I vecchi e la depressione

Journal Club, 14 settembre 2007

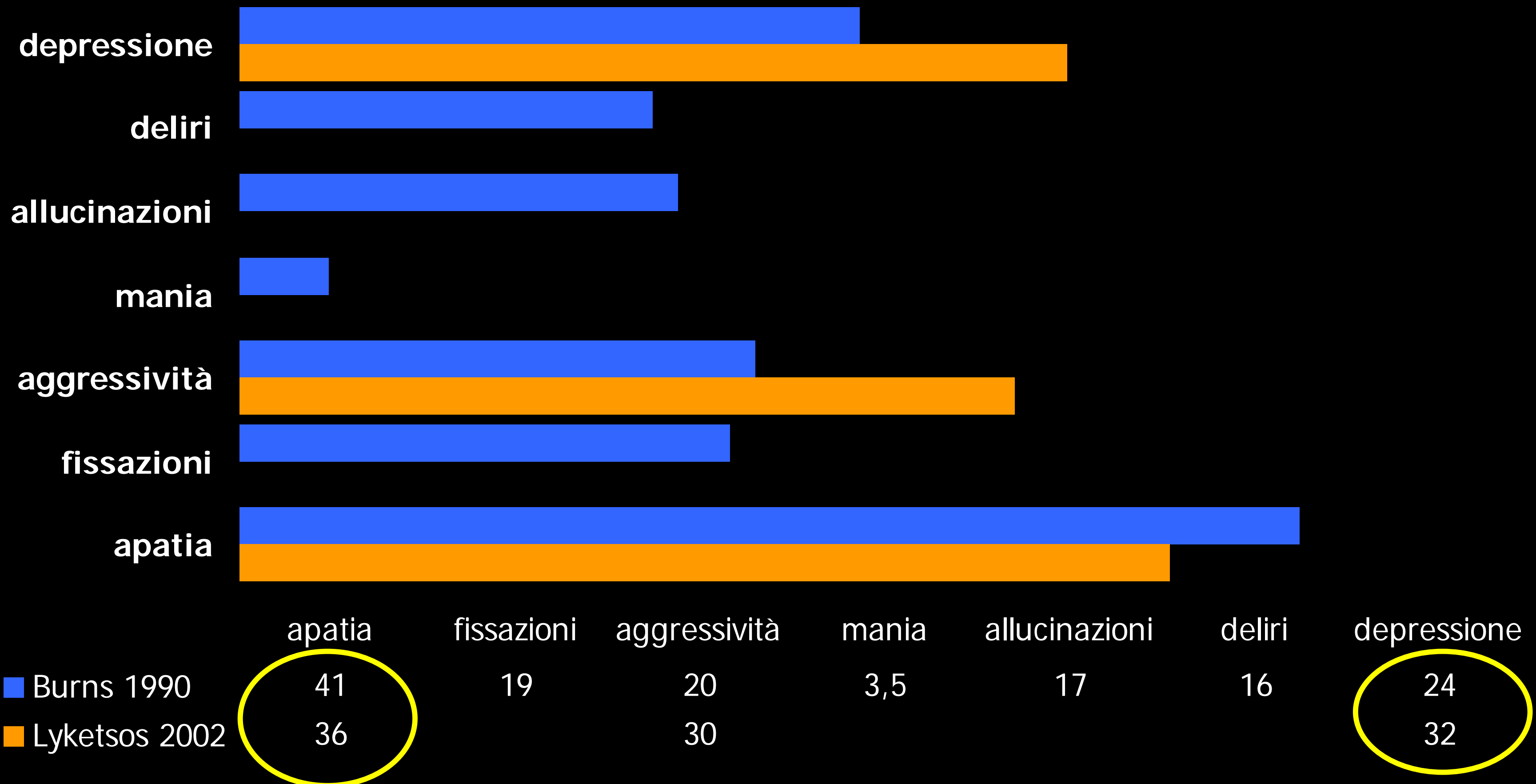
Depressione e demenza

Giuseppe Bellelli

Non-dementing psychoses in older persons

Madden J. JAMA 1952; 150:1567-70

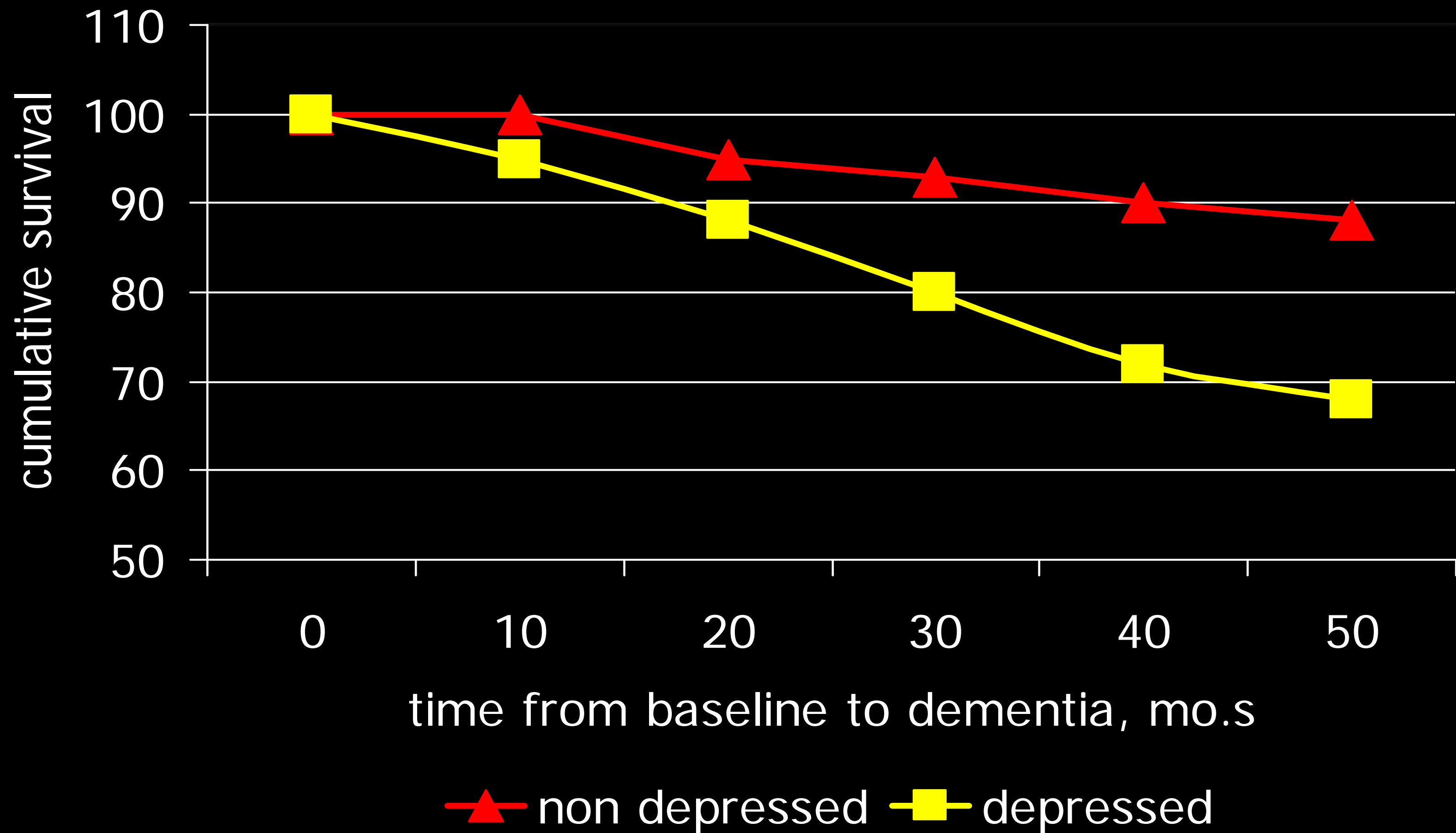
Prevalenza di sintomi psico-cognitivi nelle demenze



	apatia	fissazioni	aggressività	mania	allucinazioni	deliri	depressione
Burns 1990	41	19	20	3,5	17	16	24
Lyketsos 2002	36		30				32

