WORLD TRADE CENTER HEALTH PROGRAM

RESEARCH PRINCIPAL INVESTIGATOR

AUTUMN/WINTER MEETING

REVIEWS OF WTC-RELATED MENTAL HEALTH DISEASES

NOVEMBER 15, 2017

PARTICIPANTS

Moderators

- Benjamin J. Luft, M.D.: Stony Brook University
- Evelyn Bromet, Ph.D.: Stony Brook University

Speakers

- Robert Brackbill, Ph.D., MPH: NYC Dept. of Health
- Jennifer Yip, MPH: FDNY
- Robert Pietrzak, Ph.D.: Yale University
- Roman Kotov, Ph.D.: Stony Brook University
- Alfredo Morabia, MD, PhD.: Queens College

PARTICIPANTS (CONTINUED)

Speakers (continued)

- Sean Clouston, Ph.D.: Stony Brook University
- Pei Fen Kuan, Ph.D.: Stony Brook University
- Adriana Feder, M.D.: Mount Sinai Medical Center

Guest Participants

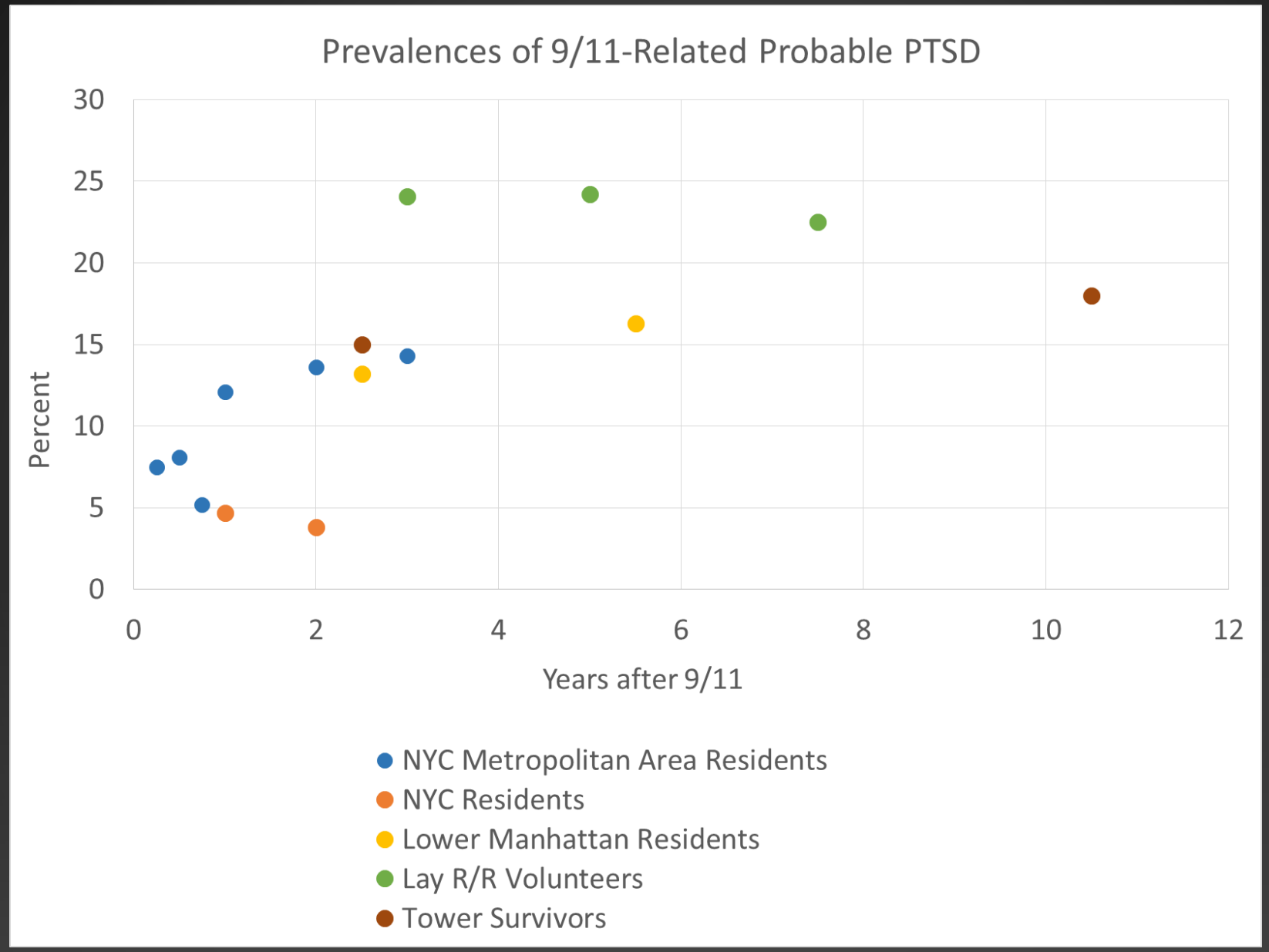
- Arieh Y. Shalev, M.D.: New York University
- Christine DeLorenzo, Ph.D.: Stony Brook University
- Rachel Yehuda, Ph.D.: Mount Sinai School of Medicine

PTSD – A COMPLEX DISORDER

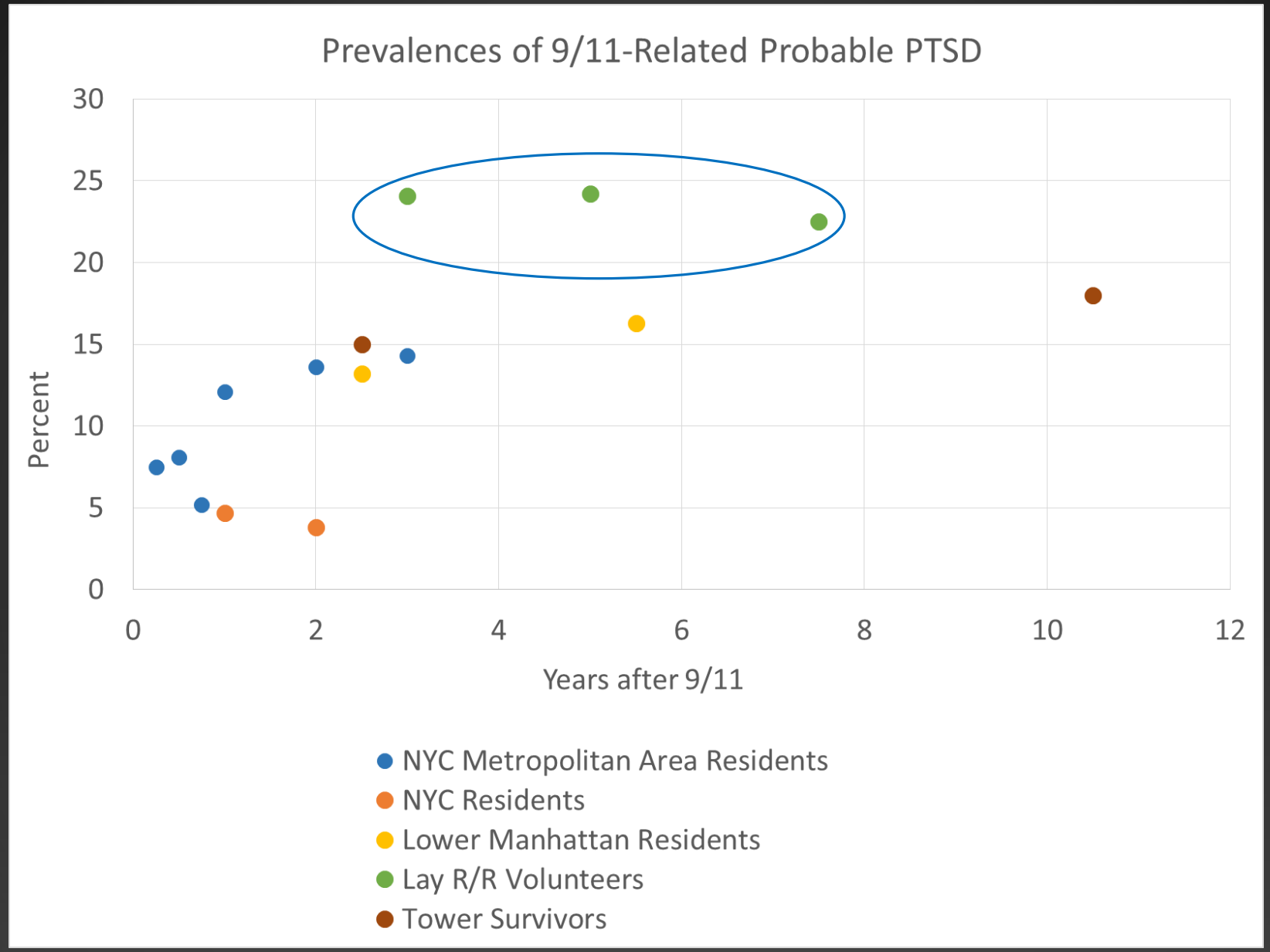
- Majority do not develop PTSD upon trauma exposure
- Multisystem disorder, comorbidity with depression, substance use, other medical conditions
- Failure to mount appropriate stress response, failure to extinguish fear responses
- Risk varies by trauma type, exposure severity, # of traumas, age at exposure(s), other stressful life events
- Genetic risk, GxE, epigenetics
- Biological mechanisms: dysfunction in stress response systems, including HPA axis, NE, endocannabinoid, inflammatory and other systems.

CONSIDERATIONS FOR PREVALENCE AND RISK FACTORS OF PTSD AND OTHER DISASTER RELATED MENTAL HEALTH CONSEQUENCES

- PTSD = signature diagnosis following disasters
- Lifetime prevalence of PTSD in US = 6.4 to 9%
- Most disaster surveys use screening scales/probable PTSD dx
- Probable PTSD prevalence = 30% to 40% in directly exposed groups over the 2 years after event
- Key risk factors: prior psychopathology; severity of exposure; pre-disaster trauma; female gender
- Few longitudinal disaster studies on long-term course of PTSD or related consequences

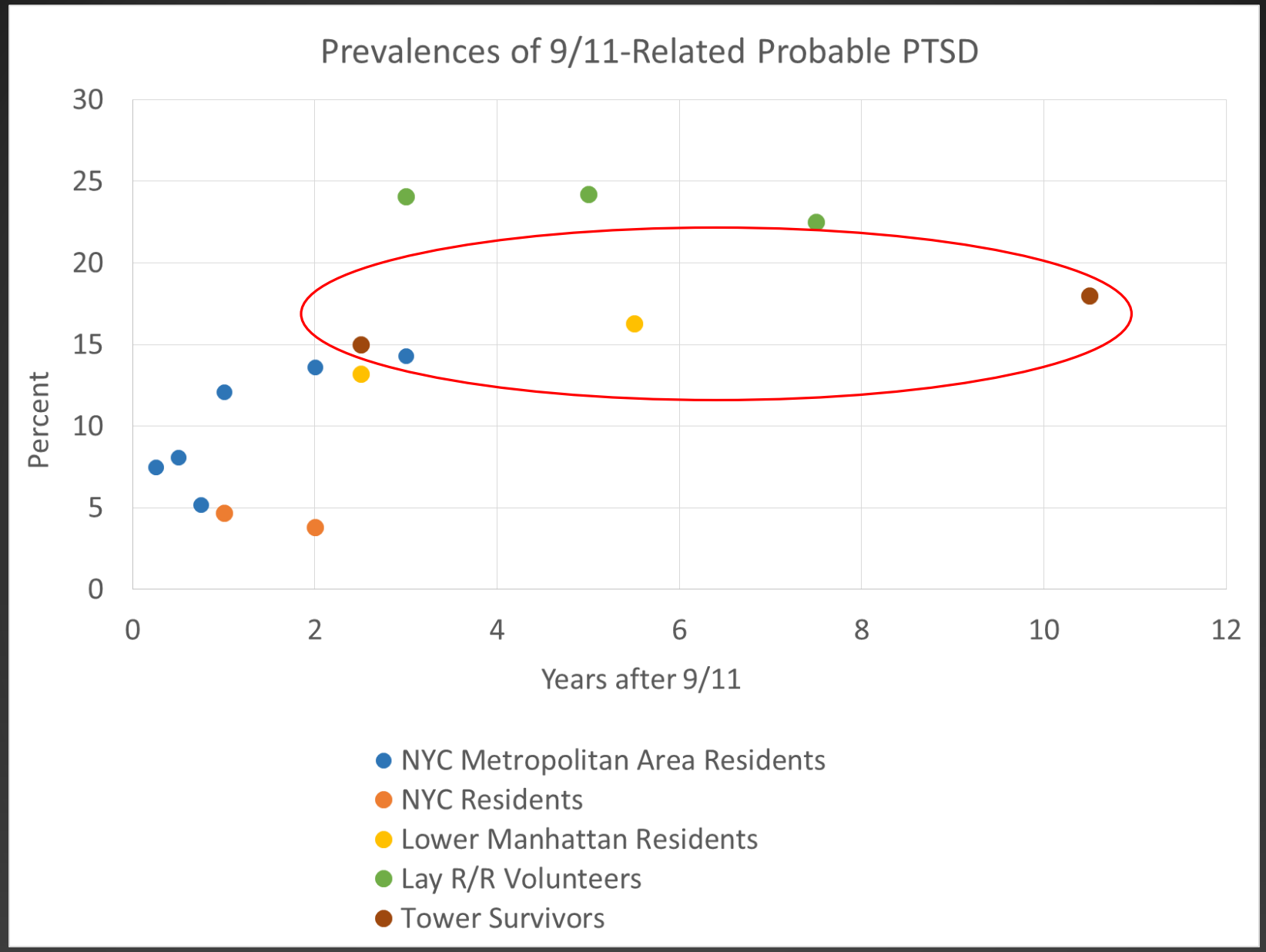


Galea et al, 2008; Brackbill et al, 2009; Galea et al.2003;Pietrzac et al, 2014;DiGrande et al, 2011;Gargano et al, 2016



