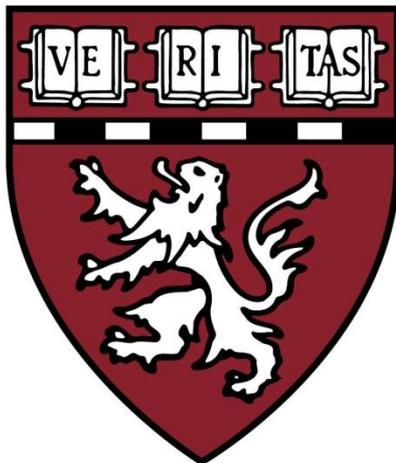
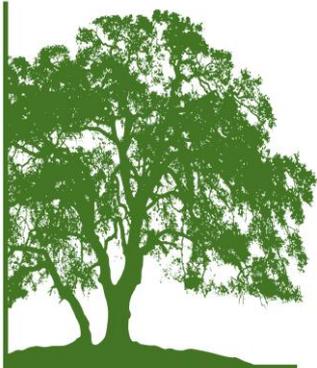


Disentangling Delirium and Dementia

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DSM5 CRITERIA FOR DELIRIUM

- Disturbance in attention and awareness
- Disturbance **develops acutely** and tends to fluctuate
- An additional disturbance in cognition, (e.g., memory deficit, language, visuoperceptual)
- **Not better explained by a preexisting dementia**
- Not in face of severely reduced level of arousal or coma
- Evidence of underlying organic etiology(-ies)

[Characteristics of transience and reversibility]

Used with permission. American Psychiatric Association, 2013

DSM5 CRITERIA FOR DELIRIUM

- Evidence of significant cognitive decline from previous level in one or more cognitive domains
- Cognitive deficits interfere with independence in everyday activities
- Deficits do not occur exclusively in the context of a delirium
- Deficits are not better explained by another mental disorder (eg, major depressive disorder, schizophrenia)

[Characteristics of chronic and progressive]

Used with permission. American Psychiatric Association, 2013

Differential Diagnosis: Delirium vs. Dementia

Feature	Delirium	Dementia
Onset	Typically abrupt	Insidious and progressive
Duration	Hours to day	Months to years
Attention	Reduced ability to sustain or shift attention	Normal unless severe dementia
Consciousness	Fluctuating, reduced level of consciousness	Generally intact
Speech	Can be incoherent, disorganized	Ordered, may have aphasia
Psychomotor subtypes	Hyperactive/hypoactive forms often present	Psychomotor changes absent or unpredictable

Oh ES...Inouye SK. JAMA 2017; 318:1161-74

Interface of Delirium and Dementia

- Often coexist clinically—delirium superimposed on dementia
- Dementia a leading risk factor for delirium
- Delirium associated with markedly increased risk for dementia (OR=12.5)
- Delirium worsens the cognitive trajectory of dementia
- Pathophysiologic overlap with shared mechanisms

Evidence for Inter-Relationship

“Stacking the Evidence”

- Epidemiologic
- Clinicopathological
- Mechanistic

-
- Biomarkers → Dr. Marcantonio
 - Neuroimaging → Dr. Asthana

Epidemiologic Evidence

Dementia: A Risk Factor for Delirium

Study	Population	Delirium (%)	Adjusted risk (95% CI)
Kennedy 2014	Emergency department, N=700	9%	OR 4.3 (2.2-8.5)
Koster 2013	Elective cardiac surgery, N=300	17%	OR 4.5 (1.9-13)
Moerman 2012	Acute hip fracture, N=378	27%	OR 2.8 (1.7-4.6)
Bo 2009	Medical or geriatric ward, N=252	11%	RR 2.1 (1.6-2.6)
Rudolph 2009	Cardiac surgery, development N=122; validation N=109	44%	RR 1.3 (1.0-1.7)
Kalisvaart 2006	Elective hip surgery, N=603	12%	RR 5.5 (3.6-8.6)
Wilson 2005	Acute medical ward, N=100	12%	OR 3.2 (1.2-9.0)
O'Keeffe 1996	Acute medical admissions, N=225	28%	OR 4.8 (2.0-11.6)
Marcantonio 1994	Elective surgery, N=1341	9%	OR 4.2 (2.4-7.3)
Pompei 1994	Acute medical/surgical, development N=432; validation N=323	15%	OR 3.6 (2.1-6.2)
Inouye 1993	Acute medical, development N=107; validation N=174	25%	RR 2.8 (1.2-6.7)

