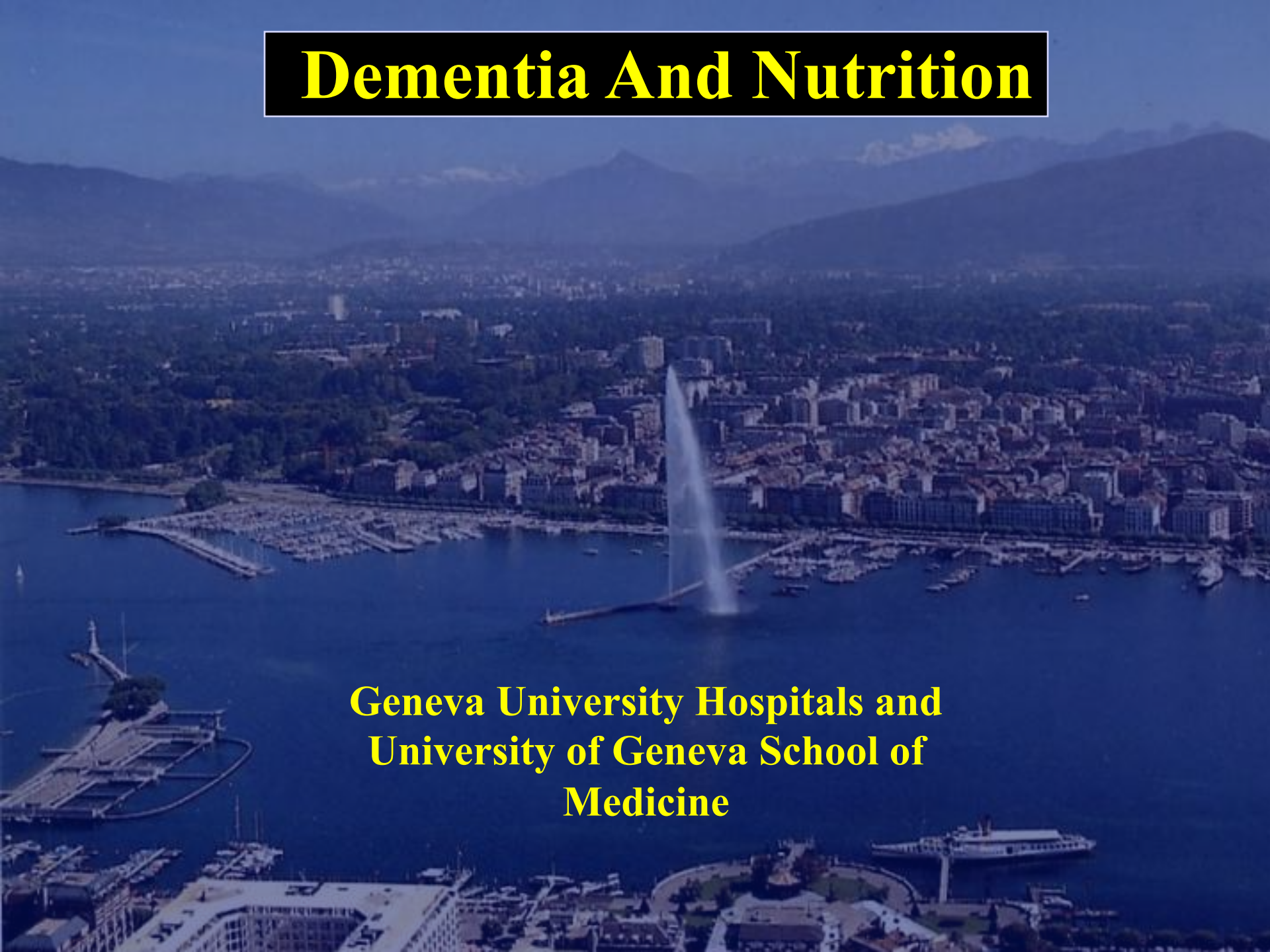
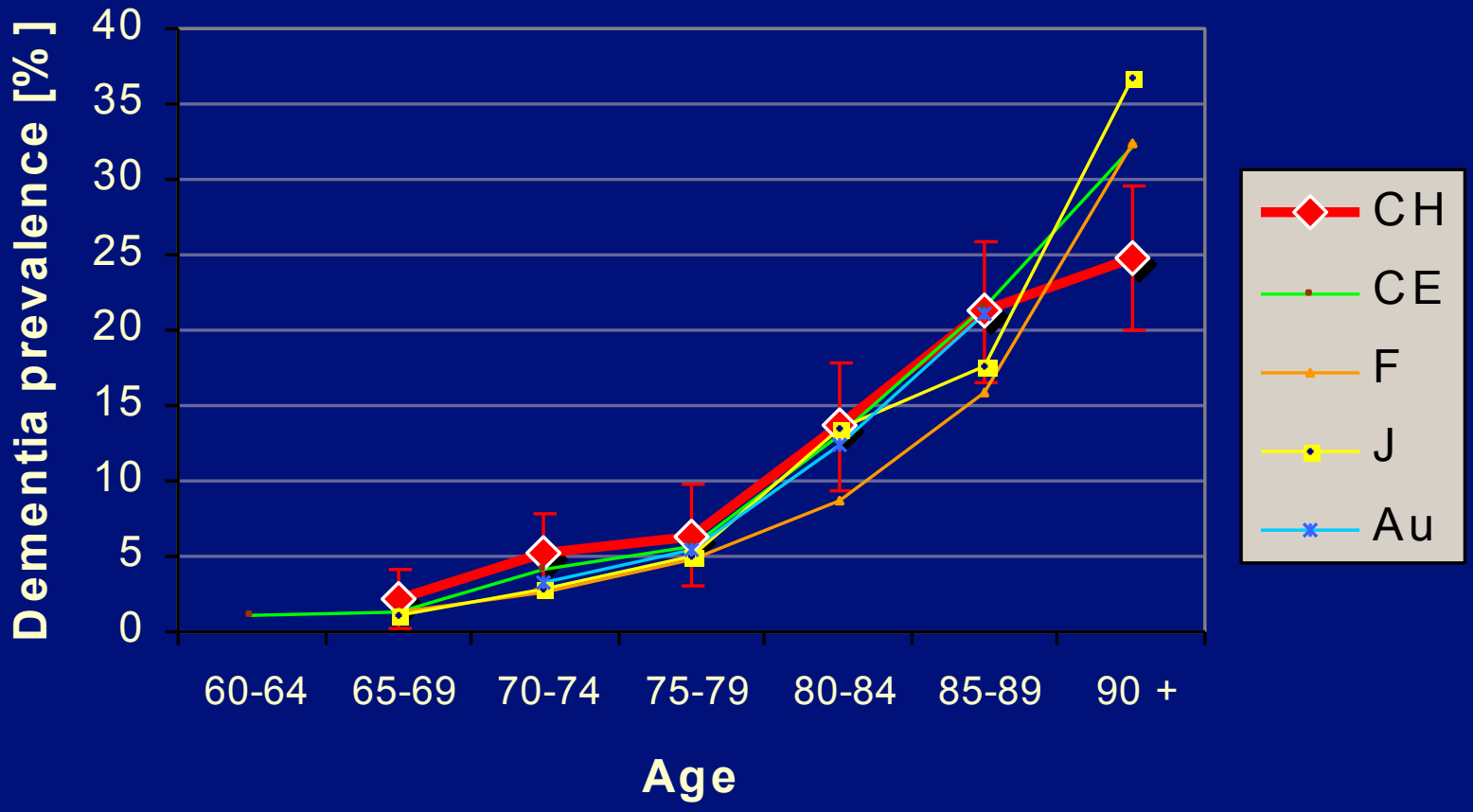
Dementia And Nutrition

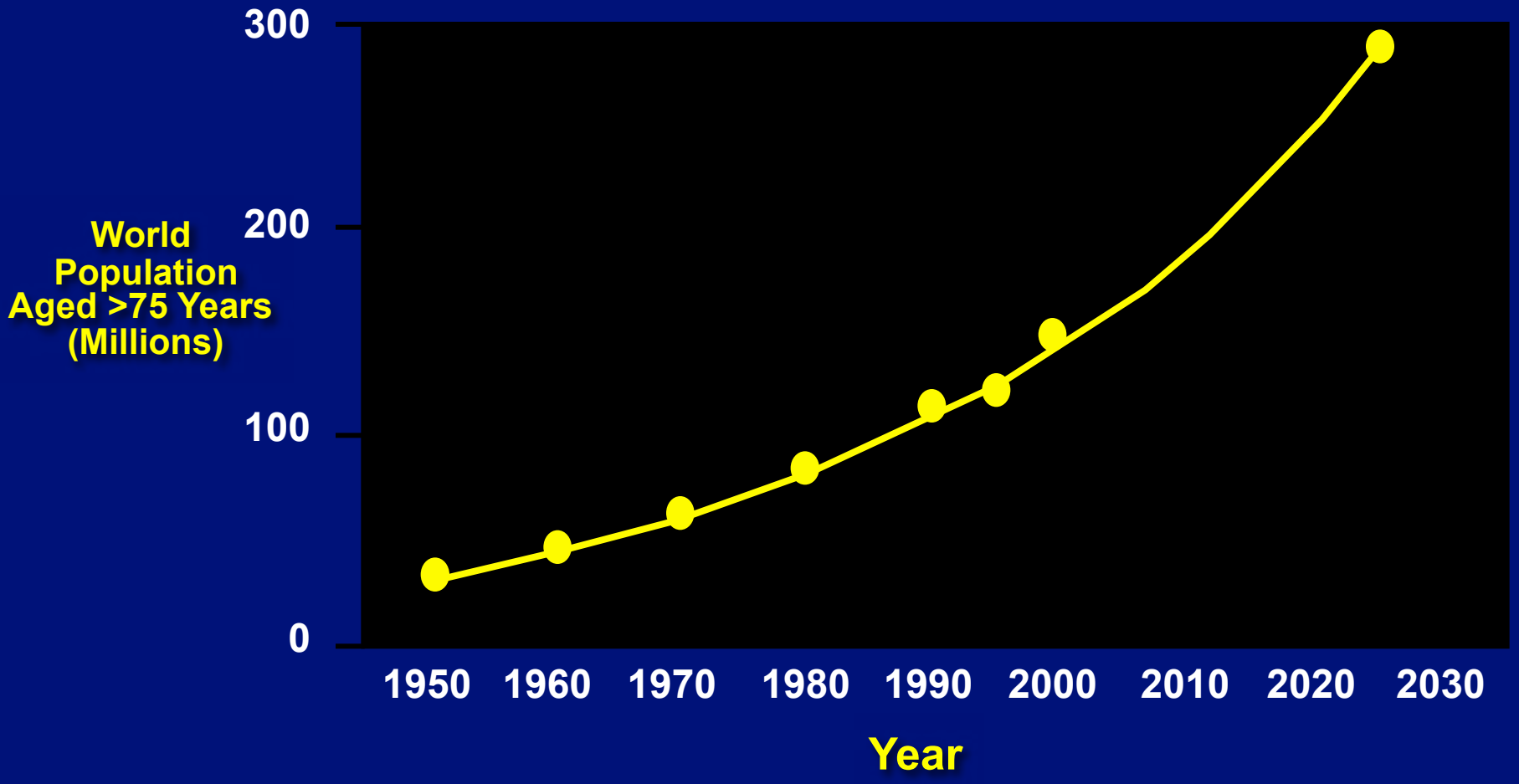


Geneva University Hospitals and
University of Geneva School of
Medicine

Prevalence of dementia



World Population Aging



Dementia
A Forgotten Diagnosis

- Screening and evaluation of 3954 patients, aged 60 + years, followed in a primary care clinic
  - Mild dementia 10,5%
  - Moderate to severe dementia 5,2%
- Cases recognized by the primary physician
  - Mild dementia 3,2%
  - Moderate to severe dementia 23,5%

Ann Int Med 1995;122:422

Dementia
A Forgotten Diagnosis

- **Individuals aged 64+ years living in Lieto, Finland. Screening and evaluation of 1260 people (82% participation)**
  - **112 patients with dementia identified**
- **Cases documented by the primary physician**
  - **Mild dementia 33%**
  - **Moderate dementia 46%**
  - **Severe dementia 73%**

Age Ageing 2003;32:606

Cognitive Deficits
Clues

- Decrease in activities/hobbies
- Difficulties keeping appointments
- Difficulties with IADL
  - Telephone
  - Public transport
  - Finances
  - Medication

Cognitive Deficits
Clues

- **Could nutritional status be an early clue to the development of dementia?**

Städt. Irren-Anstalt Frankfurt a. M.

No.

Aerztliche Acten

über

Auguste D geb: [illegible]

Alter: 51 Jahre. Religion: [illegible]

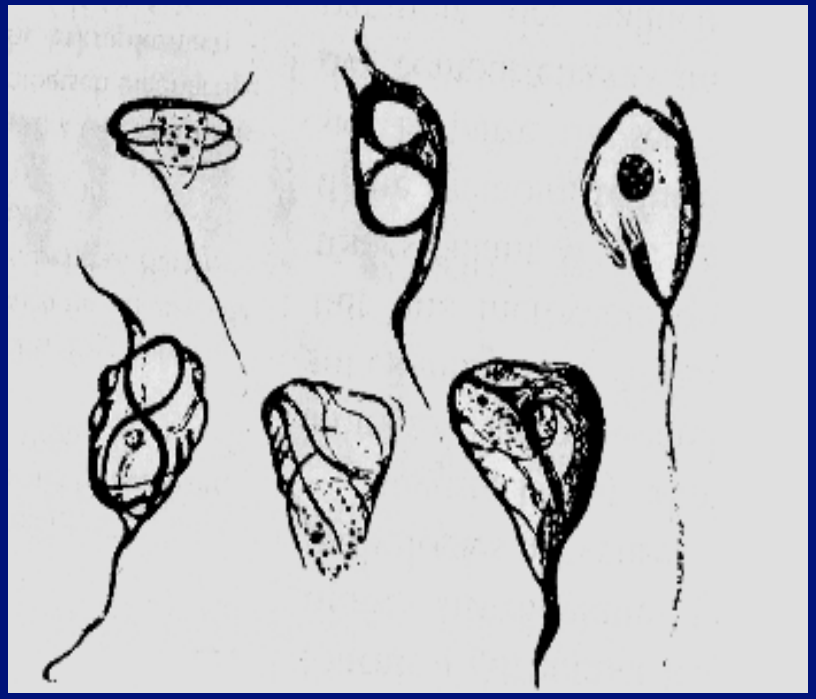
Lfd. No.	Aufgenommen	Entlassen
1.	am 25. November 1901	am
2.		
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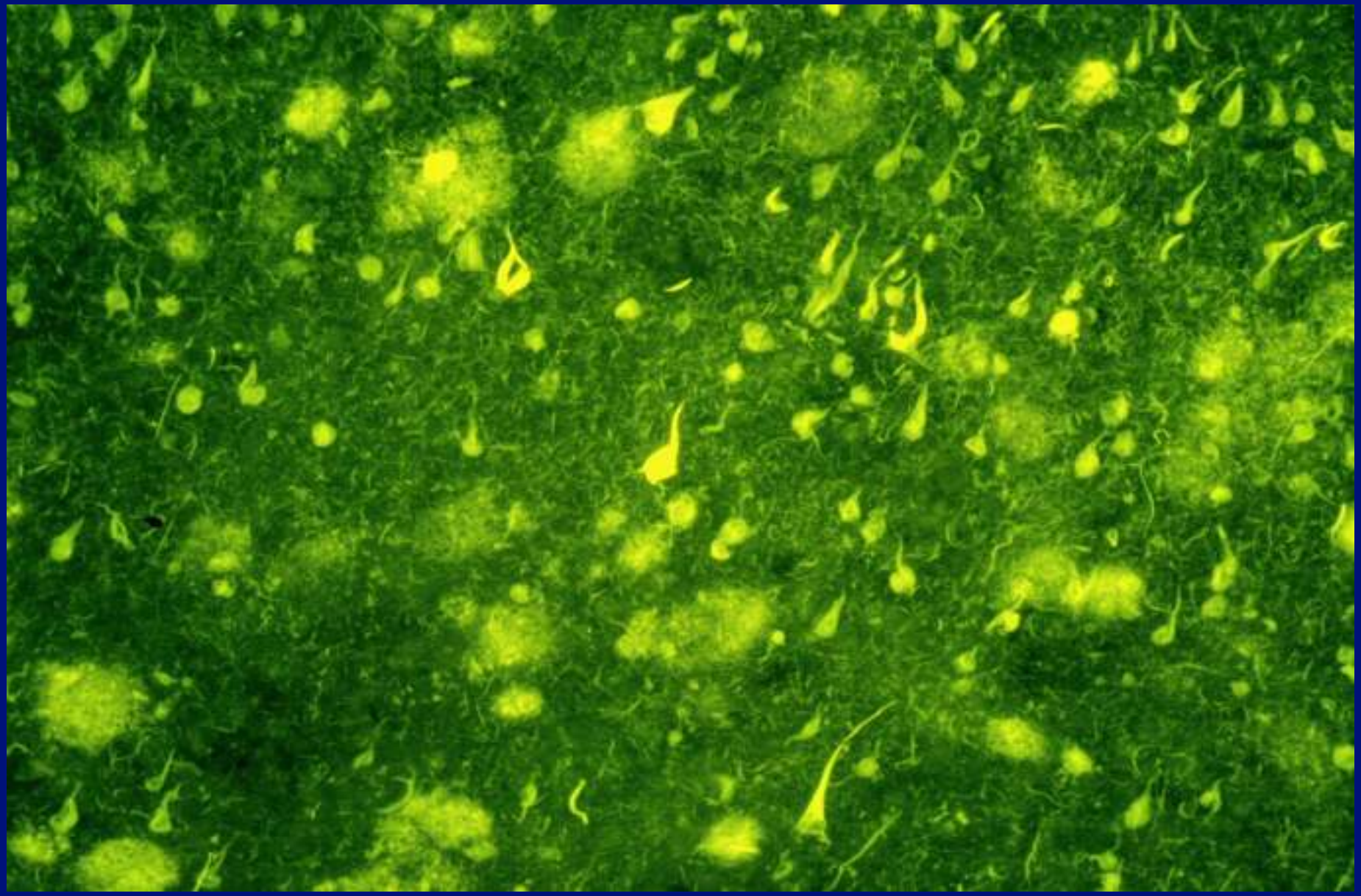
Gestorben am 8. April 1906.



