Examination of Repetitive Low-level Blast Exposure Thresholds to Predict Poor Neurobehavioral Functioning: How Many Blasts are Too Many Blasts?

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The study protocol was approved by the Walter Reed National Military Medical Center (WRNMMC) Institutional Review Board in compliance with all applicable Federal regulations governing the protection of human subjects.

Research data were derived from an approved WRNMMC Institutional Review Board protocol number 353853.

Disclosures

- Dr. Rael Lange has no relevant financial or non-financial relationships to disclose relating to the content of this activity.
- Dr. Louis French has no relevant financial or non-financial relationships to disclose relating to the content of this activity.
- The views expressed in this presentation are those of the authors and do not necessarily reflect the official policy or position of the Department of War, nor the U.S. Government.
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Background

- Past research in service members and veterans (SMVs) has demonstrated that repetitive low-level blast exposure is associated with worse self-reported postconcussion symptoms, posttraumatic stress disorder (PTSD) symptoms, and a variety of neurobehavioral (NB) symptoms such as anger, anxiety, depression, fatigue, cognitive complaints, sleep, irritability, pain, and headaches.[1]
- Consequently, in recent years, the Department of Defense has placed an increased emphasis on the need to identify thresholds of lifetime blast exposure (LBE) to identify SMVs 'at risk' for the negative effects potentially associated with repetitive low-level blast.[1]
- The purpose of this study was to examine whether a threshold of LBE could be identified that is predictive of poor NB functioning in injured SMVs with and without a history of mild traumatic brain injury (TBI).

Methods

- **Sample Size:** 340
- **Groups:** Mild TBI (n=201); Injured Controls (n=139)
- **Time Post-injury:** ≥ 24 months
- **Exclusions:** Failed SVTs (i.e., Validity-10[2])
- **Recruitment:** (a) 3 Military Medical Treatment Facilities (78%)
  (b) Community [22%; e.g., social media, flyers]
- **Age:** M=43.5 years (SD=9.7)
- **Education:** M=15.8 years (SD=2.4)
- **Gender:** 86.9% male

SVT=symptom validity testing; M=mean; SD=standard deviation

Measures

Blast Exposure Threshold Survey

TBI-Quality of Life

- Anger
- Depression
- Fatigue
- Headaches
- Cognitive Concerns–General

Measures: BETS

Blast Exposure Threshold Survey (BETS)

BETS Weapons Categories

Category 1:	Small and medium arms
Category 2:	Large arms/carried on a person
Category 3:	Artillery/missile/large arms carried by vehicle/aircraft/boat
Category 4:	Smaller explosives or grenades
Category 5:	Larger explosives or targeted explosives in close range

- The BETS is a comprehensive and well validated measure of LBE.[3]
- The BETS measures LBE in five weapons categories.[3]
- An overall value of LBE is calculated using a weighted formula; i.e., *Generalized Blast Exposure Value (GBEV).*[3]

Measures: TBI-QOL

Blast Exposure Threshold Survey (BETS)

TBI-Quality of Life (TBI-QOL)

- Anger
- Depression
- Fatigue
- Headaches
- Cognitive Concerns–General

- T-scores are generated for each scale (Mean=50, SD=10).[4]
- >1SD = 'Clinically Elevated'
- The number of clinically elevated scores across the five scales were used to create two 'NB outcome' groups.

