



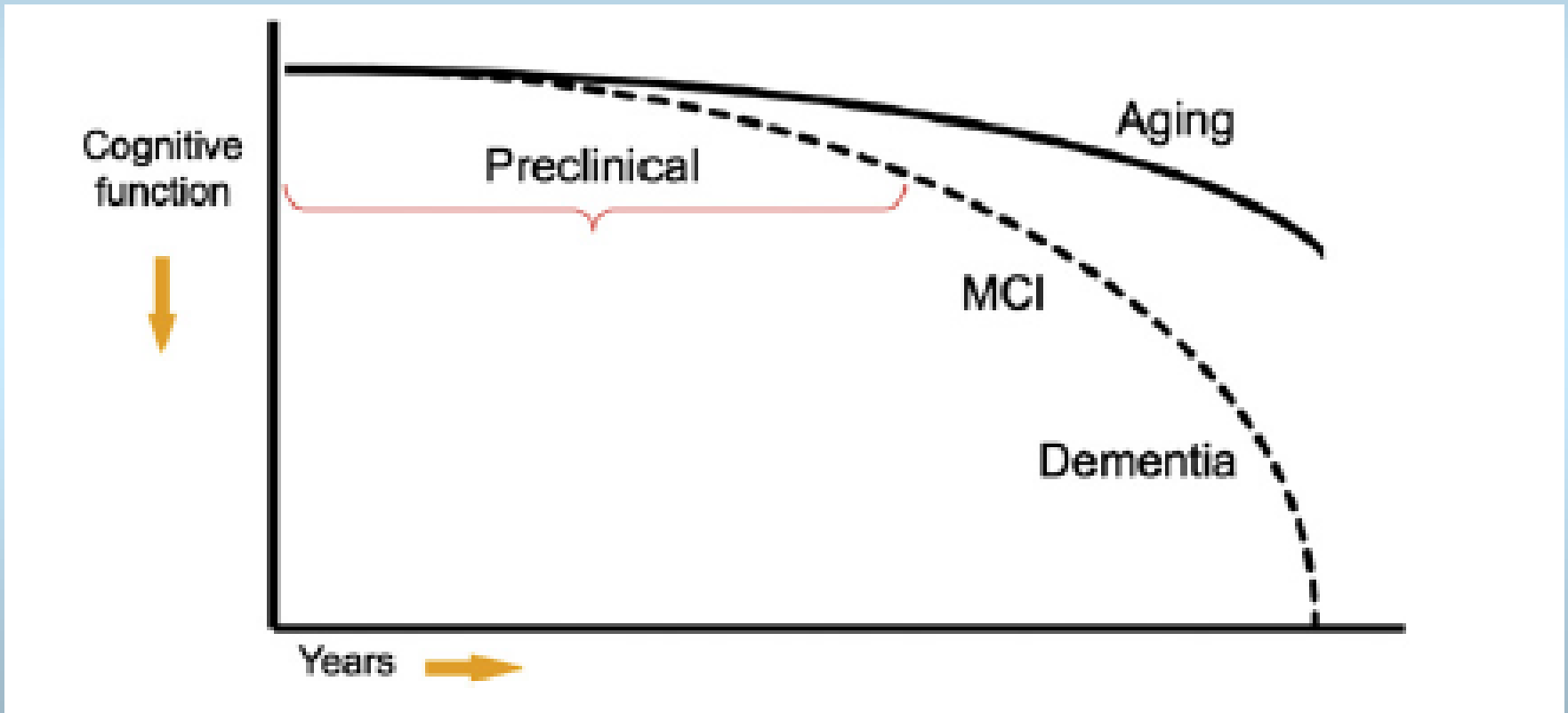
Risultati preliminari sul cortisolo e il BDNF come marcatori biologici per le funzioni cognitive ed i disturbi neuropsichiatrici degli anziani

A Martocchia, M Curto**, F Comite*, S Scaccianoce***,
F Nicoletti***, P Girardi**, P Falaschi**

*Unità di *Geriatrica, **Psichiatria, ***Farmacologia
Sapienza Università di Roma*



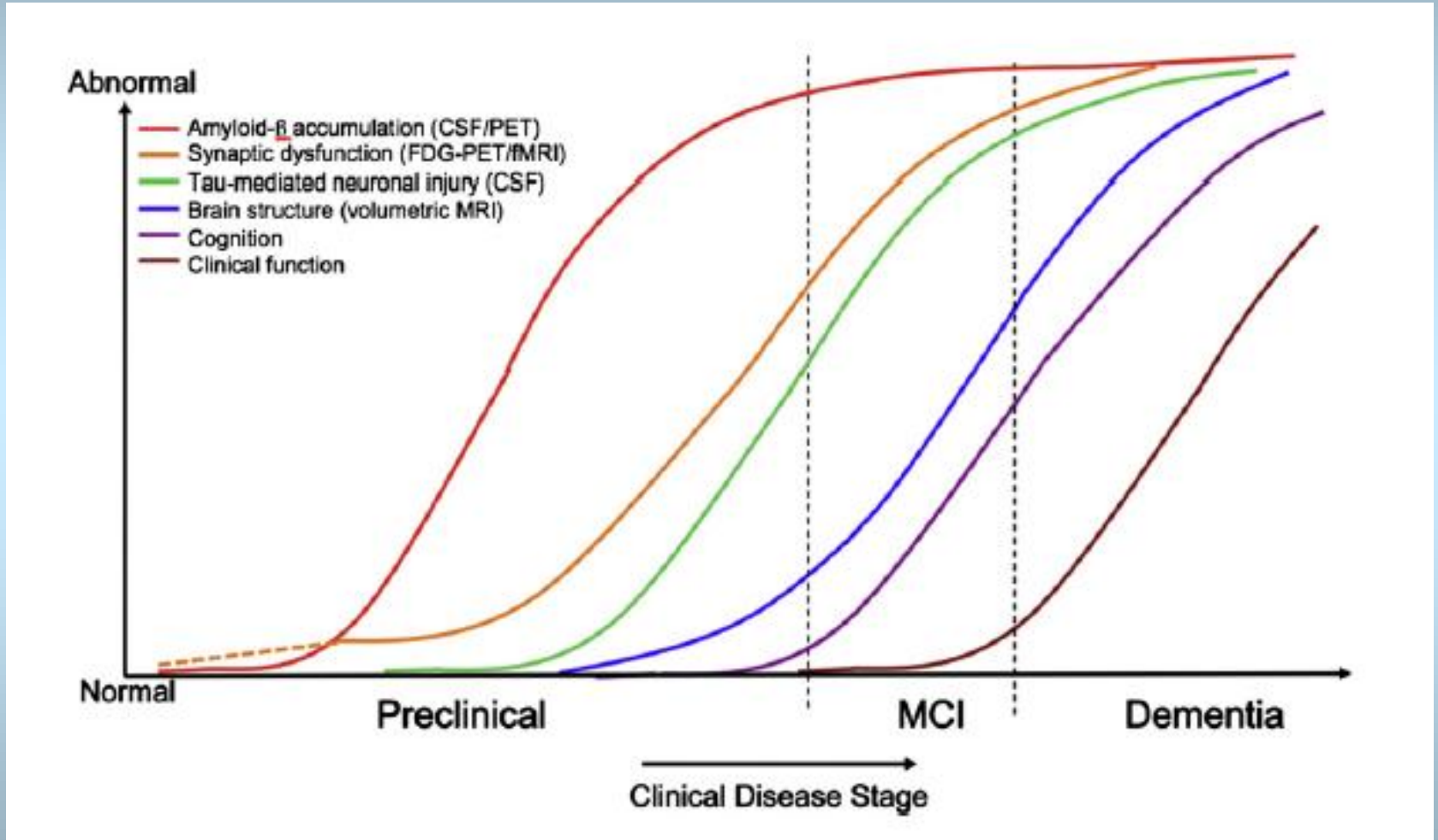
The continuum of Alzheimer's disease



(from Sperling RA et al., 2011)



Hypothetical model of dynamic biomarkers of the AD



(from Sperling RA et al., 2011)



POSSIBILI ASSOCIAZIONI TRA DEMENZA E DEPRESSIONE

Pseudodemenza (il paziente sembra demente, invece è depresso)

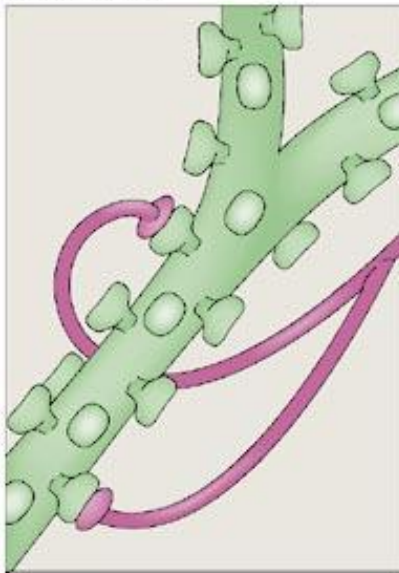
Depressione con secondaria demenza (inizia depressione e poi demenza)

