Neuropathology *vs* Neuromythology*

UNIVERSITY OF KENTUCKY

Pete Nelson

**-Thanks and apologies to Dr William Landau*

"I am delighted with your critical piece, but distressed and dismayed at your diffidence. Like God [*Sic*!], every neuropathologist is entitled to the last word, *ex officio*"

--Dr William Landau, MD
Washington University

What is Alzheimer's disease ?

What is Alzheimer's disease ?

NIA-Reagan Criteria (1997-2012)

Clinical	Cognitive impairment
Pathological	Neurofibrillary tangles
	Neuritic amyloid plaques

ELSEVIER

Alzheimer's & Dementia 8 (2012) 1–13

Alzheimer's & Dementia

Featured Articles

National Institute on Aging–Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease

Bradley T. Hyman[a], Creighton H. Phelps[b], Thomas G. Beach[c], Eileen H. Bigio[d], Nigel J. Cairns[e,f], Maria C. Carrillo[g], Dennis W. Dickson[h], Charles Duyckaerts[i], Matthew P. Frosch[j], Eliezer Masliah[k,l], Suzanne S. Mirra[m], Peter T. Nelson[n], Julie A. Schneider[o,p,q], Dietmar Rudolf Thal[r], Bill Thies[g], John Q. Trojanowski[s], Harry V. Vinters[t,u], Thomas J. Montine[v,*]

Acta Neuropathol (2012) 123:1–11
DOI 10.1007/s00401-011-0910-3

CONSENSUS PAPER

National Institute on Aging–Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease: a practical approach

Thomas J. Montine · Creighton H. Phelps · Thomas G. Beach · Eileen H. Bigio · Nigel J. Cairns · Dennis W. Dickson · Charles Duyckaerts · Matthew P. Frosch · Eliezer Masliah · Suzanne S. Mirra · Peter T. Nelson · Julie A. Schneider · Dietmar Rudolf Thal · John Q. Trojanowski · Harry V. Vinters · Bradley T. Hyman

What is Alzheimer's disease ?

NIA-AA Criteria (2012 →)

Clinical

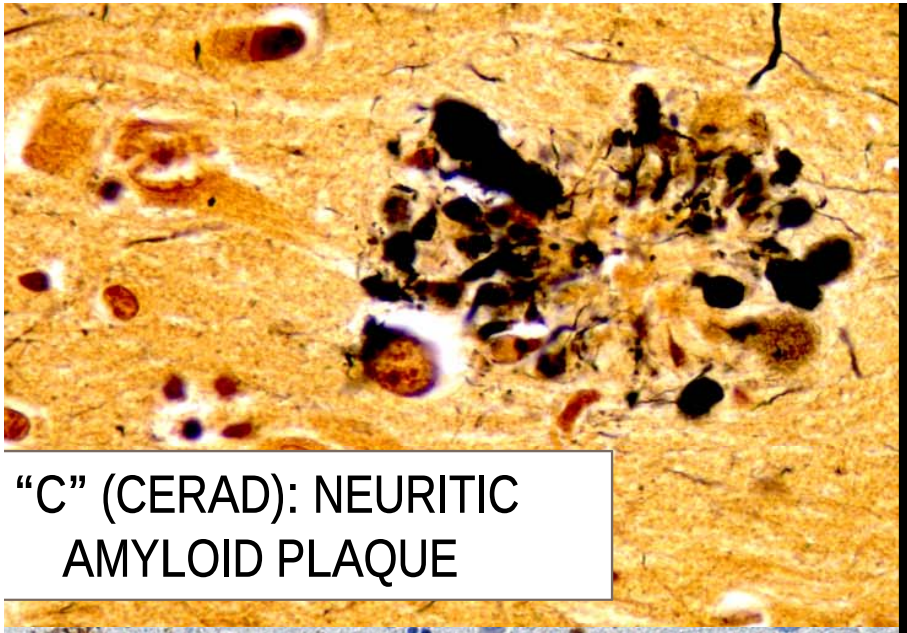
Pathological

~~Cognitive Impairment~~

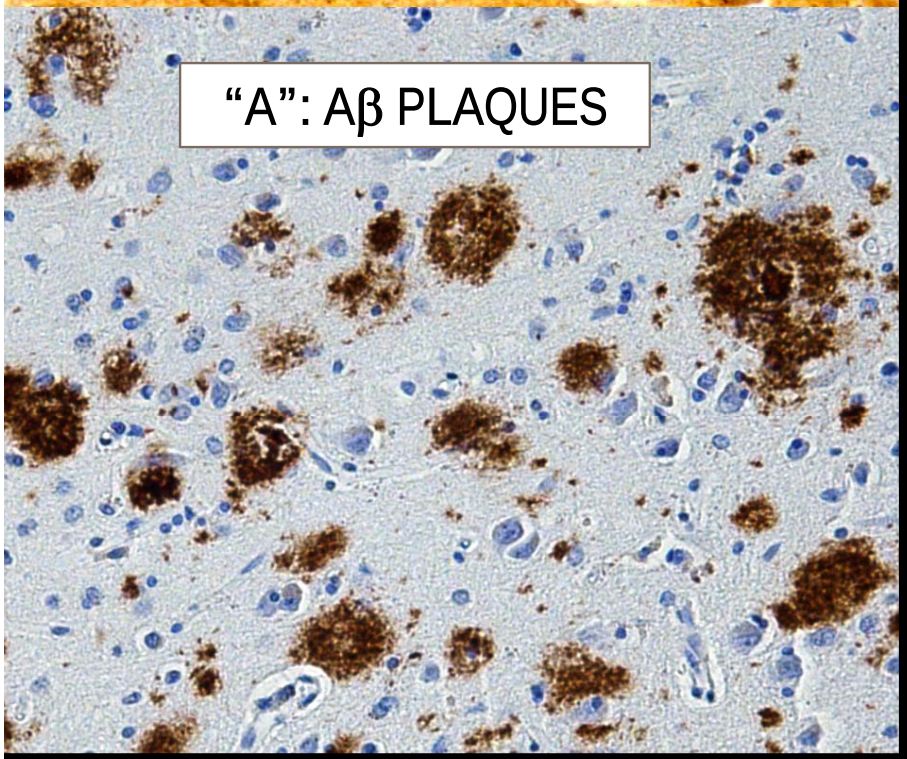
Neurofibrillary tangles

Neuritic amyloid plaques

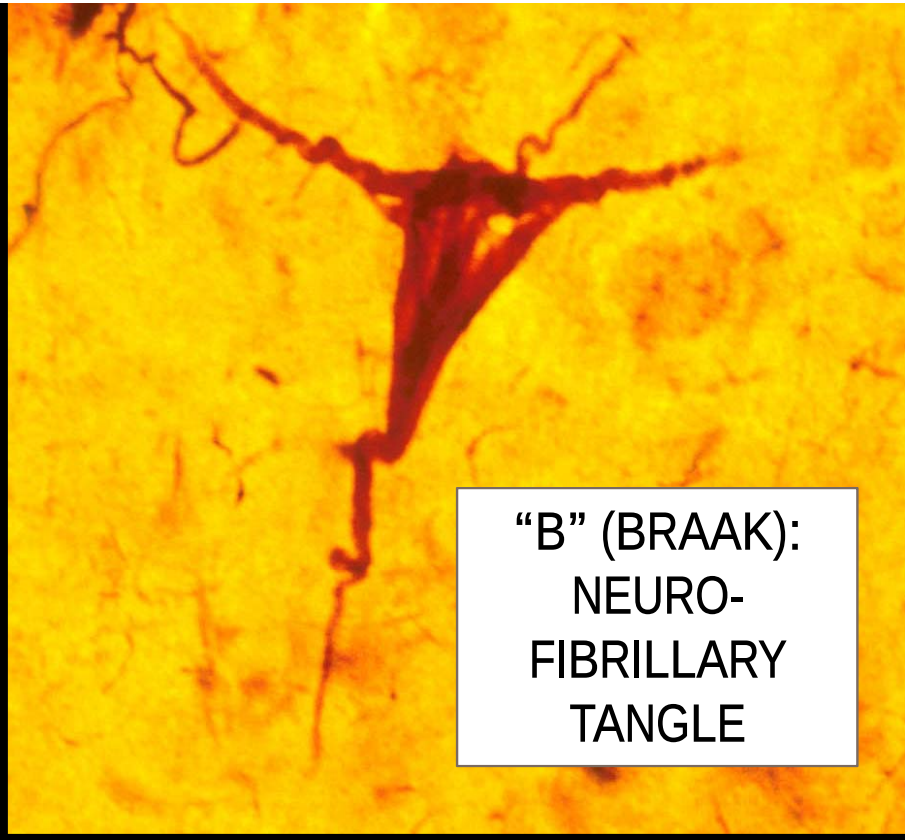
Aβ amyloid plaques



"C" (CERAD): NEURITIC AMYLOID PLAQUE

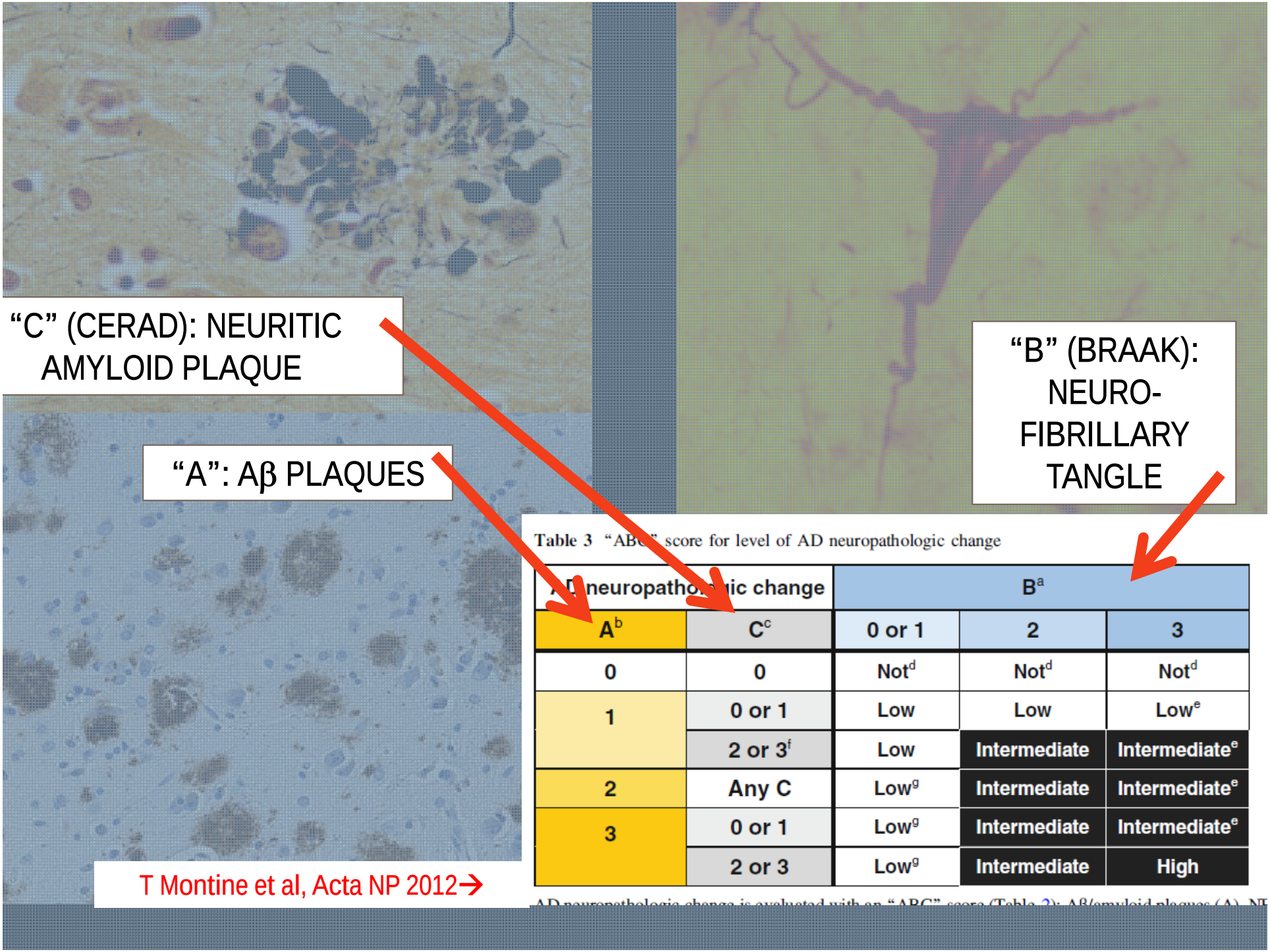


"A": Aβ PLAQUES



"B" (BRAAK): NEURO-FIBRILLARY TANGLE

AD neuropathologic hallmarks



"C" (CERAD): NEURITIC AMYLOID PLAQUE

"A": Aβ PLAQUES

"B" (BRAAK): NEURO-FIBRILLARY TANGLE

Table 3 "ABC" score for level of AD neuropathologic change

AD neuropathologic change		B[a]		
A[b]	C[c]	0 or 1	2	3
0	0	Not[d]	Not[d]	Not[d]
1	0 or 1	Low	Low	Low[e]
	2 or 3[f]	Low	Intermediate	Intermediate[e]
2	Any C	Low[g]	Intermediate	Intermediate[e]
3	0 or 1	Low[g]	Intermediate	Intermediate[e]
	2 or 3	Low[g]	Intermediate	High

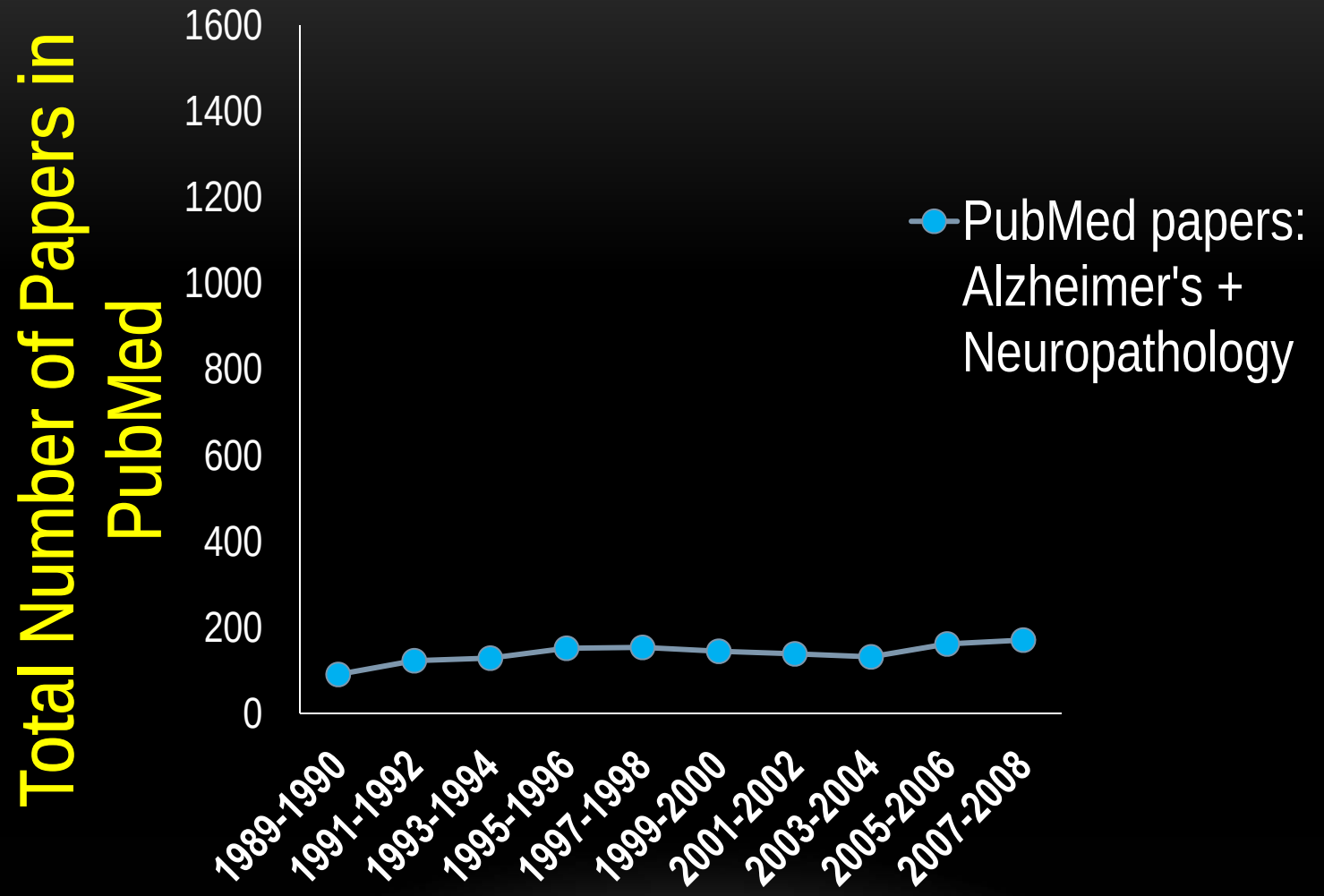
AD neuropathologic change is evaluated with an "ABC" score (Table 2): Aβ/amyloid plaques (A), NF

T Montine et al, Acta NP 2012→


DATA

Recent years have seen dramatic advancements

A central role for ADCs and NACC


Total Number of Papers in PubMed
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1400
1200
1000
800
600
400
200
0
1989-1990
1991-1992
1993-1994
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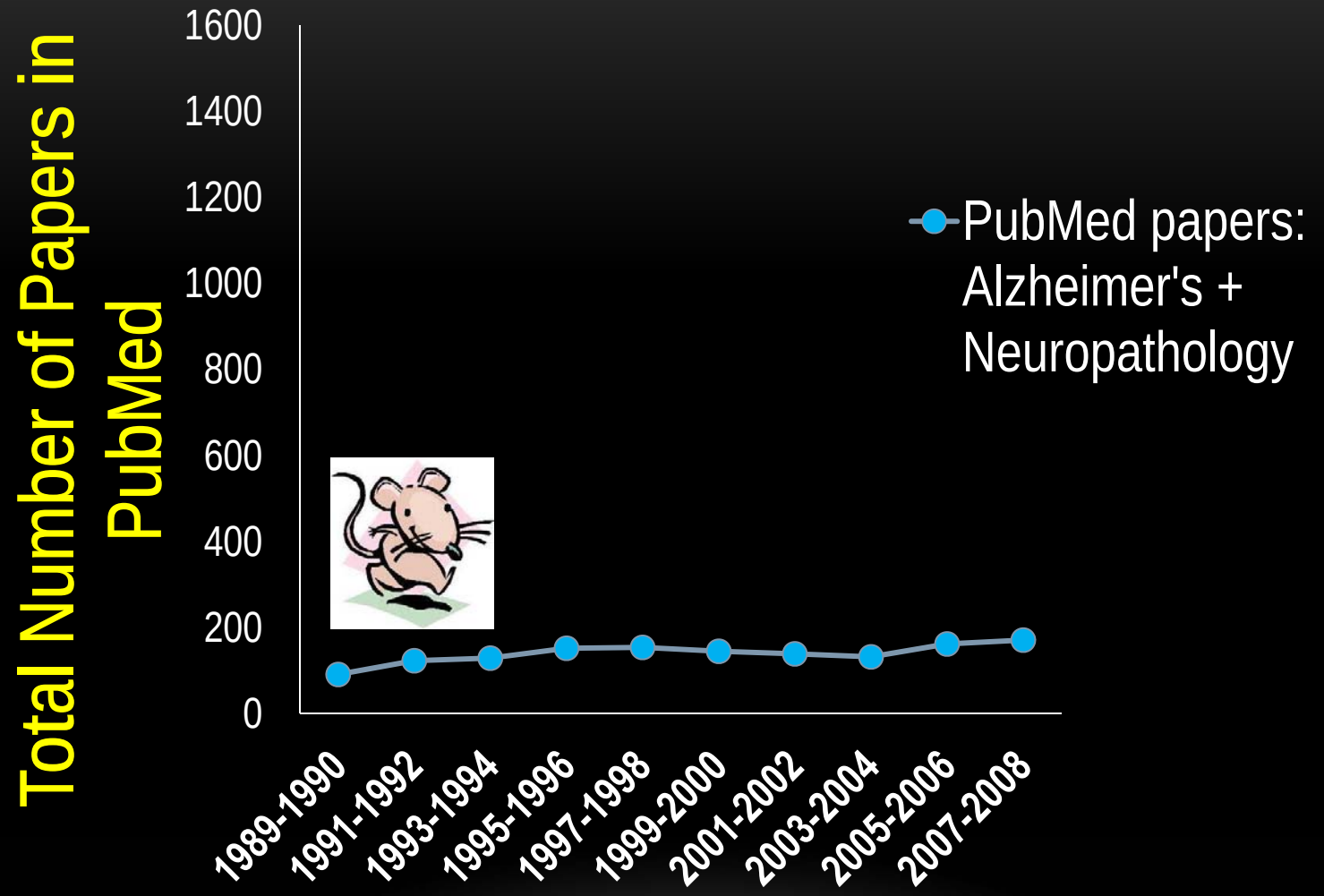
1997-1998
1999-2000
2001-2002
2003-2004
2005-2006
2007-2008
PubMed papers: Alzheimer's + Neuropathology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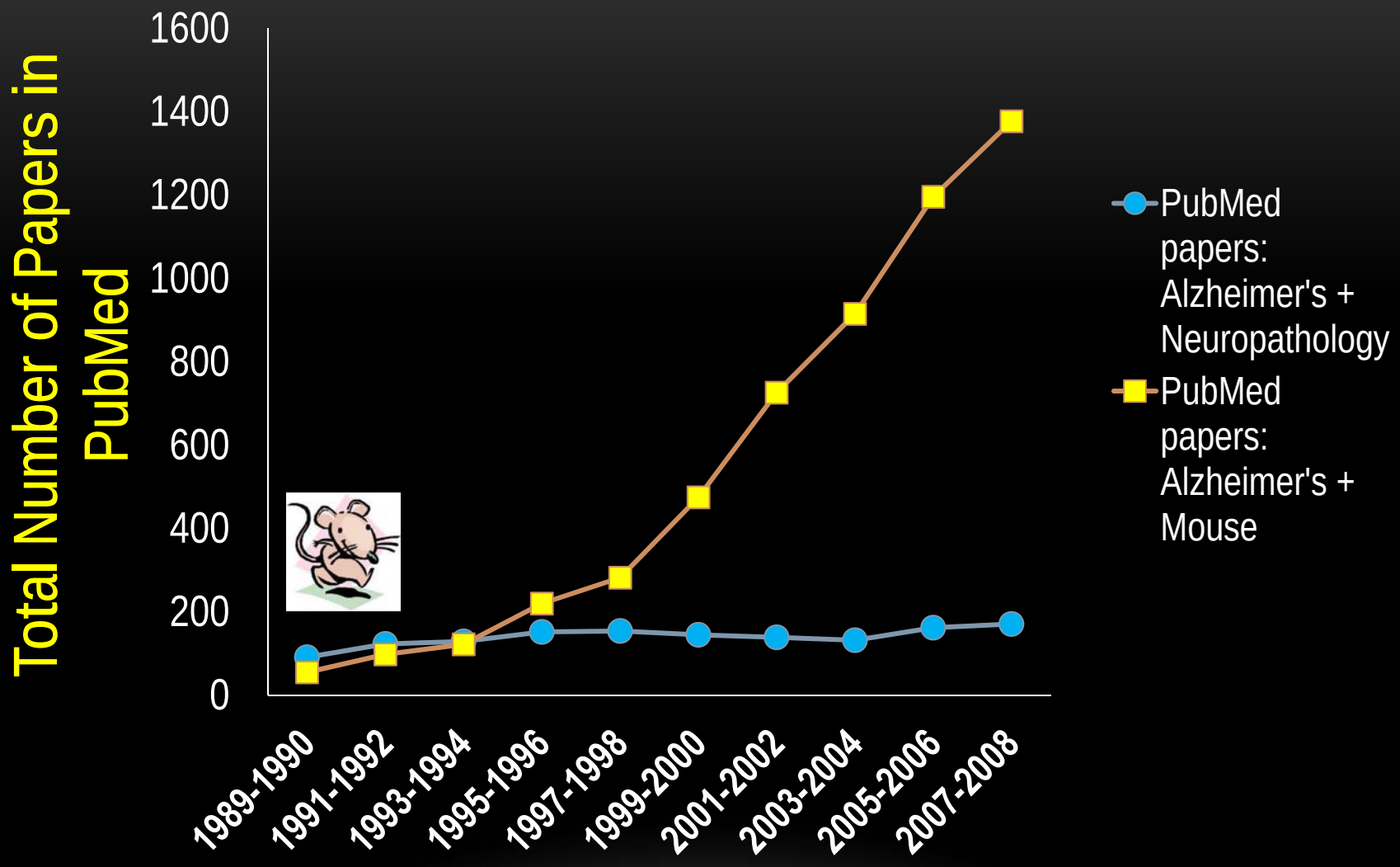
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2005-2006
2007-2008
PubMed papers: Alzheimer's + Neuropathology
PubMed papers: Alzheimer's + Mouse