Galea et al, 2002;Galea et al, 2004; Adams & Boscarino, 2006; Pietrzak et al, 2004;DiGrande, 2011;Brackbill, 2009;Gargano, 2016

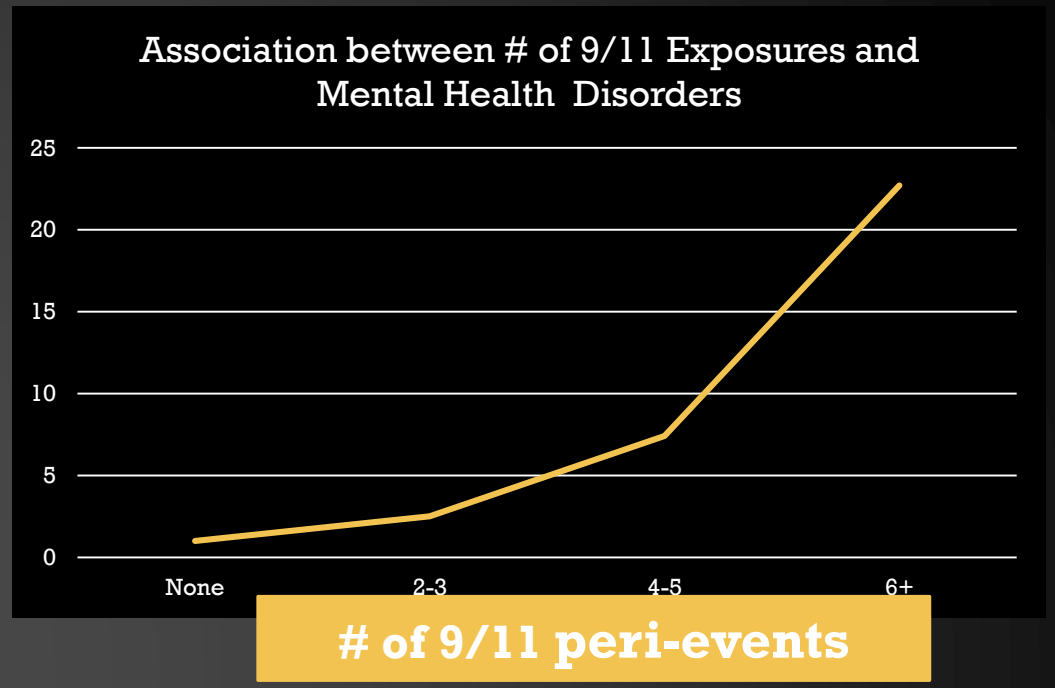
Galea et al, 2008; Brackbill et al, 2009; Galea et al.2003;Pietrzac et al, 2014;DiGrande et al, 2011;Gargano et al, 2016



Galea et al, 2002;Galea et al, 2004; Adams & Boscarino, 2006; Pietrzak et al, 2004;DiGrande, 2011;Brackbill, 2009;Gargano, 2016

Galea et al, 2008; Brackbill et al, 2009; Galea et al.2003;Pietrzac et al, 2014;DiGrande et al, 2011;Gargano et al, 2016

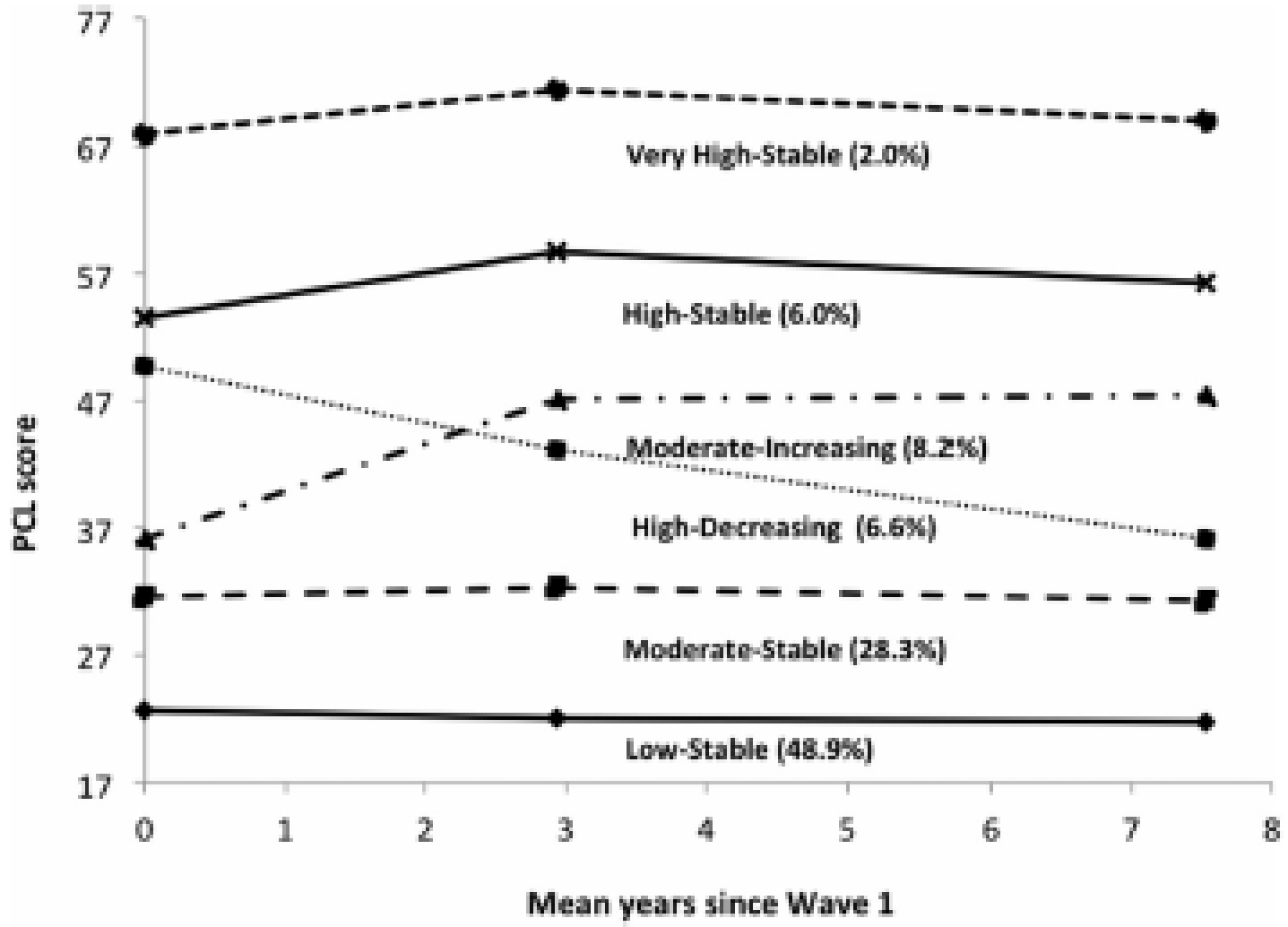
RISK FACTORS FOR WTC-PTSD (AOR/RR)



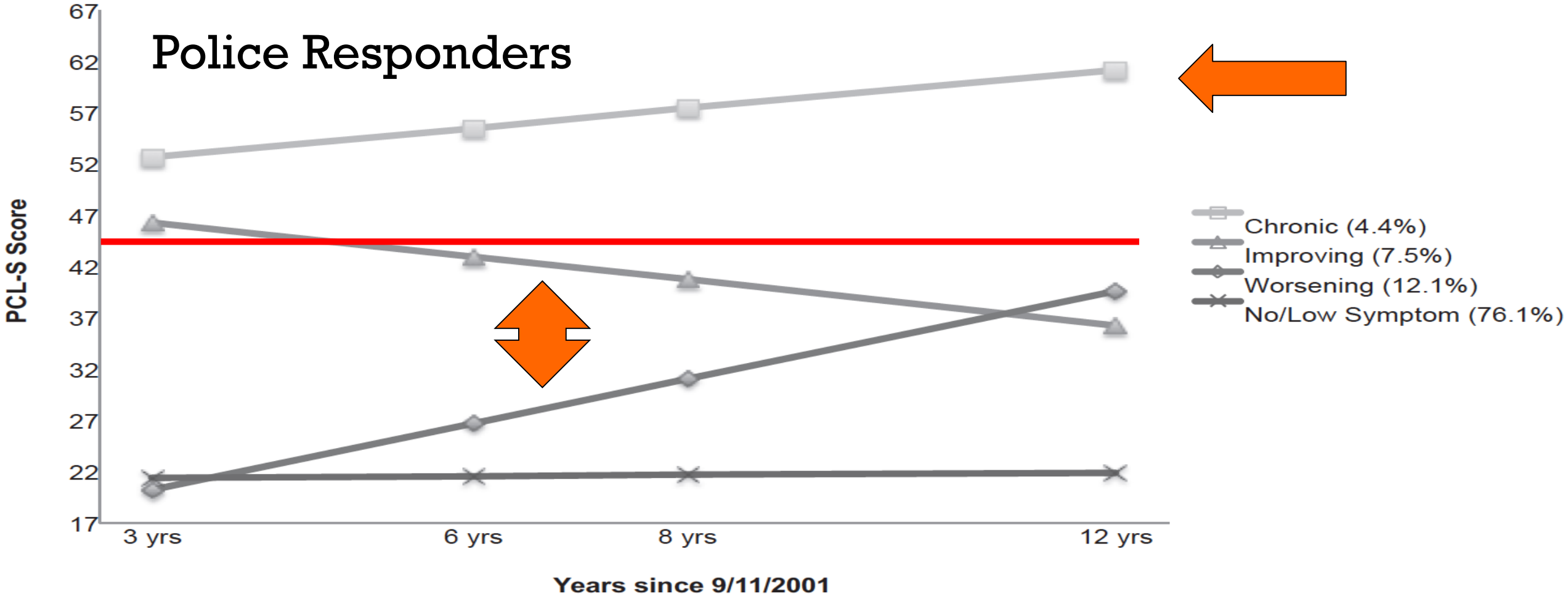
- Pre event: Female (2), Hispanic (2), prior 9/11 MH diagnosis (2)
- Peri-event: Witnessed horror (2), intense dust cloud (2), personal injury (3), panic (2); loss/death of other – 2-30 (co-worker, friend, relative, spouse)
- Post-event: Lost job b/c 9/11 (5), low social support (2-5), multiple stressful life events (2)

Galea et al, 2003;Galea et al, 2008;DiGrande et al, 2011;Brackbill et al, 2009; Brackbill et al, 2013

Welch et al.