Pseudodepressione (il paziente sembra depresso, invece è demente)

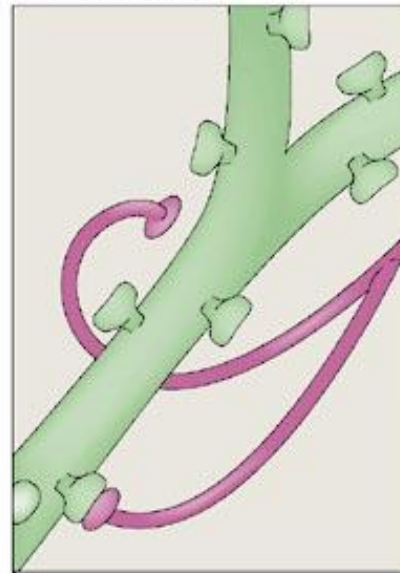
Demenza con secondaria depressione (inizia demenza e poi depressione)



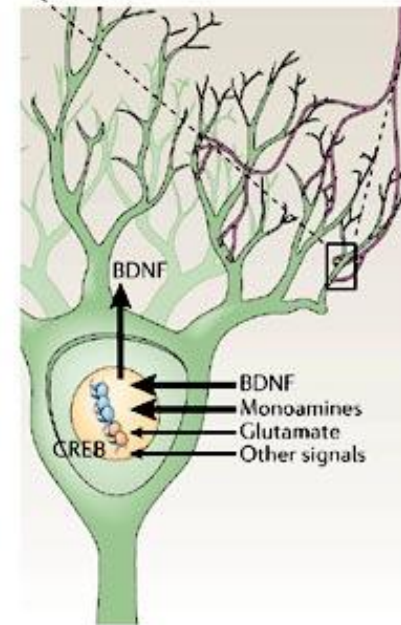
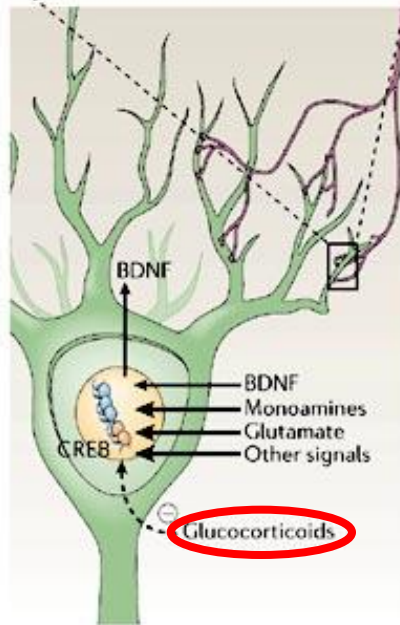
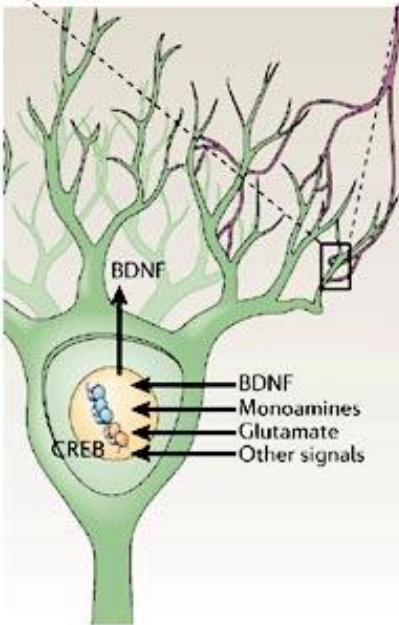
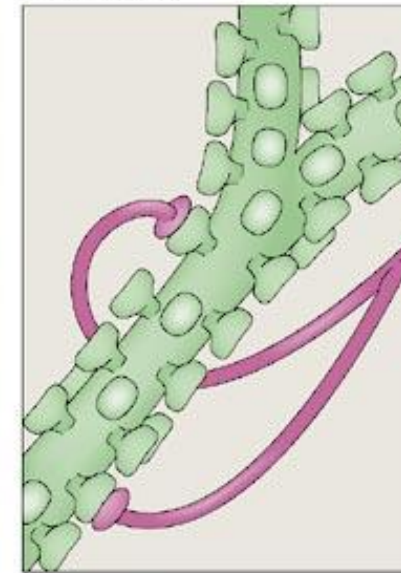
a Normal state



b Depressed state



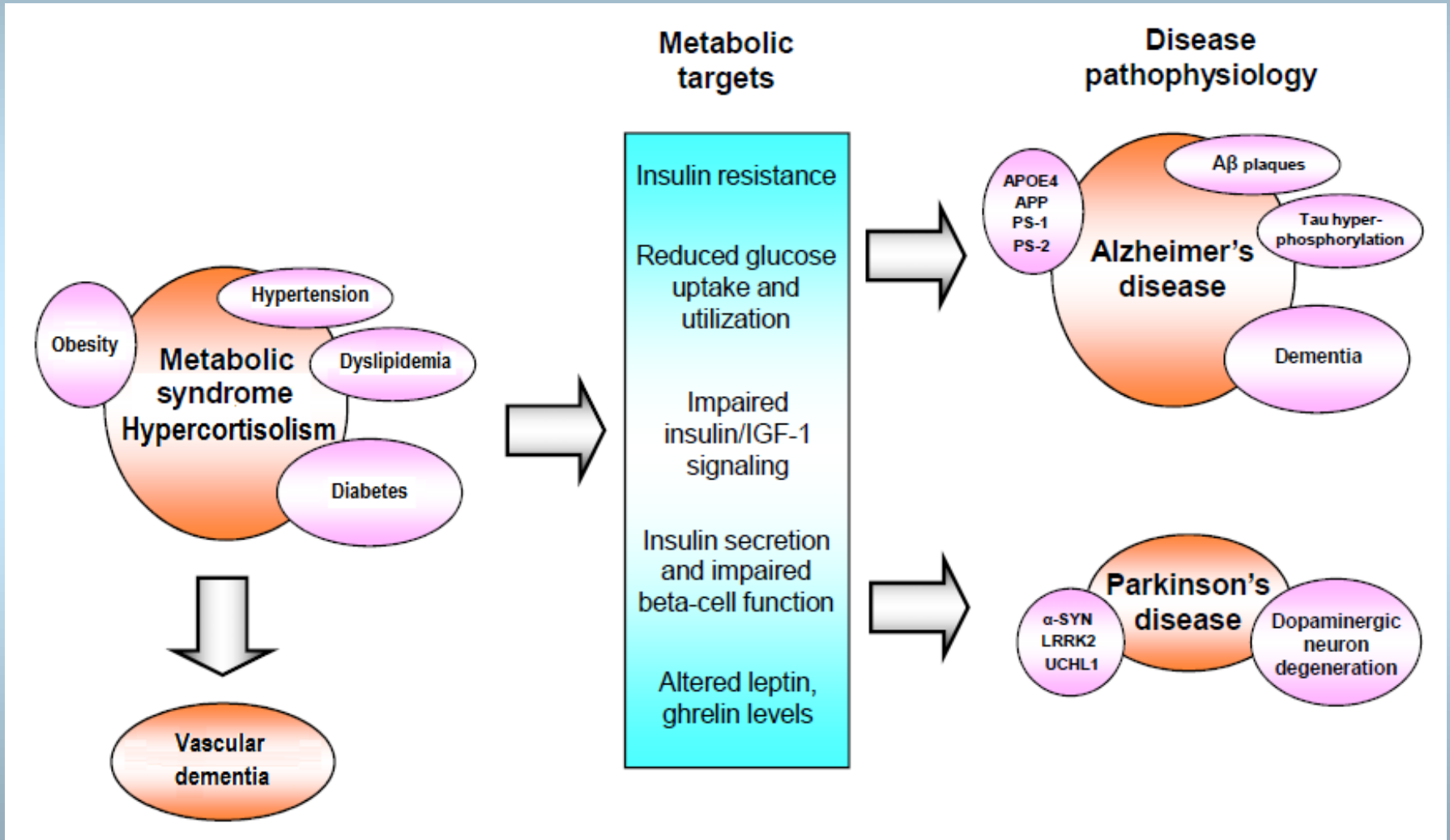
c Treated state



Neurone piramidale
ippocampale



The relationship between metabolic dysfunction, neurodegenerative diseases and vascular dementia





Brain-derived neurotrophic factor (BDNF)

It is a 13-kDa protein, member of the family of neurotrophins.

Besides its well-established roles in neuronal development, neuronal maintenance and survival as well as promoting synaptic plasticity, BDNF also plays a considerable role in regulating global metabolic function.

BDNF deficiency in rodents leads to hyperphagia, obesity, hyperinsulinemia and hyperleptinemia. BDNF deficiency in humans can lead to metabolic dysfunction.

BDNF signaling has been shown to be impaired in AD; studies have demonstrated low brain BDNF mRNA expression in hippocampus, neocortex and nucleus basalis of Meynert.