Burns. Br J Psychiatry, 1990; Lyketsos. JAMA, 2002

Development of dementia in depressed and non-depressed subjects



Devanand et al. Arch Gen Psyc, 1996

Depressive Symptoms and Cognitive Decline in Non-demented Elderly Women

Table 3. Association of Baseline Depressive Symptoms With Clinically Meaningful Cognitive Outcomes During the 4-Year Study: Results of the Unadjusted and Adjusted Analyses*

	Odds Ratio (95% CI)					
	Unadjusted			Adjusted		
	No. of Depressive Symptoms			No. of Depressive Symptoms		
Clinically Meaningful Outcome	0-2	3-5	≥6	0-2	3-5	≥6
≥3-Point decline on modified MMSE score (n = 653)	1.0	1.6 (1.3-2.1)	2.3 (1.6-3.3)	1.0	1.6 (1.2-2.1)	2.1 (1.4-3.1)
History of physician-diagnosed dementia at follow-up (n = 89)	1.0	2.3 (1.2-4.3)	3.0 (1.3-7.1)	1.0	1.7 (0.9-3.5)	2.3 (0.9-5.9)

**Adjusted for age, education, health status, exercise, alcohol use, functional status, and clinical site. CI indicates confidence interval; MMSE, Mini-Mental State Examination.*

Yaffe K, et al. Arch Gen Psych 1999

The overlap between depression & dementia

Depression = driving force → Dementia overlaps depression and cognitive deficits remit with improvements in mood

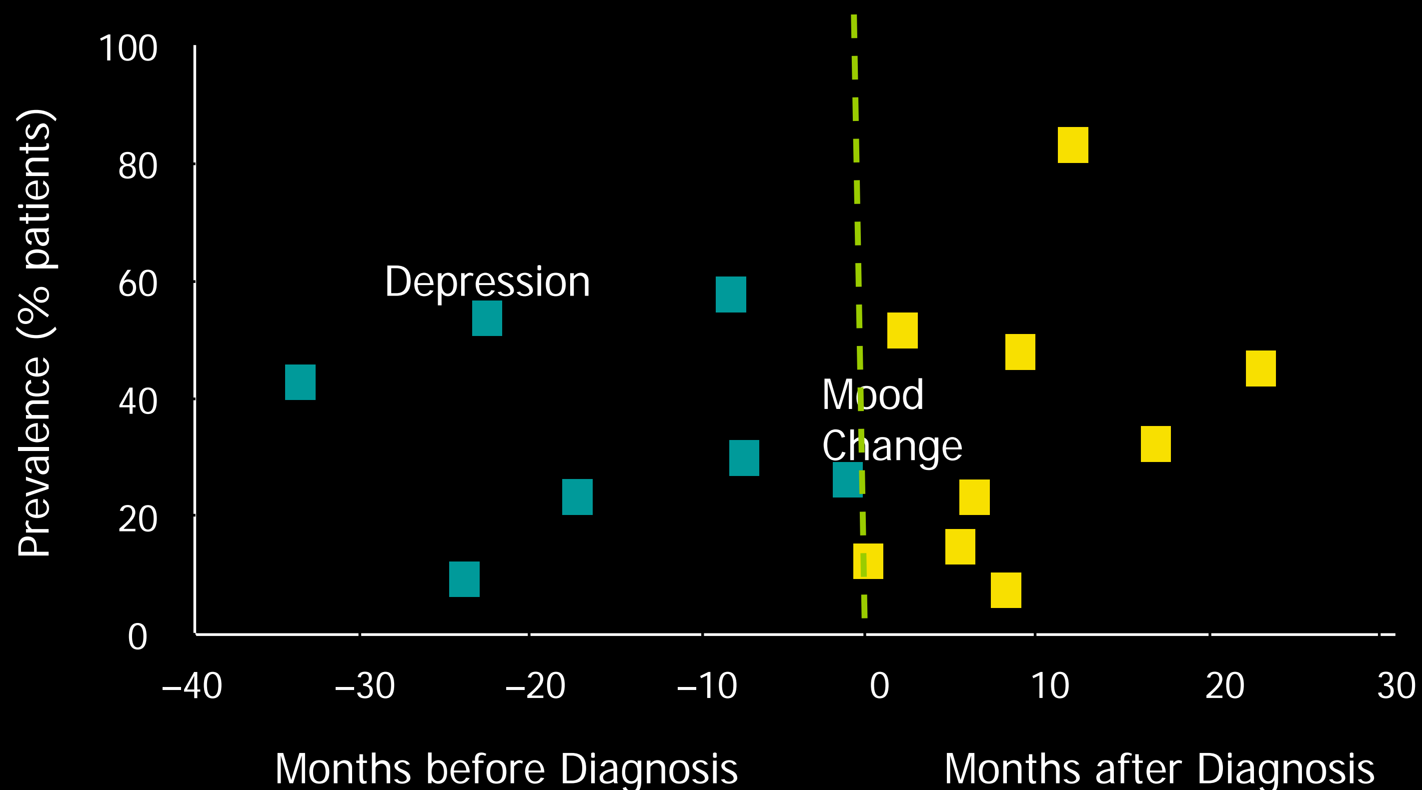
Dementia = driving force → Depression hearlds the development of an early dmentia

Depression-related cognitive impairment: possibilities for its pharmacological treatment

- Depression-related cognitive impairment (DRCI) is a condition which despite its initial treatment response, shows a progressive deterioration. No consistent therapeutic strategies have been proposed to combat this condition. This may be due to a reluctance to treat the cognitively impaired, a failure to recognise the deleterious prognosis or a poor understanding of the likely pathogenesis. Increasing evidence implicates the hypothalamo-pituitary-adrenal (HPA) axis as a key neurobiological determinant of the presentation and course of depression-induced cognitive decline. *By utilising agents which control central glucocorticoid hyperactivity over a sustained period, whilst avoiding those agents which may compromise cognitive abilities, there exists a pharmacological strategy which may minimise* the morbidity of cognitive impairment related to depressive illness.