77
67
57
47
37
27
17
PCL score
Very High-Stable (2.0%)
High-Stable (6.0%)
Moderate-Increasing (8.2%)
High-Decreasing (6.6%)
Moderate-Stable (28.3%)
Low-Stable (48.9%)
0
1
2
3
4
5
6
7
8
Mean years since Wave 1

Police Responders



Feder et al 2016

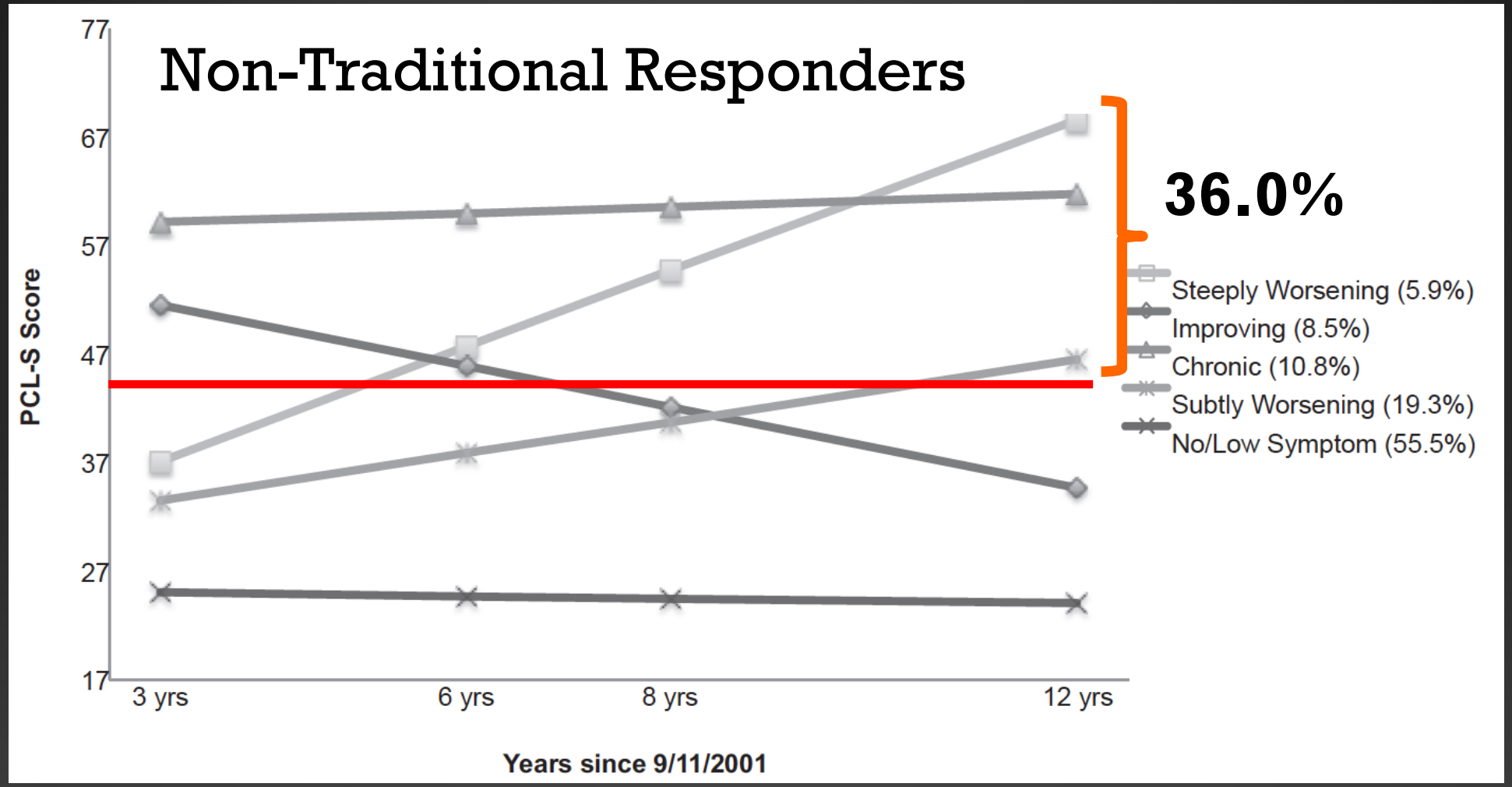
+ Ever Screen WTC-related PTSD: 11.9%

+ Current Screen WTC PTSD: 4.4%

LT PTSD in US adults: 6.8%

Current PTSD in US adults: 3.6%

National Comorbidity Survey-Replication

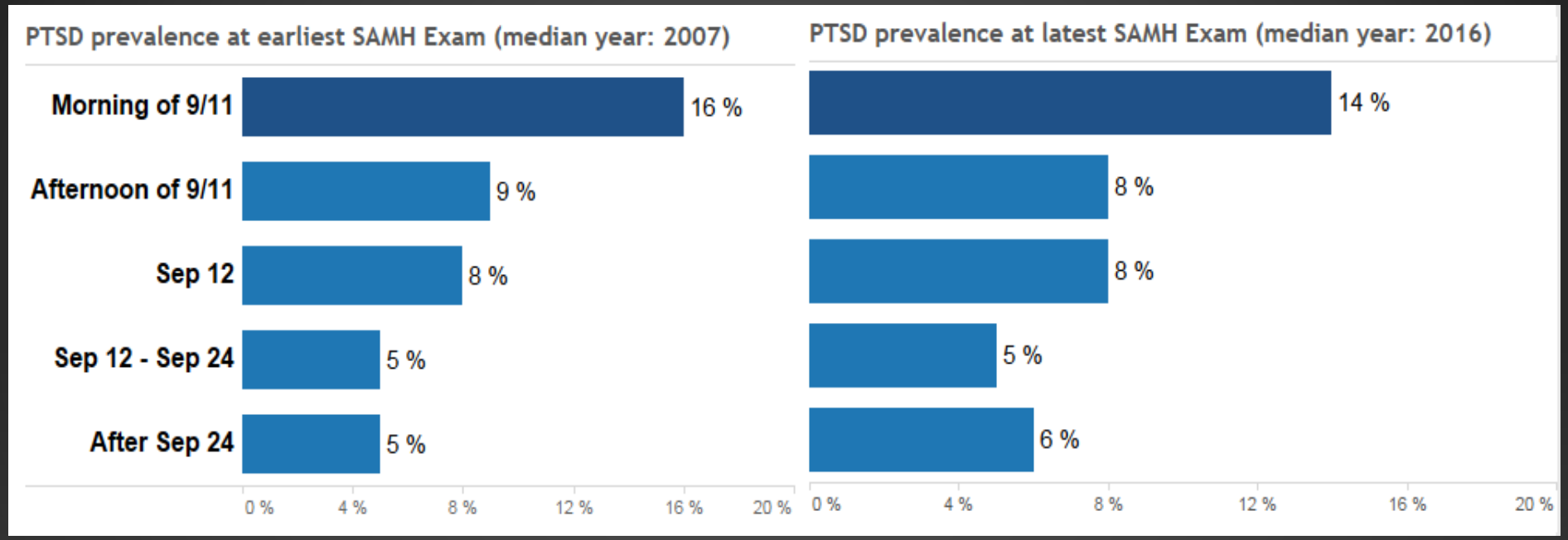


Feder et al 2016

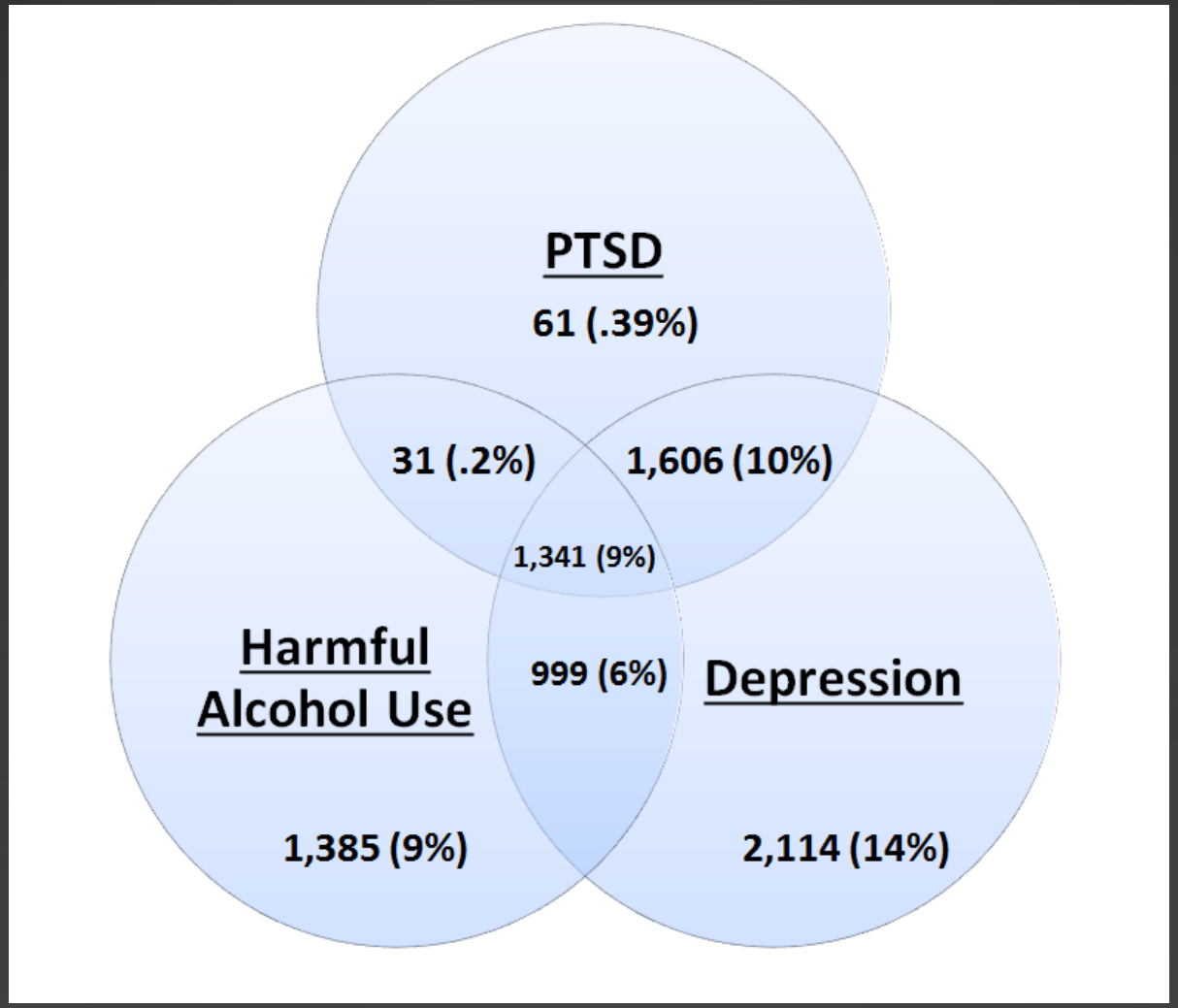
+ Ever Screen WTC-related PTSD: 44.5%
+ Current Screen WTC PTSD: 36.0%

LT PTSD in US adults: 6.8%
Current PTSD in US adults: 3.6%
National Comorbidity Survey-Replication

Arrival Time at the WTC site and PTSD prevalence



COMORBIDITY OF WTC-RELATED MENTAL HEALTH CONDITIONS



BURDEN OF PTSD-LRS COMORBIDITY

PTSD and spirometry are unrelated

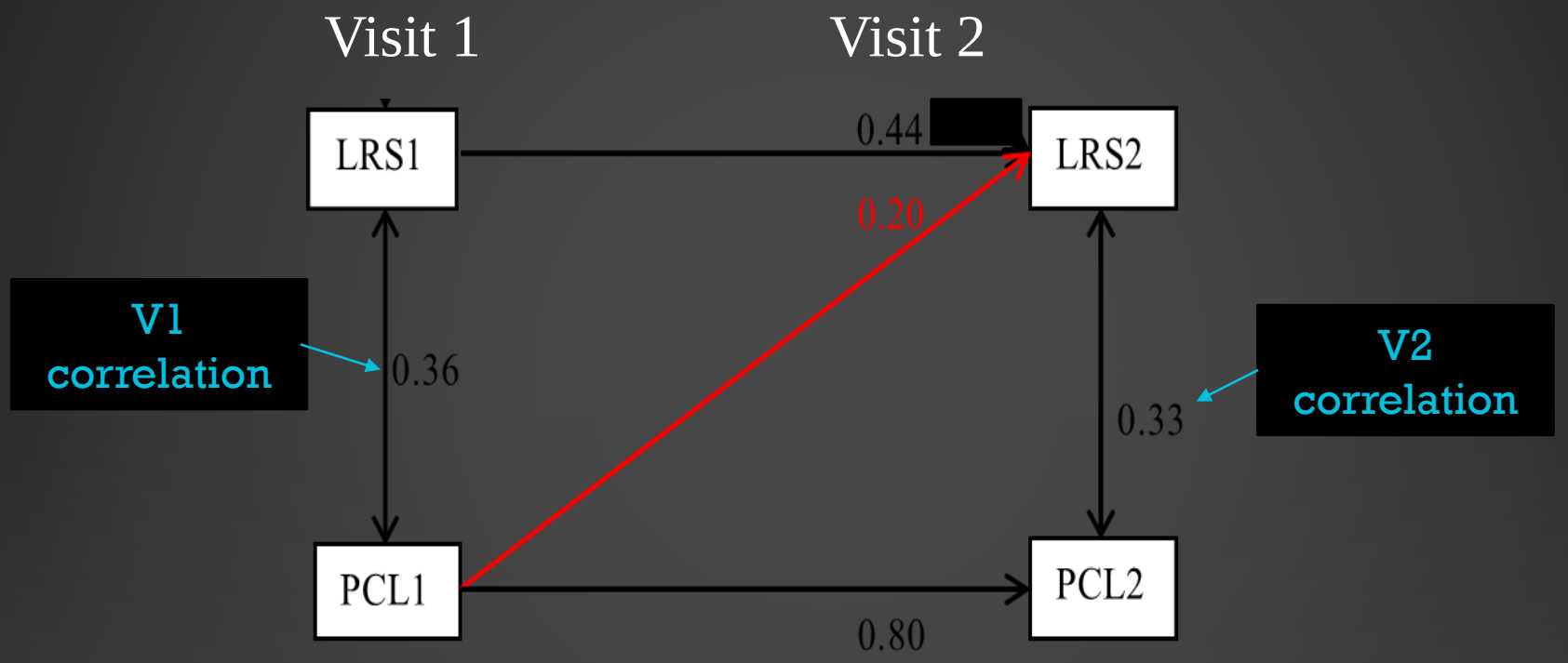
PTSD and LRS are highly correlated

N=935, Initial (2002-2003) and Recent (2013 – 2016)