Better data→ more valid conclusions

ADCs and related series: *a new standard*

- **Longitudinal assessment**
- **Improving clinical & neurocognitive evaluation**
- **Improving pathological evaluation (new diseases!)**
- **More variables, more quantitative correlation**

ADCs and related series: *a new standard*

- **Longitudinal assessment**
- **Improving clinical & neurocognitive evaluation**
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- **More variables, more quantitative correlation**

Allow us to start leaving behind studies with:

- **Overly interpreted under-evaluated patients**
- **Fewer variables, over-dichotomization**
- **“The Anecdote”**

Neuropathology
vs
Neuromythology

Myth Roundup

1. Clinicians are 90% specific in AD diagnosis
2. Plaques and tangles don't correlate with dementia
   A. End-stage AD pathology can be seen in cognitively normal individuals
   B. There is dissociation between AD pathology and cognitive impairment in "advanced old age"
   C. AD is just "brain aging", and vice versa

Myth #1

1. **Clinicians are 90% specific in AD diagnosis**

Myth #1A

1. **Clinicians are 90% specific in AD diagnosis**

Corollary myth:
There is only one disease that causes cognitive impairment in the elderly

Alagille Syndrome
Alcohol-Related Liver Disease
Alpha-1 Antitrypsin Deficiency
Autoimmune Hepatitis
Benign Liver Tumors
Biliary Atresia
Cirrhosis of unknown cause
Galactosemia
Gilbert Syndrome
Hemochromatosis
Hepatitis A-->E
Hepatocellular Carcinoma
Liver Cysts
Liver Cancer
Liver Transplant
Non-Alcoholic Fatty Liver Disease
Primary Biliary Cirrhosis (PBC)
Primary Sclerosing Cholangitis (PSC)
Reye Syndrome
Type I Glycogen Storage Disease
Wilson Disease

LIVER DISEASE !!!! (lots of em)

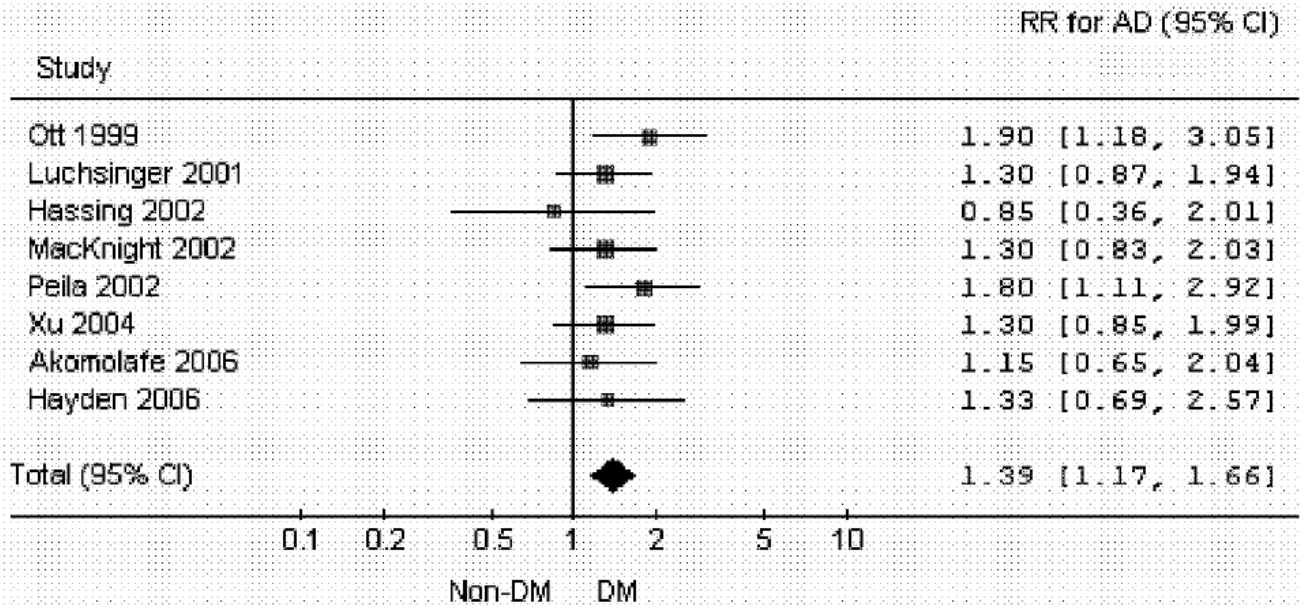
OPEN ACCESS Freely available online

PLoS one

Diabetes and the Risk of Multi-System Aging Phenotypes: A Systematic Review and Meta-Analysis

Feng-Ping Lu[1,2], Kun-Pei Lin[1,3], Hsu-Ko Kuo[1,4,5]*

1 Department of Geriatrics and Gerontology, National Taiwan University Hospital, Taipei, Taiwan, **2** Institute of Health Policy and Management, College of Public Health, National Taiwan University, Taipei, Taiwan, **3** Institute of Epidemiology, College of Public Health, National Taiwan University, Taipei, Taiwan, **4** Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan, **5** Division of Gerontology Research, National Health Research Institutes, Taipei, Taiwan



>20,000 individuals

P<<0.001

Meta-analysis of clinical (no-autopsy) studies: positive association between "Alzheimer's disease" and diabetes

Studies with brain autopsies show the opposite result

Study	Diabetics	Non-diabetics	In diabetics, versus nondiabetics	
	N	*N*	Risk of AD pathology	Risk of CVD pathology
Heitner and Dickson [89]	49	52	Not increased	Not evaluated
Peila et al. [166]	216 total autopsies		Not increased[a]	Increased
Janson et al. [98]	28	19	Not increased[b]	Not evaluated
Beeri et al. [24]	61	324	Decreased	Increased
Arvanitakis et al. [15]	36	197	Not increased	Increased
Nelson et al. [149]	50	189	Decreased	Increased
Sonnen et al. [210]	59	137	Decreased[c]	Increased
Ahtiluoto et al. [8]	70	221	Decreased	Increased
Matsuzaki et al. [135]	135 total autopsies		Not clear[d]	Not clear[d]

Nelson et al,
Acta Neuropathologica, 2011

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Diabetes is associated with increased cerebrovascular disease, ***not AD*, pathology (N>1,600)**

Acta Neuropathologica, 2011


I'LL BE THE FIRST TO ADMIT, THE RESULTS OF YOUR AUTOPSY WERE VERY SURPRISING.
4-16
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SPEEDBUMP.COM
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Crit Care. 2007;11(2):R48.
Premortem clinical diagnoses and postmortem autopsy findings: discrepancies in critically ill cancer patients.
Pastores SM, Dulu A, Voigt L, Raoof N, Alicea M, Halpern NA.

"There was a discrepancy rate of 26% between premortem clinical diagnoses and postmortem findings in cancer patients…" (26% had major missed diagnoses)

- 54% of autopsies revealed a new diagnosis with potential adverse impact on survival

JAMA. 2003 Jun 4;289(21):2849-56.
Changes in rates of autopsy-detected diagnostic errors over time: a systematic review.
Shojania KG, Burton EC, McDonald KM, Goldman L.

(based on systematic review of autopsy series)

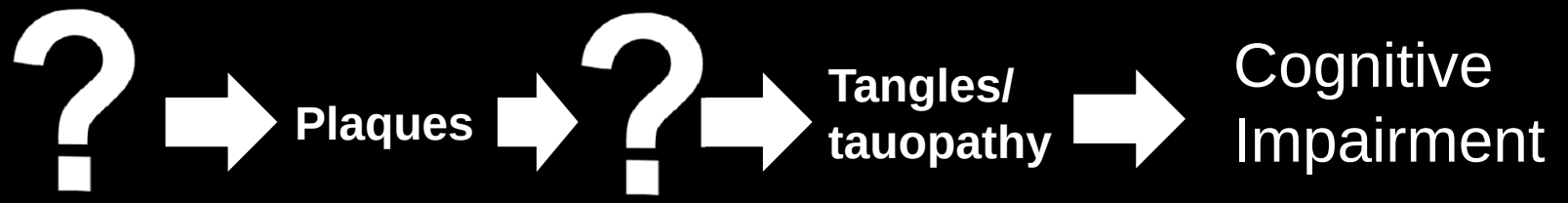
"A contemporary US institution could observe a major error (clinically MISSED diagnoses involving a 'primary cause of death') rate from 8.4% to 24.4%"

Myth #2

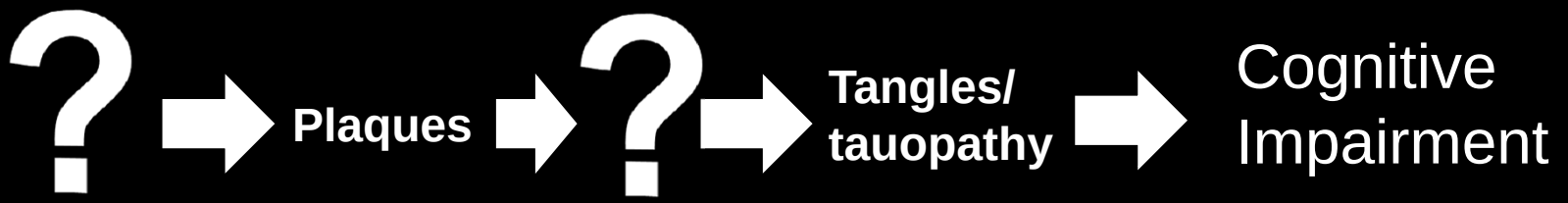
2. Plaques and tangles don’t correlate with cognitive impairment

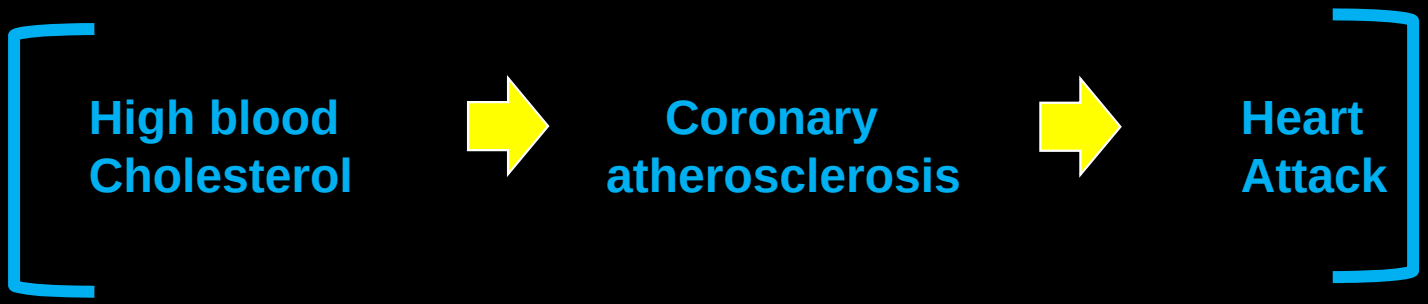
AREN'T
WE IN THE
POST-
PLAQUE & TANGLE
ERA ???????

(Hypothesis)

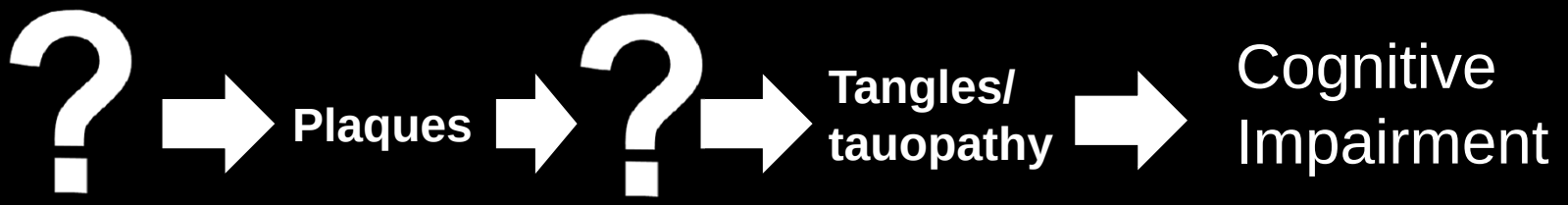


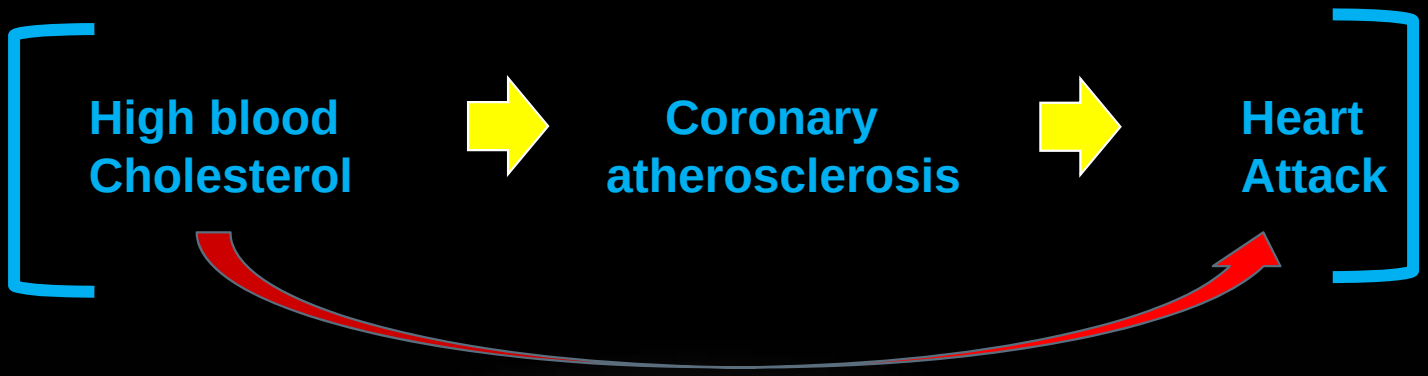
(Hypothesis)


?
Plaques
?
Tangles/
tauopathy
Cognitive
Impairment


High blood
Cholesterol
Coronary
atherosclerosis
Heart
Attack

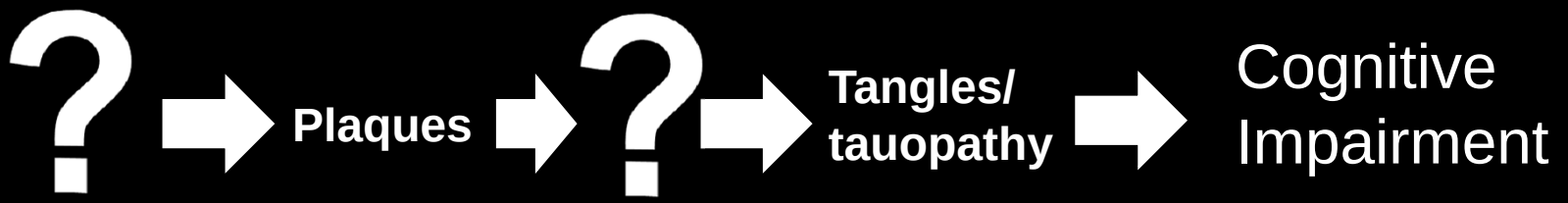
(Hypothesis)

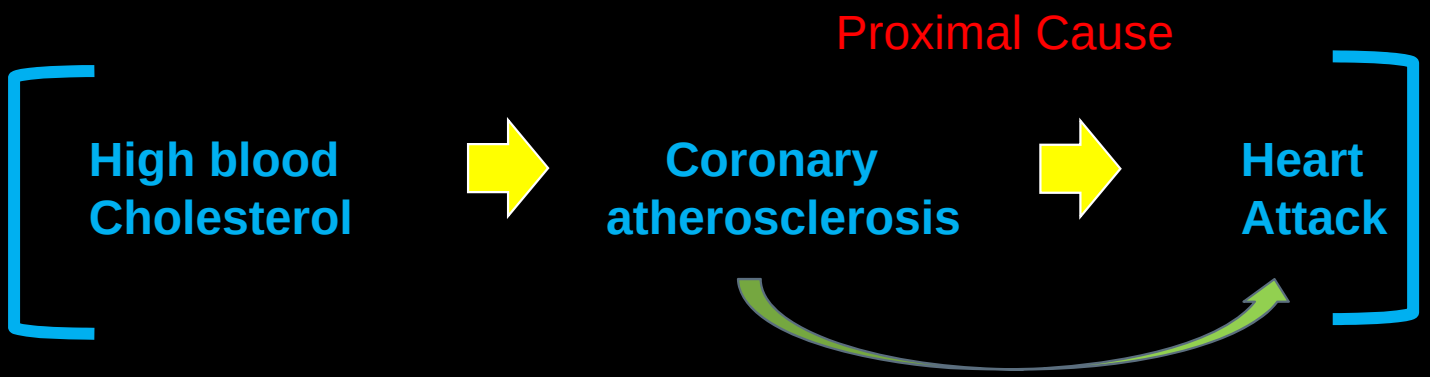




Correlation very poor

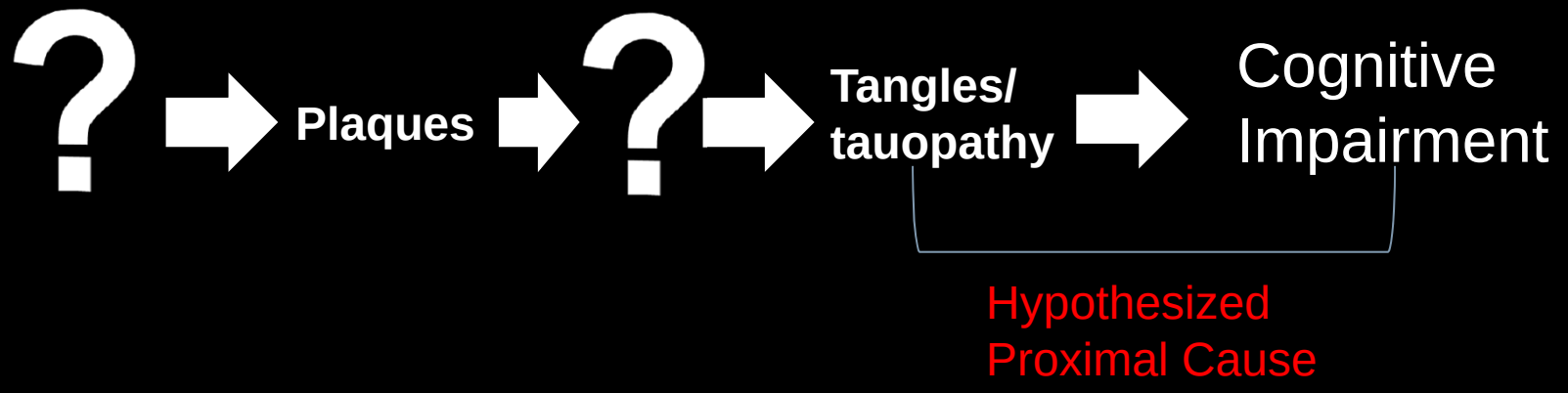
(Hypothesis)



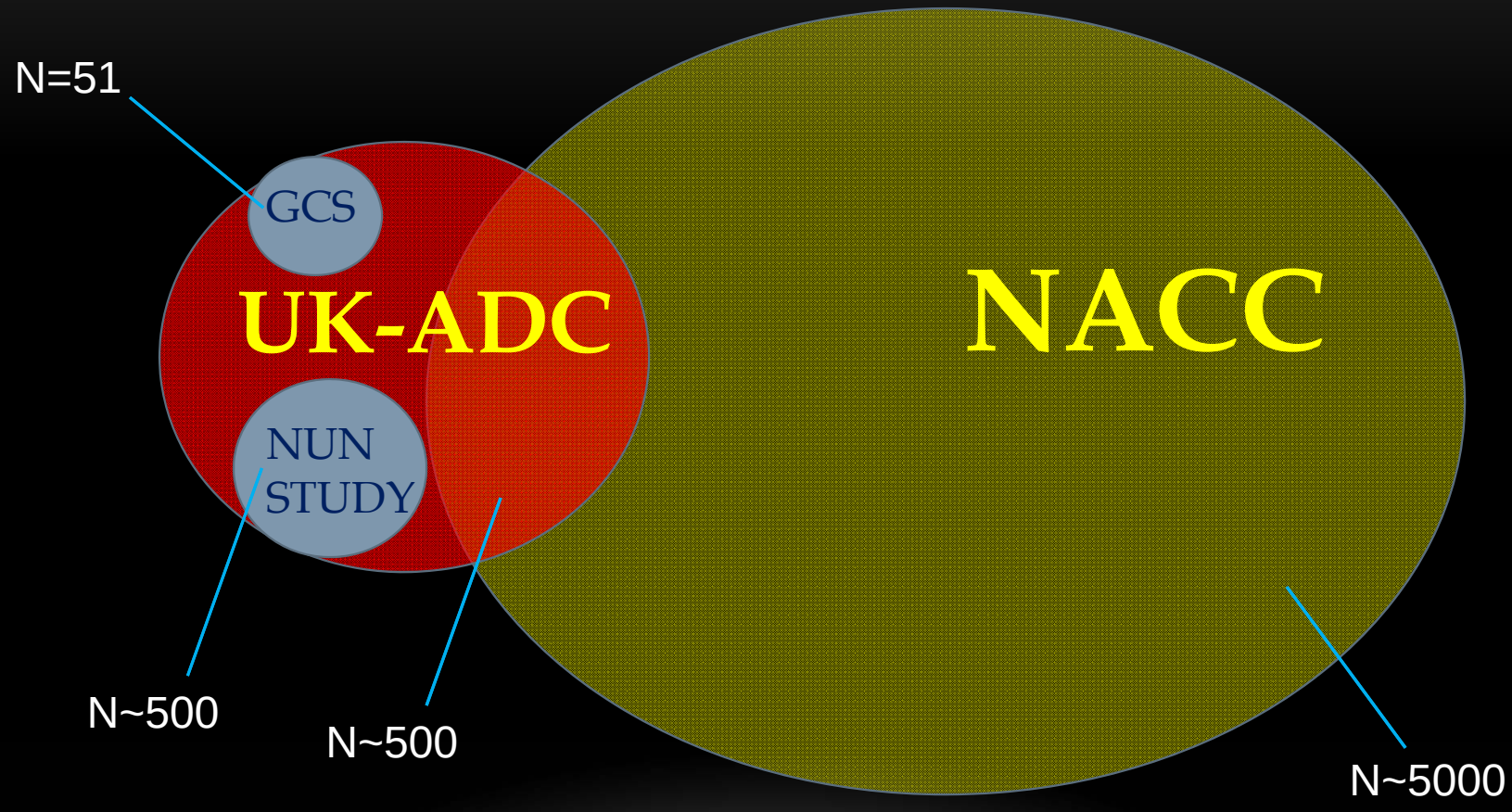


Correlation much better

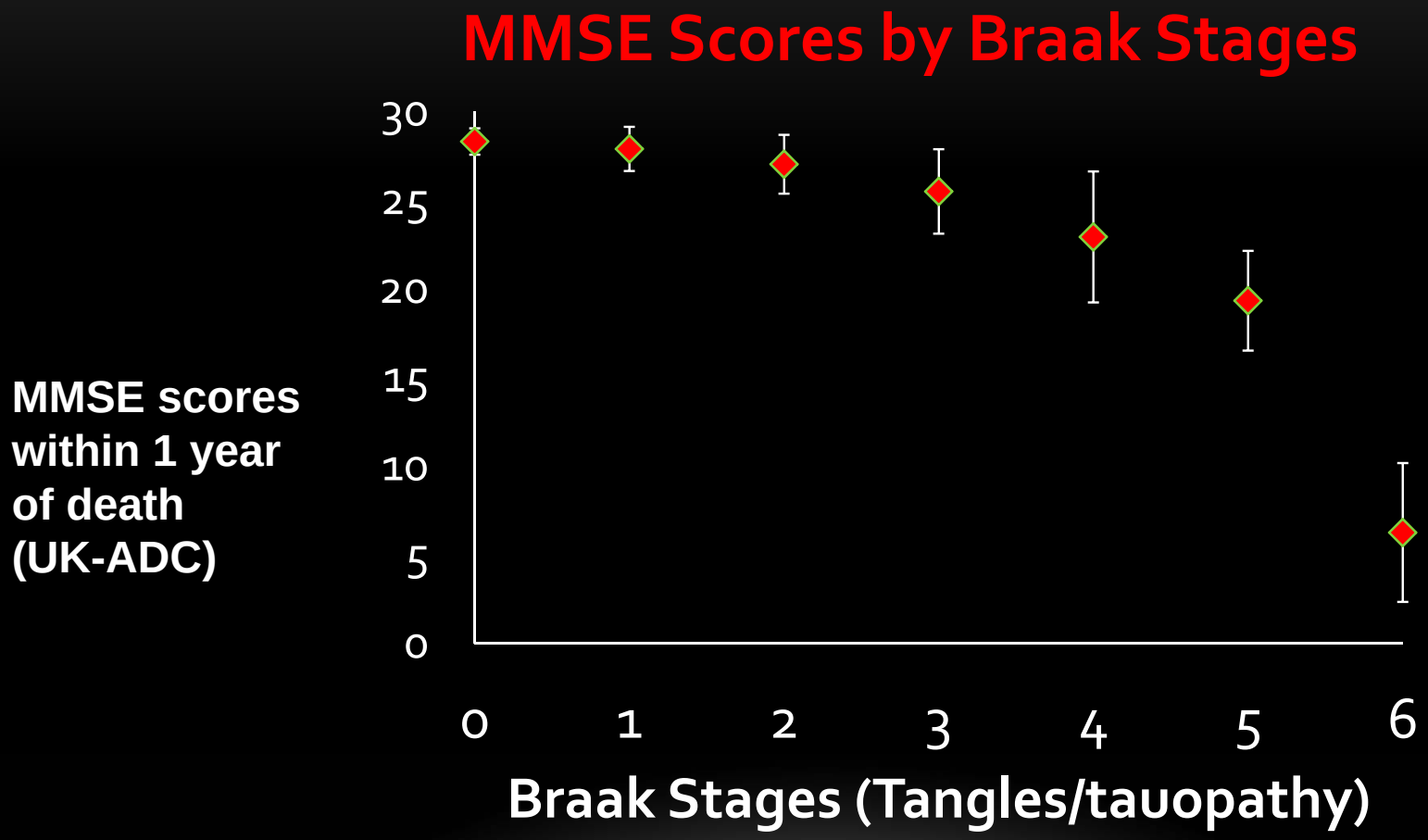
(Hypothesis)


