60° CONGRESSO NAZIONALE

NAPOLI 25-28 Novembre 2015

SOCIETÀ ITALIANA DI GERONTOLOGIA E GERIATRIA

Delirium come primo segno di demenza misconosciuta

Giuseppe Bellelli, MD

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Delirium: criteri del DSM-5

A. Disturbo dell' attenzione (i.e., ridotta capacità a dirigere, focalizzare, sostenere e shiftare l' attenzione) e consapevolezza (ridotto orientamento del se nell' ambiente).

B. Il deficit si sviluppa in un periodo di tempo relativamente breve (generalmente ore o pochi giorni), rappresenta un cambiamento dai livelli di attenzione e consapevolezza di base, e tende a fluttuare in gravità nel corso della giornata.

C. É presente un altro deficit cognitivo (es, memoria, disorientamento, linguaggio, abilità visuospaziali, o dispercezioni).

D. I deficit di cui ai criteri A e C non sono spiegabili sulla base di un preesistente (stazionario o in evoluzione) disturbo neurocognitivo e non si verificano in un contesto di grave riduzione dei livelli di arousal (es coma)

E. Vi è evidenza per storia clinica, esame obiettivo o risultati di laboratorio che il delirium è una diretta conseguenza di un problema clinico, intossicazione o sospensione di farmaci, esposizione a tossine, o è dovuto a molteplici eziologie.

Il delirium è presente se tutti e 5 i criteri sono soddisfatti

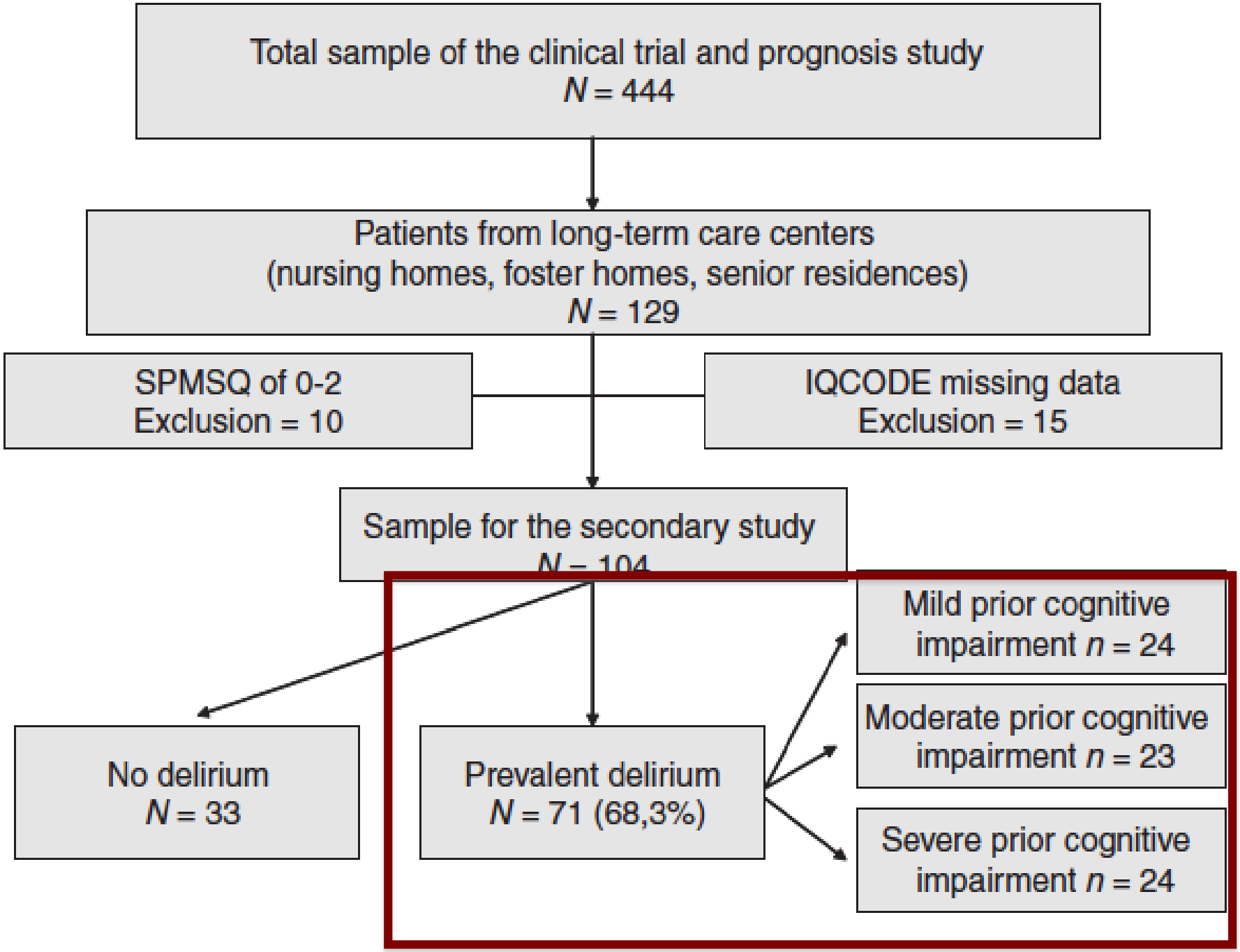
	Delirium	Dementia
Onset	Abrupt, although initial loss of mental clarity can be subtle	Insidious and progressive
Duration	Hours to days (although it can be prolonged in some cases)	Months to years
Attention	Reduced ability to focus, sustain, or shift attention is a hallmark feature that occurs early in presentation	Normal except in severe dementia
Consciousness (ie, awareness of the environment)	Fluctuating (thus assessment at multiple timepoints is necessary); reduced level of consciousness and impaired orientation	Generally intact
Speech	Incoherent and disorganised; distractible in conversation	Ordered, but development of anomia or aphasia is possible
Cause	Underlying medical condition, substance intoxication, or side-effect of drugs	Underlying neurological process (eg, amyloid β plaque accumulation in Alzheimer's disease)
Other features	Hyperactive, hypoactive, and mixed forms, as determined by the type of psychomotor disturbance, are possible; disruption in sleep duration and architecture; perceptual disturbances	Symptoms vary depending on underlying pathology (eg, fluctuations in cognition are a feature of Lewy body dementia)

These two syndromes have substantial overlapping features and can coexist in an individual patient.

