A New Frontier In Critical Care: Saving the Injured Brain

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VANDERBILT UNIVERSITY MEDICAL CENTER

VA | U.S. Department of Veterans Affairs

Disclosures

- Physician-scientist, Vanderbilt University, Nashville TN, USA
- Honoraria from Pfizer, Orion for CME Activities
- Consulting with Philips and Masimo
- PI for MIND-USA and SCCM's ICU Liberation
- NIH and VA U.S. Federal Funding

Over 20 Years of Research at Vanderbilt and VA

1998-2019…

CRITICAL ILLNESS, BRAIN DYSFUNCTION, *and* SURVIVORSHIP (CIBS) CENTER


M.D.

In ***Crime and Punishment***, Dostoyevsky used "delirium" 31 times.

“Strange to say, he seemed immediately to have become perfectly calm; not a trace of his recent **delirium** nor of the panic fear that had haunted him of late. It was the first moment of a strange sudden calm.”

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Long-Term Cognitive Impairment after Critical Illness

P.P. Pandharipande, T.D. Girard, J.C. Jackson, A. Morandi, J.L. Thompson, B.T. Pun, N.E. Brummel, C.G. Hughes, E.E. Vasilevskis, A.K. Shintani, K.G. Moons, S.K. Geevarghese, A. Canonico, R.O. Hopkins, G.R. Bernard, R.S. Dittus, and E.W. Ely, for the BRAIN-ICU Study Investigators*

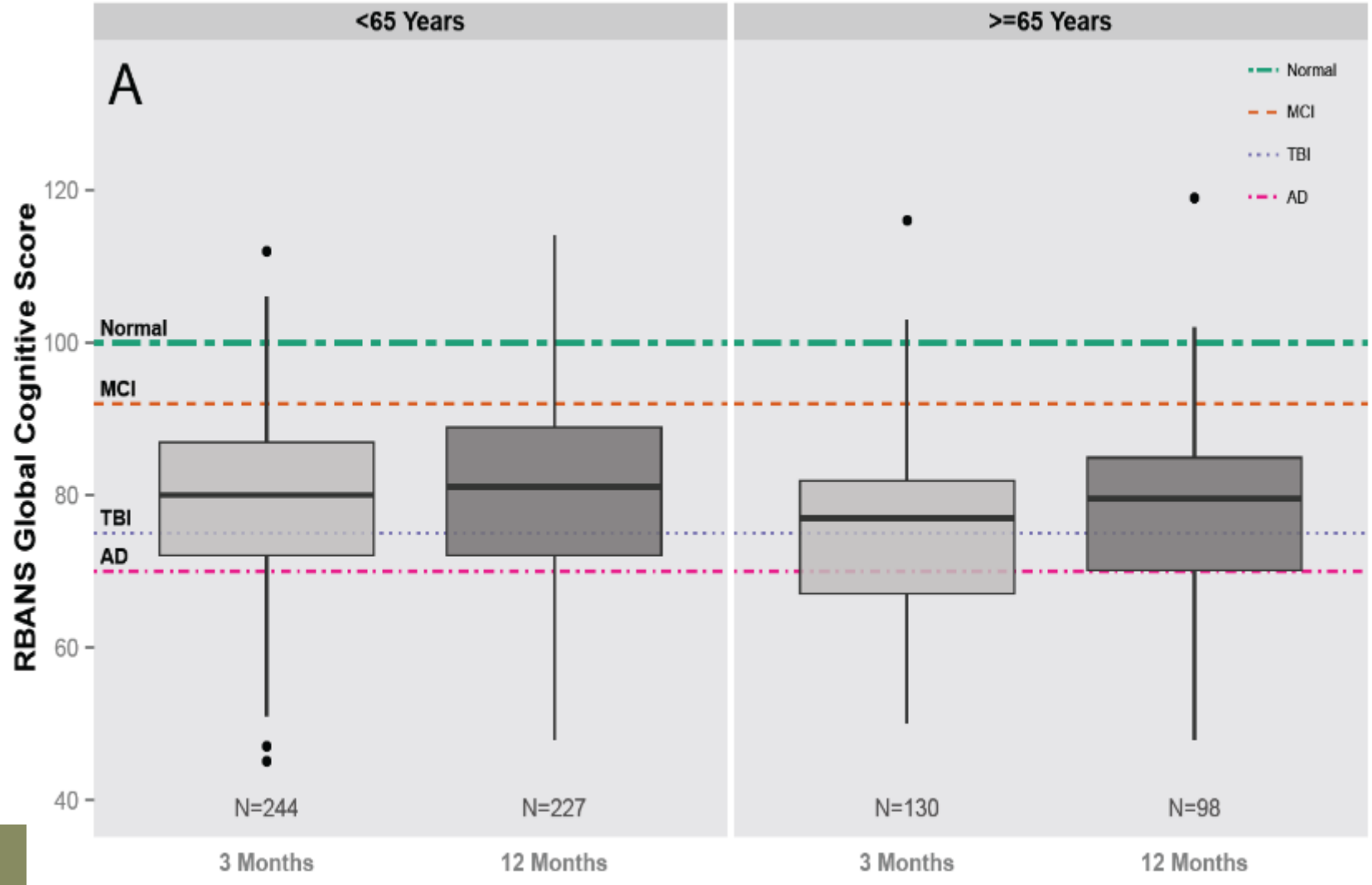
ABSTRACT

BACKGROUND

Survivors of critical illness often have a prolonged and disabling form of cognitive impairment that remains inadequately characterized.

Pandharipande, NEJM 2013;369:1306-16

The Picture of Dementia Following ICU Care



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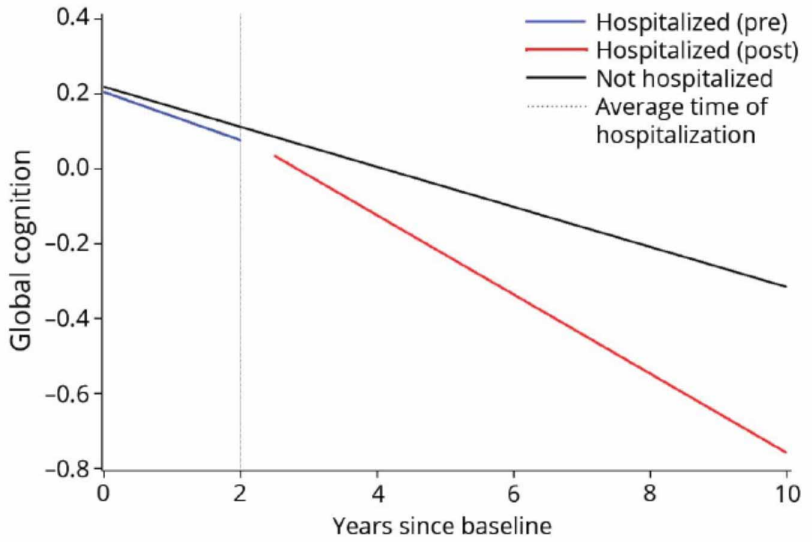
Who gets this dementia?

NIH parlance: ADRD

Alz Dz, Vascular, Lewy Body, Mixed, Frontotemporal, Creutzfeldt-Jakob, NPH, Parkinson's, Huntington's, Wernicke-Korsakoff, and Post-Critical Illness ADRD (?)

Hospitalization

Figure 2 Rate of decline in global cognition in those who had hospitalization (before and after) or no hospitalization

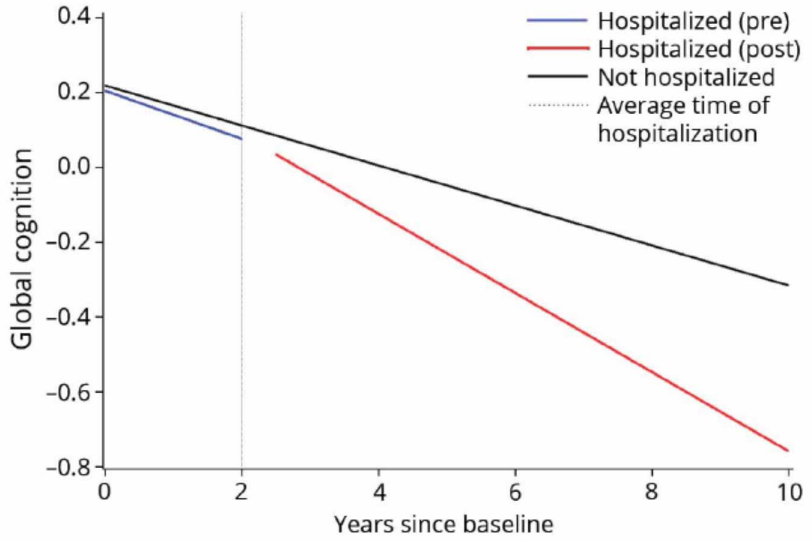


Blue line indicates mean slope before hospitalization and red line indicates mean slope after hospitalization in a person who was hospitalized, compared to the average slope in a person who was not hospitalized (black line). Dotted line indicates mean time of hospitalization. Break in line after average time of hospitalization indicates lack of observation immediately after hospitalization (mean 213 days between hospitalization and subsequent cognitive assessment).

James et al, Neurology 2019;92:1-10

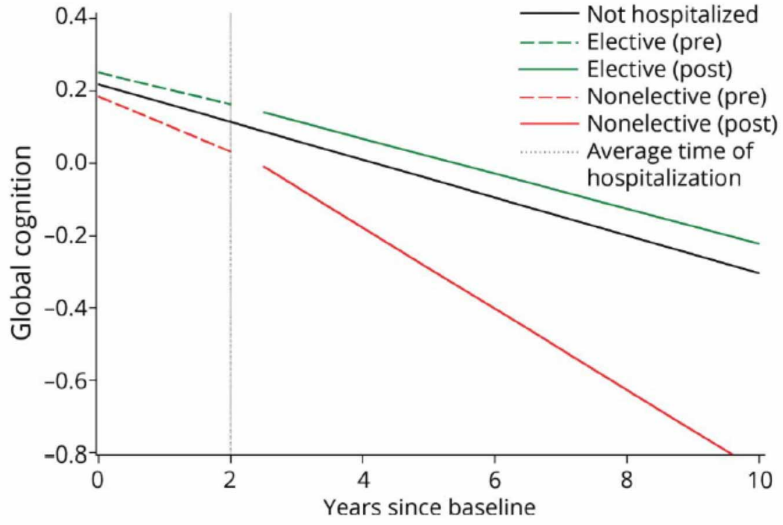
Elective vs Emergent Hospitalization

Figure 2 Rate of decline in global cognition in those who had hospitalization (before and after) or no hospitalization



Blue line indicates mean slope before hospitalization and red line indicates mean slope after hospitalization in a person who was hospitalized, compared to the average slope in a person who was not hospitalized (black line). Dotted line indicates mean time of hospitalization. Break in line after average time of hospitalization indicates lack of observation immediately after hospitalization (mean 213 days between hospitalization and subsequent cognitive assessment).