Mitchell A, J Affect Disord 1996

Disturbi comportamentali e progressione della Malattia di Alzheimer



Jost BC, Grossberg GT. *J Am Geriatr Soc.* 1996;44:1078-1081

Distinction between preclinical Alzheimer's disease and depression

- Prospective observational cohort study
  - 111 nondemented subjects with cognitive impairment >55 years without neurological or somatic causes for cognitive impairment
  - The course of cognitive impairment and dementia were assessed after 2 and 5 years
- 25 subjects had preclinical AD dementia at follow-up. 60% of these (n=15) were depressed at baseline
- Depression is common in preclinical AD. Depressed subjects with preclinical AD can be accurately differentiated from subjects with depressive-related cognitive impairment by age and severity of memory impairment

Visser PJ et al, JAGS 2000

The occurrence of depressive symptoms in the preclinical phase of AD: A population-based study

A- K. Berger, L. Fratiglioni, Y. Forsell, B. Winblad and L. Bäckman

Neurology 1999;53;1998-

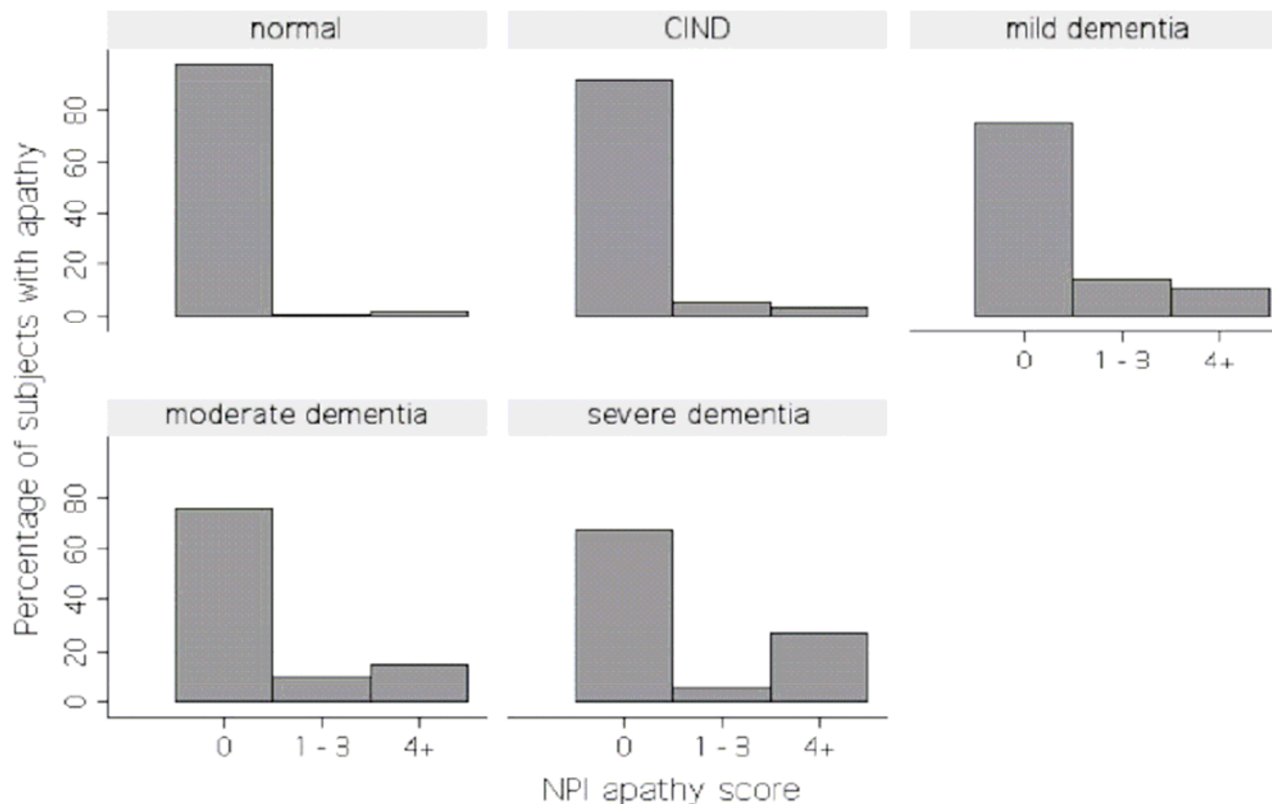
Table 2 Means and SDs in baseline depressive symptoms and subjective memory complaints of incident AD patients and nondemented persons

	Diagnosis of AD 3 years later	
Variable	Incident AD (n = 34), mean ± SD	Nondemented (n = 188), mean ± SD
Mood factor	1.18 ± 2.09	0.69 ± 1.42
Dysphoria	0.35 ± 0.66	0.21 ± 0.46
Appetite disturbance	0.24 ± 0.61	0.26 ± 0.72
Feelings of guilt	0.24 ± 0.50	0.15 ± 0.45
Thoughts of death	0.35 ± 0.88	0.07‡ ± 0.33
Motivation factor	1.38 ± 1.95	0.55‡ ± 0.95
Lack of interest	0.38 ± 0.74	0.08‡ ± 0.31
Psychomotor change	0.06 ± 0.34	0.02 ± 0.22
Loss of energy	0.53 ± 1.02	0.26* ± 0.63
Concentration difficulties	0.41 ± 0.78	0.19* ± 0.52
Sleep disturbance	1.38 ± 1.67	1.17 ± 1.46
Memory complaints	1.47 ± 1.29	0.79‡ ± 1.10

* $p < 0.05$.
‡ $p < 0.001$.

- The field has recently become more complex with the realization that these two pathways may overlap and that depression in early or mid-life may be associated with dementia or cognitive impairment many years later

Epidemiology of apathy in older adults: the Cache County Study



† $\chi^2 = 164.6$, $p < 0.001$. Graphs are plotted from data the shown. The frequency and severity of apathy increases with the severity of cognitive impairment.

CIND: Cognitive impairment, not dementia.

Chiadi U, Am J Geriatr Psychiatry 2007

Hypotheses & Key questions

- La depressione è un fattore di rischio per lo sviluppo di demenza?
- La depressione è legata alla comparsa di demenza
  - È un prodromo?
  - Ha un rapporto causativo?
- Depressione e demenza possono condividere uno o più fattori di rischio?

Depression as a risk factor for dementia

Depression as a risk factor for dementia: an updated review

- 37 cohort studies
  - 27 studies reported a statistically significant positive association in which severity of depression is a risk factor for increasing cognitive decline
  - 6 studies reported a trend towards a positive association
  - 4 studies reported no relationship
  - No studies reported an inverse relationship

Jorm A, Aust NZ J Psychiatry 2001

Articles

Proneness to psychological distress is associated with risk of Alzheimer's disease

R.S. Wilson, PhD; D.A. Evans, MD; J.L. Bienias, ScD; C.F. Mendes de Leon, PhD; J.A. Schneider, MD; and D.A. Bennett, MD

- Older Catholic clergy members
  - Annual clinical evaluations
  - Postmortem examination of the brain (n=140)
- During a mean of 4.9 years of follow-up 140 subjects developed AD. Those high in distress proneness (90° percentile) had twice the risk of developing AD than those low in distress proneness (10° percentile). Distress proneness was related to decline in episodic memory but not in other cognitive domains, with a >10-fold increase in episodic memory decline in those high in distress proneness compared with those low in the trait.
- Conclusion: proneness to experience psychological distress is a risk factor for AD, an effect independent of AD pathologic markers such as cortical plaques and tangles

Neurology 2003

Depressive symptoms, sex, and risk for Alzheimer's disease

- Risk for incident dementia and AD over a 14-year period in 1,357 community-dwelling men and women participating in the 40-year prospective Baltimore Longitudinal Study of Aging.
- Screening for depressive symptoms, medical and neuropsychological evaluations prospectively collected every 2 years.
- Premorbid depressive symptoms significantly increased risk for dementia, particularly AD in men but not in women. Hazard ratios were approximately two times greater than for individuals without history of depressive symptoms, an effect independent of vascular disease.
- We conclude that the impact of depressive symptoms on risk for dementia and AD may vary with sex.