?
Plaques
?
Tangles/
tauopathy
Cognitive
Impairment
Hypothesized
Proximal Cause

Clinical-pathological studies: incredibly rich resources with replete antemortem data and thorough autopsy information



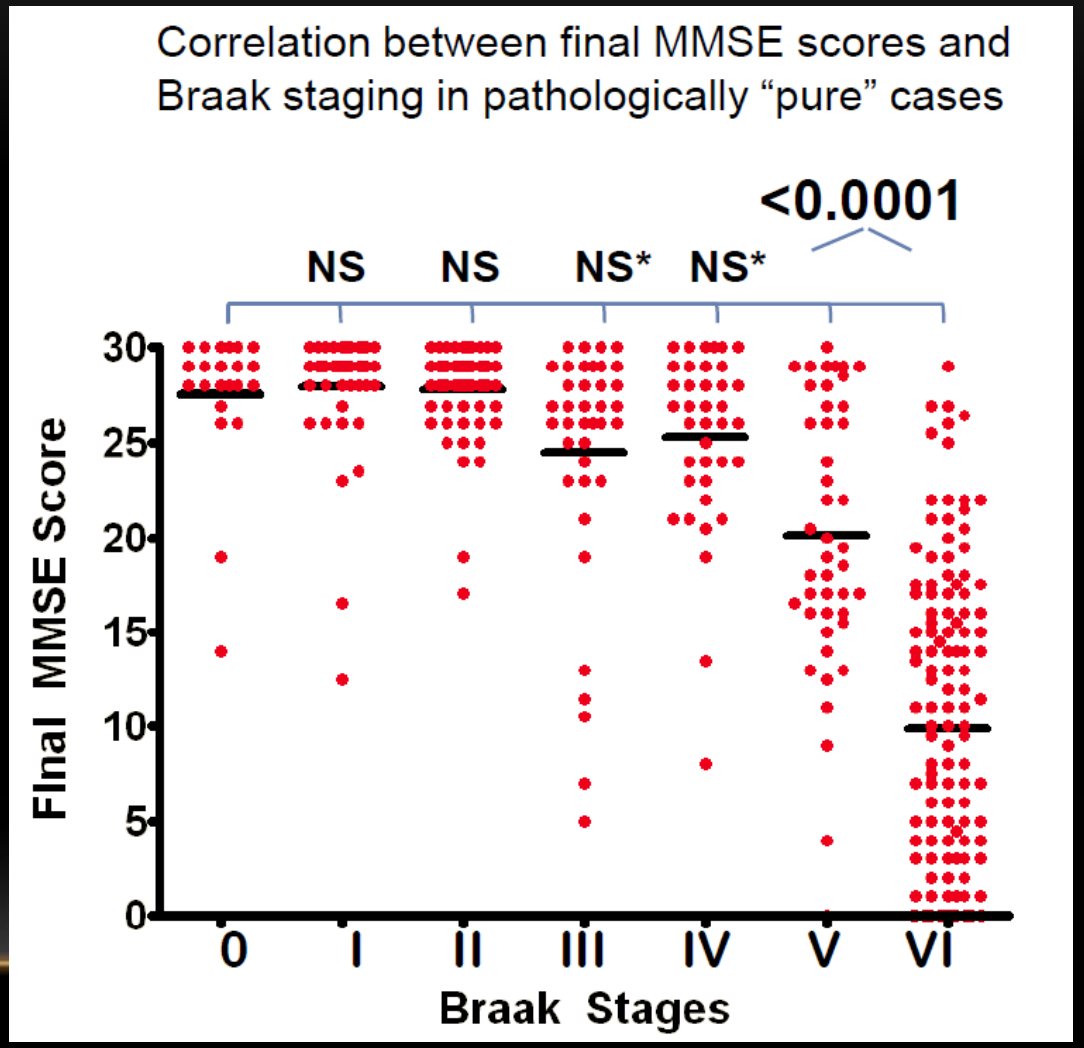
Brain pathology correlates strongly with the severity of cognitive impairment



PT Nelson, H Braak, and WR Markesbery, JNEN 2009

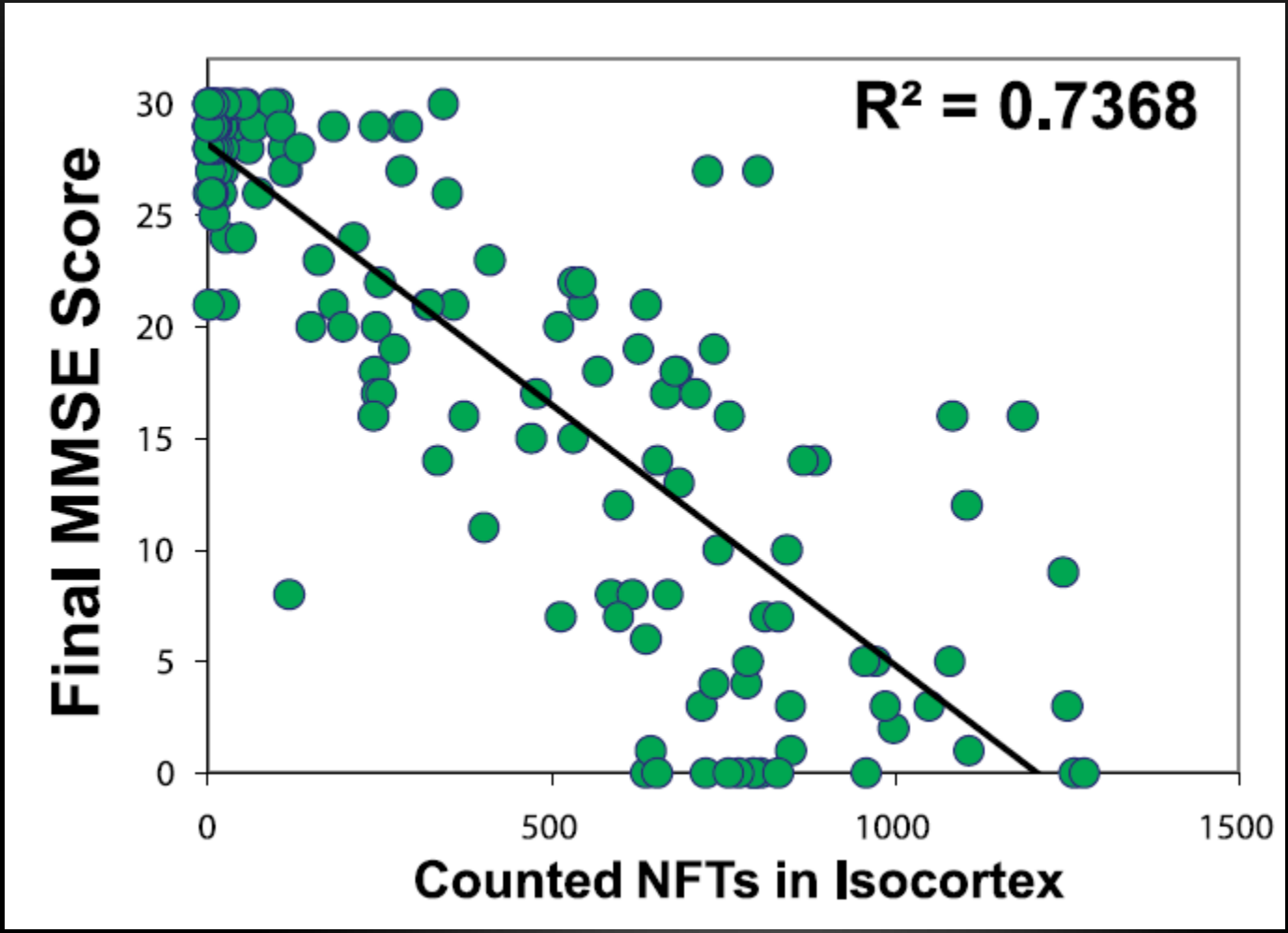
Brain pathology correlates strongly with the severity of cognitive impairment

(Nun Study)



GA Jicha et al, 2011, *Neurobiol Aging*

Best correlate with cognitive status: Neocortical NFTs



Nelson PT et al, *JNEN* 2012

Myth #2A

2. Plaques and tangles don't correlate with cognitive impairment

Corollary Myth

End-stage AD pathology can be seen in cognitively normal individuals

PT Nelson, H Braak, and WR Markesbery, JNEN 2009

10 good studies
<u>+1 case report</u>
555 nondemented Individuals

12 Braak stage V
3 Braak stage VI

2.7% with "AD path"

TABLE 2. Autopsy Series on Nondemented Persons With False-Positive Pathological Diagnosis of National Institute or Aging–Reagan Institute High Likelihood for Alzheimer Disea (Braak Stages V and VI)

Nondemented, n	Braak Stage V	Braak Stage VI	Total Braak Stage V/VI	Referer
1*	0	1*	1	(47)
49	0	0	0†	(48)
142	1	0	1	(33)
39	1	0	1	(49)
42	3	0	3	(50)
18	0	0	0†	(56)
17	0	0	0†	(55)
89	?‡	?‡	3‡	(57)
31	0	0	0	(51)
68	1	1	2	(54)
59§	3	1§	4	
n = 555			n = 15	

*Case report (47).
†Braak stages inferred.
‡Cases designated as Braak V/VI.
§From the University of Kentucky Alzheimer's Disease Center, Braak VI case v relatively low neocortical neurofibrillary tangles (Fig. 5).

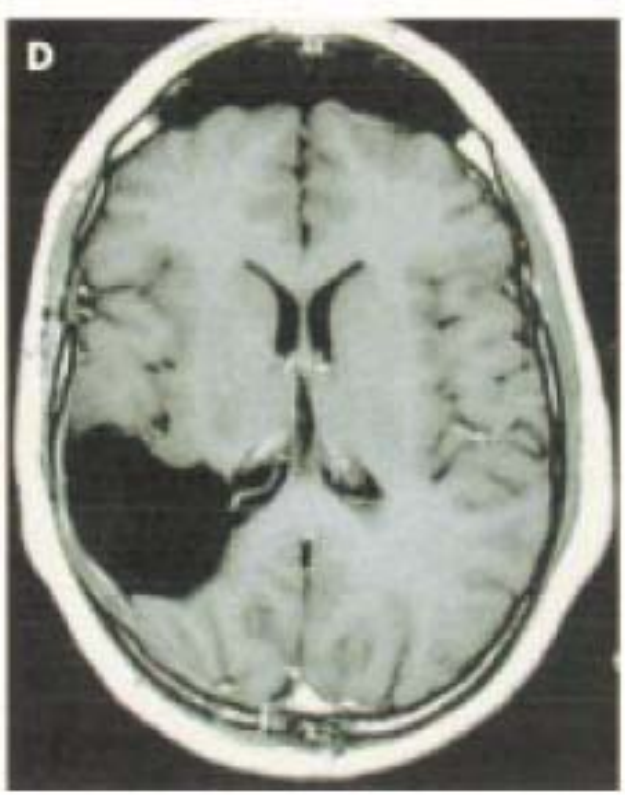
2.7% of patients thought to be “nondemented” show Braak stages V (12/555) or VI (3/555)

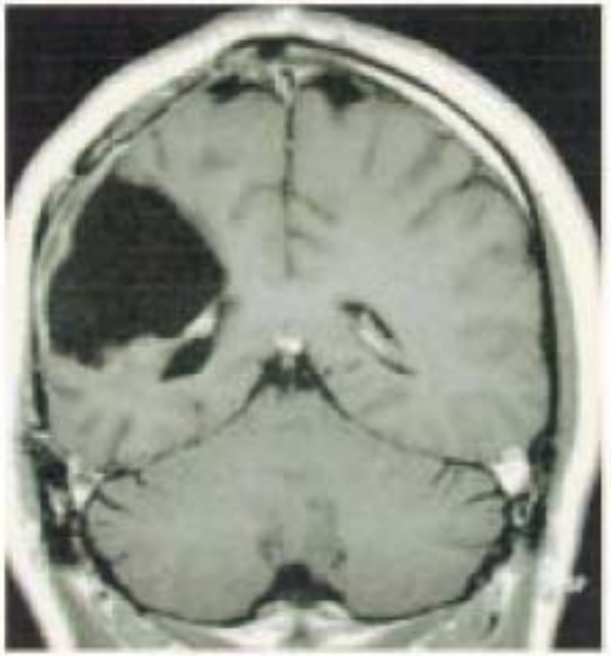
Well,

what did you expect?

Post-operative MRI following glioma resection
Post-operative MMSE score = 30/30

"Cognitive Reserve" is NOT a myth

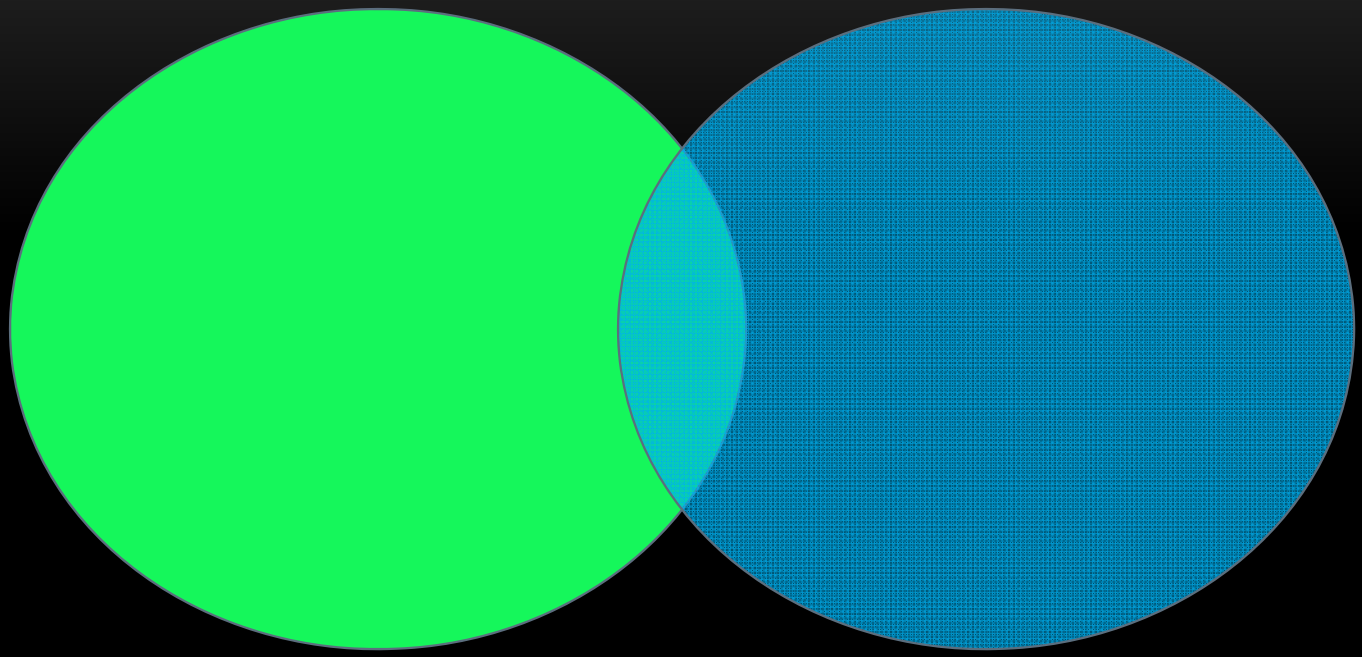




Long term reshaping of language, sensory, and motor maps after glioma resection: a new parameter to integrate in the surgical strategy

H Duffau, D Denvil, L Capelle

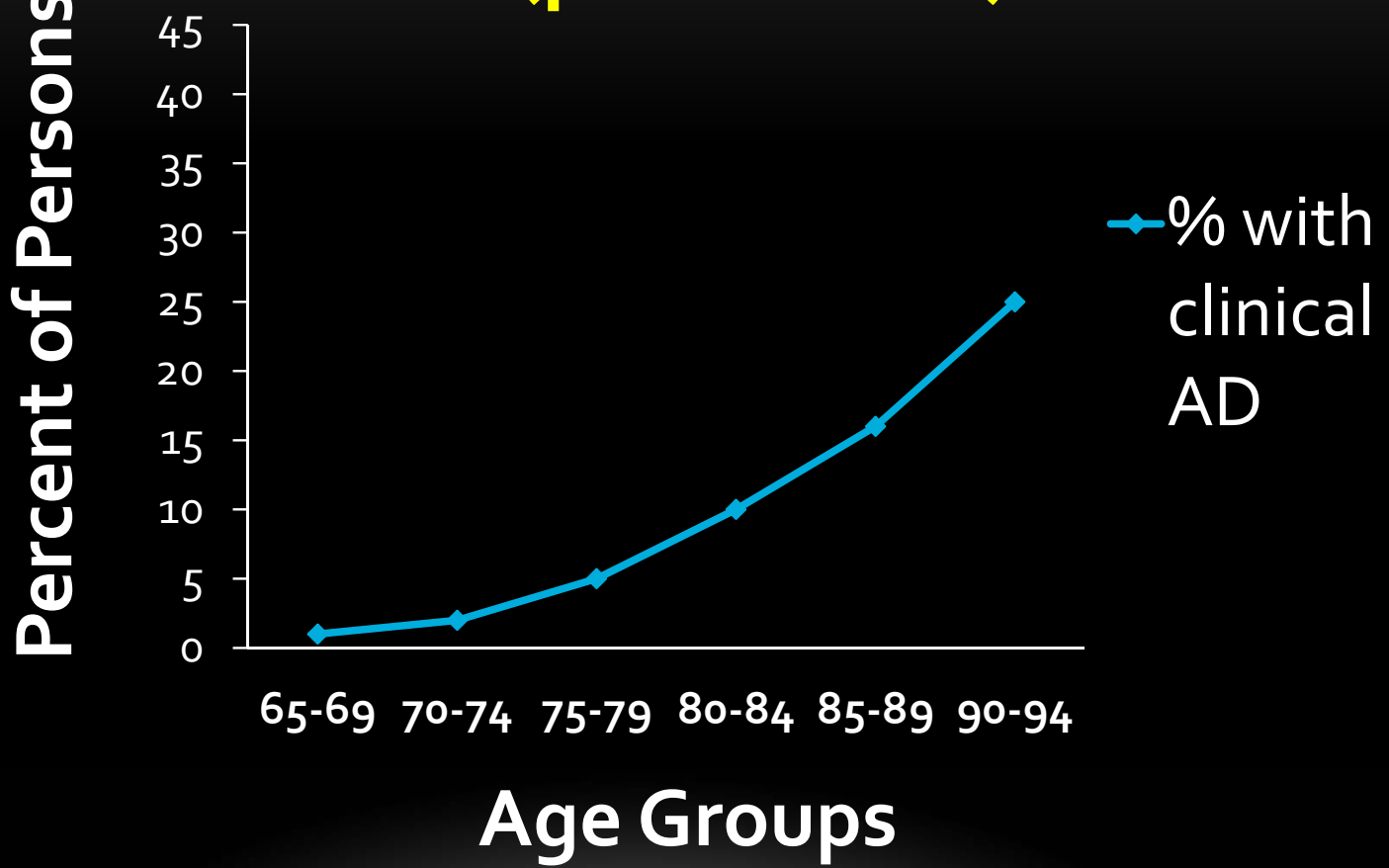
J Neurol Neurosurg Psychiatry 2002;**72**:511–516

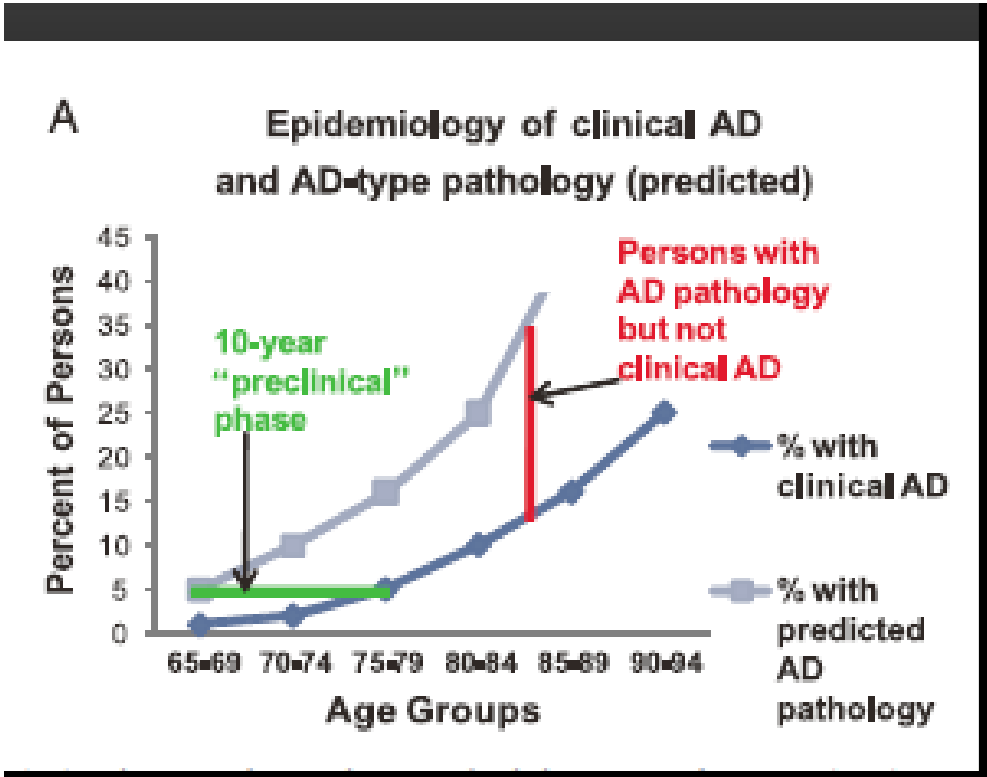


Epidemiology

Neuropathology

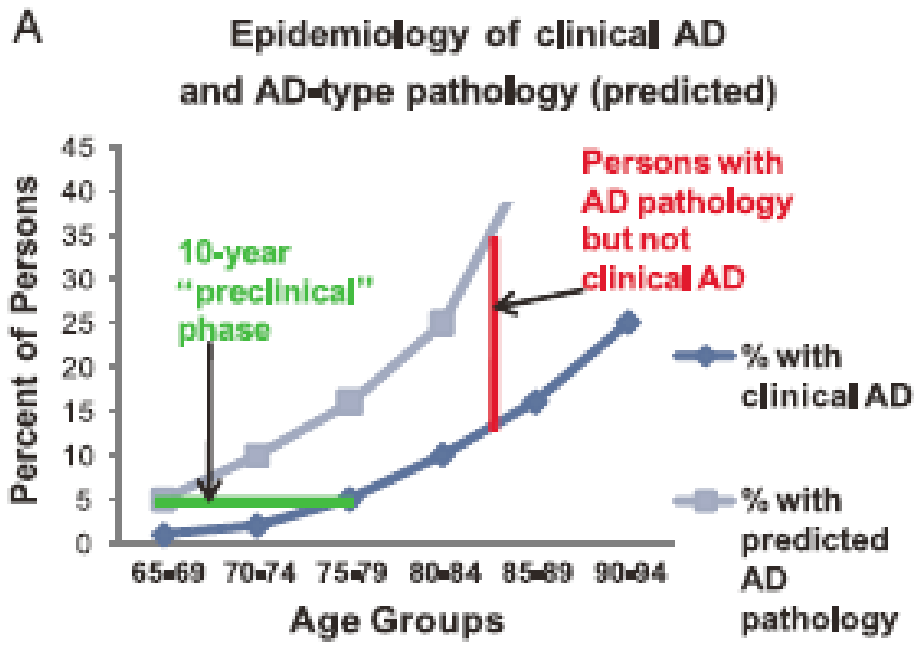
Epidemiology of clinical AD (prevalence)