Figure 3 Rate of decline in global cognition in those who had elective hospitalization, nonelective hospitalizations, or no hospitalization



Green lines indicate mean slopes before (dashed) and after (solid) the mean time of hospitalization in a person experiencing an elective hospitalization, and red lines indicate mean slopes before and after hospitalization for a person experiencing a nonelective hospitalization, compared to average slope in a person who was not hospitalized (black). Break in the after average time of hospitalization indicates lack of observation immediately after hospitalization (mean 213 days between hospitalization and subsequent cognitive assessment).

James et al, Neurology 2019;92:1-10


mindUSA
modifying the impact of ICU-associated
neurological dysfunction

Haloperidol Use for Delirium in the ICU became usual care

Fall 2018, **Mastering Intensive Care** podcast
producer Dr. Andrew Davies, Melbourne Australia

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1st Report of Haldol for ICU Delirium
40 years ago…1978

No. 395

INTRAVENOUS USE OF HALOPERIDOL FOR ACUTE DELIRIUM IN INTENSIVE CARE SETTINGS

Ned. H. Cassem, M.D. (M), *Chief, Psychiatric Consultation-Liaison Service, Massachusetts General Hospital, Boston*

SUMMARY:

Patients recovering from cardiac surgery occasionally become so delirious and agitated that immediate tranquilization is necessary. In a series of 15 patients the use of intravenous haloperidol was studied. All patients had indwelling arterial, left atrial, Swann-Ganz, and central venous pressure lines, two pacing wires each in right artrium and left ventrical, foley catheter, one or more peripheral venous lines, and often the

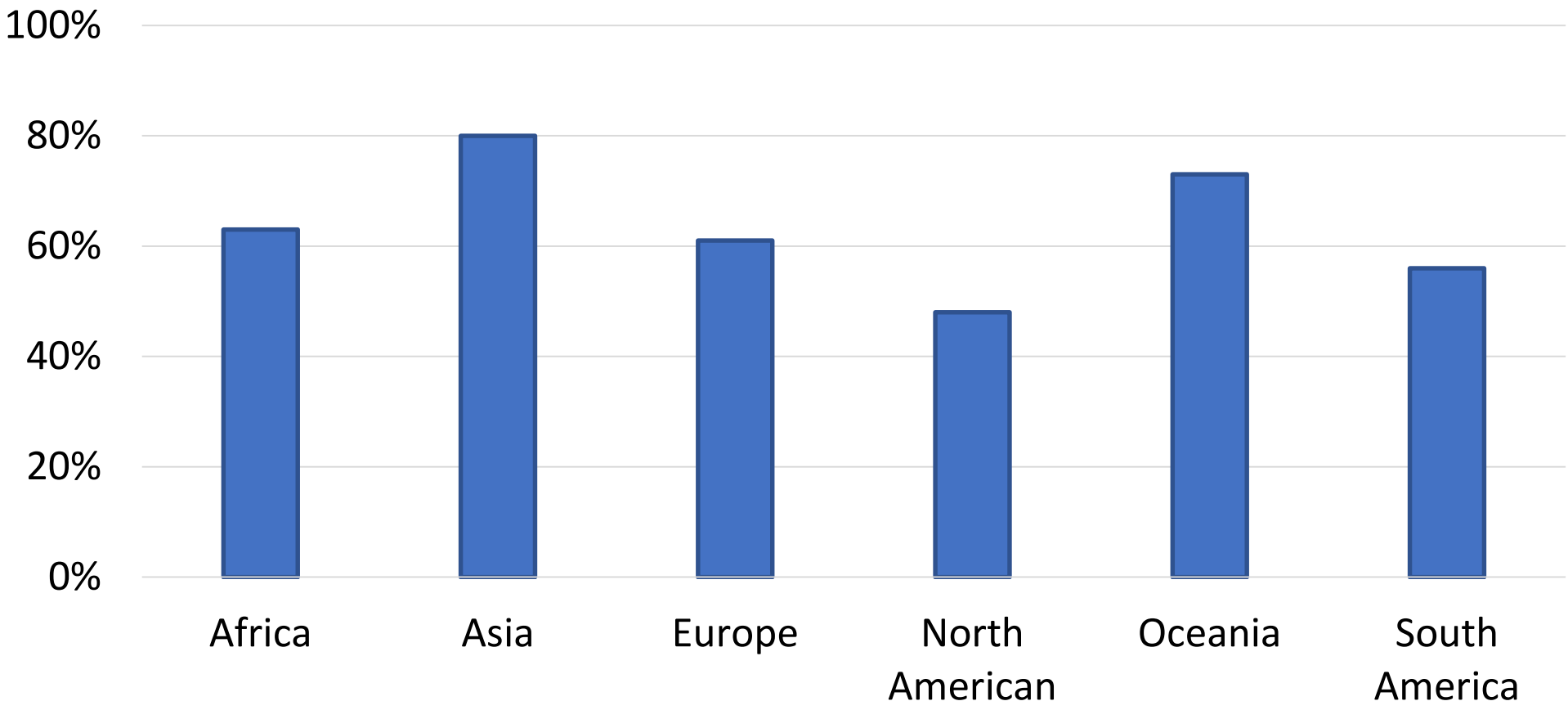
131st Annual Meeting of the American Psych Assoc, Wash DC

Haloperidol Use for Delirium in the ICU became usual care

Recommendations: Haloperidol is the preferred agent for the treatment of delirium in critically ill patients. (Grade of recommendation = C)

—2002 SCCM Guidelines

Global use of Haloperidol for ICU Delirium



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Morandi A. Crit Care Med 2017;45:e1111-22

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Risk of Death in Elderly Users of Conventional vs. Atypical Antipsychotic Medications

Philip S. Wang, M.D., Dr.P.H., Sebastian Schneeweiss, M.D., Jerry Avorn, M.D., Michael A. Fischer, M.D., Helen Mogun, and M. Alan B

Wang PS, NEJM 2005;353:2335-41

Risk of Death With Atypical Antipsychotic Drug Treatment for Dementia

Meta-analysis of Randomized Placebo-Controlled Trials

Lon S. Schneider, MD, MS
Karen S. Dagerman, MS
Philip Insel, MS

Context Atypical antipsychotic medications are widely used to treat delusions, aggression, and agitation ever, concerns have aris rapid cognitive decline,

Schneider LS, JAMA 2005;294:1934-43

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

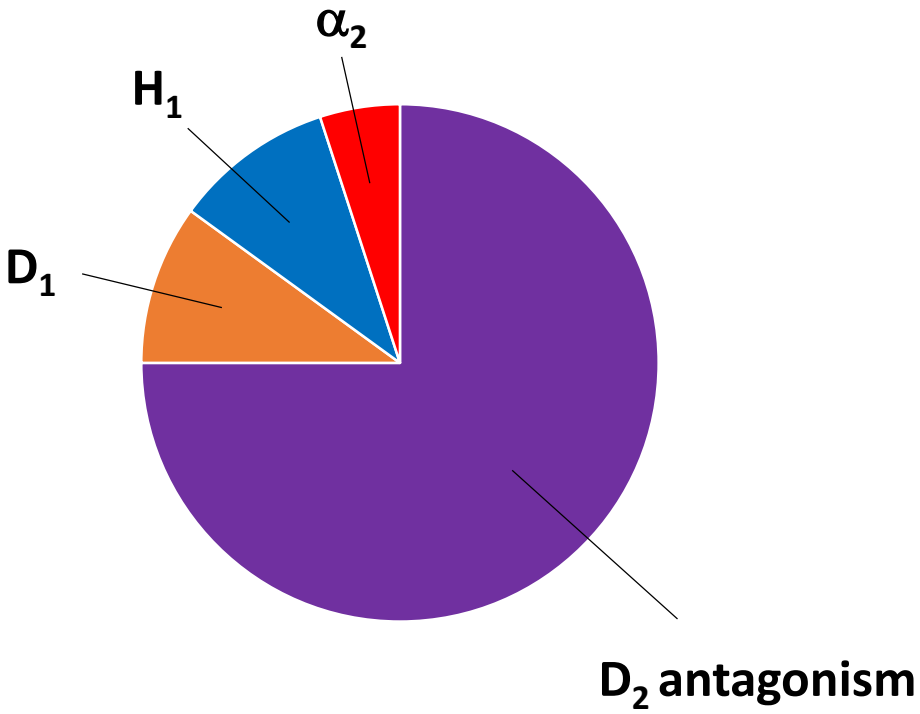
Haloperidol and Ziprasidone for Treatment of Delirium in Critical Illness

T.D. Girard, M.C. Exline, S.S. Carson, C.L. Hough, P. Rock, M.N. Gong, I.S. Douglas, A. Malhotra, R.L. Owens, D.J. Feinstein, B. Khan, M.A. Pisani, R.C. Hyzy, G.A. Schmidt, W.D. Schweickert, R.D. Hite, D.L. Bowton, A.L. Masica, J.L. Thompson, R. Chandrasekhar, B.T. Pun, C. Strength, L.M Boehm, J.C. Jackson, P.P. Pandharipande, N.E. Brummel, C.G. Hughes, M.B. Patel, J.L. Stollings, G.R. Bernard, R.S. Dittus, and E.W. Ely, for the MIND-USA Investigators*

Girard TD, et al. NEJM 2018;379:2506-16

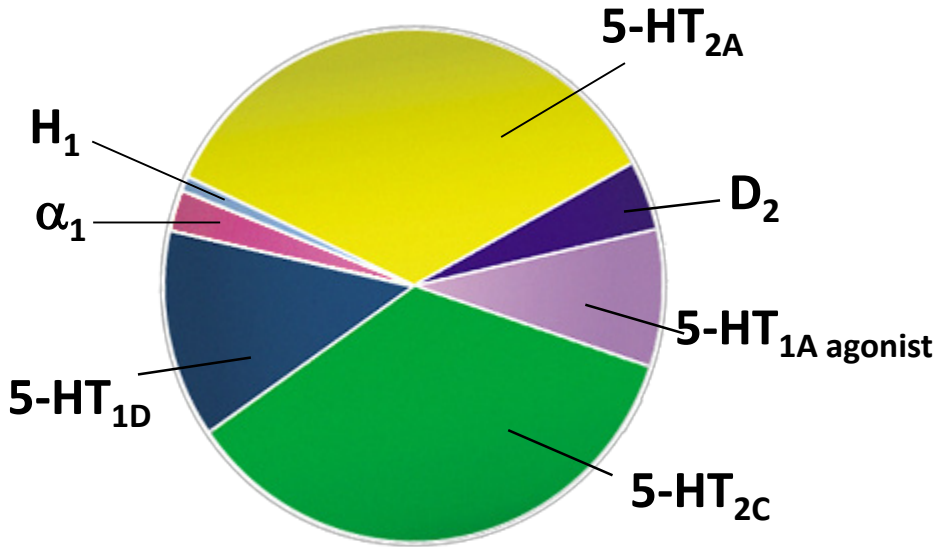
Haloperidol

mainly blocks DA



Ziprasidone

blocks 6 receptors, agonist at 1



Traditional Teaching: "Dopamine blockade in the cerebral cortex improves cognition and reduces delirium."

