CHRONIC SYMPTOMS AFTER MILD TBI(S):

EARLY RESEARCH FINDINGS FROM LIMBIC-CENC, AND HOW TO OPTIMIZE BRAIN HEALTH OF THESE INDIVIDUALS

William C. Walker, MD
Ernst & Helga Prosser Professor, Virginia Commonwealth University (VCU),
Dept. of Physical Medicine & Rehabilitation, Richmond, VA
Study Chair, LIMBIC-CENC Prospective Longitudinal Study

LIMBIC CENC

Conflict of Interest Statement

- Research to be presented was supported by **Grant funding** from:
  - Dept of Defense, Chronic Effects of Neurotrauma Consortium (CENC) Award W81XWH-13-2-0095
  - Dept of Veterans Affairs CENC Award I01 CX001135.
- **Dr. Walker has no conflicts of interest to disclose**
- **Acknowledgements:**
  - CENC Observational Study Leadership Working Group and all site staff.
  - Study participants and their families
  - The research material to be presented is based upon work supported with resources and the use of facilities at: Hunter Holmes McGuire Veterans Affairs Medical Center (VAMC) in Richmond, VA; James A. Haley Veterans Hospital (VH), Tampa, FL; Michael E. DeBakey VAMC, Houston, TX; Audie L. Murphy Memorial VH, San Antonio, TX; and is based upon work supported in part by the Defense and Veterans Brain Injury Center, US Army Medical Research and Material Command (USAMRMC).
- **Disclaimer:** The views, opinions, and/or findings contained in this article are those of the authors and should not be construed as an official Veterans Affairs or Department of Defense position, policy, or decision unless so designated by other official documentation.

LIMBIC CENC

Cyberseminar Learning Objectives

- Become familiar with the basic purpose and methods of the LIMBIC-CENC Multicenter Prospective Longitudinal Study (PLS)
- Understand the key findings from the first ‘snap-shot’ data anlaysis comparing mild TBI positive versus negative participants
- Learn and be able to apply an Integrated Clinical Approach for Patients with Persistent Post-Concussion Symptoms

LIMBIC CENC

Poll Question #1

How many mild TBIs (aka concussions) do you think that you have you had in your life:

A. None for sure (not even any questionable events that may have been a mild TBI)
B. Probably none (one or more events I'm not sure if they were mild TBI)
C. One
D. Two
E. 3 or more

LIMBIC CENC

Purpose

Background: Under CENC, the PLS established an active multicenter cohort of 1550 Servicemembers and Veterans (SM/Vs) with combat exposure who have all undergone comprehensive 360^0 evaluation of brain and neurologic health and function.

Overall Goal: With LIMBIC, we will serially assess and expand this cohort, and conduct scientific analyses to answer critical questions about:

- the long-term effects of mild traumatic brain injury (mTBI), including any evidence of neurodegeneration
- the relationship to other factors and sequalae of combat deployment

that will lead to **improved patient care and life outcomes**

LIMBIC CENC

Specific Aims under LIMBIC

- **Enroll and assess 3,000 combat-exposed SM/Vs** predominantly with mTBI(s)
  - Collect initial and longitudinal data under TBI CDE guidelines
  - Submit all data to the FITBIR informatics system
- **Investigate mTBI co-morbidities and neurologic outcomes,** including change over time
- **Identify potential differences in outcomes** between
  - Negative vs. single vs. multiple mTBI
  - Deployment-related vs. nondeployment-related mTBI
  - Pure blast vs. mixed blast-blunt vs. blunt mTBI
  - With vs. without exposure to repetitive low-level blast
- **Identify pathophysiological and biomarker signatures** for chronic mTBI subgroups with poorer recovery patterns and/or greater neurodegeneration susceptibility
- **Evaluate neuroimaging techniques** to advance the research understanding of the late effects of mTBI and determine their potential clinical use in patients

LIMBIC CENC

Methods Synopsis

- Recruit & Enroll 3,000 V/SMs with combat exposure representative of wider post-deployed population
  - Leverage Cohort for dual study enrollment

- Comprehensive, holistic, 360^0 assessment of brain and neurologic health and functioning

- Prospective follow-up (longitudinal) evaluations
  - Annual telephonic
  - Comprehensive in-person at least once every 5 years
  - Merging of retrospective (administrative) data

- Scientific analyses
  - LIMBIC internal analyses of prospective data, longitudinal and cross-sectional
  - Collaborations with other scientific stakeholders
  - Sharing of datasets directly from external requests and through the FITBIR

LIMBIC CENC

LIMBIC-CENC Prospective Longitudinal Study Enrollment & Testing Sites

#	Location	Name	PI
01	Richmond, VA	Hunter Holmes McGuire VA Medical Center	William Walker, MD David Glazier, MD
02	Houston, TX	Michael E. DeBakey VA Medical Center Baylor College of Medicine	Randall Scheibel, PhD Maya Troyanskaya, MD
03	Tampa, FL	James A. Haley Veterans' Hospital	Risa Richardson, PhD Shannon Miles, PhD
04	San Antonio, TX	South Texas Veterans' Health Care System	Carlos A. Jaramillo, MD, PhD
05	Ft. Belvoir, VA	Fort Belvoir Community Hospital Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc.	Melissa Guerra, MD
06	Portland, OR	VA Portland Health Care System	Kathleen Carlson, PhD
07	Minneapolis, MN	University of Minnesota	Scott Sponheim, PhD Nicholas Davenport, PhD
08	Boston, MA	VA Boston Healthcare System	Terri Pagoda, PhD
09	Salisbury, NC	W.G. (Bill) Hefner VA Medical Center	Sarah Martindale, PhD Jared Rowland, PhD
10	San Diego, CA	VA San Diego Healthcare System/Camp Pendleton	Amy Jak, PhD Jason Bailie, PhD
11	Fort Gordon, GA	Dwight D. Eisenhower Army Medical Center	John Rigg, MD Scott Mooney, PhD

Sites added under LIMBIC in red font

LIMBIC CENC

PLS Eligibility Criteria

- Prior Military Combat Deployment
  - Under CENC Post-911 deployment was required; Under LIMBIC: any era permitted
- Combat Exposure (CE)
  - Deployment Related Risk Inventory (DRRI-2) combat CE module of at least 1 point
- Absence of TBI severity > mild (e.g. moderate or severe TBI)
  - Both mild TBI and TBI negative (controls) are permitted
- Absence of Major Neurologic d/o (e.g. SCI) or Psychiatric d/o (e.g. schizophrenia)
  - Most neuro or psych disorders are permitted (e.g. PTSD, mini-stroke)

LIMBIC CENC

Study Significance

- Using the methods described, this study will:
  - Answer important questions about risk factors and vulnerability for early dementia or other late life neurologic effects in this at-risk population
  - Provide a national source of ready and willing research volunteers for recruitment into TBI treatment studies or other relevant research

LIMBIC CENC

Protocol Content Highlights

- Highly standardized process of
  - Mapping of **all potential concussive events (PCEs)** during lifetime
    - Modification of OSU TBI-ID Interview
    - Entire lifetime divided into deployment and non-deployment times of life
  - Determining **mTBI diagnosis for each PCE**
    - VCU retrospective Concussion Diagnostic Interview (VCU rCDI)
    - Vetting of structured algorithm diagnosis against open ended interview and medical record findings
- Emphasis placed on:
  - Efficiency of testing (participant burden)
  - Neurocognitive outcomes
  - Other features of CTE
  - Co-factors and confounders
  - Sensory impairments
  - Converging symptom, structural, physiologic, and functional outcomes

LIMBIC CENC

Poll Question #2

LIMBIC-CENC Multicenter Prospective Longitudinal study (PLS) eligibility criteria include all of the following except:

A. Prior Military Deployment
B. Combat Exposure
C. Traumatic Brain Injury
D. Absence of Major neurologic disorder other than TBI like spinal cord injury
E. None of the above (all are required for enrollment)