Auguste D (1906)







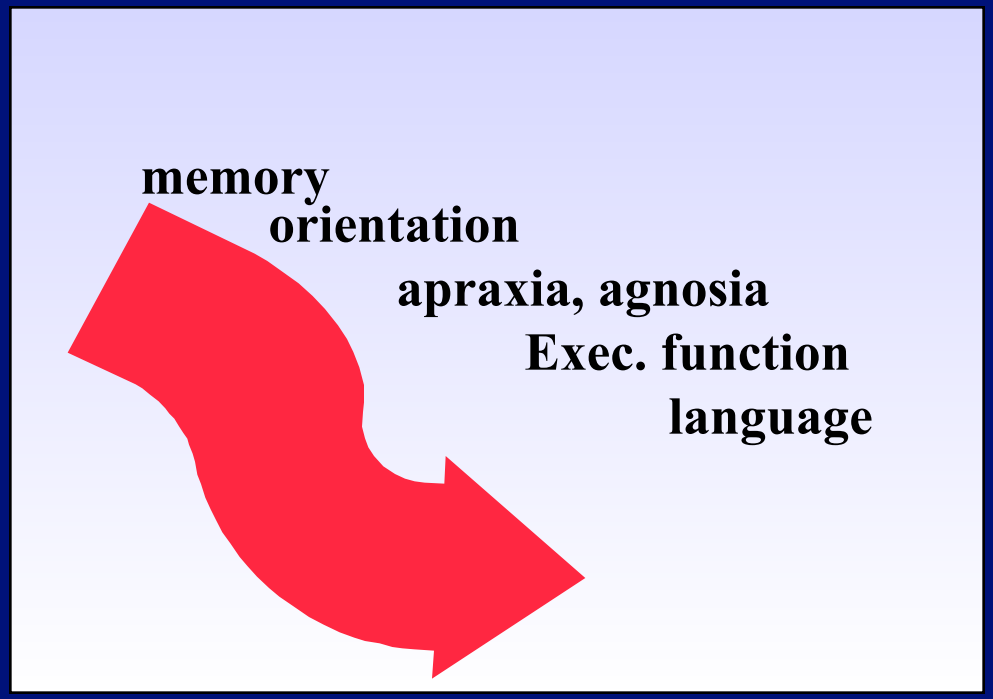
Aging brain





Superman in his later years

Alzheimer's Disease
Clinical Characteristics



- Insidious onset
- Slow progression
- No focal neurological findings

Normal brain aging and Alzheimer's Disease: Macroscopic findings

Normal brain aging is characterized by no or mild macroscopic cerebral atrophy in the absence of significant cognitive deterioration. Conversely, Alzheimer's Disease (AD) cases show, as a rule, a severe cortical atrophy involving predominantly the temporal, frontal, and parietal lobes.

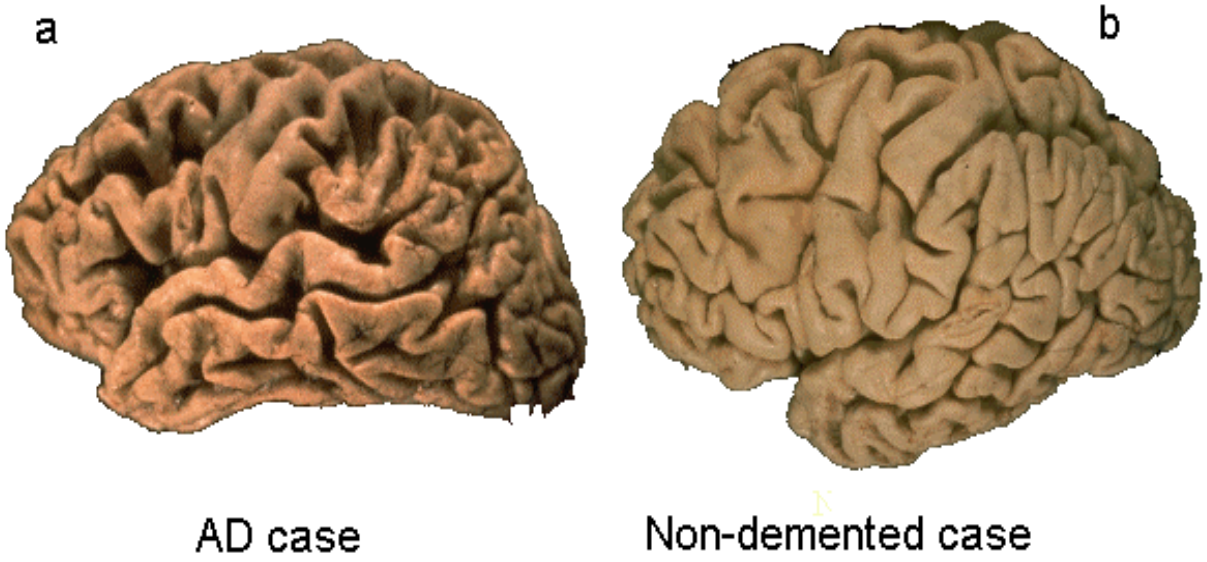
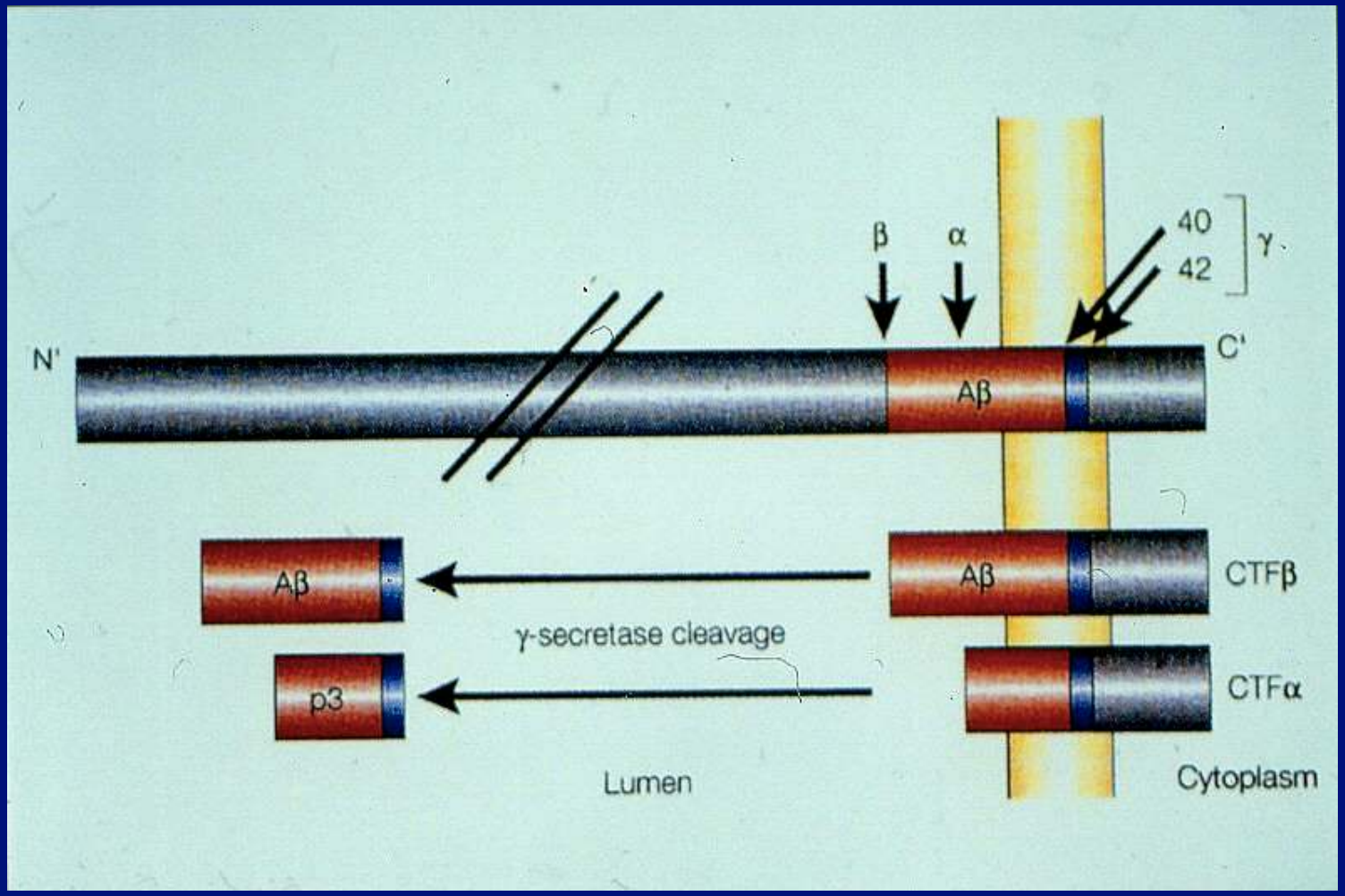
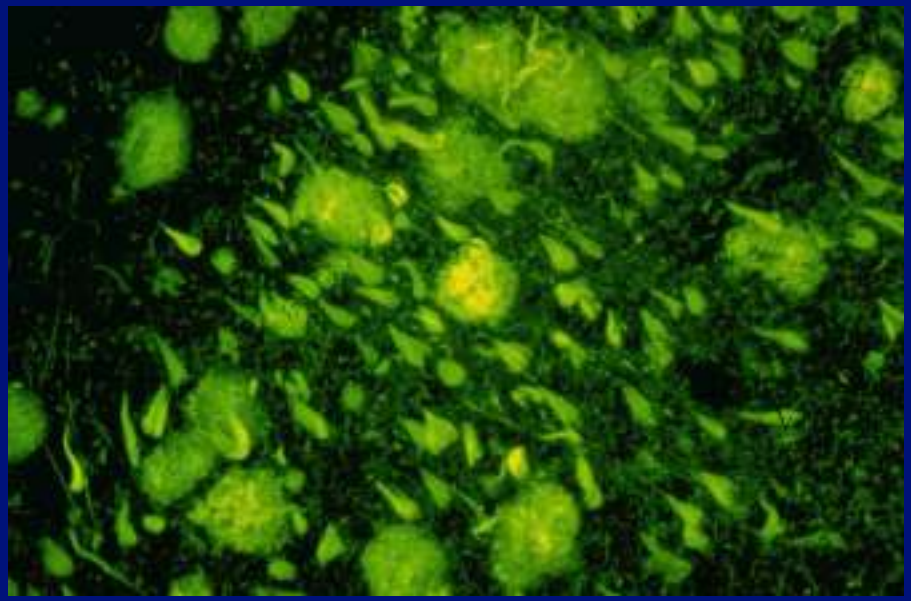


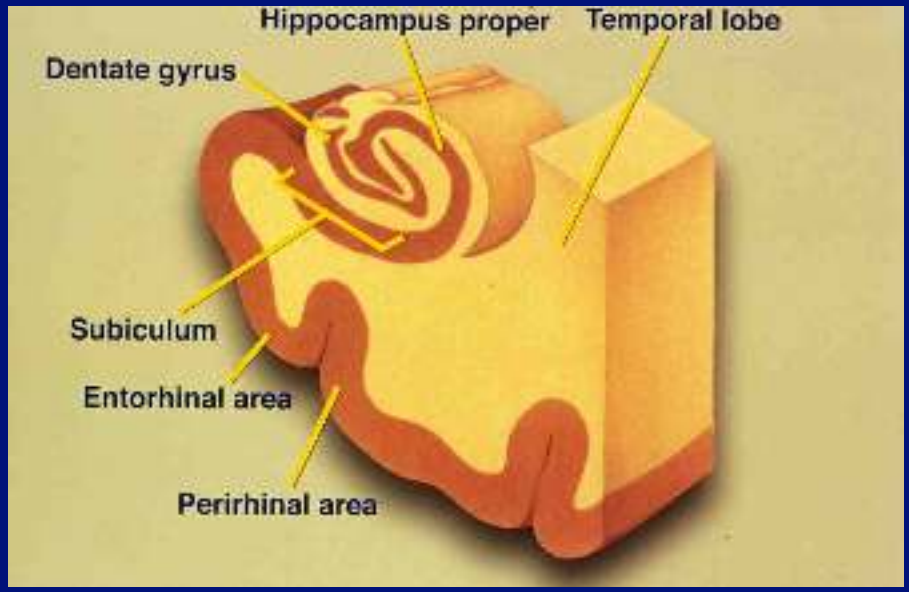
Fig. Leg. (a, b): Left cerebral hemisphere in two 78 year old patients. Note the massive cerebral atrophy in the patient with AD (a) compared to the non-demented patient (b).