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MIND-USA: Baseline Variables

Variable	Placebo N=184	Haloperidol N=192	Ziprasidone N=190
Age	59 [52-67]	61 [51-69]	61 [50-69]
APACHE II	30	28.5	28
SOFA	11	11	10
Mechanical Ventilation	175 (95%)	185 (96%)	185 (97%)
Shock on Pressors	65 (35%)	58 (30%)	64 (34%)
Medical / Surgical ICU	72% / 28%	73% / 27%	71% / 29%
Admission Diagnoses			
ARDS or Sepsis	74 (40%)	87 (45%)	68 (36%)
COPD, CHF, Cirrhosis	35 (19%)	29 (15%)	37 (19%)
Other Diagnoses	75 (41%)	76 (40%)	85 (45%)

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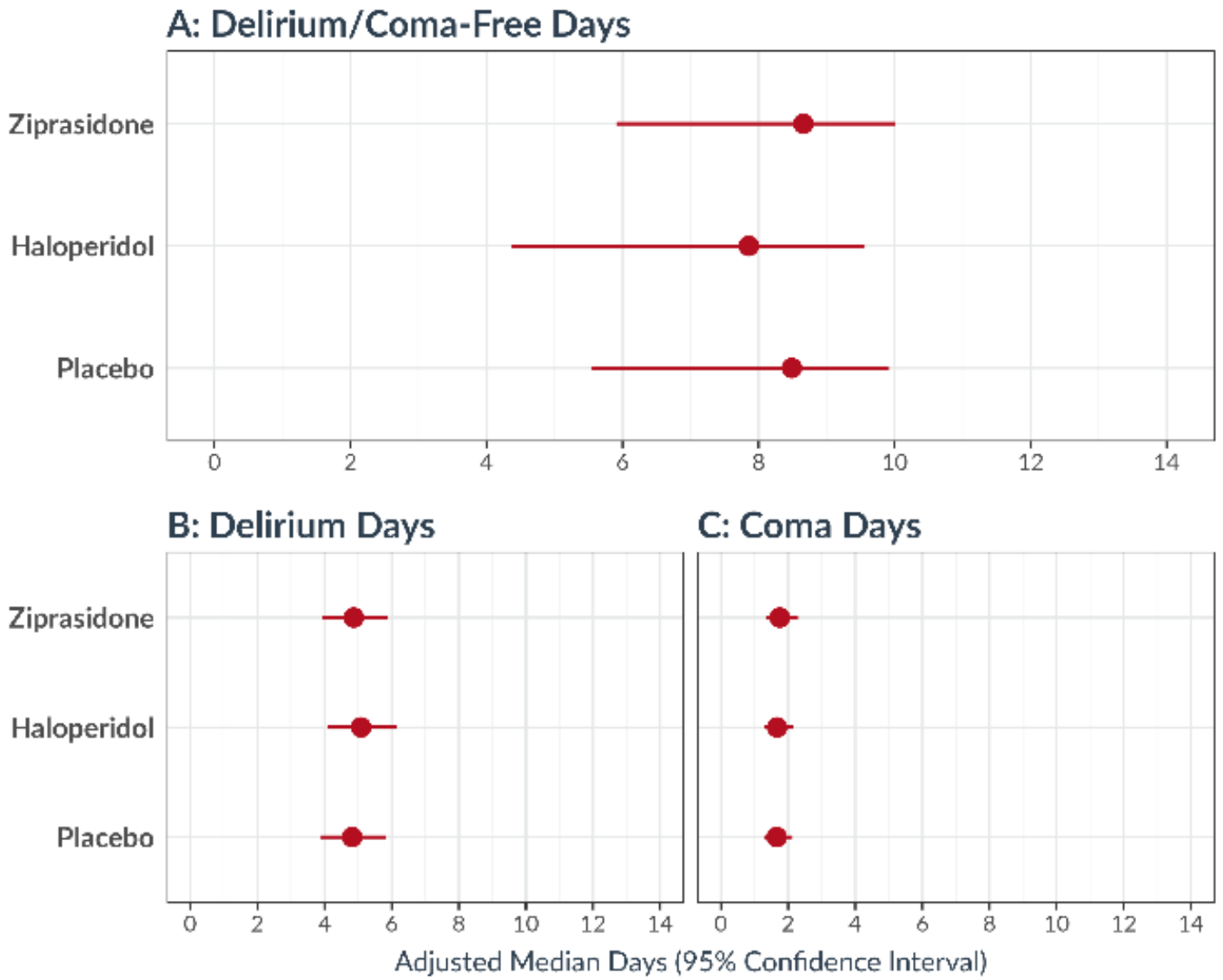
MIND-USA: primary outcome



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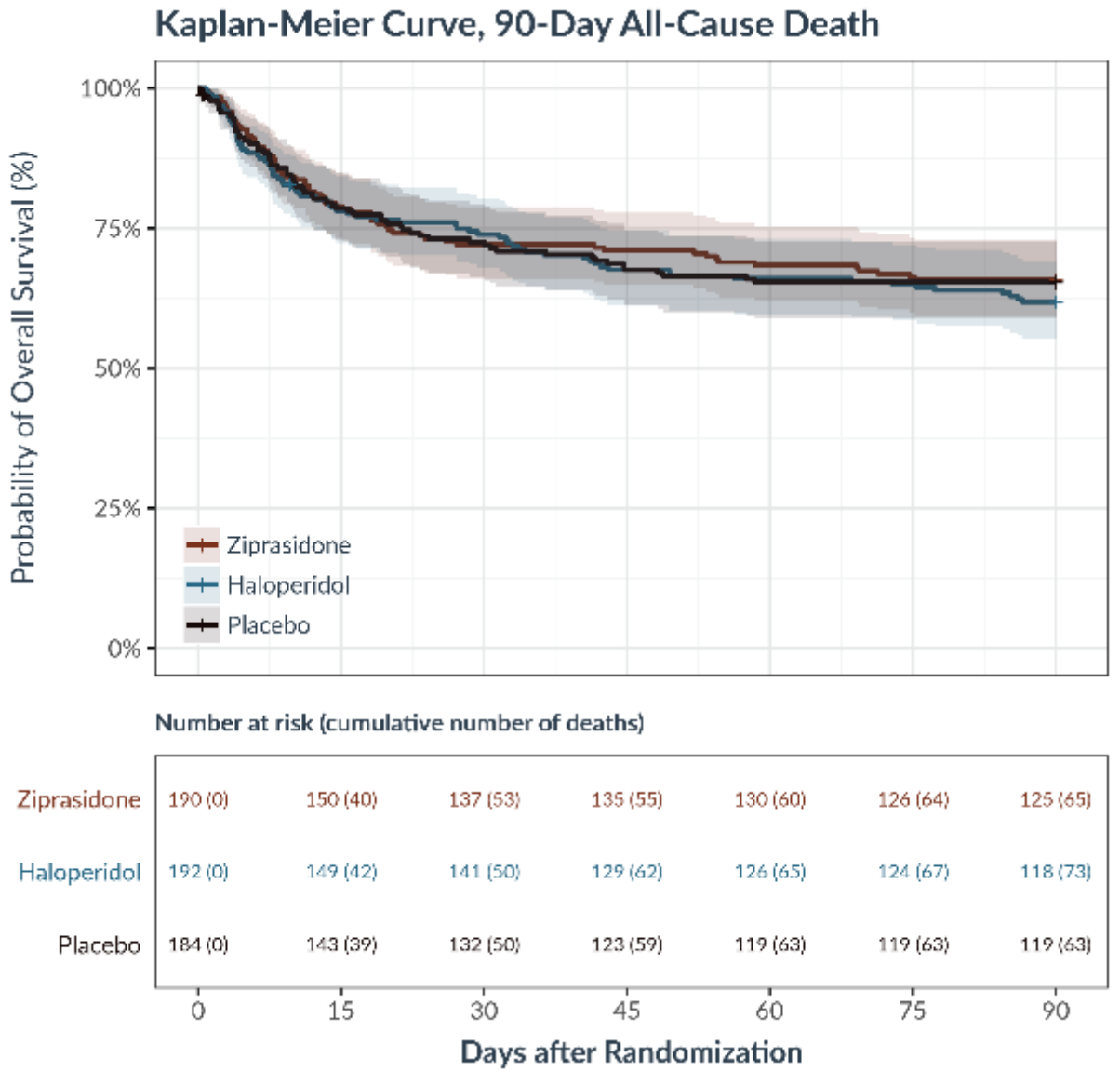
MIND-USA: 90-Day Survival