BDNF was found to be a major inducer of SORLA (sorting protein-related receptor with A-type repeats) gene transcription that regulates APP trafficking and processing into A β

Circulating plasma BDNF levels have been shown to associate with multiple cardiovascular markers of age-related pathophysiology.

It is therefore possible that a gradual decrease in BDNF levels may contribute to the increase in the risk of developing AD with advancing age.



Linear regression analysis of plasma BDNF and metabolic and cardiovascular risk factors, in the BLSA cohort

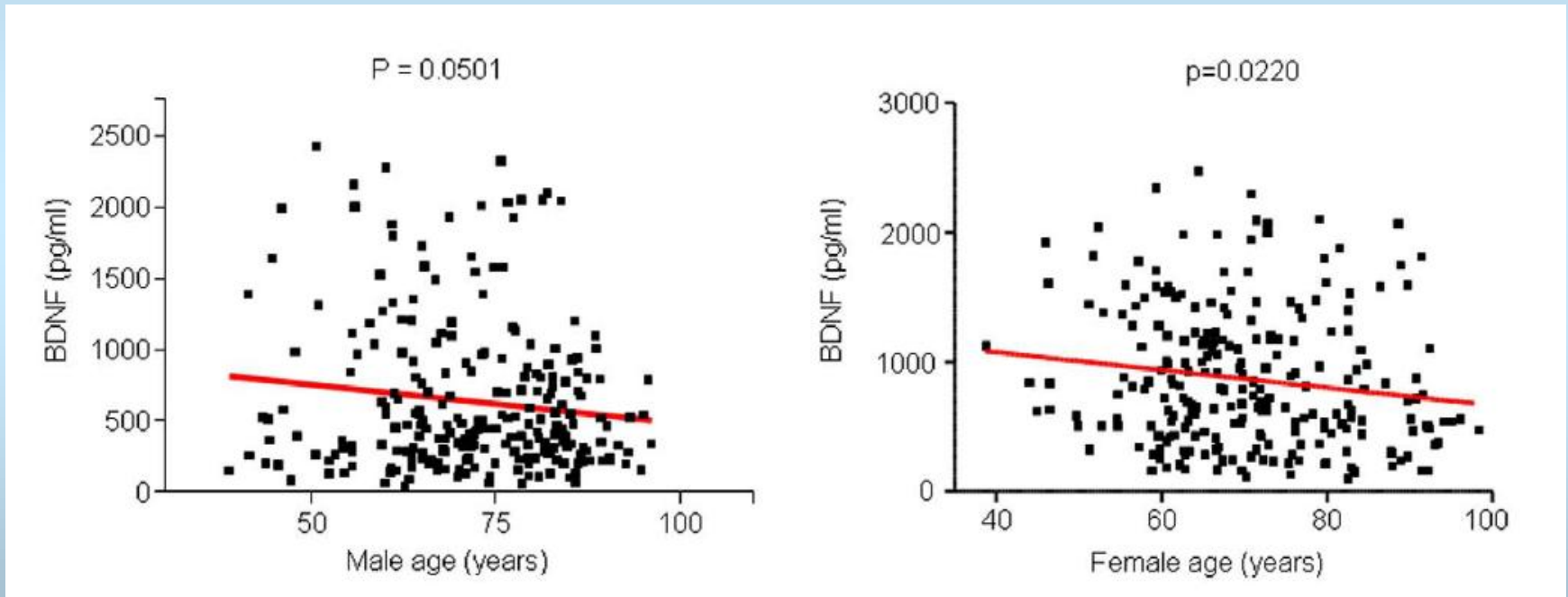
Variable	p-value	F value	DFn, DFd	R ²
Male				
Diastolic blood pressure	0.0300	4.765	1.000, 237.0	0.01971
Triglycerides	0.0289	4.834	1.000, 235.0	0.02016
Bioavailable Testosterone	0.0443	4.092	1.000, 229.0	0.01755
SHBG	0.0150	6.037	1.000, 167.0	0.03489
FT3	0.0053	7.932	1.000, 229.0	0.03348
Age	0.0501	3.878	1.000, 242.0	0.01577
Adiponectin	0.0137	6.242	1.000, 128.0	0.04650
Glucose-120	0.0460	4.037	1.000, 182.0	0.02170
Female				
Diastolic blood pressure	0.0486	3.930	1.000, 232.0	0.01666
LDL	0.0139	6.142	1.000, 227.0	0.02634
Cholesterol	0.0040	8.455	1.000, 234.0	0.03487
Folate	0.0396	4.285	1.000, 223.0	0.01885
Fat mass	0.0490	3.922	1.000, 211.0	0.01825
BMI	0.0396	4.282	1.000, 228.0	0.01843

SHBG, sex-hormone binding globulin; FT3, Free triiodo-thyronine T3; LDL, low density lipoprotein; BMI, bodymass index.
doi:10.1371/journal.pone.0010099.t002

(modified from
Golden E et al., 2010)



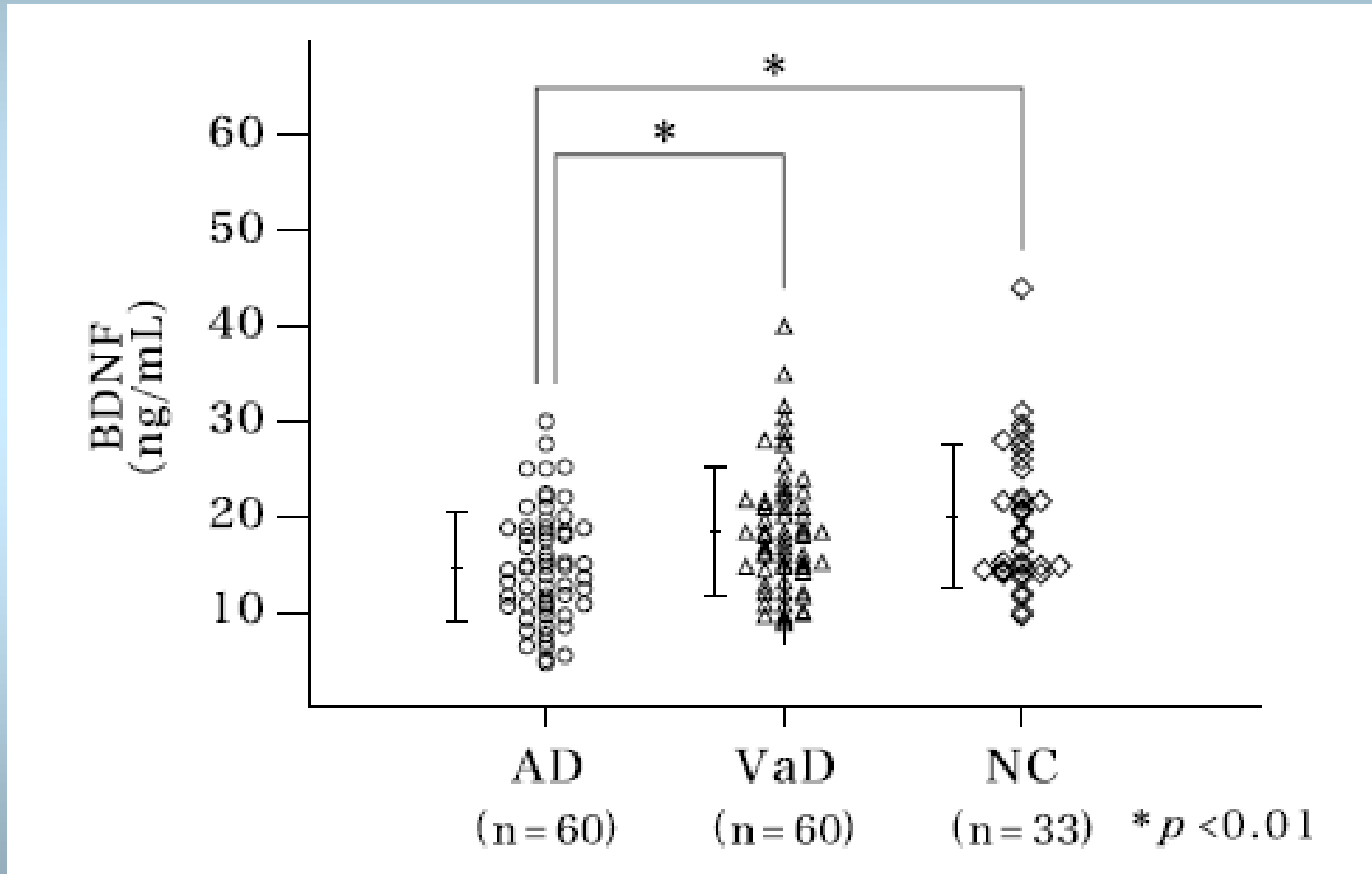
Plasma BDNF, gender and age



(modified from Golden E et al., 2010)



