Aterosclerosi e Malattia di Alzheimer

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Aterosclerosi e Malattia di Alzheimer
Giovanni Zuliani

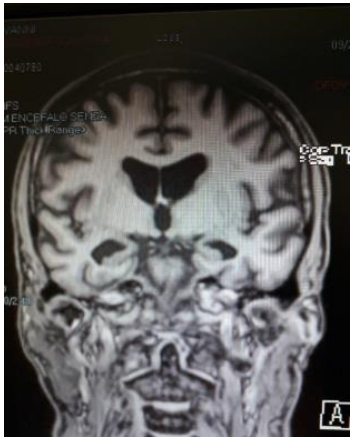
"NON HO ALCUN CONFLITTO DI INTERESSI DA DICHIARARE"

Aterosclerosi e Malattia di Alzheimer

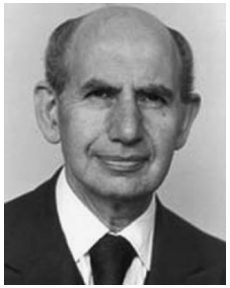
Giovanni Zuliani

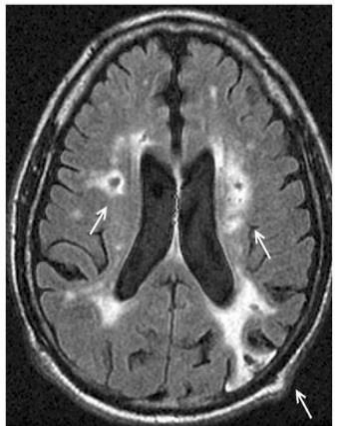
IL CONTENUTO DELLA PRESENTAZIONE NON RIFLETTE NECESSARIAMENTE LE MIE OPINIONI, MA RIPORTA DATI PROVENIENTI DALLA LETTERATURA SCIENTIFICA INTERNAZIONALE

Classificazione delle Demenze



Sir Martin Roth
(anni ‘50)