Prob.	LRS	
PTSD	Initial	Recent
Absent	62%	43%
Present	88%	83%

Prevalence of PTSD increased 1.4-fold

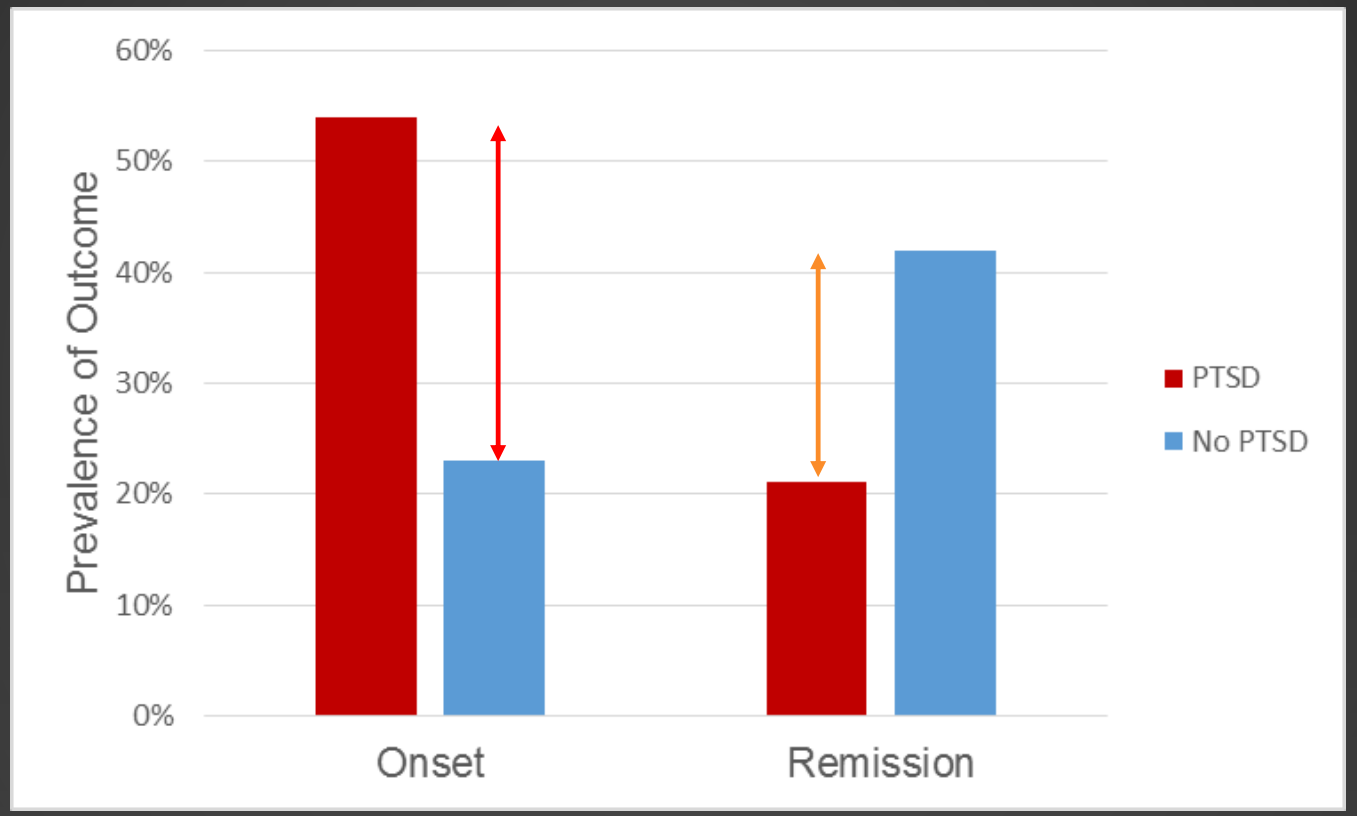
LONGITUDINAL EFFECTS (8,466 POLICE OFFICERS)



PCL = PTSD symptoms
LRS1 -> PLC2 is not significant

Kotov et al. (2015). Psychosomatic Medicine

ONSET AND REMISSION OF VISIT 2 LRS BY VISIT 1 PTSD



Visit 1 PTSD vs no PTSD: twice onsets & half remissions

Kotov et al. (2015). Psychosomatic Medicine

OVERALL

PTSD-LRS comorbidity is high and enduring

Direction: PTSD -> poor respiratory outcomes

Time scale: Effects of PTSD on LRS occur within a day

Likely mediators of PTSD effect:

- Inflammation
- Physiological hyperactivity
- Poor sleep
- Medication non-adherence

PTSD treatment improves LRS. Need to also target mediators

BIOMARKER STUDIES IN WTC RESPONDERS

Trauma exposures

↓

Gene activation (epigenetic influences)

↓

Molecular changes in stress-responsive networks

(RNA levels, protein states)

↓

PTSD risk/onset/progression/chronicity

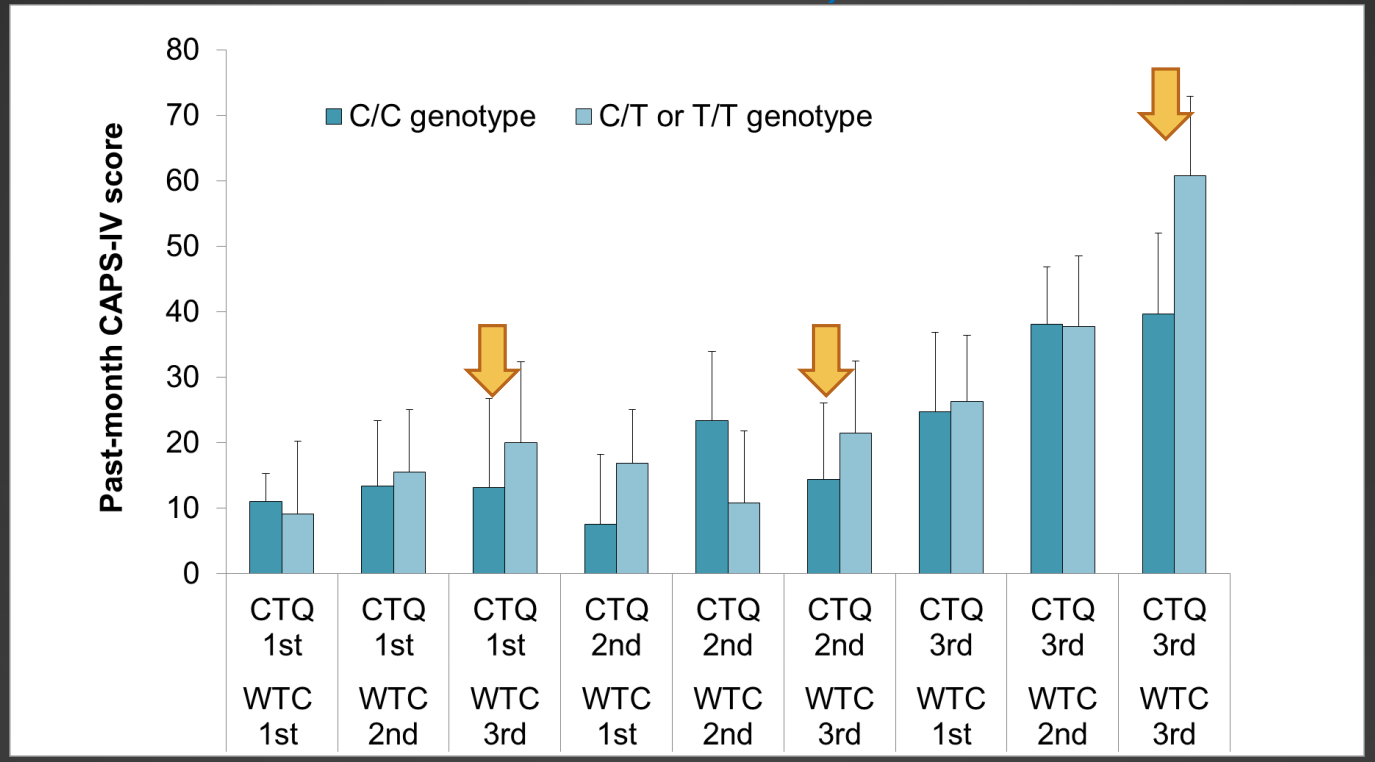
Neylan, Schadt & Yehuda 2014

MULTIPLE BIOLOGICAL LEVELS
FOCUS ON HPA AXIS AND ECB SYSTEM

- PTSD symptom trajectories in WTC responders
- Complex phenotype and life histories (in-person SCID, CAPS, childhood trauma, lifetime trauma, WTC experience, post-9/11 stressful life events)
- N=385 (Mt Sinai, NYU, Queens & UMDNJ CCEs)
- Multidimensional approach to examine HPA axis function
  - Candidate genes (GR, FKBP5), GxE
  - DNA methylation and gene expression
  - HPA axis function:
    - 24-hour urine cortisol
    - GR sensitivity in peripheral lymphocytes
    - Challenge test: DST pre-/post-DEX plasma cortisol and ACTH levels
  - Add eCB system function measures (eCB plasma levels)
- Composite additive genetic risk score

NIOSH U01 OH010407, U01 OH010986

SIGNIFICANT GENOTYPE (FKBP5 SNP RS1360780) X CHILDHOOD TRAUMA SEVERITY (CTQ) X WTC EXPOSURE SEVERITY PREDICTS CURRENT AND LIFETIME PTSD SYMPTOM SEVERITY (CAPS-IV SCORE)



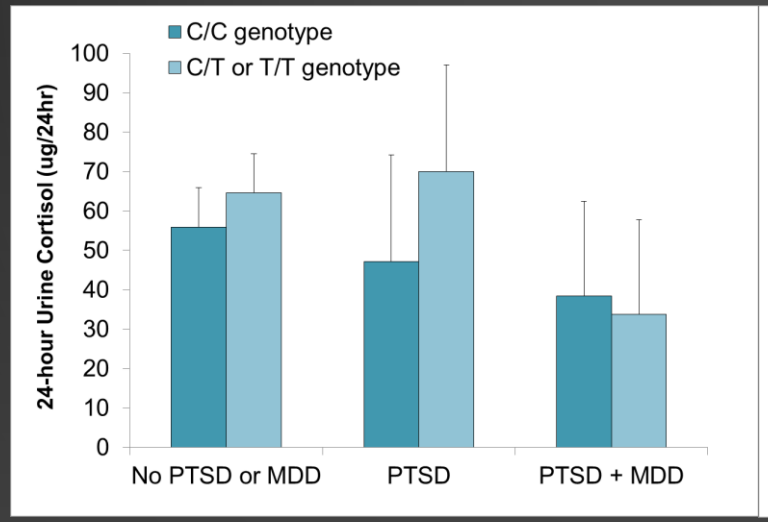
N=318 police and non-traditional WTC responders assessed face-to-face with the Clinician-Administered PTSD Scale (CAPS), from **2013 to 2017**.

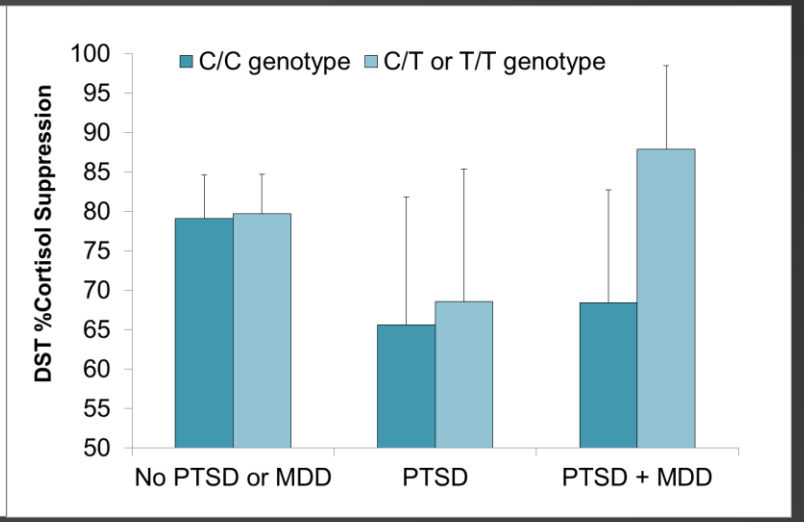
CTQ and WTC exposure **tertiles** (1st, 2nd and 3rd).