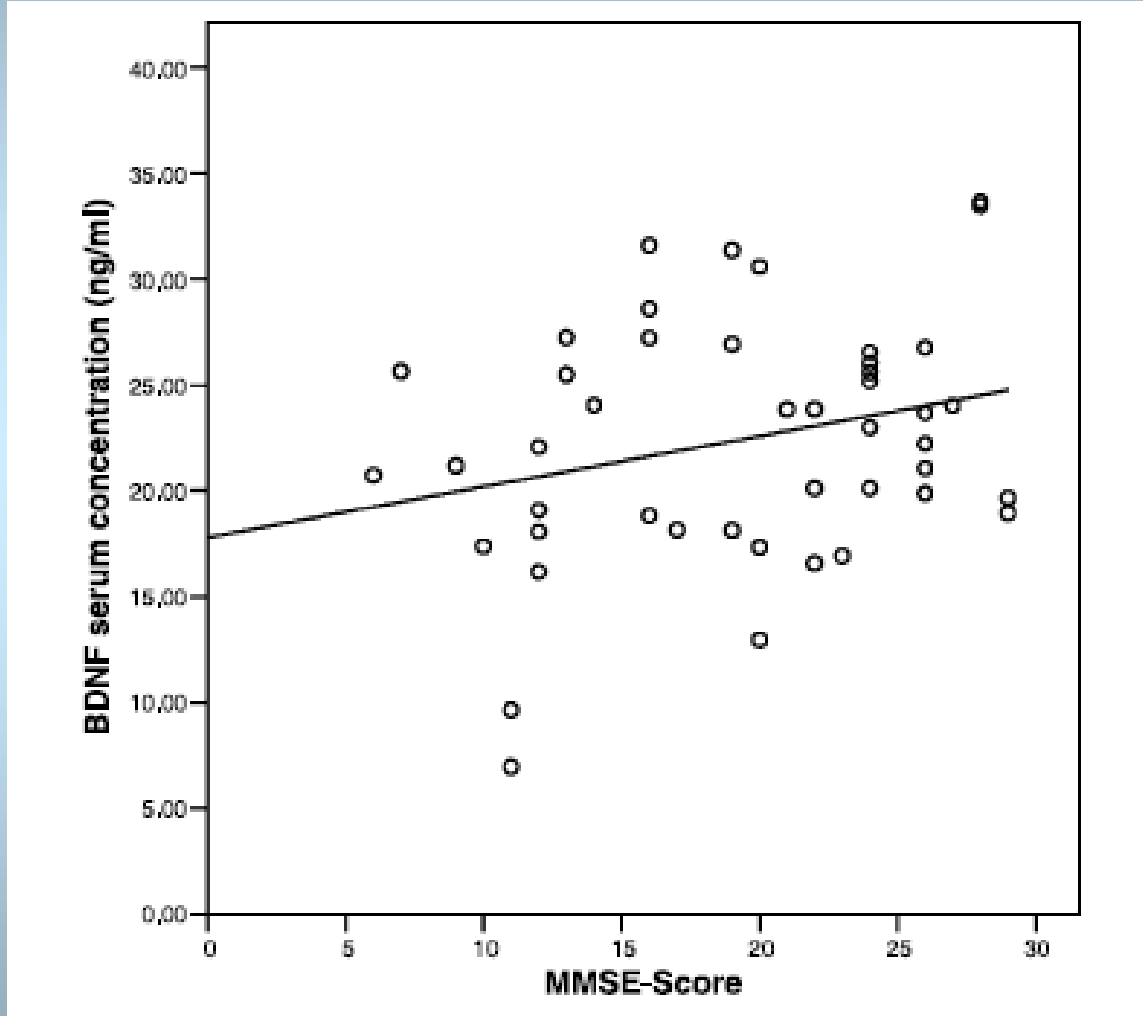
Serum BDNF in patients with Alzheimer's disease (AD), vascular dementia (VaD) and the normal control subjects (NC) * $p < 0.01$



(from Yasutake C et al., 2006)



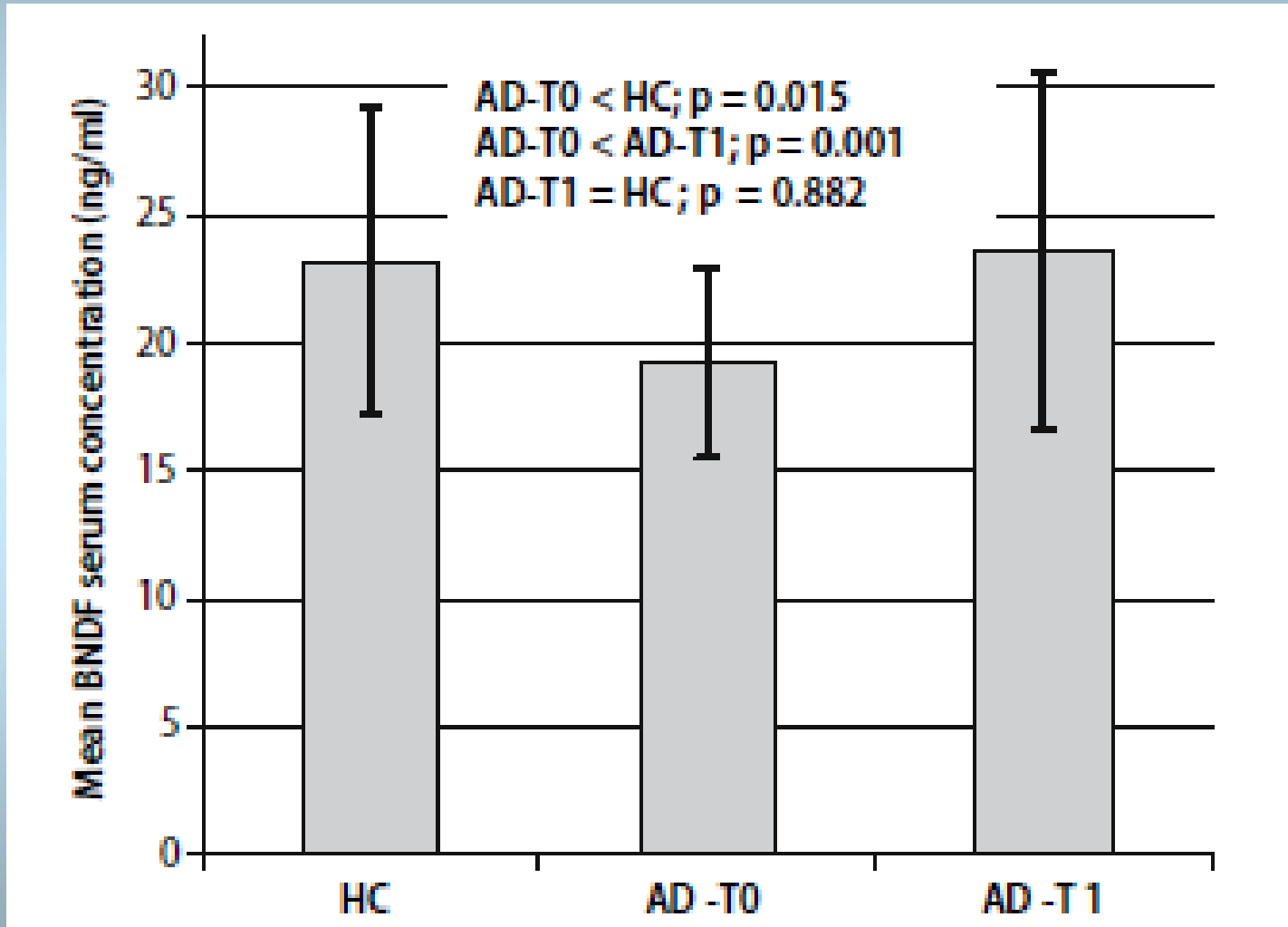
Correlation between BDNF and MMSE in AD patients ($r=0.486, p<0.0001$)



(from Laske C et al., 2006)



Serum BDNF of healthy controls (HC), Alzheimer's disease patients before treatment (AD-T0) and after 15 month of treatment with donepezil (AD-T1)



(from Leyhe T et al., 2007)