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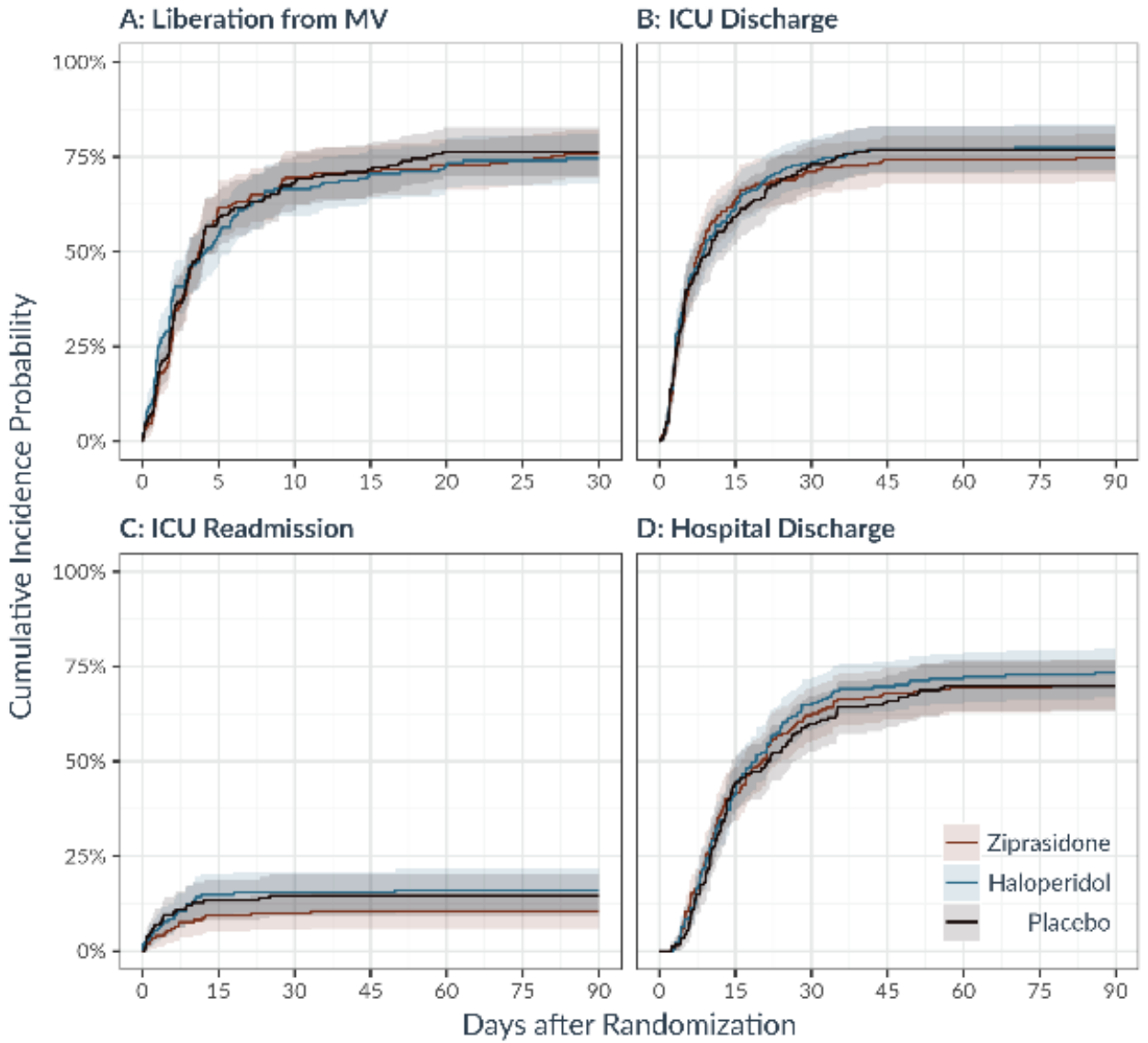
MIND-USA: Key 2° Outcomes



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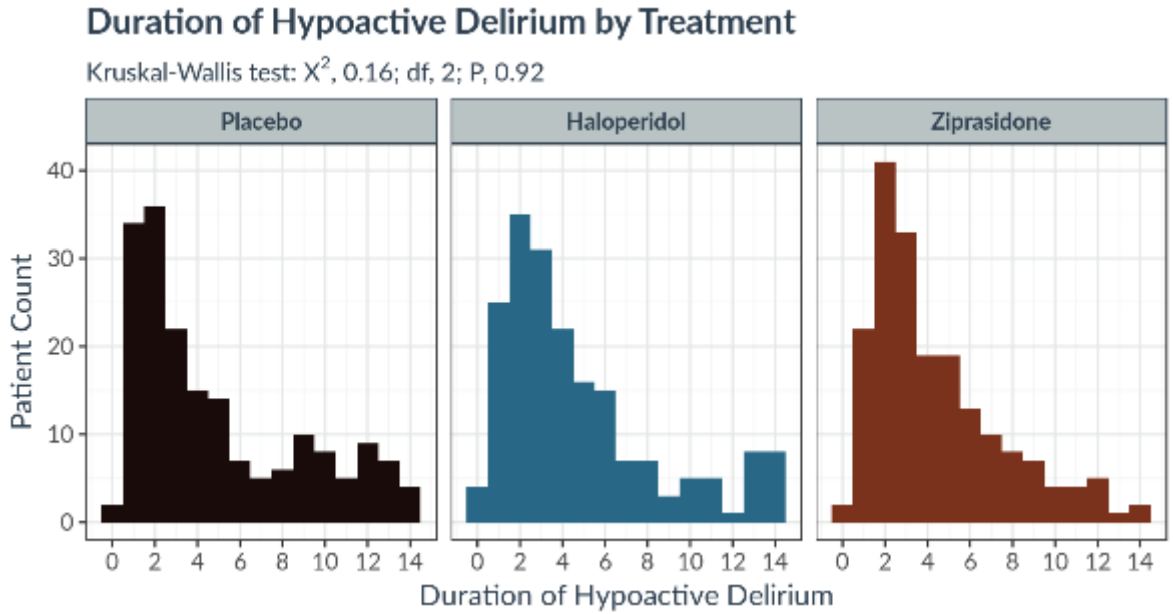
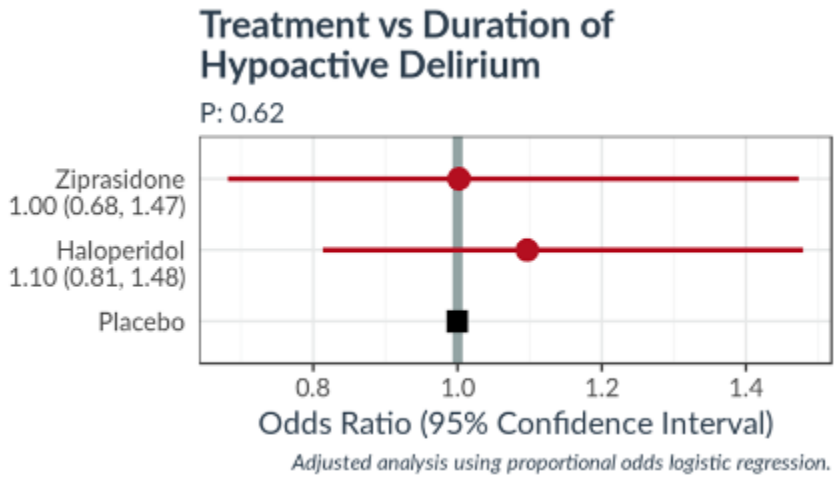
MIND-USA: Hypoactive Delirium





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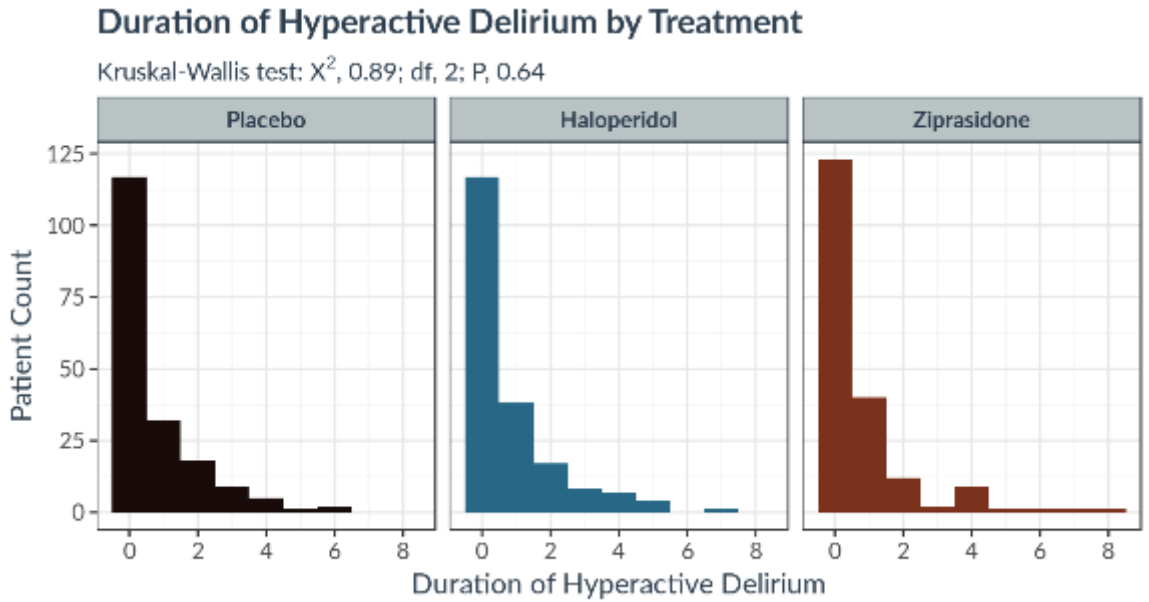
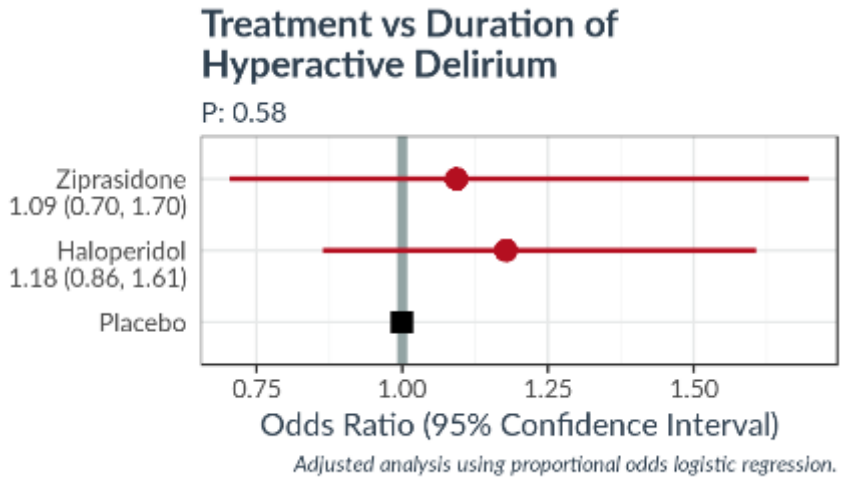
Adj P=0.62