Delirium: A Risk Factor for Dementia

Study	Population	Dementia (%)	Adjusted risk (95% CI)
CFAS 2014	Population-based, N= 2197	23%	OR 8.8 (2.8-28)
BRAIN-ICU 2013	Multi-centre ICU admissions, N=821	—	-5.6 (-9.5 - -1.8) points per delirium-day
Gross 2012	Alzheimer's clinic, N=263	27%	1.2 (0.5-1.8) points per year
Saczynski 2012	Elective CABG or valve surgery, N=225	—	Prolonged recovery
Vantaa 85+ 2012	Population-based, N=553	42%	OR 8.7 (2.1-35)
Fong 2009	Alzheimer's clinic, N=408	—	2.4 (1.0-3.8) points per year
Bickel 2008	Elective hip surgery, N=200	53%	OR 41 (4.3-396)
Lundstrom 2003	Acute hip fracture, N=78	88%	OR 5.7 (1.3-24)

Adverse Outcomes with Delirium: Dementia

Outcome	Rate When Delirium:		No. Studies	Risk (95% CI)
	Present n/N (%)	Absent n/N (%)		
Mortality	217/714 (30%)	616/2243 (27%)	7	HR= 2.0 (1.5-2.5)
Institutionalization	176/527 (33%)	219/2052 (11%)	9	OR=2.4 (1.8-3.3)
Dementia	35/56 (63%)	15/185 (8%)	2	OR = 12.5 (1.9-84)

Ref: Witlox J et al. JAMA 2010;304:443-51

Clinicopathological Evidence

- VANTAA 85+ study: population-based, N=553
- Strongest relationship between incident dementia and pathologic measures (tau, amyloid, vascular, Lewy body) in persons *without delirium*
- When delirium included in models, no association with pathologic markers detectable
- Suggestion that pathologic substrates for delirium may be different from conventional dementia pathology.

Davis DH et al. Brain 2012; 135: 2809-16.

Mechanistic Evidence

- Animal models and tissue culture studies
- Inflammation: animal models with vulnerable brains administered inflammatory challenge--
Lipopolysaccharide (LPS) or polyinosinic:polycytidylic acid (poly I:C) –leading to neuronal death/microglial activation and persistent cognitive deficits
- Microglial priming: Cox 1 and prostaglandin inhibitors protect against LPS-induced cognitive deficits
- Inhalational anesthetics: may induce apoptosis and neurotoxicity, along with changes consistent with AD