Classification of Outcome Categories

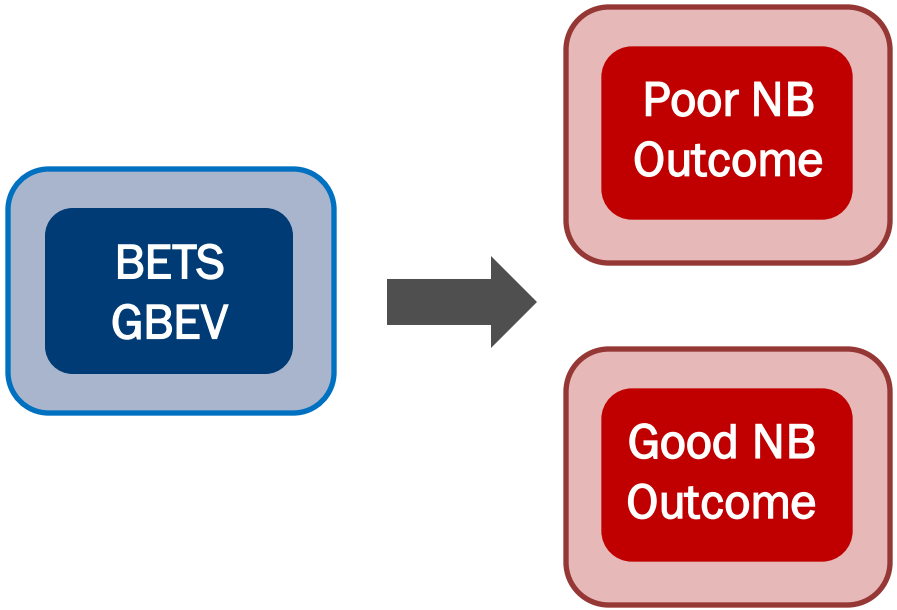
Poor NB Outcome

2-or-more Clinically Elevated Scores

Good NB Outcome

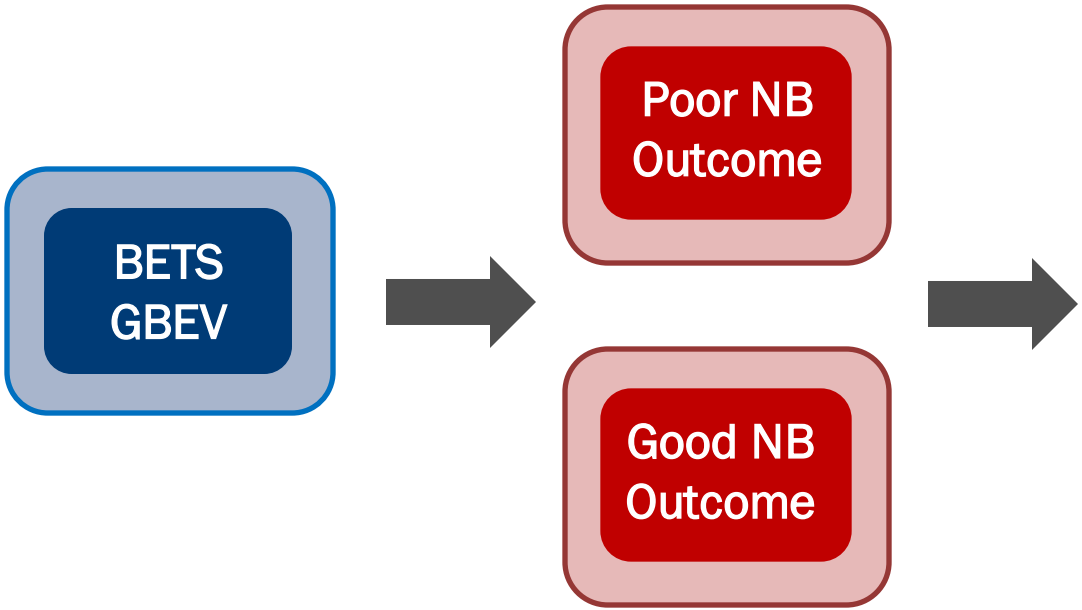
0 or 1 Clinically Elevated Score

Statistical Analysis



Receiver operating curve (ROC) analysis was used to identify optimal LBE thresholds (using GBEV) to predict Poor versus Good NB outcome in the mild TBI and control groups separately.