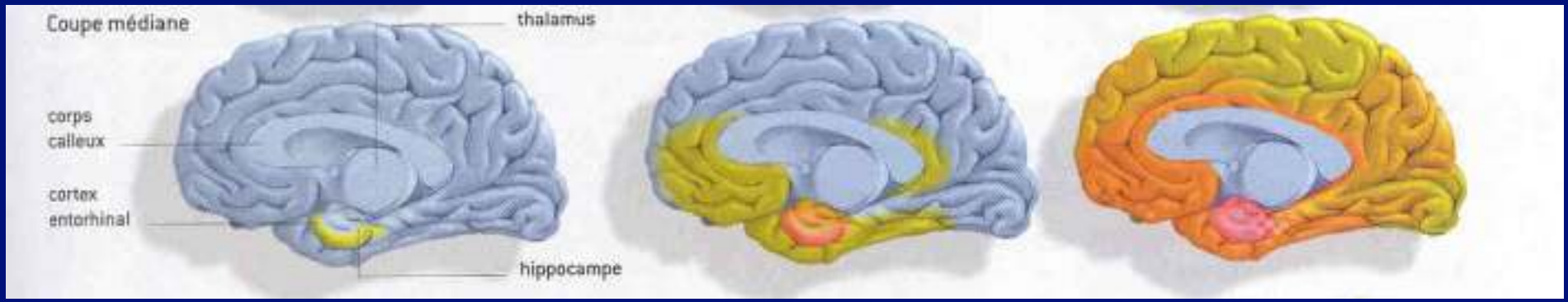





β
α
40
42
γ
N'
C'
Aβ
Aβ
Aβ
CTFβ
γ-secretase cleavage
p3
CTFα
Lumen
Cytoplasm

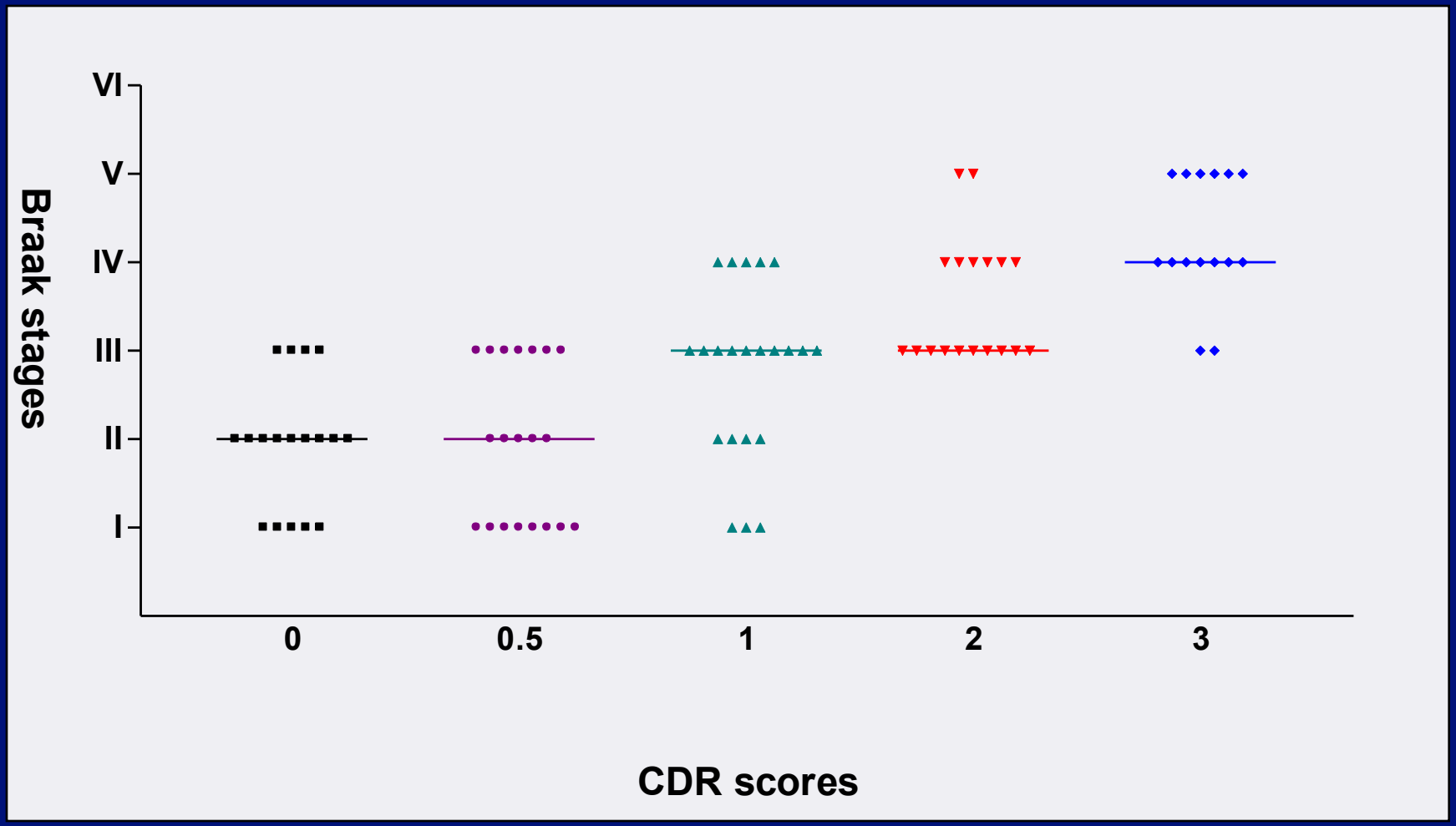



Hippocampus proper
Temporal lobe
Dentate gyrus
Subiculum
Entorhinal area
Perirhinal area


Coupe médiane
thalamus
corps calleux
cortex entorhinal
hippocampe

Alzheimer et Corrélations Clinicopathologiques

Stades de Braak et CDR



J Neuropathol Exp Neurol 2001;60:946

Correlation between clinical severity (CDR) and neuropathological staging
-Univariate Model-

- NFT staging accounted for 26.5% of the variability in clinical severity, Abeta protein deposition staging accounted for 13.0% and age for 4.4%

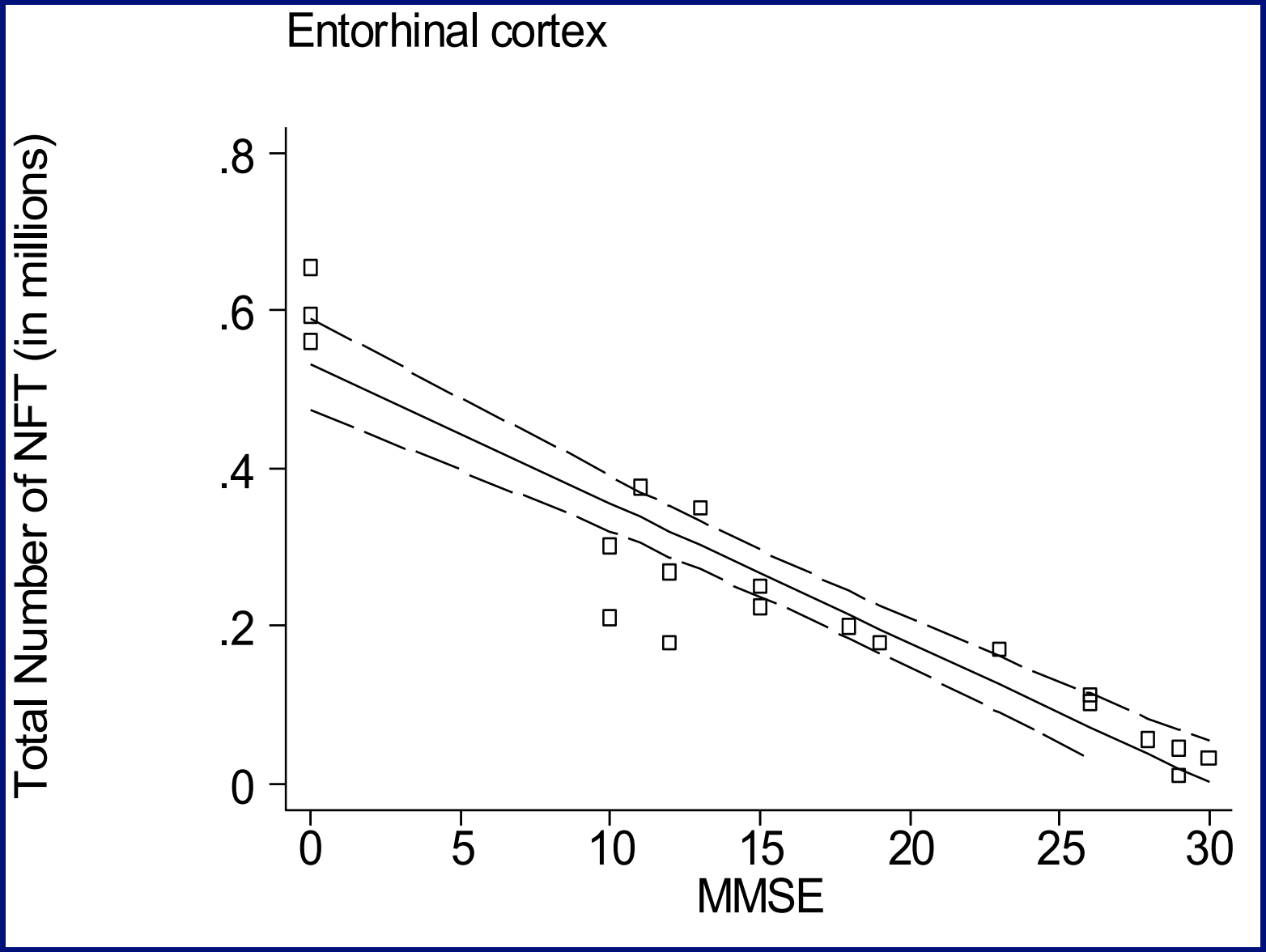
J Neuropathol Exp Neurol 2001;60:946

Correlation between clinical severity (CDR) and neuropathological staging
-Multivariate Model-

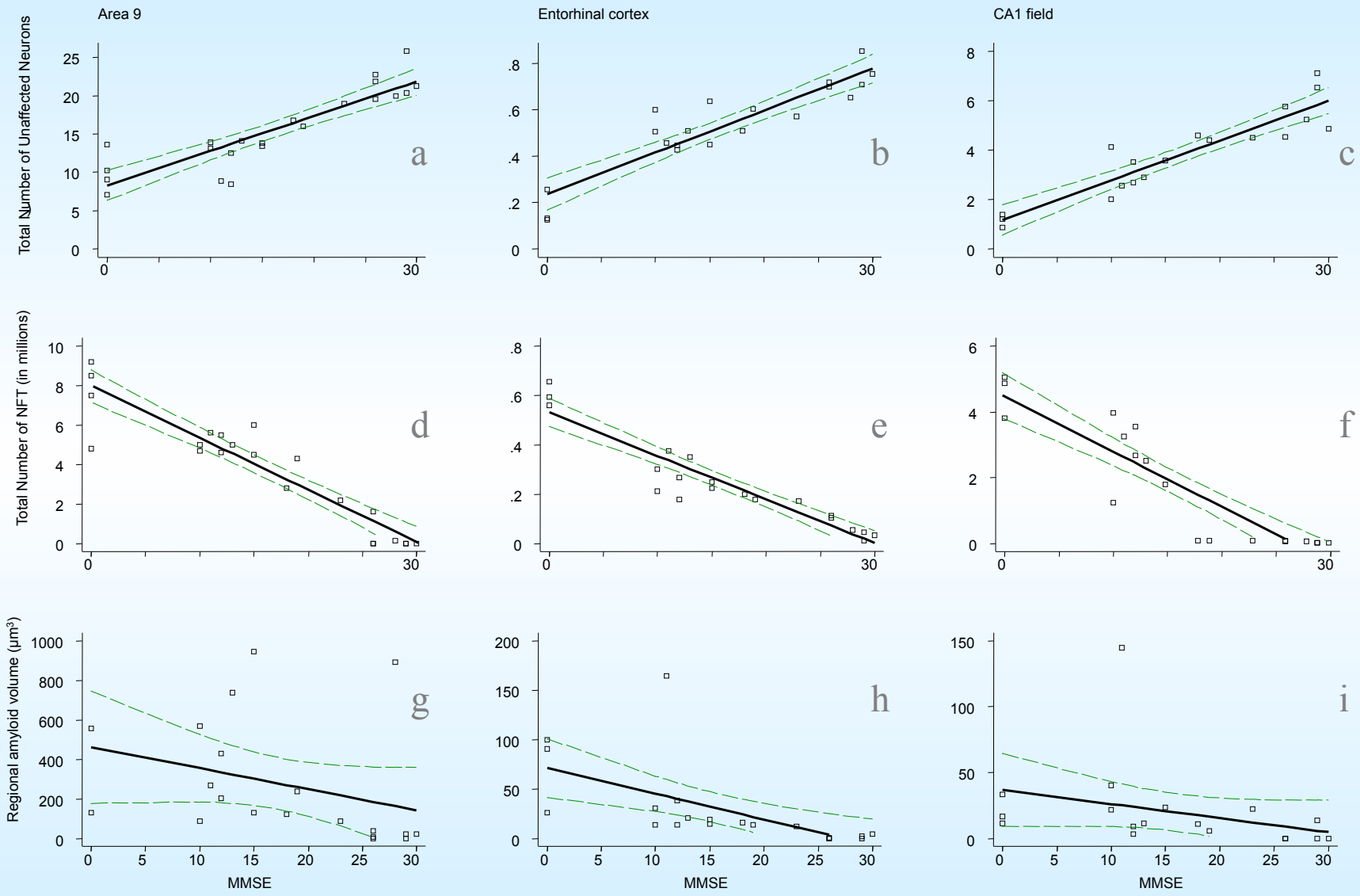
- NFT and age together accounted for 27.2% of the variability in CDR scores

- the addition of Abeta-protein staging to the model could only explain an extra 2.9% of the clinical variability

