

# **Delirium in Older Persons: An Investigative Journey**

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# Goals

- Overview my investigative journey in delirium research—not a global overview of all delirium research
- Discuss unanswered questions and future areas of investigation in delirium

# *The Beginning...*

- Six cases during my first attending stint
- Poring over medical records to figure out “what went wrong”
- Convincing others that this was an important area for research
- In the process, convincing myself

# What is Delirium?

(Acute Confusional State)

## Definition:

- Acute decline in attention and cognition

## Why is delirium important?

- Common problem
- Serious complications
- Often unrecognized
- 40-50% cases preventable

In U.S. hospitals today

***5 older patients become delirious every minute***

2.6 million older adults develop delirium each year

U.S. Dept HHS, AoA Report, Profile of Older Americans 2011

# **Step 1: Figure out how to** **measure delirium**

# Measuring the Outcome

- Needed a strong measure for the outcome: reliable, valid, and sensitive to change
- Developed the Confusion Assessment Method (CAM) for measurement of delirium
- For clinicians and lay interviewers
- Both clinical and research settings
- Prospective validation study against criterion standard (geriatric psychiatrist ratings)

# Development of a Delirium Instrument

Ref: Inouye SK, et al. Ann Intern Med.  
1990, 113: 941-8.



# Key Features of Delirium

- 1) Acute onset and fluctuating course
- 2) Inattention
- 3) Disorganized thinking
- 4) Altered level of consciousness

Note: disorientation and inappropriate behavior not useful diagnostically

# Simplified Diagnostic Criteria

- Uses 4 criteria assessed by CAM:
  - (1) acute onset and fluctuating course
  - (2) inattention
  - (3) disorganized thinking
  - (4) altered level of consciousness
- The diagnosis of delirium requires the presence of criteria:
  - (1), (2) and (3) or (4)

# Validation of CAM

	<u>Site I</u>	<u>Site II</u>
	(n=30)	(n=26)
Sensitivity	10/10 (100%)	15/16 (94%)
Specificity	19/20 (95%)	9/10 (90%)
Positive predictive accuracy	10/11 (91%)	15/16 (94%)
Negative predictive accuracy	19/19 (100%)	9/10 (90%)
Likelihood ratio (positive test)	20.0	9.4