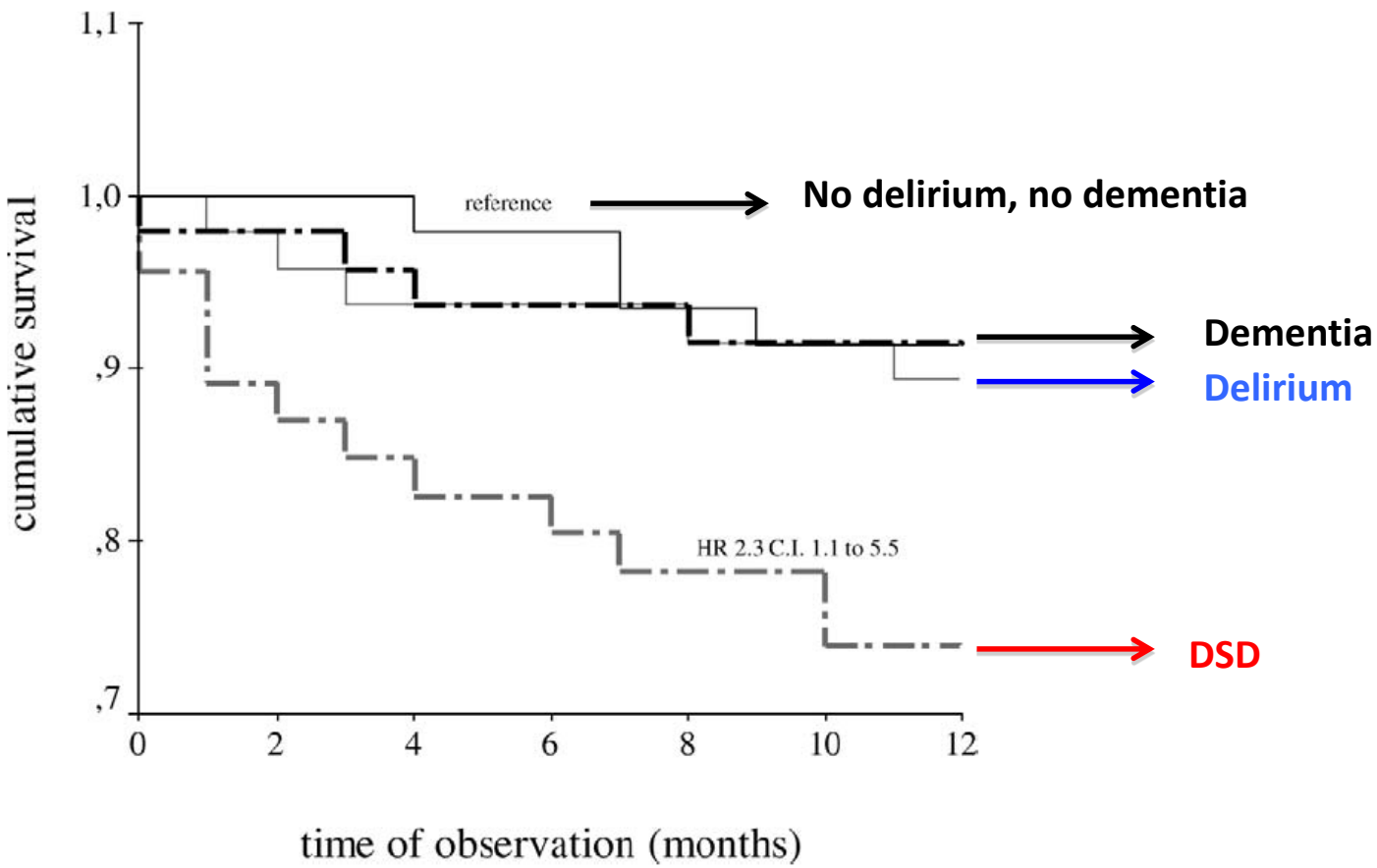
Table 1: Comparative features of delirium and dementia

Fong T et al Lancet Neurol 2015

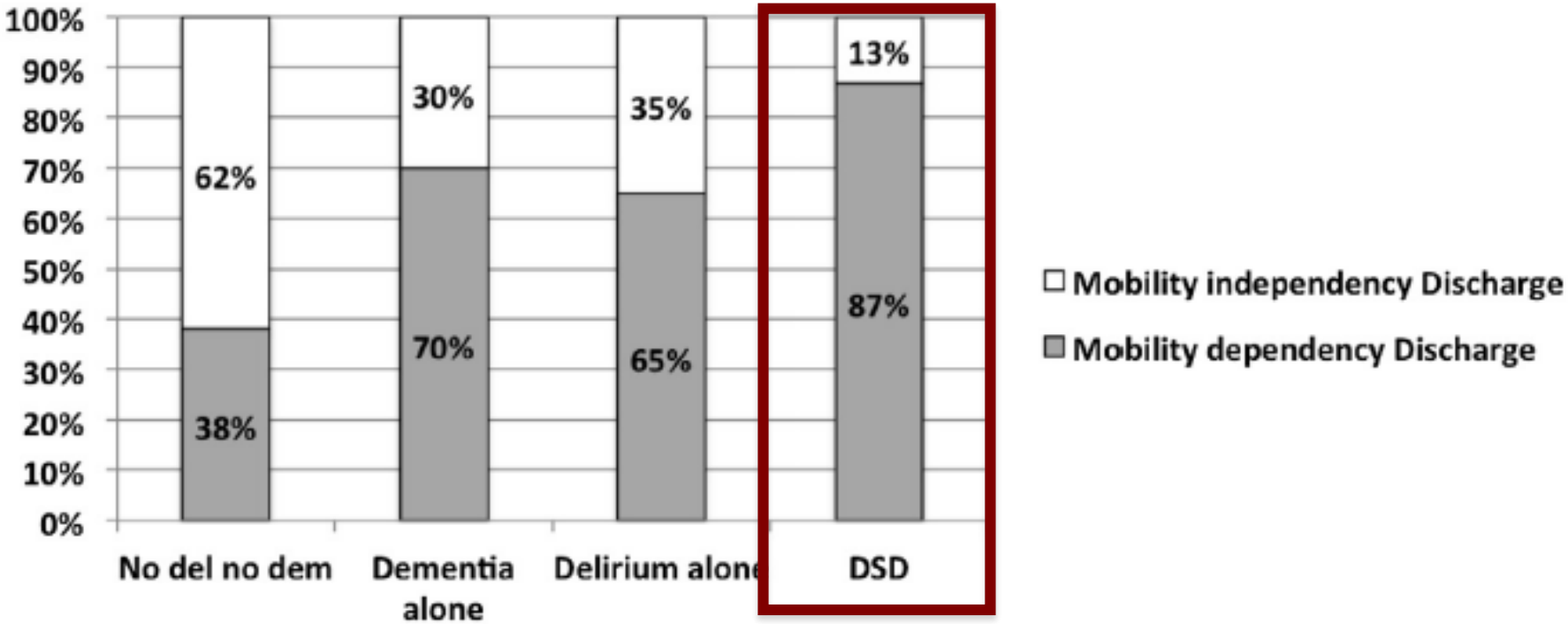
	All Patients (n = 203)	Dementia Subtype			P Value
		Alzheimer Disease (n = 48)	Vascular Dementia (n = 96)	Parkinsonism-Related Dementia (n = 59)	
Age, years	77.6 ± 6.0	77.6 ± 6.0	78.0 ± 6.1	77.1 ± 5.9	0.664
Gender, male/female	111/92	22 / 26	53 / 43	36 / 23	0.289
Admission frequencies in 4 years (total)	2.3 ± 1.8 (472)	1.8 ± 1.2	2.5 ± 1.9	2.5 ± 2.0	0.056
Average stay per hospitalization (days)	15.4 ± 13.6	10.2 ± 9.2	16.8 ± 12.9*	17.4 ± 16.5*	0.010
Death	9 (4.4%)	2 (4.2%)	3 (3.1%)	4 (11.9%)	0.559
Cerebrovascular risk factor					
Diabetes mellitus	67 (33.3%)	10 (20.8%)	33 (34.4%)	24 (40.7%)	0.088
Hypertension	130 (6.4%)	28 (58.3%)	67 (69.8%)	35 (59.3%)	0.269
Hyperlipidemia	33 (16.3%)	8 (16.7%)	17 (17.7%)	8 (13.6%)	0.791
Coronary artery disease	16 (7.9%)	4 (8.3%)	6 (6.3%)	6 (10.2%)	0.673
Presence of stroke	103 (50.70%)	0 (0.0%)**	96 (100%)	7 (11.9%)**	<0.001
Chronic systemic disease					
Liver disease	5 (2.5%)	0 (0.0%)	2 (2.1%)	3 (5.1%)	0.228
Chronic kidney disease	29 (14.3%)	4 (8.3%)	13 (13.5%)	12 (20.3%)	0.202
Chronic obstructive pulmonary disease	14 (6.9%)	1 (2.1%)	9 (9.4%)	4 (6.8%)	0.266
Mix gastroenteric disease	11 (5.4%)	1 (2.1%)	6 (6.3%)	4 (6.8%)	0.500
Five primary etiology for admission					
Acute delirium	91 (44.8%)	32 (66.7%)	35 (36.5%)*	24 (40.7%)*	0.002
Newly onset stroke	49 (24.1%)	5 (10.4%)**	33 (34.4%)	11 (18.6%)**	0.003
Pneumonia	36 (17.7%)	5 (10.4%)	19 (19.8%)	12 (20.3%)	0.314
Fall-related hip fracture	17 (8.4%)	1 (2.1%)**	14 (14.6%)	2 (3.4%)**	0.010
Urinary tract infection	15 (7.3%)	3 (6.2%)	8 (8.3%)	4 (6.8%)	0.883