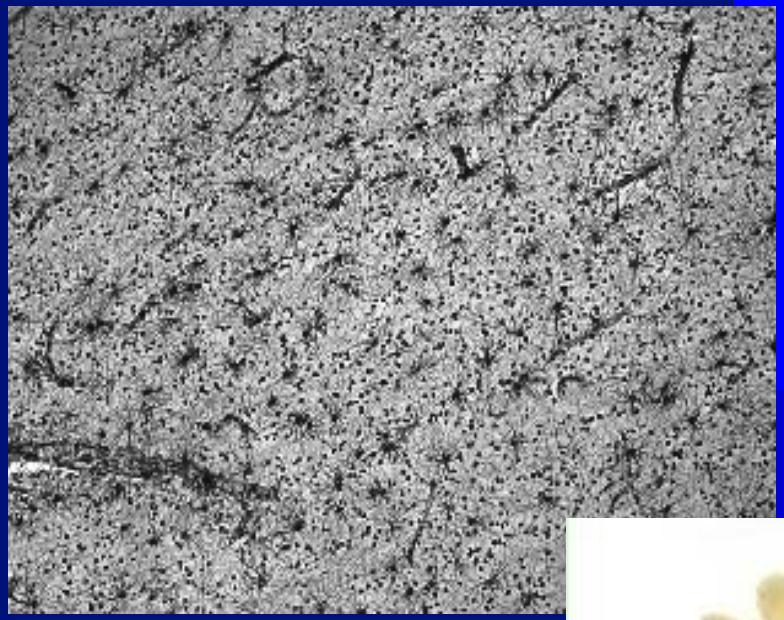
J Neuropathol Exp Neurol 2001;60:946



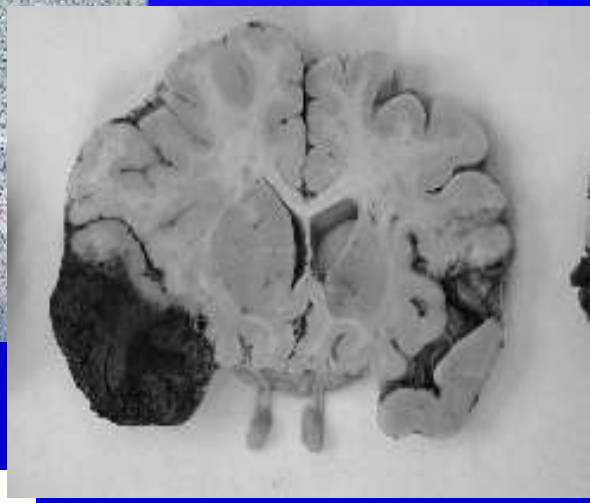
Neurology 2003;60:1495-1500

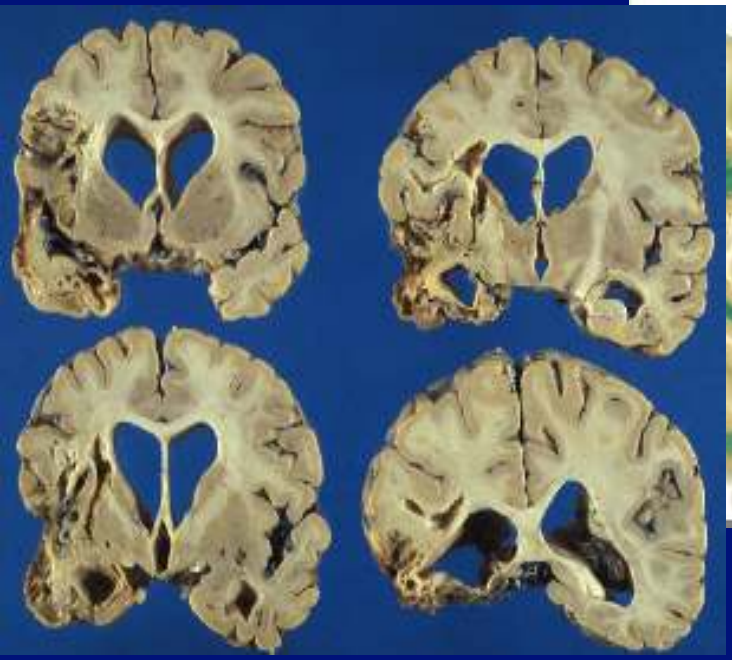


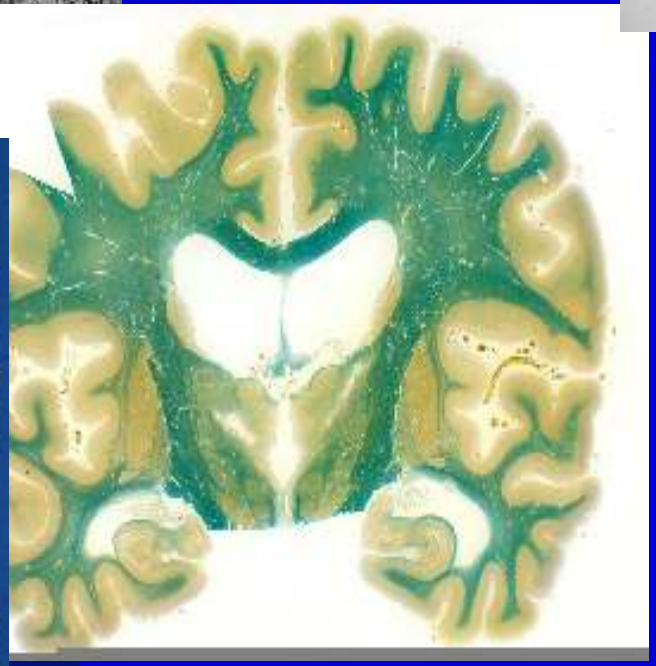
Neurology 2003;60:1495-1500









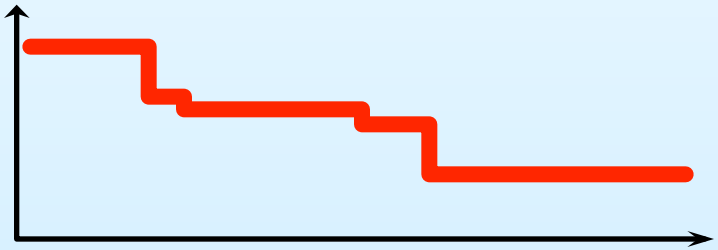




Vascular Dementia
Clinical Characteristics

Vascular Dementia

- Abrupt onset
- Stepwise deterioration
- Focal neurologic findings
- History of stroke



Alzheimer



Neuropsychological Profile

- Impaired attention, concentration and executive function
- Memory is less impaired than in AD
- Improved retrieval with cueing

- The neuropsychological profile is not specific for VaD
- Studies did not include neuropathological verification

Neurology 1999;53:670
J Neurol Sci 2002:203:17

Vascular Dementia
Diagnosis

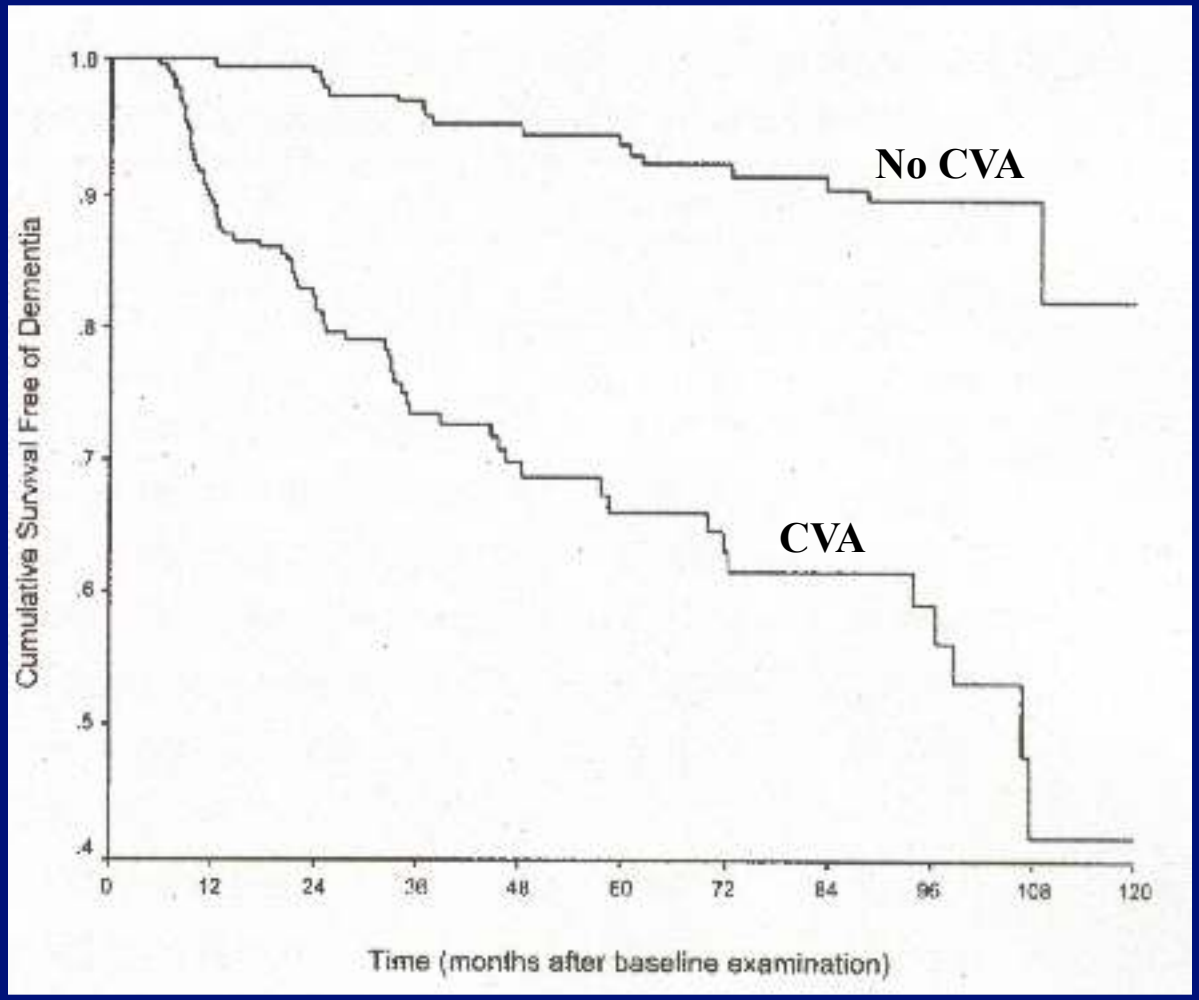
- Dementia
- Evidence of cerebrovascular pathology
- Link between the two

Post Stroke Dementia

- **Vascular dementia is 4 to 10 times more common in individuals who have suffered a stroke**
- **Increased risk of dementia in the months following a stroke (1/4 of the patients are demented 3 months post CVA)**

Neurology 2000;54:1124

Post Stroke Dementia



Stroke 2002;33:254





Auguste D (1906)

Die Arteriosklerotische Atrophie Des Gehirns.
Alzheimer A. et al. *Allg Z Psychiatr Psych Gerichtl Med* **1895**; 51:1809-1812

Mixed Dementia
First Mention

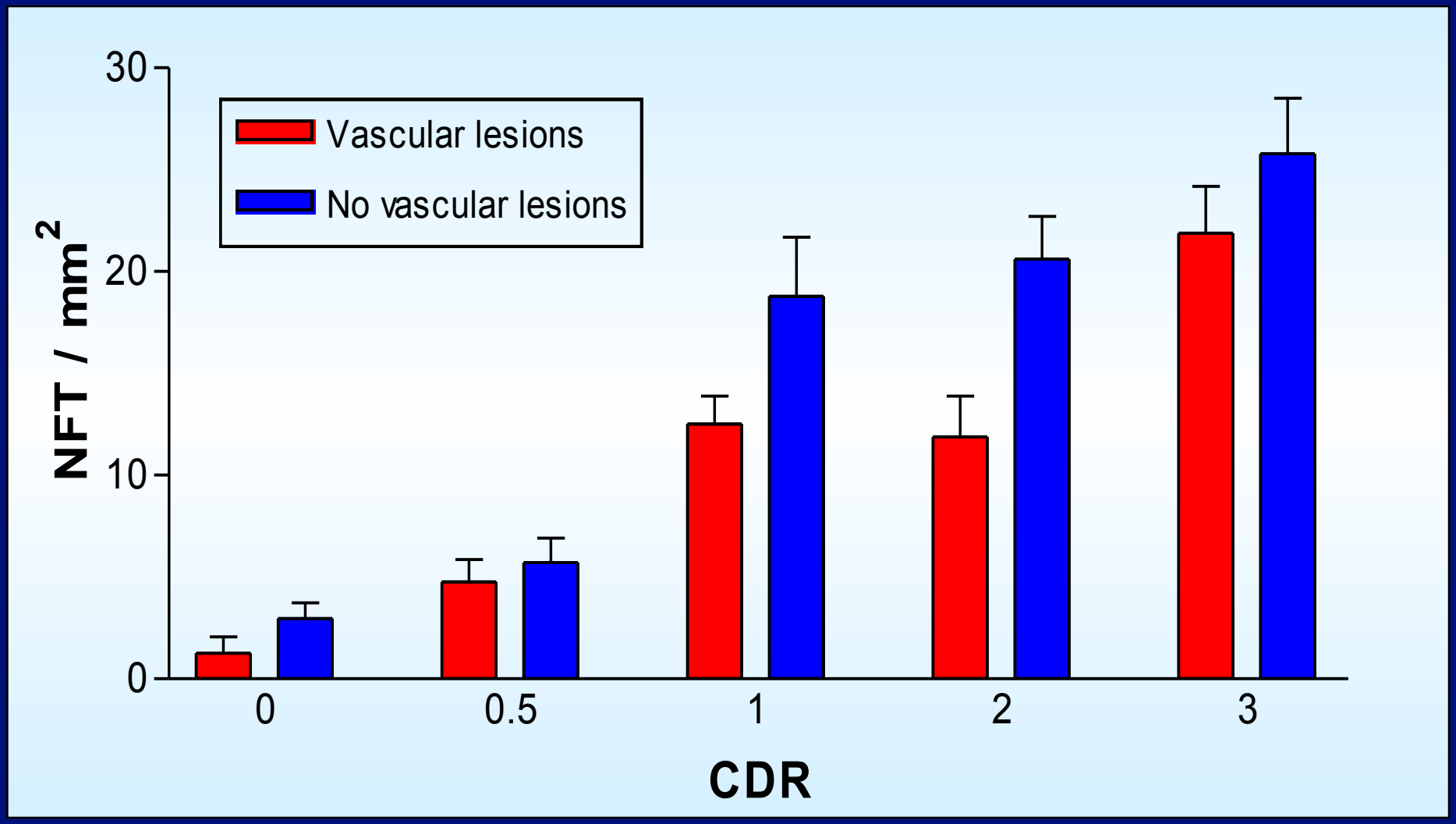
- **1962: Senile Mixed Dementia (Delay et Brion)**
  - **Co-existence of vascular and degenerative lesions in a demented person.**

Mixed Dementia Neuropathological Studies

- **MRC CFAS 209 autopsies**
  - **Mean age at death 85 years (men) and 86 years (women)**
  - **cerebrovascular pathology (hemorrhage, infarct, lacunes, small vessel disease) 78%**
  - **NFT or SP: 70%**

Lancet 2001;357:169

Cognition and NFT counts in elderly individuals with and without vascular lesions



Conceptual Challenges

- Do all ischemic lesions affect cognition?
- What characteristics are most important?
  - Type
  - Size
  - Location

Conceptual Challenges

- How do we interpret the impact of different ischemic lesions on cognition
  - Hemorrhages
  - Macroscopic infarcts
  - Lacunes
  - Microscopic infarcts
  - Gliosis (focal, diffuse)
  - White matter disease (periventricular or deep)

Cognition and Infarct Size

- A volume of damaged cerebral tissue > 50cc nearly always results in dementia (J Neurol Sci 1968; 7: 331)

Cognition and Infarct Size

- Cognitive decline rate was no different in patients with AD and infarcts < 10cc compared to cases with AD and no infarcts (Arch Neurol 2000;57:1474 and Arch Neurol 2001; 58:250)
- Microvascular lesions may be greater determinants of VaD than macrovascular lesions (Ann NY Acad Sci 2000;903:239)

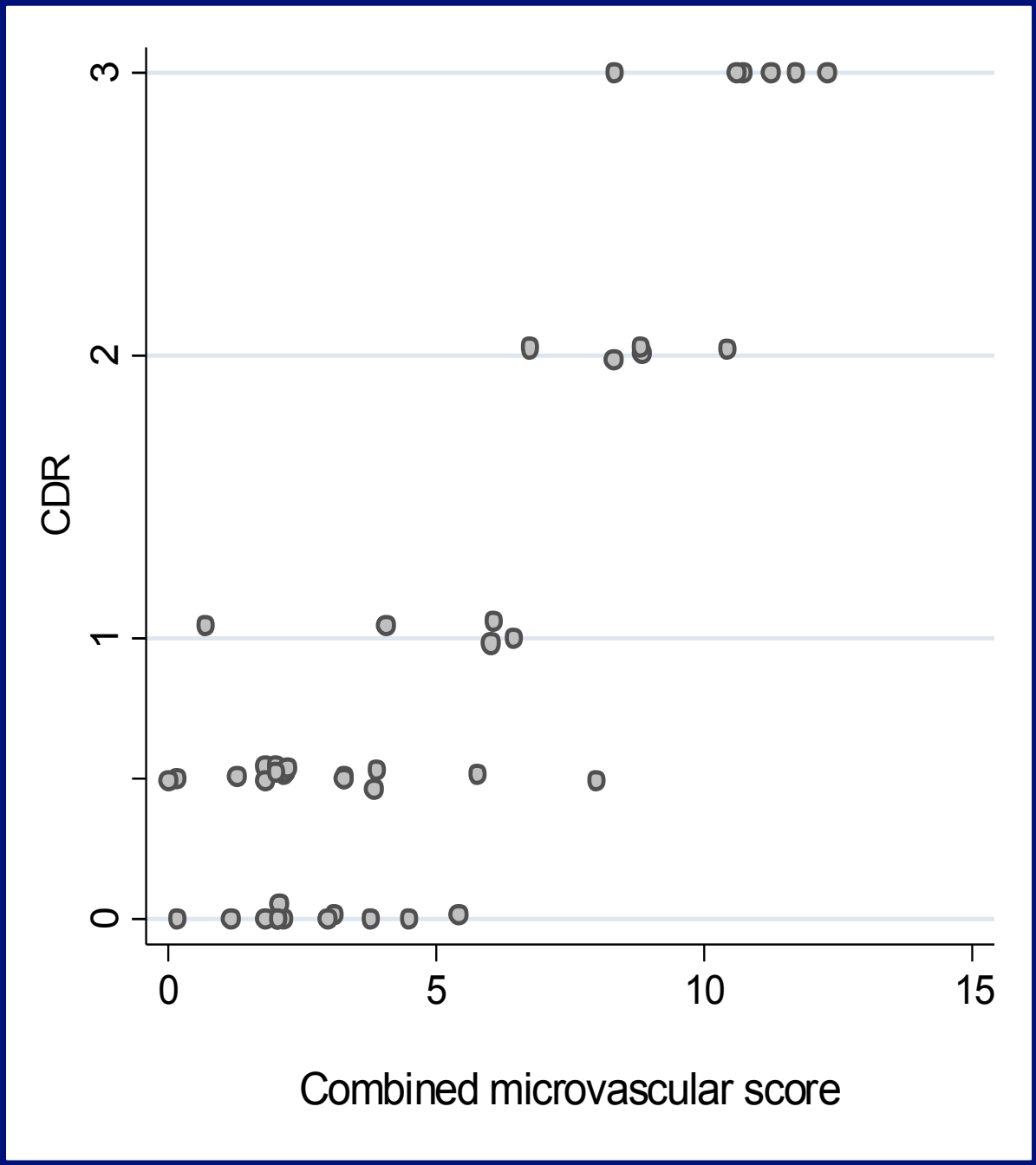
Study Population

- 45 autopsied cases
  - with microscopic ischemic lesions
  - no macroscopic ischemic lesions
  - no significant NFT pathology (Braak stages I and II)
  - no other central nervous system disorders (i.e., tumors, Parkinson disease, Lewy body disease)
- Cognitive function assessed by CDR
  - No dementia: 13 cases
  - Questionable dementia: 16 cases
  - Dementia: 16 cases