MIND-USA: Hyperactive Delirium





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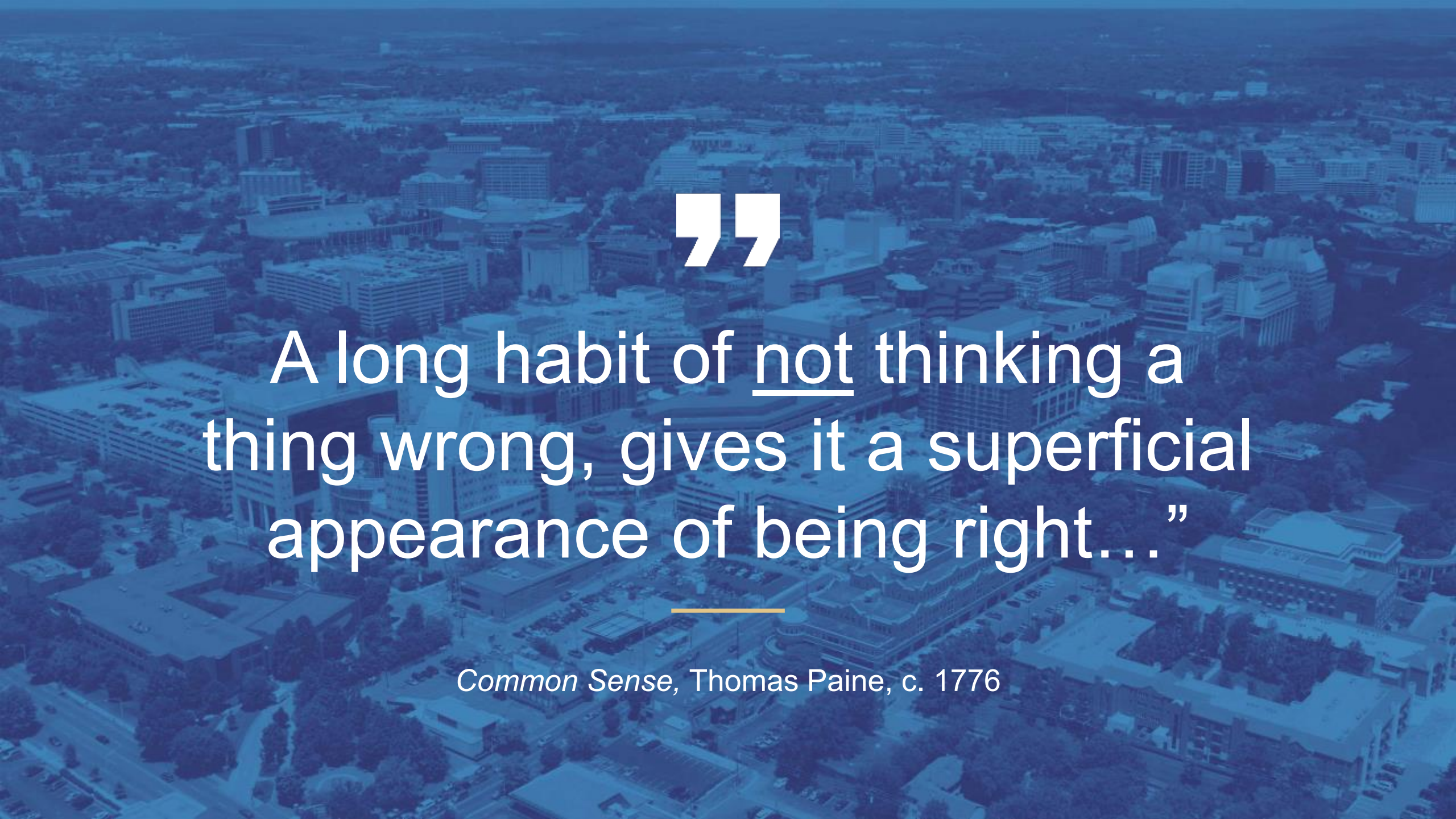
Adj P=0.58



”A long habit of not thinking a thing wrong, gives it a superficial appearance of being right…”

Common Sense, Thomas Paine, c. 1776

How To Prevent Brain-Sapping Delirium In The ICU

npr.org

Richard Harris, Senior NPR Science Reporter, Oct 8, 2018

ABCDEF Bundle: Science & Philosophy

(based on 40 Lancet, JAMA, NEJM papers + ~350 others)

- **A**nalgesia: Assess, Prevent, Manage Pain
- **B**oth SATs and SBTs: Stop Drugs, Stop Vent
- **C**hoice of Analgesia and Sedation
- **D**elirium: Assess, Prevent, Manage
- **E**arly Mobility and Exercise, Environment
- **F**amily Engagement and Empowerment

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A-E and A-F Bundle References

ABCDE Bundle

1. Pandharipande P, Crit Care, 2010;14:157-59
2. Vasilevskis EE, Chest, 2010;138:1224-33
3. Morandi A, Curr Opin Crit Care, 2011;17:43-49
4. Balas MC, Crit Care Nurse, 2012;32:40-47
5. Carrothers KM, Crit Care Med, 2013;41:S128-35
6. Trogrlić Z, Crit Care, 2015;19:157
7. Boehm LM, Am J Crit Care, 2017;26:e18-28
8. Boehm LM, Am J Crit Care, 2017;26:e38-47

ABCDEF Bundle

9. Balas MC, Crit Care Med, 2014;42:1024-36
10. Barnes-Daly MA, Crit Care Med, 2017;45:171-78
11. Ely EW, Crit Care Med, 2017;45:321-30
12. Marra A, Crit Care Clin, 2017;33:225-43
13. Morandi A, Crit Care Med, 2017;45:e1111-22
14. Barnes-Daly MA, World Evid Based Nurs, 2018;15:206-16
15. Pun BT, Crit Care Med 2019;47:3-14
16. Stollings, Crit Care Nurse 2019;39:36-45.
17. Balas MC, Crit Care Nurse 2019;39:46-60
18. Hsieh SJ, CCM 2019;47:885-93

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Liberated…?

Liberated…

ABCDEF…Early Mobility and Family in Poland:

Ventilated Patient and Her Husband with Shopping Cart

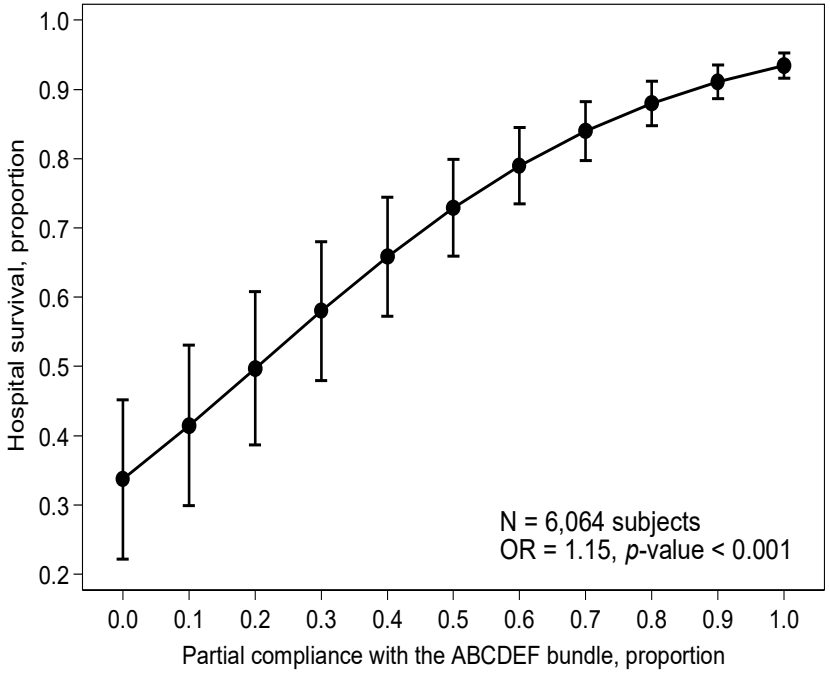
Ely EW CCM 2017;45:321-30

Courtesy of Dr. Kasia Kotfis in Szczecin, Poland

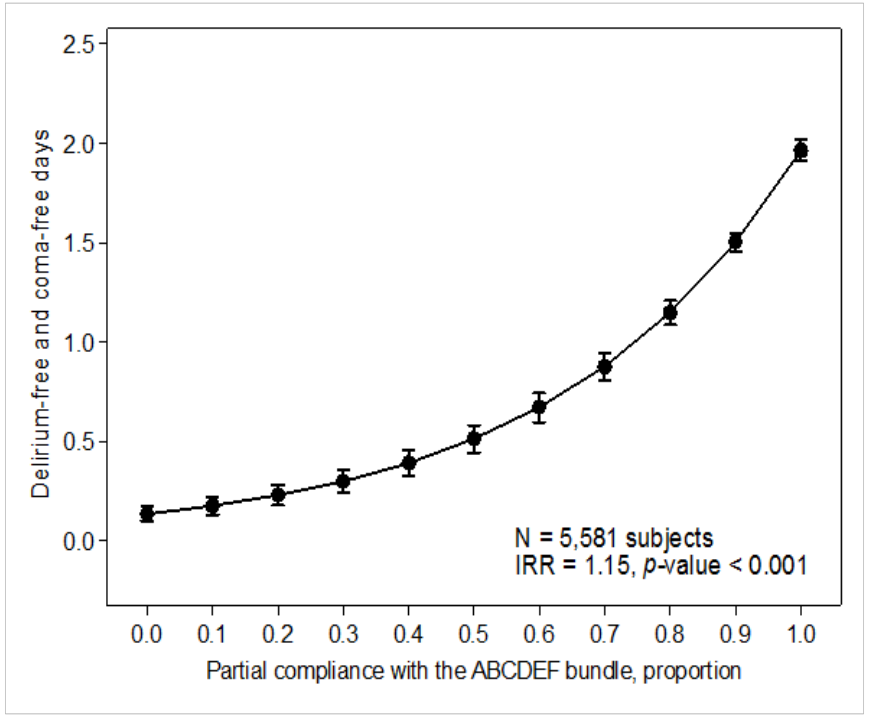
Mr. D and Wanda

Survival and Delirium-Coma Freedom

Implementing ABCDEF Bundle in >6,000 patients



Mortality Improvement



Delirium and Coma Freedom

NOTE: Adjusted for age, APACHE III, and mechanical ventilation
7 California Hospitals, Interprofessional QI Implementation project