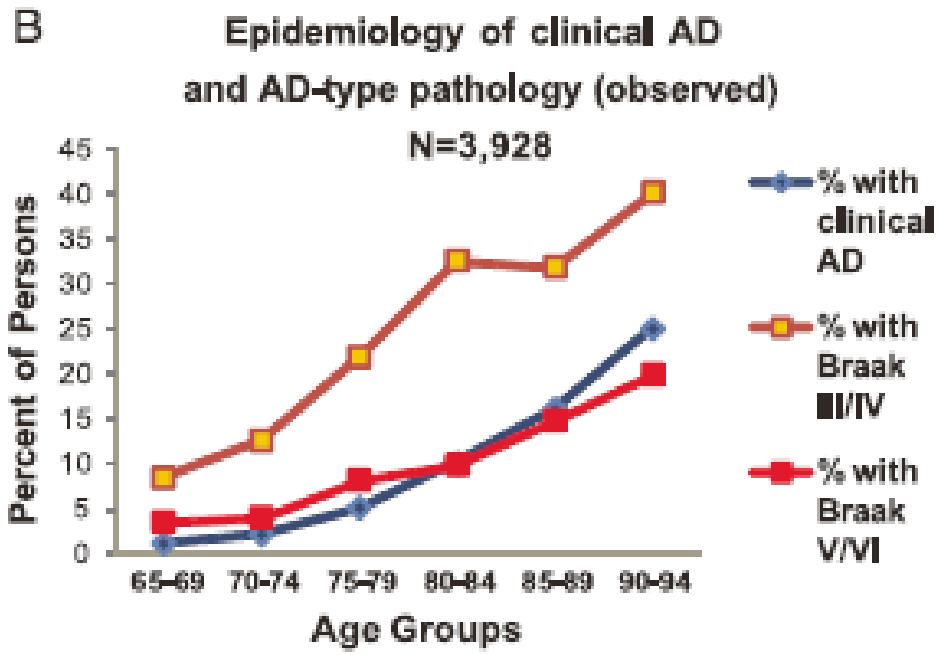




THEORETICAL PREDICTIVE MODEL OF AD PATHOLOGY

PT Nelson, H Braak, and WR Markesbery, JNEN 2009



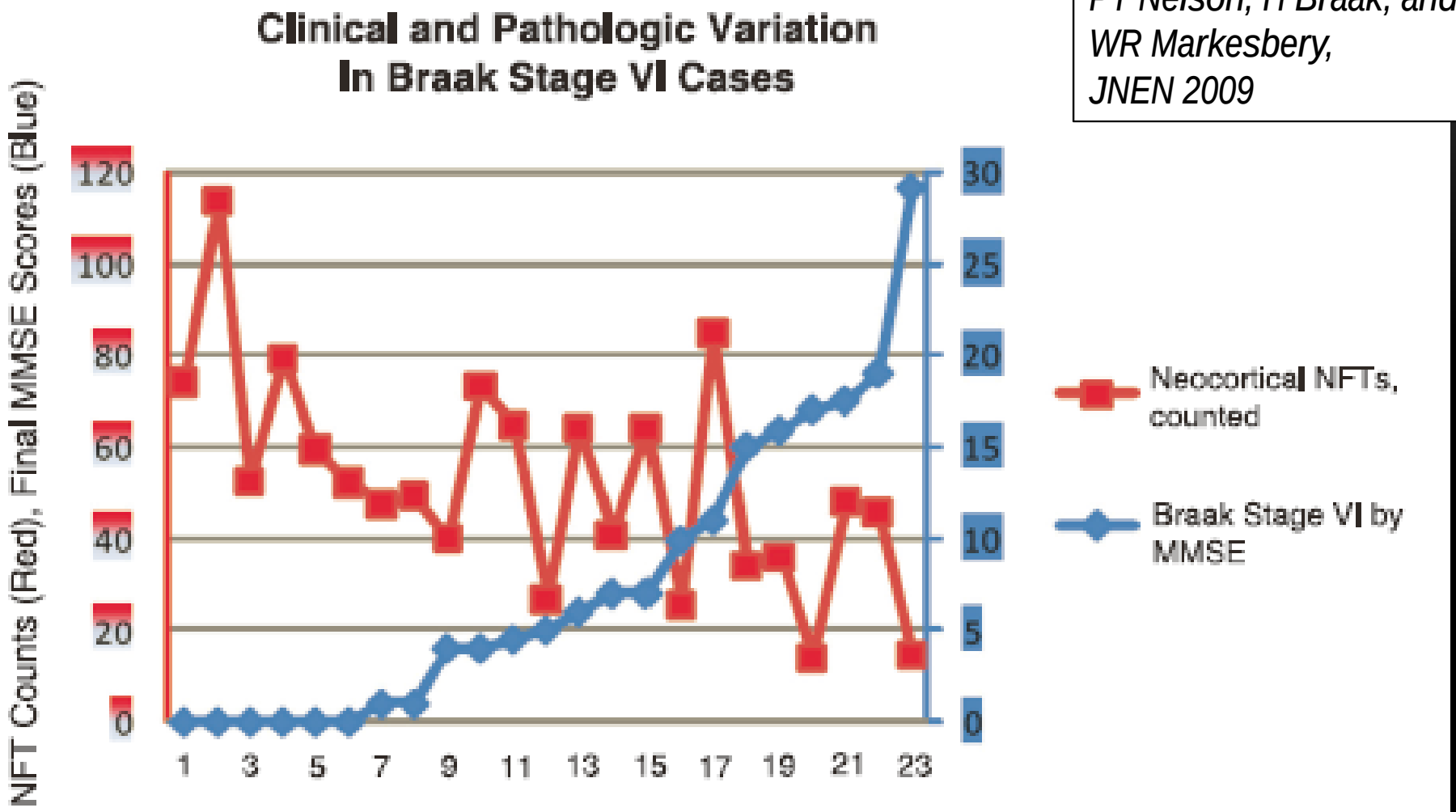


EXPECTED AND ACTUAL OBSERVATIONS OF AD PATHOLOGY MATCH WELL

PT Nelson, H Braak, and WR Markesbery, JNEN 2009

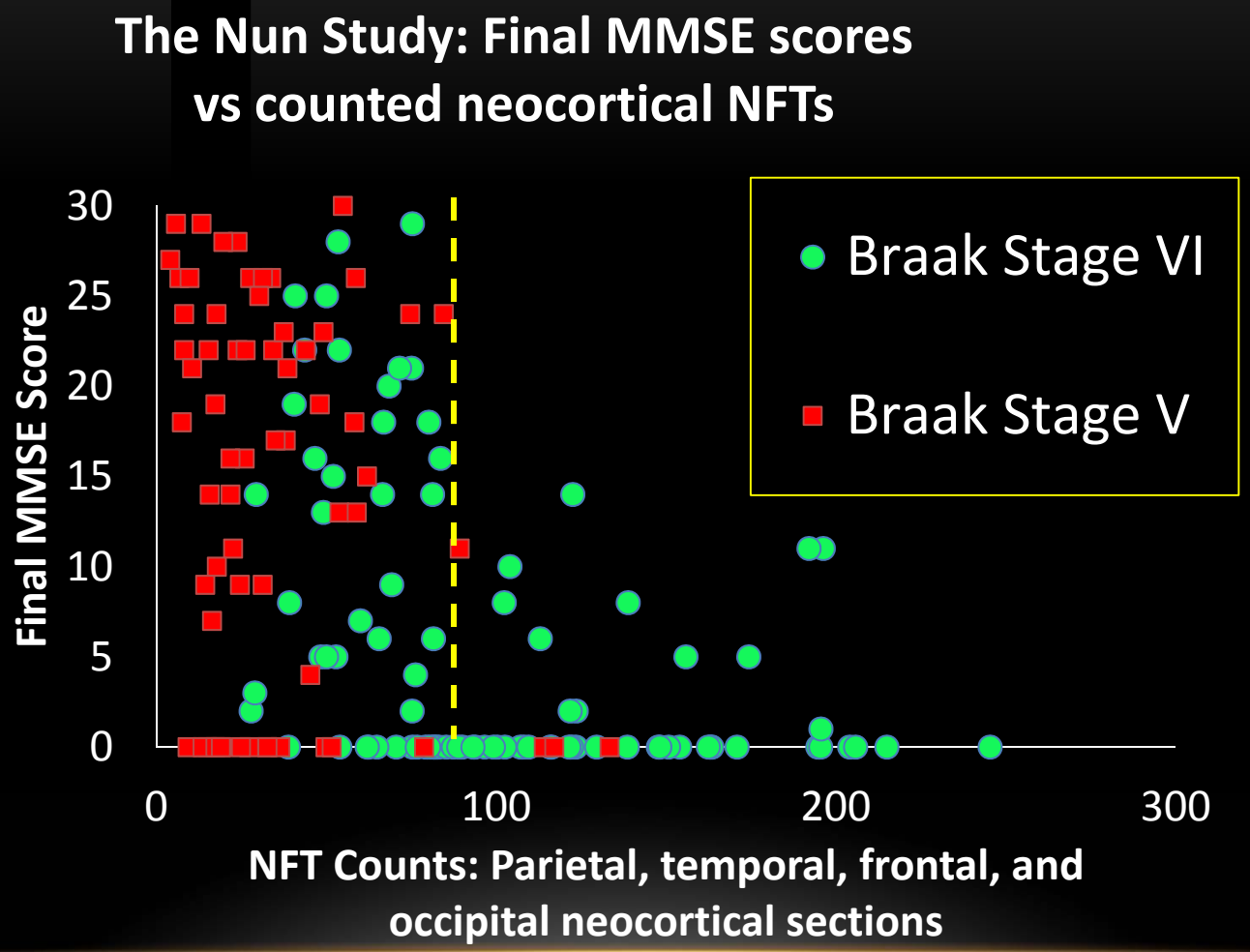
Are there “cognitively intact” patients with true“end-stage” type (SEVERE Braak stage VI) neocortical neurofibrillary pathology?

PT Nelson, H Braak, and WR Markesbery, JNEN 2009



There is heterogeneity among "Braak stage VI" cases with the "high cognitive function" cases corresponding to the lower numbers of neocortical NFTs

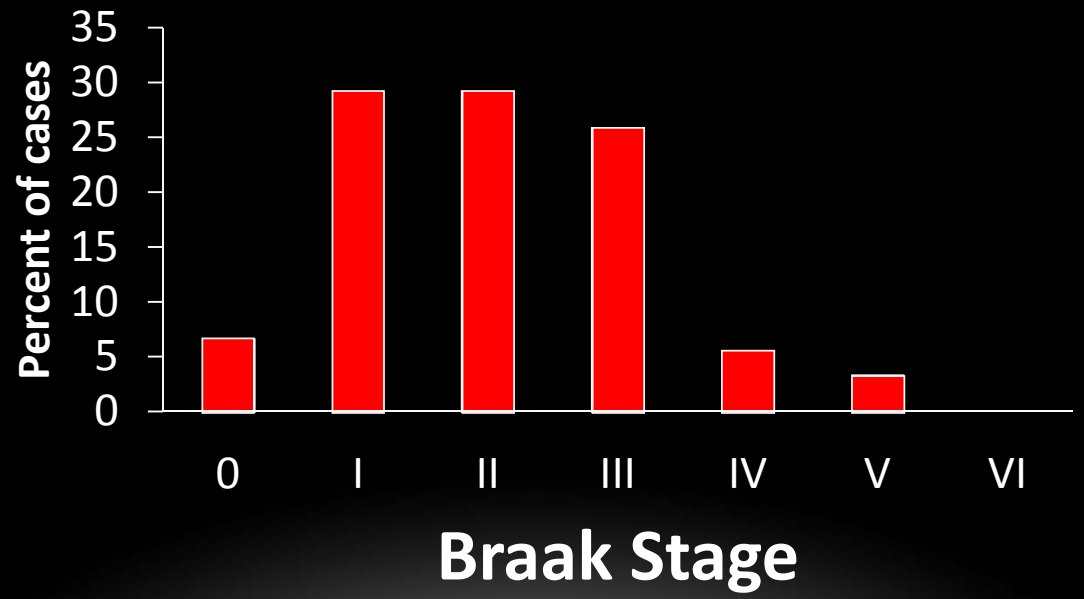
Neocortical NFTs over a certain threshold ALWAYS→dementia



E Abner et al, JAD, 2011

Braak stages in cognitively intact individuals

NACC (combined) datasets:
Braak stages (%)
with final MMSE score of 30 within last year of life



E Abner et al, JAD, 2011

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†Braak stages inferred.
‡Cases designated as Braak V/VI.
§From the University of Kentucky Alzheimer's Disease Center, Braak VI case with relatively low neocortical neurofibrillary tangles (Fig. 5).

Nelson et al JNEN 2009

OBSERVATION

Dissociation of Neuropathologic Findings and Cognition

Case Report of an Apolipoprotein E ε2/ε2 Genotype

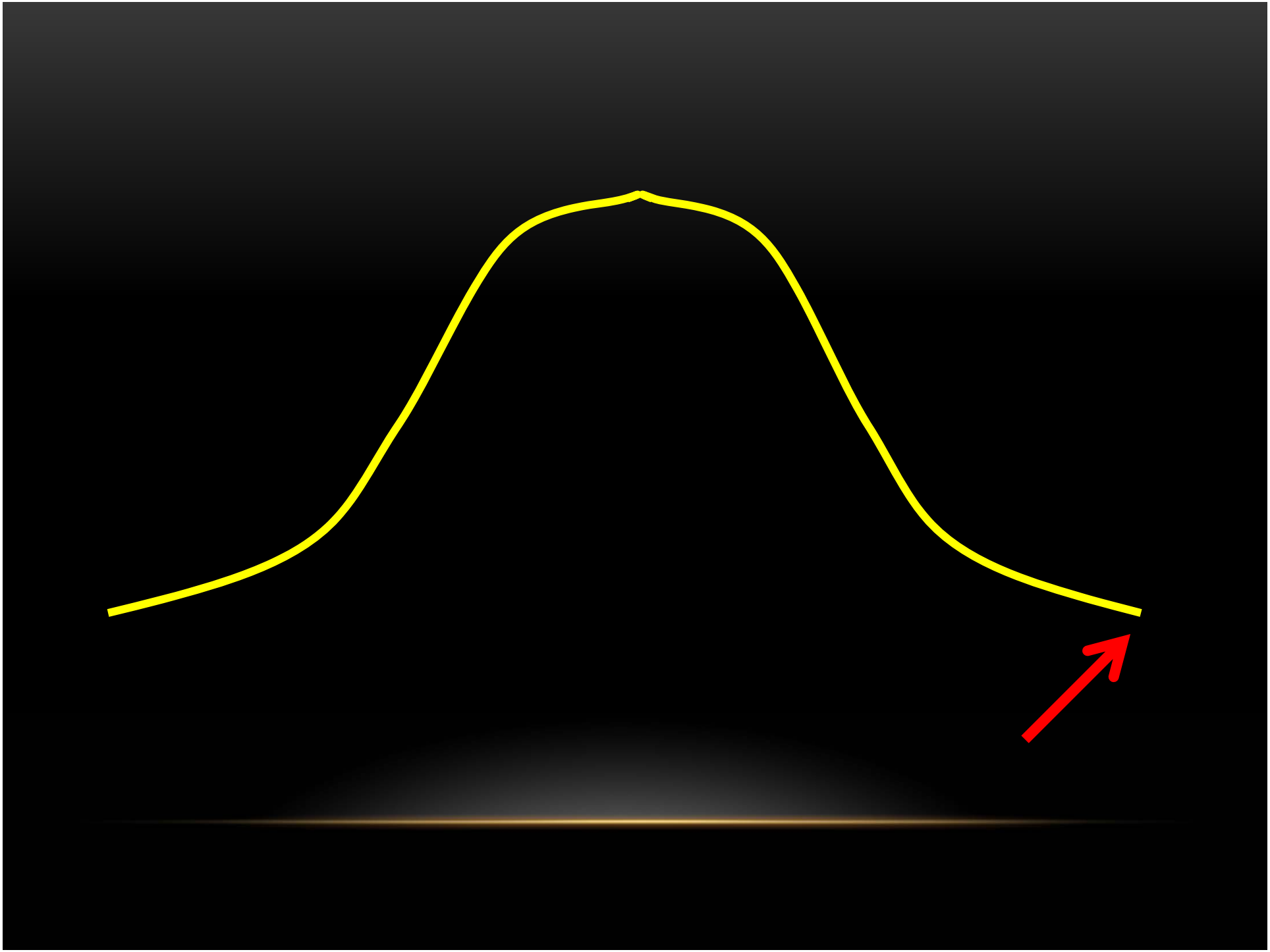
Daniel J. Berlau, PhD; Kristin Kahle-Wrobleski, PhD; Elizabeth Head, PhD; Matthew Goodus, BA; Ronald Kim, MD; Claudia Kawas, MD

Table. Neuropsychological Test Scores 6 Months and 1 Month Before Death

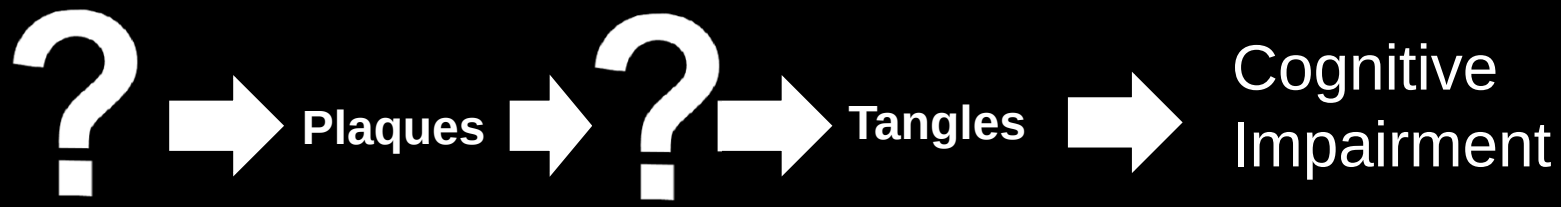
Test		November 4, 2004 Raw Score	November 4, 2004 Percentile[a]
MMSE		28/30	
Digit Span, forward		15	99
Digit Span, backward		4	20
Boston Naming Test, 15 items		12	52
Fluency tests, No. of words in 1 min			
Animal		21	97
Letter *F*		7	15
CVLT, 9 items, No. of words			
Trial 1		5	71
Trial 4		6	38
10-Minute delay		6	71
CERAD copy total, 11 possible points		9	55
Clocks (11:10) total, 8 possible points		6	60
Trail Making Test, total s			
Part A		80	30
Part B	ND	300[b]	10
Part C	ND	47	25

Case report: Patient <=20th %ile on three separate cognitive tests prior to death

neuropsychological tests were performed 6 months and

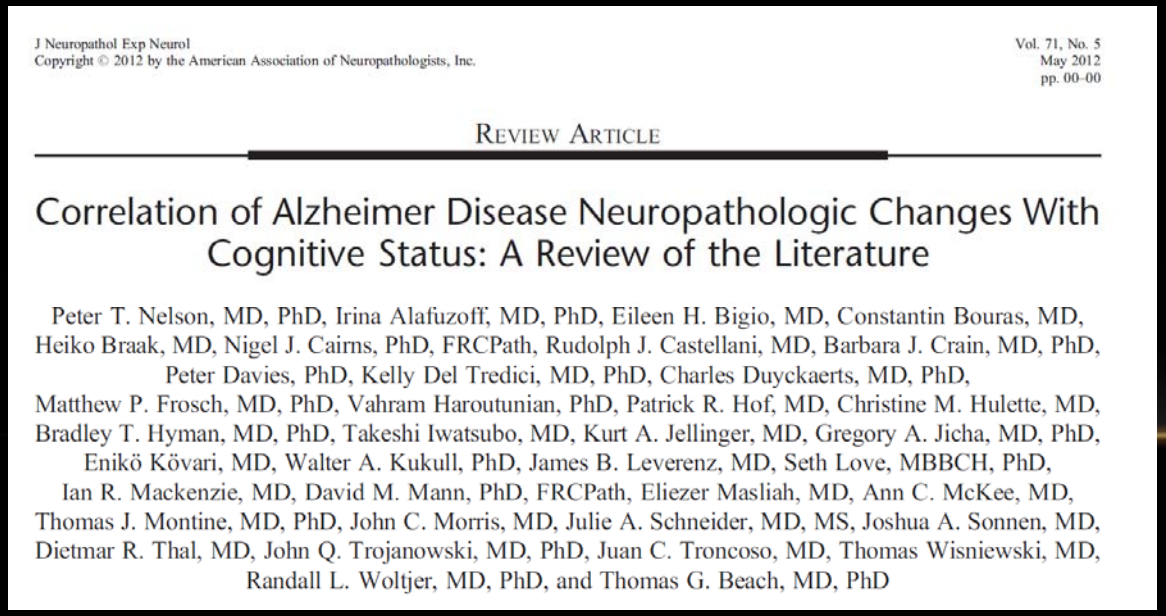


Plaques and Tangles in Alzheimer's disease: Clinicopathological correlation studies are compatible with the hypothesis that these lesions contribute to cognitive impairment



Plaques and Tangles in Alzheimer's disease: Clinicopathological correlation studies are compatible with the hypothesis that these lesions contribute to cognitive impairment

? → **Plaques** → ? → **Tangles** → Cognitive Impairment



J Neuropathol Exp Neurol
Vol. 71, No. 5
May 2012
pp. 00–00

REVIEW ARTICLE

Correlation of Alzheimer Disease Neuropathologic Changes With Cognitive Status: A Review of the Literature

Peter T. Nelson, MD, PhD, Irina Alafuzoff, MD, PhD, Eileen H. Bigio, MD, Constantin Bouras, MD, Heiko Braak, MD, Nigel J. Cairns, PhD, FRCPath, Rudolph J. Castellani, MD, Barbara J. Crain, MD, PhD, Peter Davies, PhD, Kelly Del Tredici, MD, PhD, Charles Duyckaerts, MD, PhD, Matthew P. Frosch, MD, PhD, Vahram Haroutunian, PhD, Patrick R. Hof, MD, Christine M. Hulette, MD, Bradley T. Hyman, MD, PhD, Takeshi Iwatsubo, MD, Kurt A. Jellinger, MD, Gregory A. Jicha, MD, PhD, Enikö Kövari, MD, Walter A. Kukull, PhD, James B. Leverenz, MD, Seth Love, MBBCH, PhD, Ian R. Mackenzie, MD, David M. Mann, PhD, FRCPath, Eliezer Masliah, MD, Ann C. McKee, MD, Thomas J. Montine, MD, PhD, John C. Morris, MD, Julie A. Schneider, MD, MS, Joshua A. Sonnen, MD, Dietmar R. Thal, MD, John Q. Trojanowski, MD, PhD, Juan C. Troncoso, MD, Thomas Wisniewski, MD, Randall L. Woltjer, MD, PhD, and Thomas G. Beach, MD, PhD

***JNEN*, 2012**

Myth roundup

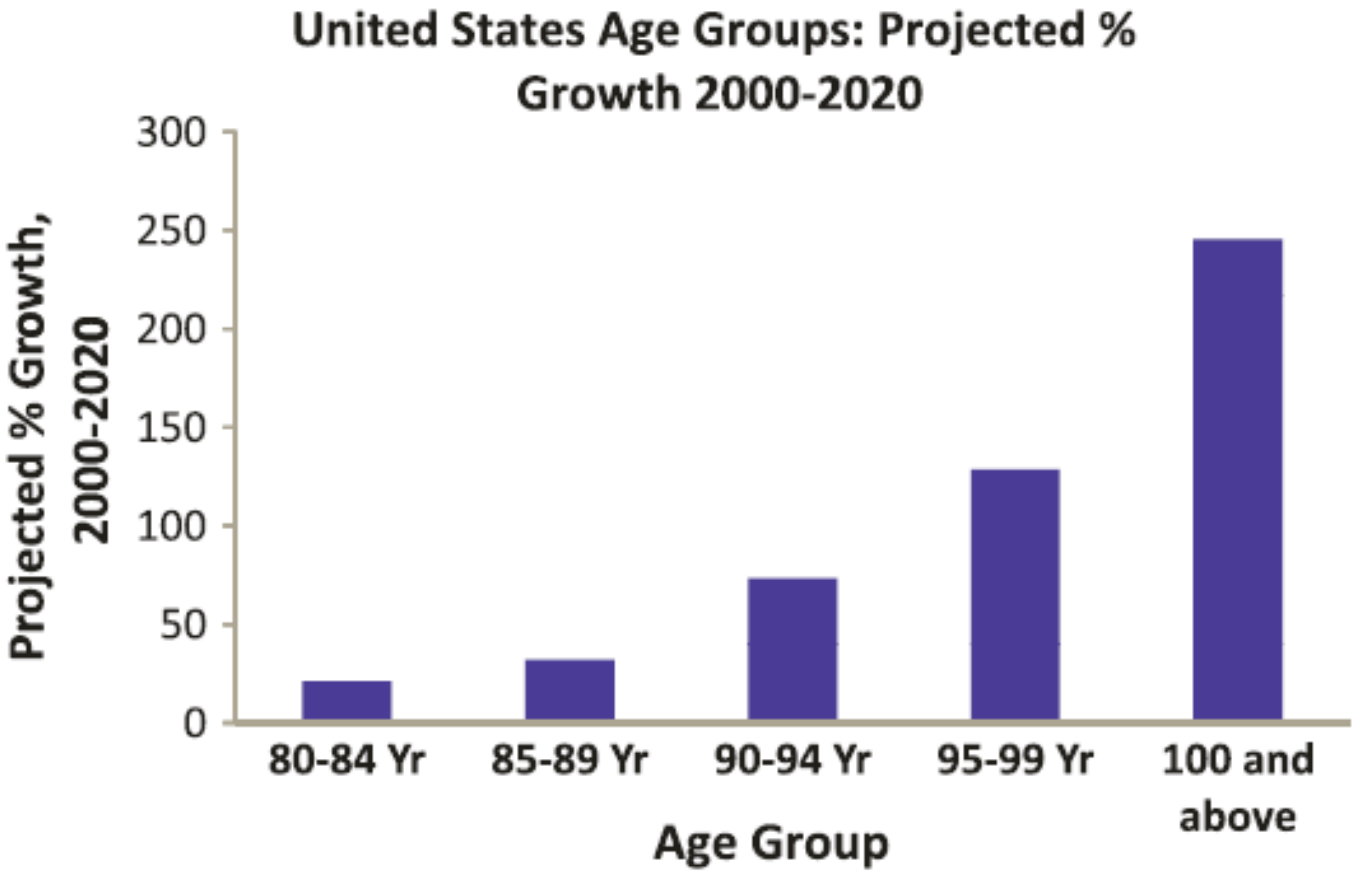
2. Plaques and tangles don’t correlate with cognitive impairment

Myth #2B

2. Plaques and tangles don't correlate with cognitive impairment

Corollary Myth

There is dissociation between AD pathology and cognitive impairment in "advanced old age"



An important and topical issue!!