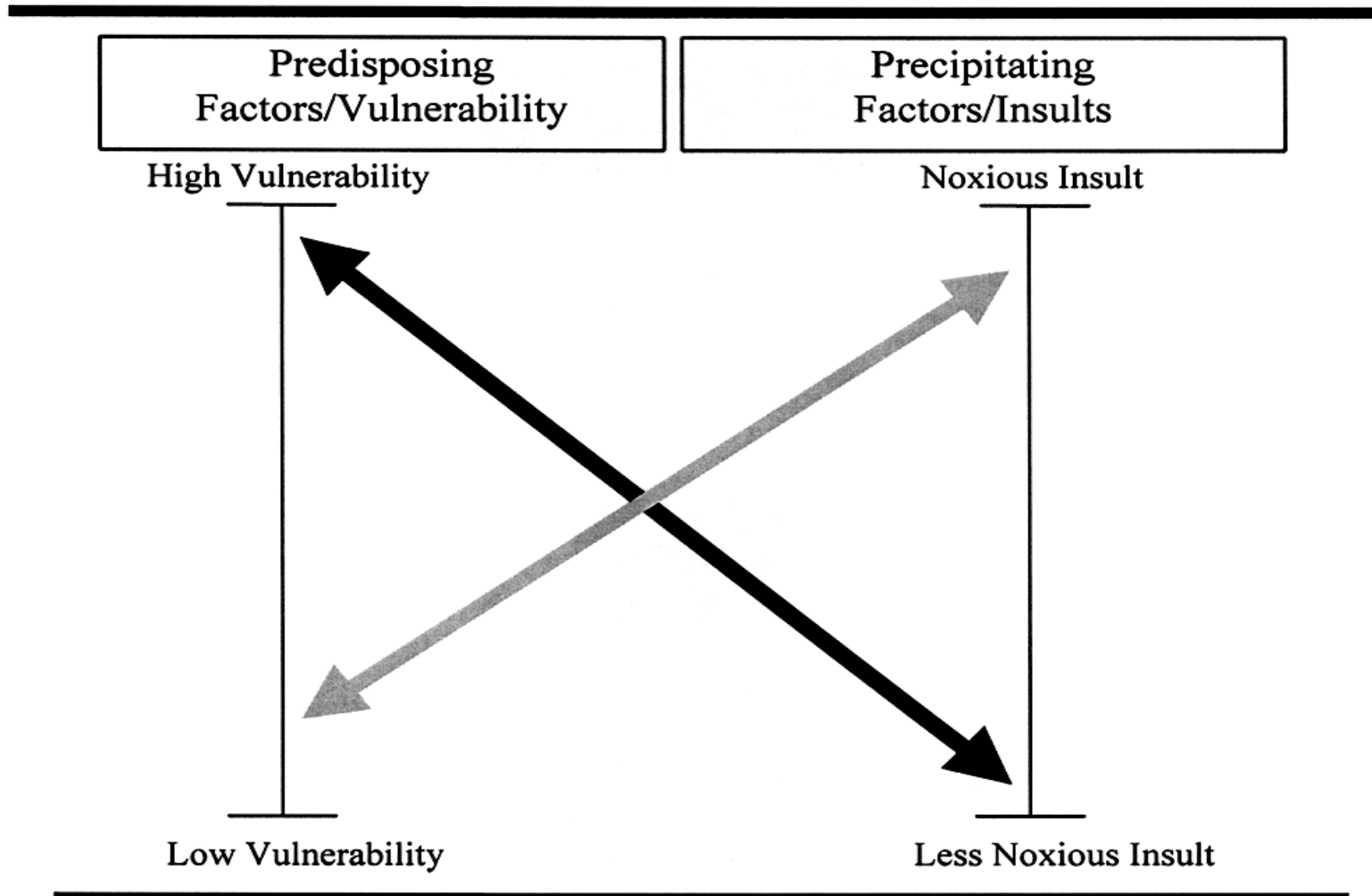
# CAM Significance

- Helped to improve recognition of delirium
- Widely used standard tool for clinical and research purposes nationally and internationally
- Validated in over 1000 patients with sensitivity 94% and specificity of 89%
- Translated into over 20 languages
- Used in over 4000 original published studies
- Many adaptations (CAM-ICU, CAM-ED, BCAM)

Ref: Wei LA et al. JAGS 2008;56:823-30

# **Step 2: Identify who is at risk for delirium**

# MULTIFACTORIAL MODEL OF DELIRIUM IN OLDER PERSONS



# **Baseline Vulnerability**

## Development and Validation of a Predictive Model for Delirium Based on Admission Characteristics

Ref: Inouye SK, et al. Ann Intern Med 1993;119:474-81.

# Methods

- Design: Prospective cohort study
- Patients: 2 consecutive cohorts of patients age  $\geq 70$  years on the medicine service (N=107 and 174)
- Exclusions: delirium at baseline
- Assessments: Daily patient and nurse interviews, with CAM ratings



# Development of the Predictive Model

- 13 potential risk factor variables with  $RR \geq 1.5$  entered into a stepwise multivariable model
- 4 risk factors selected for the final predictive model

# Independent Risk Factors for Delirium

(N=107)