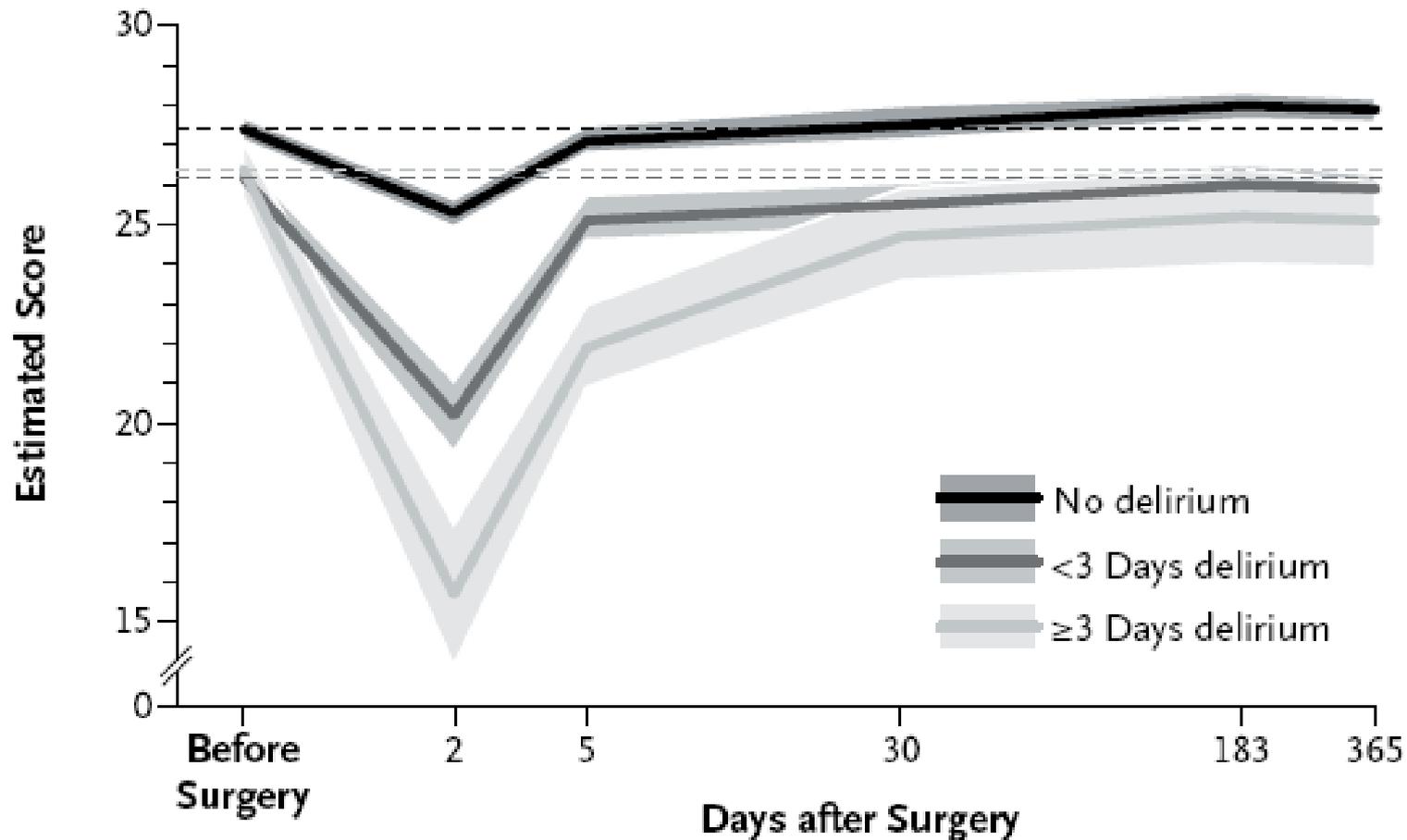
***Does delirium lead to long-term
cognitive decline?***

Impact of Delirium at 12 months

- Aims: Examine cognitive function over 12 months in 225 patients following elective cardiac surgery.
- Main Results:
 - Delirium occurred in 46% patients
 - Cognitive trajectory (by MMSE) characterized by abrupt initial decline followed by gradual recovery over 6 months
 - ***Patients with prolonged delirium did not get fully back to baseline at 12 months***

Impact of Delirium at 12 months

(N=225 cardiac surgery patients)