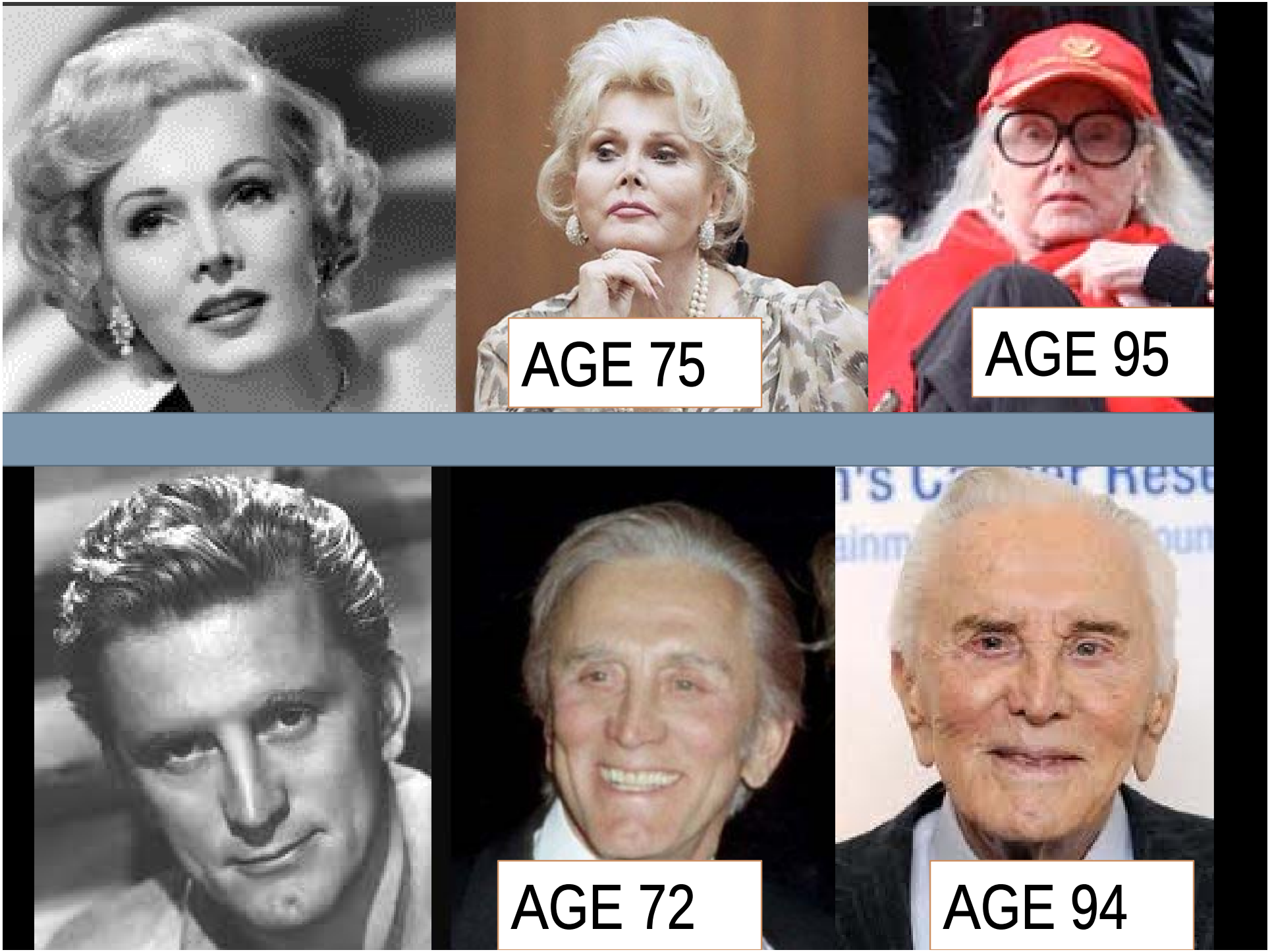
Source: U. S. Census Bureau

Acta Neuropathologica, 2011

In advanced old age…
(individuals beyond 90 years old)


AGE 75


AGE 72

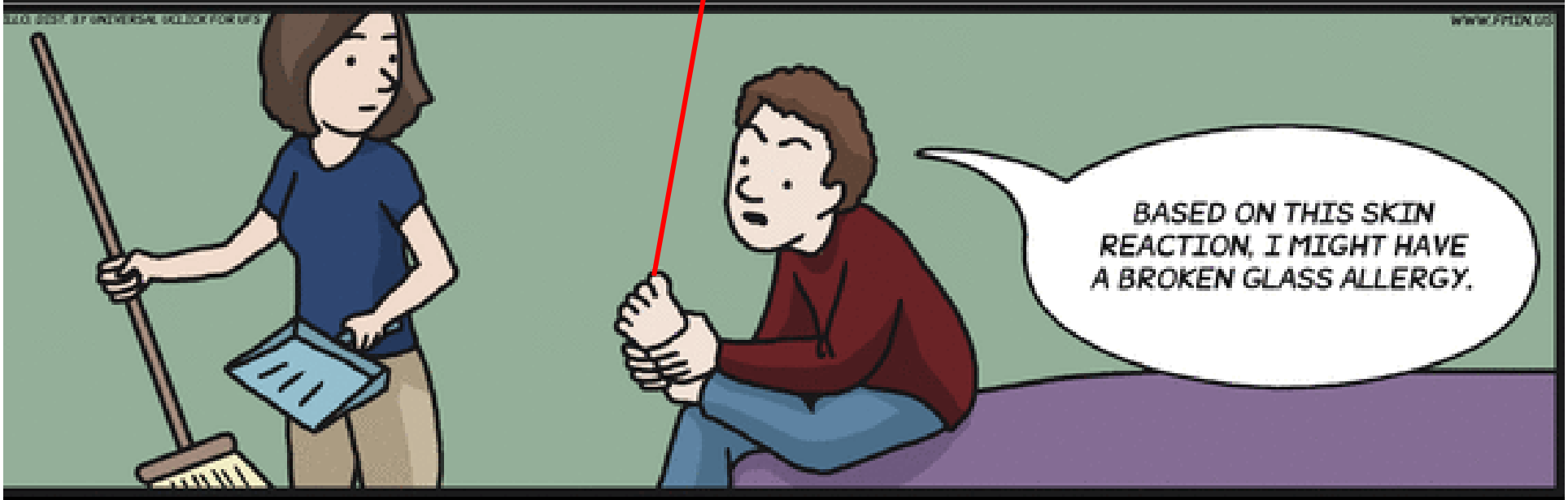

AGE 75
AGE 95
AGE 72
AGE 94

In advanced old age…
(individuals beyond 90 years old)

1. …some cognitive impairment is usual;
2. …mild/moderate hippocampal tangles is universal (and is NOT AD);
3. …other high-morbidity pathologies occur with prevalence that approximates AD prevalence.

“F-minus” by Tony Carrillo

Red inflamed toe does not necessarily = allergy



“F-minus” by Tony Carrillo

Apologies to “F-minus” by Tony Carrillo

Apologies to “F-minus” by Tony Carrillo

Hippocampal NFTs does not necessarily = AD

“F-minus” by Tony Carrillo

Tangles and no plaques is *not* AD

Table 3 "ABC" score for level of AD neuropathologic change

AD neuropathologic change		B[a]		
A[b]	C[c]	0 or 1	2	3
0	0	Not[d]	Not[d]	Not[d]
1	0 or 1	Low	Low	Low[e]
	2 or 3[f]	Low	Intermediate	Intermediate[e]
2	Any C	Low[g]	Intermediate	Intermediate[e]
3	0 or 1	Low[g]	Intermediate	Intermediate[e]
	2 or 3	Low[g]	Intermediate	High

AD neuropathologic change is evaluated with an "ABC" score (Table 2): Aβ/amyloid plaques (A), NF

T Montine et al, *Acta Neuropathologica*, 2012

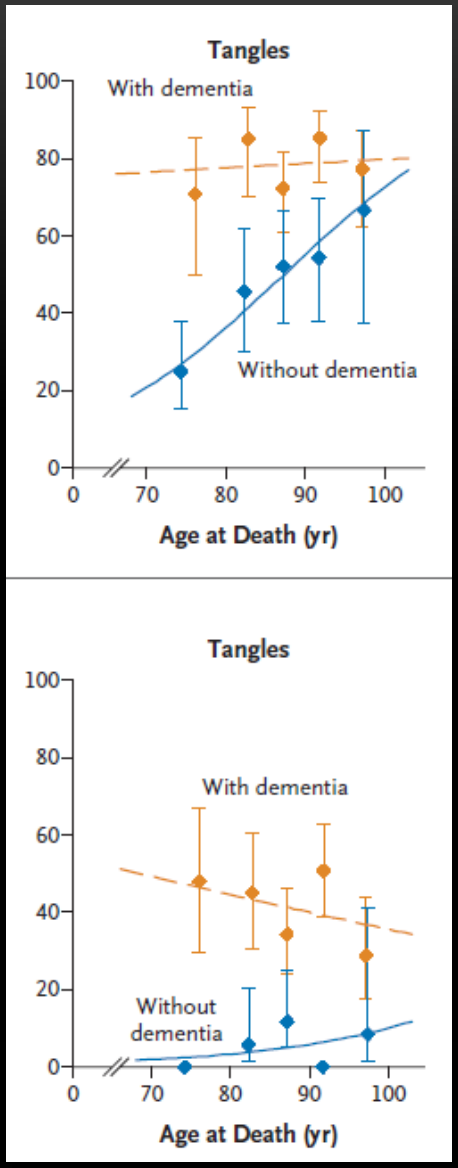
Savva et al (*NEJM 2009*):

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Age, Neuropathology, and Dementia

George M. Savva, Ph.D., Stephen B. Wharton, F.R.C.Path., Paul G. Ince, M.D., Gillian Forster, B.Sc., Fiona E. Matthews, Ph.D., and Carol Brayne, M.D., for the Medical Research Council Cognitive Function and Ageing Study



…possible dissociation between AD pathology and cognitive impairment in “very old persons”

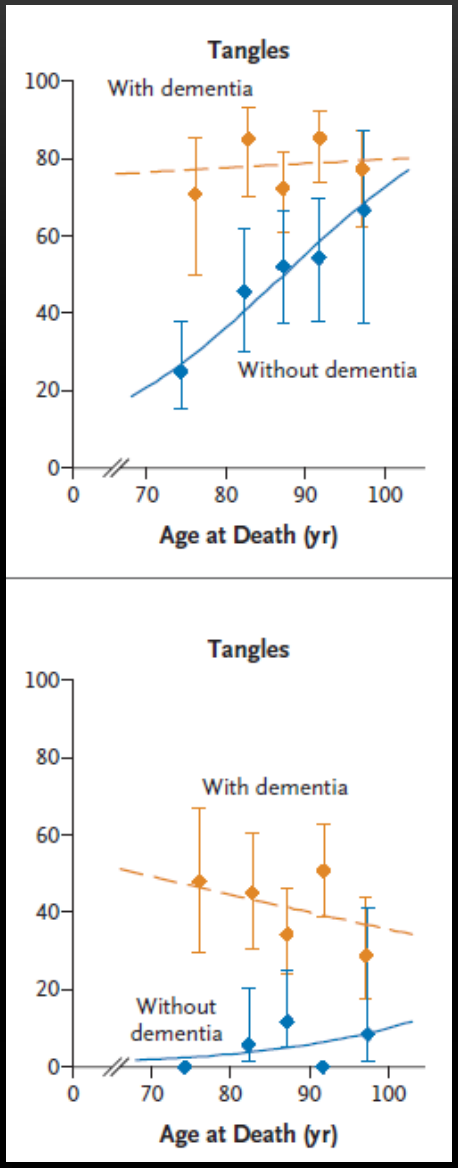
Savva et al (*NEJM 2009*):

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Age, Neuropathology, and Dementia

George M. Savva, Ph.D., Stephen B. Wharton, F.R.C.Path., Paul G. Ince, M.D., Gillian Forster, B.Sc., Fiona E. Matthews, Ph.D., and Carol Brayne, M.D., for the Medical Research Council Cognitive Function and Ageing Study



>90 year olds:

-Difficulty dichotomizing "dementia"
-Poor correlation between plaques and dementia
-Hippocampal NFTs without AD (or overt dementia)
-Non-AD pathologies that cause dementia

In advanced old age…

1. …some cognitive impairment is usual;
2. …mild/moderate hippocampal tangles is nearly universal (and is NOT AD).
3. …other high-morbidity pathologies occur with prevalence that approximates AD prevalence.

In advanced old age…

1. …some cognitive impairment is usual;
2. …mild/moderate hippocampal tangles is nearly universal (and is NOT AD).
3. …other high-morbidity pathologies occur with prevalence that approximates AD prevalence.
4. HOWEVER, advanced AD pathology (neocortical plaques+tangles) still always correlates with cognitive impairment

Myth #2C

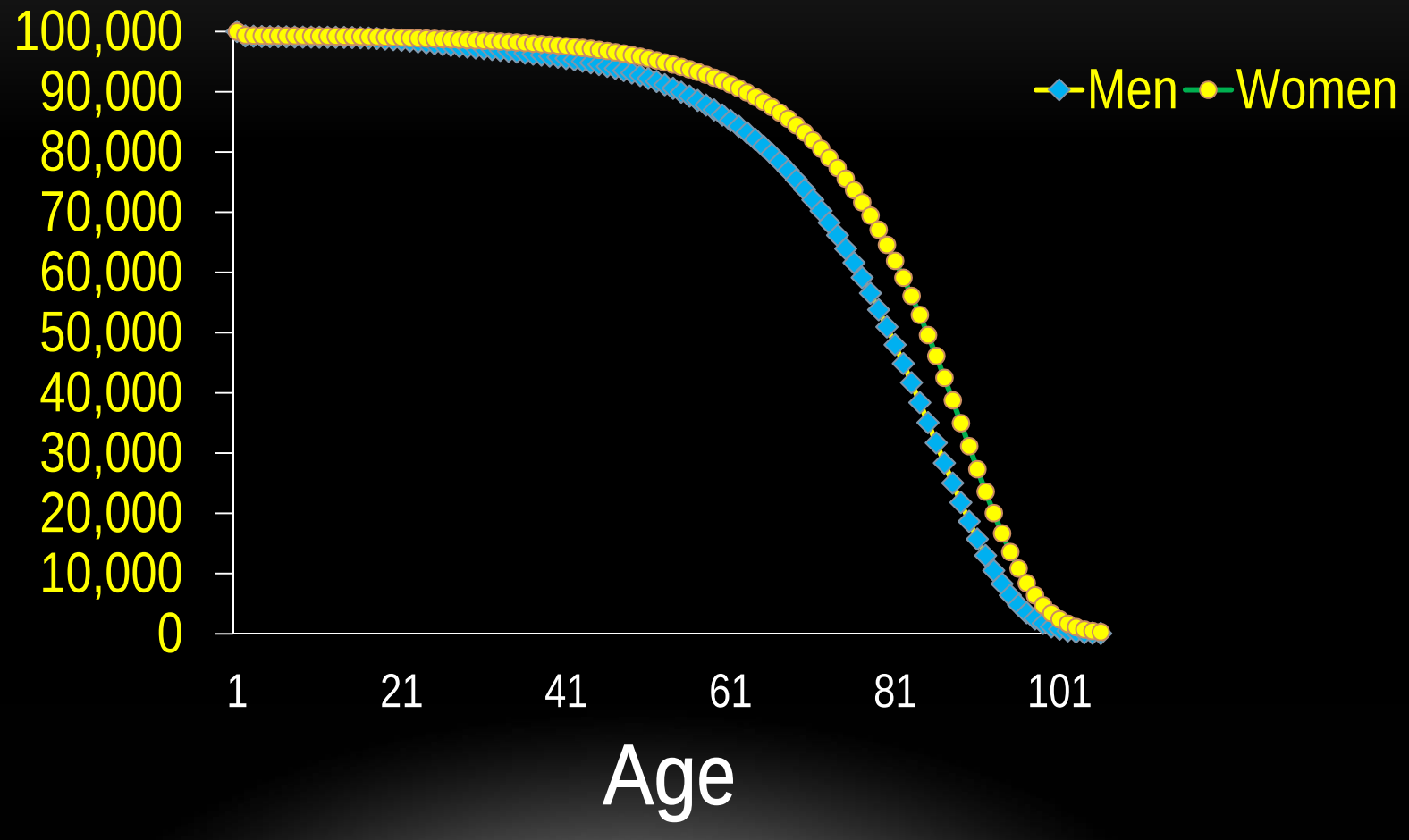
1. Plaques and tangles don't correlate with cognitive impairment

Corollary Myth

AD is just "brain aging", and vice versa (everyone gets AD if they live long enough)

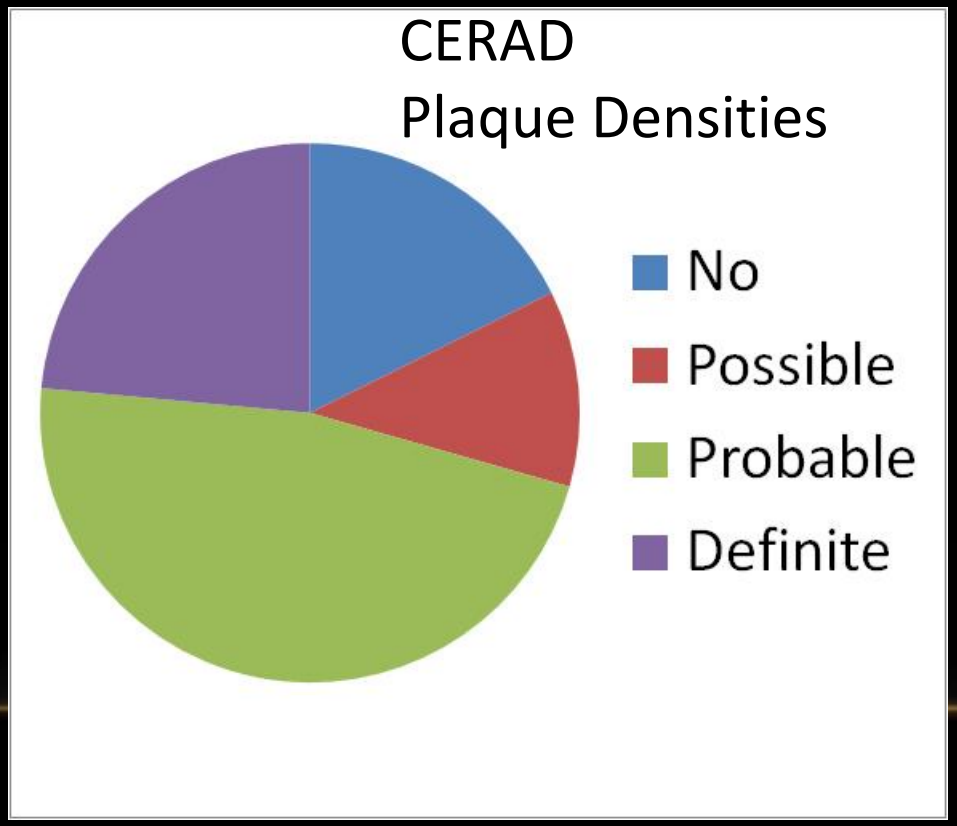
Alive per 100,000 population, U.S.