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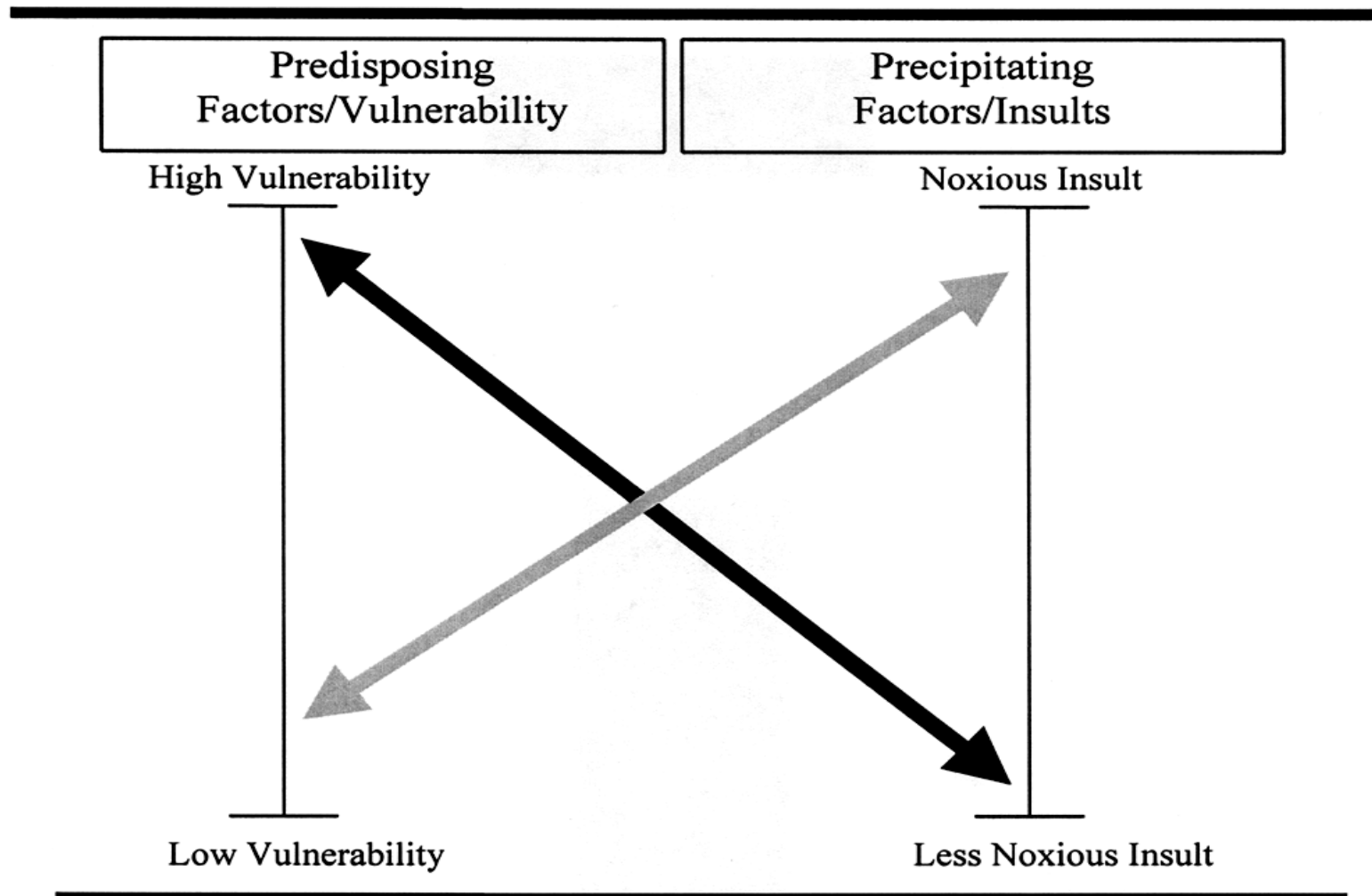
Risk Factor	Adjusted Relative Risk (95% CI)
Vision Impairment	3.5 (1.2, 10.7)
Severe Illness	3.5 (1.5, 8.2)
Cognitive Impairment	2.8 (1.2, 6.7)
BUN/Cr Ratio $\geq$ 18	2.0 (0.9, 4.6)