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

Impact of Delirium at 36 months: SAGES Study

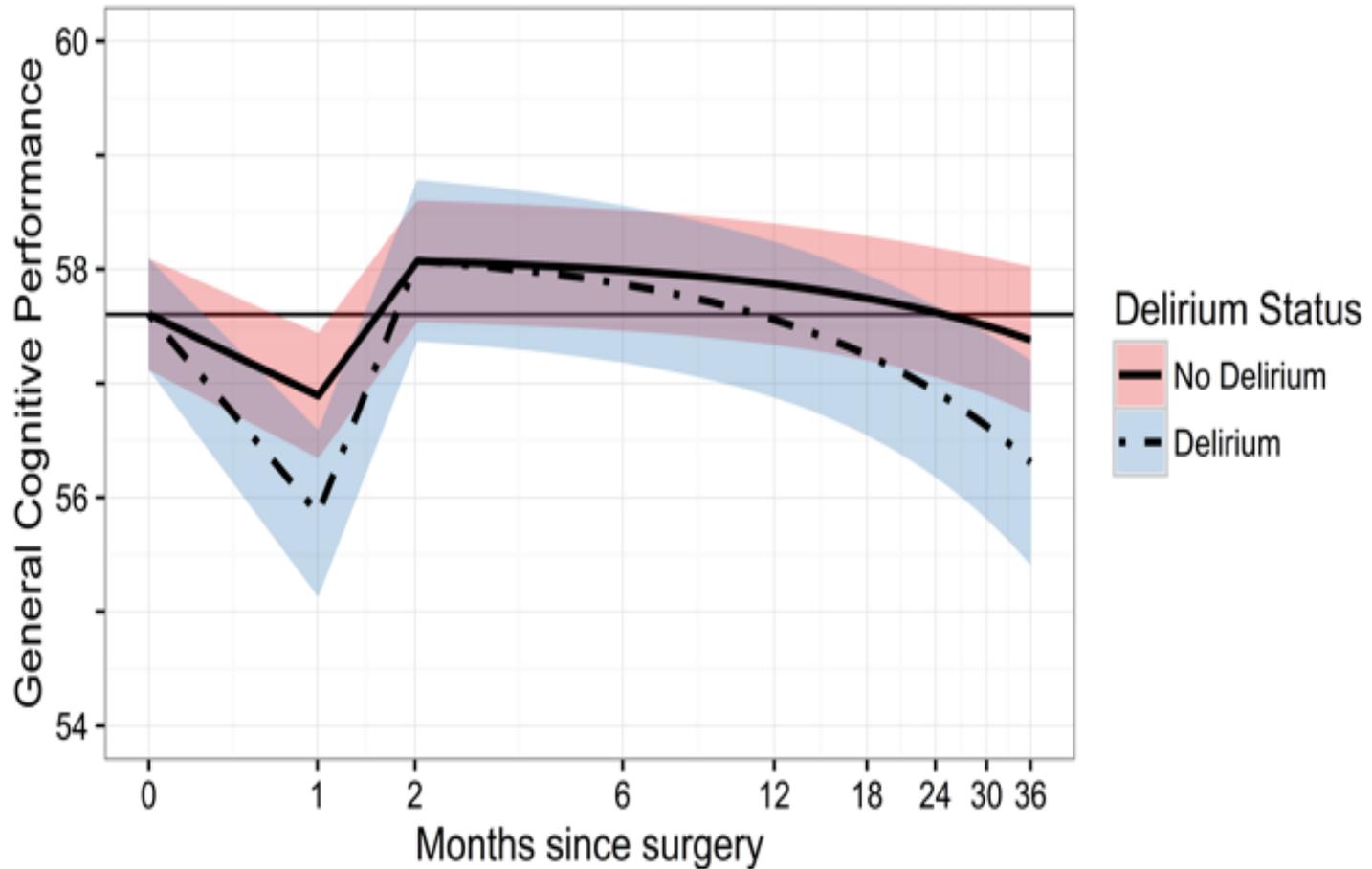
Aims: Examine cognitive trajectory over 36 months in 560 patients without dementia undergoing major elective surgery

Major results:

- Delirium occurred in 24% patients following major elective surgery. Cognitive function measured by GCP composite
- In delirium and non-delirium groups, acute cognitive decline at 1 month
- Non-delirium group, recovers above baseline at 2 months, then gradual decline out to 36 months (above baseline)
- Delirium group, recovers above baseline at 2 months, then ***gradual decline out to 36 months substantially below baseline, with a slope equivalent to that seen in MCI***