Dal Forno G. Ann Neurol 57: 381-7, 2005

Rates of depression in individuals with pathologic but not clinical Alzheimer Disease are lower than those in individuals without the disease: findings from the Baltimore Longitudinal Study on Aging

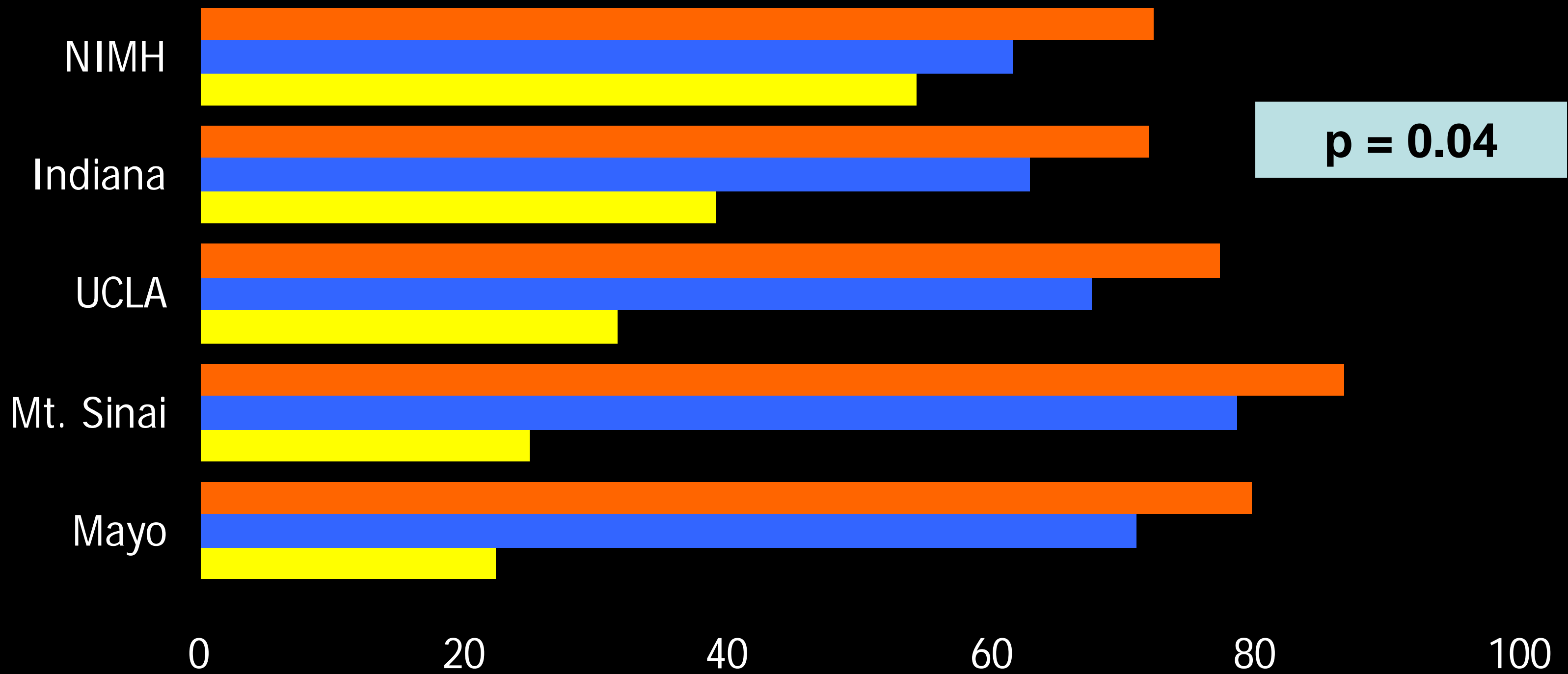
- Individuals with Alzheimer pathology but no cognitive decline before death had significantly lower rates of depression than cognitively normal controls with no Alzheimer pathology and individuals with Alzheimer pathology plus clinical diagnoses of dementia. These findings suggest that depression is a risk factor for AD in the presence of AD pathology, but depression is not a risk factor for AD pathology

Morgan M et al, Alzh Dis Associat Disord 2007

La depressione è un prodromo della malattia di Alzheimer?

- MIRAGE study, Green R et al, Arch Neur 2003
  - Strongest association between current AD and prior depression in the 3 years leading up to a formal diagnosis of AD
  - The strength of association declined with increasing separation of depression and dementia
- PAQUID study, Fuhrer R et al, JAGS 2003
  - Depressive symptoms associated with an increased risk of dementia only in the short term and then only for men

Prevalenza di depressione maggiore associata a precocità di esordio AD



	Mayo	Mt. Sinai	UCLA	Indiana	NIMH
età studio	79,7	86,7	77,3	72	72,4
età inizio	71	78,6	67,7	62,9	61,6
% DM	22,5	25	31,7	39,1	54,4

Zubenko GS et al. Am J Psychiatry 2003

La depressione ha un link "causativo" con la demenza (di Alzheimer)?

- Differenze alla baseline nelle dimensioni dell'ippocampo sx in una coorte di pazienti depressi che successivamente svilupparono AD
  - Non correlazioni di questo tipo in pazienti che svilupparono demenza senza essere depressi alla baseline
    - » Steffens DC, Am J Geriatr Psychiatry 2002
- I dati non sono stati replicati nello studio "PATH Through life project" ed in altri 2 studi indipendenti

Depressione in pz con MCI aumenta il rischio di AD?