Total sample of the clinical trial and prognosis study
N = 444
Patients from long-term care centers
(nursing homes, foster homes, senior residences)
N = 129
SPMSQ of 0-2
Exclusion = 10
IQCODE missing data
Exclusion = 15
Sample for the secondary study
N = 104
No delirium
N = 33
Prevalent delirium
N = 71 (68,3%)
Mild prior cognitive impairment n = 24
Moderate prior cognitive impairment n = 23
Severe prior cognitive impairment n = 24

Delirium Superimposed on Dementia (DSD) increases mortality



Bellelli G, et al. J Gerontol A BiolSciMedSci 2007;62:1306-1309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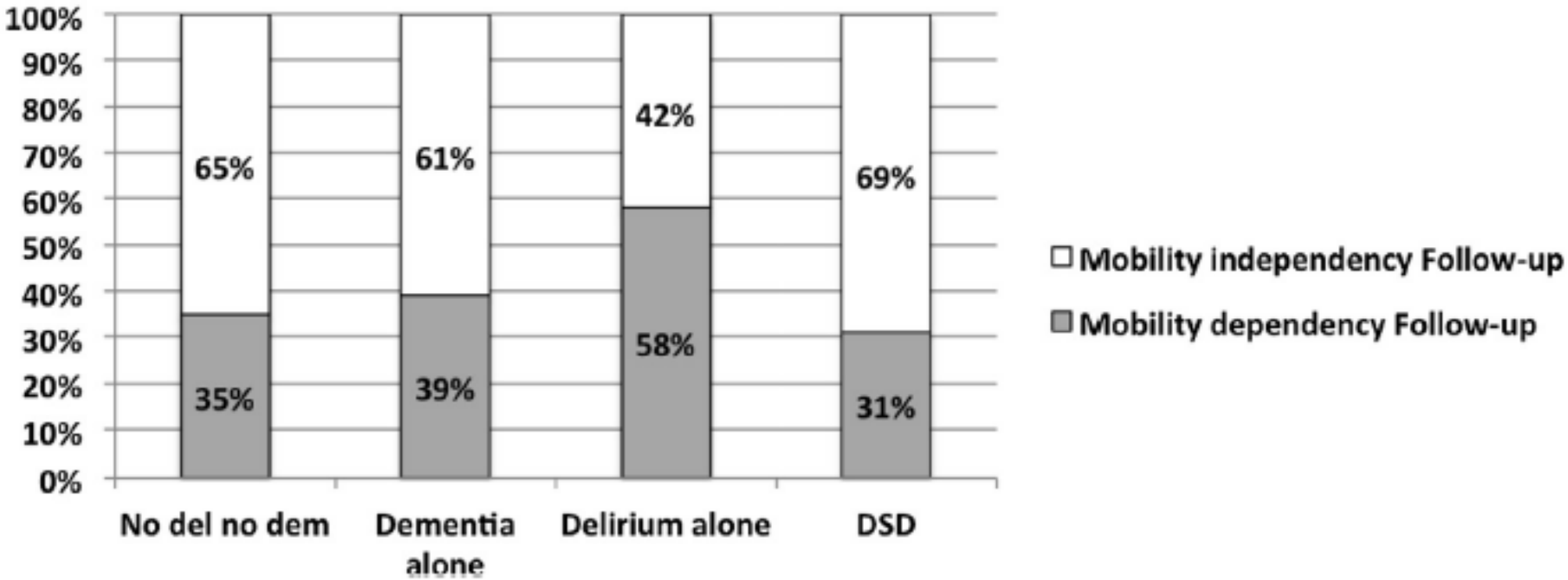
Dementia alone
Delirium alone
DSD
Mobility independency Discharge
Mobility dependency Discharge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58%
69%
31%
No del no dem
Dementia alone
Delirium alone
DSD
Mobility independency Follow-up
Mobility dependency Follow-up