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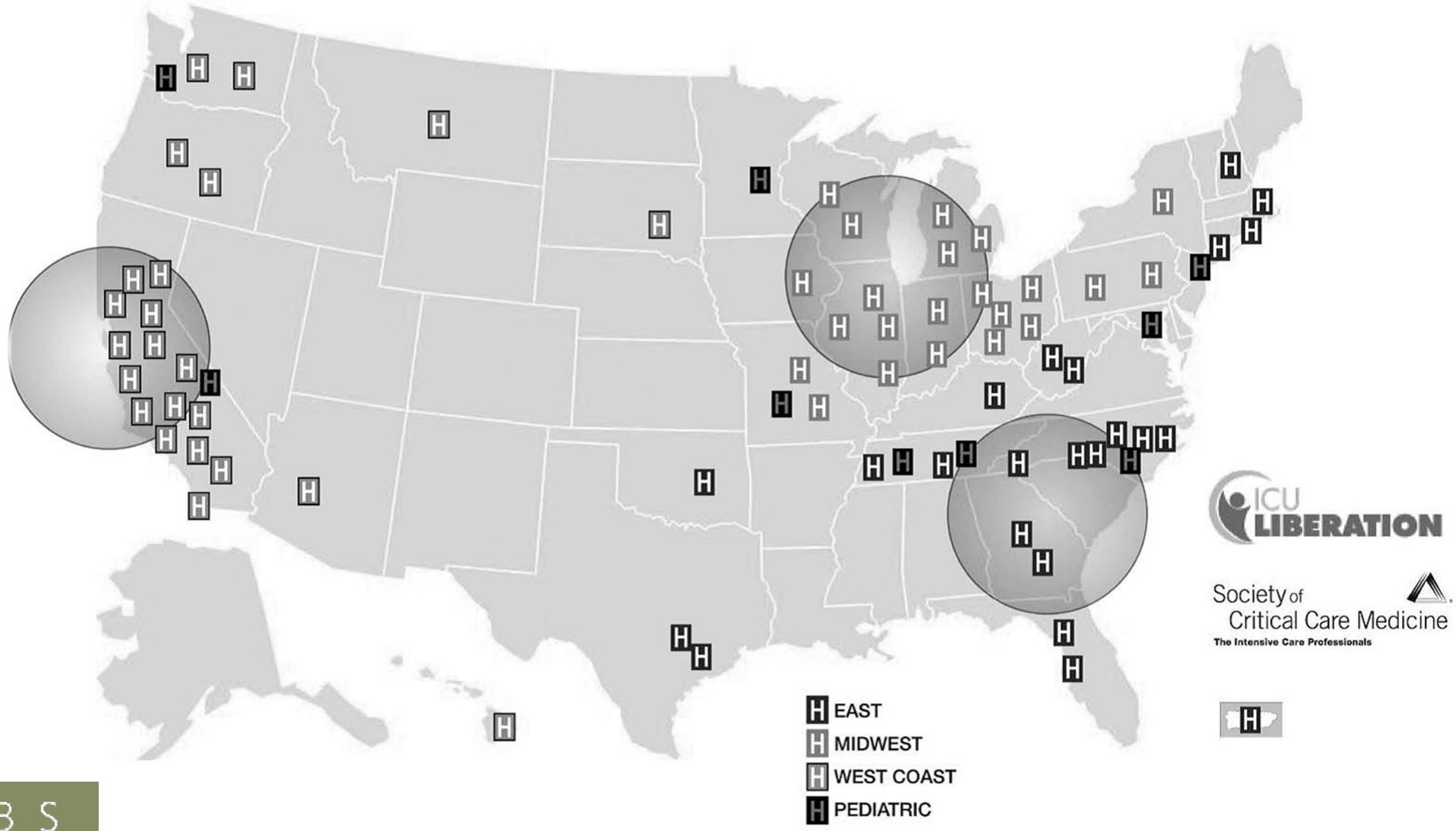
Barnes-Daly MA, CCM 2017;45:171-8

Caring for Critically Ill Patients with the ABCDEF Bundle: Results of the ICU Liberation Collaborative in Over 15,000 Adults

Brenda T. Pun, DNP, RN, FCCM[1]; Michele C. Balas, PhD, RN, CCRN-K, FCCM, FAAN[2,3]; Mary Ann Barnes-Daly, MS, RN, CCRN-K, DC[4]; Jennifer L. Thompson, MPH[5]; J. Matthew Aldrich, MD[6]; Juliana Barr, MD, FCCM[7,8]; Diane Byrum MSN, RN, CCRN-K, CCNS, FCCM[9]; Shannon S. Carson, MD[10]; John W. Devlin, PharmD, FCCM[11]; Heidi J. Engel, PT, DPT[12]; Cheryl L. Esbrook, OTR/L, BCPR[13]; Ken D. Hargett, MHA, FAARC, FCCM[14]; Lori Harmon, RRT, MBA[15]; Christina Hielsberg, MA[15]; James C. Jackson, PsyD[1]; Tamra L. Kelly, BS, RRT, MHA[4]; Vishakha Kumar, MD, MBA[15]; Lawson Millner, RRT[16]; Alexandra Morse, PharmD[4]; Christiane S. Perme, PT, CCS, FCCM[14]; Patricia J. Posa, BSN, MSA, CCRN-K[17]; Kathleen A. Puntillo, PhD, RN, FAAN, FCCM[18]; William D. Schweickert, MD[19]; Joanna L. Stollings, PharmD, FCCM[20]; Alai Tan, PhD[2]; Lucy D'Agostino McGowan, PhD[21]; E. Wesley Ely, MD, MPH, FCCM[1,22]

Pun BT, et al. Crit Care Med. 2019;47:3-14
Sponsored by the SCCM via The Moore Foundation

ICU Liberation Hospitals and Regions



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ICU Liberation Collaborative

- Gordon Moore Foundation (Intel Billionaire)
- SCCM (Sepsis, ICU Liberation, Thrive)
- Aug 2015 to April 2017
- 68 Adult American ICUs, 10 Pediatric
- Medical, Surgical, Cardiac, Neuro ICUs
- ABCDEF Bundle implementation
- 15,226 patients
- All regression models adjusted for 18 confounders chosen *a priori*

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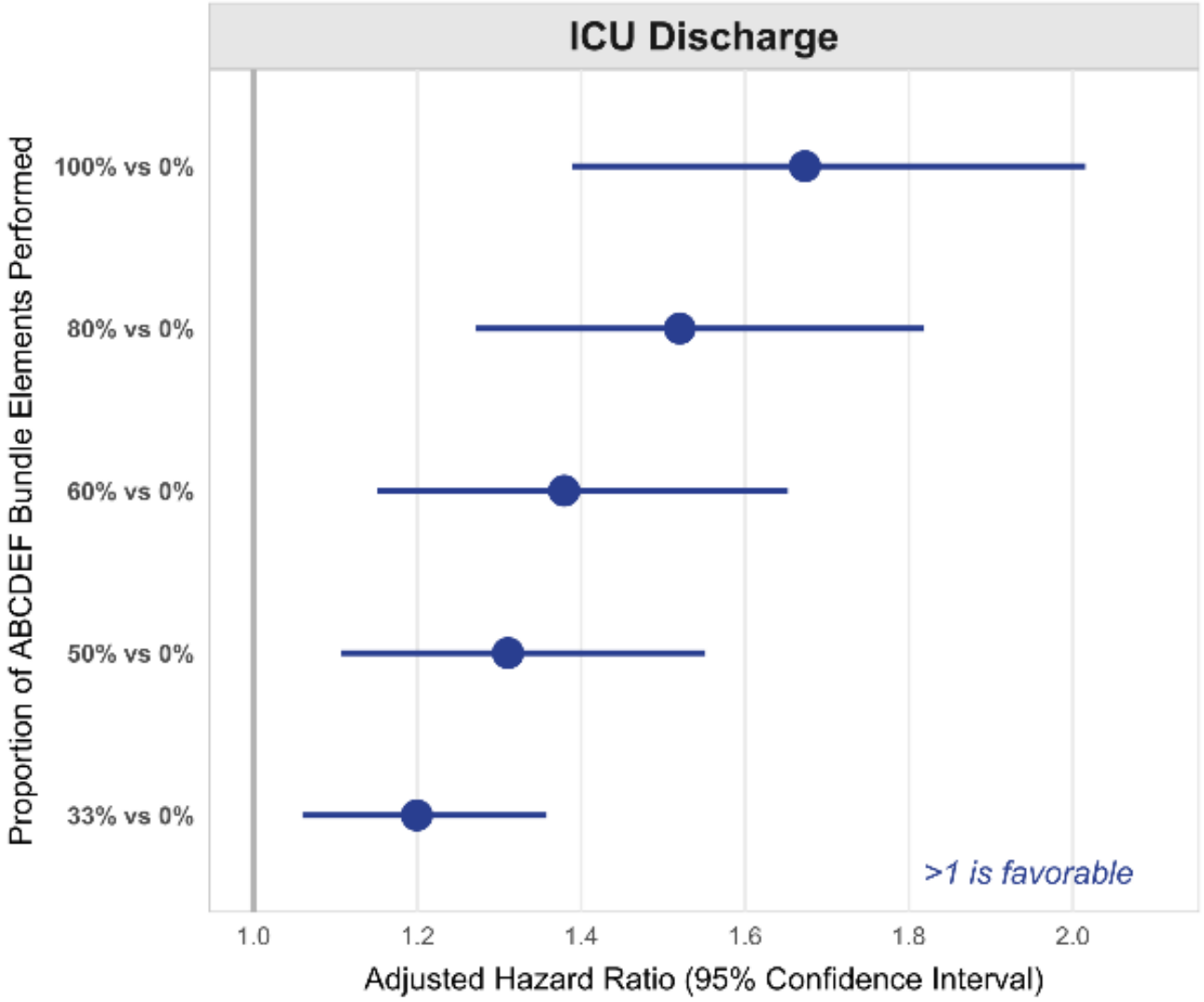
ABCDEF bundle performance… improves ICU discharge



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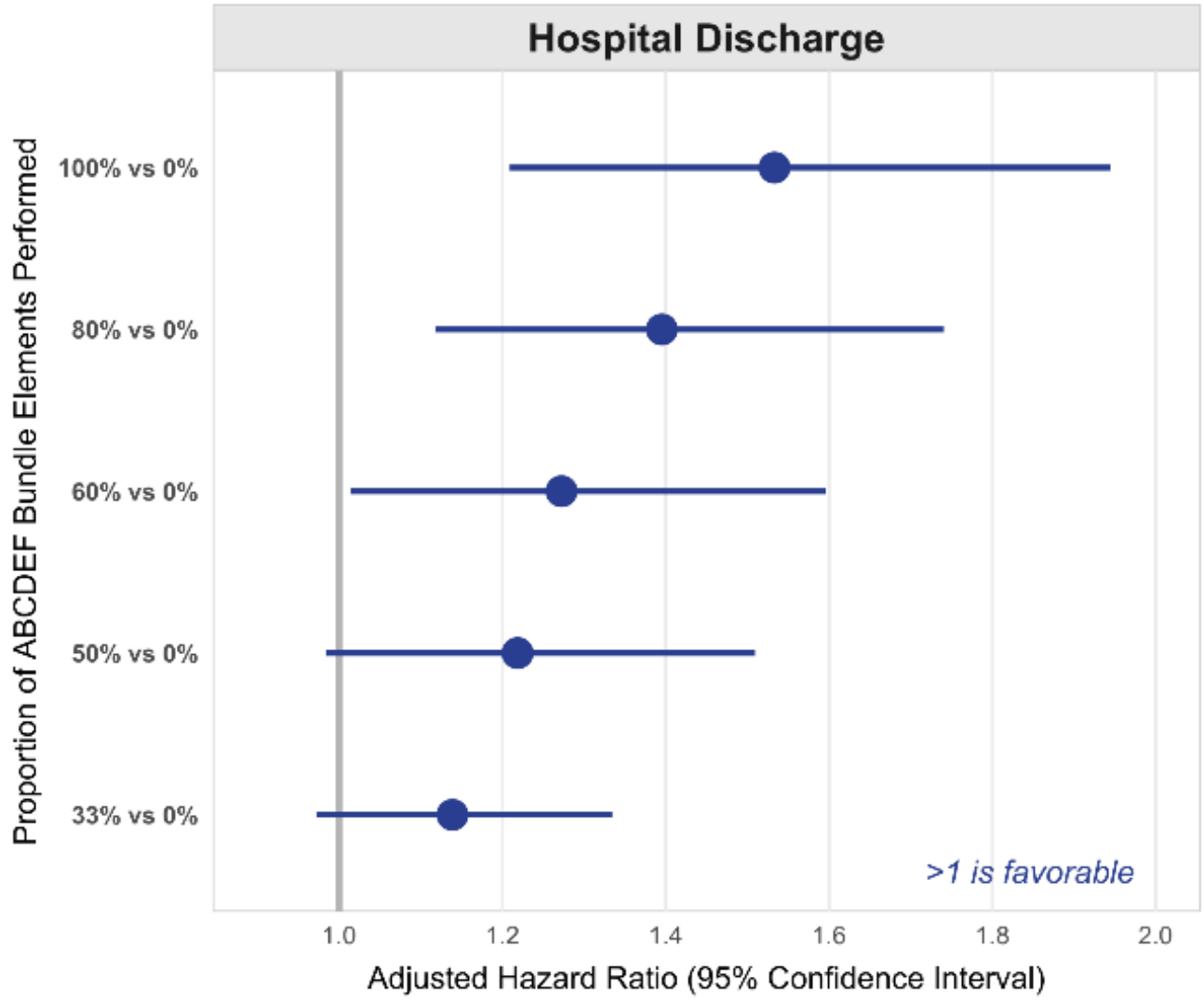
ABCDEF bundle performance… improves hospital discharge