114 pz con MCI

Follow-up di 3 anni

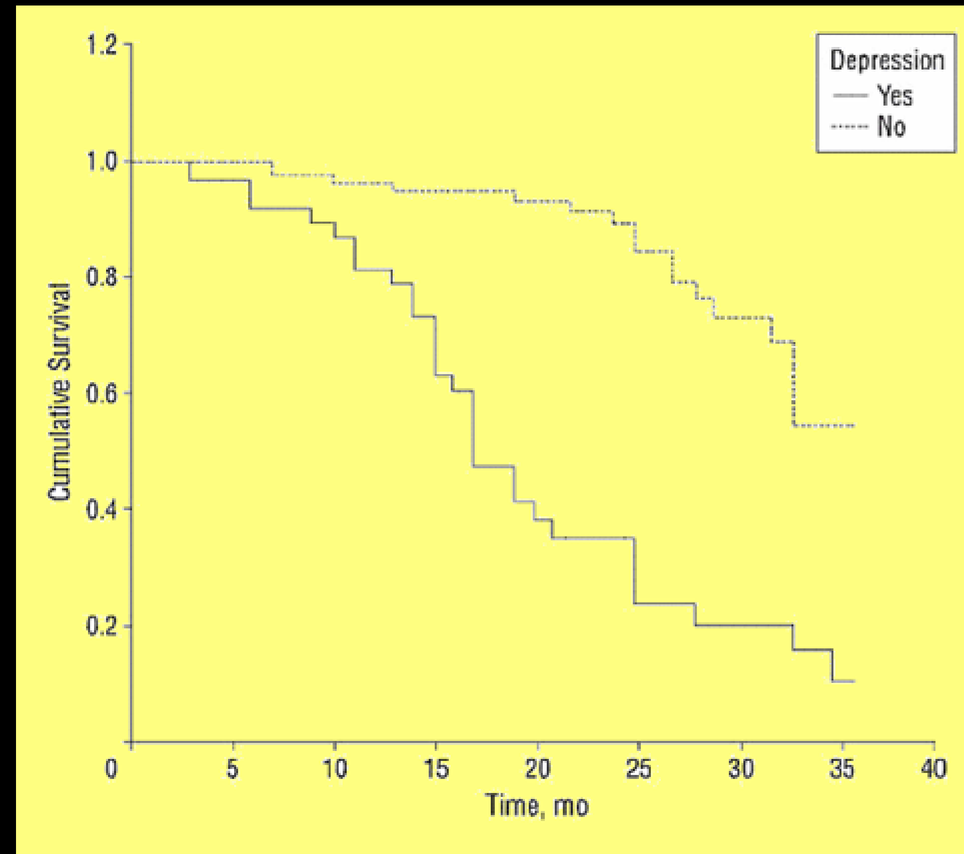
36% depressione basale

Demenza:

- 85% dei depressi
- 32% dei non depressi

Sviluppo demenza più precoce nei depressi

Maggior rischio per pz con scarsa risposta agli AD



Modrego et al., Arch Neurol 2004

Depression is unrelated to conversion to dementia in patients with mild cognitive impairment.

Rozzini L, Vicini Chilovi B, Trabucchi M, Padovani A

Arch Neurol. 2005.

Our results provide no support to this hypothesis but show that depression could have a different pathophysiological basis from AD, as demonstrated in a recent paper showing that depressive symptoms neither correlated with summary measures of plaque and tangle pathology in cortical regions nor altered the relation of these pathologic indices to clinical disease.

La demenza di Alzheimer è più frequente in coloro che sviluppano depressione in tarda età?

PRO

71 depressed patients and 50 surgical controls; 10 depressed and no controls have dementia at follow-up; presence of dementia was predicted by older age at baseline

Brodaty et al, Psychol Med 2003

Global cognitive score declined a mean of 0.030 unit per year (SE 0.005, *p* 0.001). Annual rate of decline increased about 7%

Wilson et al, Neurology 2003

CONTRO

227 mentally healthy and 62 with DSM III R depression, followed for 3 years. The higher incidence of dementia in those with early onset major depression may be due to a longer lifetime duration of depression

Palsson S , Br J Psychiatry 1999

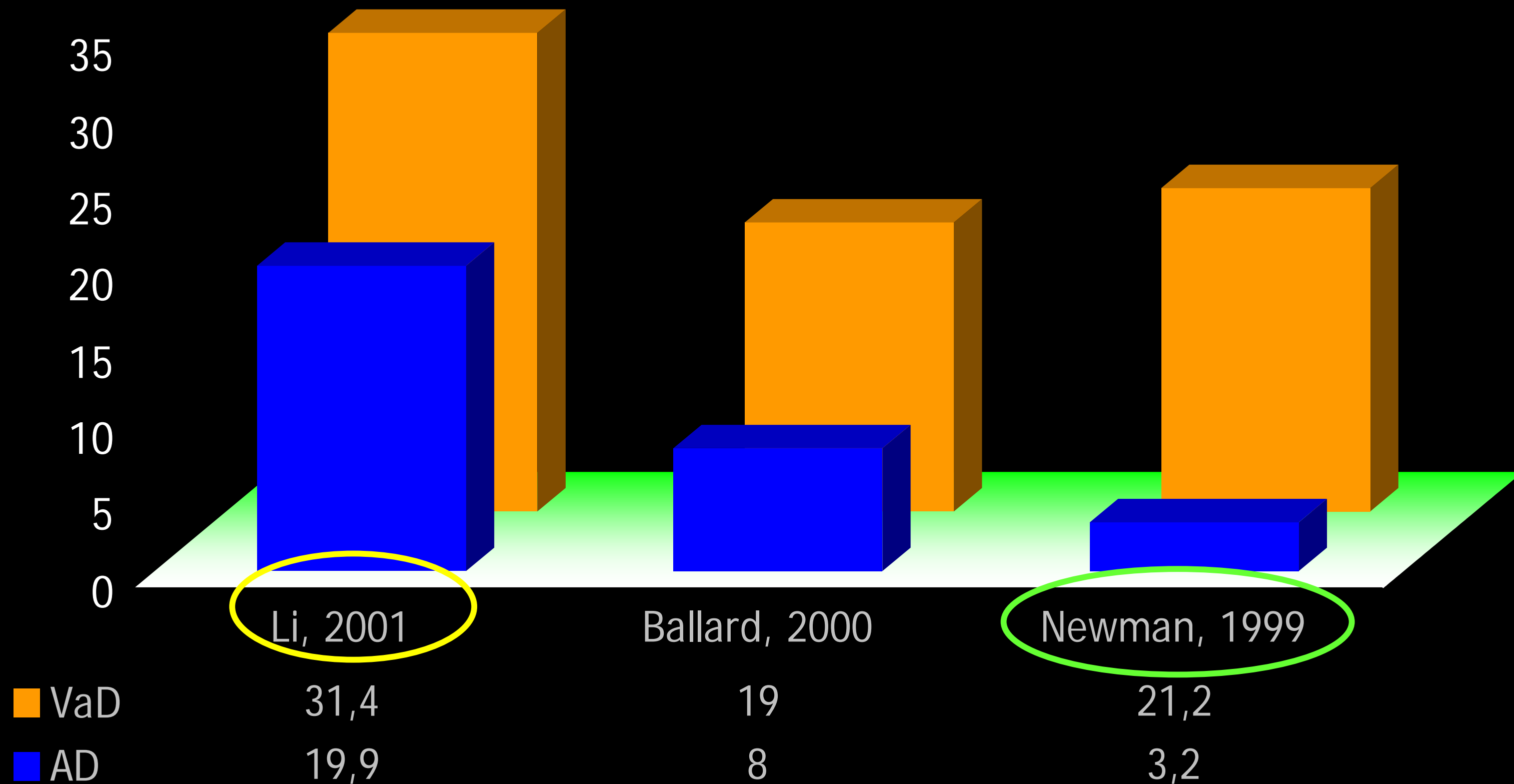
Does cognitive impairment itself act as a risk factor for future depression in mood?