DEMENZE NEURODEGENERATIVE

↓

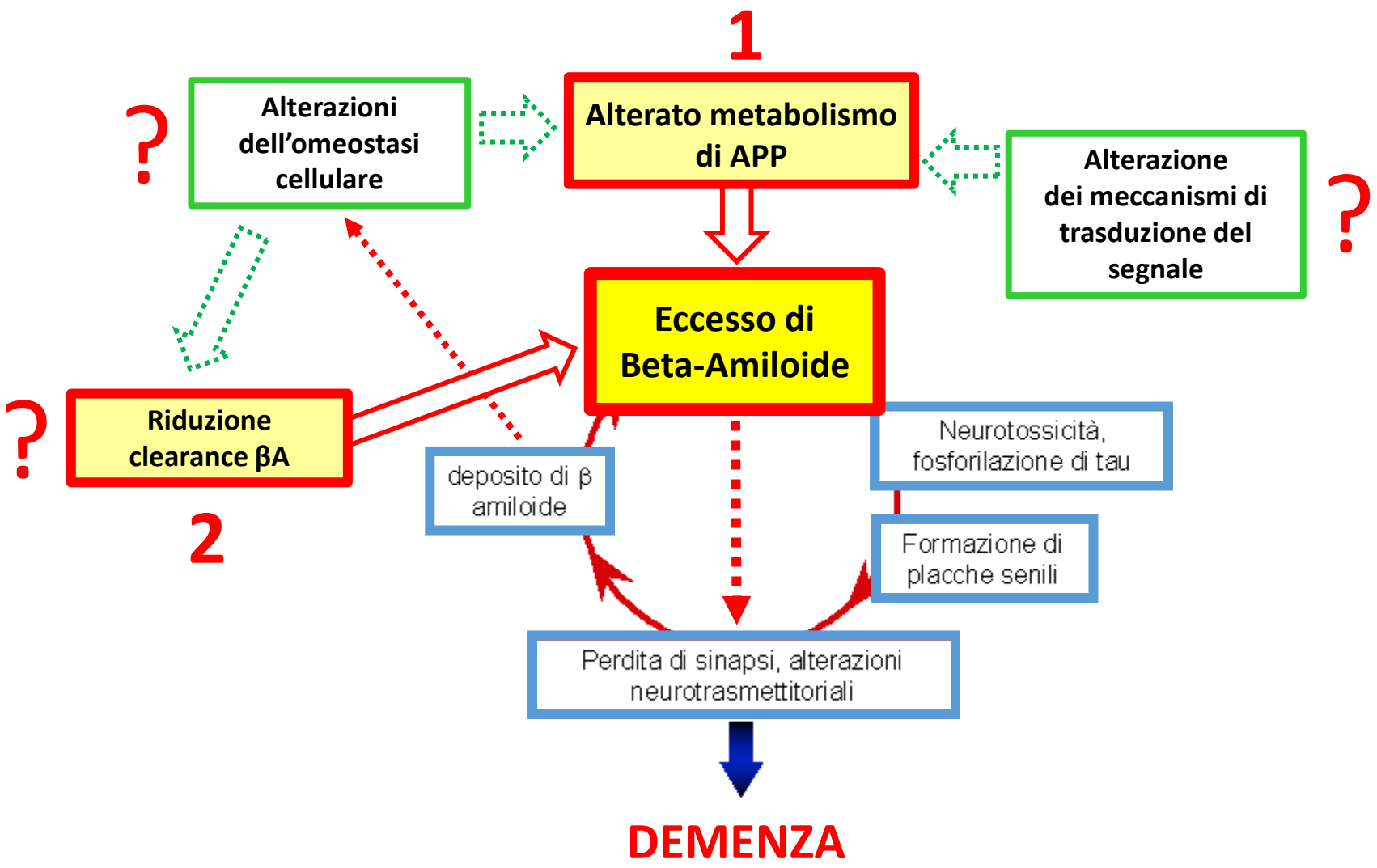
Pattern clinico specifico

DEMENZA VASCOLARE

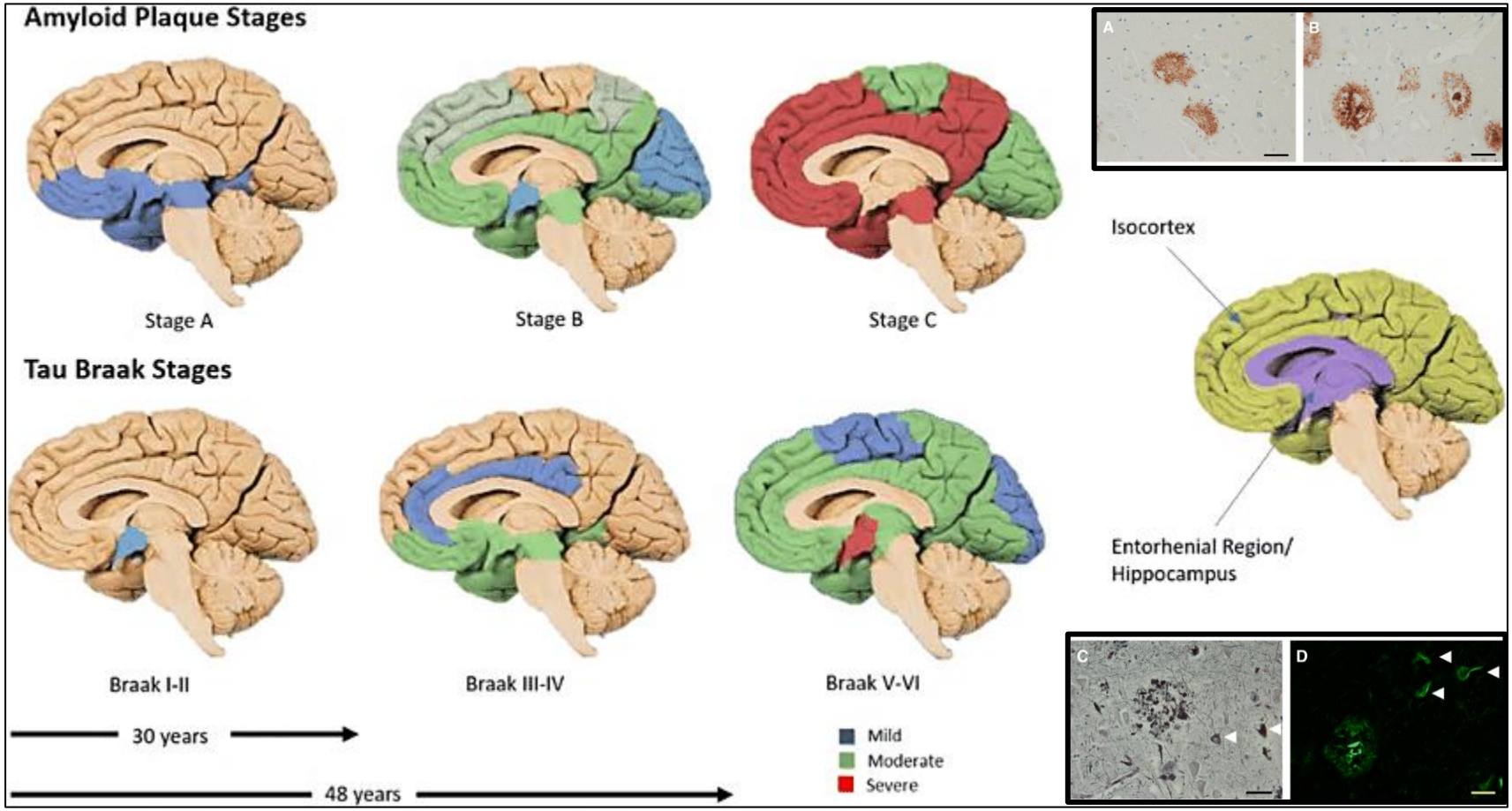
↓

Pattern clinico specifico

Malattia di Alzheimer
Ipotesi patogenetica semplificata



La diagnosi di Alzheimer è tuttora basata su βA e NFT: *«NO AMILOIDE, NO ALZHEIMER…»*