Source: 2007 Actuarial Tables



Centenarians

Mean Age at death:
102.2 +/- 2.5yrs
N=52



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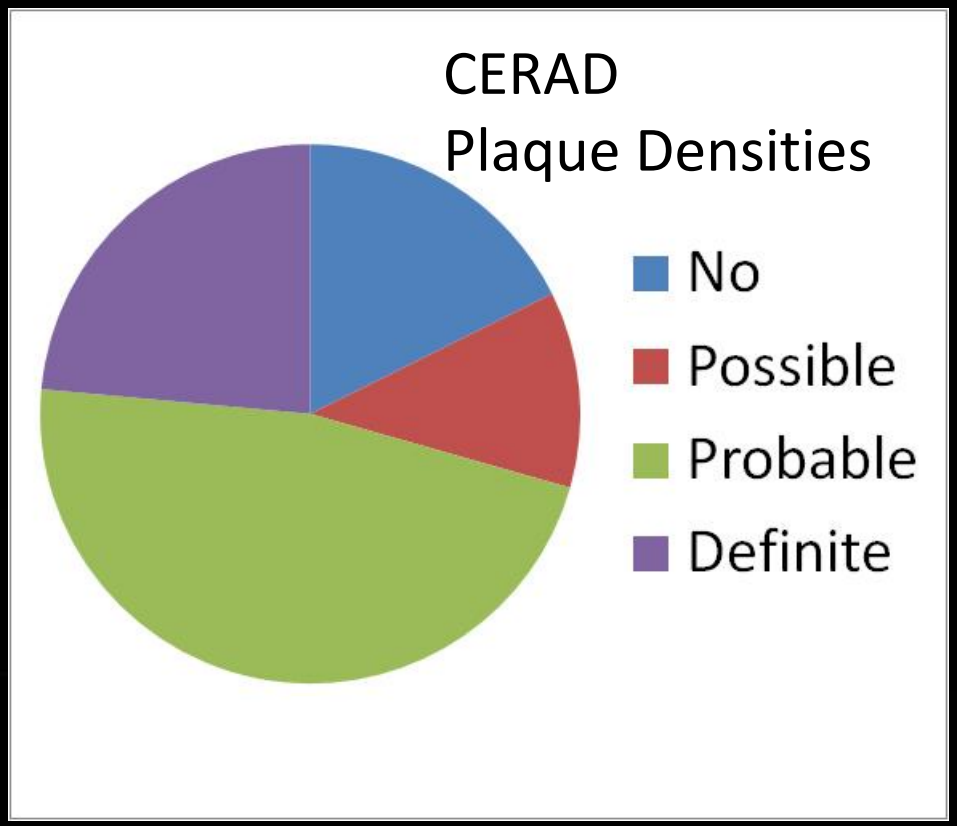
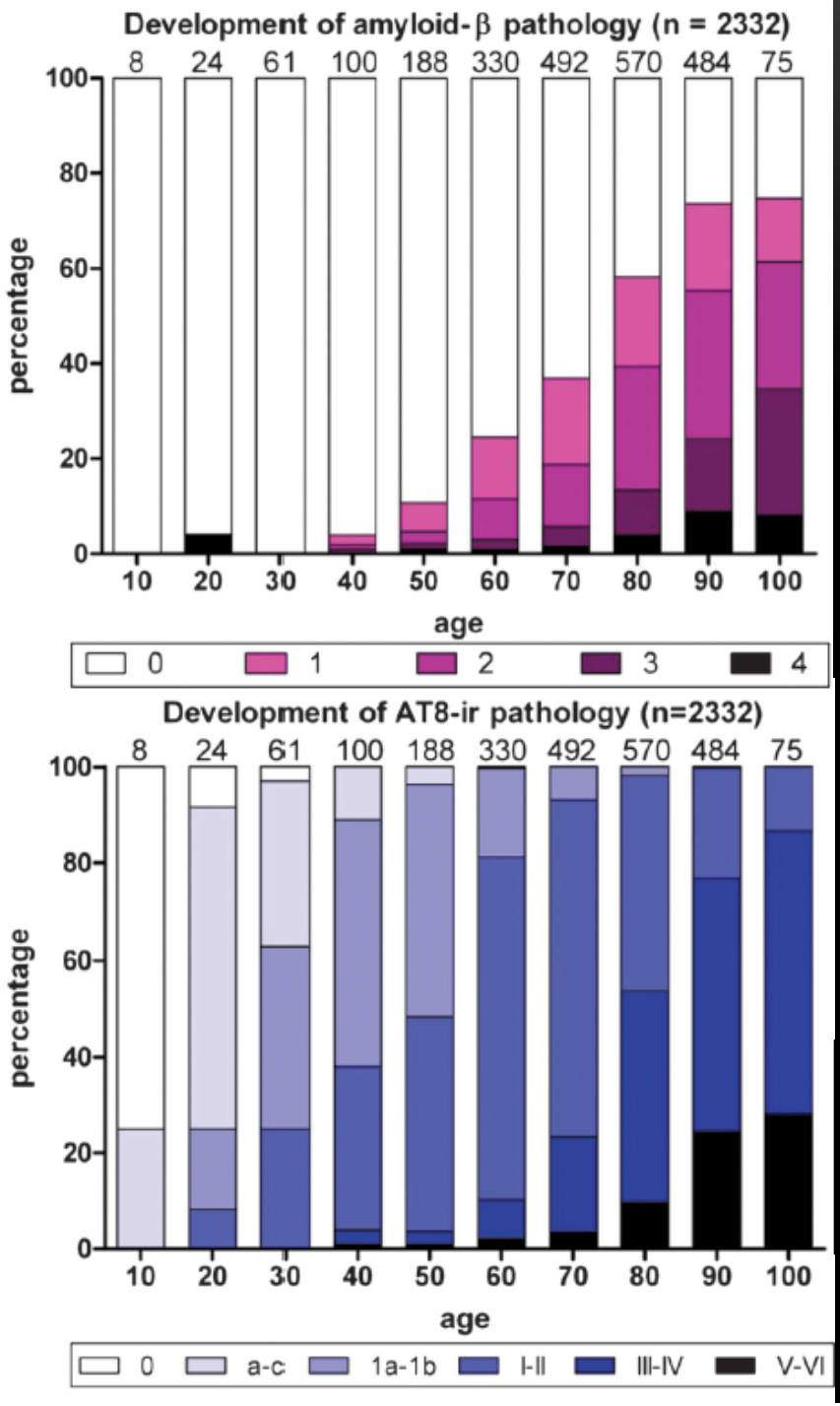


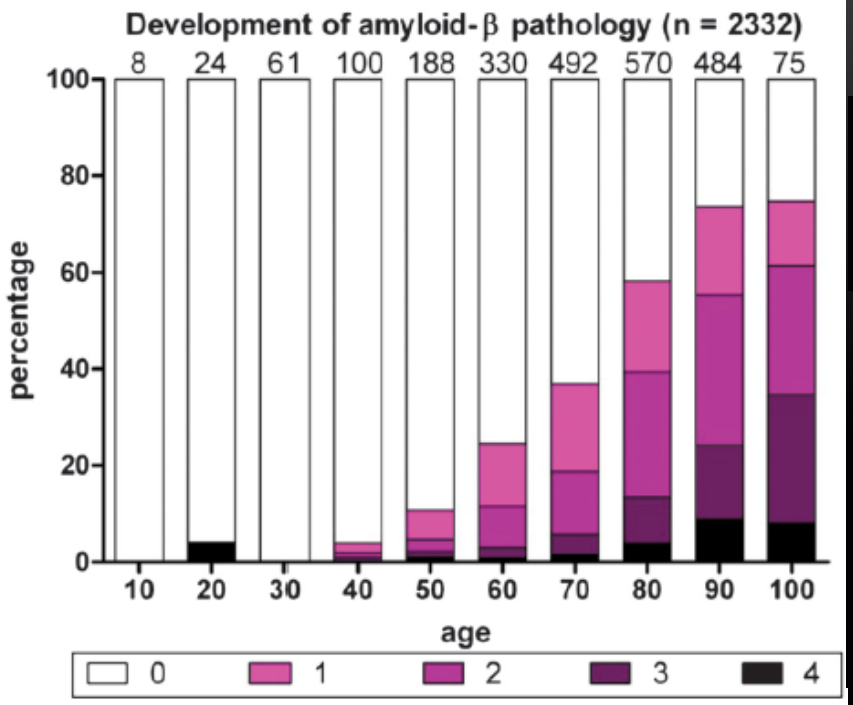
Not everyone gets AD

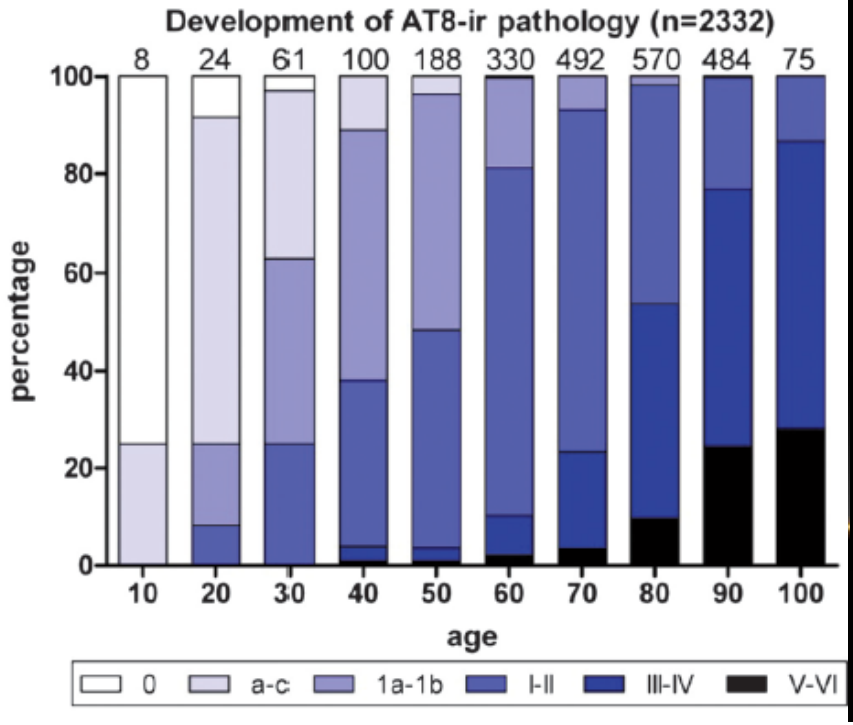


Other large datasets agree:

It is by no means inevitable for centenarians to get AD

Braak H, et al,
J Neuropathol Exp Neurol. 2011





← Plaques

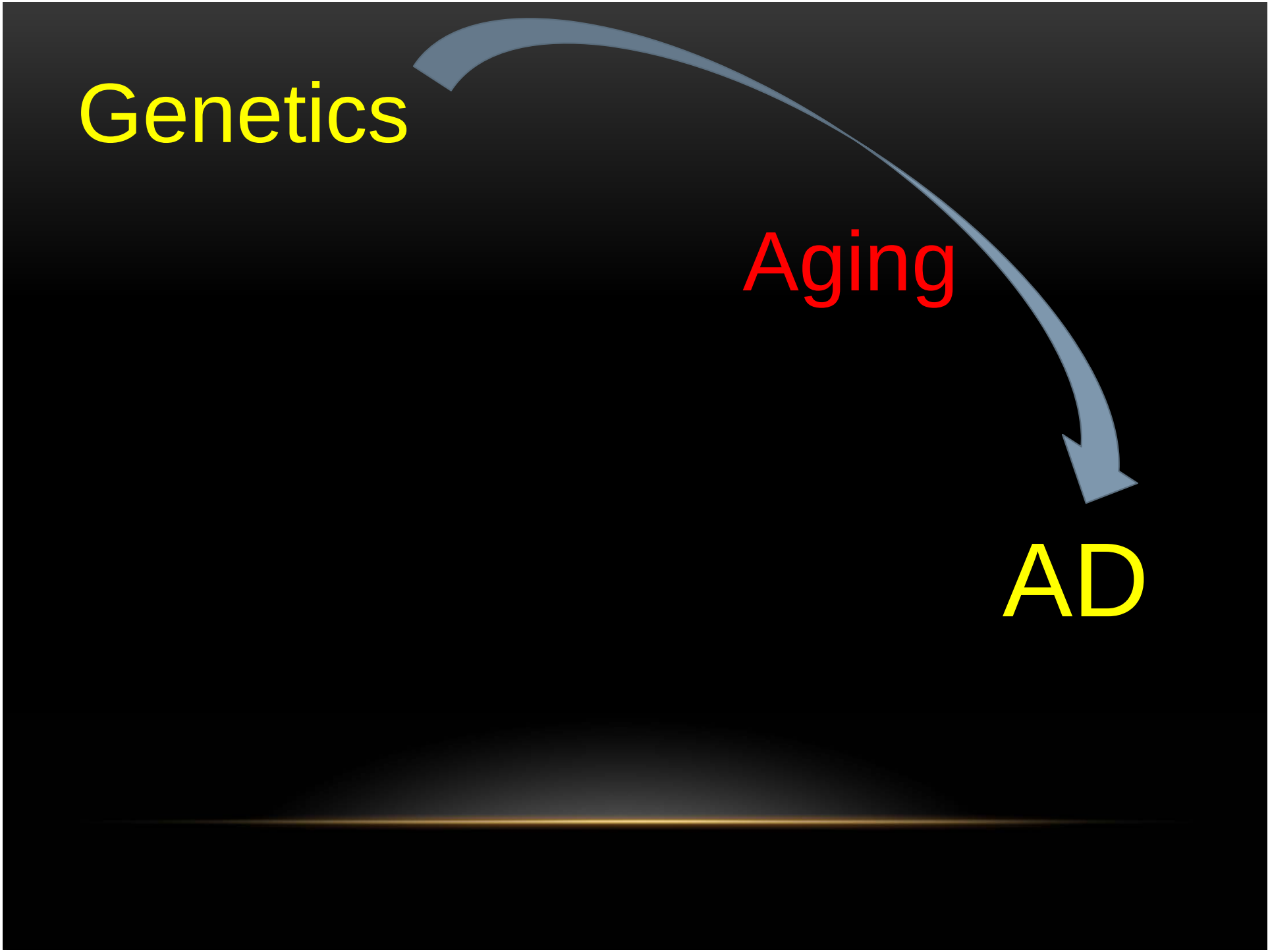
Other large datasets agree:

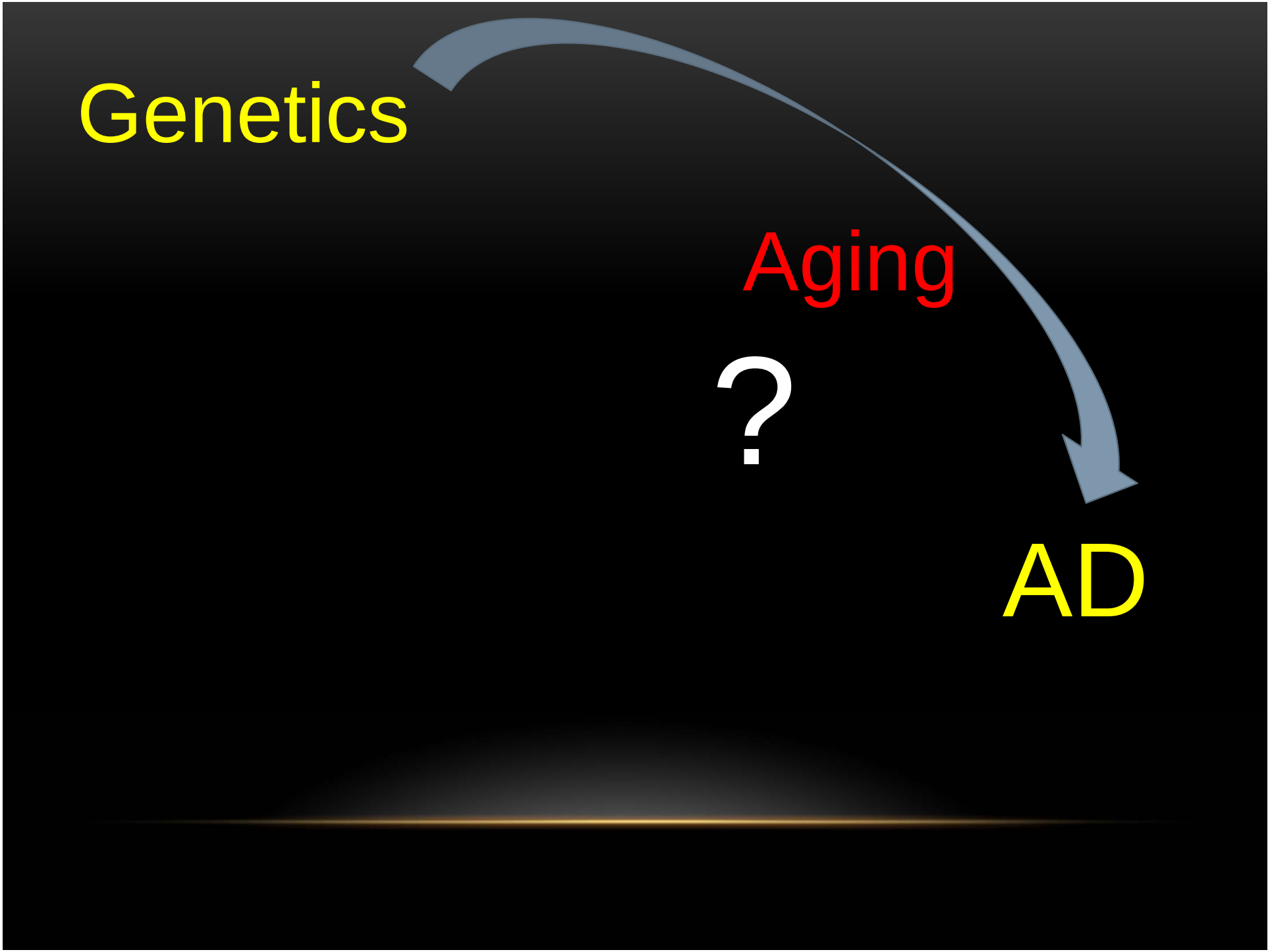
It is by no means inevitable for centenarians to get AD

← Tangles

Braak H, et al,
J Neuropathol Exp Neurol. 2011

Genetics


Genetics
Aging
AD


Genetics
Aging
?
AD

Progerias, human diseases with “accelerated aging”:

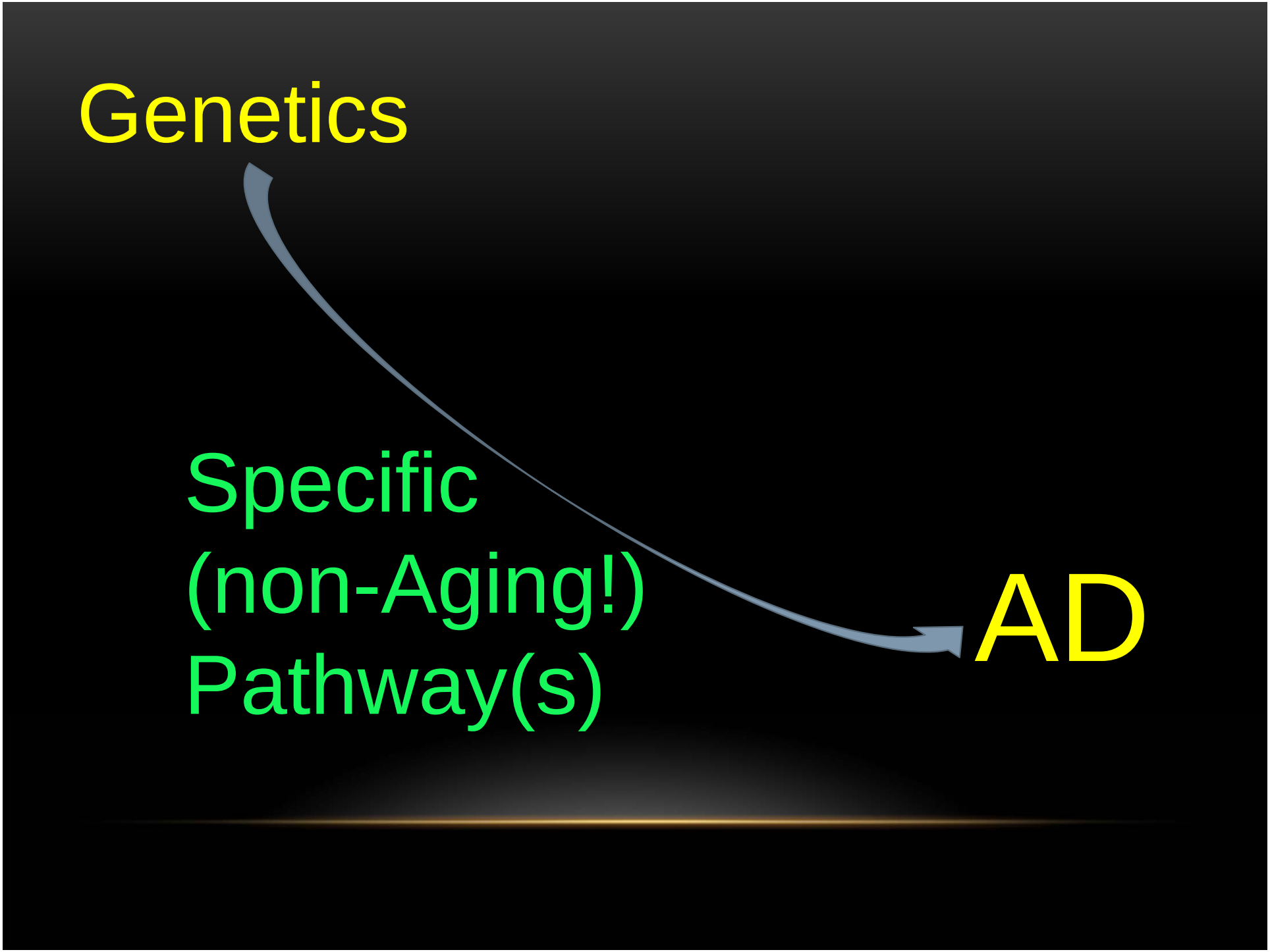
Accelerated aging syndromes
Werner syndrome
Hutchinson-Gilford progeria syndrome
Cockayne syndrome
Trichothiodystrophy

Progerias, human diseases with “accelerated aging”:
Any increase in AD pathology?

Accelerated aging syndromes
Werner syndrome
Hutchinson-Gilford progeria syndrome
Cockayne syndrome
Trichothiodystrophy

Progerias, human diseases with “accelerated aging”:
No established increase in AD pathology

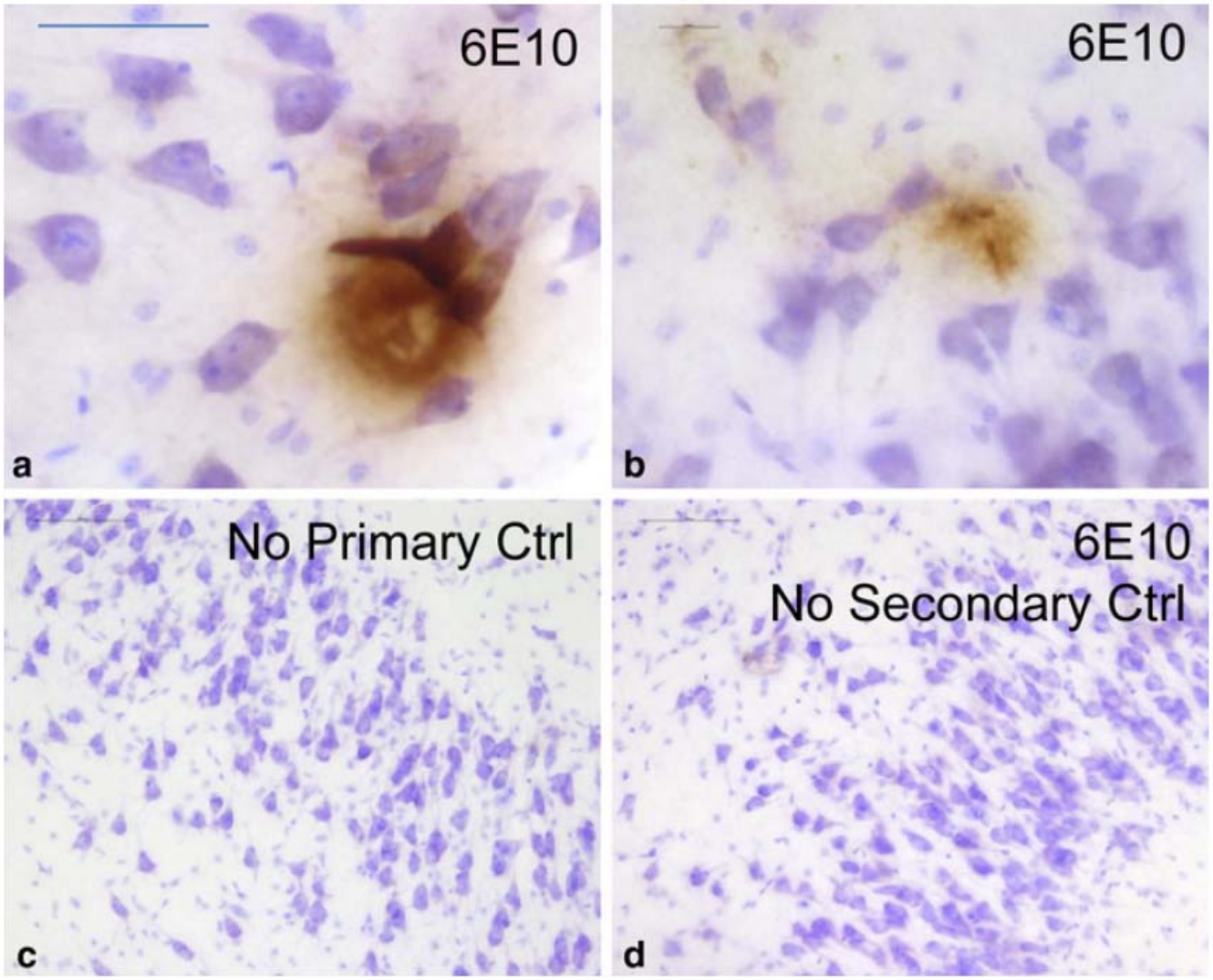
Accelerated aging syndrome	Increase of AD pathology?
Werner syndrome	No
Hutchinson-Gilford progeria syndrome	No
Cockayne syndrome	No
Trichothiodystrophy	No


Genetics
Specific
(non-Aging!)
Pathway(s)
AD

5-month old with Down Syndrome

(thanks to Dr. Elizabeth Head)