Inouye SK et al. SAGES Study, *Alzheimers Dement.* 2016; 12:766-75

LONG-TERM COGNITIVE TRAJECTORY AFTER ELECTIVE SURGERY



Inouye SK et al. SAGES Study, *Alzheimers Dement.* 2016; 12:766-75

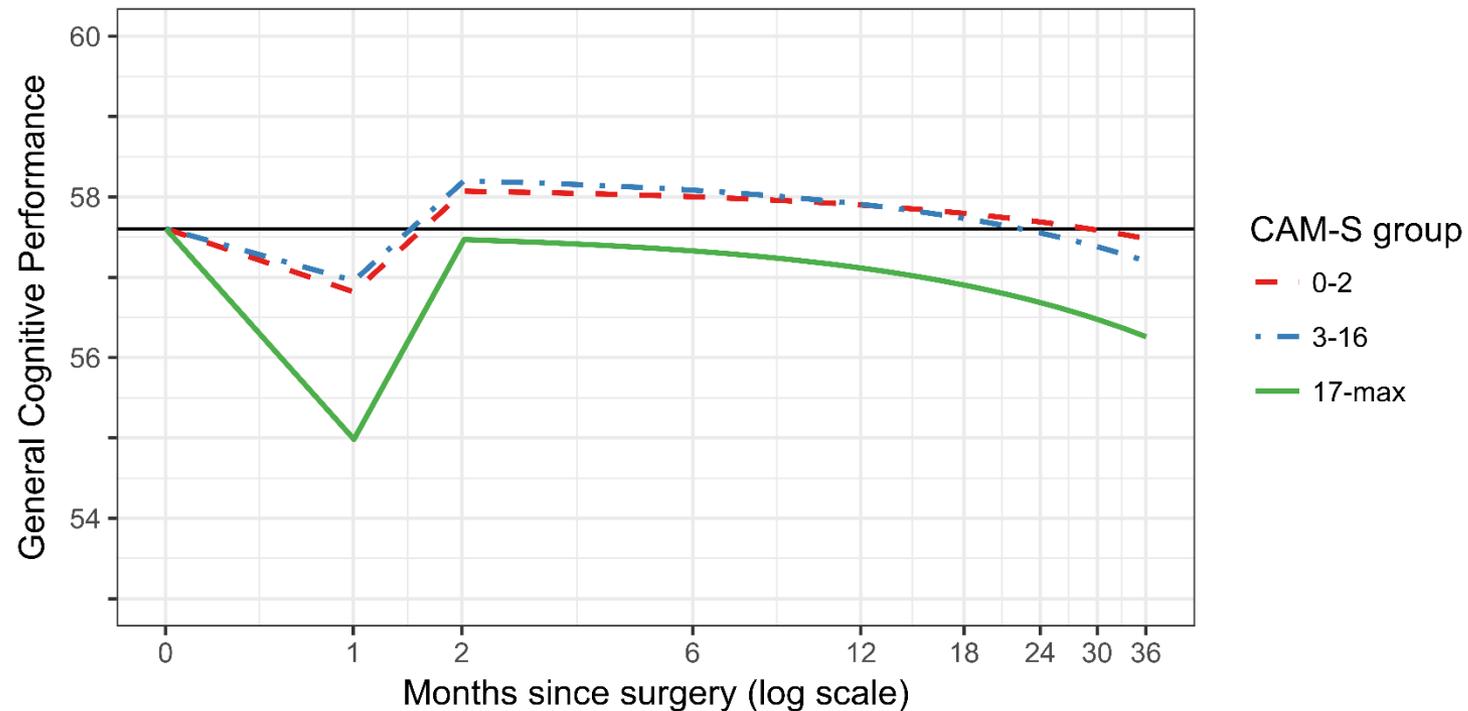
Impact of Delirium Severity over 36 months: SAGES Study

Aims: Examine cognitive trajectory over 36 months in 560 SAGES patients without dementia—stratified by tertiles of delirium severity (CAM-S peak)

Major results:

- Delirium occurred in 24% patients following major elective surgery. Long-term cognitive decline (LTCD) measured by slope of GCP composite
- Delirium severity demonstrates a threshold effect with the highest level of severity (sum of CAM-S ≥ 17) being associated with greatest degree of LTCD at 36 months
- All other groups were not significantly different
- ***Slope of cognitive decline in highest severity group is $-.82$ GCP points/year—equivalent to that of dementia. Important exposure-response relationship.***