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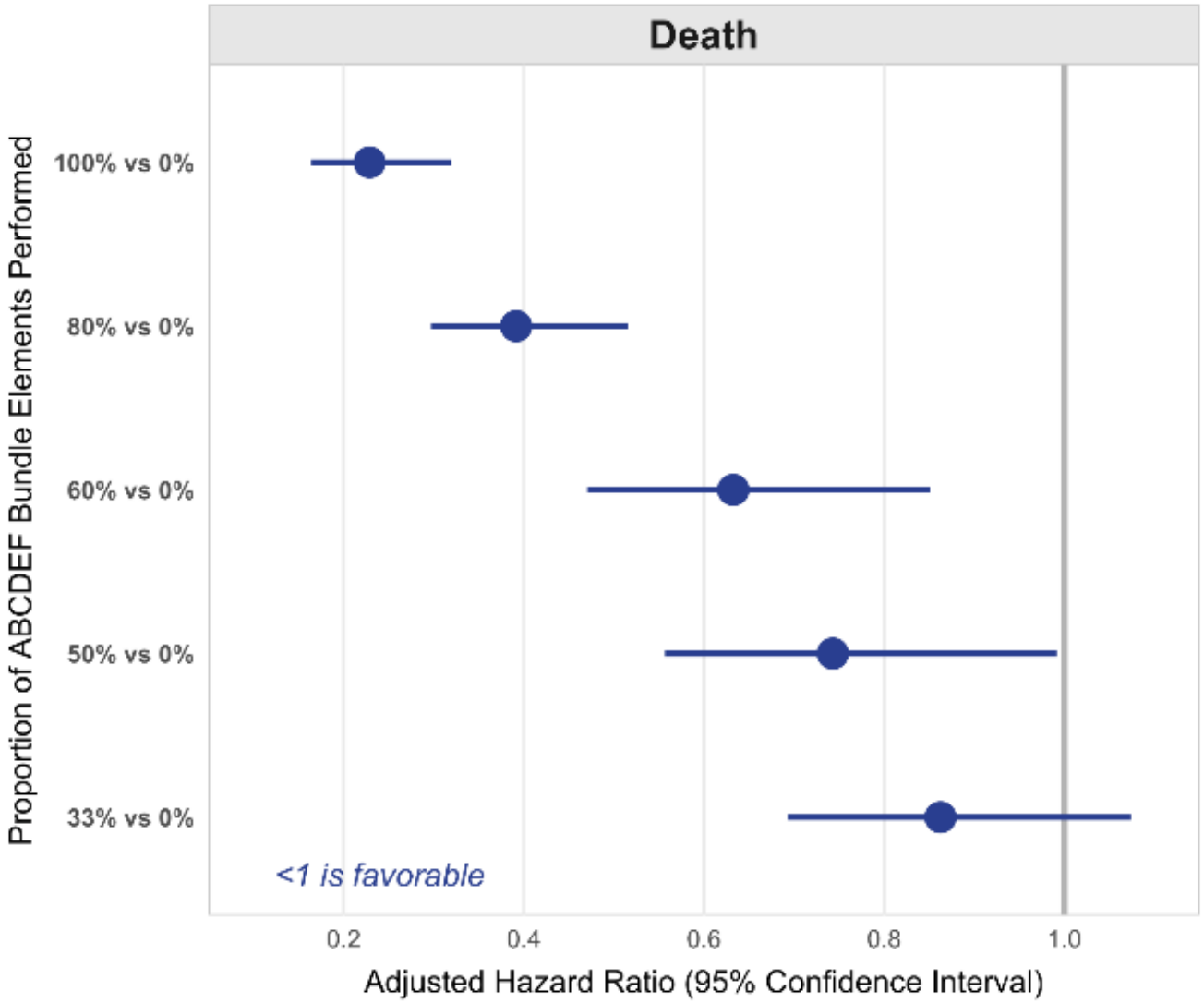
Performance…reduces death



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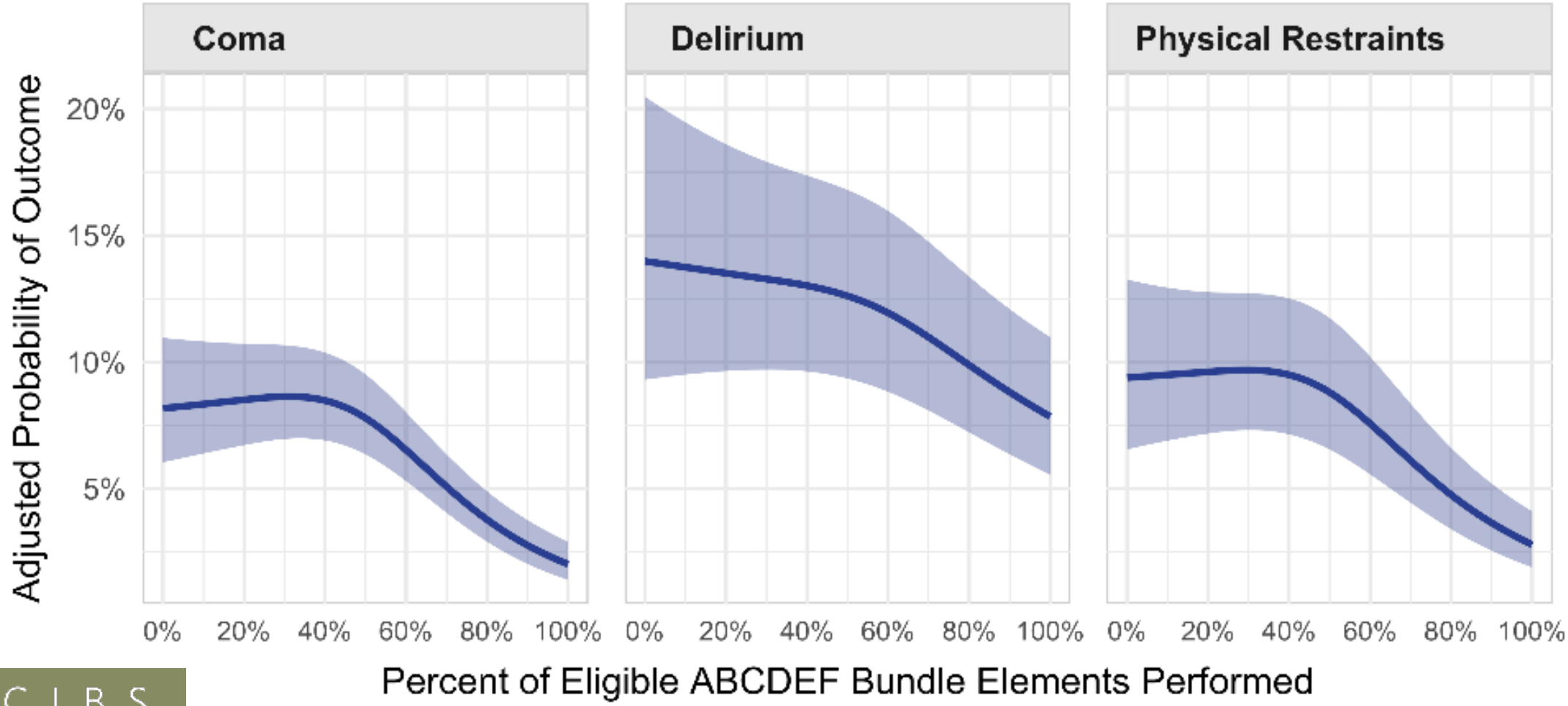
Performance improves… coma, delirium, restraints