# Performance of the Predictive Model

## Development of Delirium

No. of Risk Factors	<u>Initial Cohort</u>			<u>Validation Cohort</u>		
	n/N	(%)	RR	n/N	(%)	RR
0	3/33	(9)	1.0	1/30	(3)	1.0
1-2	14/61	(23)	2.5	16/103	(16)	4.7
3-4	10/12	(83)	9.2	12/38	(32)	9.5

# Multifactorial Model of Delirium in Older Persons



# Precipitating Factors

## Development and Validation of a Predictive Model for Delirium Based on Hospitalization – Related Factors

Ref: Inouye SK, et al. JAMA 1996;275:852-7.

## INDEPENDENT PRECIPITATING FACTORS FOR DELIRIUM

(N = 196)

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Precipitating Factor	Adjusted Relative Risk (95% CI)
Use of physical restraints	4.4 (2.5 - 7.9)
Malnutrition	4.0 (2.2 - 7.4)
> 3 medications added	2.9 (1.6 - 5.4)
Use of bladder catheter	2.4 (1.2 - 4.7)
Any iatrogenic event	1.9 (1.1 - 3.2)

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## **PERFORMANCE OF PREDICTIVE MODEL**

Development Cohort, N = 196

No. Factors	Delirium rate, by person	RR	Delirium rate, per 100 person-days	RR
0	2/76 (3%)	1.0	2/673 (.3)	1.0
1-2	20/98 (20%)	7.8	20/559 (3.6)	12.0
≥ 3	13/22 (59%)	22.7	13/61 (21.3)	71.0

# INTER-RELATIONSHIP OF BASELINE AND PRECIPITATING FACTORS

Development Cohort, N = 196

RATE OF DELIRIUM (per 100 person-days)

Baseline Risk Group

		<u>Precipitating Factors Group</u>			
		Low	Int	High	Total
Low		0	0	0	0
Int		0	3.2	13.6	1.6
High		1.4	4.9	26.3	5.6
Total		.3	3.6	21.3	



# **IDENTIFICATION OF RISK FACTORS:** **SIGNIFICANCE**

- Helped determine which risk factors to address
- Identified patients at high risk for delirium—to target for future preventive efforts
- Provided groundwork needed for clinical programs and intervention trials

# **The Yale Delirium Prevention** **Trial**

Inouye SK. N Engl J Med. 1999;340:669-76.

# **Risk Factors for Delirium**

- Cognitive Impairment
- Sleep Deprivation
- Immobilization
- Vision Impairment
- Hearing Impairment
- Dehydration

# Yale Delirium Prevention Program

Multicomponent intervention strategy targeted at 6 delirium risk factors

<u>Risk Factor</u>	<u>Intervention</u>
Cognitive Impairment.....	Reality orientation Therapeutic activities protocol
Sleep Deprivation.....	Nonpharmacological sleep protocol Sleep enhancement protocol
Immobilization.....	Early mobilization protocol Minimizing immobilizing equipment
Vision Impairment.....	Vision aids Adaptive equipment
Hearing Impairment.....	Amplifying devices Adaptive equipment and techniques
Dehydration.....	Early recognition and volume repletion

# Yale Delirium Prevention Trial: Methods

- Design: controlled clinical trial with individual matching from 3/25/95 – 3/28/98
- Subjects: patients  $\geq 70$  years old without evidence of delirium, but at moderate to high risk for developing delirium. Sample size = 852 (426 intervention, 426 controls)
- Units: one intervention and 2 control (usual care) units
- Procedures: baseline, daily, and 1 mo, 6 mo, 12 mo follow-up interviews by trained clinical research staff, blinded to study hypotheses and interventional nature