- An accellerated annual increase of depressive symptoms during follow-up was associated with impaired attention, pooreer immdiate recall at baseline

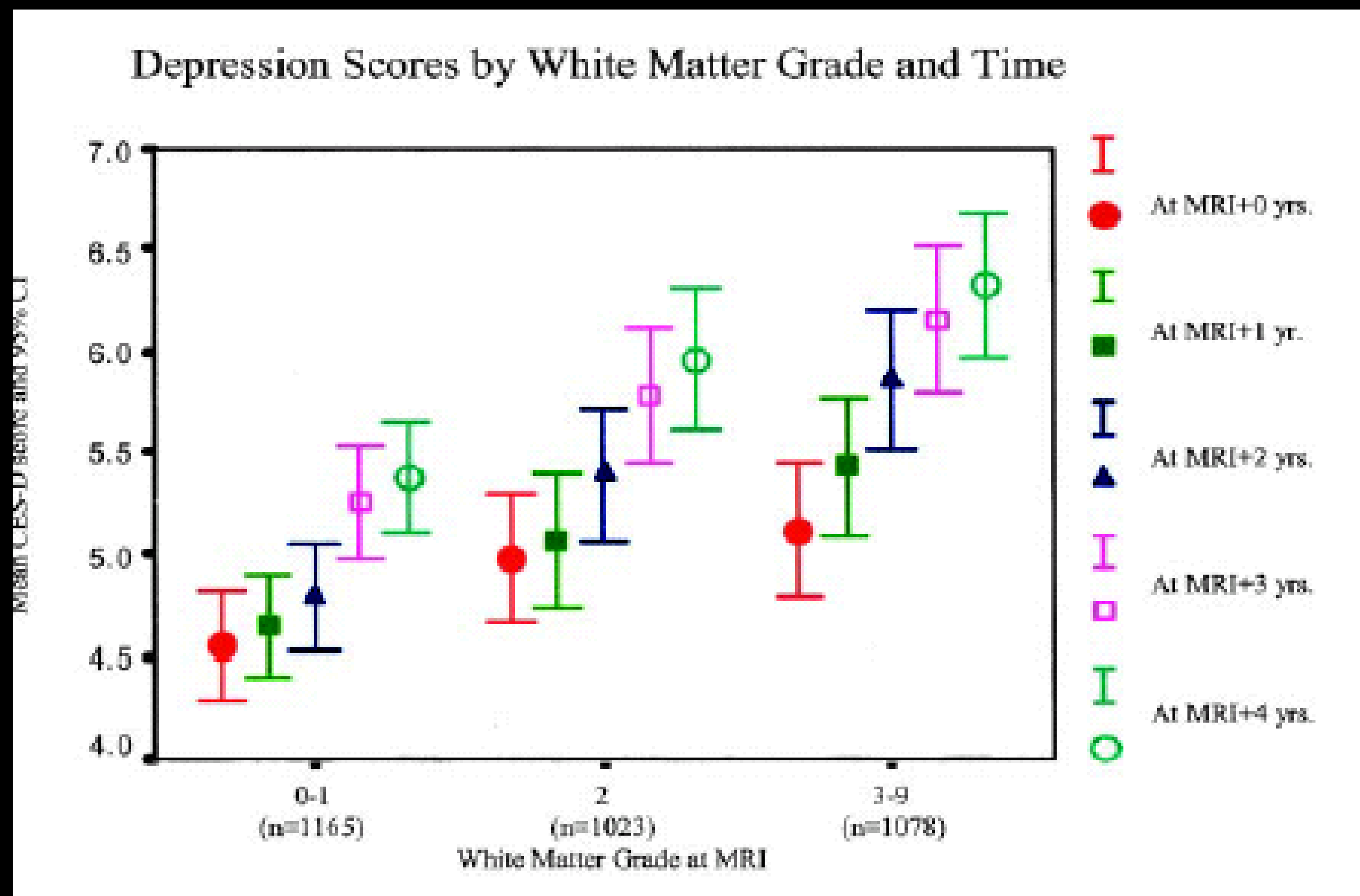
Vinkers DJ, The Leiden 85 plus study BMJ 2004

La depressione è più frequente in associazione con la demenza di Alzheimer o con la demenza vascolare?

Depressione più frequente nella demenza vascolare rispetto all'Alzheimer



Relationship between CES-D scores & white-matter MRI



Steffen D, Stroke 2002

Biological substrates supporting the relationship between depression and cerebrovascular diseases

- White-matter hyperintensities (WMH) in late-onset depression
  - Krishnan, 1998
- Silent stroke in 94% of patients with late-onset depression in absence of family history or psychosocial stressors
  - Fujikawa 1994

The vascular depression hypothesis

- Late age at onset (after age 65) or change in course after early onset
- Persistent symptoms
- Association of such depression with vascular disease or risk factors and diffuse multifocal lesions

Alexopoulos Arch Gen Psych 1997

How might such lesions cause depression?

- There are five frontal subcortical systems connecting the frontal lobe to the basal ganglia; vascular disconnection of these frontal "executive" areas from input areas could result in changes in attention and cognition; vegetative and somatic symptoms; and mood, cognitive, and autonomic responses

  (Blazer et al. *Journal of Gerontology*, 2003)

- Proposed two mechanisms for such disconnections:
  - small direct lesions might themselves disrupt critical brain pathways;
  - an accumulation of lesions could eventually reach a threshold level, perhaps then conferring a predisposition to depression

  (Alexopoulos et al. *Arch Gen Psych*, 1997)

Clinically defined vascular depression

- Cerebrovascular lesions usually occur at areas receiving blood from perforating arteries supplying the basal ganglia or at the borders of vascular territories. For this reason, patient with vascular risk factors may have lesions at the basal ganglia.
- Damage of the basal ganglia and their connections to prefrontal structures has been associated with depression as well as a frontal lobe syndrome that includes retardation, lack of insight, and impaired executive functions. Therefore, we would expect vascular depression to be accompanied by these symptoms and signs.
- Since vascular lesions usually are not limited to the basal ganglia and the pefrontal areas, a broader spectrum of cognitive impairment and disability may occur in vascular depression

Alexopoulos et al, Am J Psychiatry 1997

Executive dysfunction and depressive symptoms in cerebrovascular disease

Bellelli G, et al, J Neurol Neurosurg Psyc, 2002

Cerebrovascular disease and executive dysfunction in geriatric depression

	Total (n=209)	None mild sCVD (N=104)	Mod- severe sCVD (N=105)	p
Age, years	79.6±6.3	78.6±6.7	80.6±5.7	.021
Gender (% of female)	80.4	76.9	83.8	.140
Education (years)	6.0±3.1	5.9±3.0	6.1±3.2	.559
Geriatric Depression Scale (0-15)	6.8±3.6	6.3±3.7	7.3±3.4	.044
Mini Mental State Ex (0-30)	22.6±3.5	23.6±3.2	21.6±3.6	.000
Memory Span FW	4.4±0.7	4.4±0.7	4.3±0.7	.381
Memory Span BW	2.3±0.8	2.4±0.9	2.3±0.7	.728
Semantic Verbal Fluency (z score)	-1.2±0.8	-1.0±0.9	-1.4±0.8	.001
% of perseverative errors in SVF	29.9±42.8	23.7±25.7	36.0±54.0	.041
Attention sustained (z score)	-1.6±1.0	-1.4±1.0	-1.7±1.0	.040
Babcock Test (z score)	-1.4±1.3	-1.4±1.4	-1.5±1.2	.576

Lucchi E, Bellelli G, Magnifico F, Guerini F, Trabucchi M. J Gerontol 2006

Depression–Executive Dysfunction Syndrome in Stroke Patients

Vataja et al. *Am. J. Geriatr. Psychiatry.*2005;

Quale l’espressione clinica della depressione in associazione alla demenza?