Impact of Delirium Severity over 36 months: SAGES Study



Delirium outcomes in persons with Alzheimer's disease

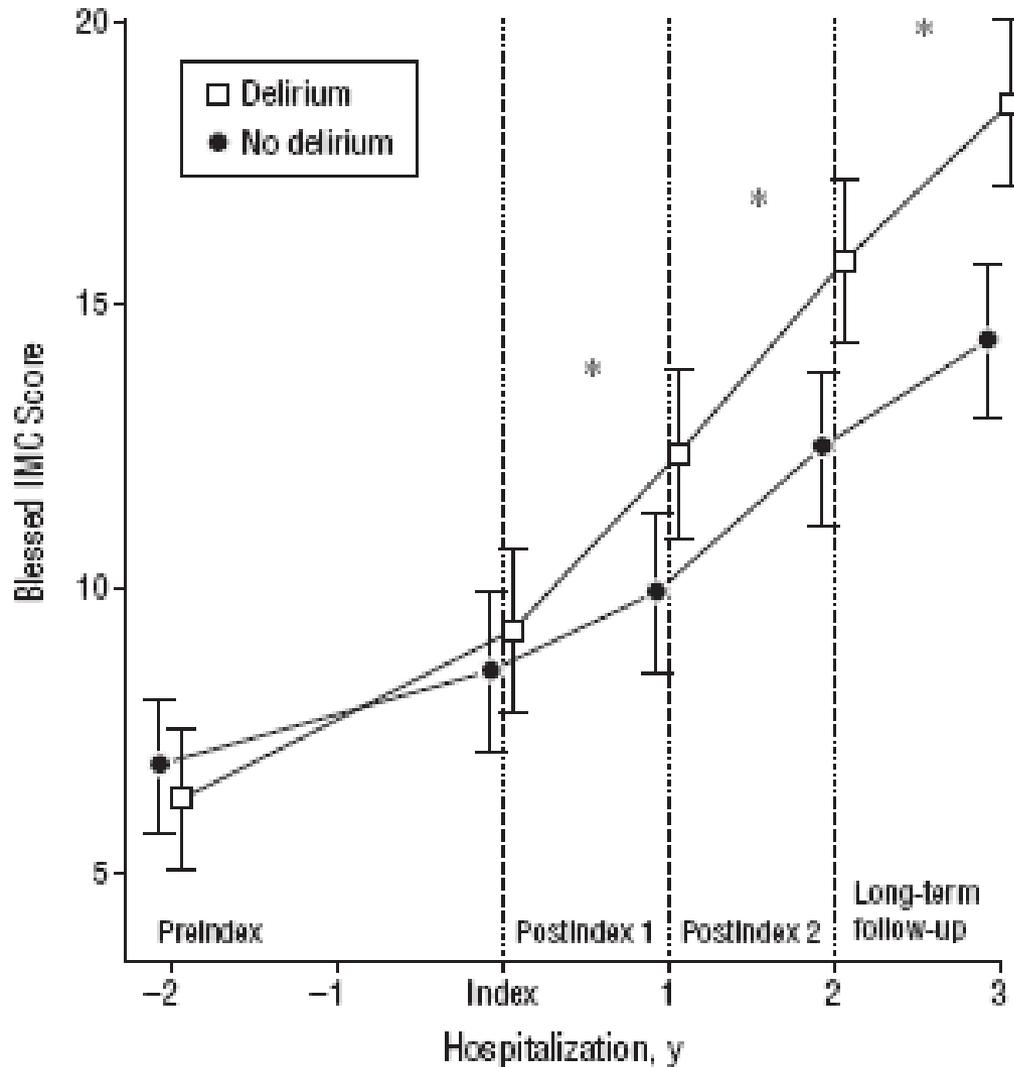
(N=771 ADRC patients)

Adverse Outcomes at 12 months	Adjusted Relative Risk (95% CI)	Attributable Risk %	Risk Attributable to Delirium
Death	5.4 (2.3-12.5)	6.2	1 in 16
Institutionalization	9.3 (5.5-15.7)	15.2	1 in 7
Cognitive Decline at 1-year	1.6 (1.2-2.3)	20.6	1 in 5
Any Adverse Outcome	2.2 (1.8-2.7)	12.4	1 in 8

Ref: Fong TG et al. Ann Intern Med 2012;156:848-56

Delirium Accelerates Cognitive Decline Trajectory in Dementia

[Nested cohort of 263 hospitalized patients with AD]



Gross AL *Arch Intern Med* 2012; 172; 1324; Fong TG *Neurology*. 2009;72:1570

What we don't know

- Concept of *complicated delirium*: Delirium that leads to long-term cognitive decline (Akin to injurious falls)
 - Who is at-risk?
 - What are the causes/mechanisms?
 - Are there complex, multifactorial relationships (genetic, environmental, mediation effects between vulnerability and precipitating factors)?
 - How do we prevent?
 - How do we treat?

Preventing delirium may offer the unprecedented opportunity to prevent or ameliorate future cognitive decline.