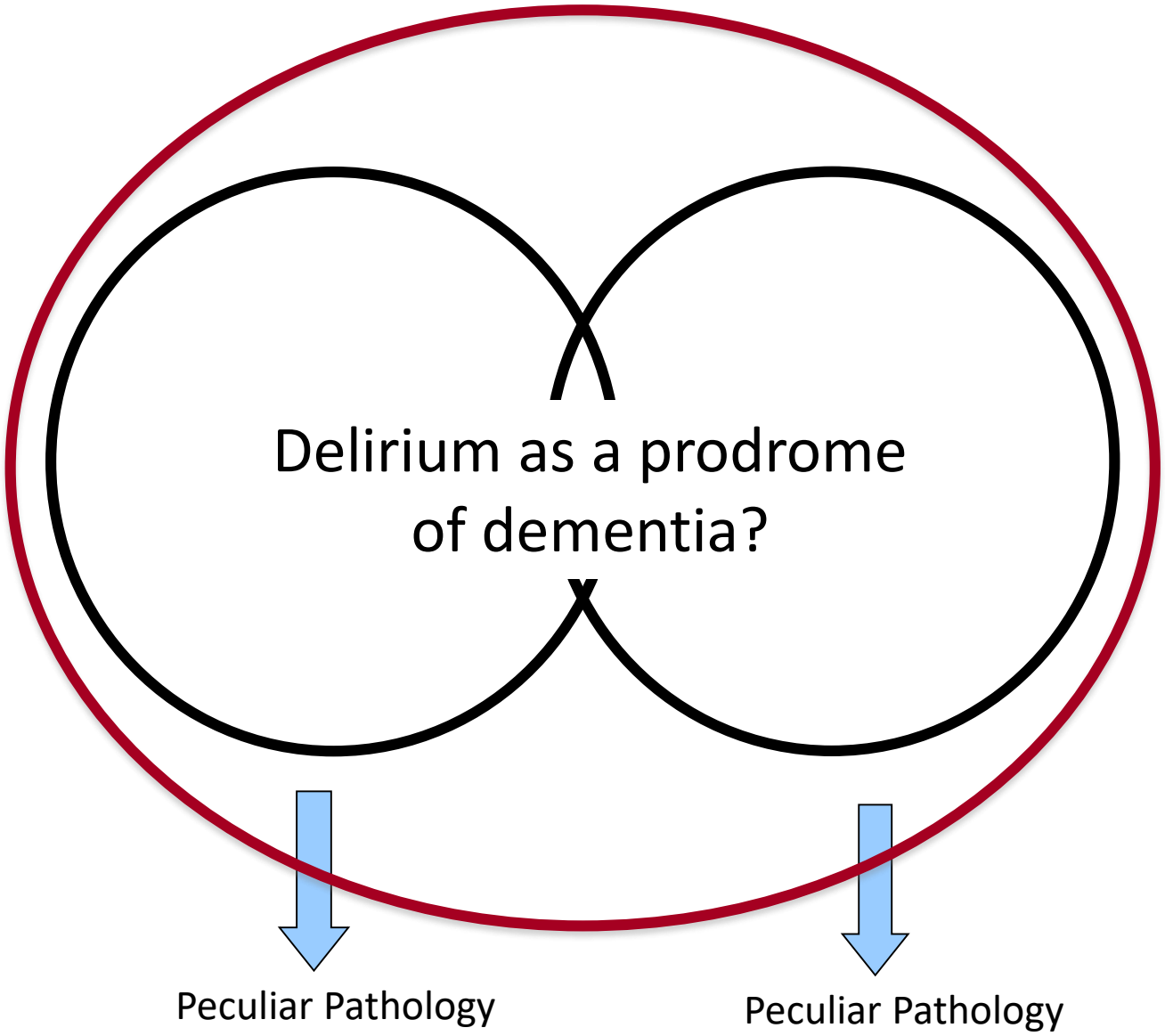
Journal of Gerontology: MEDICAL SCIENCES
2005, Vol. 60A, No. 6, 748–753

Delirium Superimposed on Dementia in a Community-Dwelling Managed Care Population: A 3-Year Retrospective Study of Occurrence, Costs, and Utilization

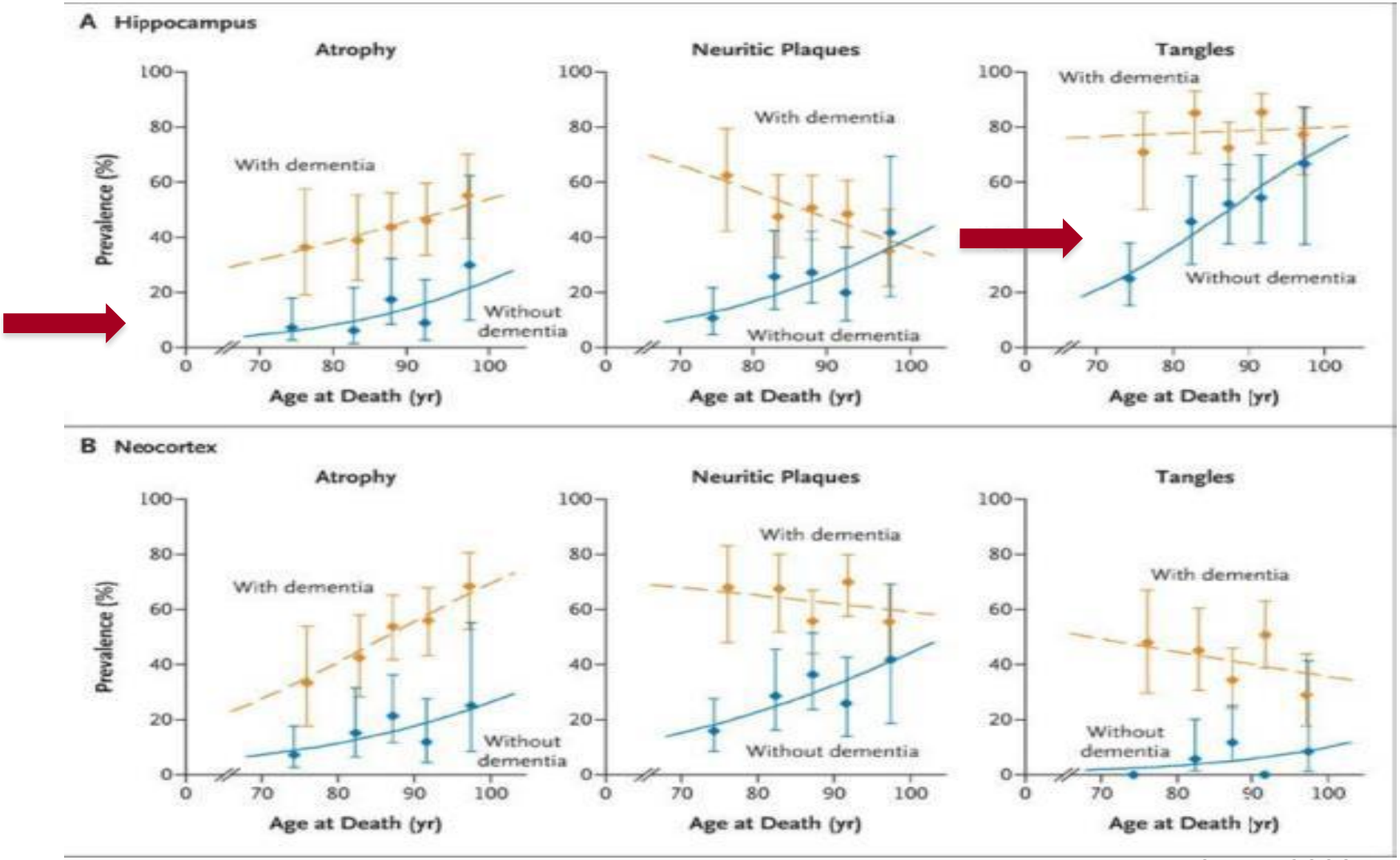
Donna M. Fick,[1,2,3] Ann M. Kolanowski,[3] Jennifer L. Waller,[1] and Sharon K. Inouye[4]