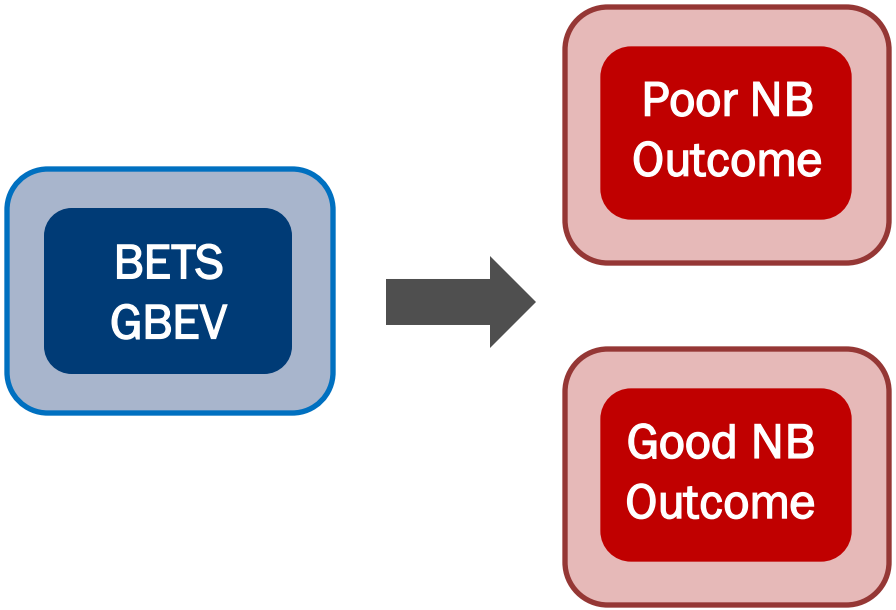
Output of Interest from ROC Analysis



A range of GBEV cutoff scores and two important clinical utility metrics: Sensitivity and Specificity.

GBEV	Sensitivity	Specificity
4,074	.95	.28
4,857	.89	.29
14,589	.84	.40
24,888	.81	.50
35,257	.76	.53
66,394	.70	.57
79,464	.65	.58
90,148	.60	.59
98,909	.54	.59
119,777	.49	.59
150,208	.46	.66
286,459	.41	.76
489,273	.35	.77
833,550	.30	.86
1,096,481	.24	.87
1,150,403	.22	.87
2,084,275	.16	.87
3,379,751	.11	.88
5,320,926	.05	.91

Inclusion of Two Important Metrics



ROC output does not include positive and negative predictive power (PPP and NPP)

GBEV	Sensitivity	Specificity	PPP	NPP
4,074	.95	.28	.41	.90
4,857	.89	.29	.40	.83
14,589	.84	.40	.43	.82
24,888	.81	.50	.47	.83
35,257	.76	.53	.46	.80
66,394	.70	.57	.47	.78
79,464	.65	.58	.45	.75
90,148	.60	.59	.44	.73
98,909	.54	.59	.41	.70
119,777	.49	.59	.39	.68
150,208	.46	.66	.42	.69
286,459	.41	.76	.47	.70
489,273	.35	.77	.45	.69
833,550	.30	.86	.54	.70
1,096,481	.24	.87	.51	.68
1,150,403	.22	.87	.48	.67
2,084,275	.16	.87	.41	.66
3,379,751	.11	.88	.33	.65
5,320,926	.05	.91	.25	.64

Primer on Clinical Utility Metrics

- PPP and NPP provides us with data that is more useful in the clinical setting (n=1). PPP and NPP tells us how confident we can be, in terms of a percentage, that a given score on a test/measure *(obtained from a single person)*, actually predicts what the test/measure is designed to predict.[5]
- Sensitivity and Specificity simply tells us the true positive and true negative rate of a test/measure to identify the target condition in any given group.
  - ✓ These values provide limited 'clinically-relevant' information for prediction purposes.
- However, all four metrics are very important in order to establish any cutoff scores that could be used clinically.