LIMBIC CENC

CENC MULTI-CENTER OBSERVATIONAL STUDY: INTERIM ANALYSIS COMPARING PERSONS WITH VS WITHOUT HISTORICAL MTBI

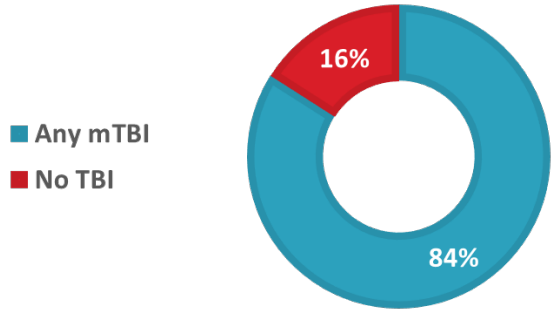
William C. Walker, MD[1,2], Tracy Nolen, DrPh[3], Harvey Levin, PhD[4], William Carne, PhD[1,2], Shawn Hirsch[3], Rick Williams, PhD[3], Sidney R. Hinds MD[5], David X. Cifu, MD[1,2], and the CENC Observational Study Work Group

1 (Virginia Commonwealth University, Richmond, VA)
2 (Hunter Holmes McGuire VA Medical Center, Richmond, VA)
3 (Research Triangle Institute, RTP, NC)
4 (Baylor College of Medicine, Houston, TX)
5 (US Army Medical Research and Materiel Command, FT Detrick, MD)

LIMBIC CENC

Synopsis of this Early Analysis

- Comparison of Mild TBI positive vs negative groups
- Unadjusted analyses



- ‘Snapshot’ sample of first 492 enrollees, all SM/Vs with post-911 deployments
- Takeaways: Compared to controls, those with prior mild TBI had greater:
  - Symptoms
  - Perceived life difficulties
  - Comorbidity burden

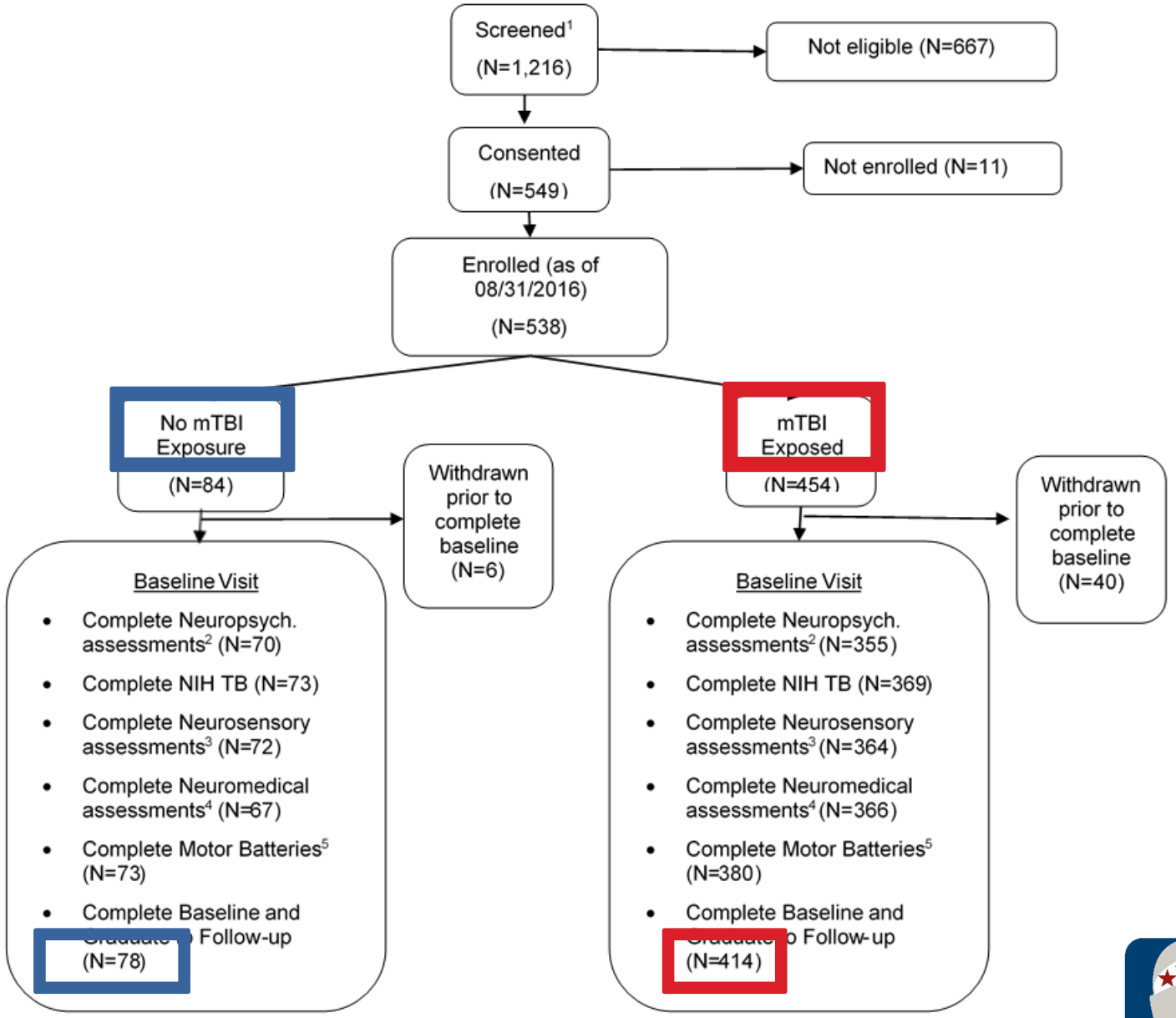
But <u>objective measures were almost entirely equal</u>

LIMBIC CENC

PLS Sites that enrolled into 1st Snapshot Dataset

#	Location	Name	PI
01	Richmond, VA	Hunter Holmes McGuire VA Medical Center	William Walker, MD David Glazier, MD
02	Houston, TX	Michael E. DeBakey VA Medical Center Baylor College of Medicine	Randall Scheibel, PhD Maya Troyanskaya, MD
03	Tampa, FL	James A. Haley Veterans' Hospital	Risa Richardson, PhD Shannon Miles, PhD
04	San Antonio, TX	South Texas Veterans' Health Care System	Carlos A. Jaramillo, MD, PhD
05	Ft. Belvoir, VA	Fort Belvoir Community Hospital Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc.	Melissa Guerra, MD
06	Portland, OR	VA Portland Health Care System	Kathleen Carlson, PhD
07	Minneapolis, MN	University of Minnesota	Scott Sponheim, PhD Nicholas Davenport, PhD
08	Boston, MA	VA Boston Healthcare System	Terri Pagoda, PhD
09	Salisbury, NC	W.G. (Bill) Hefner VA Medical Center	Sarah Martindale, PhD Jared Rowland, PhD
10	San Diego, CA	VA San Diego Healthcare System/Camp Pendleton	Amy Jak, PhD Jason Bailie, PhD
11	Fort Gordon, GA	Dwight D. Eisenhower Army Medical Center	John Rigg, MD Scott Mooney, PhD