I costi medi totali in un periodo di 3 anni pari a $ 9,565 per il gruppo DSD, 7,556 per il gruppo con sola demenza, $ 9,422 per il gruppo con solo delirium e $ 4,765 per il gruppo di controllo.

Is delirium a separate process from dementia?


Delirium as a prodrome
of dementia?
Peculiar Pathology
Peculiar Pathology

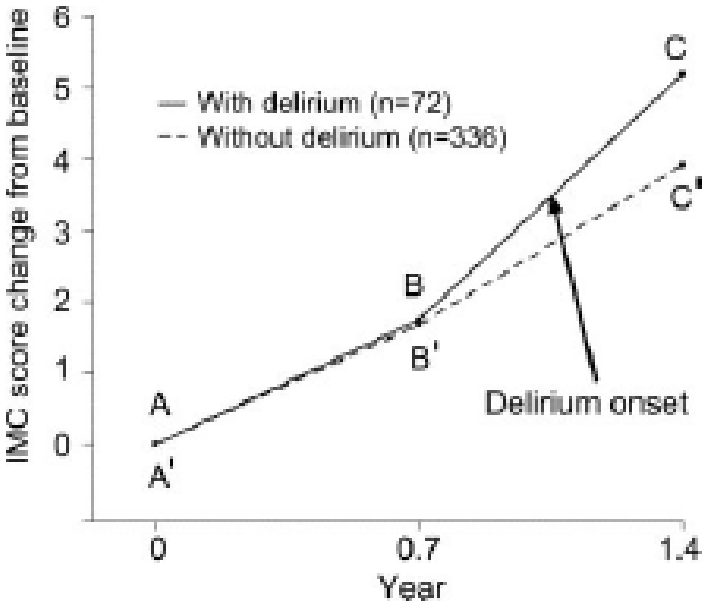
Modeled and Observed Prevalence of Moderate or Severe Pathological Lesions According to Age



Savva 2009 NEJM

Delirium accelerates cognitive decline in hospitalized elderly patients

Figure Cognitive trajectories of patients with Alzheimer disease with and without delirium



. Neurology® 2009;72:1570-1575

Table 3. Adjusted and Unadjusted Relative Risks for Death, Institutionalization, Cognitive Decline, and Any Adverse Outcome*

Variable	Relative Risk (95% CI)	
	Hospitalized Patients Without Delirium†	Hospitalized Patients With Delirium†
Death (*n* = 771)		
Unadjusted	5.3 (2.2–12.8)	8.9 (4.0–20.0)
Adjusted‡	4.7 (1.9–11.6)	5.4 (2.3–12.5)
Institutionalization (*n* = 771)		
Unadjusted	7.3 (4.3–12.5)	10.8 (6.5–18.0)
Adjusted‡	6.9 (4.0–11.7)	9.3 (5.5–15.7)
Cognitive decline (*n* = 480)		
Unadjusted	0.9 (0.6–1.3)	1.6 (1.2–2.2)
Adjusted‡	0.9 (0.6–1.4)	1.6 (1.2–2.3)
Any adverse outcome (*n* = 590)		
Unadjusted	1.8 (1.4–2.2)	2.5 (2.0–3.0)
Adjusted‡	1.7 (1.4–2.2)	2.2 (1.8–2.7)

Ann Intern Med. 2012;156:848-856.