COMBINING BIOMARKERS TO UNCOVER PTSD BIOTYPES

- Stratification of patient populations into biological subtypes
- Future mapping of biotypes to specific treatments (Neylan et al 2014)

Association between Group and DST Percent Cortisol Suppression is Moderated by FKBP5 rs1360780 Genotype; but not for 24-hour Urinary Cortisol



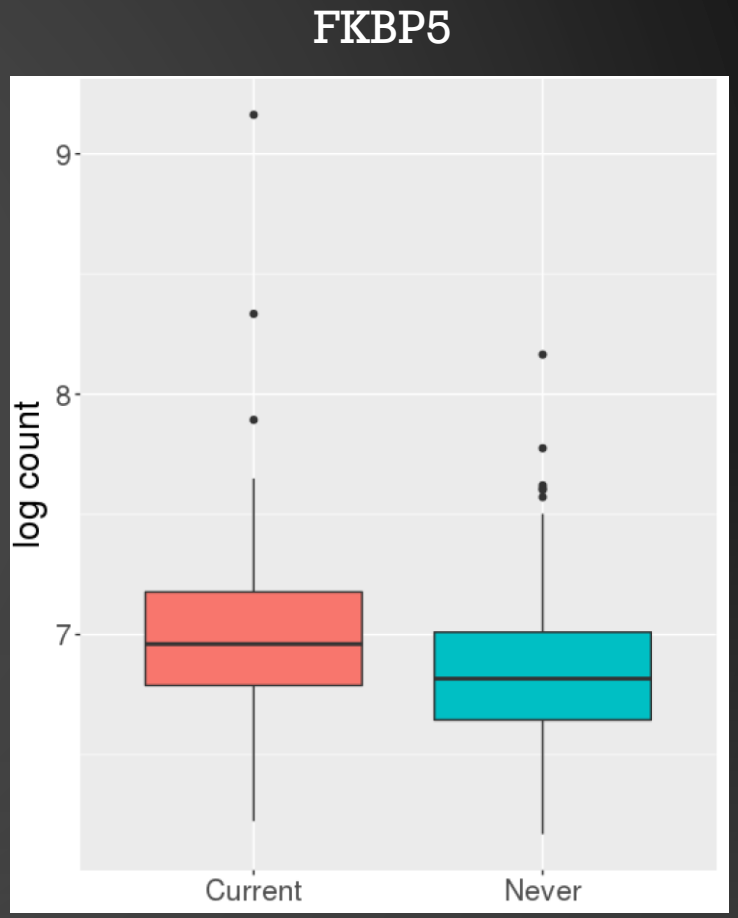


"Extreme" groups: n = 161, 12, 24

WTC WELLNESS PROGRAM

GENE EXPRESSION RESULTS

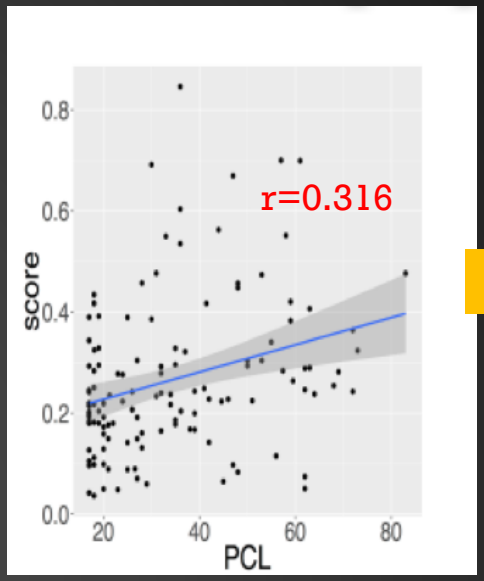
- ~100 genes associated with PTSD
- Top gene FKBP5: regulation of the glucocorticoid receptor and immunological responses to stress
- Top pathway: glucocorticoid receptor signaling



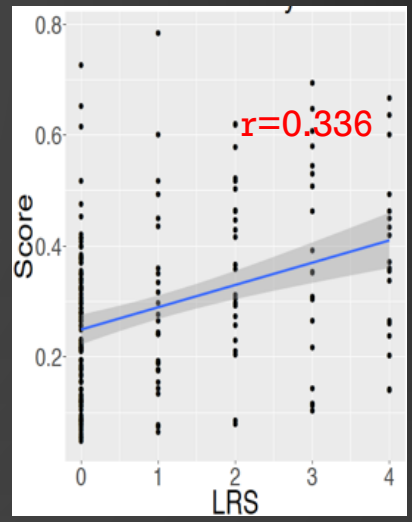
WTC WELLNESS PROGRAM

GENE EXPRESSION (GE) RESULTS

- A prediction model for PTSD was constructed using machine learning tools
- GE score (GES) computed from the model achieves AUC 0.764 (vs best single gene AUC 0.64), and is positively associated with PCL and LRS



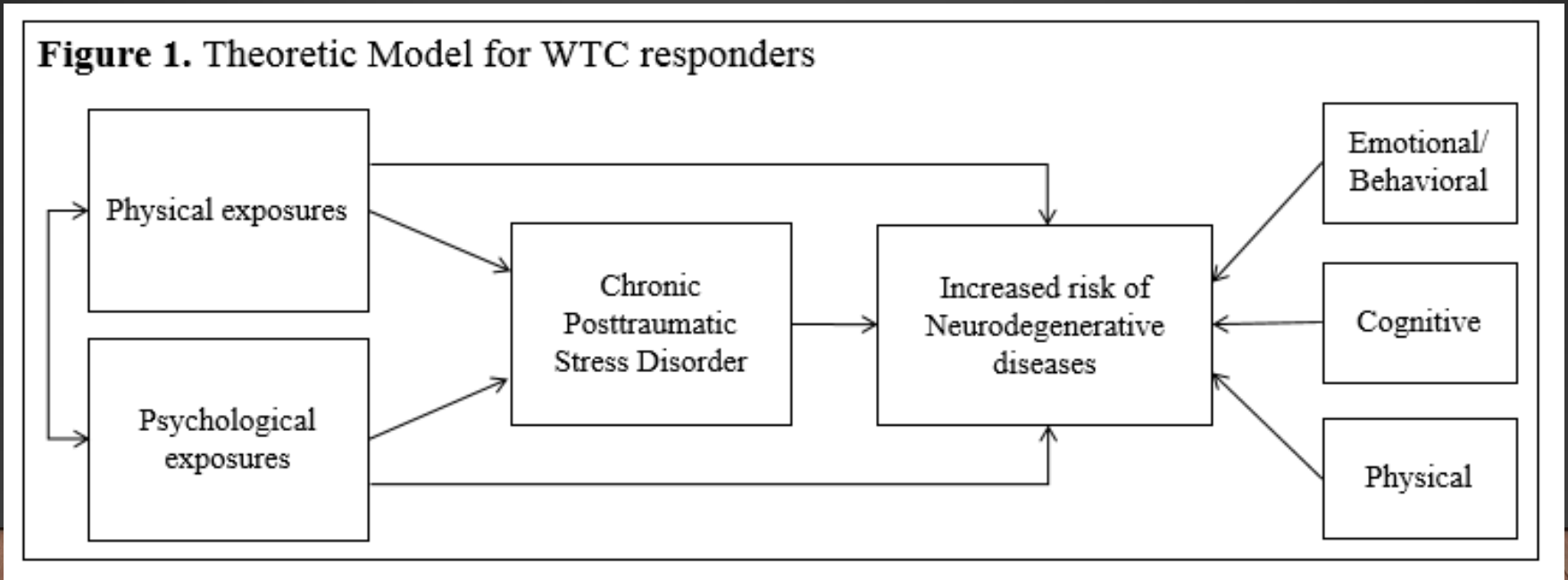
GES vs PCL



GES vs LRS

PTSD MAY CAUSE NEURODEGENERATION (ND)

- Extends results from: VA studies, stress research at the Einstein Aging study, Holocaust survivors, Nuns study, Longitudinal Aging Study Amsterdam, and the Whitehall study
- Two possible pathways from WTC experiences to brain aging
- We must also note the impact of ND across domains of functioning



Clouston et al. WTC Nov 2017

COGNITIVE IMPAIRMENT (CI) IS COMMON IN WTC RESPONDERS

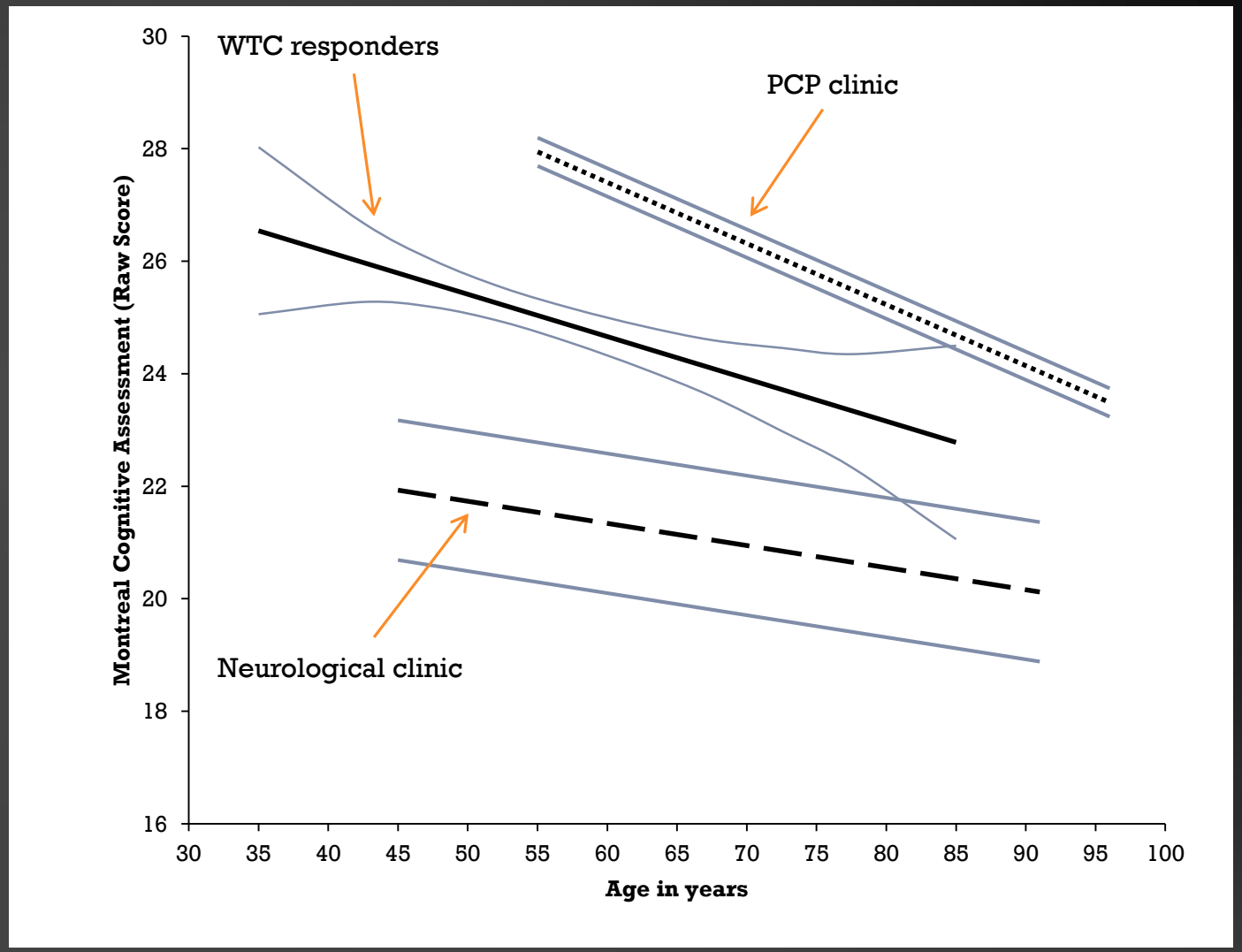
WTC Responders may be aging more quickly than healthy comparison (but slower than neurologically impaired)

12.8% screen positive for any CI

1-2% have severe cognitive impairment (SCI)