Criteri diagnostici per la depressione nella malattia di Alzheimer

- **A.** Tre (o più) dei seguenti sintomi devono essere presenti da un periodo di 2 settimane e devono rappresentare un cambiamento significativo rispetto al funzionamento precedente: almeno un sintomo deve essere o 1) umore depresso o 2) diminuzione dell'affettività o del piacere:
  - 1. umore significativamente depresso
  - 2. diminuzione dell'affettività o del piacere in risposta a contatti sociali e ad attività familiari
  - 3. isolamento o ritiro sociale
  - 4. disregolazione dell'appetito
  - 5. disregolazione del sonno
  - 6. cambiamenti psicomotori (agitazione)
  - 7. irritabilità
  - 8. senso di fatica e perdita di energia
  - 9. sentimenti di indegnità, sfiducia o eccessivo o inappropriato senso di colpa
  - 10. pensieri ricorrenti di morte, ideazione o pianificazione di suicidio
- **B**. I criteri per malattia di Alzheimer (DSM IV TR) devono essere soddisfatti

Am J Geriatr Psychiatry, 2002

Criteri diagnostici per la depressione nella malattia di Alzheimer

- **C.** I sintomi devono causare significativa difficoltà o disregolazione nel funzionamento
- **D.** I sintomi non devono essere presenti esclusivamente nel corso di un delirium
- **E.** I sintomi non devono essere dovuti agli effetti diretti di una sostanza
- **F.** I sintomi non devono spiegare altre condizioni (depressione maggiore, disturbo bipolare, lutto, schizofrenia, disturbo schizoaffettivo, psicosi, disturbi d'ansia, disturbi da abuso di sostanza). Non sono da includere sintomi che, a giudizio del clinico, sono chiaramente dovuti a altre condizioni mediche o che sono diretta conseguenza di sintomi della demenza non connessi all'umore (es. perdita di peso dovuta a difficoltà di assunzione di cibo).
- *Specificare*:
  - se l'inizio dei sintomi è antecedente, contemporaneo o ritardato rispetto ai sintomi della malattia di Alzheimer.
  - se i sintomi sono associati a psicosi, ad altri segni o sintomi comportamentali significativi, con precedente di disturbi dell'umore.

Am J Geriatr Psychiatry, 2002

Proposed criteria for vascular depression

- **A.** Major depression occurring in the context of clinical and/or neuroimaging evidence of cerebrovascular disease or neuropsycghological impairment and at least one of:
- **B1**. clinical manifestation may include history of stroke or transient ischaemic attacks, or focal neurological signs or symptoms (e.g. exaggeration of deep tendom reflexes, extensor plantar response, pseudobulbar palsy, gait disturbance, weakness of extremity
- **B2**. Neuroimaging findings may include white or grey matter hyperintensities (e.g. Lesions > 5 mm in diameter and irregular in shape), confluent white matter lesions, or cortical or subcortical infarcts
- **B3.** cognitive impairment manifested by disturbance of executive function (e.g., planning, organizing, sequencing, abstracting), memory or speed of processing information

Steffens & Krishnan, Biol Psych 1998

Proposed criteria for vascular depression

- **Supportive features**
  - Depression onset after age 50 or change in course of depression after onset of vascular disease
  - Marked loss of interest or pleasure
  - Psychomotor retardation
  - Lack of family history of mood disorders
  - Marked disability in instrumental or self maintenance of daily living

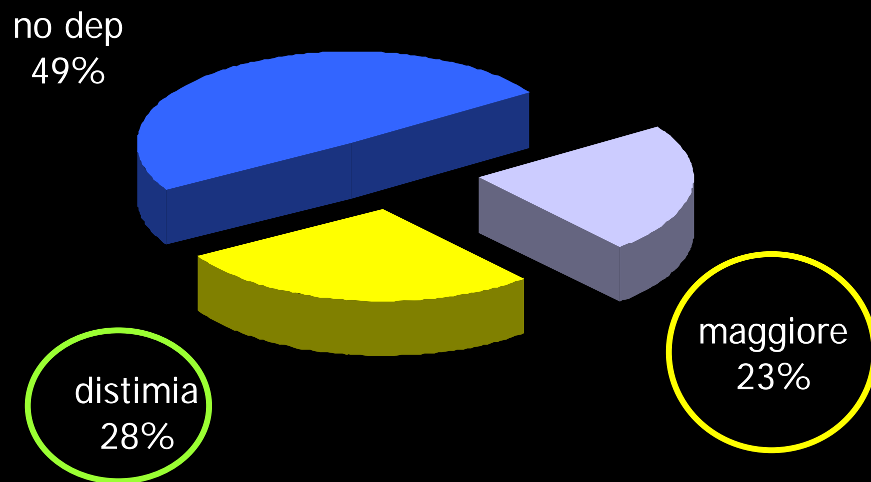
Steffens & Krishnan, Biol Psych 1998

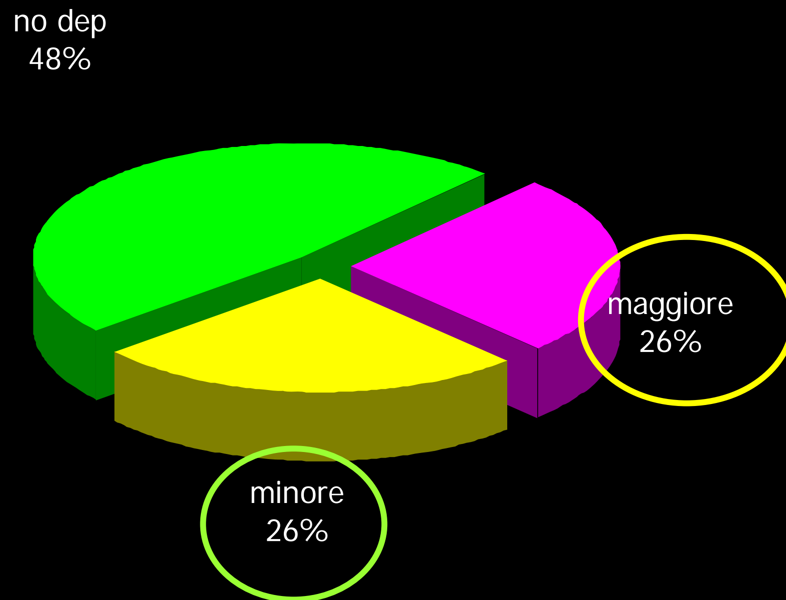
Prevalenza forme di depressione in AD

103 casi con probabile Alzheimer

(51% con depressione)

670 casi con probabile Alzheimer





Migliorelli et al. Am J Psychiatry 1995

Starkstein et al. Am J Psychiatry, 2005

Quali le espressioni cliniche della depressione nei soggetti dementi?