LIMBIC CENC

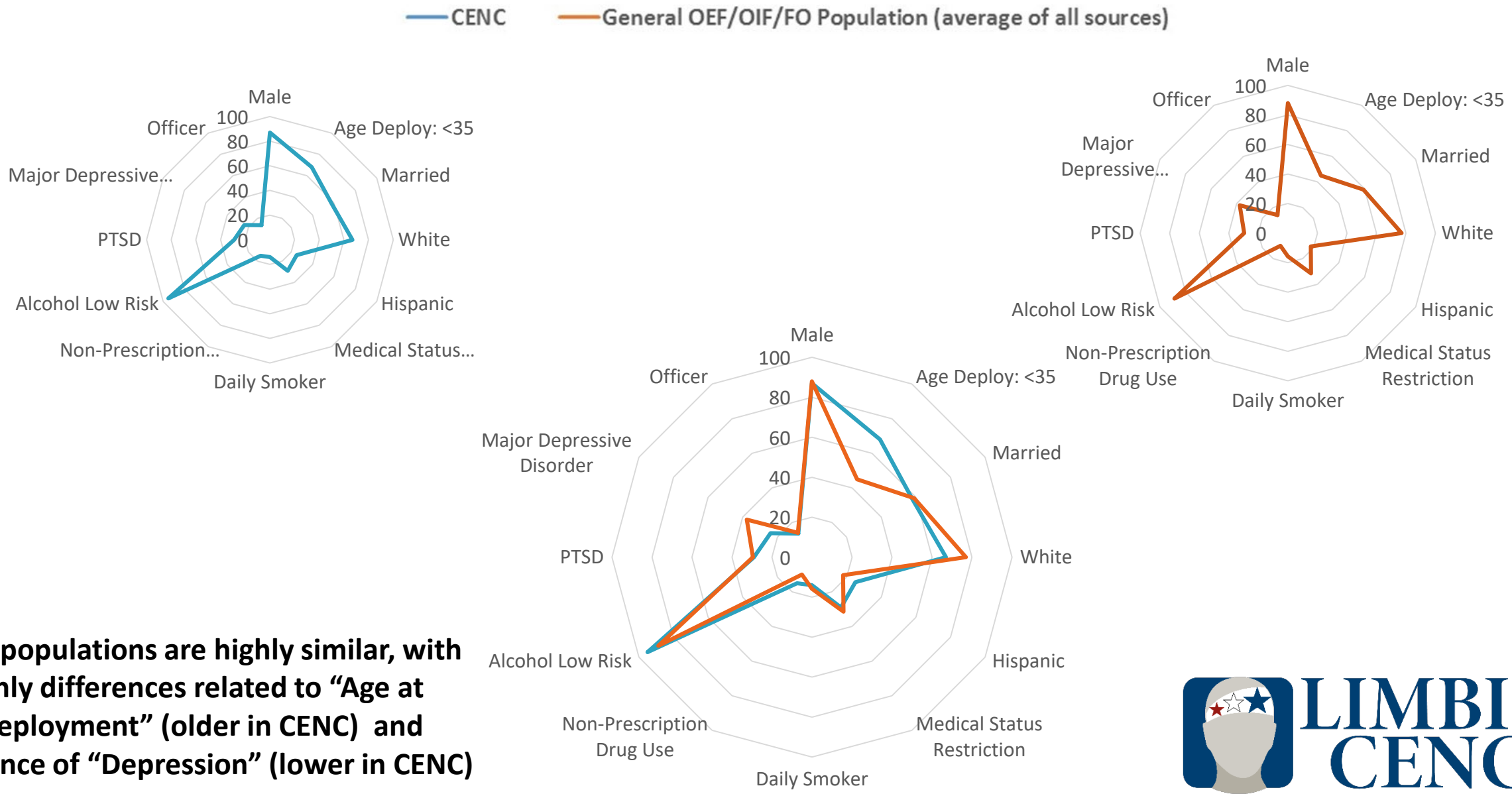

Screened[1] (N=1,216)
Not eligible (N=667)
Consented (N=549)
Not enrolled (N=11)
Enrolled (as of 08/31/2016) (N=538)
No mTBI Exposure (N=84)
Withdrawn prior to complete baseline (N=6)
mTBI Exposed (N=454)
Withdrawn prior to complete baseline (N=40)
Baseline Visit
Complete Neuropsych. assessments[2] (N=70)
Complete NIH TB (N=73)
Complete Neurosensory assessments[3] (N=72)
Complete Neuromedical assessments[4] (N=67)
Complete Motor Batteries[5] (N=73)
Complete Baseline and Follow-up (N=78)
Baseline Visit
Complete Neuropsych. assessments[2] (N=355)
Complete NIH TB (N=369)
Complete Neurosensory assessments[3] (N=364)
Complete Neuromedical assessments[4] (N=366)
Complete Motor Batteries[5] (N=380)
Complete Baseline and Follow-up (N=414)

LIMBIC CENC

Demographics & Environmental Factors with No Differences

	+ TBI	No TBI	P value
Race	66.2% White	69.2% White	0.751
Ethnicity	23.4% Hispanic	30.8% Hispanic	0.175
Education	36.2% College Grad	39.7% College Grad	0.485
Current Military	6.1% Yes	9.1% Yes	0.325
Age enrolled, mean (std)	39.0 (19.1)	40.8 (10.7)	0.149
Marital Status	58.9% Married	55.1% Married	0.531
Years since Index Event, mean (std)	9.0 (4.5)	8.9 (4.5)	0.815
Years since Last TBI, median	8.2	n/a	n/a
Service Branch	69.5% Army	66.2% Army	0.520
Years in Military, mean (std)	14.0 (8.9)	15.2 (9.5)	0.317
Combat deployments [Q1,Q3]	2 [1, 12]	1 [1, 5]	**0.069**

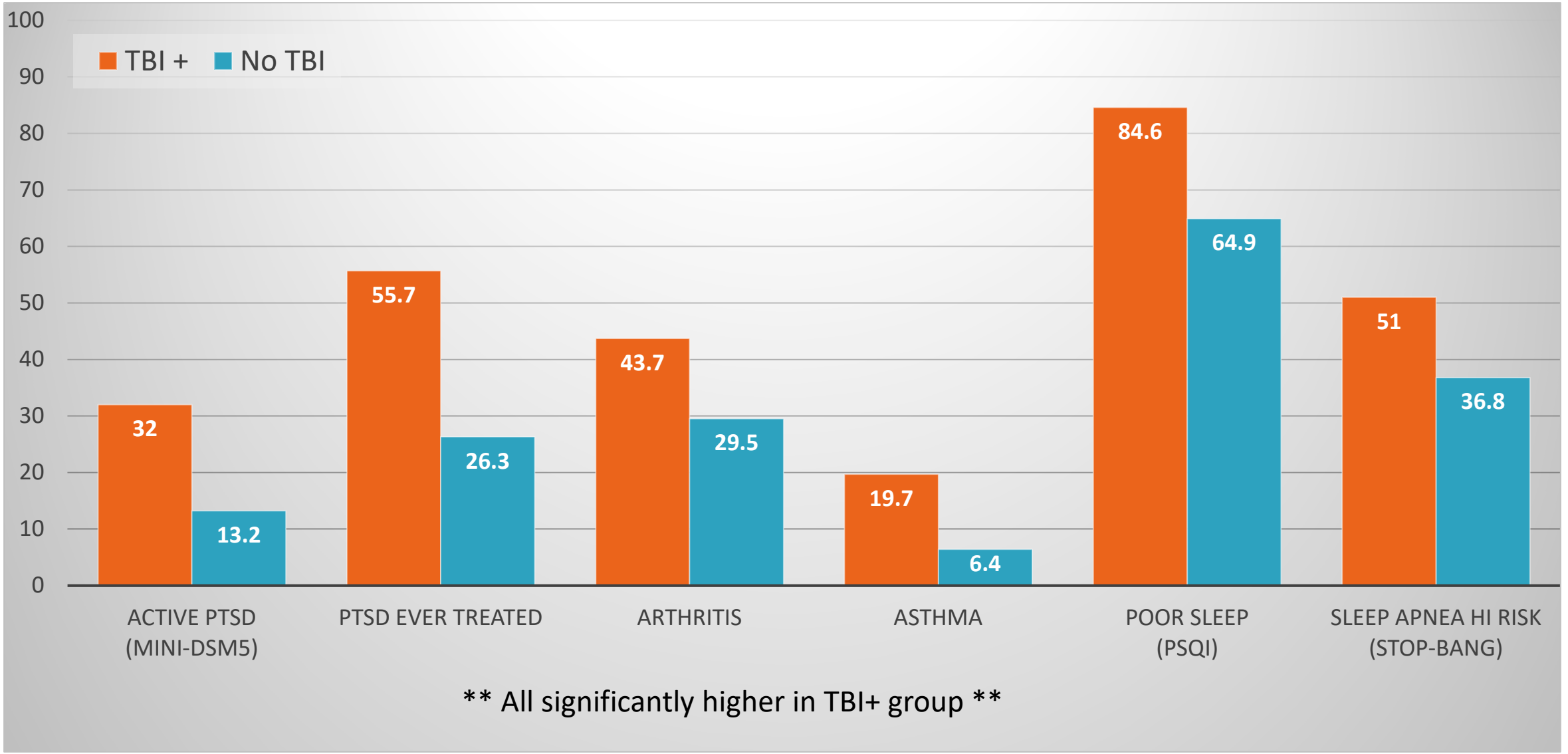
Population at a Glance (% with each characteristic)