Clinical Utility Metrics for GBEV to Identify Good versus Poor Neurobehavioral Outcome: Mild TBI Group

GBEV	Sensitivity	Specificity	PPP	NPP
2,328	.95	.10	.36	.79
10,596	.89	.19	.37	.77
31,115	.85	.30	.39	.78
60,909	.80	.35	.40	.76
73,990	.75	.36	.39	.72
124,192	.70	.41	.39	.72
240,646	.65	.44	.38	.70
353,159	.60	.48	.38	.69
603,000	.55	.58	.42	.71
1,088,200	.51	.62	.42	.70
1,428,808	.46	.62	.39	.68
1,885,280	.41	.65	.39	.67
2,225,620	.35	.67	.37	.66
2,873,272	.30	.70	.35	.65
4,691,427	.25	.77	.37	.66
8,700,757	.20	.88	.47	.67
11,737,605	.16	.89	.43	.66
21,627,889	.10	.90	.34	.65
26,357,565	.06	.92	.28	.64

N=201

Data has been condensed by omitting some rows

Wish List for Clinical Utility Metrics

Useful Predictor: Poor and Good Outcome	Useful Screener: Poor Outcome (Rule-in)	Useful Screener: Good Outcome (Rule-out)
High Sensitivity	High Sensitivity	--
High Specificity	--	High Specificity
High PPP	High PPP	--
High NPP	--	High NPP

Clinical Utility Metrics for GBEV to Identify Good versus Poor Neurobehavioral Outcome: Rule-in and Rule-out

Useful Predictor: Poor NO Good Outcome

High Sensitivity

High Specificity

High PPP

High NPP

GBEV	Sensitivity	Specificity	PPP	NPP
2,328	.95	.10	.36	.79
10,596	.89	.19	.37	.77
31,115	.85	.30	.39	.78
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11,737,605	.16	.89	.43	.66
21,627,889	.10	.90	.34	.65
26,357,565	.06	.92	.28	.64

N=201, Mild TBI

Wish List for Clinical Utility Metrics: Rule-in

Useful Predictor: Poor NO Good Outcome	Useful Screener: Poor Outcome (Rule-in)
High Sensitivity	High Sensitivity
High Specificity	--
High PPP	High PPP
High NPP	--

Clinical Utility Metrics for GBEV to Identify Good versus Poor Neurobehavioral Outcome: Rule-in

Useful Screener: Poor Outcome (Rule-In)

NO

High Sensitivity

–

High PPP

–

GBEV	Sensitivity	Specificity	PPP	NPP
2,328	.95	.10	.36	.79
10,596	.89	.19	.37	.77
31,115	.85	.30	.39	.78
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21,627,889	.10	.90	.34	.65
26,357,565	.06	.92	.28	.64

N=201, Mild TBI

Wish List for Clinical Utility Metrics: Rule-out

Useful Predictor: Poor NO Good Outcome	Useful Screener: Poor NO Outcome (Rule-in)	Useful Screener: Good Outcome (Rule-out)
High Sensitivity	High Sensitivity	--
High Specificity	--	High Specificity
High PPP	High PPP	--
High NPP	--	High NPP

Clinical Utility Metrics for GBEV to Identify Good versus Poor Neurobehavioral Outcome: Rule-out

Useful Screener: Good Outcome (Rule-out)

NO

–

High Specificity

–

High NPP

GBEV	Sensitivity	Specificity	PPP	NPP
2,328	.95	.10	.36	.79
10,596	.89	.19	.37	.77
31,115	.85	.30	.39	.78
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26,357,565	.06	.92	.28	.64