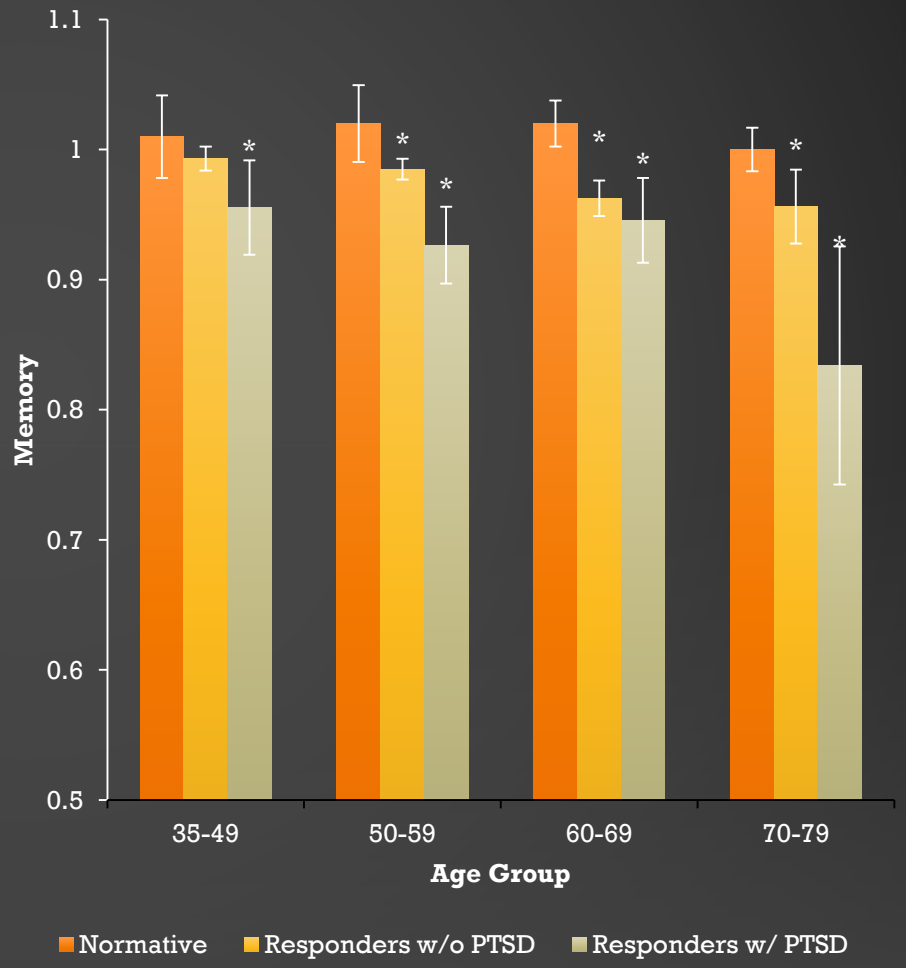
Risk and severity of CI is significantly ssociated with PTSD

- Most strongly with PTSD symptom severity measured at enrollment



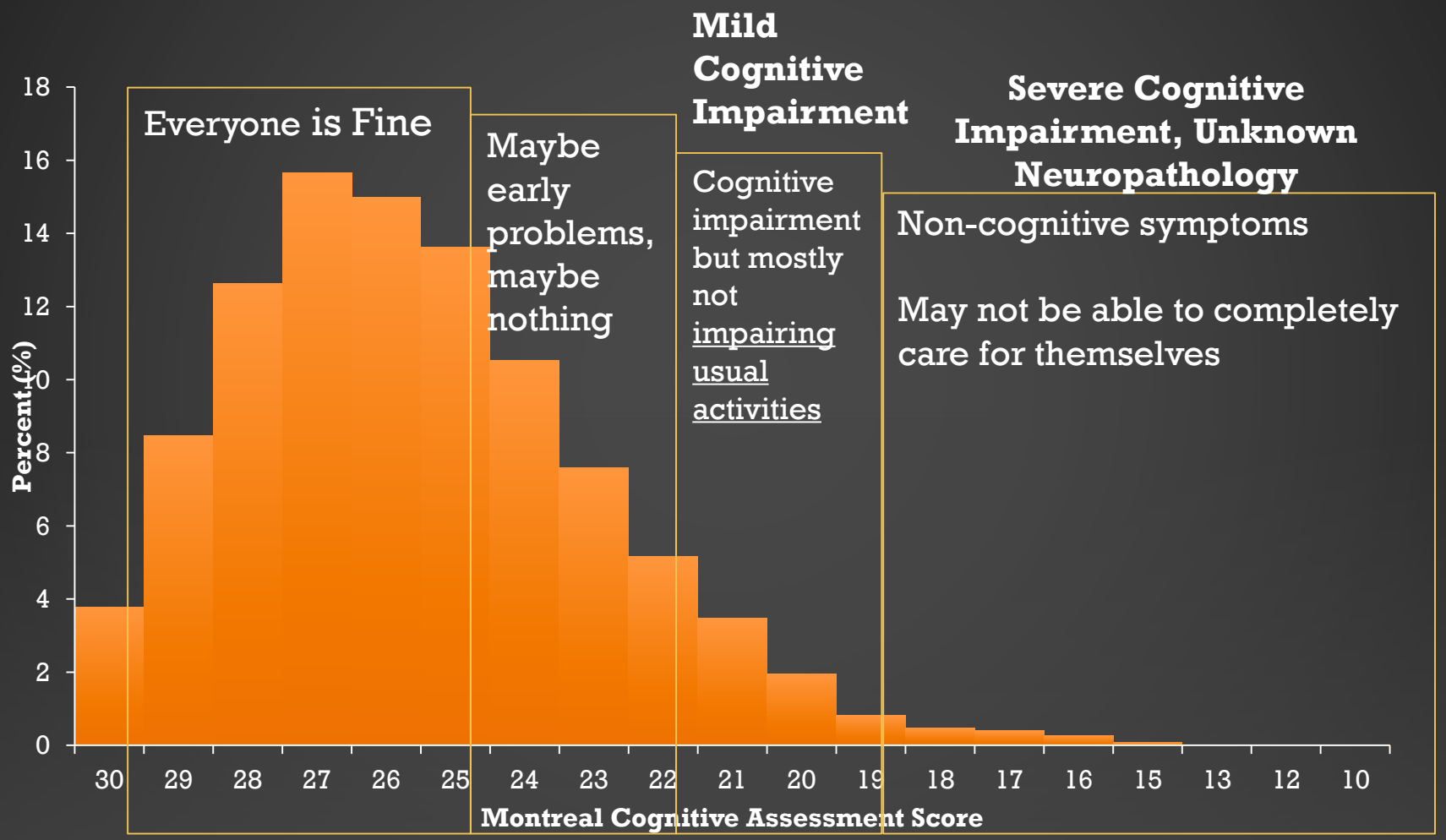
COGNITIVE DOMAINS LINKED TO ND DIMINISHED IN PTSD

- WTC responders were worse than age-matched norms
- PTSD was strongly associated with cognitive dysfunction
- WTC exposures moderately associated with cognitive dysfunction
- Same increase in depressive symptoms over time among those with cognitive dysfunction



Clouston et al. WTC Nov 2017

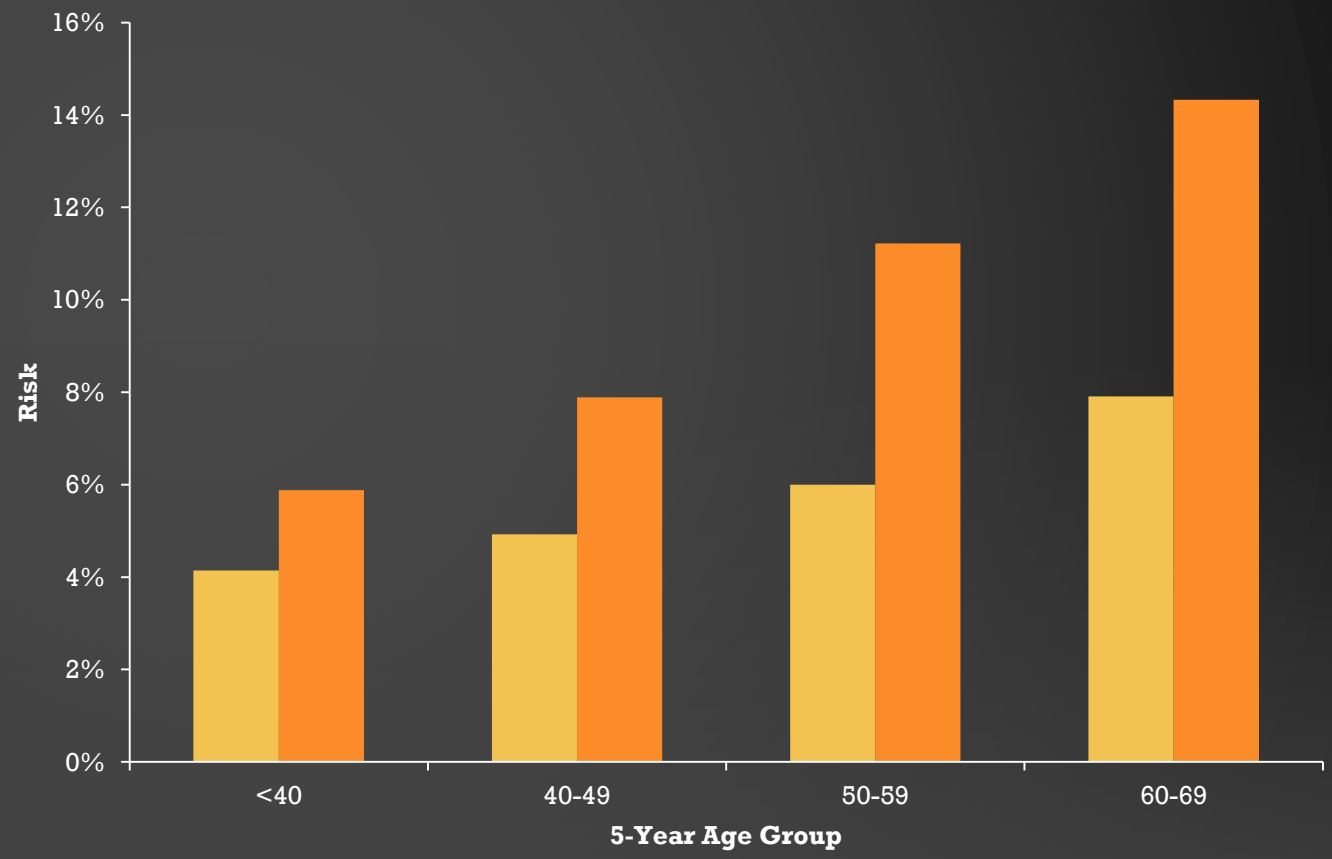
MANY RESPONDERS HAVE "REAL" TROUBLES



THE RISK OF CI INCREASES AS RESPONDERS AGE

- We find that both prevalent CI (at baseline) and CI with evidence of decline (MCI) are age-graded

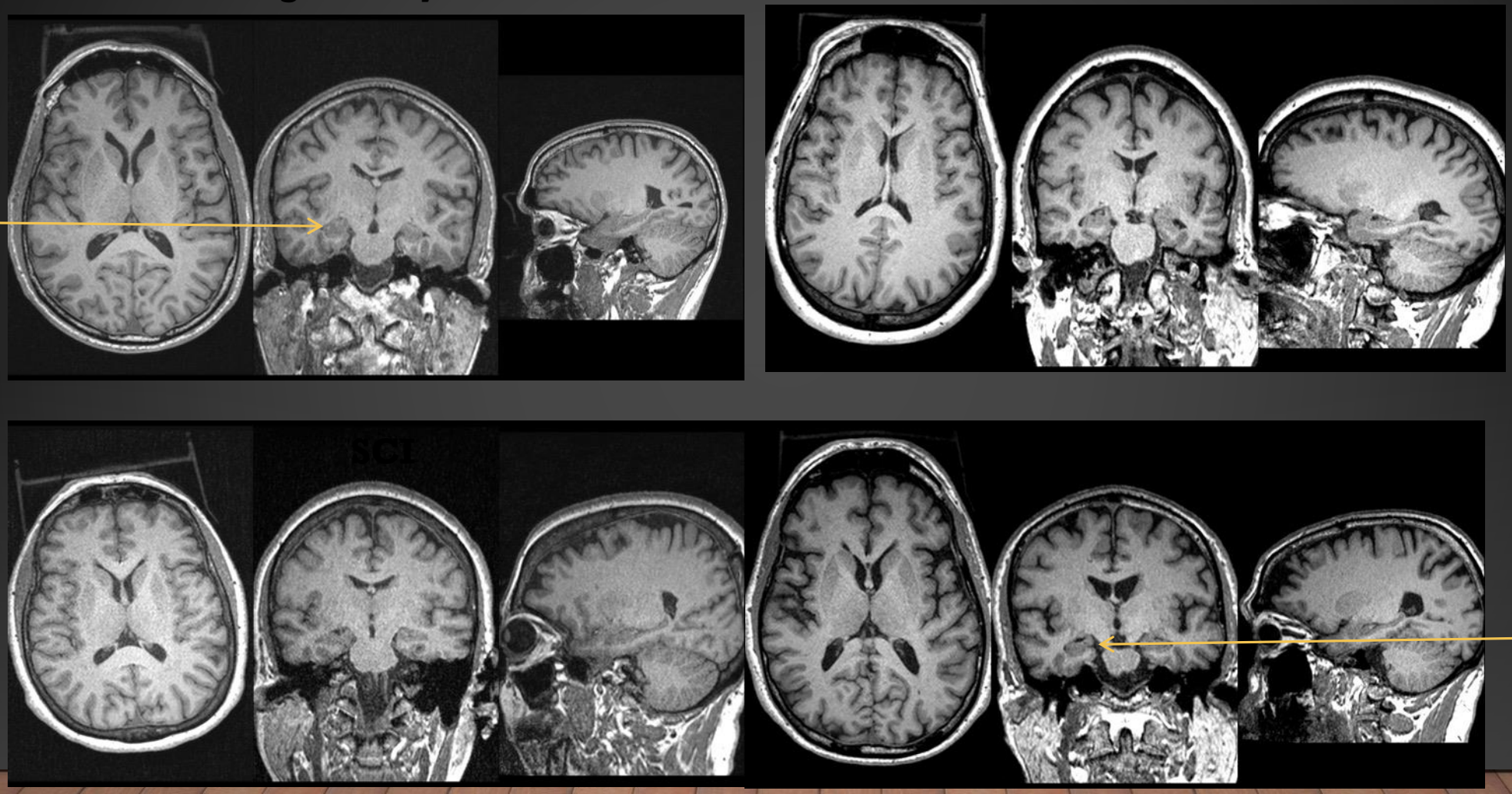
- Increase in risk is around 3% per year for MCI