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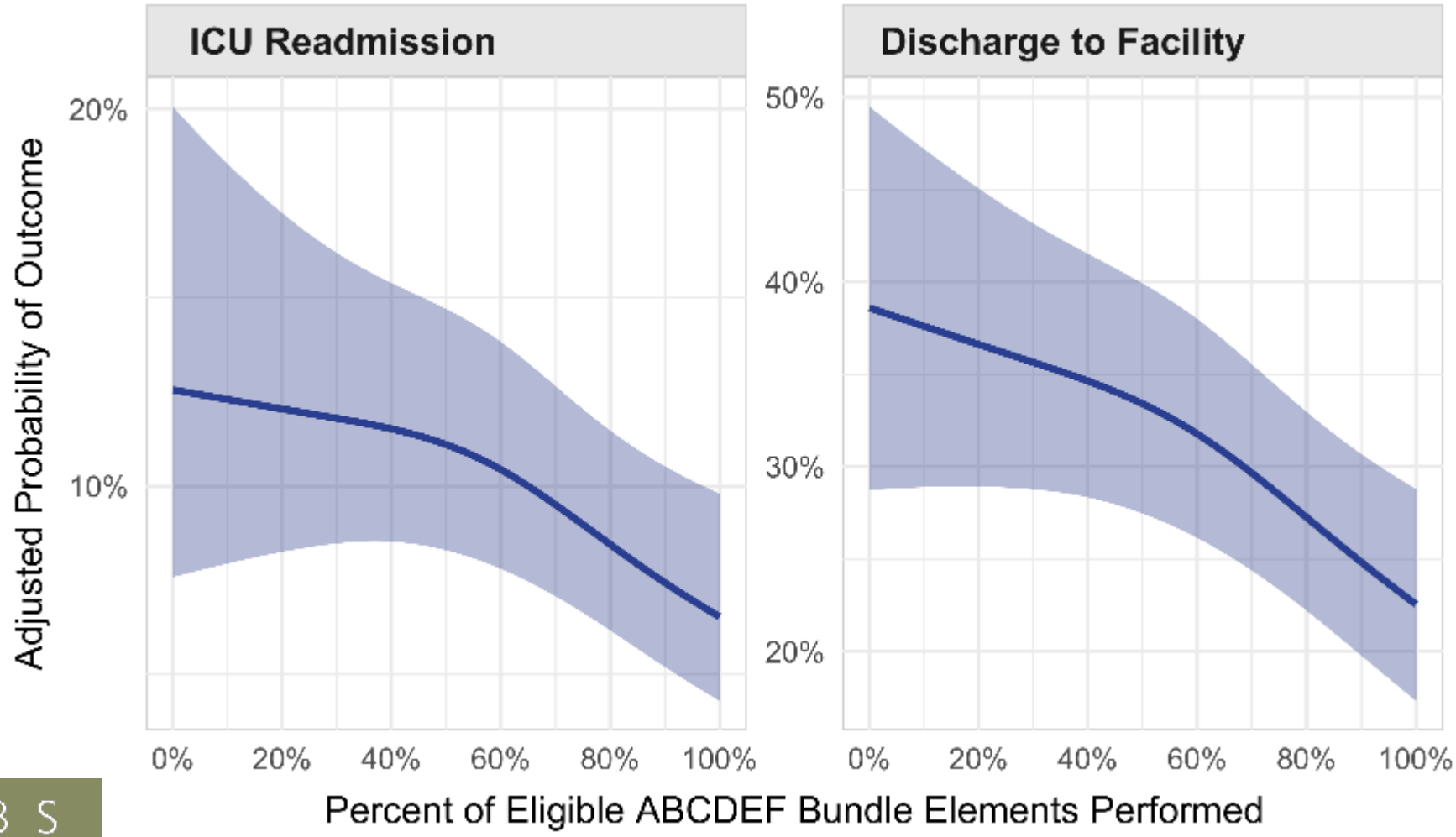
Performance reduces… ICU readmission and NH transfers



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Future Directions

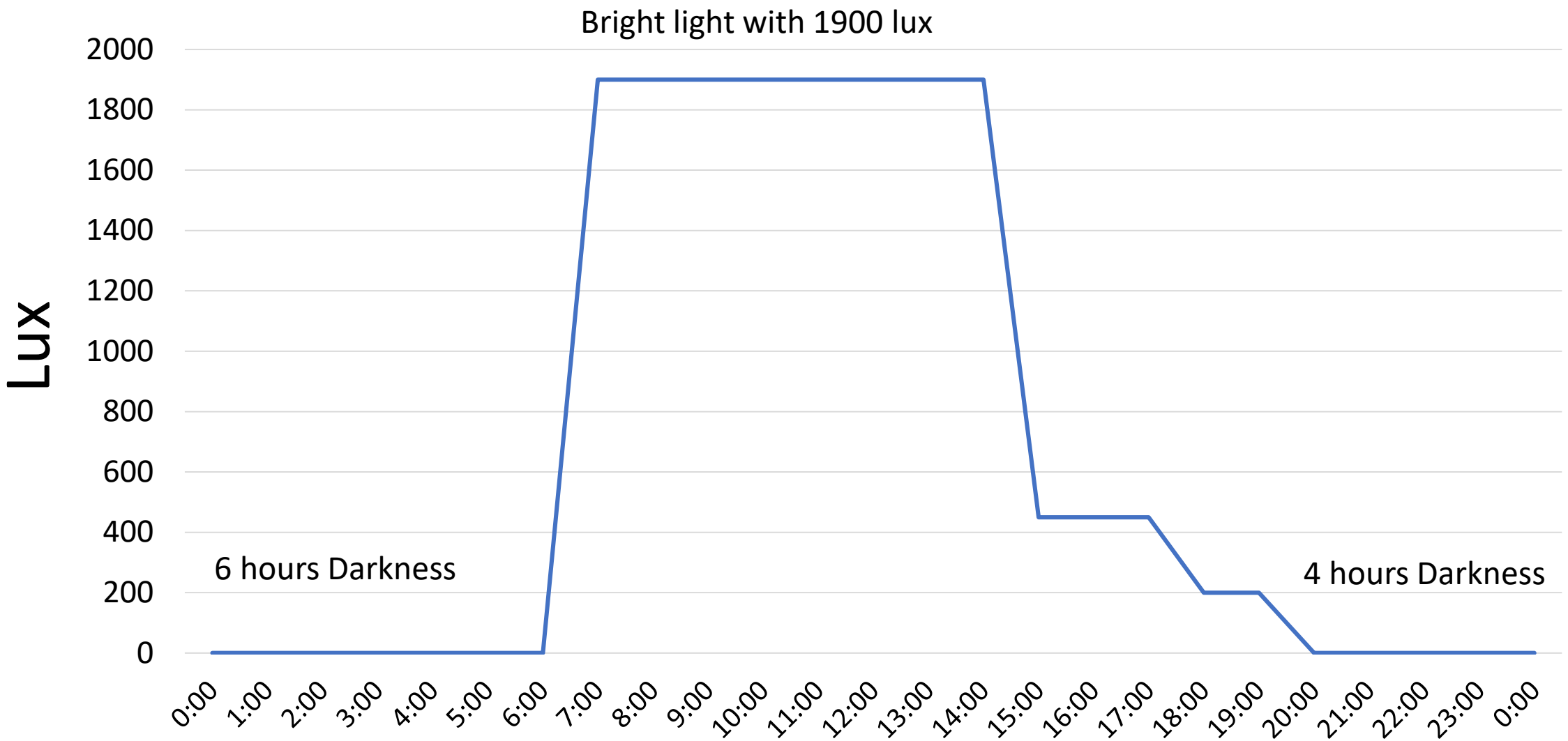
Mobilizing the Brain with Sudoku & Scrabble

Providing Lux to Restore Circadian Rhythm

VitalSky Basic

VitalSky Advanced

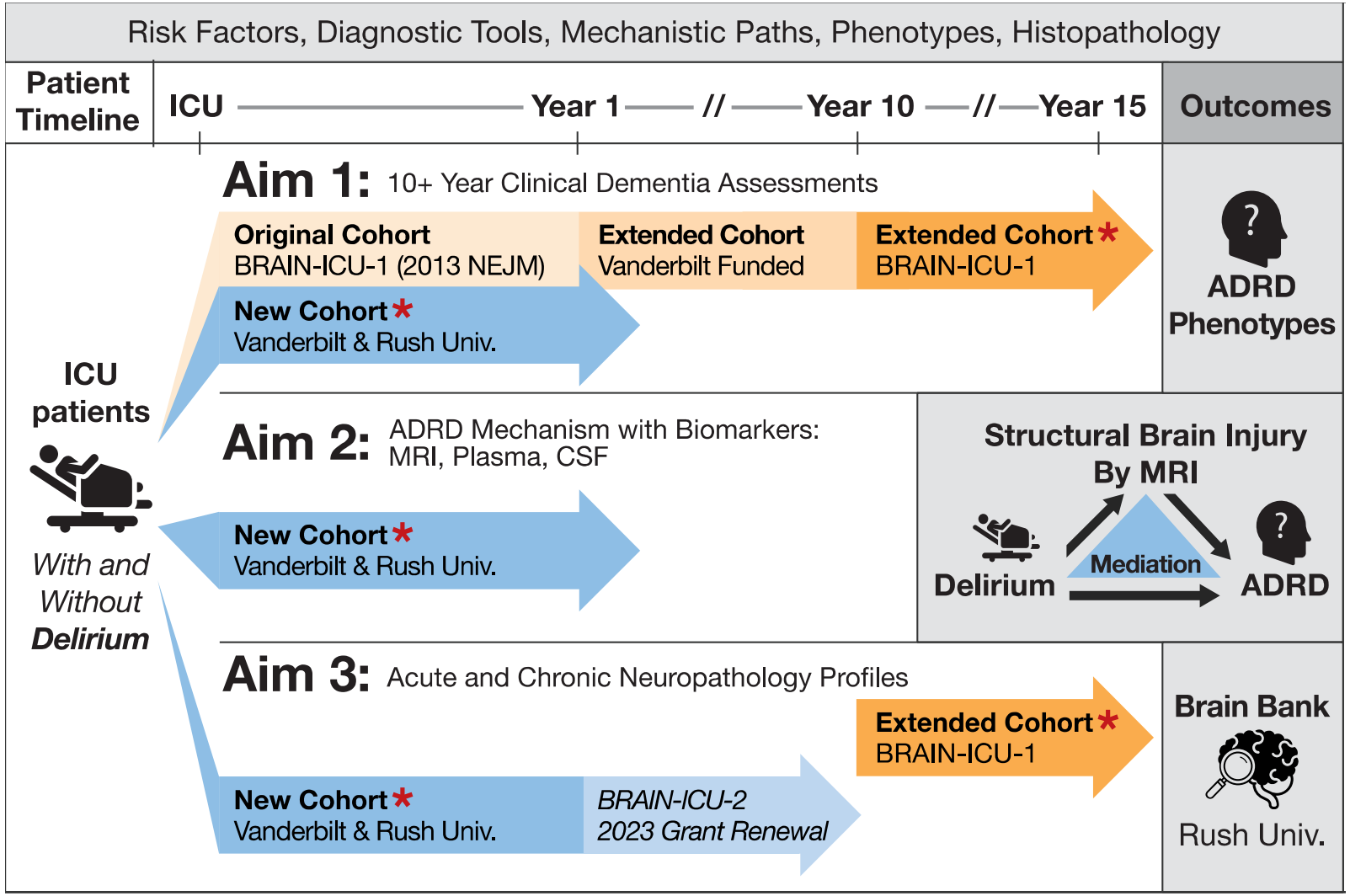
Circadian-effective white light



BRAIN2

BRAIN2 Study Overview

Clarifying the Relationship between Delirium and ADRD (NIA PAR-18-029)



Legend: * *This RO1 Proposal (2019-2023)*

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CIBS Collaborators

Surgery

Anesthesia

Medicine

Neurology

Psychiatry

Biostatistics

Epidemiology

Pharmacology

Radiology

Pediatrics

Biomedical Informatics

VU Engineering

VUIIS

Health Policy

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