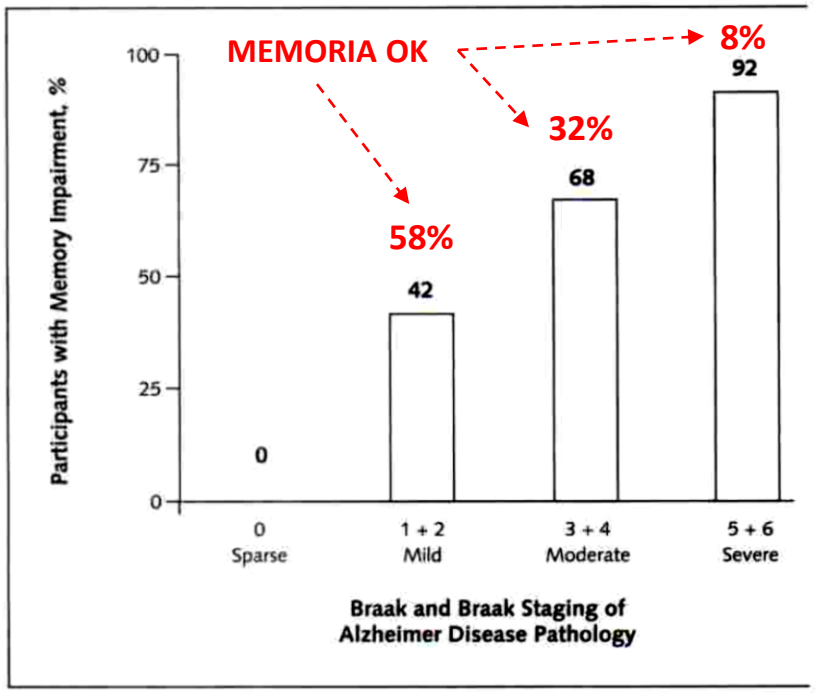


Braak & Braak – CERAD - NIA-Reagan

Healthy aging and dementia: findings from the Nun study

Il 30% DEI SOGGETTI CON DIAGNOSI ANATOMO-PATOLOGICA DI AD NON HA DEFICIT MNESICO

Figure 2. The relationship between the Braak and Braak staging of the degree or spread of Alzheimer disease neurofibrillary pathology and the prevalence of impairments in short-term memory (delayed word recall) at the last examination before death.



LA NEUROPATOLOGIA AD (BA + TAU) E' NECESSARIA MA NON SUFFICIENTE

Snowdon Ann Intern Med 2003

Objective subtle cognitive difficulties predict future amyloid accumulation and neurodegeneration

Method: 747 ADNI participants (305 CN, 153 Obj-SubCognDiff, 289 MCI) underwent **neuropsychological testing** and serial **amyloid PET** and **structural MRI.**

Objective Subtle Cognitive Difficulties are:

- associated with faster amyloid accumulation and vulnerability of entorhinal cortical thinning.

- identified PRIOR to or during the pre-clinical stage of amyloid deposition.

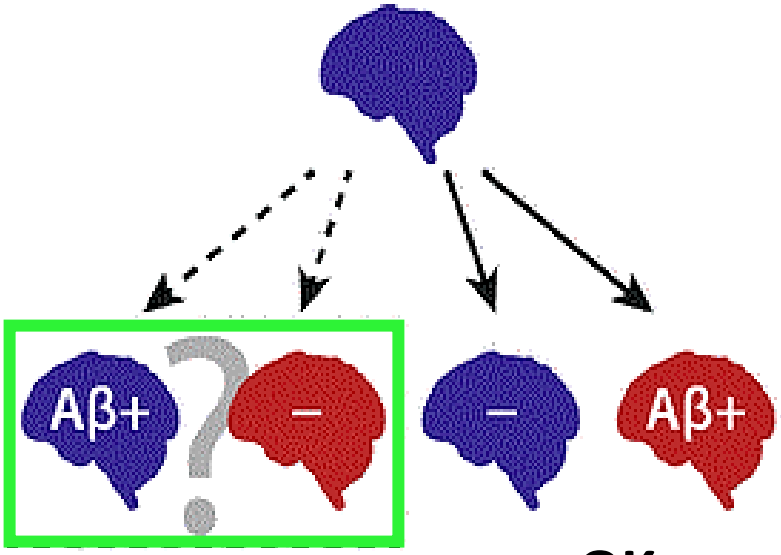
"Cognitive changes may be occurring BEFORE significant levels of amyloid have accumulated … It seems we may need to focus on treatment targets of pathologies other than amyloid …