EARLY RESULTS IDENTIFY ND IN NEUROIMAGING

Cognitively Normal

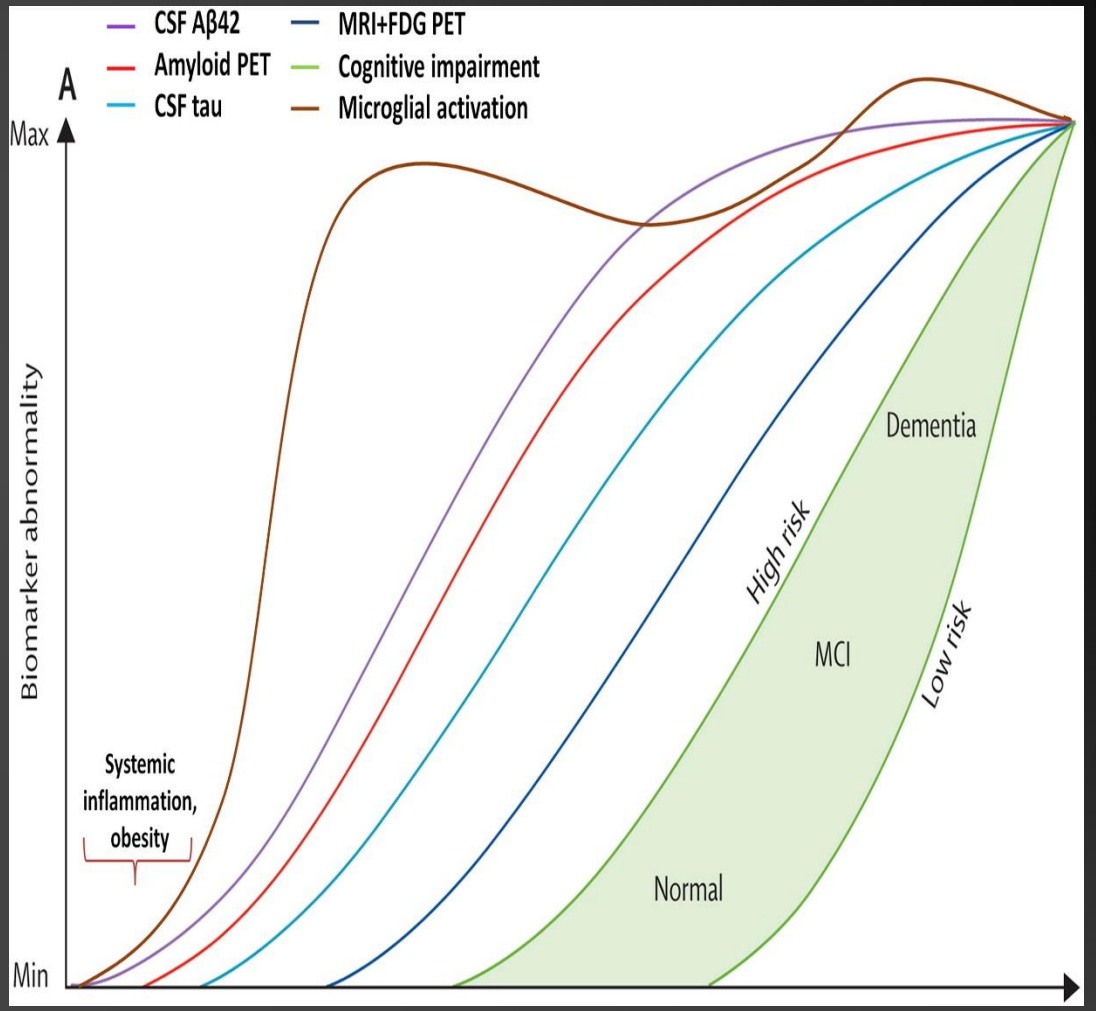
Hippocampus



Hippocampus

WE NEED TO UNDERSTAND THE PATHOLOGY OF CI

- Severe and Mild forms of CI are sometimes different–
  - We really need to know how many WTC responders have signs of neurodegeneration
  - We also need to know whether Severe and Mild CI look similar
- Early markers of neural dysfunction can be informative –
  - There is potential for neuroinflammation among responders with PTSD
  - Does neuroinflammation relate to MCI in this population
  - How common is neuroinflammation
- Are MCI-related impairments pathognomonic of Alzheimer's or another disorder?
- *We need to identify the pathology*



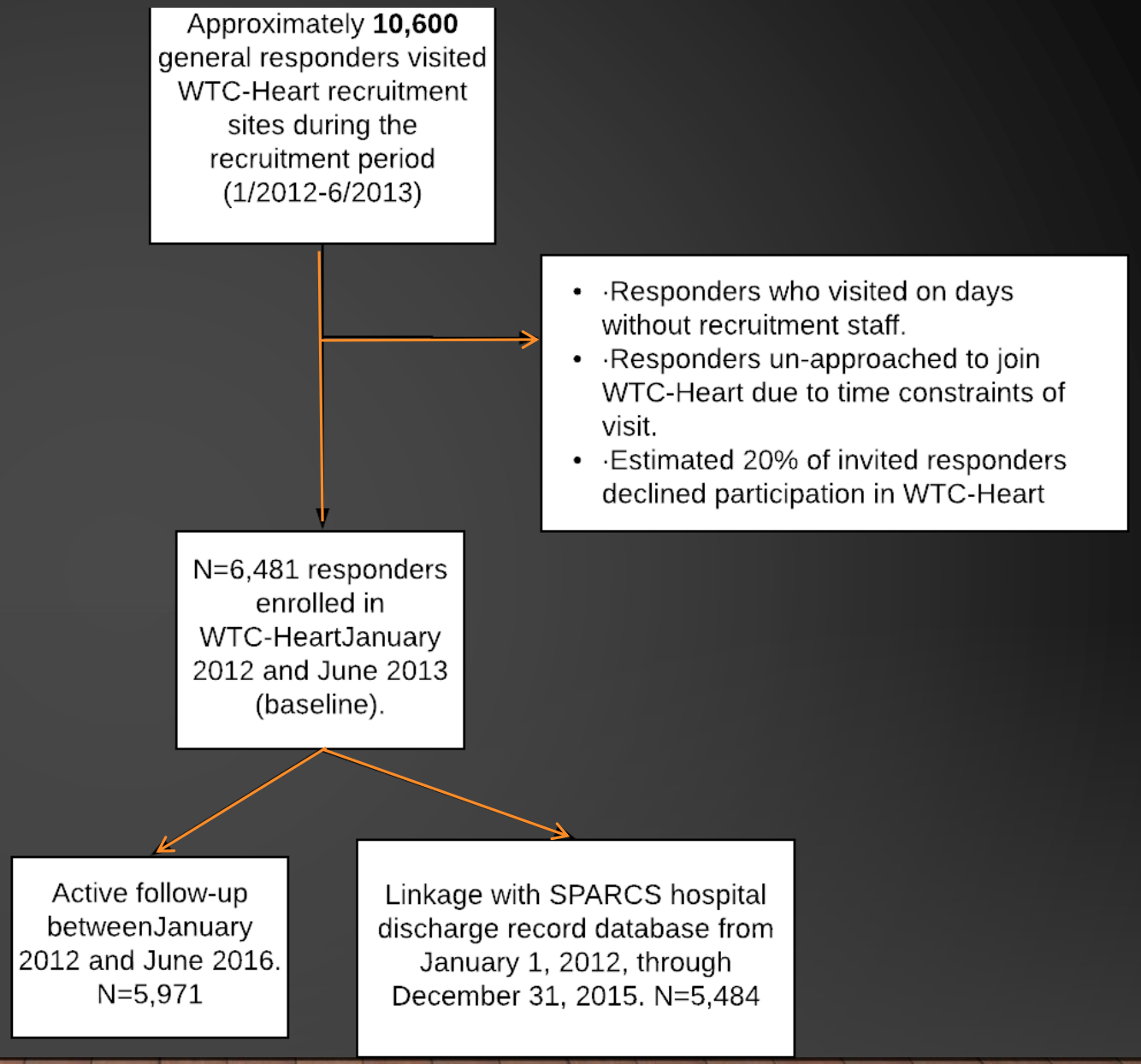
Clouston et al. WTC Nov 2017

PTSD & CARDIOVASCULAR DISEASES IN MALE AND FEMALE FIRST-RESPONDERS: THE WORLD TRADE CENTER-HEART COHORT STUDY

WTC-HEART

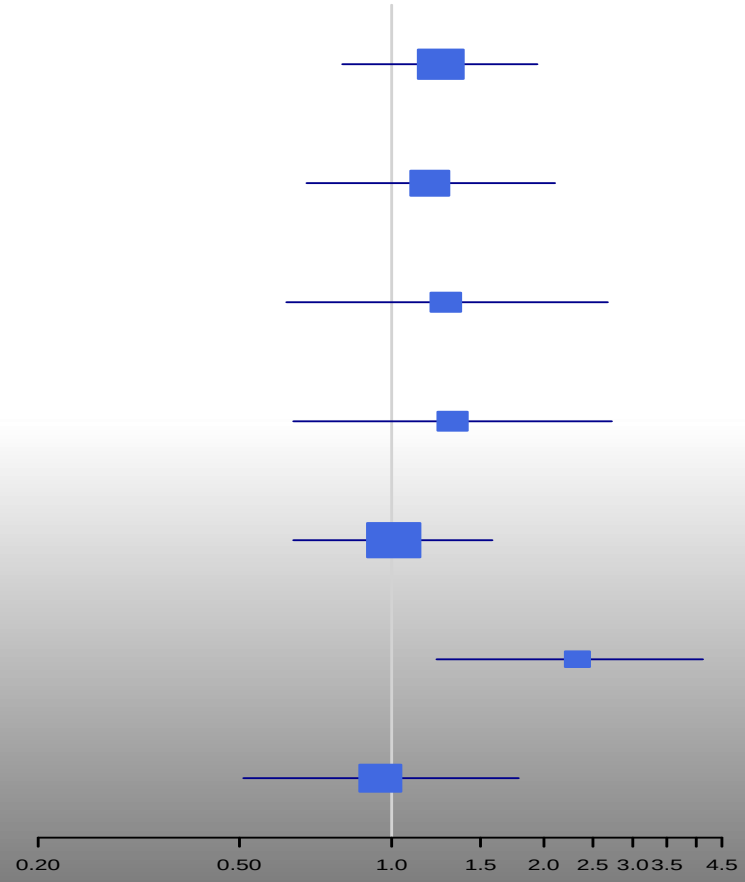
- Prospective, fixed cohort of 6481 WTC first responders recruited within WTCHP
- Active follow-up for incident and recurrent CVD from January 2012 until June 2016, remotely via email, mail, and phone interviews in English, Spanish, and Polish.
- Also linked with the NY State hospitalization database, SPARCS
- Common singular exposure in 2001-2 (Natural experiment)
- Active follow-up for incident and recurrent events
- Middle-aged
- Measured CVD risk factors
- High prevalence of PTSD