N=201, Mild TBI

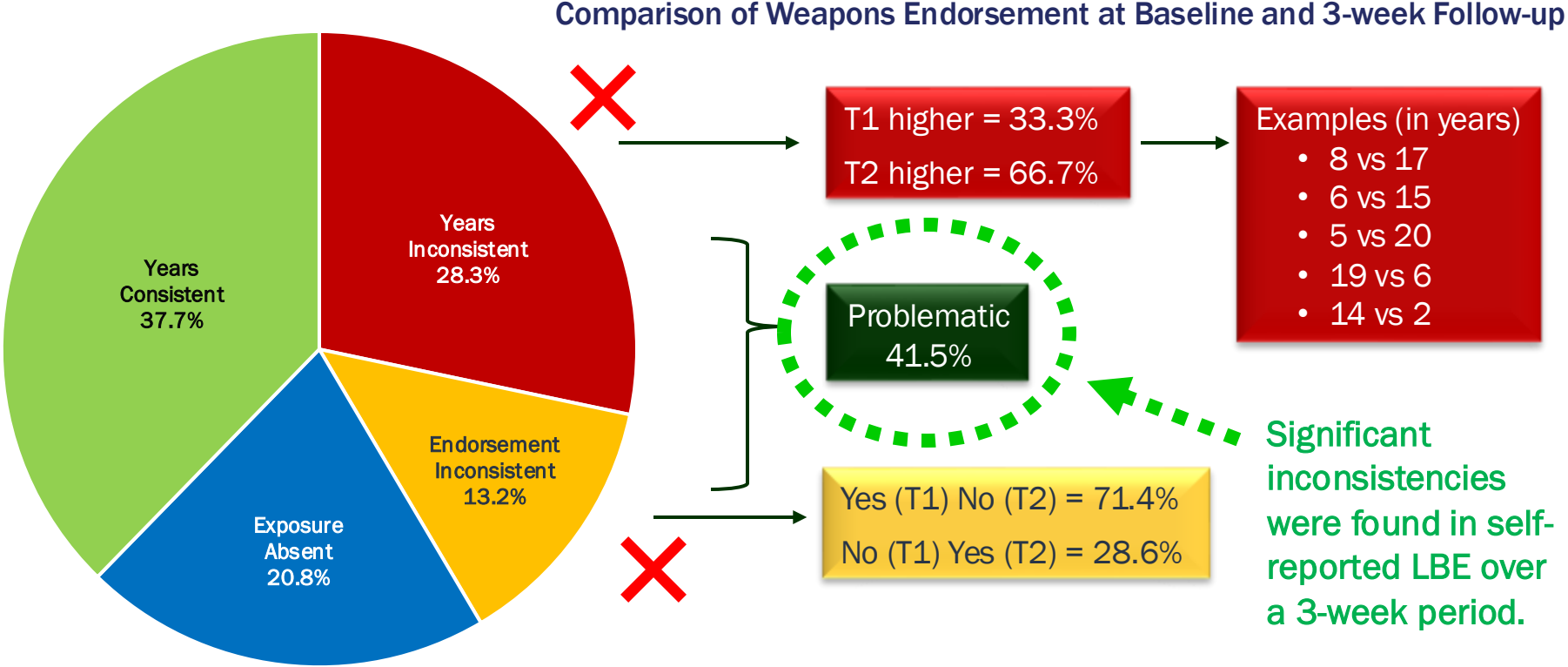
Wish List for Clinical Utility Metrics: Summary

Conclusions (1 of 4)

- Past research has established a relationship between high LBE and worse NB functioning in SMVs.[1]
- However, this study was unable to identify a threshold of LBE that could be used as a confident *predictor* or *screener* of poor NB functioning.
- There may be a number of reasons for these findings:
  1. ***Measuring LBE is challenging!*** Measurement relies on a person's retrospective recall of blast exposure over many years which is highly prone to bias.[6] It is possible that the information gathered is simply not accurate.

Conclusions (2 of 4)