Two populations are highly similar, with only differences related to "Age at Deployment" (older in CENC) and presence of "Depression" (lower in CENC)

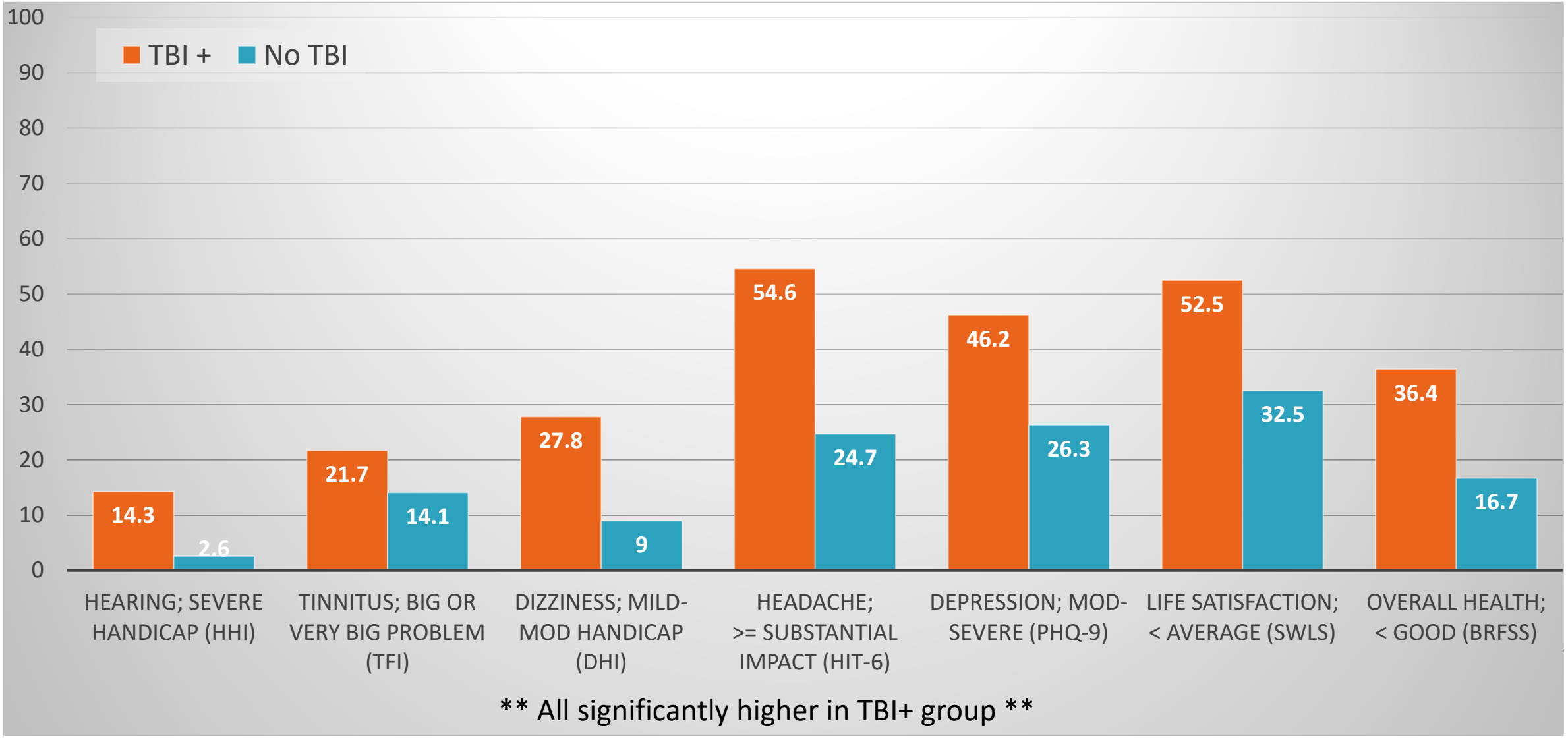
LIMBIC CENC

Comorbidity Differences ($p < 0.05$); Categorical Variables



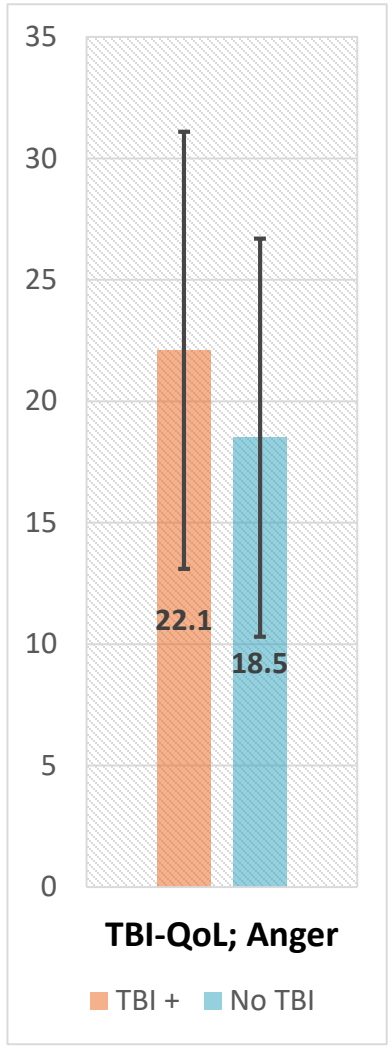
** All significantly higher in TBI+ group **

Symptom and Self-Report Outcomes with Differences ($p < 0.05$); Categorical Variables