Clinical Variability Explained by Each Lesion – Univariate Model

Age	5.4%	P<0.05
A beta deposition stage	8.0%	P<0.05
Microinfarcts	36.1%	P<0.01
Periventricular white matter lesions	10.6%	P<0.01
Deep white matter lesions	4.6%	P<0.05
Focal gliosis	-	NS
Diffuse gliosis	-	NS

Stroke 2004;35:410

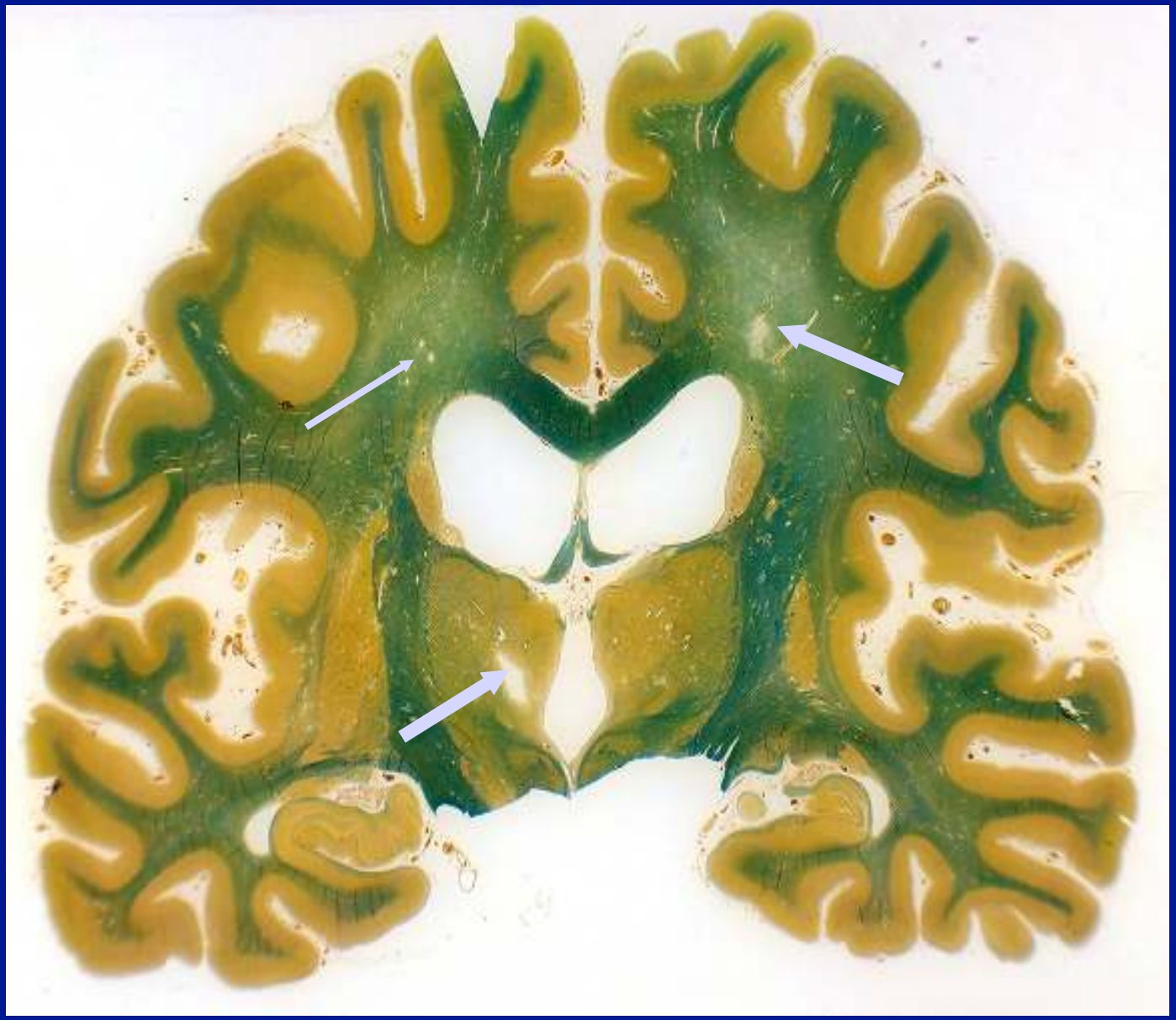

CDR
3
2
1
0
0
5
10
15
Combined microvascular score

Clinical Variability Explained by the Various Lesions – Multivariate Model

- Age and A beta stage: 10.4%
- Age and A beta stage and MI: 30.3% (+ 19.9%)
- Age and A beta stage and PVD: 20,1% (+9.7%)
- Age and A beta stage and DWMD: 15.8% (+5.4%)
- Age and A beta stage and Combined Ischemia Score: 38.2% (+27.8%)

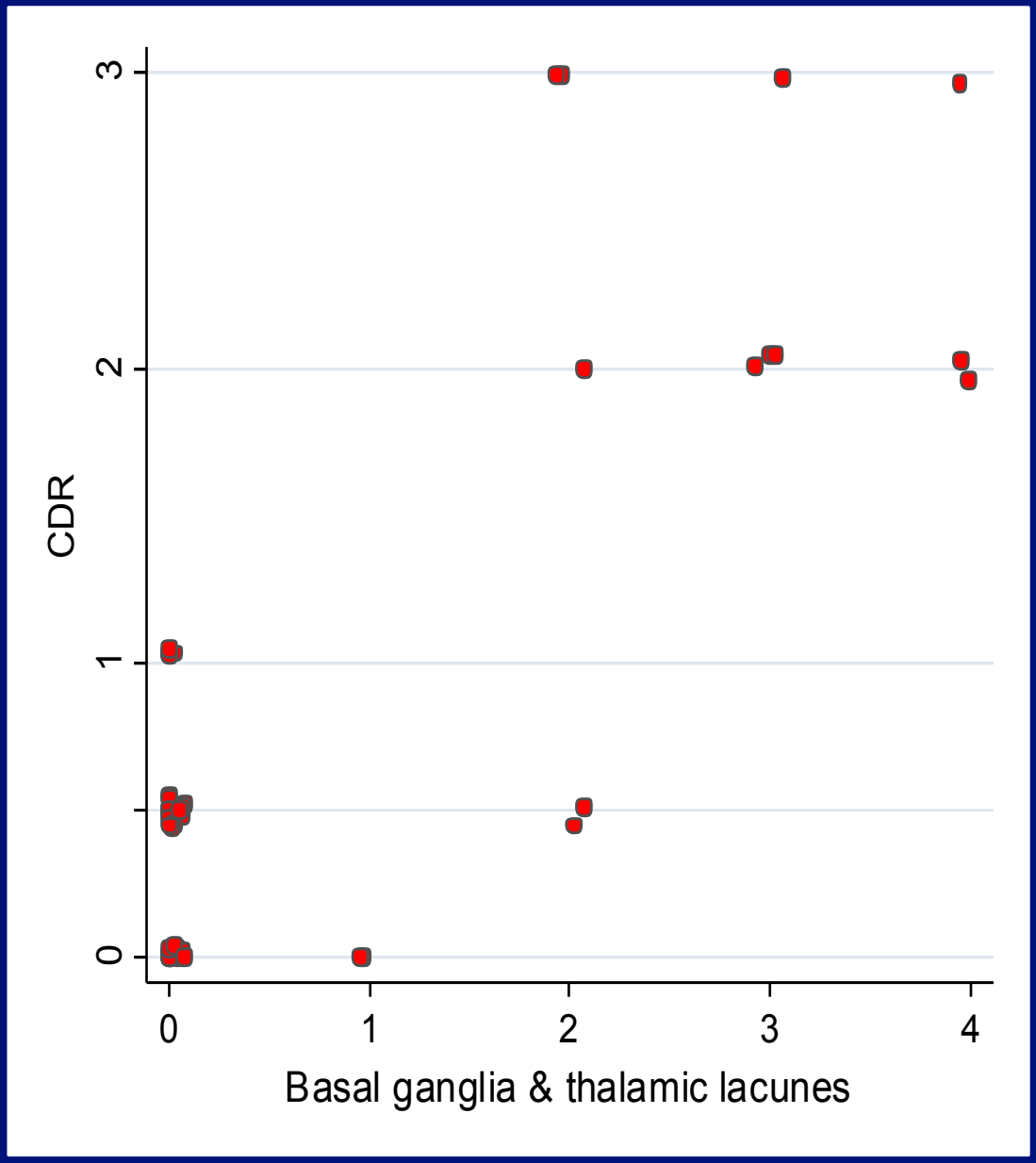
Stroke 2004;35:410

Lacunes and Cognition in Brain Aging



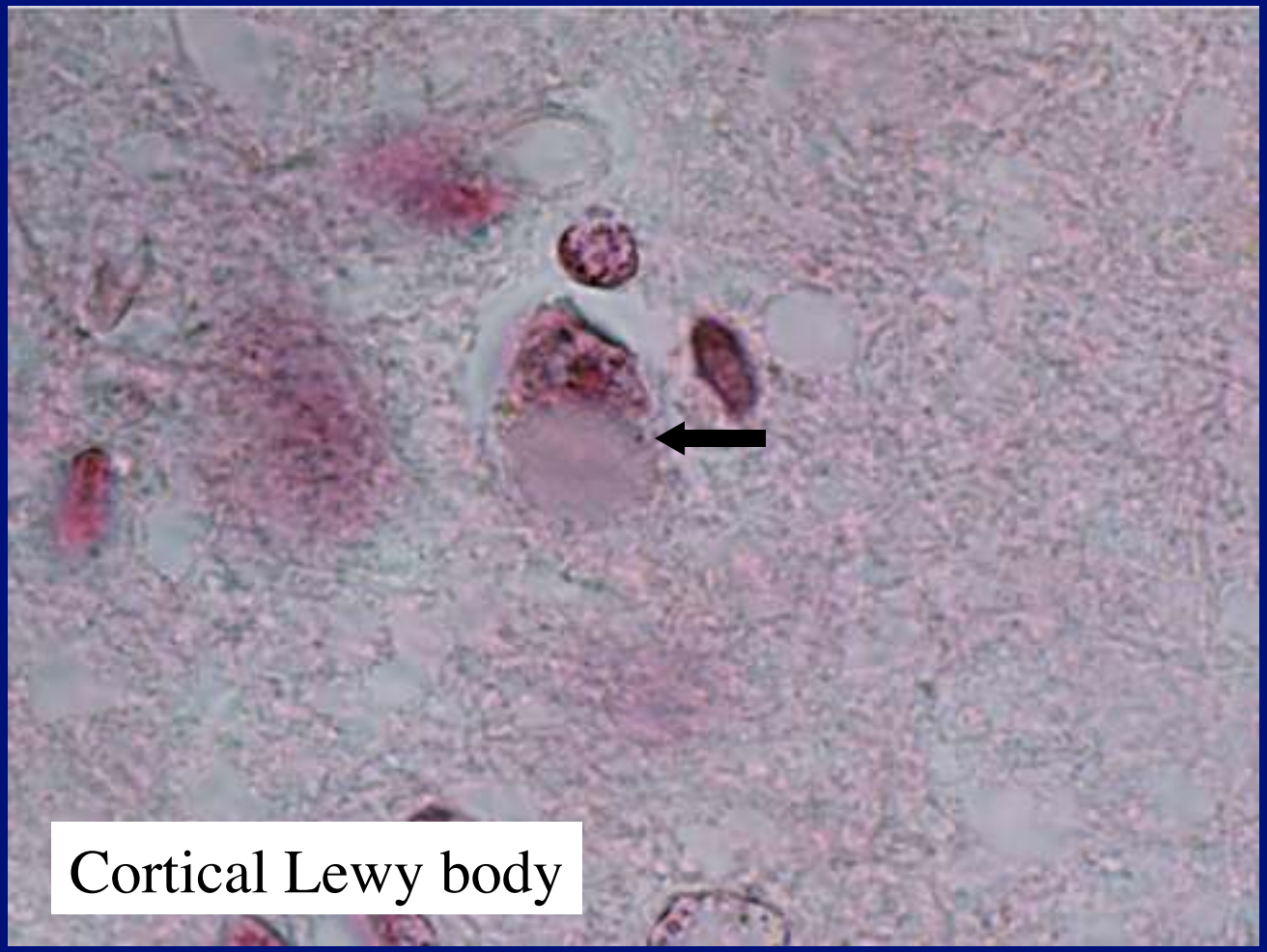
Study Population

- 47 autopsied cases
  - with no or minimal microscopic ischemic lesions
  - no macroscopic ischemic lesions other than lacunes
  - no significant NFT pathology (Braak stages I and II)
  - no other central nervous system disorders (i.e., tumors, Parkinson disease, Lewy body disease)
- Cognitive function assessed by CDR
  - No dementia: 15 cases
  - Questionable dementia: 18 cases
  - Dementia: 14 cases

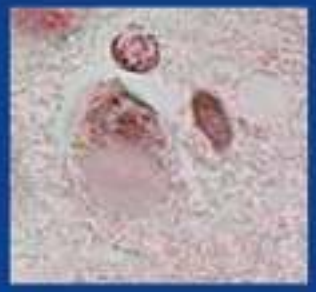

CDR
0
1
2
3
0
1
2
3
4
Basal ganglia & thalamic lacunes

Clinical Variability Explained by Each Lesion – Univariate Model

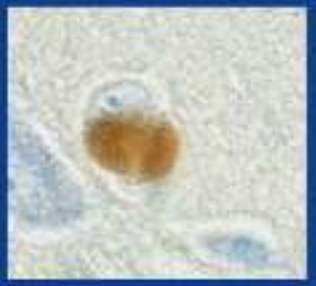
Age	-	NS
A beta deposition stage	6.7%	P<0.01
Basal ganglia lacunes	17.2%	P<0.01
Thalamic lacunes	13.2%	P<0.01
Deep white matter lacunes (frontal, temporal, parietal)	-	NS