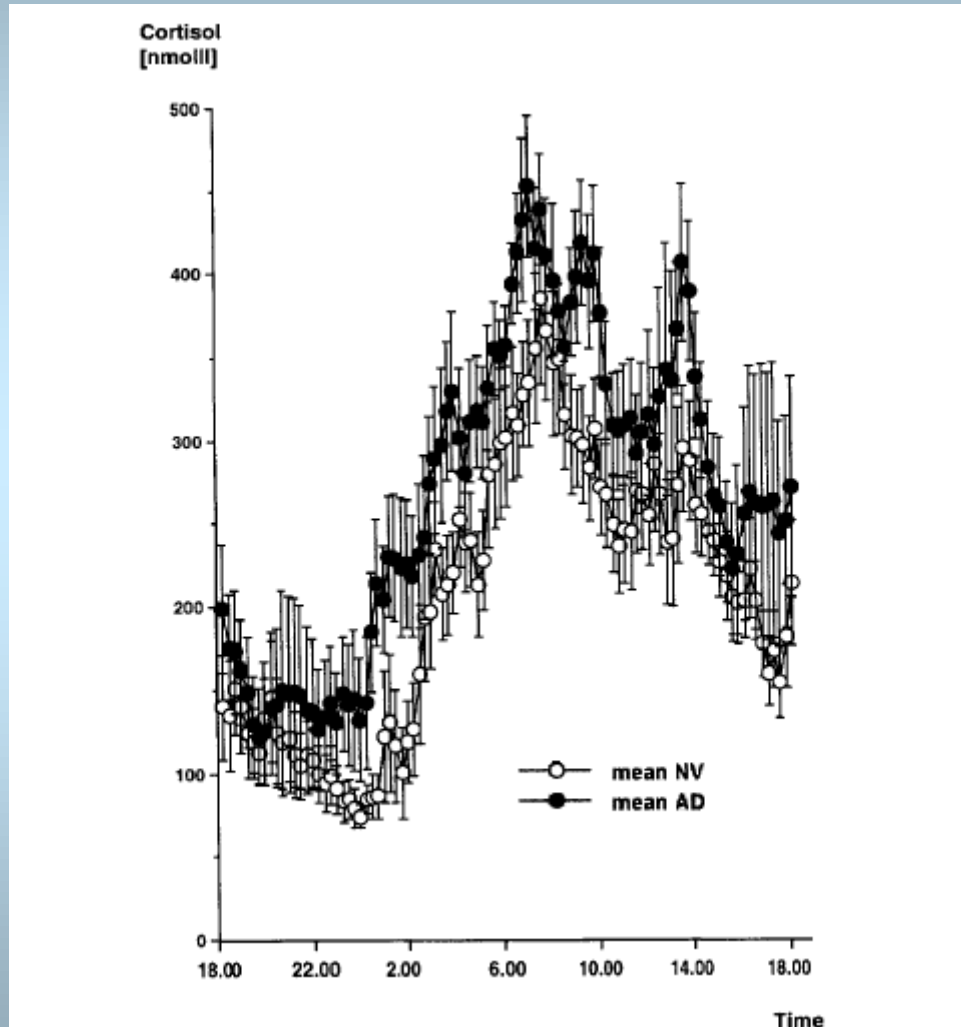
Med Hypotheses 2008, 71: 703-705.

Subclinical Cushing's syndrome is a potential cause of metabolic dementia and rapidly progressive Alzheimer-type dementia.

Guldiken S, Guldiken B



Mean 24-h plasma cortisol concentration in normal volunteers (NV) and Alzheimer's disease (AD)



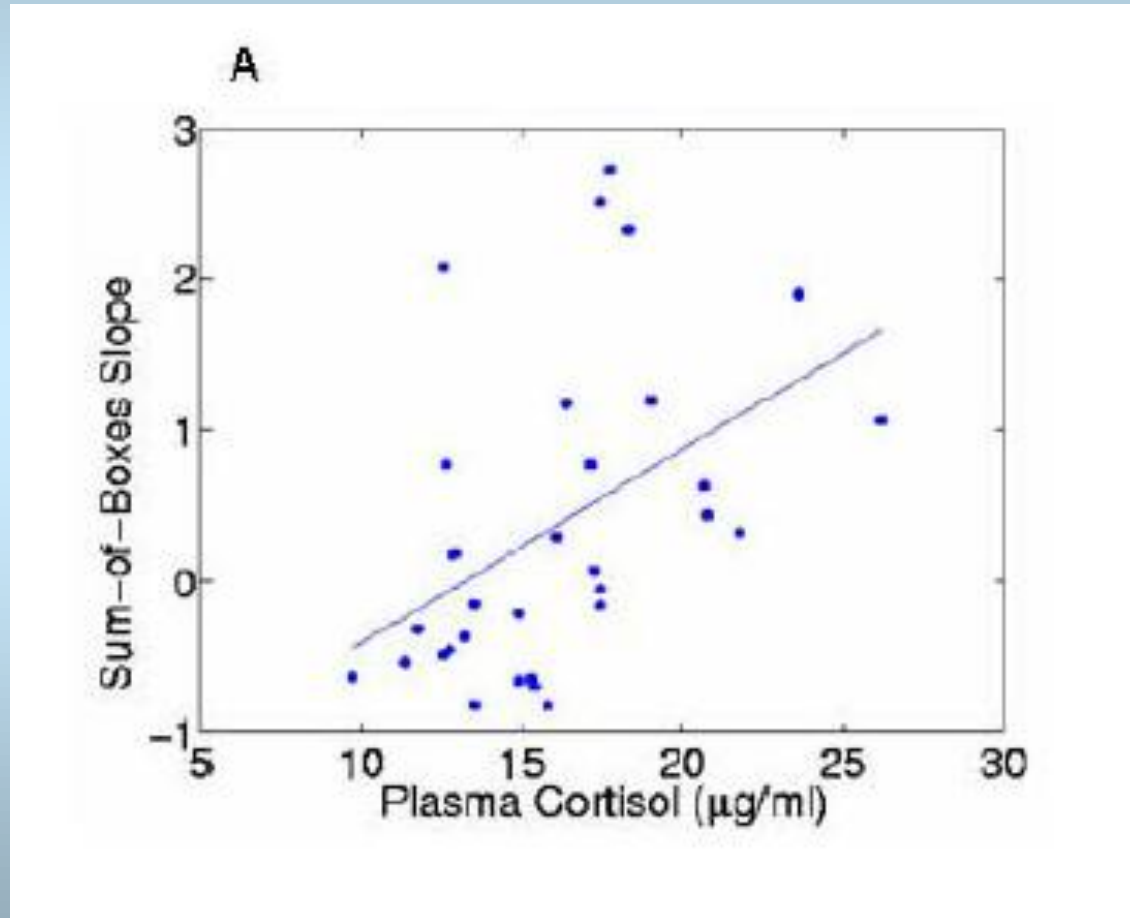
(from Hartmann A et al., 1997)



Correlations between plasma cortisol and measures of disease progression (4 years) in subjects with very mild (CDR=0.5) to mild (CDR=1) AD

CDR rates the cognitive impairment on a 5 point scale (0, 0.5, 1, 2, 3 - none to severe) in 6 domains or “boxes”:

- 1) memory,
- 2) orientation,
- 3) judgment and problem solving,
- 4) function in the community,
- 5) function at home and hobby
- 6) personal care.