ADNI
Alzheimer's Disease Neuroimaging Initiative

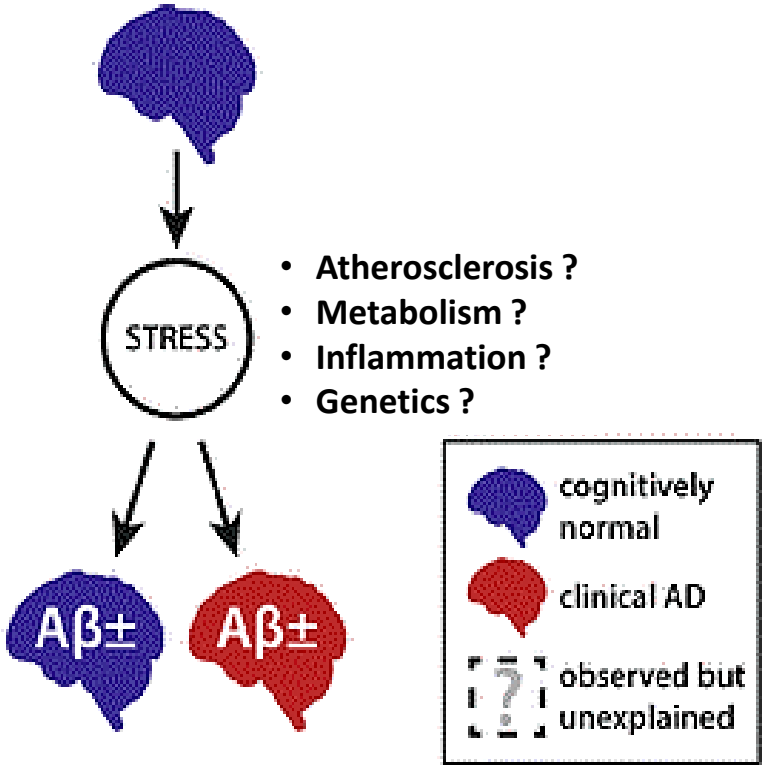
Thomas et al. Neurology 2020

Ipotesi patogenetica della Malattia di Alzheimer

A. Amyloid Hypothesis

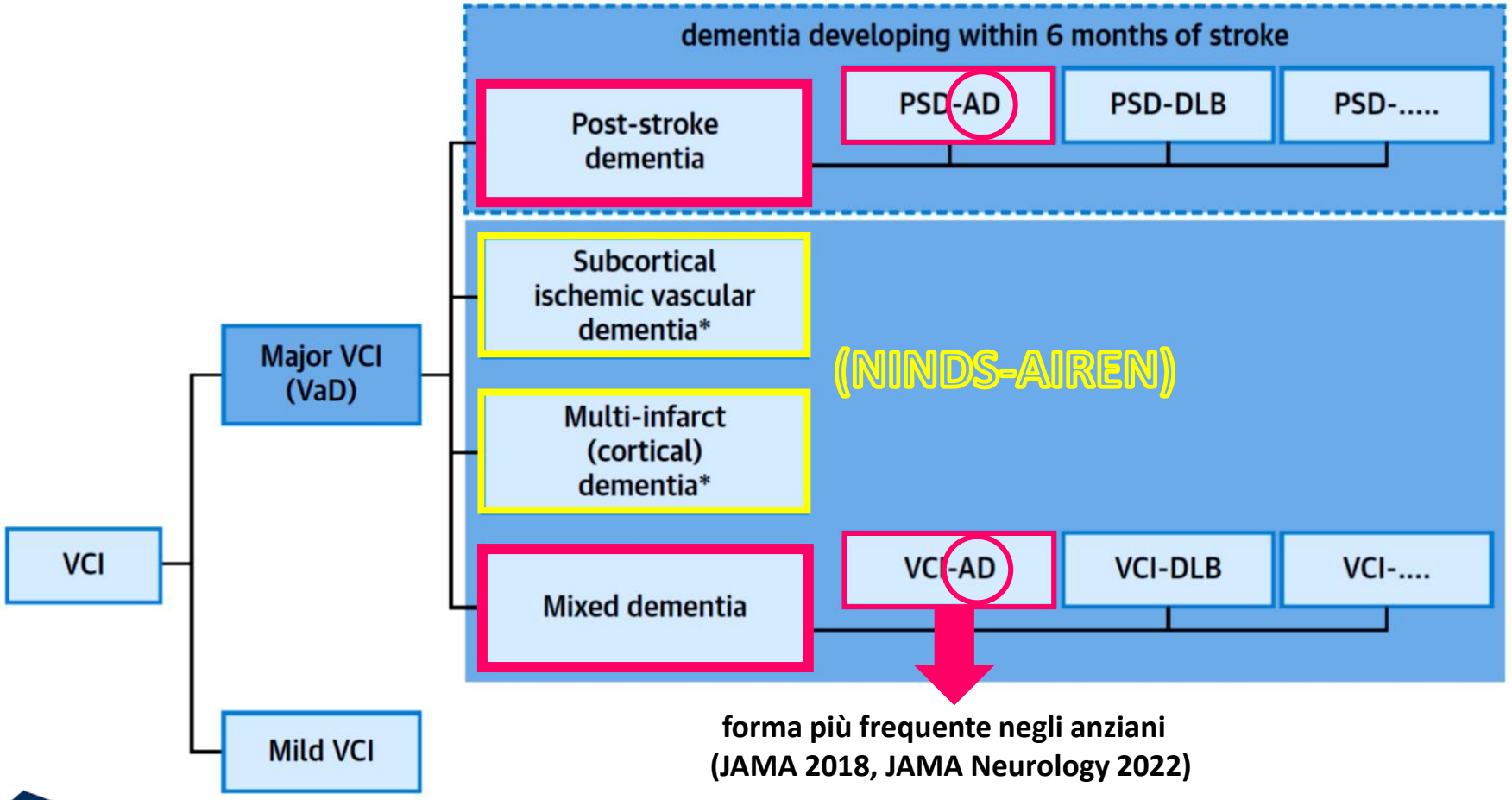


B. «Adaptative Response» Hypothesis»



Vascular Cognitive Impairment and Dementia

JACC Scientific Expert Panel - 2019



forma più frequente negli anziani
(JAMA 2018, JAMA Neurology 2022)

Iadecola et al. JACC 2019

JAMA Neurology | Original Investigation

Frequency and Underlying Pathology of Pure Vascular Cognitive Impairment