WTC-HEART -- DESIGN

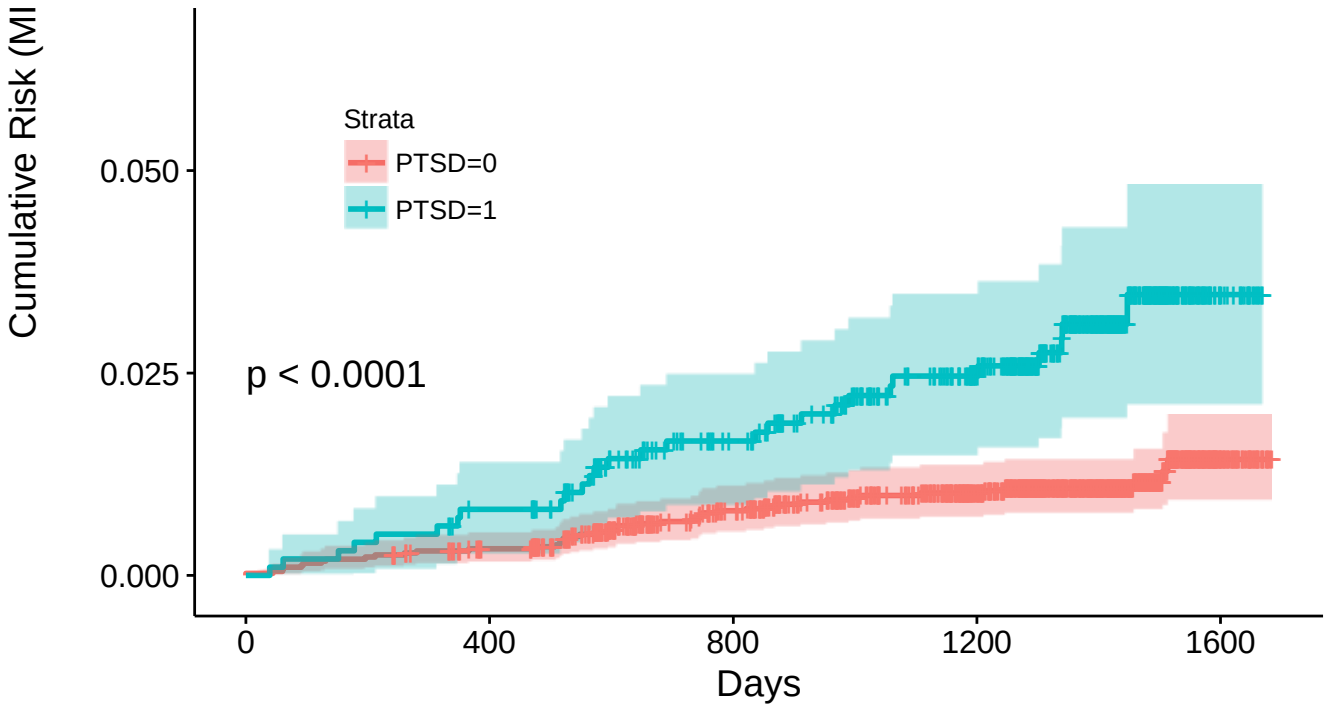


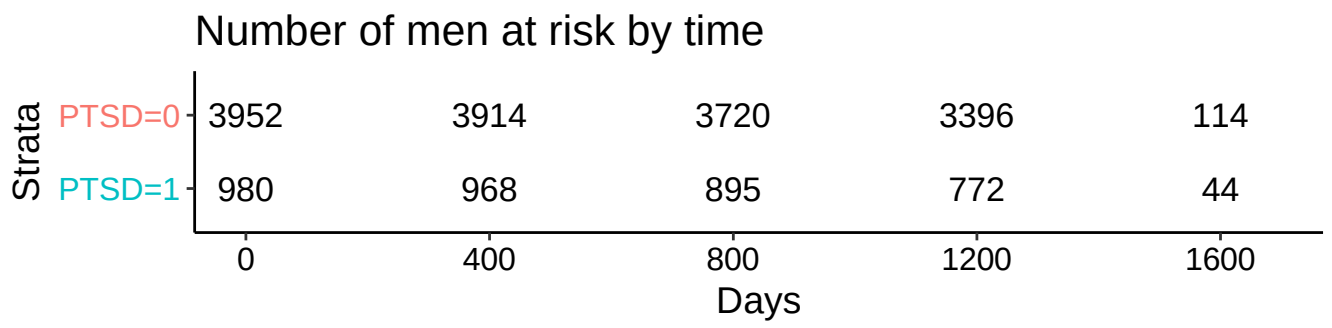
WTC-HEART – RISK FACTORS

Risk Factors	Comparisons	aHR
Blood Pressure	High/Normal	1.25
Total Cholesterol	High/Normal	1.19
BMI	Overweight/Normal	1.28
	Obese/Normal	1.32
Cigarettes	Former/Never	1.01
	Current/Never	2.33
Used Respirator	yes/no	0.95

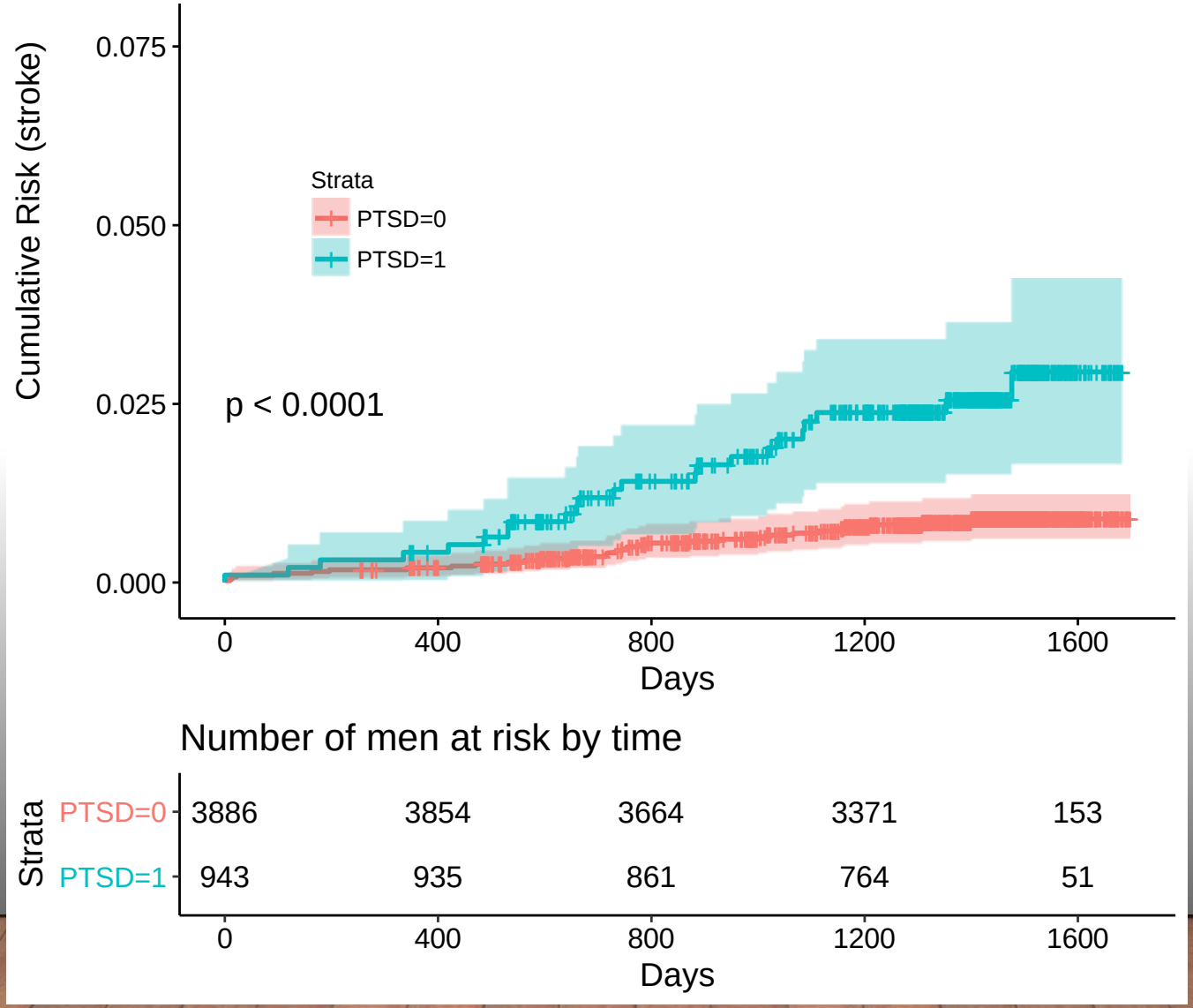


WTC-HEART – PTSD & MI





WTC-HEART – PTSD & STROKE



WTC-HEART – PTSD & MI/STROKE

			PTSD		Age-adjusted			Multivariate*		
Gender	**Outcome**	**Measure**	**yes**	**No**	**HR**	**95% CI**		**HR**	**95% CI**	
			Cases			**LL**	**UL**		**LL**	**UL**
Men	MI	Incident	23	38	2.29	1.36	3.85	2.22	1.25	3.94
	Stroke	Incident	19	27	2.71	1.25	3.94	2.76	1.48	5.13
	MI or Stroke	Incident	41	61	2.55	1.71	3.79	2.46	1.60	3.78

WTC-HEART – PTSD & MI/STROKE

			PTSD		Age-adjusted			Multivariate*		
Gender	**Outcome**	**Measure**	**yes**	**No**	**HR**	**95% CI**		**HR**	**95% CI**	
			Cases			**LL**	**UL**		**LL**	**UL**
Men	MI	Hospitalization	34	47	2.79	1.78	4.34	2.89	1.75	4.76
	Stroke	Hospitalization	26	35	2.62	1.56	4.39	2.94	1.69	5.12
	MI or Stroke	Hospitalization	56	78	2.57	1.82	3.63	2.77	1.90	4.05

WTC-HEART -- CONCLUSIONS

- Because of its design, this cohort study offers unique and strong evidence that WTC attack-related PTSD is a risk factor for MI and stroke, in men and women, and independently of recognized cardiovascular risk factors and depression.

- Relevant for first responders for other disasters?

SUMMARY

- PTSD is the most common psychiatric disease in this population of patients.
- PTSD affects (between 4.4 to 36%), to varying degrees, all the population groups studied including police, firefighters, civilian volunteers, community members and children.
- Four disease trajectories have been identified in this patient populations: (1) survivors/responders with persistent symptoms of PTSD since 9/11/2001; (2) individuals whose symptoms gradually improved; (3) individuals whose symptoms worsened over time; and (4) those with minimal/low symptoms across time.

SUMMARY (CONTINUED)

- There is significant comorbidity with depression, anxiety, and substance abuse.
- PTSD is co-morbid with and predictive of medical conditions including respiratory disease and GERD.
- Significant association has been found between 9/11-related PTSD and myocardial infarction and stroke have been found.
- Mild to severe cognitive impairment is occurring with increased frequency in the responder population. This has been shown to be associated with PTSD and exposure severity. Results are replicable across instruments, and appear to be worsening with time.

RECOMMENDATIONS

1. Expanding the monitoring exam to include a broader array of lifetime risk factors, such other traumatic experiences, history of mood, anxiety, and substance use disorder, medical conditions, psychosocial disability and subsequent trauma.
2. Expanding the scope of the monitoring program to screen for cognitive and physical impairment, indicative of accelerated aging, as well as cardiovascular disease.
3. Undertaking a formal review of the quality of mental health treatment interventions in the WTC Health Program as a first step in understanding the persistence of PTSD symptoms in responders receiving treatment. This review would determine whether responders are receiving evidence-based treatments according to the American Psychiatric Association treatment guidelines as well as catalog all forms of treatments received.

RECOMMENDATIONS (CONTINUED)

4. Focusing future statistical analyses on:
   a. Links between exposure, PTSD and other systemic conditions to determine whether these conditions should be classified as WTC-connected conditions.
   b. Expanding the model of PTSD to incorporate the trajectories, psychosocial determinants, and the ensuing disability.
   c. Real time biological measures to further refine the classification, which is currently heterogeneous, and thus identify more homogeneous subgroups with different forms of PTSD.
5. Increasing its support of research on the biologic links between PTSD and the earlier than expected onset of aging-related conditions, particularly cardiovascular disease, cognitive dysfunction, and level of physical functional limitations.
6. Developing a biomedical model of disease that pulls together the multiple impacts of PTSD on medical and psychological outcomes as well as biologic, physiologic and endocrinologic changes that occur concurrently.

RECOMMENDATIONS (CONTINUED)

7. Encouraging the use of neuroimaging modalities to further define the various phenotypes found in PTSD and to correlate these to biologic markers (e.g. genetic, endocrinologic) of disease.
8. Develop RCT trials that are individualized to specific symptom clusters rather than treating PTSD as a homogeneous disorder.
9. Developing biobanks and analyzing whether specific biomarkers (e.g., immune, molecular, proteome, metabolomics, imaging) change over time or are indicators or response to specific treatments, with a special focus on potentially modifiable markers.