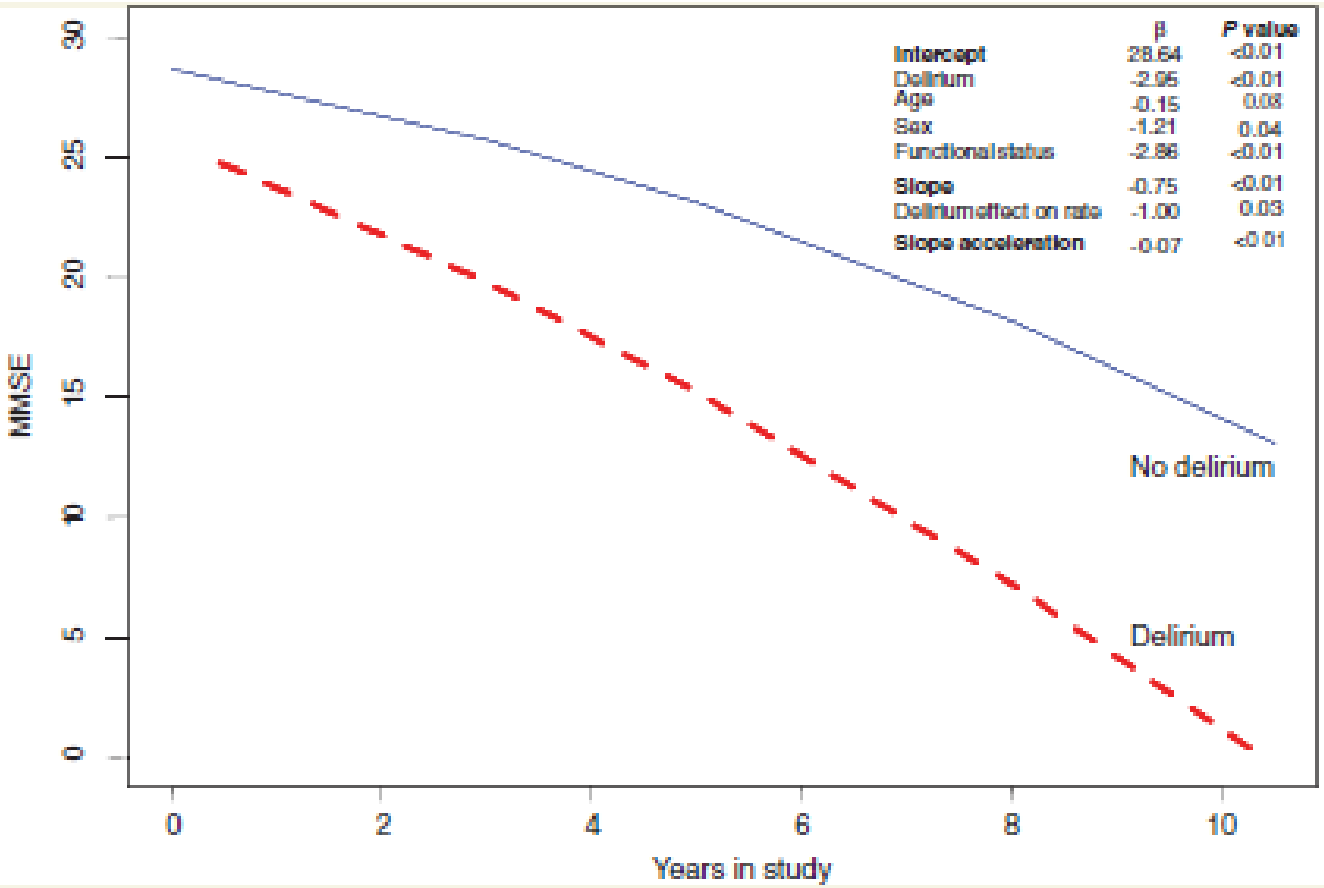
Vantaa 85+ Cohort Study

- Population-based
- Southern Finland
- All residents age ≥85 years
- Recruited 1991
- Follow-up 1994, 1996, 1999, 2001
- Cognitive and functional assessment each wave
- 52% autopsy
- Retrospective delirium assessments

Table 1 Clinical characteristics of participants at baseline

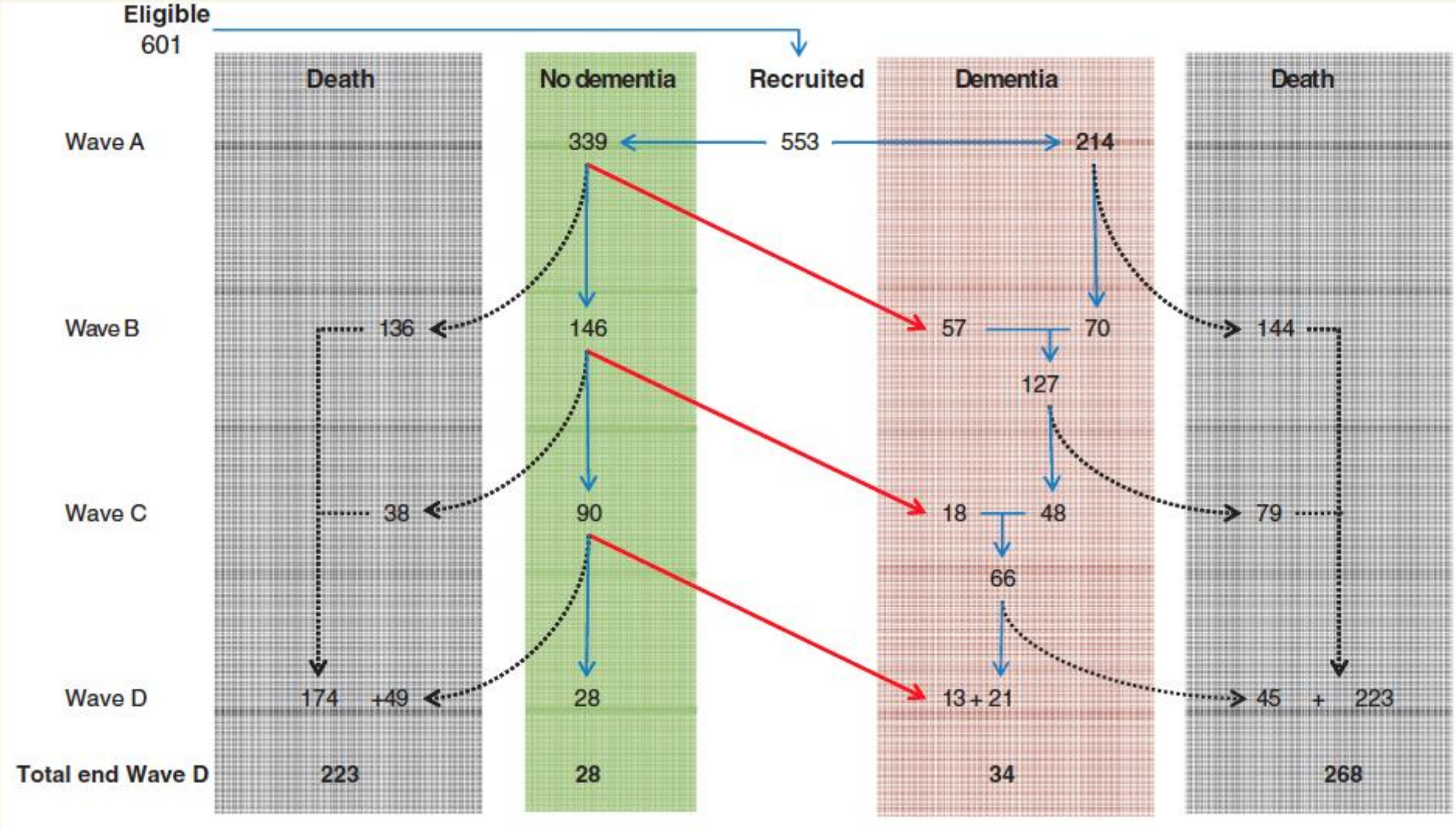
	No history of delirium	⩾ 1 episode of delirium	*P*-value
n at baseline (%)	482 (87)	71 (13)	
Person years	1901	164	
Mean age (SD)	88 (2.9)	90 (3.1)	1.00
Sex (% females)	385 (80)	55 (77)	0.64
Proportion with >4 years education (%)[a]	98 (23)	10 (17)	0.31
Mean time in study (years, IQR)	3.2 (1.6–5.9)	1.9 (0.9–3.2)	<0.01
Co-morbidity score at baseline (IQR)[b]	3 (1–4)	3 (2–5)	<0.01
Functionally independent at baseline (%)	321 (67)	24 (34)	<0.01
Prevalent dementia	159 (33)	55 (77)	<0.01
MMSE			
Baseline (IQR)	21 (17–26)	15 (10–19)	<0.01
Last follow-up (IQR)	19 (11–24)	13 (9–17)	<0.01

A total of 121 participants experienced delirium at any time during the study (22%). Of these, 58 were brain donors (48%) and 232 brain donors had no history of delirium (54%) ($P = 0.26$).