1767 Soggetti – 67% donne – età media alla morte 89 anni

PATOLOGIA CEREBRALE:

- ***56% MISTA***
- ***21% solo VASCOLARE***
- ***23% solo NEURODEGENERATIVA***

DETERIORAMENTO COGNITIVO:

- ***78% nel gruppo MISTA***
- ***67% nel gruppo NEURODEGENERATIVA***
- ***42% nel gruppo VASCOLARE***

Oveisgharan et al. JAMA Neurology 2022

JAMA Neurology | Original Investigation

Frequency and Underlying Pathology of Pure Vascular Cognitive Impairment

NEL GRUPPO VASCOLARE:

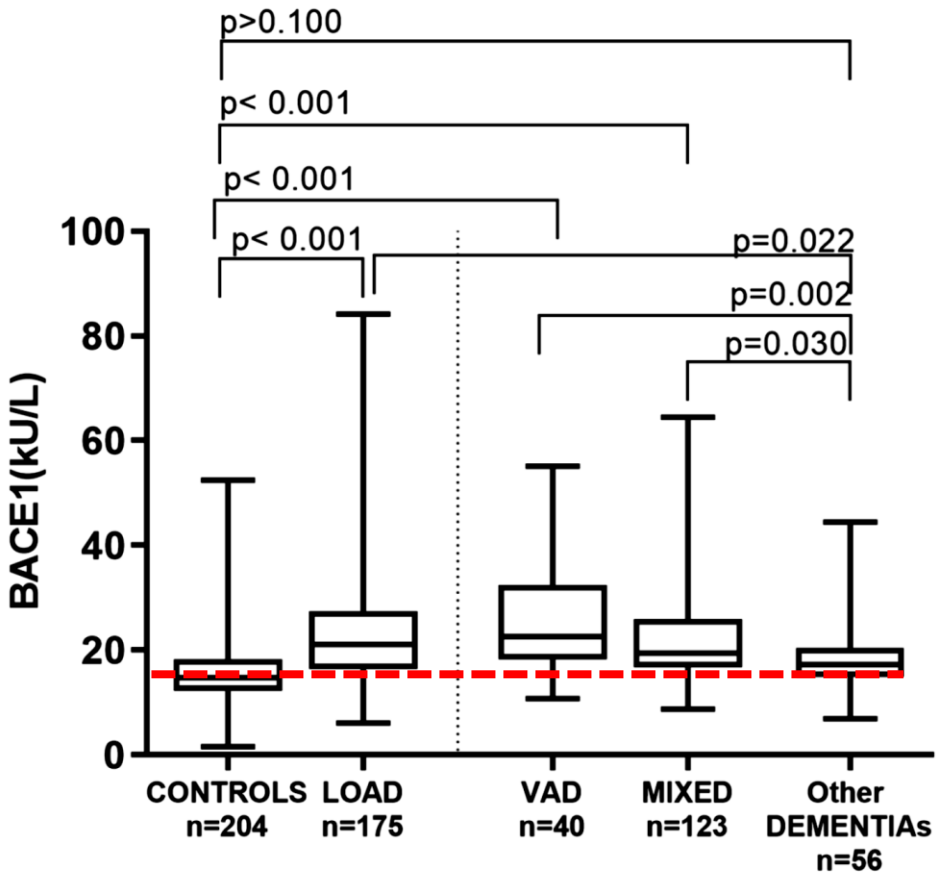
La patologia cerebrovascolare spiega solo il 10% della variabilità del declino cognitivo …