Cortical Lewy body

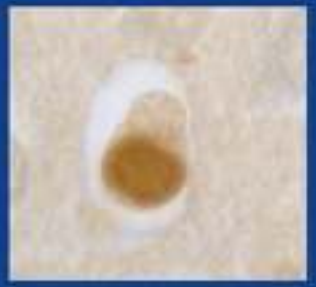
Cortical LB



HE



anti-α-synuclein



anti-ubiquitin

Lewy Body Dementia

- **Progressive impairment of cognitive function:**
  - **memory (70% des cas)**
  - **Slowing, attention deficits**
  - **fluctuations**

Lewy Body Dementia

- **Extrapyramidal syndrome**
  - **Moderate and symetrical**
  - **Poor response to L-dopa**
  - **Great sensitivity to neuroleptics**

Lewy Body Dementia

- **Visual hallucinations (80% of the case)**
  - **persistent**
  - **complex**
  - **criticized**

Correlation between LB scores and CDR stages

Areas	*Spearman's coefficient*	*Statistical significance*
	0.48	P < 0.01
21	0.53	P < 0.005
24	0.60	P < 0.001
41	0.52	P < 0.005
Entorhinal	0.69	P < 0.001
Total	0.71	P < 0.001

Acta Neuropathologica 2003;106:83

Dementia In Older Populations

- Several different types of dementia
- Different clinical presentations
- Different pathological correlates
- Different and many times unkown underlying pathophysiological mechanisms

Weight Loss And AD

- Patients and methods
  - **mild to moderate AD patients (N=362) and controls (N=317) with two or more weight measurements per year**
  - **the average follow up was > 2 years**
- Results
  - **nearly twice as many AD patients experienced weight loss of 5% or more when compared to controls (men P=. 003 ; women, P=.001)**
  - **in a multivariate model, a diagnosis of AD remained a significant predictor of ≥ 5% weight loss (P<<0.001)**

JAGS 1996;44:265

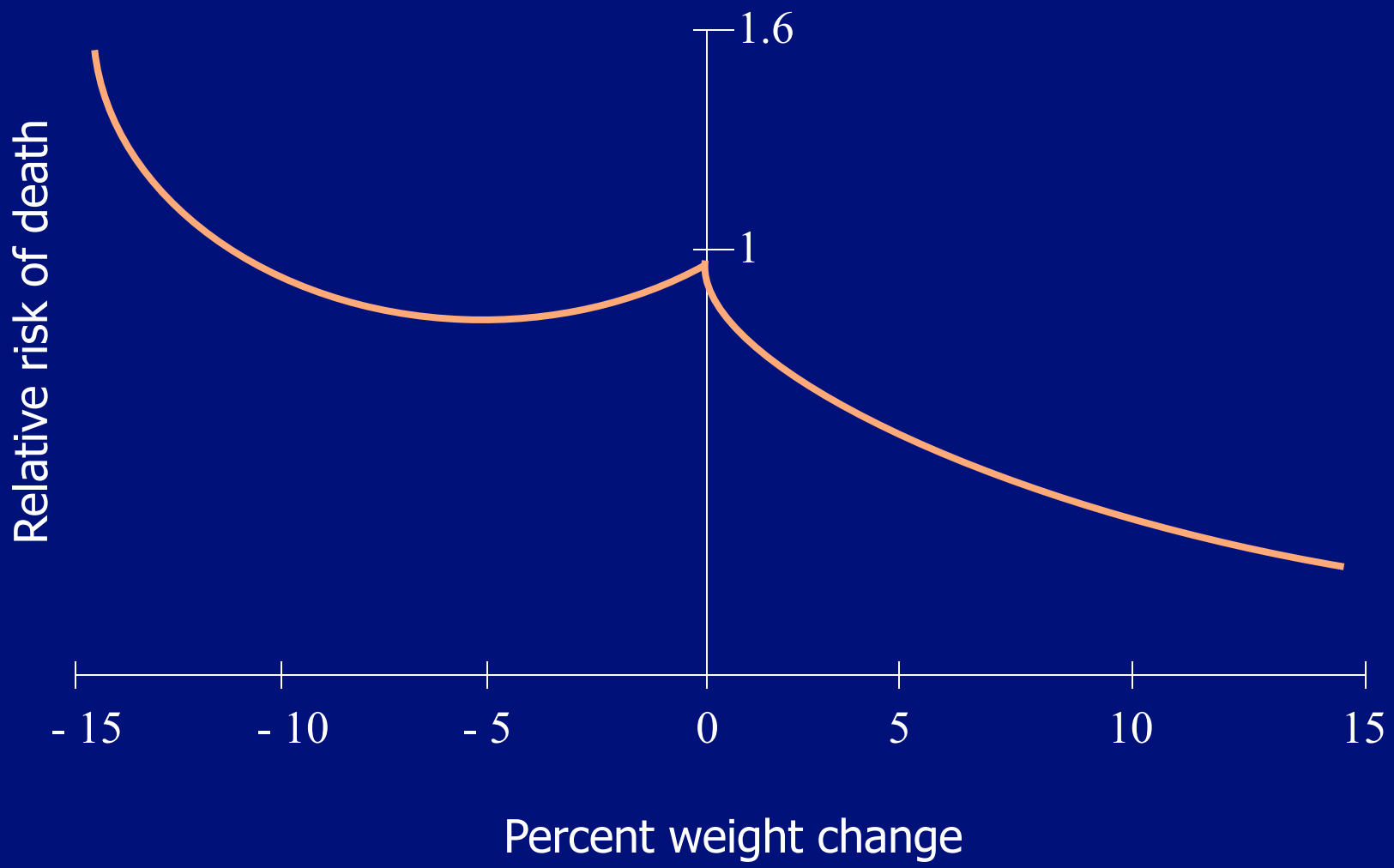
Weight Loss And AD

- Risk of weight loss increases with dementia severity
- Weight loss is not confined to severe cases
- Some cases gain weight

J Am Geriatr Soc 1998;46;1223

Am J Clin Nutr 2000;71:637S

Weight Change and Mortality in AD



J Am Geriatr Soc 1998;46;1223

AD and Weight Loss
A Multifactorial Process

- Social supports
- Changes in taste and smell
- Affective disorders
- Behavioural disorders
- Functional Impairments
- Swallowing Difficulties
- Medications
- Co-Morbidities

AD, Feeding Difficulties and Caregiver Burden

- 224 community dwelling AD patients and their caregivers
- One year follow up
- Feeding difficulties at baseline related to AD severity
- Increase in feeding difficulties over 1 year strongly related to caregiver burden

Int J Geriatr Psychiatry 2002;17:950

AD, Weight and Acetylcholinesterase Inhibitors

	Galantamine 24mg	Galantamine 12mg	Placebo
Weight loss (kg) over 5 months	1.3	0.5	0.1

Neurology 2000;54;2269

Caloric Intake and AD

- 51 AD and 27 « controls »
- 3 day food intake diary (foods weighed)
- AD cases weighed less and had poorer nutritional status
- AD cases did not eat less calories
- AD cases had less physical activity

J Neurol 2004;251:314

Folate And Vitamin B12

- Most studies report similar B12 levels in AD and controls
- MMA and Homocystein higher in AD than controls
- Varying results for serum folate, RBC folate lower in AD

J Gerontol Med Sci 1997;52A:M76
Arch Neurol 1998;55:1449
J Gerontol Med Sci 2001;56A:M675
Am J Clin Nutr 2004;80:114

Micronutrients, Trace Elements And AD

- 35 « patients »
  - Controls (11), CIND (8), AD (8), VaD (8)
  - Low Se, Co and Cr in CIND, AD and VaD
  - Increased Cu in AD and VaD
  - Increased aluminium in AD
- 44 AD patients received either supplements or supplements + micronutrients (Mg, Zn, Arginine, Cu, vit. C E B12, folate) for 6 months
  - No difference in cognition
  - No difference in nutritional status

Arch Gerontol Geriatr 2004; Suppl 9:393

Clin Nutr 2004;23:265

Fish and AD

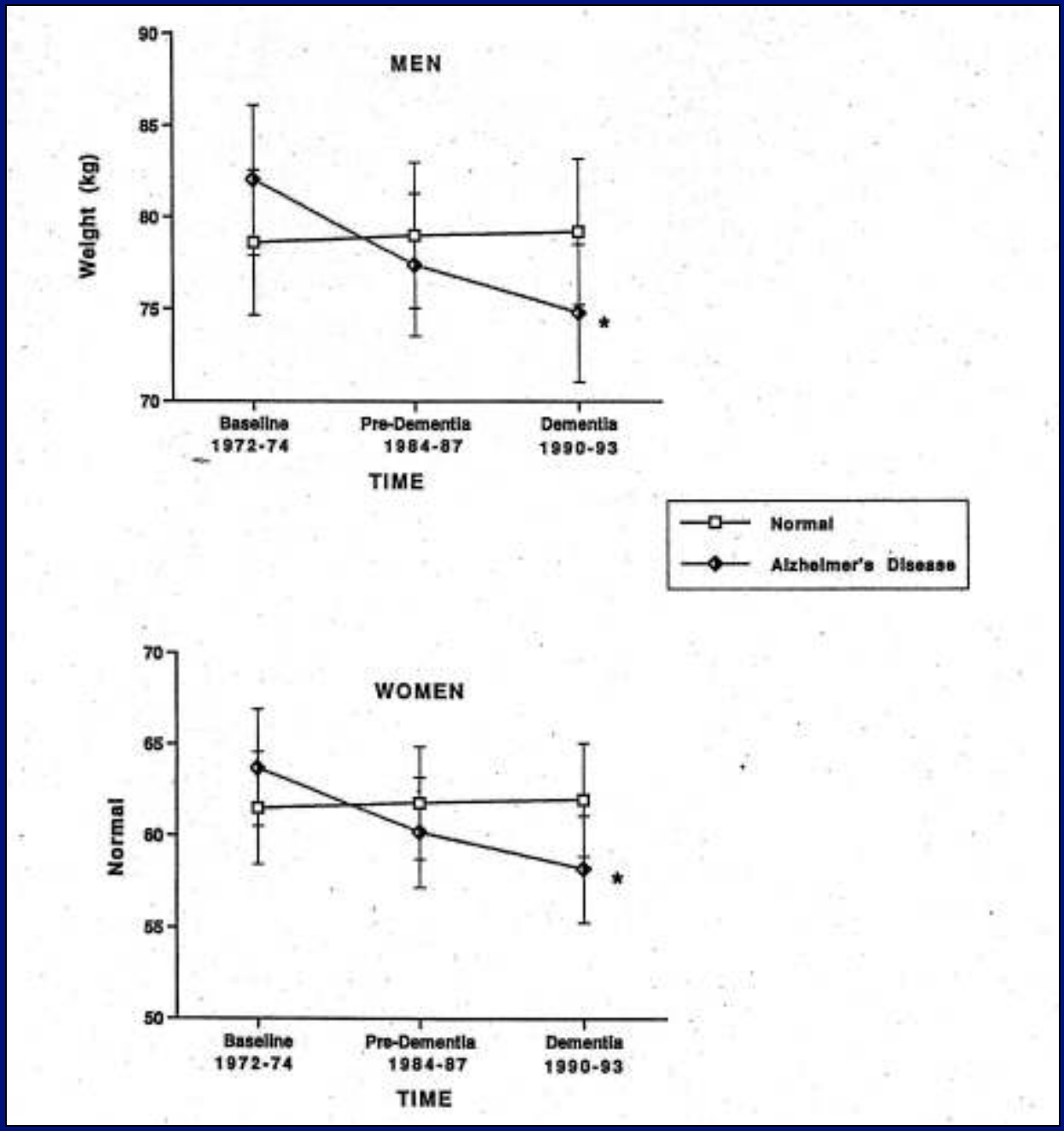
- **Fish consumption once a week or more decreases AD risk by 60% over approximately 4 years**

J Am Geriatr Soc 2003;51:1143

Weight Change and AD

- Older community-dwelling men (N=134) and women (N=165) were followed for 20 years before they were diagnosed as cognitively intact or demented.
- Weight was measured at three clinic visits between 1972-74, 1984-87, 1990-93

Barrett-Connor et al, JAGS, 1996



Barrett-Connor et al, JAGS, 1996

Weight Change and AD

- Patients and methods
  - **older community-dwelling men (N=134) and women (N=165) were followed for 20 years before they were diagnosed as cognitively intact or demented.**
  - **weight was measured at three clinic visits between 1972-74, 1984-87, 1990-93**
- Results
  - **50% of men and women who developed dementia had lost 5 kg since their first evaluation 20 years previoulsy compared with about 25% of subjects who were cognitively intact.**

Barrett-Connor et al, JAGS, 1996

Paquid Study
BMI and Development of Dementia

Table 2 Incidence of dementia during follow-up according to initial body mass index

	BMI category				
	< 21	21–22	23–26	≥ 27	Total % (n)
Incidence rate of dementia					
*At 1 year: % (n)	1.7 (5)	0.9 (3)	0.8 (6)	0.9 (4)	1.0 (18)
At 3 years: % (n)	6.1 (22)	5.0 (20)	2.8 (26)	2.9 (17)	3.7 (85)
At 5 years: % (n)	4.3 (13)	1.9 (7)	2.9 (24)	1.6 (8)	2.6 (52)
At 8 years: % (n)	5.1 (11)	5.1 (14)	4.2 (27)	3.7 (14)	4.4 (66)

* In the Gironde region only.

BMI = body mass index.

Nourhashemi et al., Neurology ,2003

BMI and Development of Dementia

- **392 non demented individuals followed from age 70 to 88 years**
- **Women who developed dementia between 79 and 88 had higher BMI at age 70 (27.7 vs 25.7 p=0.007), 75 (27.9 vs. 25.1 p<0.01) and 79 (26.9 vs. 25.0 p<0.02)**