# Yale Delirium Prevention Trial: Results

Outcome	Intervention Group (N=426)	Usual Care Group (N=426)	Matched OR (CI) or p-value
Incident delirium, n (%)	42 (9.9%)	64 (15.0 %)	.60 (.39 -.92) p= .02
Total delirium days	105	161	p=.02
No. delirium episodes	62	90	p=.03
Delirium severity score	3.9	3.5	p=.25
Recurrence rate	13 (31.0%)	17 (26.6%)	p=.62

# Delirium Prevention Trial: Significance

- First demonstration of delirium as a preventable medical condition
- Practical, real-world intervention strategy targeted towards evidence-based risk factors
- Primary prevention of delirium likely to be most effective treatment strategy
- Targeted, multicomponent strategy works

# **THE HOSPITAL ELDER LIFE PROGRAM** **(HELP)**

## **A Model of Care to Prevent Delirium and Functional Decline in Hospitalized Older Patients**

Inouye SK, et al. J Am Geriatr Soc. 2000;48:1697-1706.



# HELP Impact on Outcomes

Reference	No. of Patients	Rate in HELP	Rate in Controls	Improvement with HELP
<b>PREVENTION OF DELIRIUM</b>				
Rubin 2011	>7,000	18%	41%	23%
Chen 2011	179	0%	17%	17%
Caplan 2007	37	6%	38%	32%
Rubin 2006	704	26%	41%	15%
Inouye 1999	852	10%	15%	5%
<b>REDUCED COGNITIVE DECLINE (MMSE decline by 2+ points)</b>				
Inouye 2000	1,507	8%	26%	18%
<b>REDUCED FUNCTIONAL DECLINE (ADL decline by 2+ points)</b>				
Inouye 2000	1,507	14%	33%	19%
<b>DECREASED HOSPITAL LENGTH OF STAY</b>				
Rubin 2011	>7,000	5.3 days	6.0 days	0.7 days
Caplan 2007	37	22.5 days	26.8 days	4.3 days
Rubin 2006	704	---	---	0.3 days
<b>REDUCED INSTITUTIONALIZATION</b>				
Caplan 2007	37	25%	48%	23%
<b>DECREASED FALLS</b>				
Inouye 2009	--	2%	4%	2%
Inouye 2009	--	3.8/1000 p-y	11.4/1000 p-y	7.6/1000 p-y
Inouye 2009	--	1.2/1000 p-y	4.7/1000 p-y	3.5/1000 p-y
Caplan 2007	37	6%	19%	13%
<b>DECREASED SITTER USE</b>				
Caplan 2007	37	330 hours	644 hours	314 hours