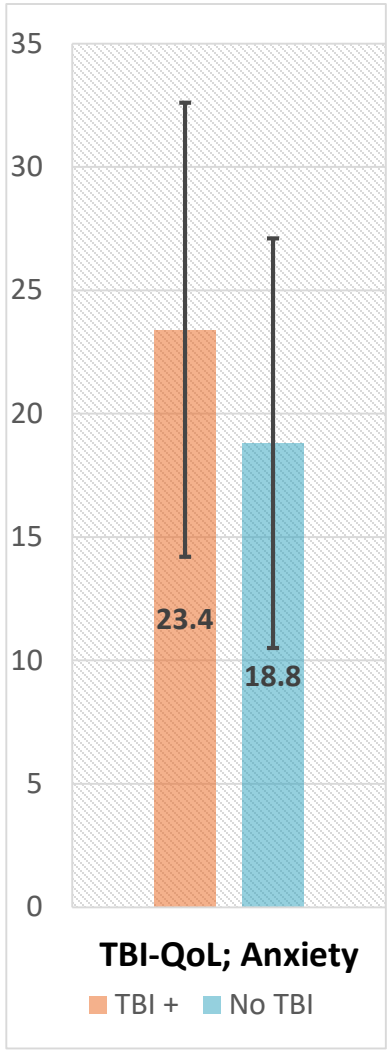


** All significantly higher in TBI+ group **

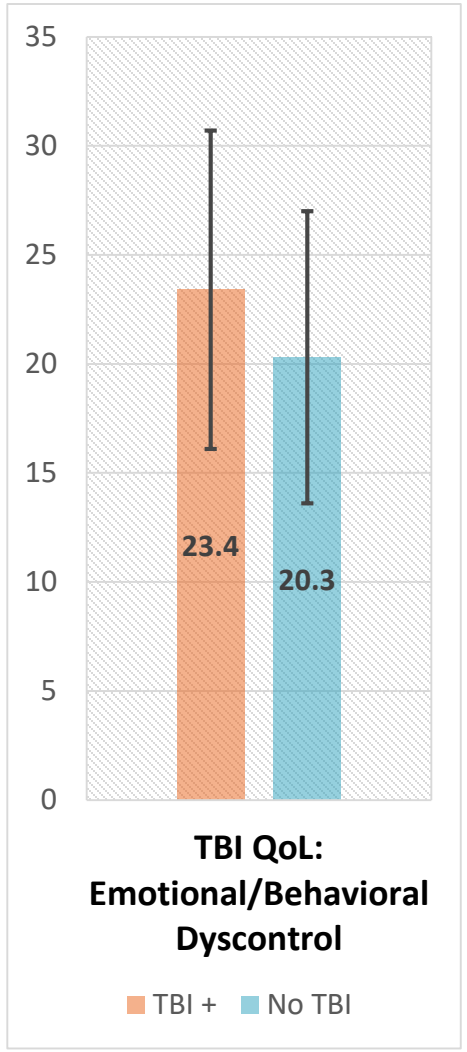
Symptom Outcomes with Differences ($p < 0.05$); Continuous Variables



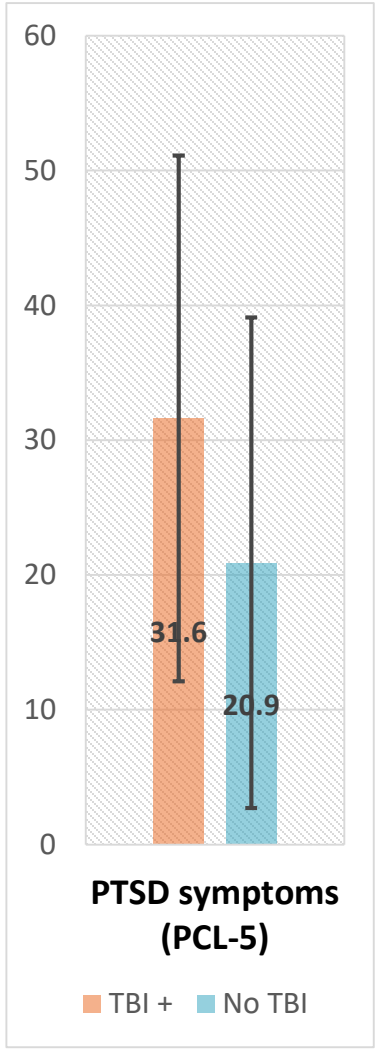
Mean (SD)



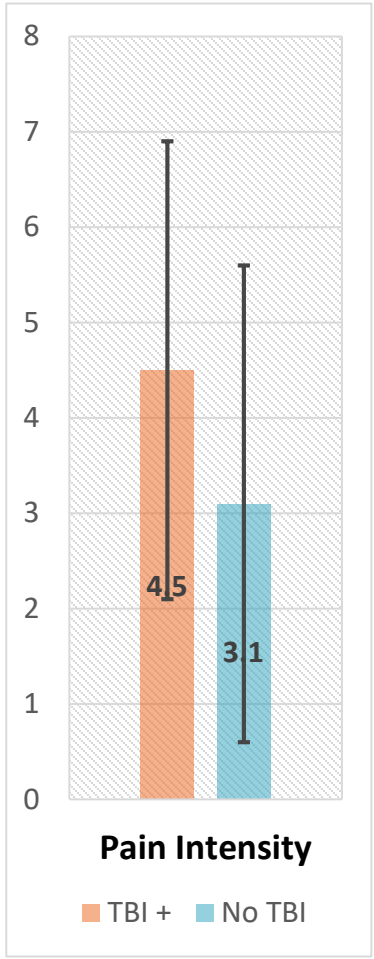
Mean (SD)

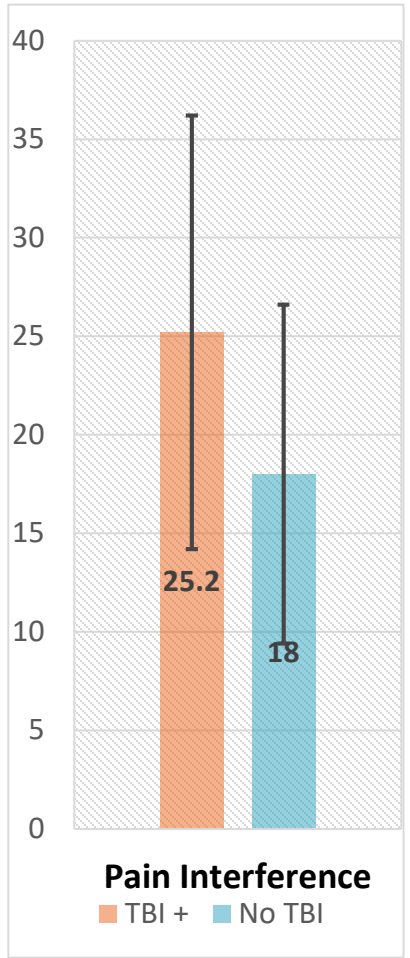


Mean (SD)



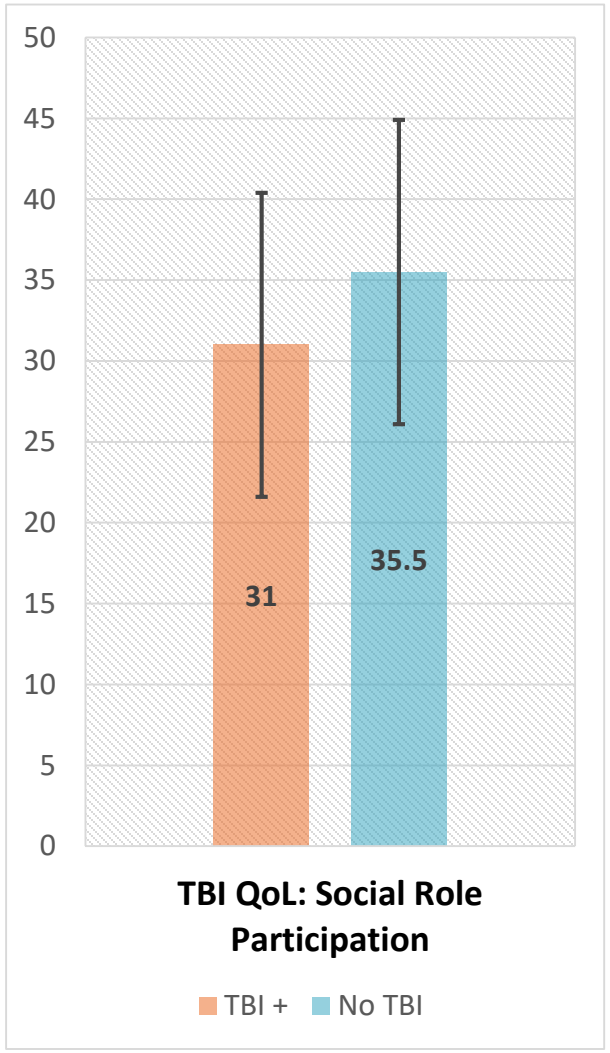
Mean (SD)