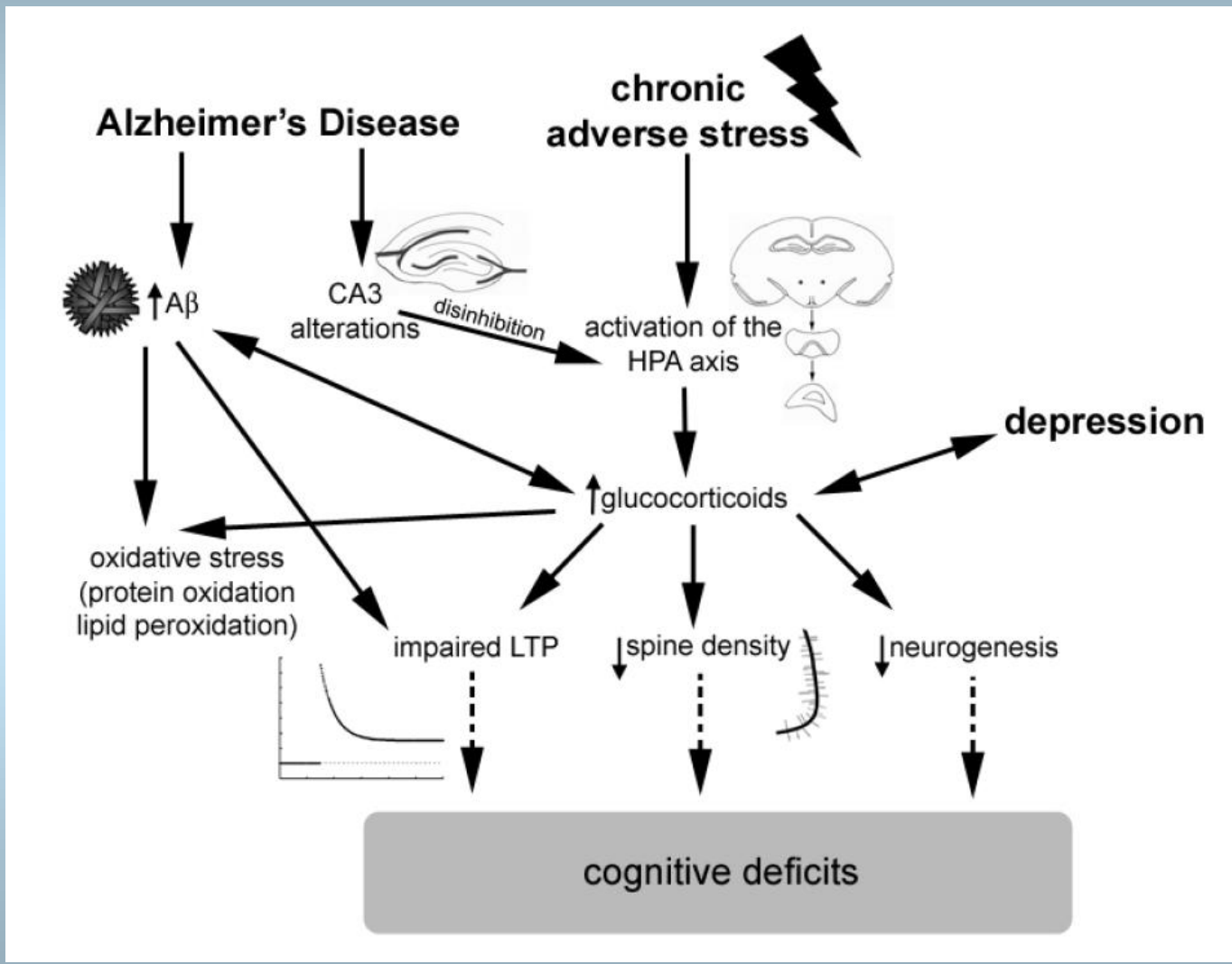


CDR score of 0 indicates no dementia and CDR scores of 0.5, 1, 2, 3 indicate very mild, mild, moderate and severe dementia, respectively. Box scores can be totaled to yield a sum-of-boxes total score that ranges from 0 (0x6) to 18 (3x6).

(modified from Csernansky JG al., 2006)



Pathways through which AD and chronic adverse stress potentially lead to cognitive impairments



(from Rothman SM, Mattson MP 2010)



Glucocorticoid-related genetic susceptibility for Alzheimer's disease

A rare haplotype in the 5' regulatory region of the gene encoding 11 β -hydroxysteroid dehydrogenase type 1 (HSD11B1) was associated with a 6-fold increased risk for sporadic AD

(from De Quervain DJF et al., 2004)



Scopo dello studio

Valutare il ruolo del BDNF e del cortisolo nella malattia di Alzheimer (AD), nella depressione (D) o in AD e D in comorbidità rispetto ad un gruppo di controllo



Materiali e metodi

Sono stati valutati:

- pazienti affetti da AD (n=18) probabile secondo NINCDS-ADRDA,
- pazienti affetti da D (n=17) secondo i criteri del DSM-IV,
- pazienti affetti da AD e D (n=17) in comorbidità,
- soggetti anziani (>65 anni) (n=18) di controllo,
- soggetti giovani (n=18) di controllo.

Sono stati esclusi i pazienti in trattamento con farmaci antidepressivi o inibitori delle colinesterasi/memantina.

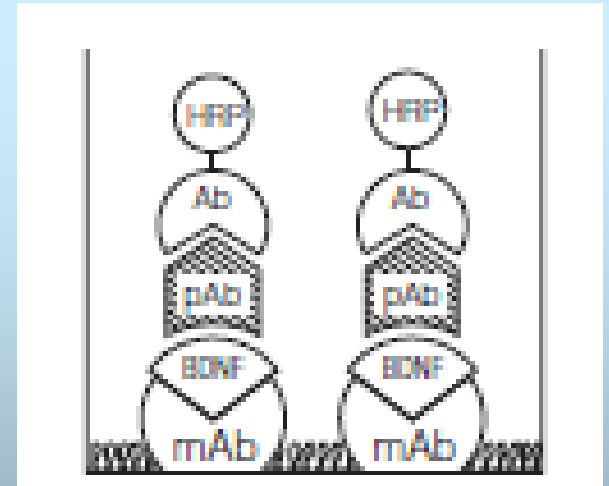


Materiali e metodi

Ogni paziente è stato sottoposto ad una valutazione multidimensionale comprensiva di Mini Mental State Examination (MMSE), Geriatric Depression Scale (GDS) o Cornell Scale (per la depressione in demenza, se $MMSE < 20$). I pazienti AD sono stati inclusi con $MMSE < 24$; i pazienti D sono stati inclusi con $GDS > 5$ o Cornell Scale > 10 .

Il BDNF ematico (h.8-9) è stato dosato con metodica ELISA (Promega). \longrightarrow

E' stata eseguita una raccolta urinaria frazionata (h.8-20 e h.20-8) per la misurazione del cortisolo notturno, standardizzato per l'escrezione della creatinina.





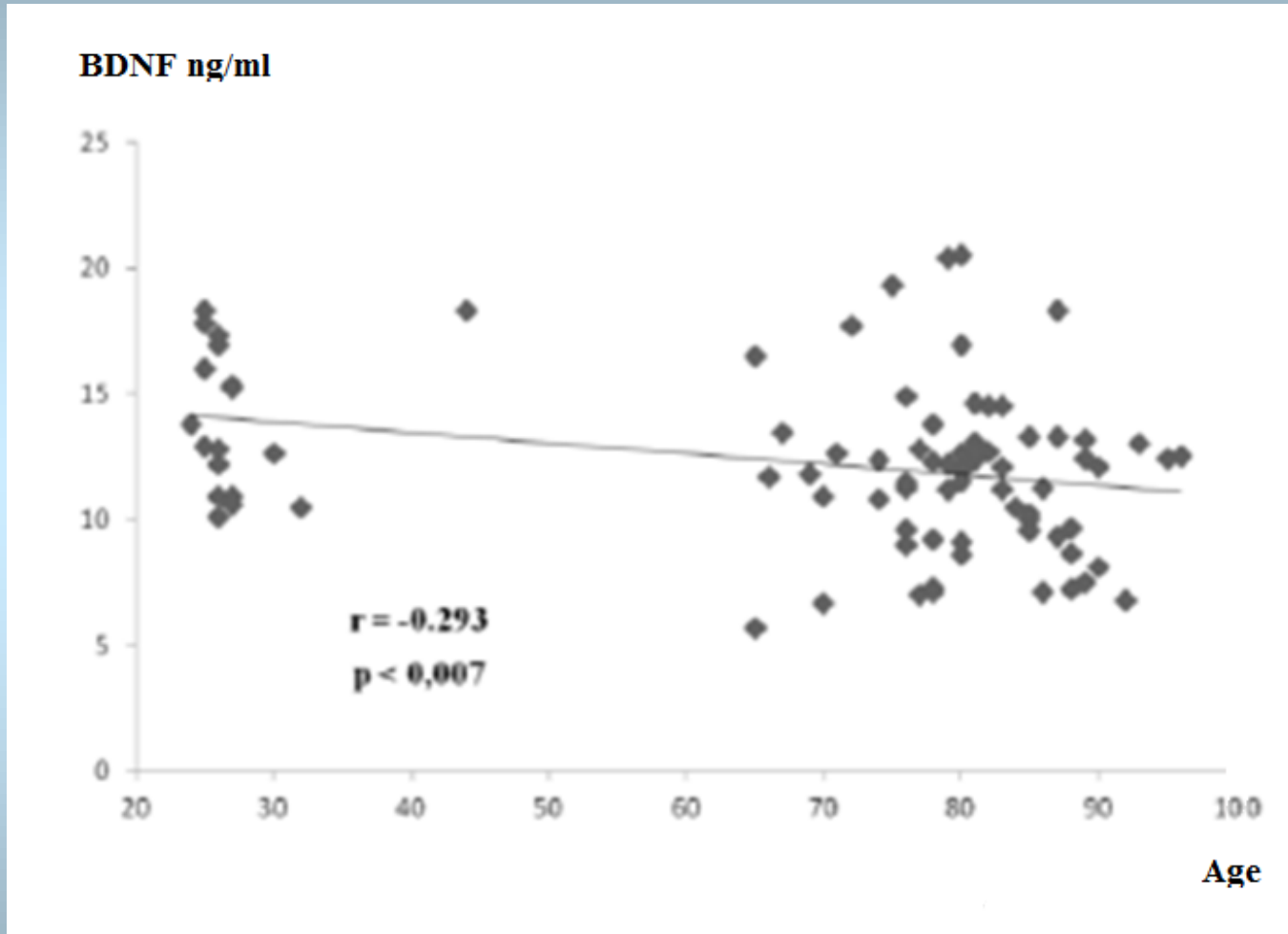
Risultati

	MA	D	MA e D	Controlli Anziani	Controlli Giovani
	(n=18)	(n=17)	(n=17)	(n=18)	(n=18)
Sesso(M/F)	3/17	5/11	5/13	15/4	9/9
Età (anni)	86,4±3,5	76,6±7,9	79,4±5,4	80,1±4,3	27,4±4,5
MMSE	11,3±9,3	25,5±3,2	18,2±6,2	28,3±1,2	30
GDS	4,2±1,5	8,6±2,6	9,3±1,7	1,4±1,2	0
BDNF(ng/ml)	10,1±2,5	12±3,3	11,7±,6	13,7±3,7	14±2,9