# HELP Impact on Costs

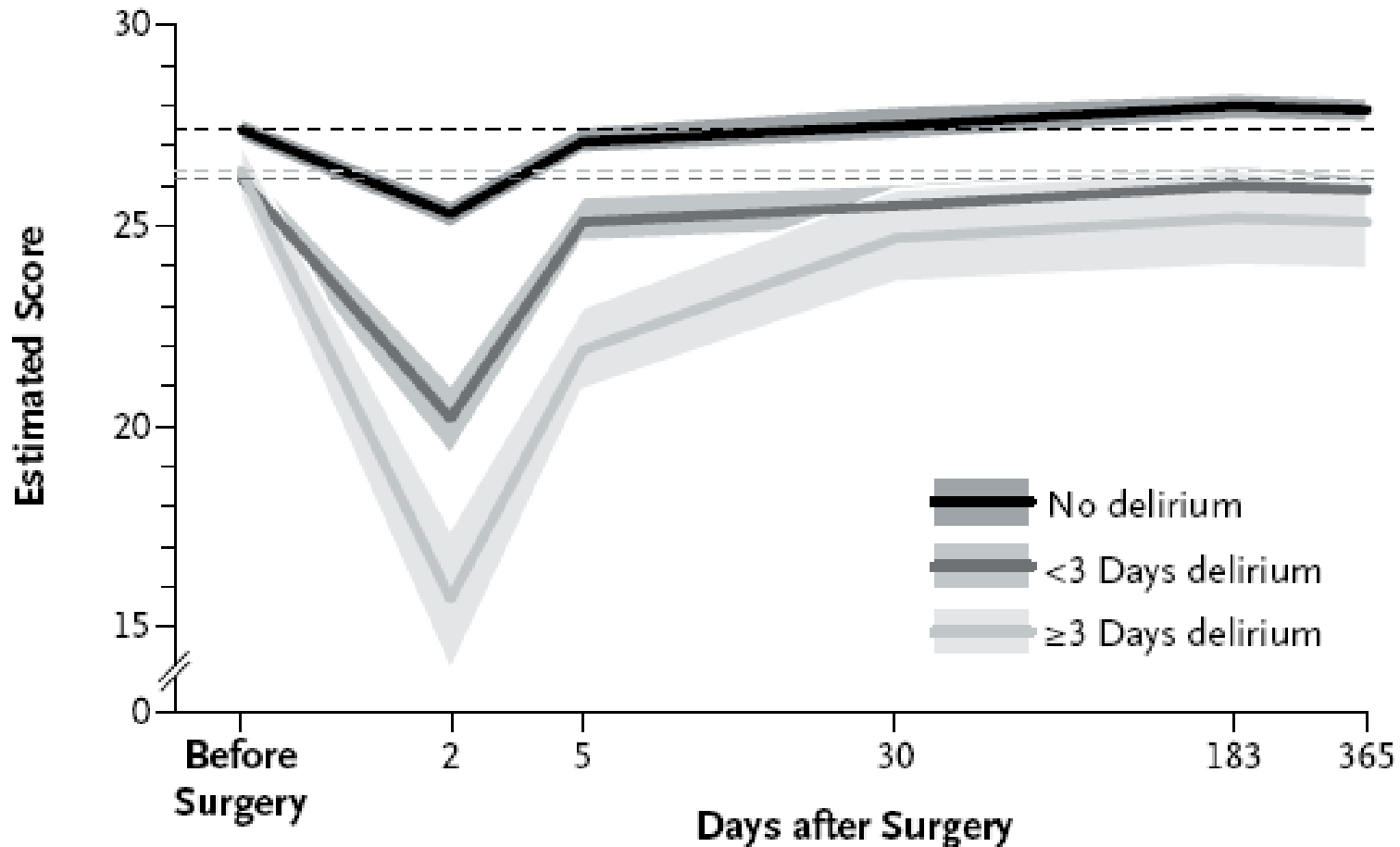
Reference	No. of Patients	Impact on Cost
Rubin 2011	>7,000	>\$7.3 million per year savings in hospital costs (> \$1000 savings per patient)
Rizzo 2001	852	\$831 cost savings per person-yrs in hospital costs
Leslie 2005	801	\$9,446 savings per person-yrs in long-term nursing home costs
Caplan 2007	111	\$121,425 per year savings in sitter costs

# Overview of the SAGES Study

- SAGES: Successful AGing after Elective Surgery
- Funded by NIH Grant P01AG031720
- Goal is to examine the epidemiology, risk markers, and long-term outcomes of delirium (ongoing prospective cohort study of over 560 surgical patients and 120 nonsurgical controls)

# Short-Term Impact of Delirium

(N=225 cardiac surgery patients)