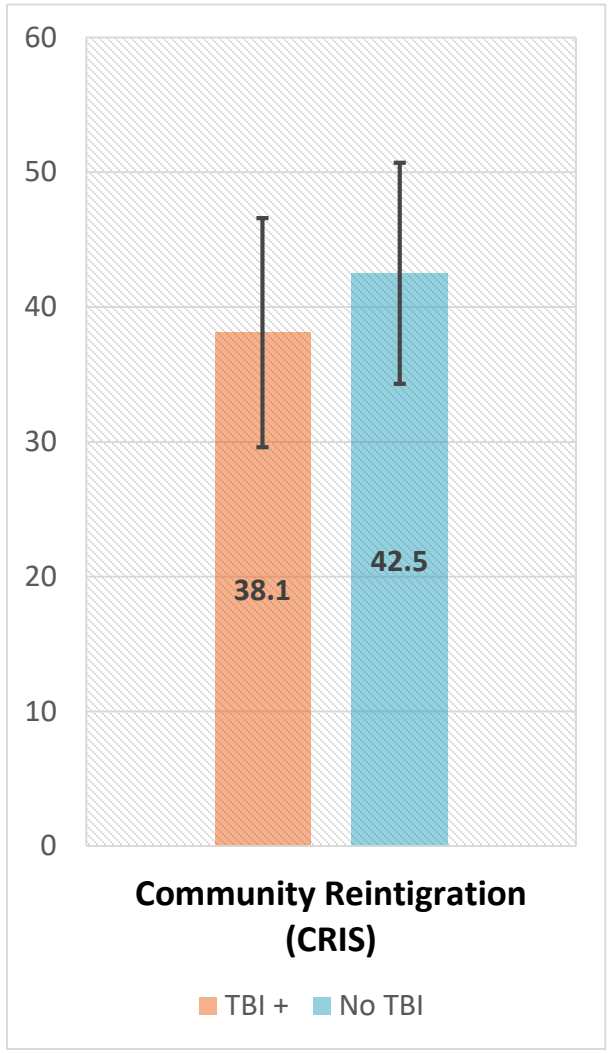


LIMBIC CENC

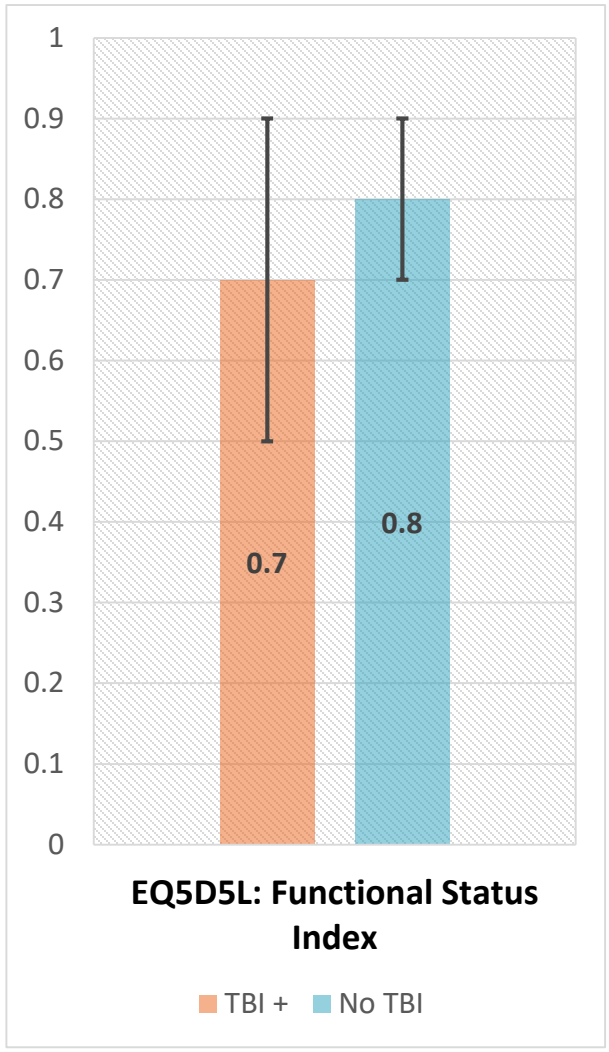
Functional/Participation/Global Self-Report Outcomes with Differences ($p < 0.05$)



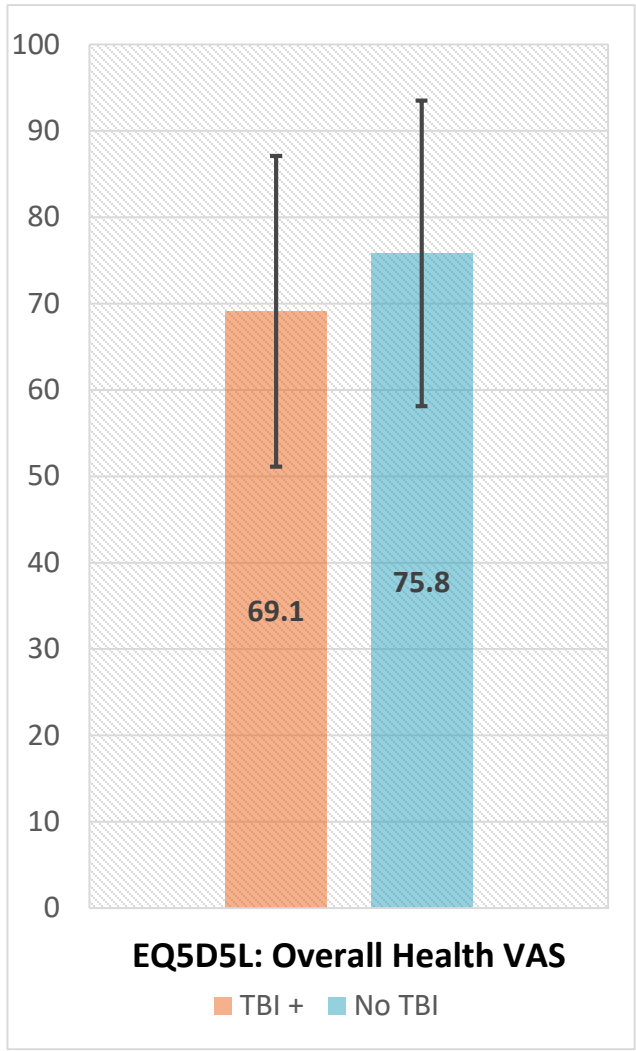
Mean (SD)



Mean (SD)

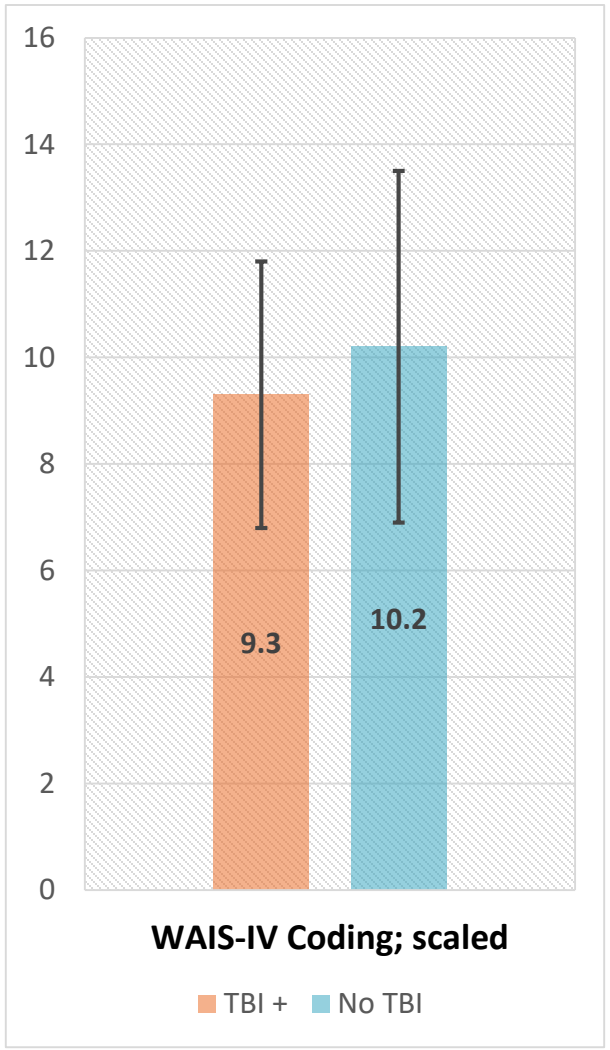


Mean (SD)