Example Study 1: Test-retest Reliability of the BETS



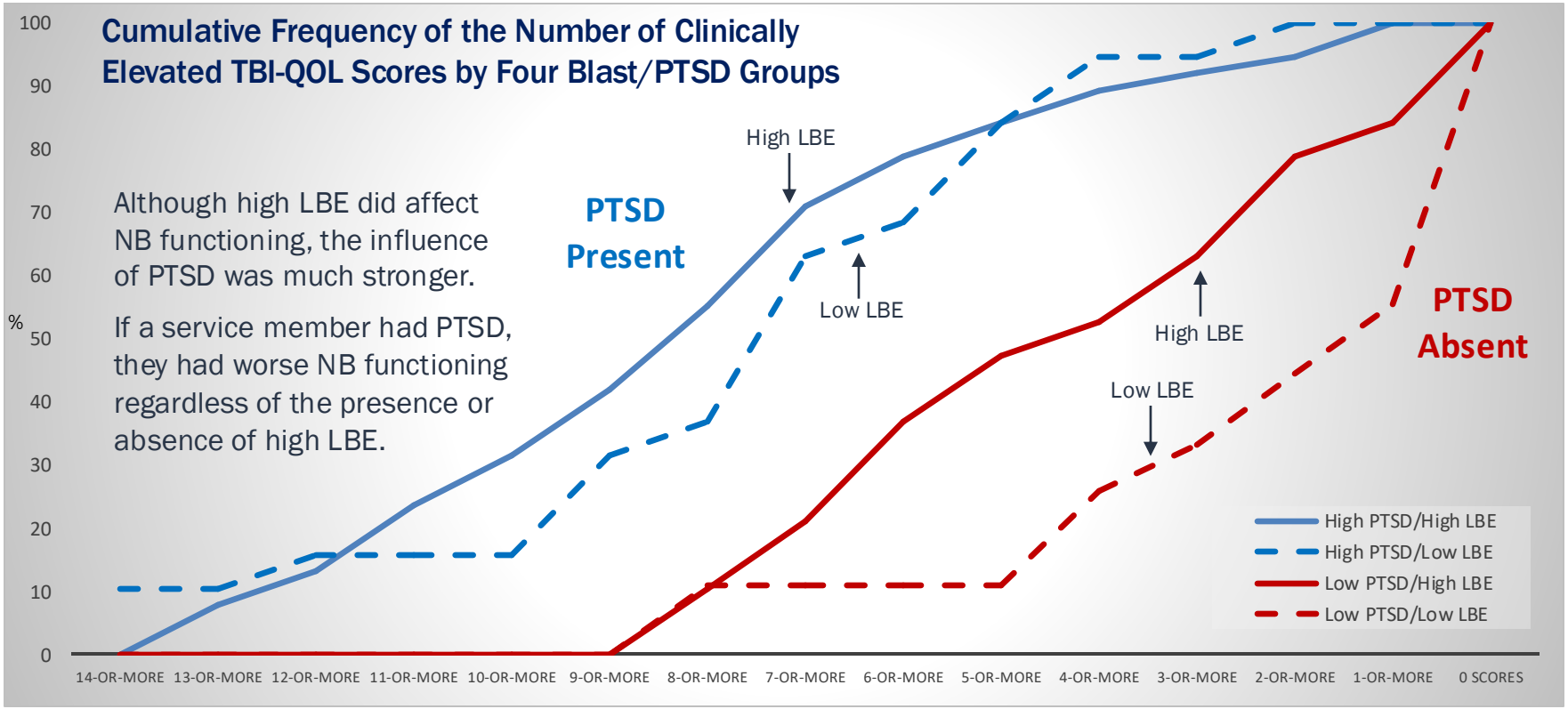
Lange RT, et al. *J Neurotrauma*. 2026;43(11-12):916-925. doi: 10.1177/08977151251394741

Conclusions (3 of 4)

- Past research has established a relationship between high LBE and worse NB functioning in SMVs.[1]
- However, this study was unable to identify a threshold of LBE that could be used as a confident *predictor* or *screener* of poor NB functioning.
- There may be a number of reasons for these findings:
  1. ***Measuring LBE is challenging!*** Measurement relies on a person's retrospective recall of blast exposure over many years which is highly prone to bias.[6] It is possible that the information gathered is simply not accurate.
  2. ***A patient's clinical presentation is complicated!*** There are many known factors that can potentially influence NB functioning (e.g., PTSD, poor family functioning, poor sleep, low resilience, etc.)[1,7] It is possible that factors other than blast exposure are simply more clinically relevant or influential.

Conclusions (4 of 4)

Example Study 2: Influence of LBE and PTSD on TBI-QOL



Lange RT, et al. *J Neurotrauma*. 2024;41(1-2):186-198. doi: 10.1089/neu.2023.0133

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Questions?