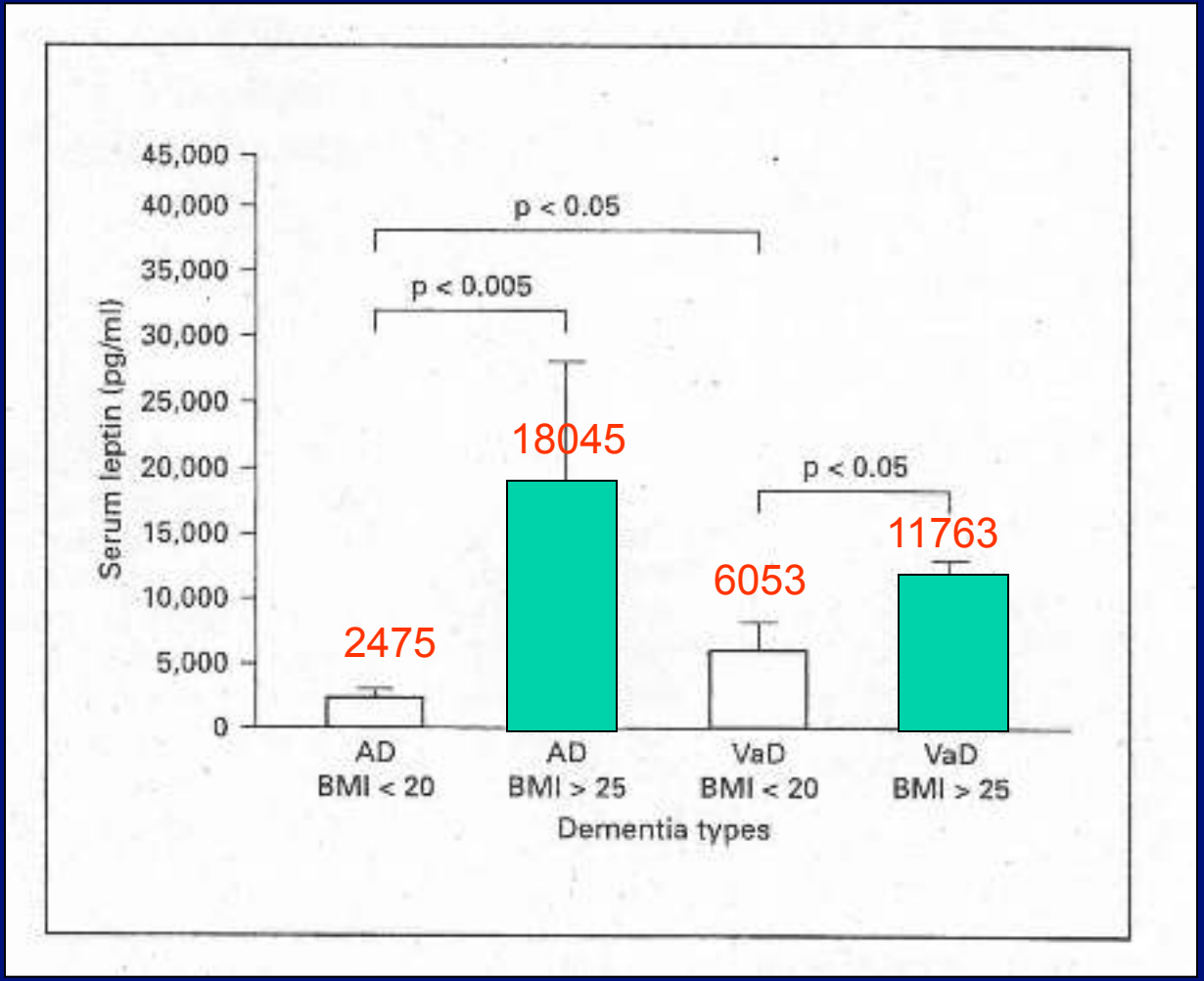
Arch Int Med 2003;163:1524

BMI and Leptin levels in AD and VaD

16 VaD :

MMSE :15

16 AD:
MMSE : 13,5



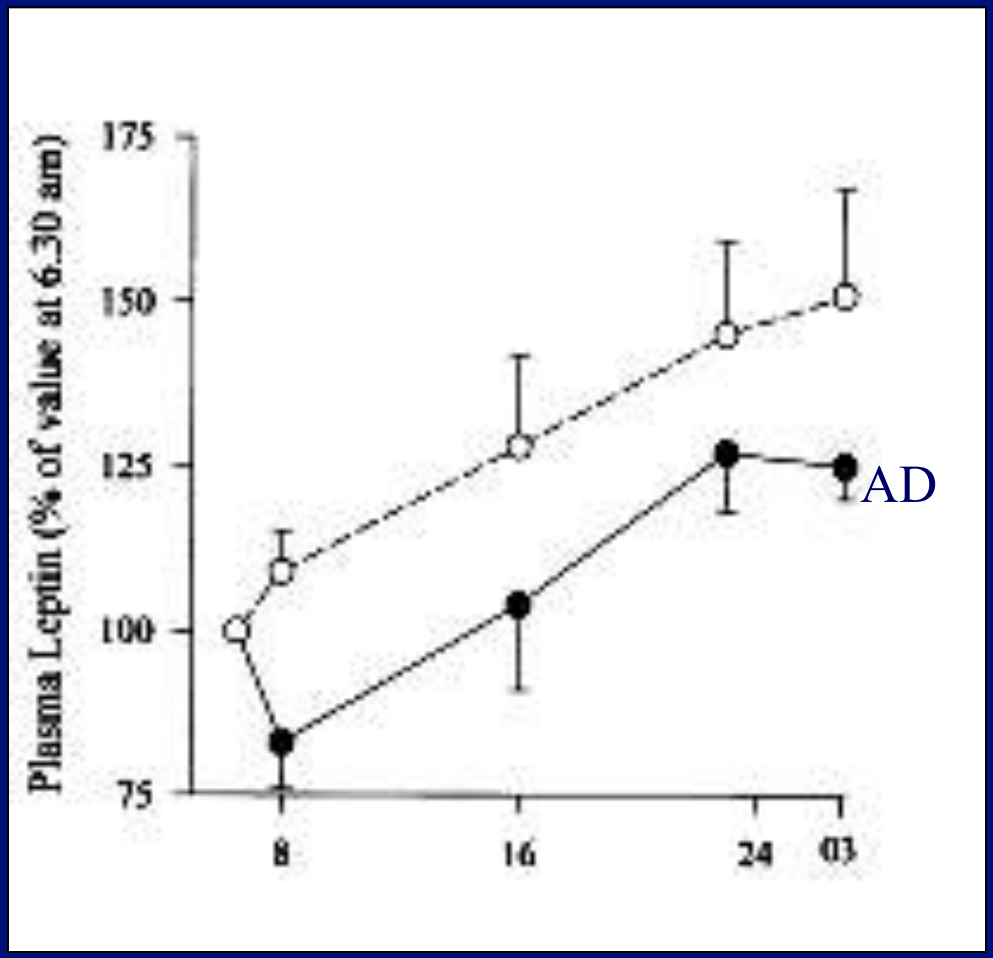
Power D et al, Dement Geriatr Cogn Disord,2002

Leptin Levels and Circadian Rhythm in AD (n=5) and Aged Controls (n=5)

	AD 3F/2H	Controls 3F/2H
Age	76,8±2,3	75,2±3,3
BMI	24,3 ±1,2	24 ±1,8
Serum leptin (ng/ml)	11,6 ±3,3	14,3 ±6,2
% Variation in leptin levels (3AM/6.30 AM)	52 ±16 p=0,034	26 ±6 p=0,011

Olsson, et al., Biol Psychiatry, 1998

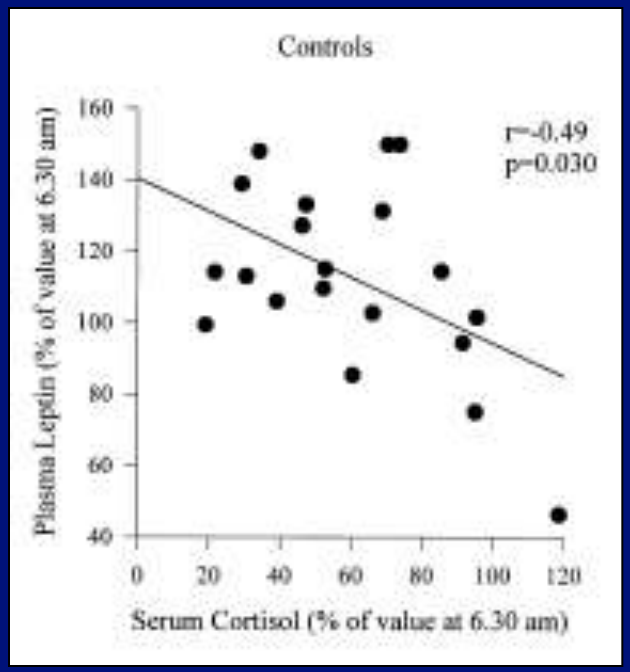
Leptin Circadian rhythm in AD (n=5) and Aged Controls (n=5)



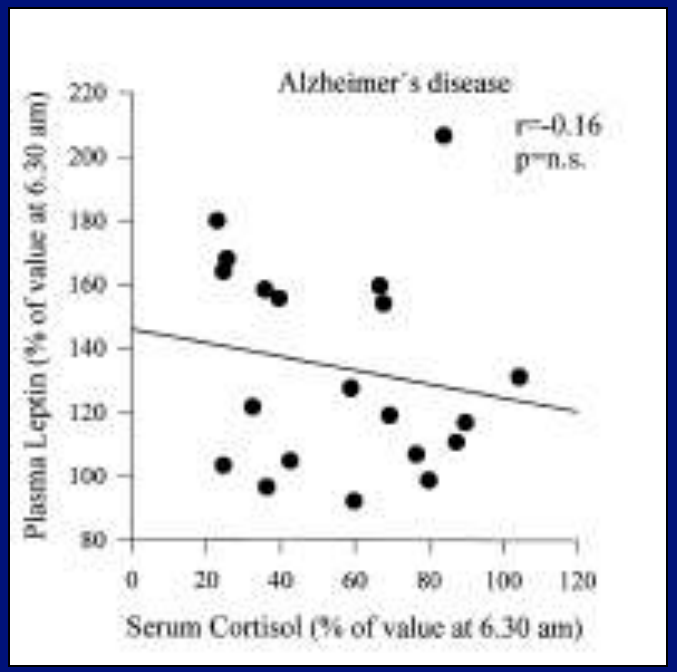
Olsson, et al., Biol Psychiatry, 1998

Cortisol and Leptin in AD and Controls

5 controls



5 AD



Similar BMI in both groups

Olsson, et al., Biol Psychiatry, 1998

Glucose Intolerance and Cognitive Function

	No GInt (n=506)	GInt (n=80)	p value
Age (années)	73,3±2,9	72,9± 3,0	ns
Education	7,0±3,6	6,6±3,8	ns
BMI	26,3±3,9	28,7±5,3	<0,001
Blood glucose (mmol/l)	5,4±0,5	6,0±0,6	<0,001
Insulin levels (pmol/l)	62,4±31,2	90,6±1,0	<0,001
MMSE	26,6±2,3	25,9±3,0	0,012
G&B*	23,5±11,8	22,1±22,12,6	0,026

* Grober & Buschke

Diabetes care,1998:398-402

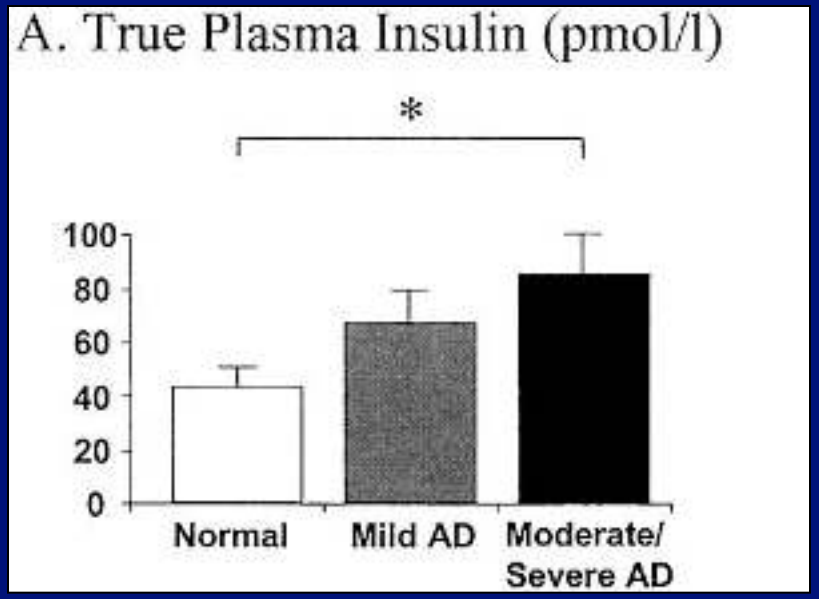
Insulin and AD

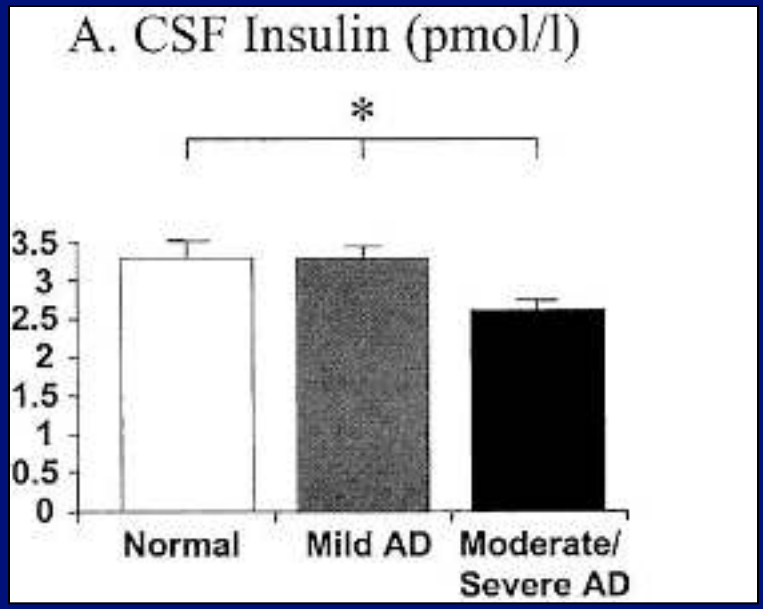
25 AD

Mean age : 71.2 years

14 controls

Mean age :72.4 years





Neurology,1998:164-168

Tube feeding

Tube Feeding in Advanced Dementia

- Does not prolong life in hospitalized patients or nursing home residents
- No clear evidence for decreased risk of aspiration pneumonia
- No evidence for increased patient comfort (restraints)

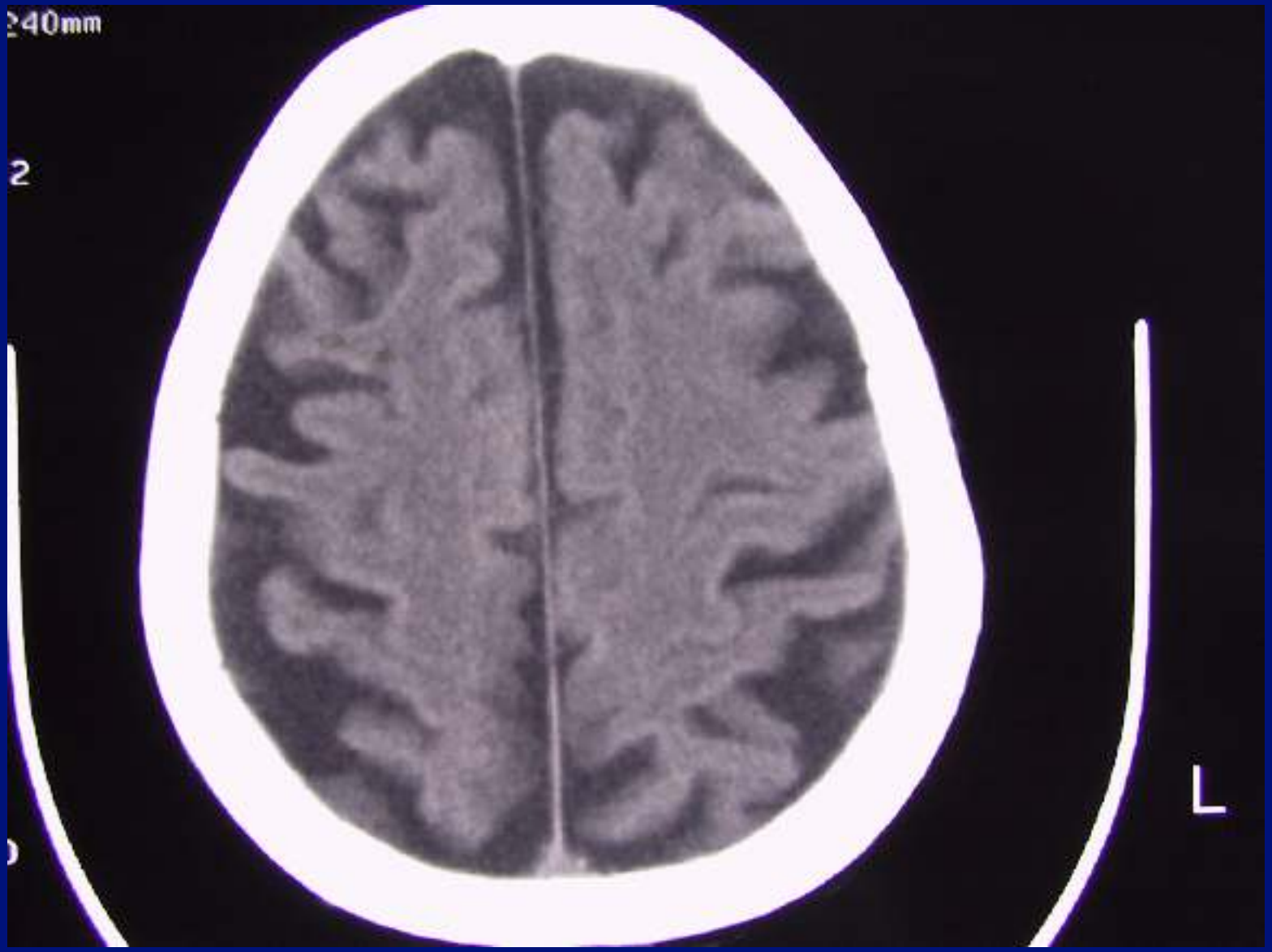
NEJM 2000;342:206

Arch Int Med 2001;161:594

Nutrition and Dementia Conclusions

- All dementias are not equivalent, results for AD cannot be automatically extrapolated to all other dementias
- Weight loss is more common in AD than aged matched controls and is associated with increased mortality
- Weight loss is multifactorial and pathophysiological mechanisms are not well known
- Weight loss may precede the onset of AD (but also obesity)
- Decisions regarding tube feeding should take into account published data and ethical principles