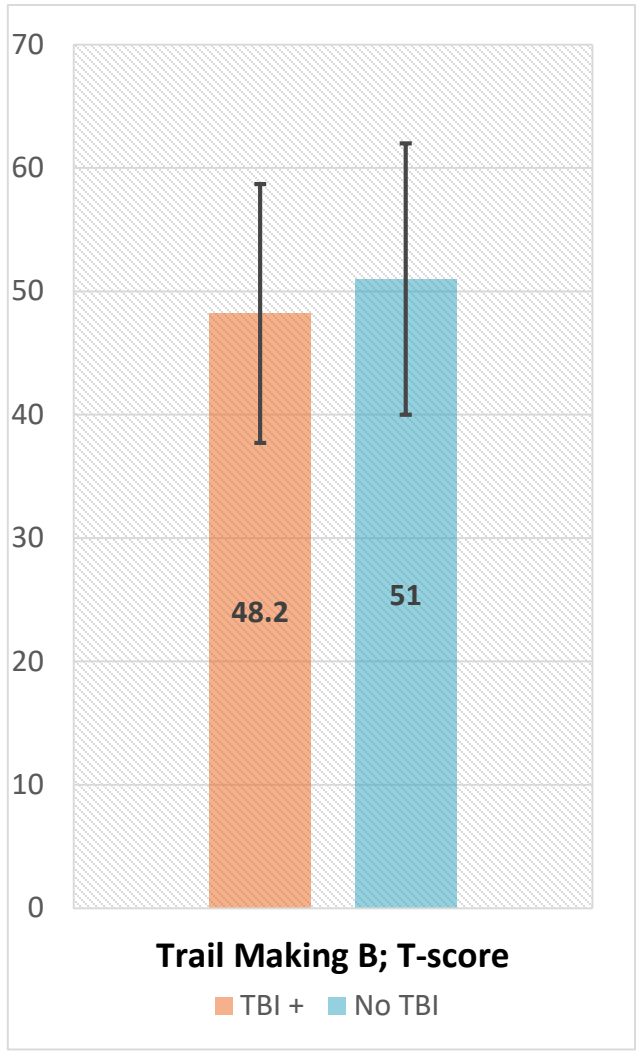


Mean (SD)

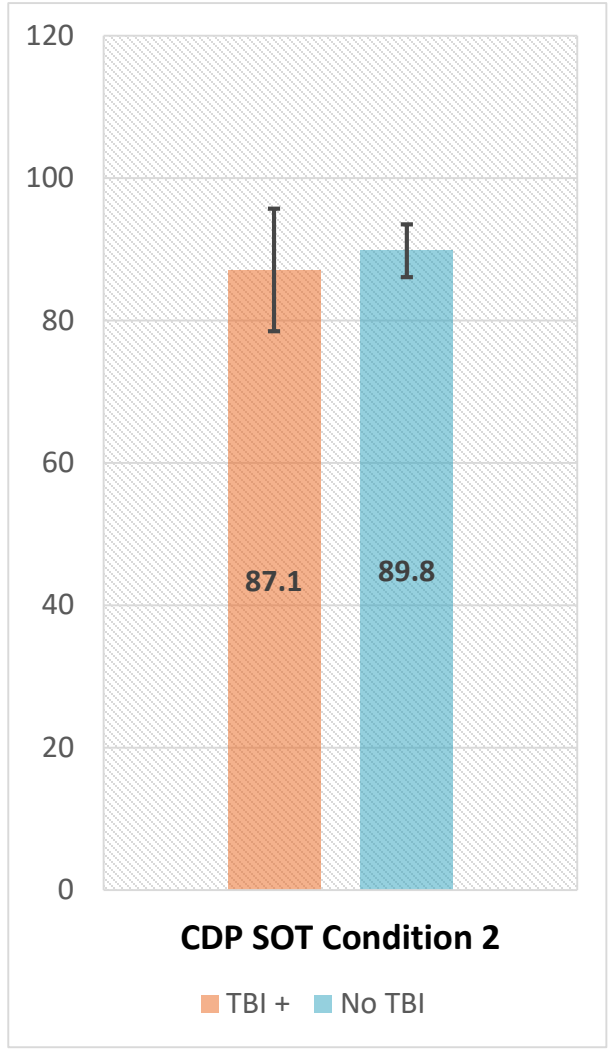
A few Performance Outcomes had statistical difference ($p < 0.05$) with small effect sizes



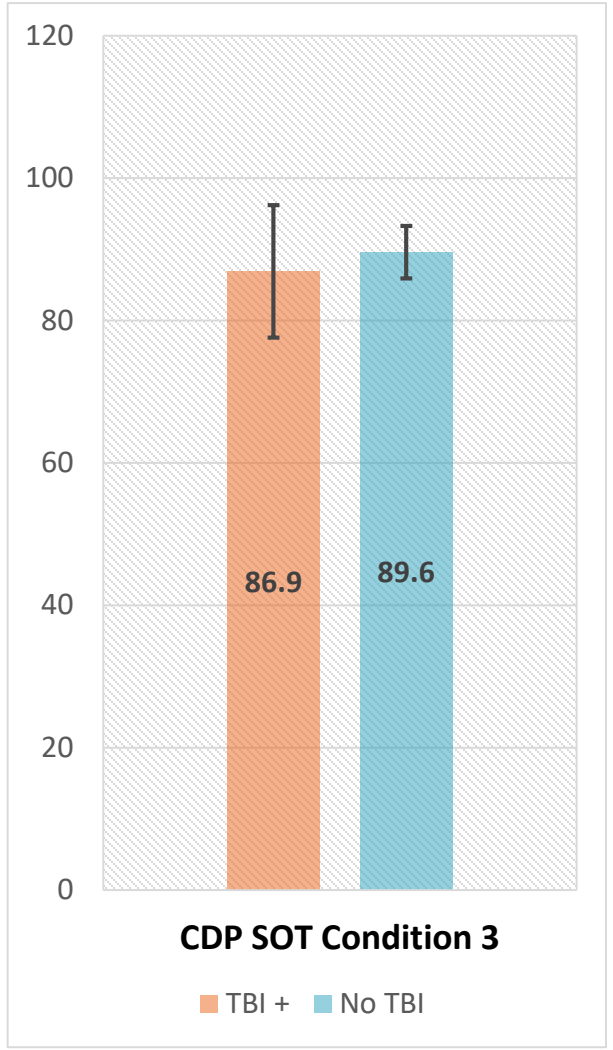
Mean (SD)



Mean (SD)



Mean (SD)



Mean (SD)

Notable Objective Tests with No Between Group Differences

- NIH Toolbox Cognition battery
  - Fluid Composite [primary outcome]
  - All sub-scores
- Traditional Neuropsychology tests
  - Other WAIS-IV scores (digit span, L/N sequence, symbol search, visual puzzle)
  - CVLT-II, D-KEFS verbal fluency, TMT A/B, BVMT-R
- Sensory Systems
  - Visual acuity
  - Verticality (SVV)
  - Smell (BSIT)
  - Central Auditory processing (SCAN-3)
- Neuroendocrine labs
  - Thyroid stimulating hormone
  - Testosterone
  - Insulin-like growth factor
- Epilepsy
  - Self-report screen
  - Medical record code
- Motor System
  - 4 Meter Walk
  - Parkinson's motor exam (UPDRS)
  - Posturography SOT Conditions 1, 4, 5, 6

LIMBIC CENC

Limitations of Snapshot Overall Findings Analyses

- mTBI subtypes not examined
- Unadjusted analyses only
  - mTBI positive versus mTBI positive groups differed in combat exposure level and comorbidities
- Not all baseline measures were included (e.g. imaging, eye-tracking, EEG)
- Cross-sectional data only (Longitudinal data not analyzed)
- Data from only first third of currently accrued cohort

LIMBIC CENC

Conclusions of Snapshot Overall Findings Analyses

- Among former post-911 military combatants, those with a positive mTBI history have more severe widespread symptoms and poorer perceived life functioning.