(Curto M, Martocchia A, Comite F, Scaccianoce S, Ferracuti S, Girardi P, Nicoletti F, Falaschi P, 2012)



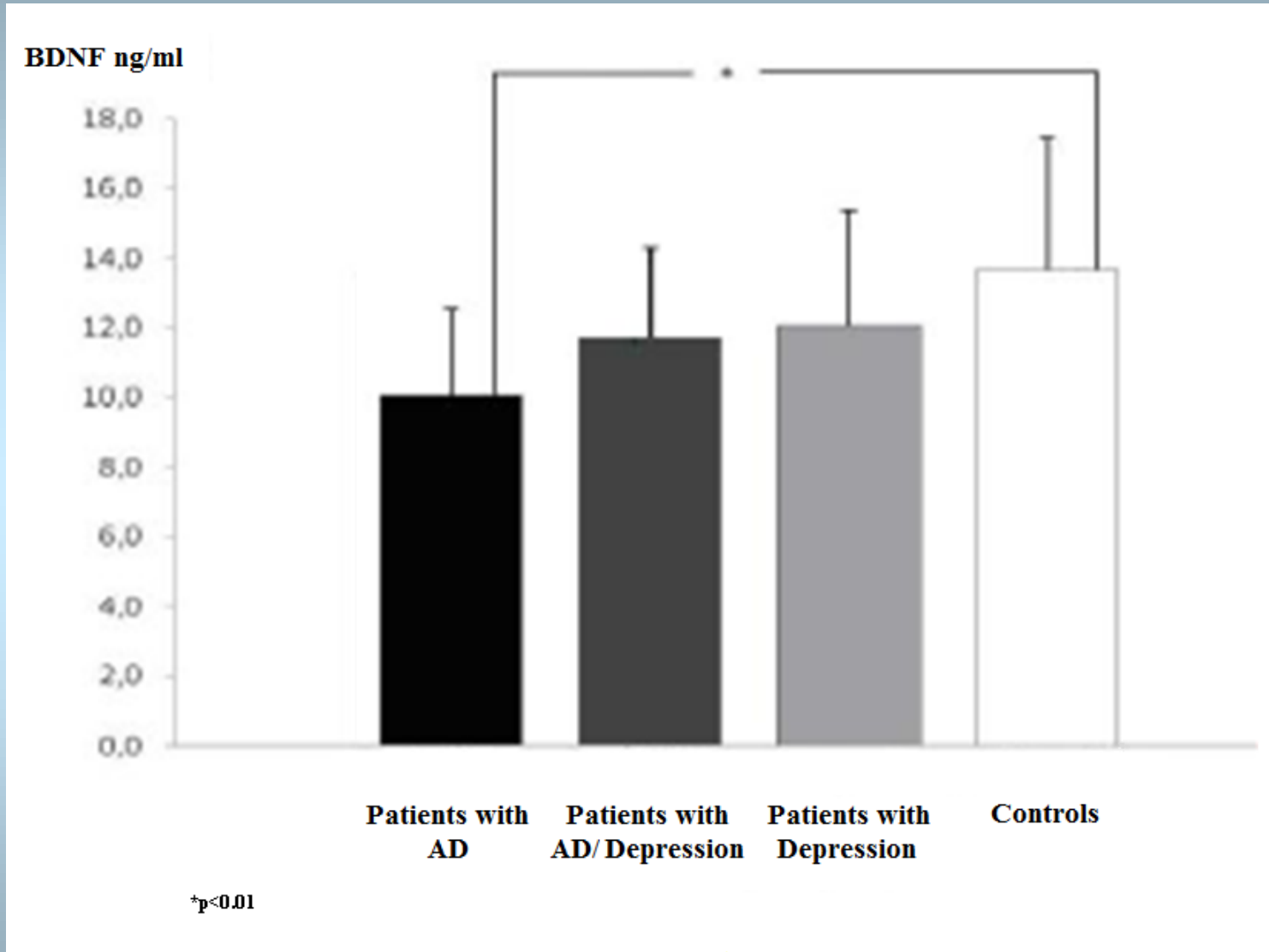
Correlazione fra BDNF ed età



(Curto M, Martocchia A, Comite F, Scaccianoce S, Ferracuti S, Girardi P, Nicoletti F, Falaschi P, 2012)



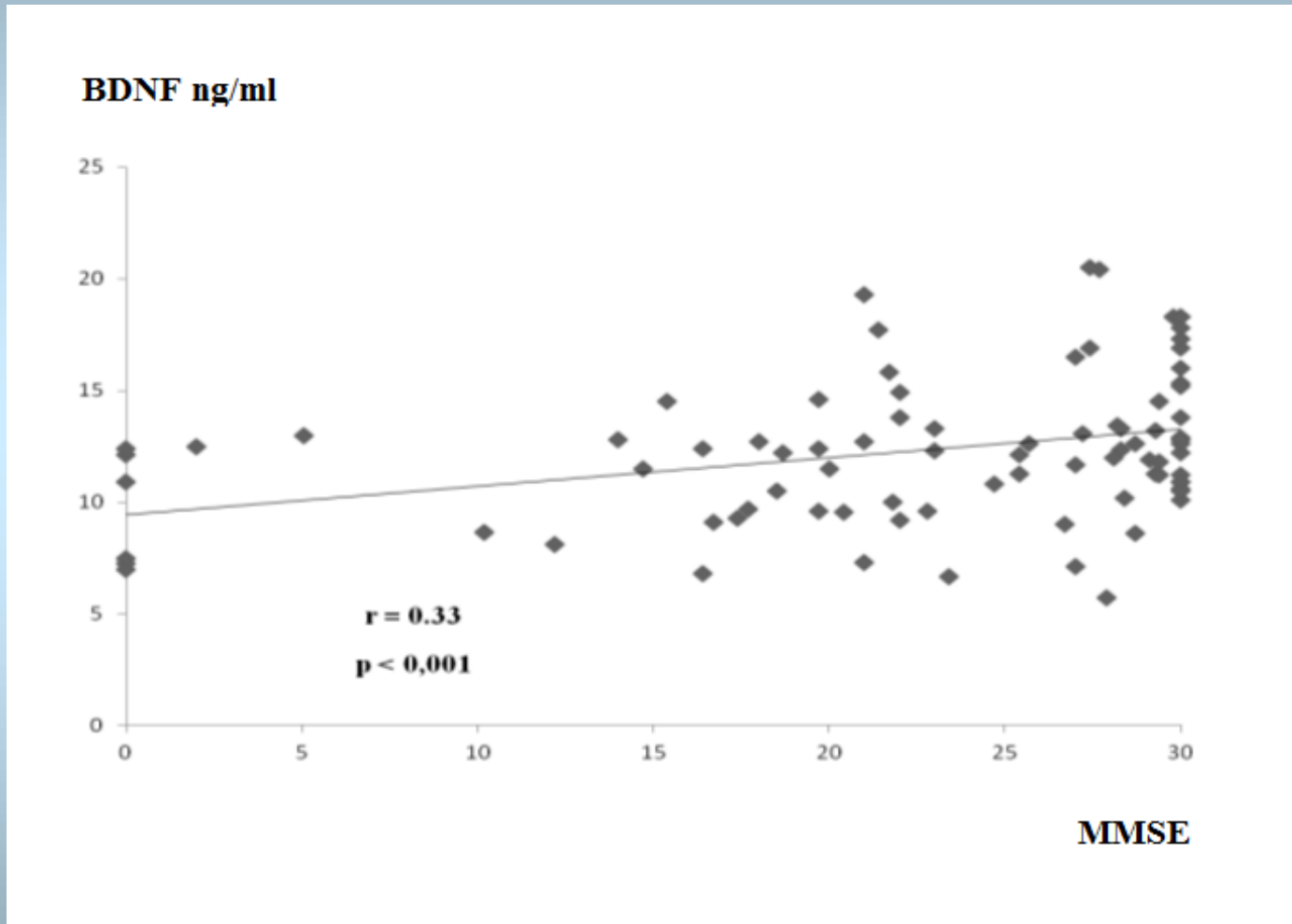
BDNF nei vari gruppi (controlli anziani)



(Curto M, Martocchia A, Comite F, Scaccianoce S, Ferracuti S, Girardi P, Nicoletti F, Falaschi P, 2012)