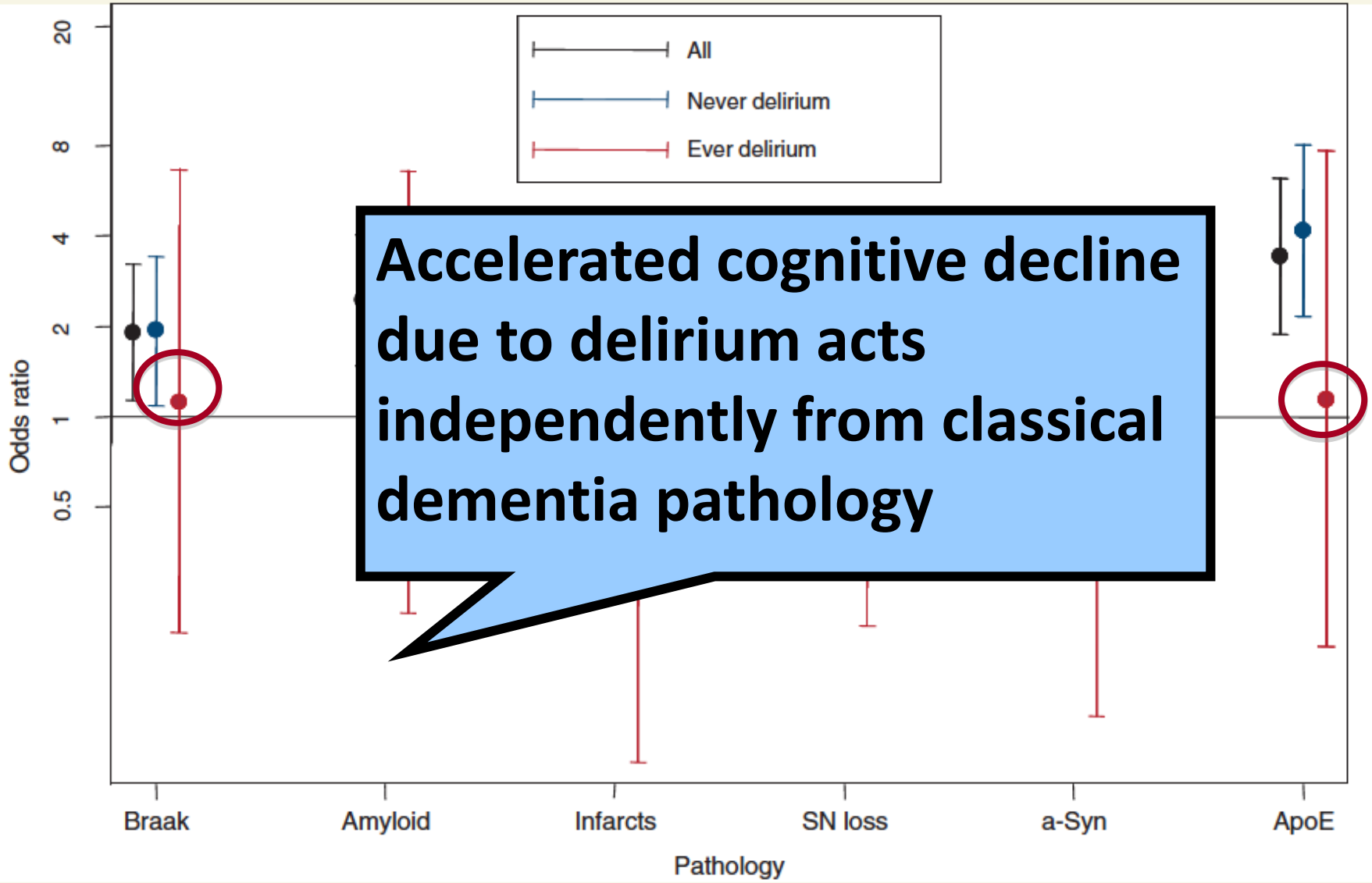
	N			95% CI	P
Dementia	311	OR	8.7	(2.1 to 35)	<0.01
Worse CDR	264	OR	3.1	(1.5 to 6.3)	<0.01

Flow diagram of follow-up in the Vantaa study. Illustration enumerating dementia and mortality events in Vantaa over time.



Wave A = 1991; Wave B = 1994; Wave C = 1996 and Wave D = 1999.

Relationship between delirium, dementia and neuropathology/genotype



Accelerated cognitive decline due to delirium acts independently from classical dementia pathology

Worsening Cognitive Impairment and Neurodegenerative Pathology Progressively Increase Risk for Delirium

Daniel H.J. Davis, M.R.C.P., Ph.D., Donal T. Skelly, Ph.D., Carol Murray, M.Sc., Edel Hennessy, B.A., Jordan Bowen, M.B., B.S., Samuel Norton, Ph.D., Carol Brayne, M.D., Terhi Rahkonen, M.D., Raimo Sulkava, M.D., David J. Sanderson, Ph.D., J. Nicholas Rawlins, Ph.D., David M. Bannerman, Ph.D., Alasdair M.J. MacLullich, M.R.C.P., Ph.D., Colm Cunningham, Ph.D.

- For every MMSE point lost, risk of incident delirium increased by 5% (p ¼ 0.02).
- LPS precipitated severe and fluctuating cognitive deficits in 16-week ME7 mice but lower incidence or no deficits in 12-week ME7 and controls, respectively. This was associated with progressive thalamic synaptic loss and axonal pathology