- La depressione potrebbe essere la conseguenza (ipotesi “reattiva”) dell’impairment cognitivo?
- Consapevolezza di AD non associata con depressione
  - Arkin, 2001
  - Ballard, 1993
- Non associazione tra gravità AD e rischio di depressione
  - Payne, 1998

La coesistenza di depressione & demenza impatta (con effetto sinergico) sugli outcomes?

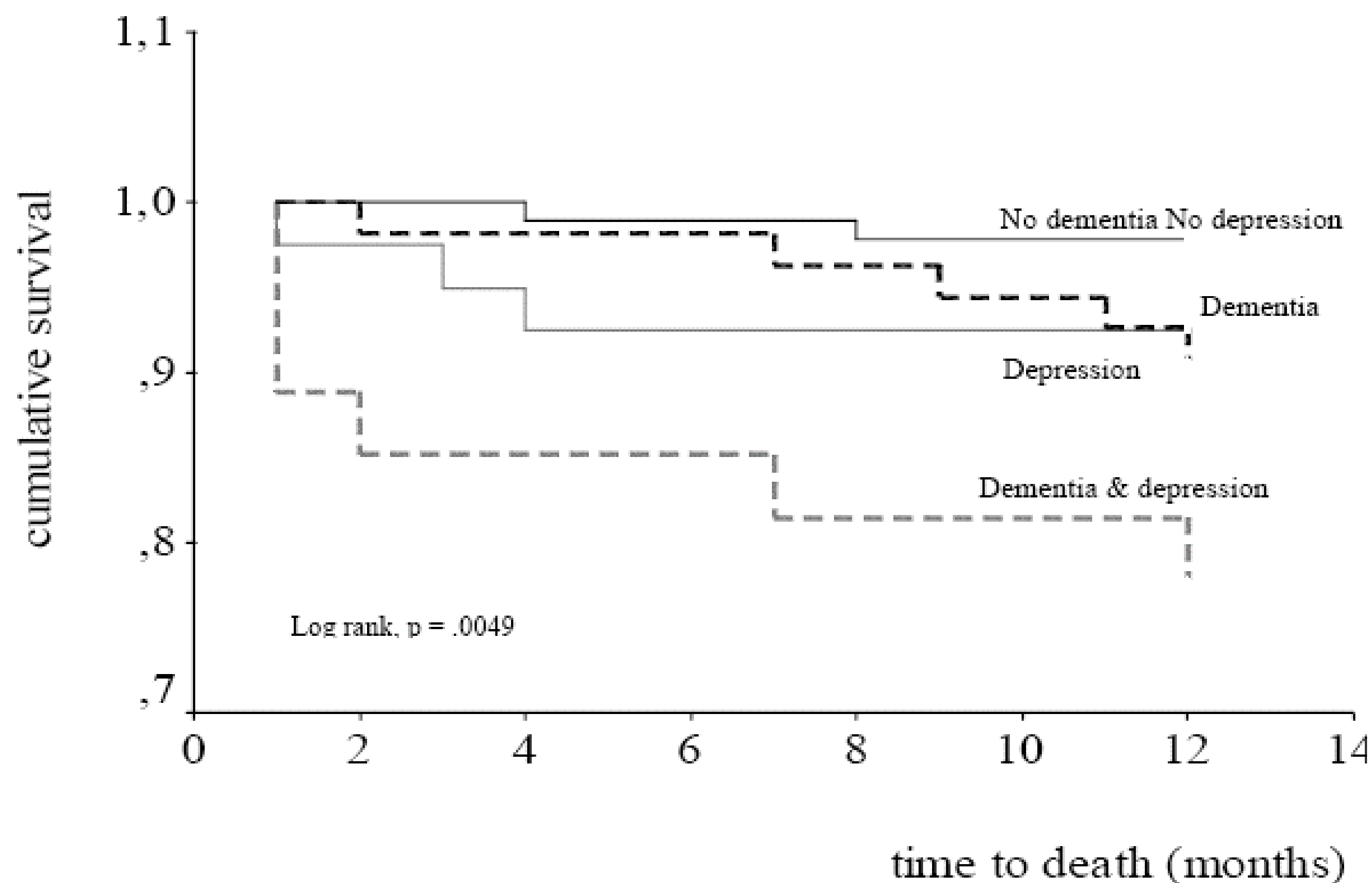
La depressione e la demenza in pazienti con frattura di femore

- Nell' Amsterdam Study of the Elderly depressione e demenza identificano un sottogruppo di pazienti con prognosi peggiore
  - » *Geerlings MI et al, Psychol Med 1999*
- Late onset depression è associata ad un rate più elevato di mortalità e demenza
  - » *Baldwin R, Int J Geriatr Psych 2006*
- La coesistenza di demenza e depressione si associa ad una mortalità più elevata a 15 mesi in soggetti colpiti da stroke
  - » *Pohjiasvaara et al, Cerebrov Dis 2002*
- Gli studi più recenti non chiariscono se l'associazione di depressione e demenza aumenti il rischio di mortalità nel breve-medio periodo, nonostante entrambe queste condizioni cliniche, singolarmente, siano gravate da un ridotto tasso di sopravvivenza

Depressione & demenza: i nostri dati

- 327 pazienti ricoverati c/o RACU Ancelle della Carità (gennaio 2002-aprile 2006) per riabilitazione frattura di femore
- 211 pazienti screenati per sintomi depressivi (MMSE > 16/30)
- 172 pazienti [90 né depressi né dementi, 54 depressi, 40 dementi, 27 depressi & dementi]
- Follow-up ad 1 anno

Depression associated to dementia impact on 1-year survival in elderly patients after hip fracture



	Unadjusted	Adjusted			
	B	B	HR	95% CI	p
No depression no dementia	0	0	1.00	Reference	
Depression (n=54)	1.4	1.7	5.3	1.0 to 29.3	.06
Dementia (n=40)	1.2	1.2	3.4	0.5 to 23.3	.20
Depression and dementia (n=27)	2.4	2.2	8.7	1.5 to 48.5	.01

Summarizing results

- La depressione notoriamente incrementa la mortalità mediante meccanismi patogenetici noti (tono cardiaco autonomico, asse ipotalamico pituitario, attivazione piastrinica, livelli anomali di catecolamine); da altri è considerata marker di frailty
- La demenza aumenta il rischio di morte attraverso infezioni e ridotti meccanismi adattativi
- Depressione e demenza hanno un effetto additivo (con meccanismi patogenetici che agiscono in modo sinergico) sulla mortalità ad 1 anno (apatia?)

Conclusioni

- Depressione e demenza coesistono molto spesso
- Sembrerebbe esistere una relazione molto forte tra depressione e demenza allorquando compaiano in tempi ravvicinati
- L′importanza di un ruolo prodromico e/o causativo della depressione non deve essere sottovalutato
- I criteri per valutare la depressione nel soggetto con decadimento cognitivo sono differenti da quelli comunemente utilizzati
- Depressione e demenza sembrano avere un ruolo additivo nell′aumentare il rischio di mortalità in pazienti con frattura di femore