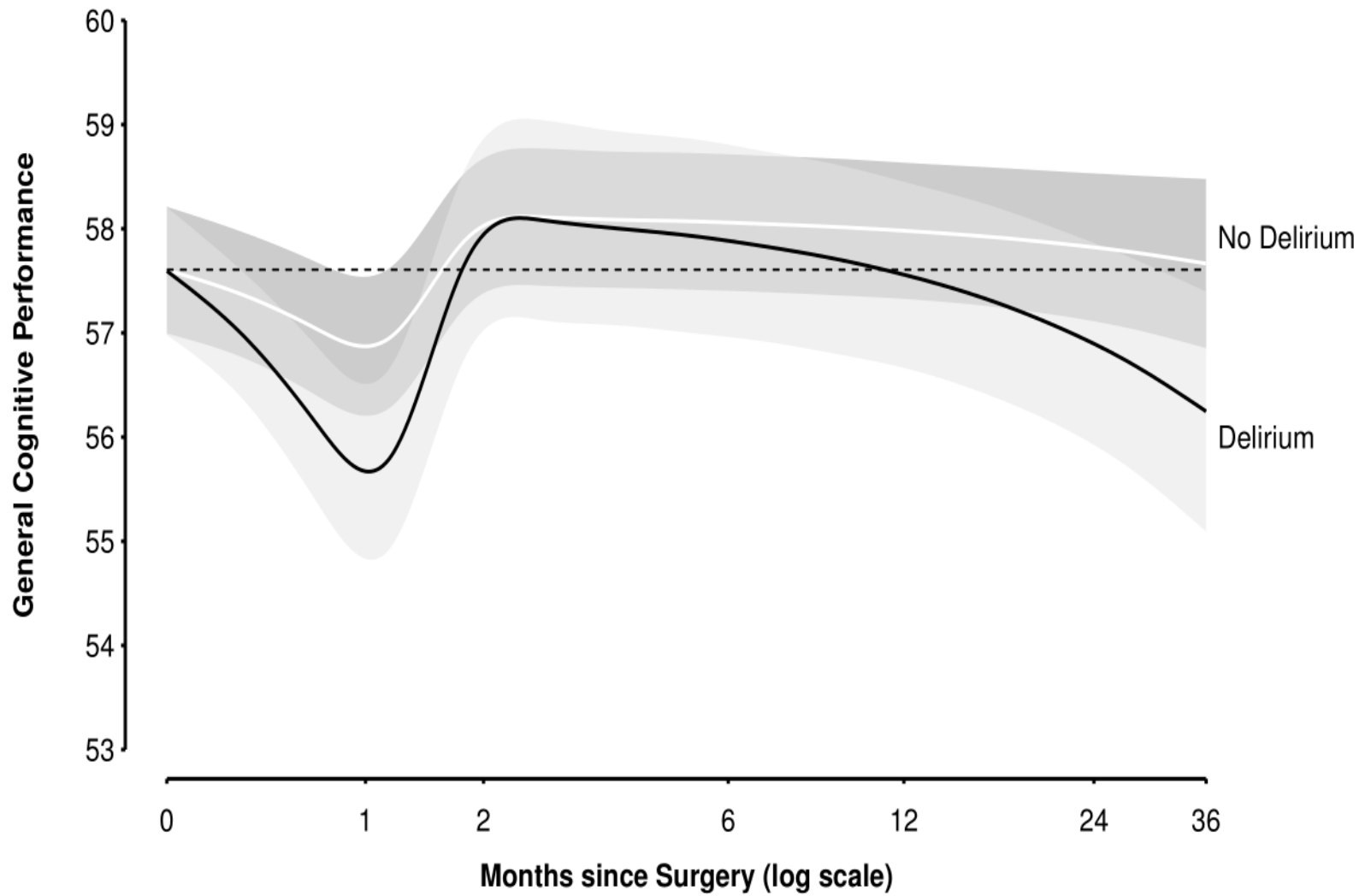
Saczynski JS et al. N Engl J Med. 2012; 367:30-9

Presented at NIDUS Delirium Boot Camp 2017,  
Posted with permission.

# Short-Term Impact of Delirium

- Delirium occurred in 46% patients following cardiac surgery in 225 patients
- Cognitive trajectory characterized by abrupt initial decline followed by gradual recovery over 6 months
- Patients did not get fully back to baseline even at 1 year
- Delirium potentially preventable in 30-40% cases.