The disease of plaques and tangles (AD) begins at young age among individuals with high genetic risk



PT Nelson et al, *Acta Neuropathologica*, 2011

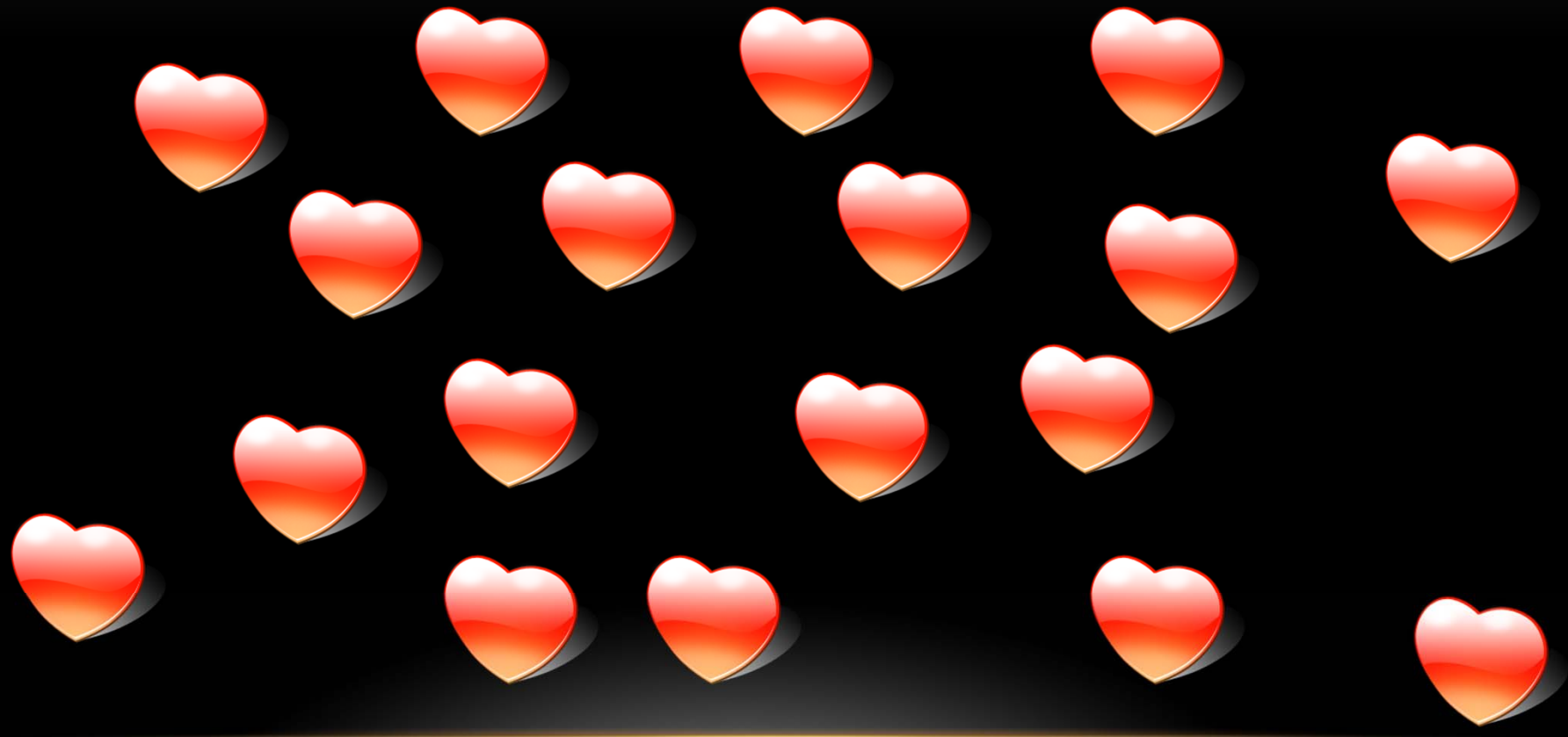
So what is the main reason that clinical-pathologic correlation is so imperfect?


©2010 VIKTOR BORS

Scott Adams's "Dilbert"

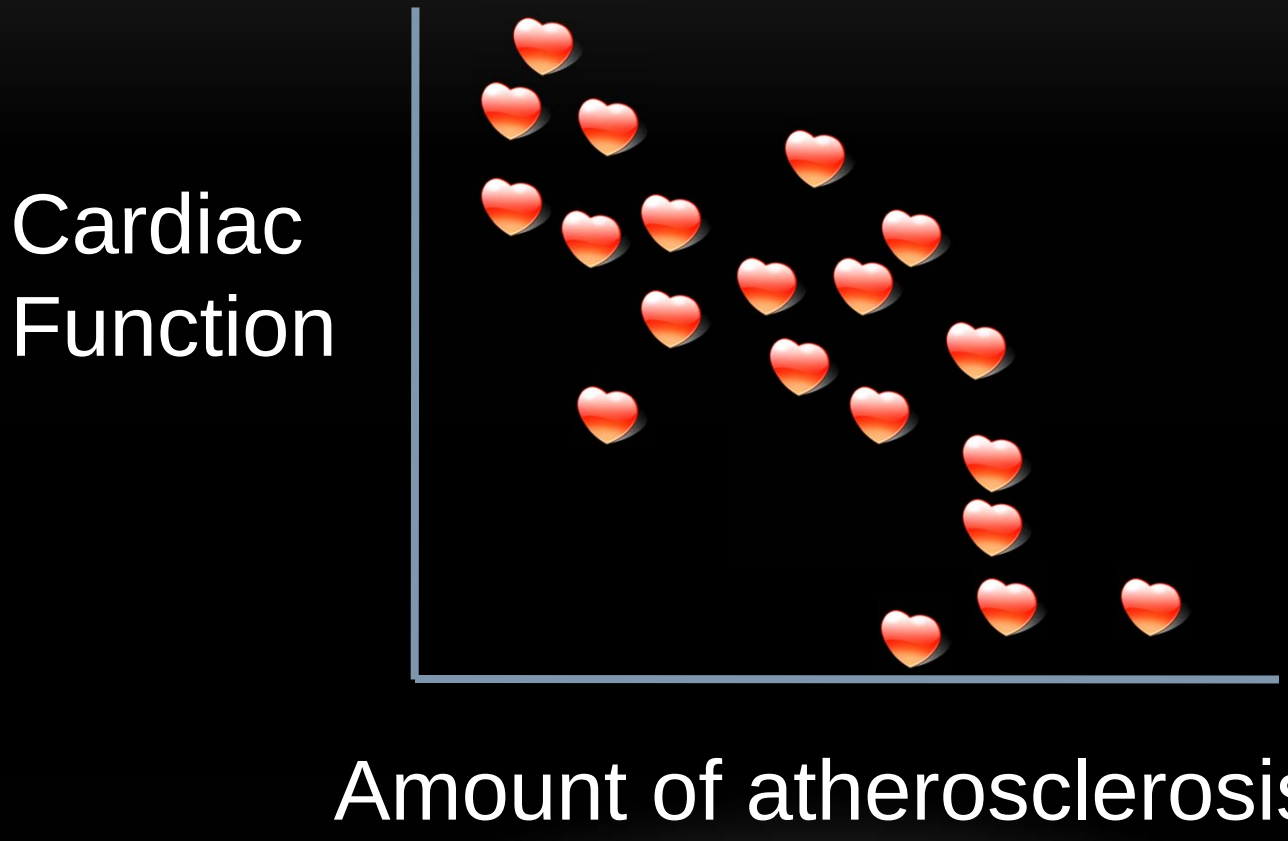
Thought experiment:

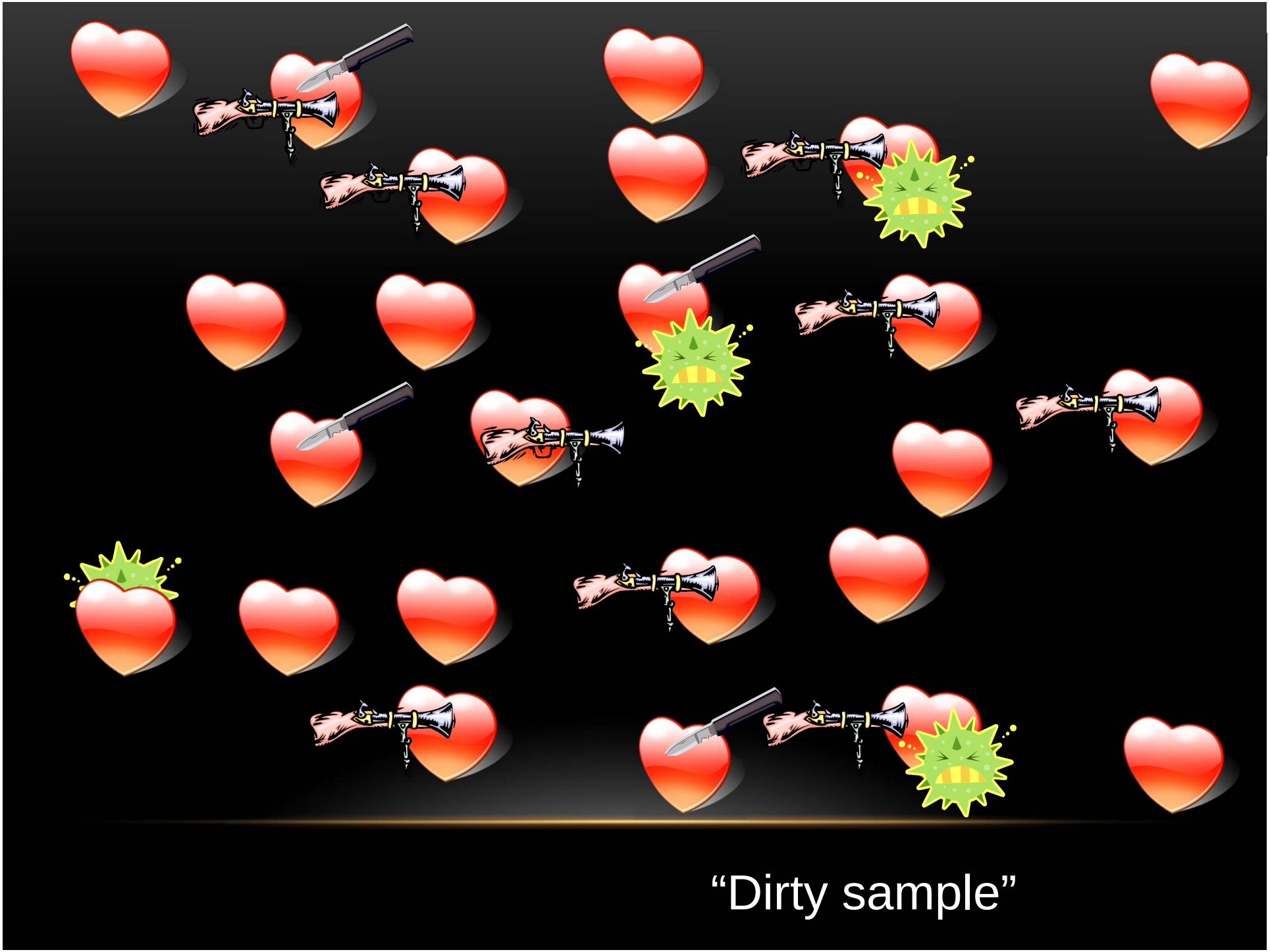
Could you detect a clinico-pathological relationship in heart disease if testing the correlation of atherosclerosis and cardiac health?



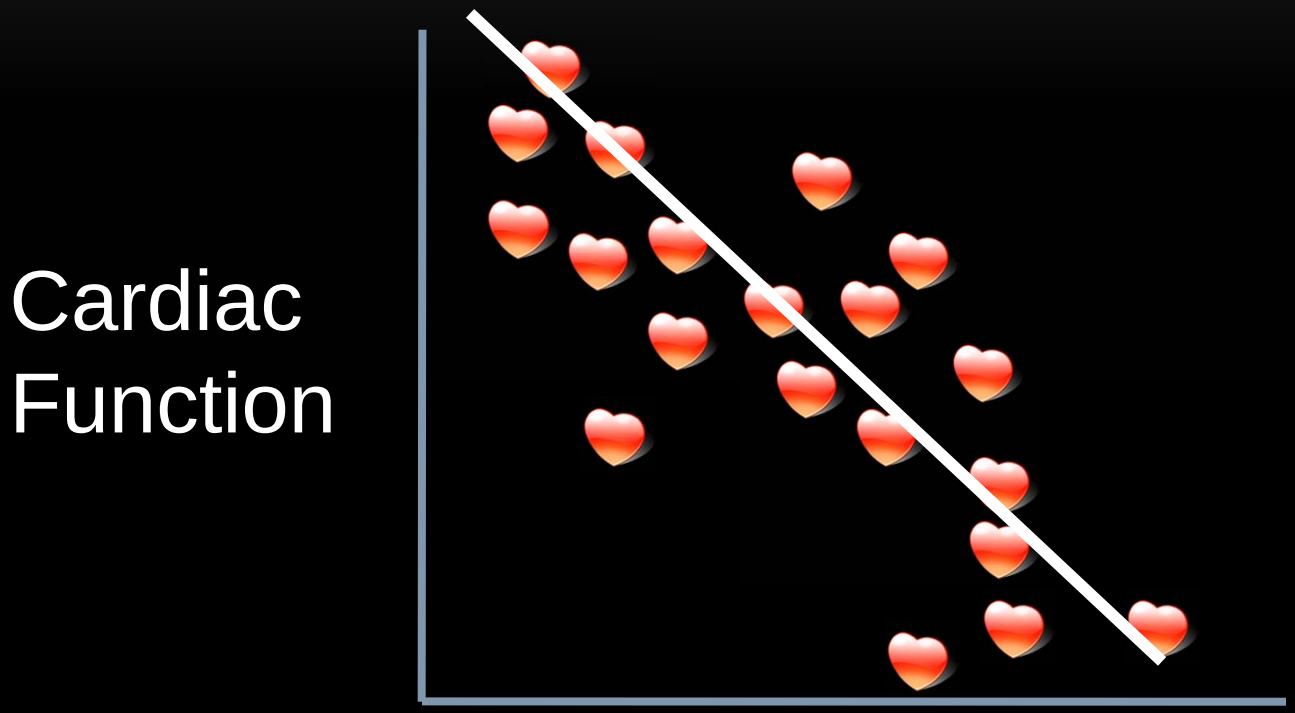
"Clean sample"

Clean sample – good correlation



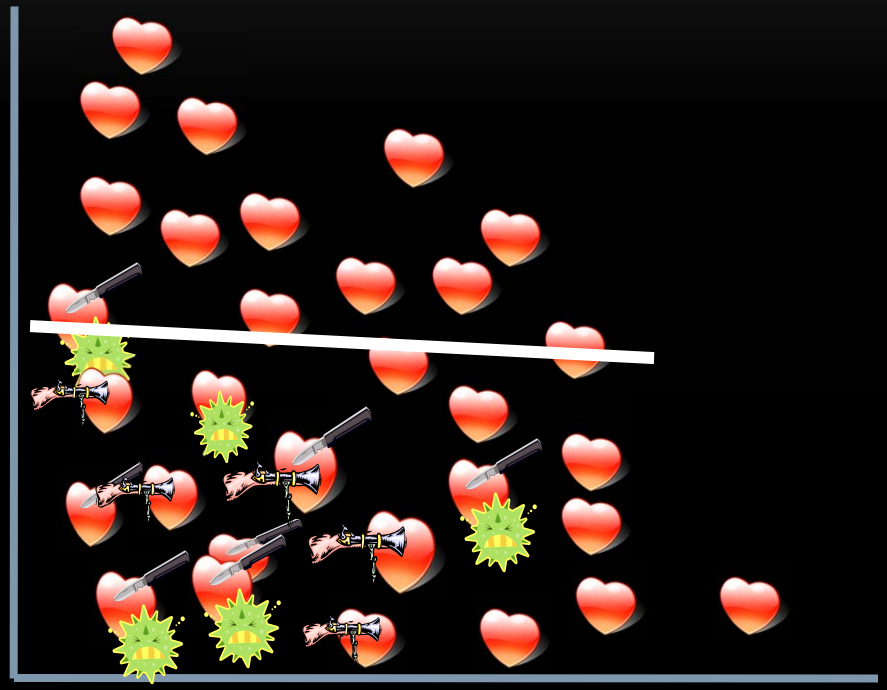

“Dirty sample”

Clean sample – good correlation

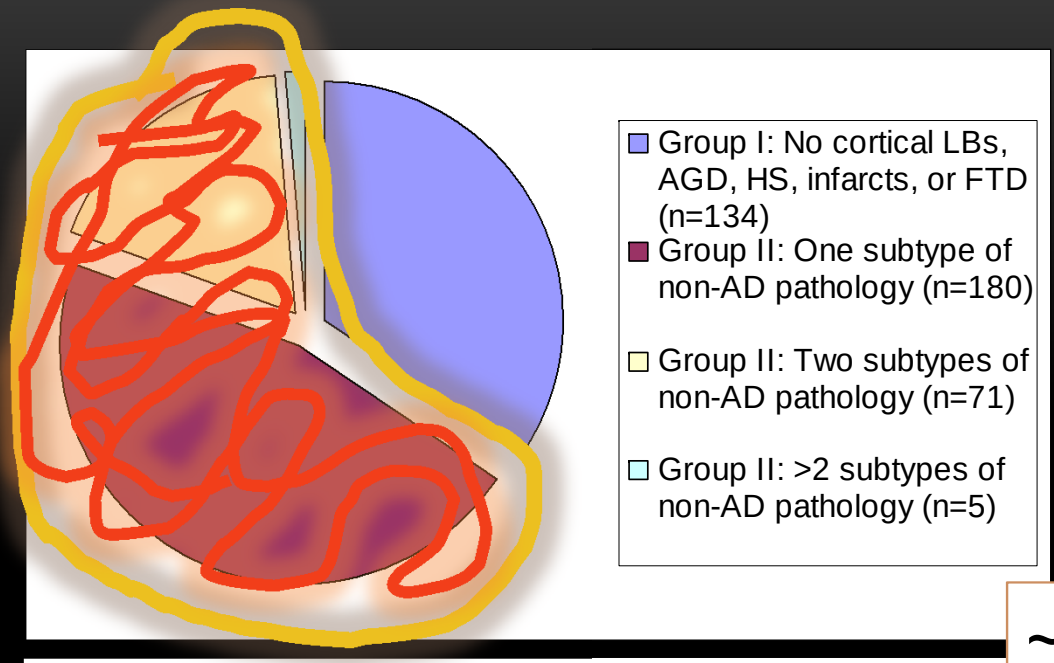


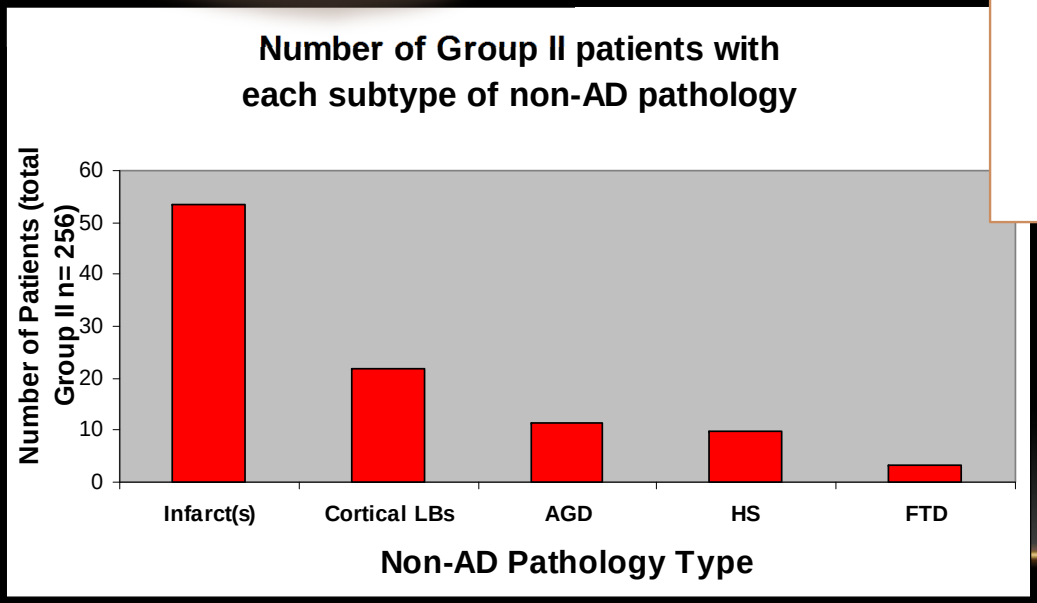
Dirty sample – poor correlation

Cardiac Function



Amount of atherosclerosis





~2/3rd of UK ADC cohort have important non-AD pathology

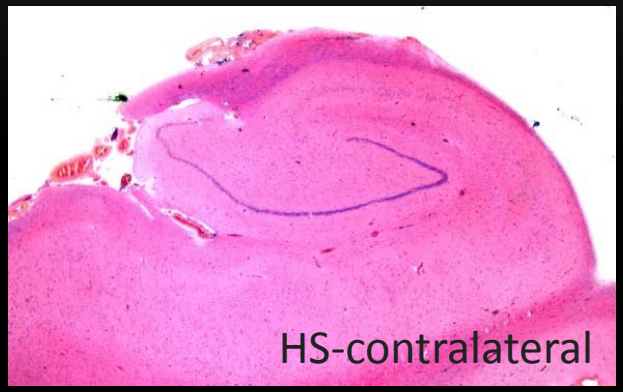
Nelson PT et al, *JNEN* 2007

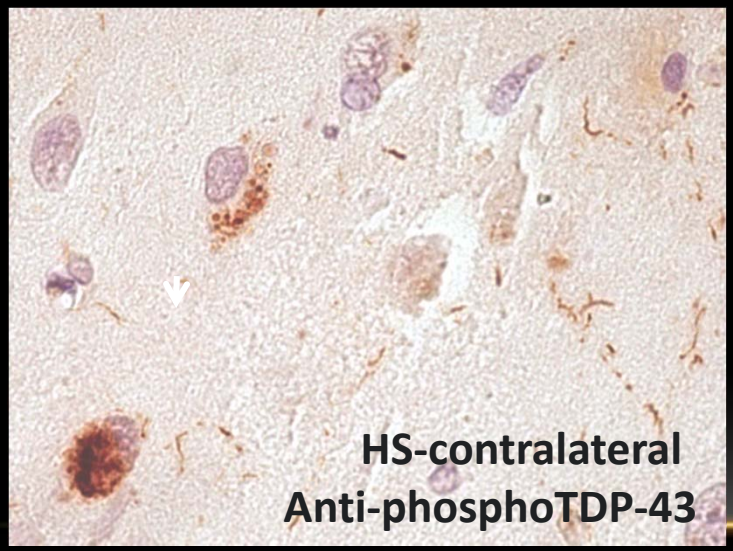
Key point:

In advanced old age, it is the norm for human brains to exhibit impactful, non-Alzheimer's pathology

Scott Adams's "Dilbert"