Correlazione fra BDNF e MMSE

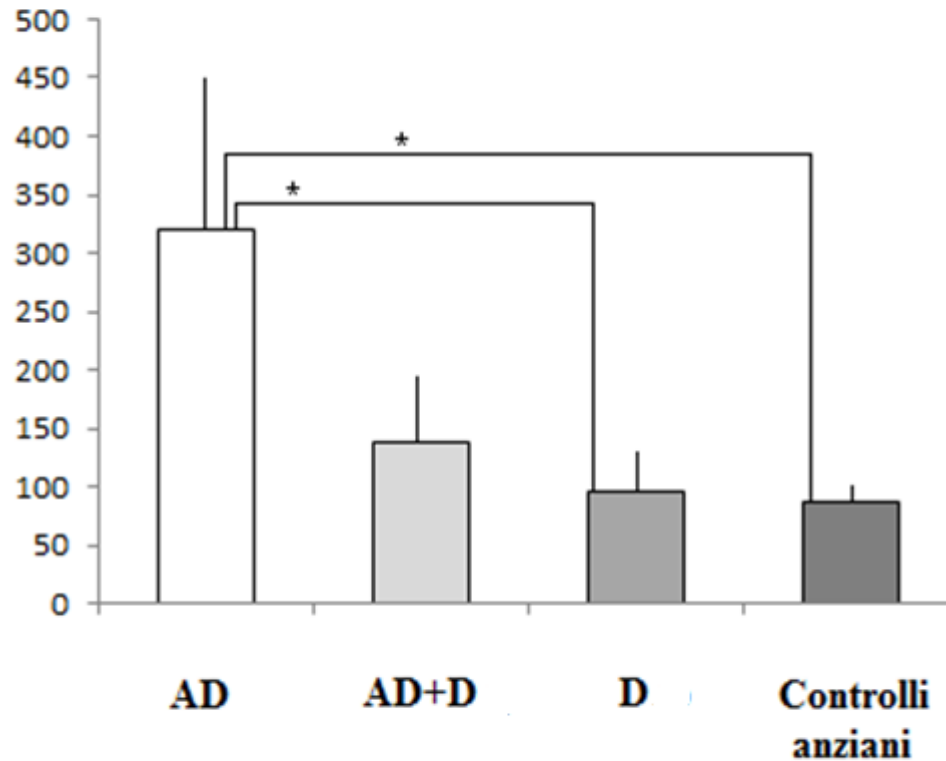


(Curto M, Martocchia A, Comite F, Scaccianoce S, Ferracuti S, Girardi P, Nicoletti F, Falaschi P, 2012)



Cortisolo urinario notturno nei vari gruppi (controlli anziani)

Cortisolo/creatinina urinaria (mcg/gr)

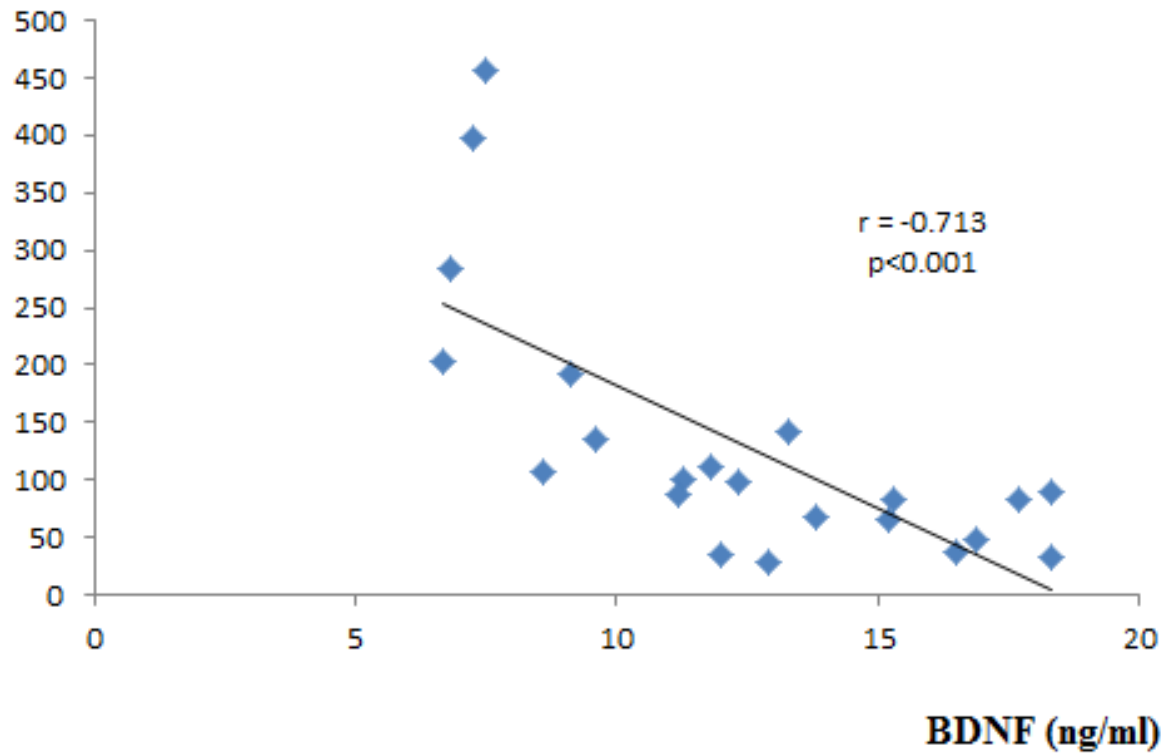


* $p < 0.025$



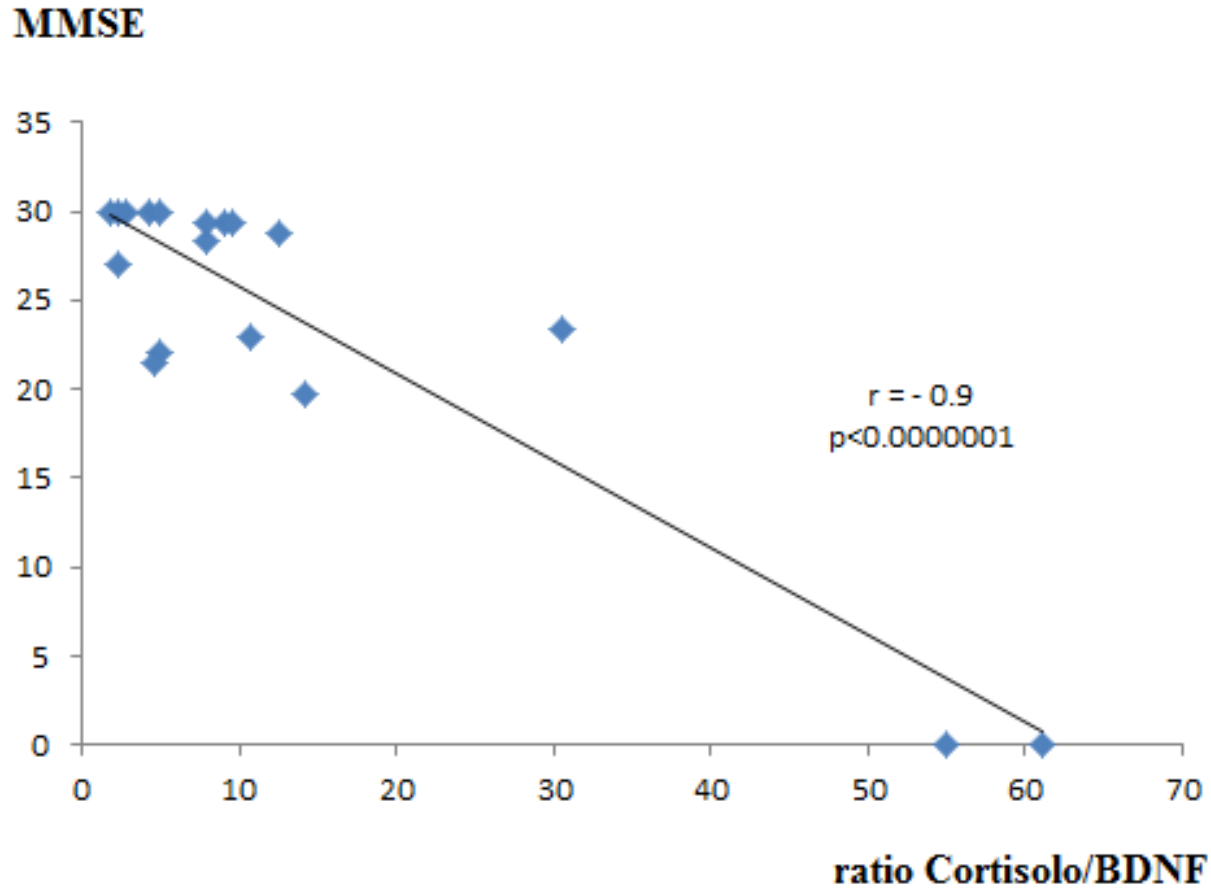
Correlazione tra cortisolo urinario e BDNF ematico

**Cortisolo/creatinina urinaria
(mcg/g)**





Correlazione tra MMSE e ratio cortisolo urinario/BDNF ematico





Conclusioni

Il cortisolo urinario ed il BDNF ematico sono candidati promettenti come marcatori biologici per la valutazione dei disturbi neuropsichiatrici e del declino cognitivo nei soggetti anziani.

Il loro impiego in associazione come rapporto (cortisolo urinario notturno standardizzato per creatinina urinaria/BDNF ematico) sembra migliorarne sensibilmente la correlazione con il MMSE.