- Actual Performance measures were largely the same
  - Differences did emerge in several domains warranting future research focus: processing speed, visual-motor integration and executive function, and postural control.

- Differences in many other attributes not directly linked to TBI between the mTBI positive and negative individuals must be considered before causal inferences can be made.

- **A wide range of rigorous, adjusted analyses of cross-sectional data from the entire cohort, analyses of mTBI subgroups, inclusion of the brain imaging, biofluid, EEG, eye-tracking data, as well as longitudinal assessments are under way.**

LIMBIC CENC

Poll Question #3:

These analyses found that compared to TBI negative controls, **combat exposed SM/Vs with prior mild TBI(s) have**:

A. More PTSD diagnoses and PTSD type symptoms
B. More TBI type symptoms
C. Poorer life satisfaction
D. Worse self-reported functional status
E. All of the above

LIMBIC CENC

Poll Question #4:

Which types of measures showed minor or no differences?

A. Cognitive performance
B. Demographic variables
C. Motor and sensory performance
D. All of the above
E. None of the above

How does a clinician use this information?

Patients with mTBI histories often are distressed with high symptom levels and poor perceived life functioning but have little to no objective abnormalities.

Provide Holistic Care via:

- ✓Empathy
- ✓Common goal setting
- ✓Symptom based approach
- ✓Education
- ✓Counseling on lifestyle factors
- ✓Progressive physical exercise
- ✓Address comorbidities (PTSD, chronic pain)

What to Avoid:

- × Prolonged passive therapies
- × Medications with cognitive or other significant side effects (e.g. benzodiazepines, gabapentin)
- × PolyPharmacy
- × Inferring patient's condition is not 'real'
- × Inferring you will 'fix' patient's condition (instead, let them know that you will help them to better manage their lives)

LIMBIC CENC

Education Touchstones

- Movement; physical activity level throughout day (aim for 4,000+ steps/day)
- Structured physical exercise
  - encourage aerobic component & consider formal physical therapy for focal difficulties
- Sleep hygiene (aim for 7 hours/night of sleep)
- Stress (mental/emotional) reduction
  - encourage use of relaxation training program
- Nutrition (increase consumption of vegetables, fiber and nuts)
- EtOH, tobacco and illicit substance use
  - encourage cessation program
- Role of Medications; discuss options and why you are advising for or against
  - When using: Counsel on goals, when to take, what good and bad may result; at f/u confirm usage
- Cognitive & Communication compensatory strategies

LIMBIC CENC

Physical Exercise with Emphasis on Aerobics and Daily Movement

Aerobic ('cardio') Exercise Dosing Recommendations

- ≥150 minutes low-moderate intensity aerobic activity per week
- OR ≥ 75 minutes high-intensity activity per week
- OR equivalent combination
- Caveat: There is no magic threshold

Advise to promote more movement during daily life activities

- Take stairs instead of elevators
- Skip the moving walk-way in airport
- Park further from destination
- Do gardening or yard-work yourself
- Some may benefit from step tracker to set goals

LIMBIC CENC

Healthy Diet Guidelines

Enjoy plant-based and fish diet

- Fruits: ≥ 3 servings/day
- Vegetables: ≥ 3 servings/day
- Fish: ≥2 servings/week
- Whole grains: ≥ 3servings/day
- Okay foods in general: basic dairy, nuts, legumes, extra virgin olive oil

Limit meats and refined food

- Refined grains: ≤1.5servings/day
- Processed meats: ≤ 1 serving/week
- Unprocessed red meats: ≤ 1.5 servings/week
- Bad foods in general: highly processed, added sugars, deep fried, saturated fats

Add Calorie Control if unhealthy weight/BMI despite above plan

LIMBIC CENC

Limit Alcohol consumption

- Women: Up to 1 drink-equivalent/day
- Men: Up to 2 drinks/day

- 1 drink-equivalent defined as 14g (or 0.6 ounce) of pure alcohol.
- To calculate drink-equivalents in ounces, multiply the volume in ounces by the alcohol content in percent and divide by 0.6 ounces of alcohol per drink-equivalent:
- Examples
  - Wine: 5 oz of 12% ABV wine=0.85 drink-equivalents,
  - Beer: 12 oz 5% ABV beer = 1 drink-equivalents,
  - Spirits: 1.5 oz (shot) of 40% ABV spirits = 1 drink-equivalents,
  - 50ml fortified wine= 0.56 drink-equivalents,

LIMBIC CENC

Sleep Hygiene

- Set bedtime early enough to get > 7 hours of sleep.
- Consistent time into and out of bedtime every day
- If you don't fall asleep after 20 minutes, get out of bed.
- Get exposure to natural light during the day.
- Establish regular relaxing bedtime routine (e.g. warm shower or bath, reading a book, or light stretches).
- Avoid emotionally upsetting conversations and activities before attempting to sleep.
- Don't go to bed unless you are sleepy.
- Use your bed only for sleep and sex.
- Limit exposure to bright light in the evenings.
- Turn off electronic devices > 30 min before bedtime.
- Exercise regularly and maintain a healthy diet.
- Reduce your fluid intake before bedtime

Promote a pleasant sleep environment

- The bedroom should be cool (60 to 67 F) – for optimal sleep.
- Turn off bright lights from lamps, cell phone and TV screens
- Consider using blackout curtains, eye shades, ear plugs, "white noise" machines, humidifiers, fans and other devices that can make the bedroom more relaxing.

AVOID

- Daytime naps: *if nap, Max 30 minutes.*
- Caffeine after mid-afternoon.
- Strenuous workouts close to bedtime.
- Alcohol before bedtime
- Large meal before bedtime: *If you are hungry at night, eat a light, healthy snack.*

LIMBIC CENC

Stress Management

- Relaxation Strategies; find one that works for you and practice regularly
  - Examples: Yoga, Meditation, Controlled breathing, Heart Rate Variability training (ideally taught with biofeedback)
- Devote at least 10 minutes of social activity every day.
  - Any activity that brings you joy, be it reading, drawing or even writing.
- Smile frequently
- Engage in counseling (psychotherapy) and/or seek mental health care if stress, anxiety or depression not controlled well with the above strategies

LIMBIC CENC

Cognitive Compensatory Strategies

Memory Problems

- Maintain a schedule and routine
  - Unless PRN, take meds at same time(s) of day every day.
  - Make a 'to do' list every night and review every morning.
  - Keep commonly-used important items in consistent spot.
  - Place a large display where you often see it to keep important information such as appointments.
- Use proven strategies to aid memory and avoid confusion or mistakes
  - Allow time for memory consolidation after learning new info
  - Keep info simple and repeat it to yourself frequently.
  - Use repeat back method for verifying verbal communication
  - Break activities in the simple steps
  - Always check written work in the same order such as left to right, up and down

Attention and Concentration Problems

- Avoid multitasking
- When pausing from task, write down what was done and what still remained
- Use self-coaching techniques such as talking yourself through a task.
- Consistently check over your work very carefully.
- Schedule frequent breaks during the day.
- Try to avoid interruptions.

LIMBIC CENC

Key Messages that should be conveyed to chronically distressed individuals with mTBI

- **Clinician will partner and guide patient with their wisdom**

- **Realistic goals are lower distress level and higher functional level**

Also convey (with care and sensitivity):

- Total cure is not a realistic goal
- There are no magic bullets
  - Clinician's actions (medications, device, therapy) by themselves rarely cure
- The patient must take an active role
  - Getting better takes hard work

LIMBIC CENC

Poll Question #5:

What strategy is least helpful for patients with mTBI and persistent distressing and widespread symptoms?

A. Physical exercise
B. Stimulant medication
C. Socialization
D. Meditation
E. Repeating back important information heard

LIMBIC CENC

The End

Questions?

LIMBIC CENC