HIPPOCAMPAL SCLEROSIS – *WHAT IS IT?*





Cell death and gliosis in hippocampus

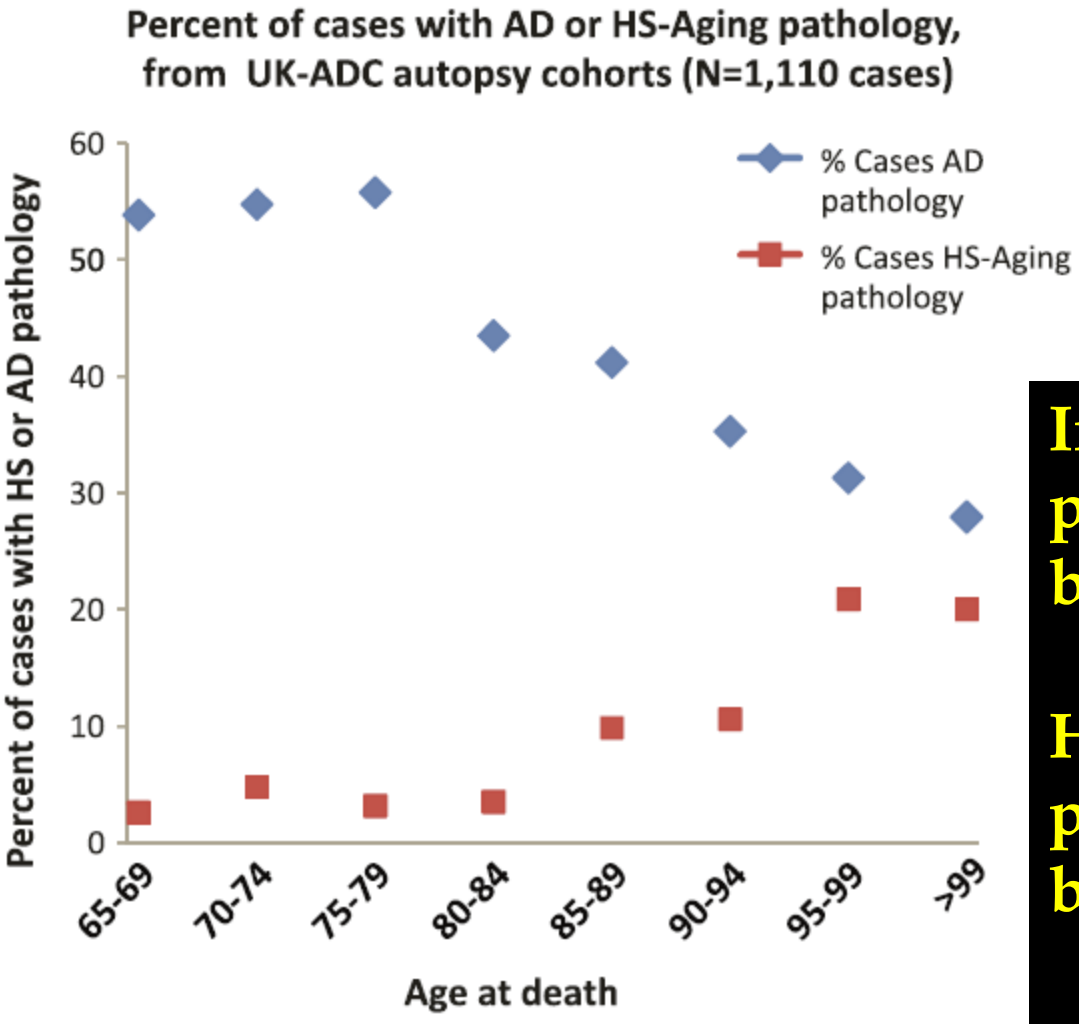
Probably not related to AD

Aberrant TDP-43 usually

No biomarker or specific clinical feature

Definite cognitive impact

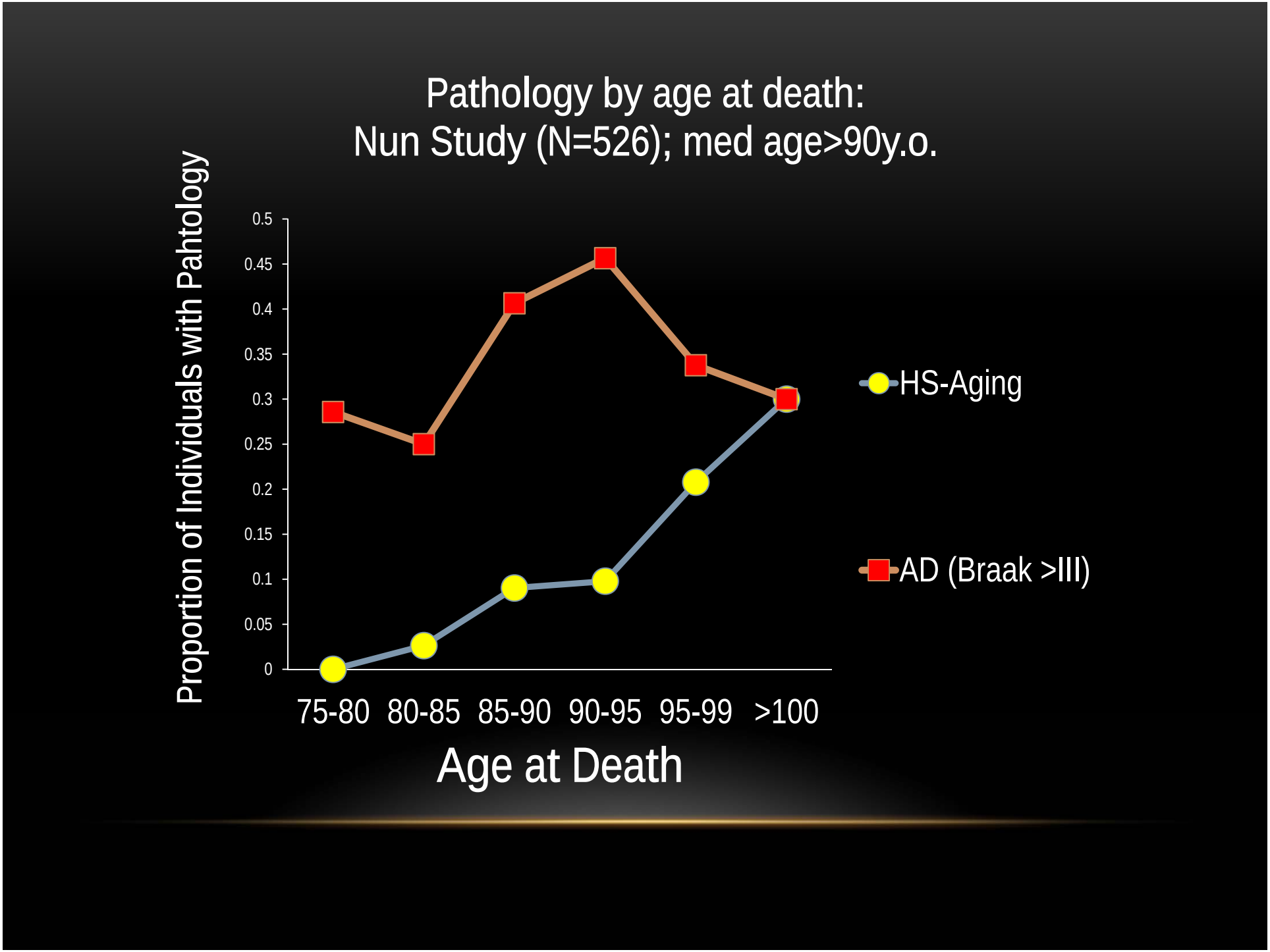
Autopsy diagnosis required



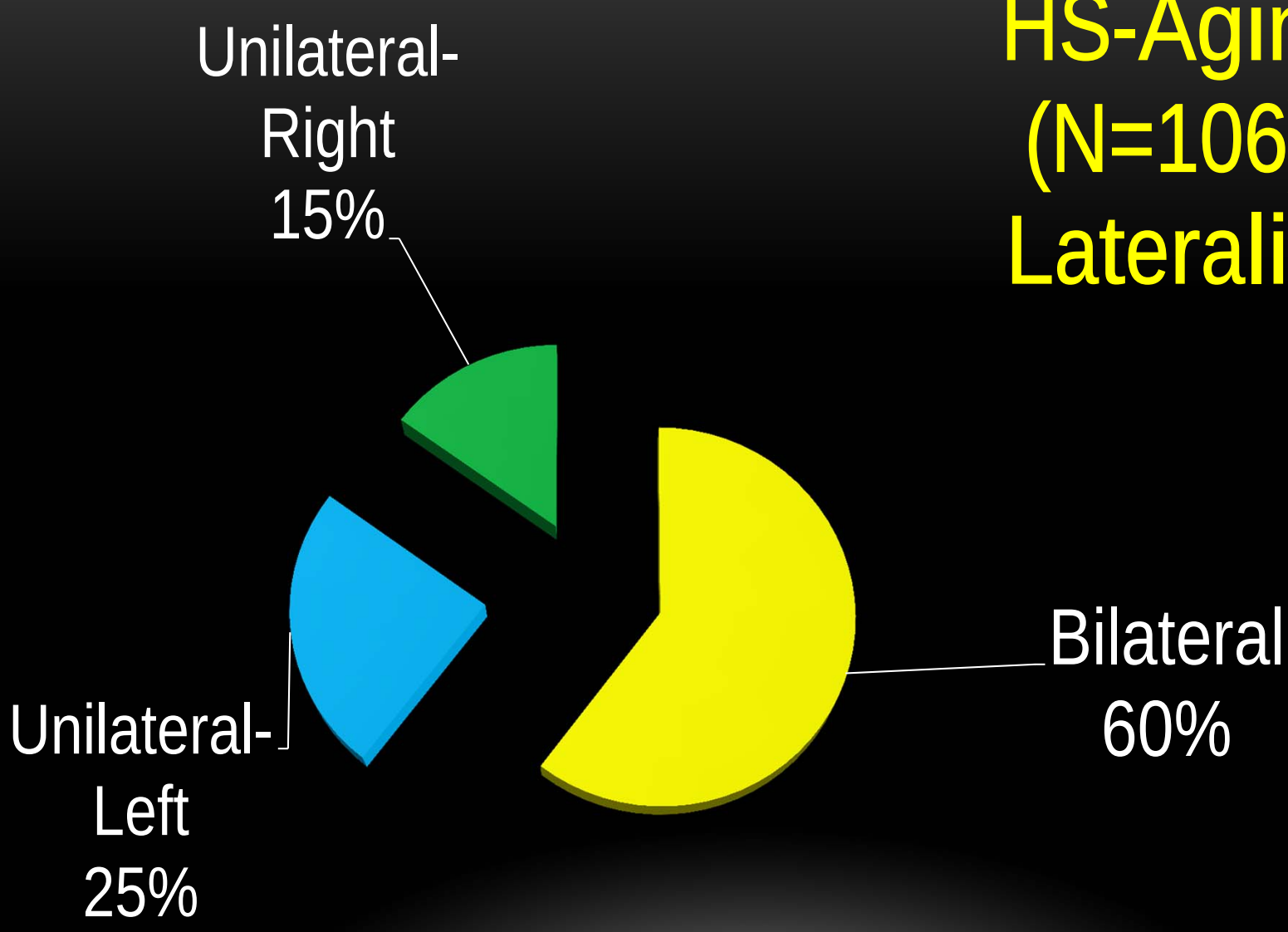
In extreme old age, AD pathology becomes LESS prevalent

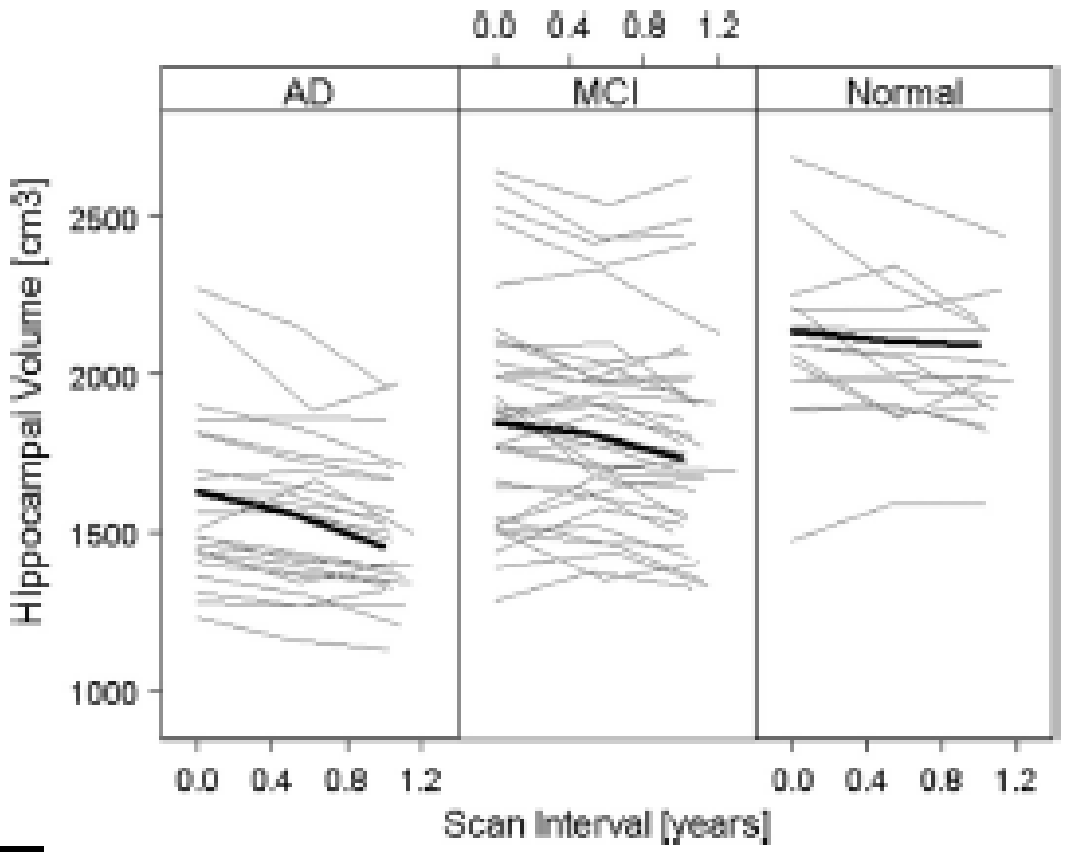
Hippocampal sclerosis pathology becomes MORE prevalent

Acta Neuropathologica, 2011
Brain, 2011


Pathology by age at death:
Nun Study (N=526); med age>90y.o.
Proportion of Individuals with Pahtology
0.5
0.45
0.4
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
75-80
80-85
85-90
90-95
95-99
>100
Age at Death
HS-Aging
AD (Braak >III)

HS-Aging (N=106): Laterality





A large proportion of MRI-visualized hippocampal atrophy is NOT AD!

ELSEVIER

Alzheimer's & Dementia

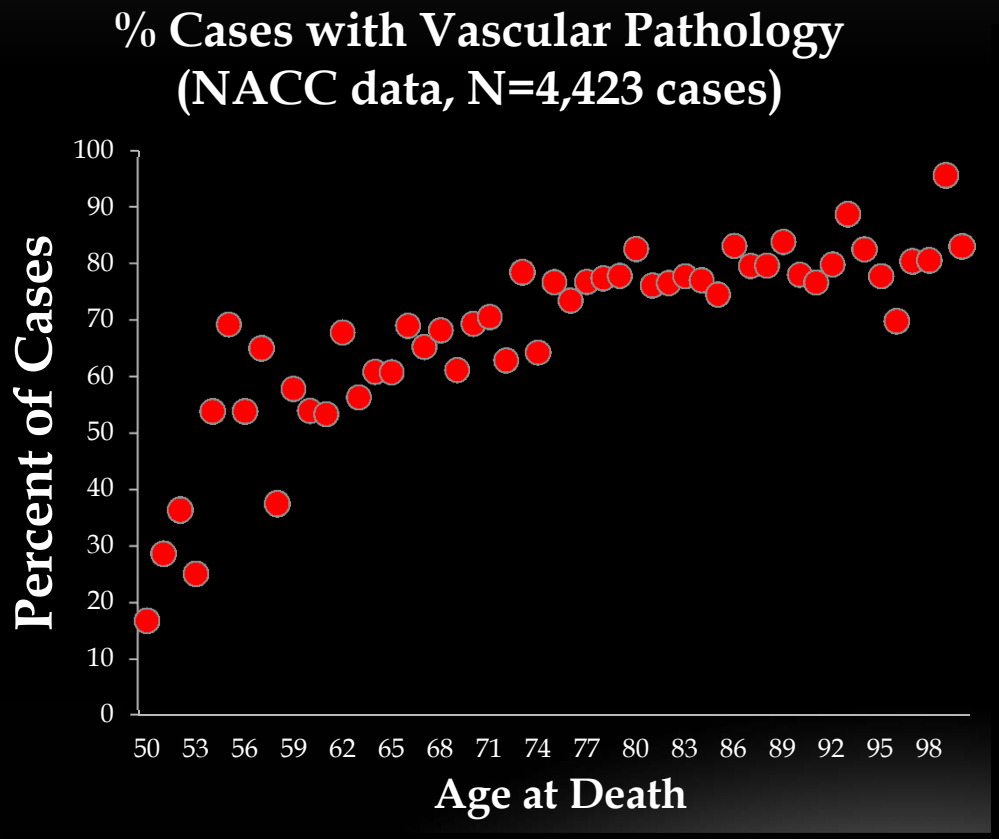
Alzheimer's & Dementia 8 (2012) S1–S68

Review Article

The Alzheimer's Disease Neuroimaging Initiative: A review of papers published since its inception

Michael W. Weiner[a,b,c,d,e,*], Dallas P. Veitch[a], Paul S. Aisen[f], Laurel A. Beckett[g], Nigel J. Cairns[h,i], Robert C. Green[j], Danielle Harvey[g], Clifford R. Jack[k], William Jagust[l], Enchi Liu[m], John C. Morris[f], Ronald C. Petersen[n], Andrew J. Saykin[o,p], Mark E. Schmidt[q], Leslie Shaw[r], Judith A. Siuciak[s], Holly Soares[t], Arthur W. Toga[u], John Q. Trojanowski[r,w,x,y], Alzheimer's Disease Neuroimaging Initiative

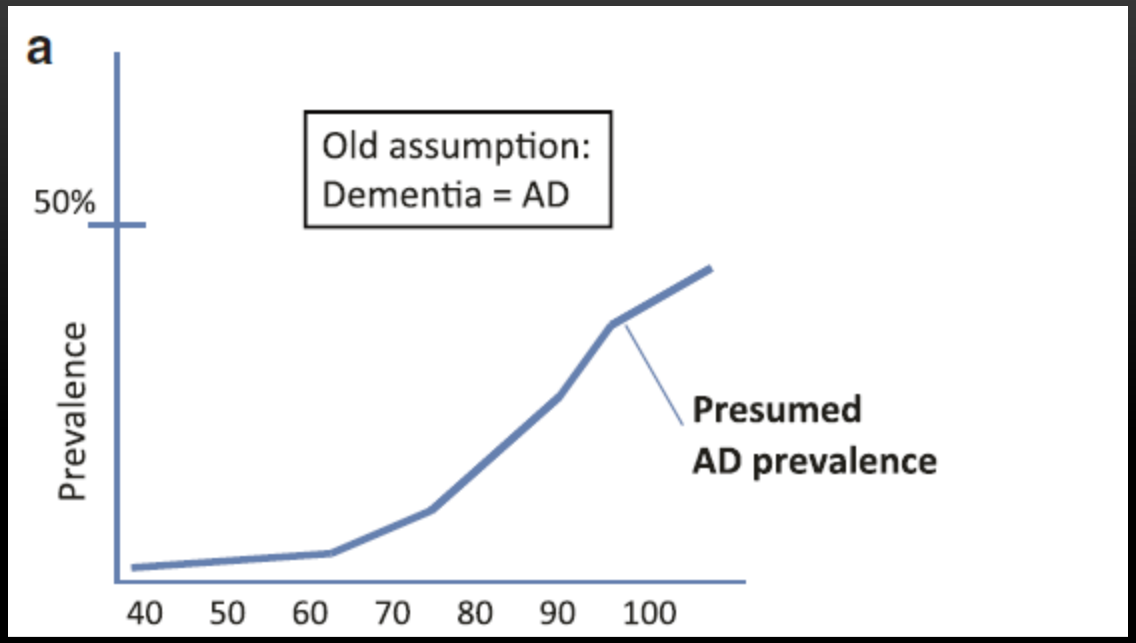
Cerebrovascular Disease



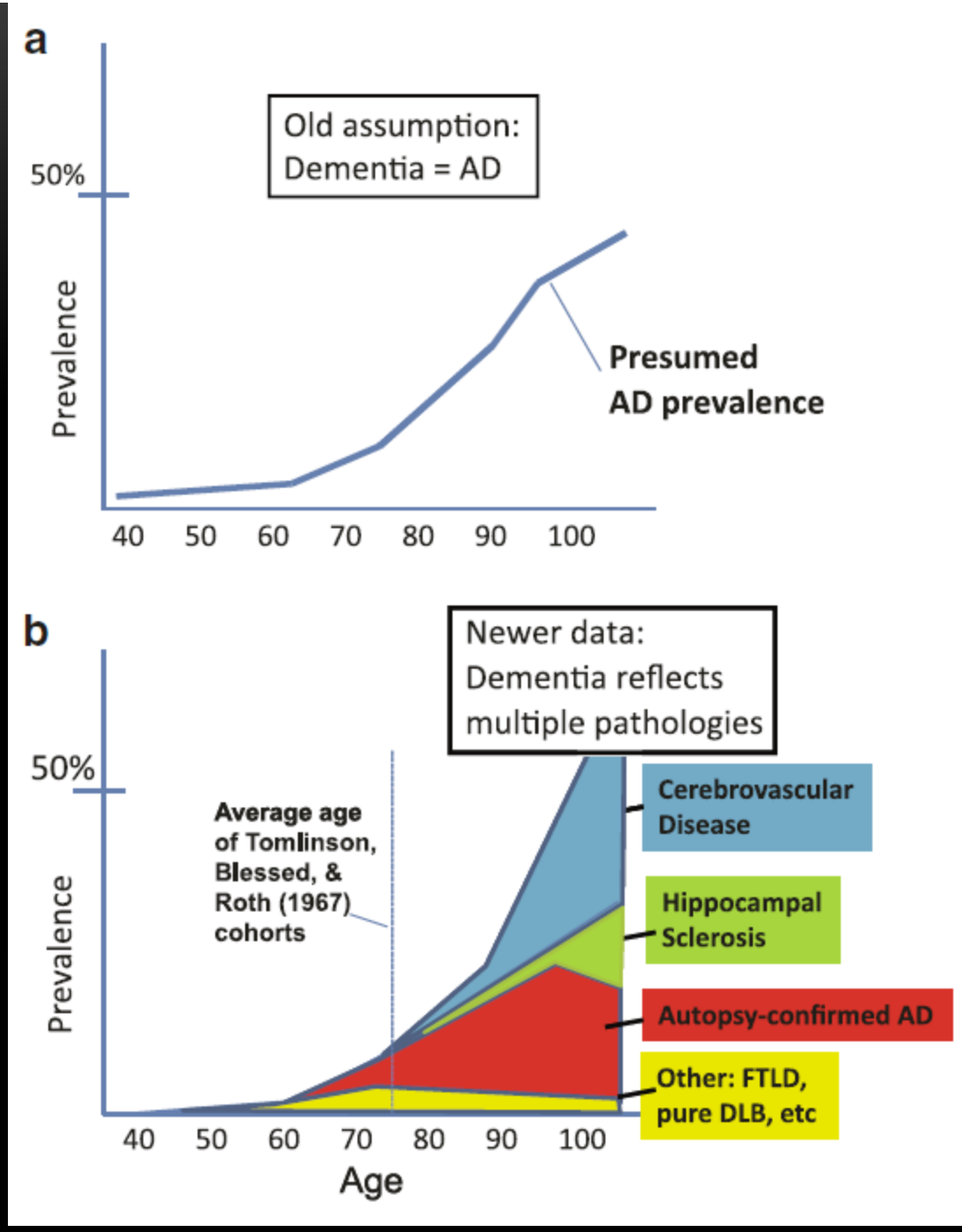
In old age, cerebrovascular pathology becomes MORE prevalent & practically ubiquitous

(although AD pathology becomes LESS prevalent)

Acta Neuropathologica, 2011



Additional pathologies in advanced old age require an overhaul of prior assumptions



In advanced old age, non-AD diseases underlie much of clinical dementia

"Classic" clin-path studies addressed much younger cohorts.

Acta Neuropathologica, 2011

AD is not “brain aging”; there are abundant evidences for a specific plaque+tangle disease with strong genetic contribution

Density of neocortical tangles correlates strongly with cognitive impairment

No “dissociation” between AD pathology and cognitive impairment

Many diseases in aged human brains

Conclusions

1. **Neuropathology (NP) is complicated**

2. **Consideration of NP necessary to optimize management of**
   -patients, clinical trials, biomarkers, animal models, etc

3. **NP has become more, not less, relevant and important**

Obvious fact:

Obvious fact:

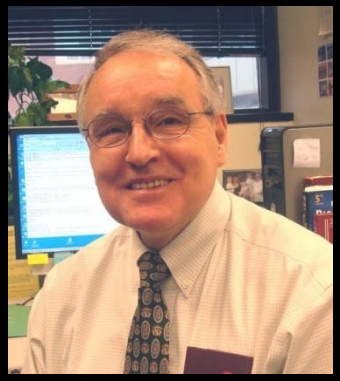
We’re not done yet

UK-ADC Neuropathology Core

Erin Abner, MPH

Greg Jicha, MD PhD

Dick Kryscio, PhD



Fred Schmitt, PhD

Linda Van Eldik, PhD

Thanks

Dr. William Markesbery

NIH/NIA	Pilot Grant
NIH/NINDS	K08 Grant
NIH/NINDS	R01 Grant
NIH/NIA	R21 Grant
NIH/NIA ADC NP Core	P30 Grant
Alzheimer's Association	NIR Grant

Editorial comment:

Editorial comment:

Autopsy diagnosis
is the gold standard for
neurodegenerative
disease diagnosis and severity