240mm
2
L

Correlation between clinical severity (CDR) and neuropathological staging
-Univariate Model-

- NFT staging accounted for 26.5% of the variability in clinical severity, Abeta protein deposition staging accounted for 13.0% and age for 4.4%

J Neuropathol Exp Neurol 2001;60:946

Correlation between clinical severity (CDR) and neuropathological staging
-Multivariate Model-

- NFT and age together accounted for 27.2% of the variability in CDR scores

- the addition of Abeta-protein staging to the model could only explain an extra 2.9% of the clinical variability

Gold et al. J Neuropathol Exp Neurol 2001;60:946

Vascular Dementia
Diagnostic criteria

- Hachinski Ischemic Score, Loeb, Rosen
- DSM-IV
- ICD 10
- NINDS-AIREN
- ADDTC

Vascular Dementia Criteria Clinicopathological Correlations

	Sensitivity	Specificity
ADDTC possible	0.70	0.78
NINDS-AIREN possible	0.55	0.84
DSM-IV	0.50	0.84
Hachinski Ischemic Scale	0.43	0.88
ADDTC probable	0.25	0.91
NINDS-AIREN probable	0.20	0.93
ICD-10	0.20	0.94

Neurology 1997; 49:690 Am J Psychiatry 2002;159:82

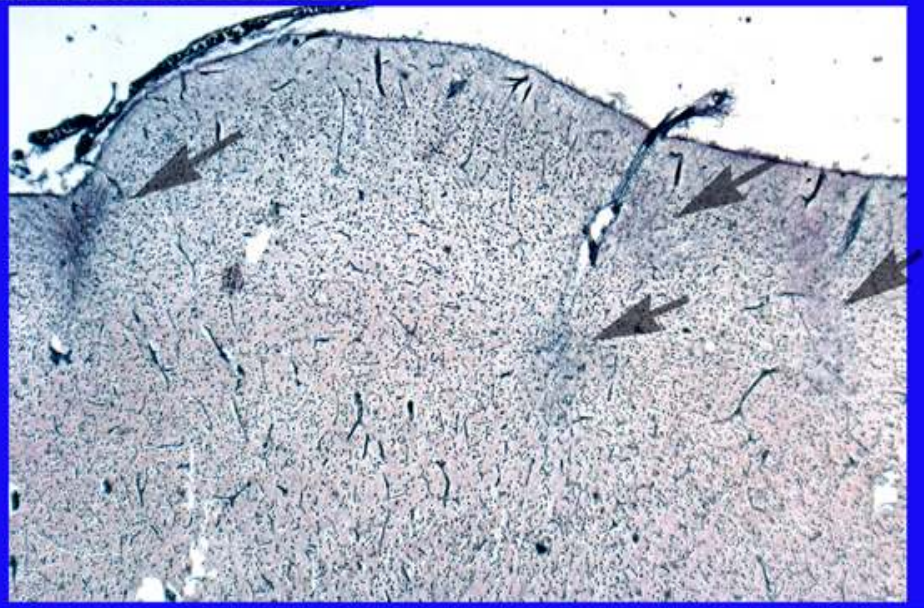
Vascular lesions and Cognition In Mixed Cases

- Individuals with AD neuropathology have a lower MMS if infarcts or lacunes are present
- The presence of vascular lesions decreases cognitive performance in early stages of AD
- For an identical clinical severity, AD lesions are decreased in cases with vascular lesions

JAMA 1997;2777:815
Lancet 1999; 354:919
Acta Neuropathol 2002;103:481

Microinfarcts

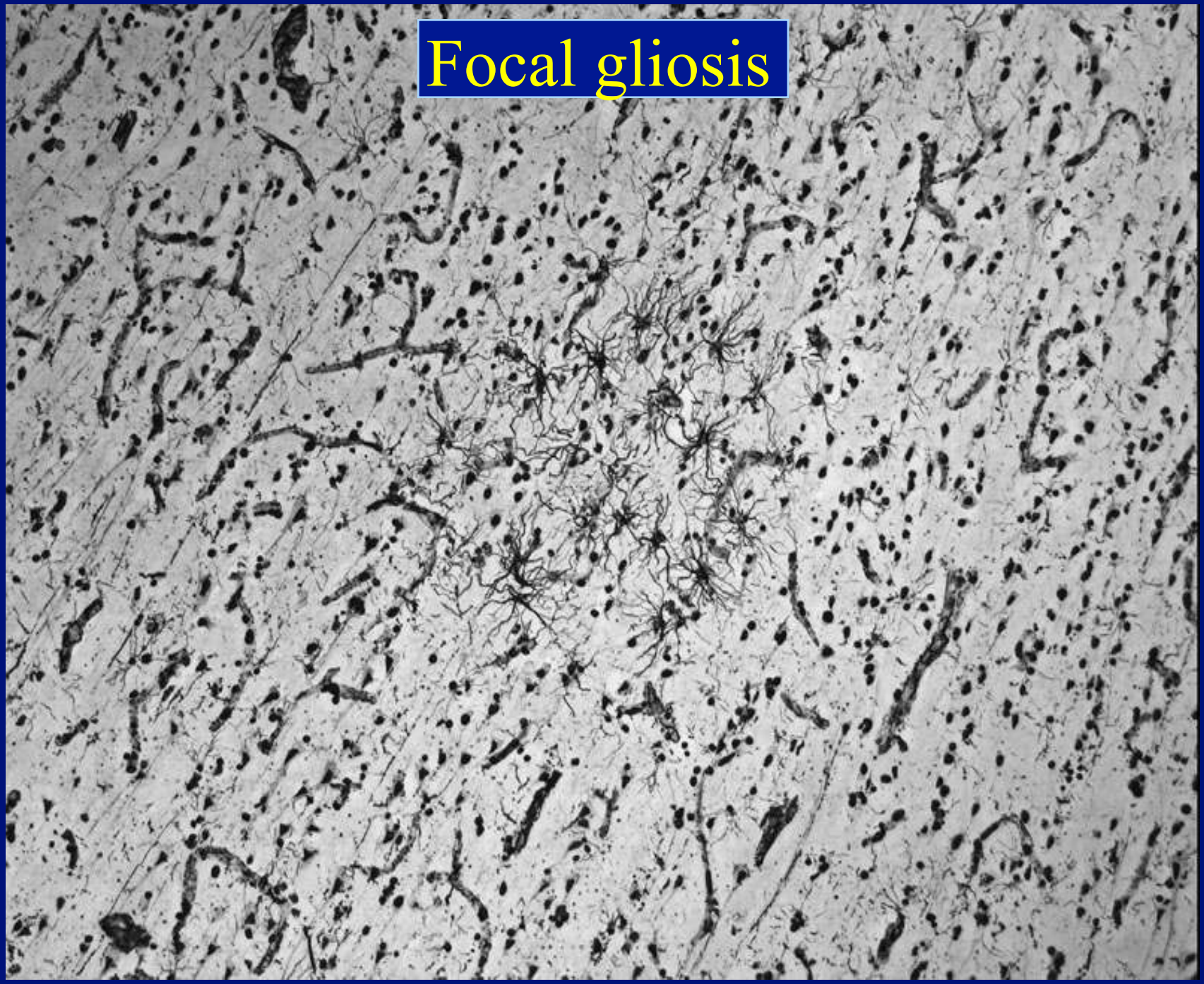




Diffuse White Matter Gliosis

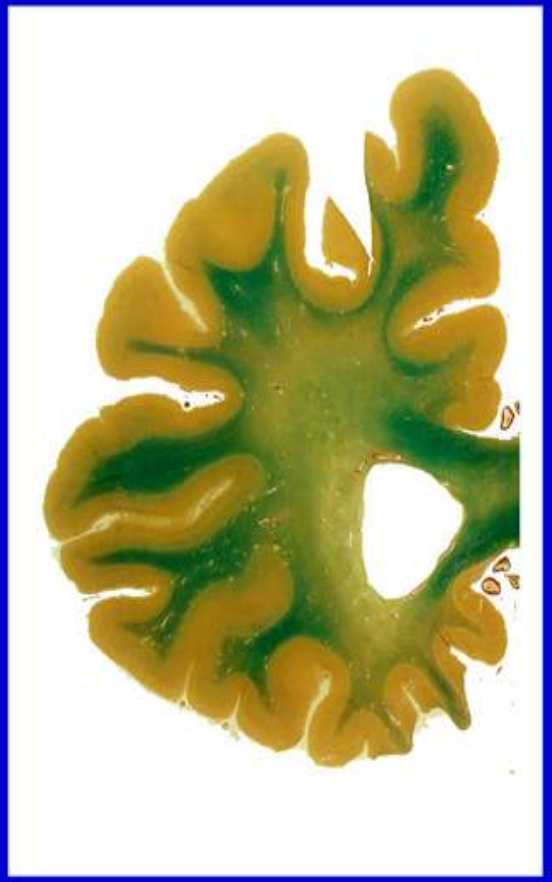


Focal gliosis



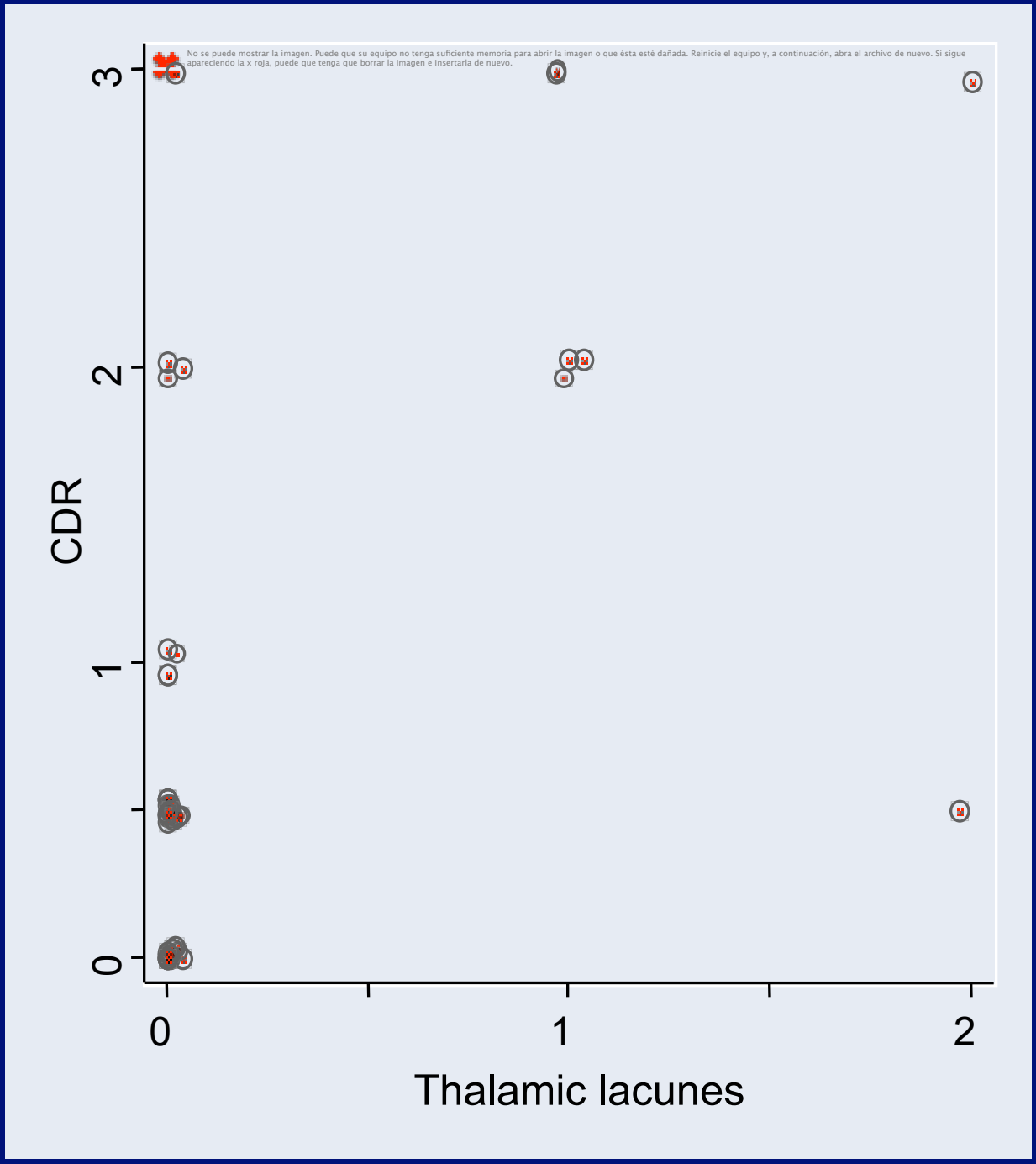
Demyelination





Cognition and Infarct Size Methodological Issues

- **Concomitant AD pathology may mask the consequences of microscopic ischemic lesions**
- **Ischemic lesions are heterogenous and different types of lesions may have different cognitive impacts**
- **Ischemic lesions can be diffuse, locations vary and assessment should thus be performed bilaterally in areas that are likely to be involved in cognition**


No se puede mostrar la imagen. Puede que su equipo no tenga suficiente memoria para abrir la imagen o que ésta esté dañada. Reinicie el equipo y, a continuación, abra el archivo de nuevo. Si sigue apareciendo la x roja, puede que tenga que borrar la imagen e insertarla de nuevo.
CDR
0
1
2
3
0
1
2
Thalamic lacunes

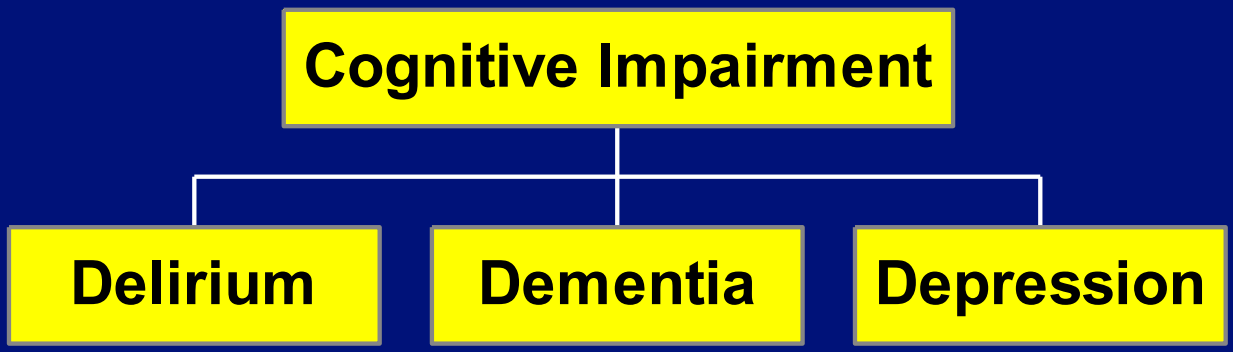
Vascular Lesions and Dementia

- Multi-infarct dementia
- Single infarct dementia
- Small vessel disease
- Hypoperfusion
- Hemorrhage

Cognitive Deficits Screening

- MMS
- Clock drawing

Differential Diagnosis of Cognitive Impairment




DFOV 240mm
STD
12
0
R
L
V 120
A 250
OSTERIOR FOSSA/U

Mixed Dementia

- **Presence of both AD and vascular lesions that have clinical consequences on cognitive function.**