Am J Ger Psych 2014

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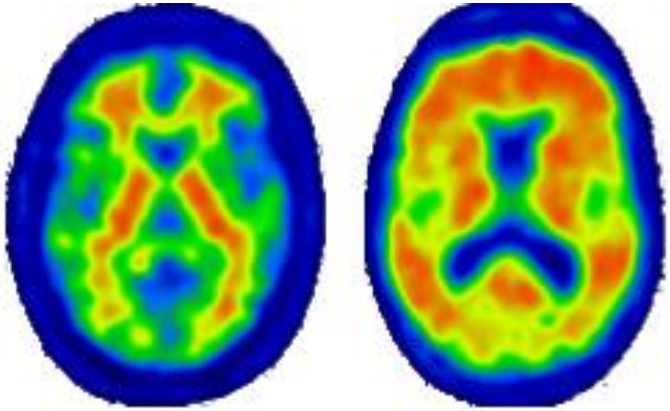
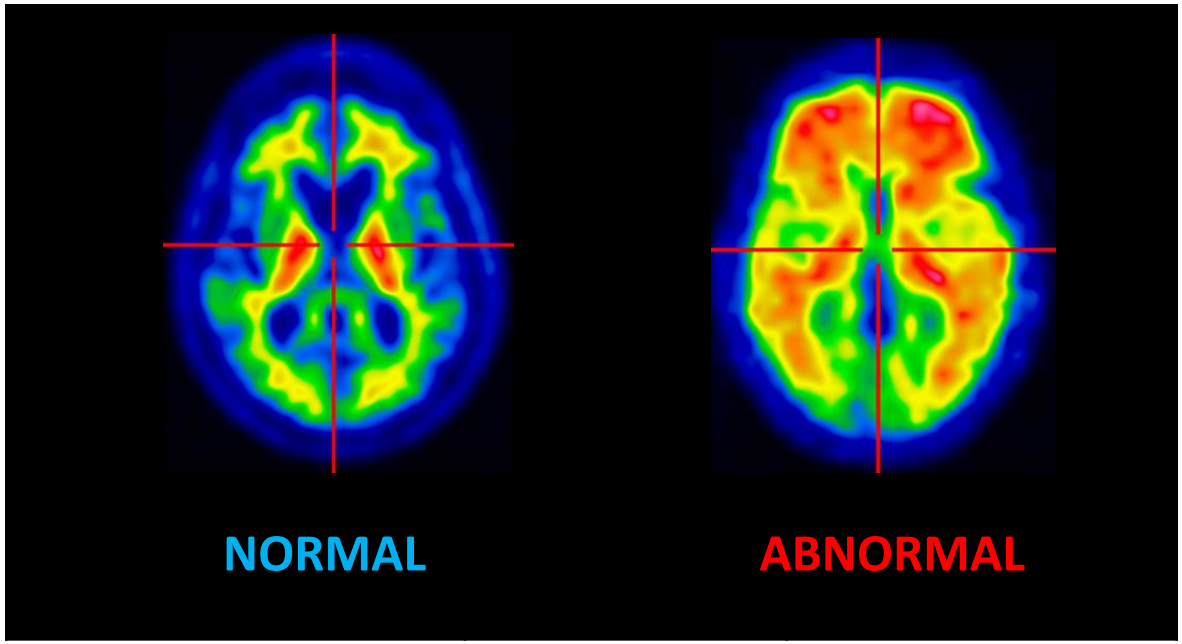
Am J Ger Psych 2014

Relationship between 18-Flutemetamol amyloid imaging and post-surgery delirium in elderly:

THE AMYDEL STUDY



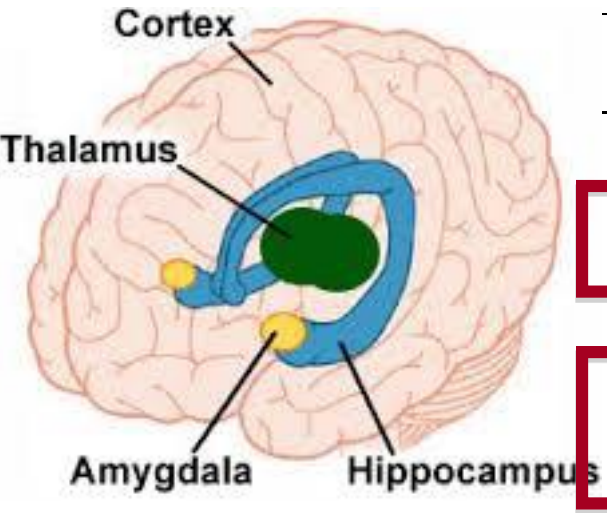
In vivo Brain Amyloid Load in Delirium Patients – 18F-Flutemetamol PET

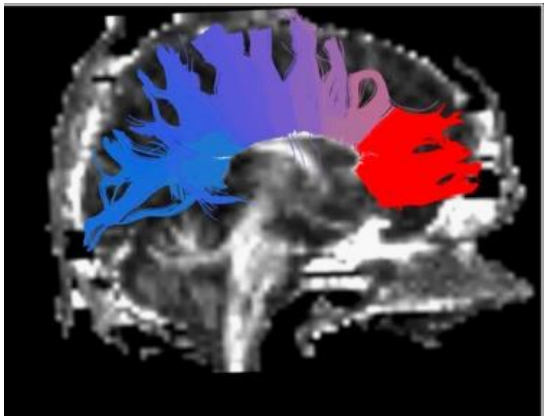


	D- N=12	D+ N=6	*p**
Flutemetamol-PET			
Amyloid positivity	5 (42%)	3 (50%)	1.00

*p values indicate significance Fisher's Exact Test.

Sucortical Brain Atrophy in Delirium Patients





| | D−
N=11 | D+
N=6 | *p** |
|---|---|---|---|
| | | | |
| **Subcortical Volumes (mm³)** | | | |
| Hippocampus | 3170 ± 435 | 2617 ± 622 | 0.08 |
| Lateral Ventricle | 18846 ± 8737 | 23103 ± 9381 | 0.19 |
| Amygdala | 1315 ± 186 | 938 ± 184 | **0.00** |
| Thalamus | 6069 ± 426 | 5180 ± 1343 | 0.09 |
| | | | |
| **White Matter Tracts** | | | |
| *Mean Diffusivity* | | | |
| Cingulate Gyrus R | 1.23 ± 0.17 | 1.62 ± 0.34 | **0.022** |
| Cingulate Gyrus L | 0.85 ± 0.042 | 0.86 ± 0.066 | 0.220 |
| *Radial Diffusivity* | | | |
| Genu Corpus Callosum | 0.44 ± 0.06 | 0.53 ± 0.10 | **0.069** |
| Cingulate Gyrus R | 1.14 ± 0.15 | 1.46 ± 0.31 | **0.016** |
| Cingulate Gyrus L | 1.16 ± 0.20 | 1.44 ± 0.40 | 0.263 |
| *Axial Diffusivity* | | | |
| Cingulate Gyrus R | 1.40 ± 0.29 | 1.97 ± 0.43 | **0.056** |
| Cingulate Gyrus L | 1.40 ± 0.21 | 1.59 ± 0.35 | 0.263 |

Conclusions

- Delirium and dementia are strictly related, i.e., delirium is a determinant of cognitive decline and dementia
- In an autoptic study delirium seems to have a pathophysiological link which is independent (though additive) to classical dementia pathology
- A recent neuroimaging study seems to confirm previous finding, i.e., delirium and dementia are not the same phenomenon

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- Alessandro Morandi

Amydel STUDY
Participating Centers:

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Ordine Ospedaliero di S. Giovanni di Dio - Fatebenefratelli
Sistema Sanitario Regione Lombardia
CENTRO S. GIOVANNI DI DIO - FATEBENEFRATELLI
ISTITUTO DI RICOVERO E CURA A CARATTERE SCIENTIFICO

FONDAZIONE POLIAMBULANZA
Istituto Ospedaliero

Azienda Ospedaliera
San Gerardo

Flutemetamol (18F) supply:

GE Healthcare