# LONG-TERM COGNITIVE TRAJECTORY AFTER ELECTIVE SURGERY



# Long-Term Impact: SAGES Study

- Delirium occurred in 24% patients following major elective surgery
- In both groups, acute cognitive decline at 1 month
- Non-delirium group, recovers above baseline at 2 months, then gradual decline out to 36 mos (above baseline)
- Delirium group, recovers above baseline at 2 months, then gradual decline out to 36 months substantially below baseline (equal to MCI).

# Inflammatory Biomarkers for Delirium

- Two recent studies from Successful Aging after Elective Surgery (SAGES) study:
  - IL-6 as an important disease marker for delirium, markedly elevated at postop day 2
  - CRP as a risk and disease marker for delirium at pre-op, immediate postop, and post day 2

Vasunilashorn SM, J Gen Intern Med 2015; Dillon ST, J Biol Psych 2016



## Relationship of AD and Delirium

- SAGES cohort (free of dementia at baseline) :
  - APOE-E4 not a risk factor for delirium in SAGES
  - MRI volumetric changes typical of AD not a risk factor for delirium in SAGES
- Thus, in SAGES important risk factors for AD do not confer increased risk for delirium—suggesting separate pathways.

Vasunilashorn, AJGP 2015; Cavallari, Neurobiol Aging. 2015

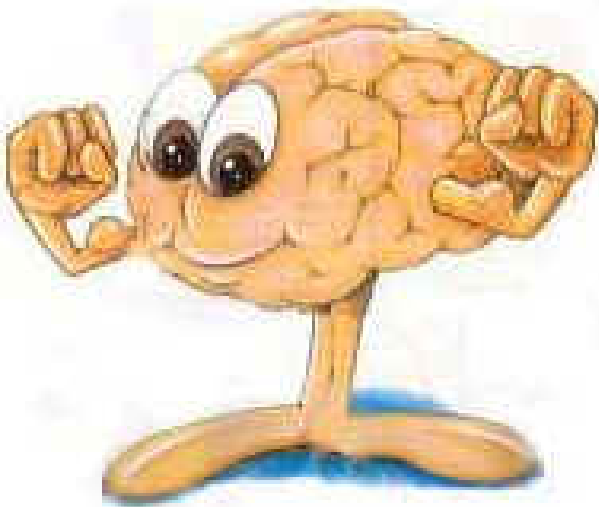
# Where We are Going...

Area	Research priorities
Recognition	<ul style="list-style-type: none"><li>•Better measurement methods (severity, subtypes)</li><li>•Cost-effective approaches to evaluation</li></ul>
Epidemiology	<ul style="list-style-type: none"><li>•Long-term outcomes</li><li>•Permanent changes, relationship to dementia</li></ul>
Pathophysiology	<ul style="list-style-type: none"><li>•Cellular and molecular mechanisms/animal models</li><li>•Biomarkers</li><li>•Neuroimaging</li><li>•Etiologic subtypes/heterogeneous syndrome</li></ul>
Treatment	<ul style="list-style-type: none"><li>•Personalized treatment approaches—based on genetic/pathophysiologic mechanisms</li><li>•Efficacious approaches that impact delirium outcomes: trials of targeting etiologies, drug reduction, nonpharmacologic approaches</li></ul>

# Why is addressing delirium important?

- Tremendous clinical impact
- Healthcare costs and policy implications
- Indicator of quality of care for elders
- Helps us better understand the brain—  
including normal functioning and functioning  
under stress (reserve)

***Most important:  
Preventing delirium may offer the  
unprecedented opportunity to  
prevent or ameliorate future  
cognitive decline.***



# Interested in Learning More?

- Delirium prevention-HELP
  - [www.hospitalelderlifeprogram.org](http://www.hospitalelderlifeprogram.org)
- Delirium research-NIDUS (Network for Investigation of Delirium: Unifying Scientists)
  - <https://deliriumnetwork.org/>
- Contact us:
  - [AgingBrainCenter@hsl.harvard.edu](mailto:AgingBrainCenter@hsl.harvard.edu)
- Follow us: @sharon\_inouye  
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