Oveisgharan et al. JAMA Neurology 2022

OPEN

Increased blood BACE1 activity as a potential common pathogenic factor of vascular dementia and late onset Alzheimer's disease

Giovanni Zuliani[1], Alessandro Trentini[2], Valentina Rosta[2], Remo Guerrini[3], Salvatore Pacifico[3], Stefania Bonazzi[1], Anna Guiotto[2], Angelina Passaro[1], Davide Seripa[4], Giuseppe Valacchi[2,5] & Carlo Cervellati[1]✉



2020
nature
SCIENTIFIC REPORTS

Person-specific contribution of neuropathologies to cognitive loss in old age

1079 partecipanti a *Religious Orders Study* o *Memory and Aging Project* (70% MCI/demenza, 30% normali).

1.	ALZHEIMER	65.3% (NIA Reagan)
2.	Chronic macroscopic infarcts:	36.0%
3.	Cerebral amyloid angiopathy:	35.8%
4.	TDP-43:	34.9%
5.	Atherosclerosis:	32.2%
6.	Arteriolosclerosis:	31.3%
7.	Chronic microinfarcts:	30.0%
8.	Neocortical Lewy bodies:	13.3%
9.	Hippocampal sclerosis:	10.4%

236 combinazioni neuropatologiche diverse

Annals of NEUROLOGY
An Official Journal of the American Neurological Association and the Child Neurology Society
ANA AMERICAN NEUROLOGICAL ASSOCIATION

Boyle et al. Annals of Neurology 2018

Person-specific contribution of neuropathologies to cognitive loss in old age

Contributo medio (%) al disturbo cognitivo:

- **Pathologic AD: >50%**
  (dal 22.3% al 100% a seconda della presenza delle altre neuropatologie)
- **Lewy bodies: 41.0%**
- **Hippocampal sclerosis: 24.9%**
- **Macroscopic infarcts: 20.1%**
- **Amyloid angiopathy: 15.7%**
- **Atherosclerosis: 18.5%**
- **Arteriolosclerosis: 19.8%**

La AD "pura" è rara = 9%

Annals of NEUROLOGY An Official Journal of the American Neurological Association and the Child Neurology Society

Boyle et al. Annals of Neurology 2018

Quale rapporto tra aterosclerosi e Malattia di Alzheimer ?

BRAIN INFARCTION and the Clinical Expression of Alzheimer Disease. The Nun Study

LA NEUROPATOLOGIA AD (BA + TAU) E' NECESSARIA MA NON SUFFICIENTE

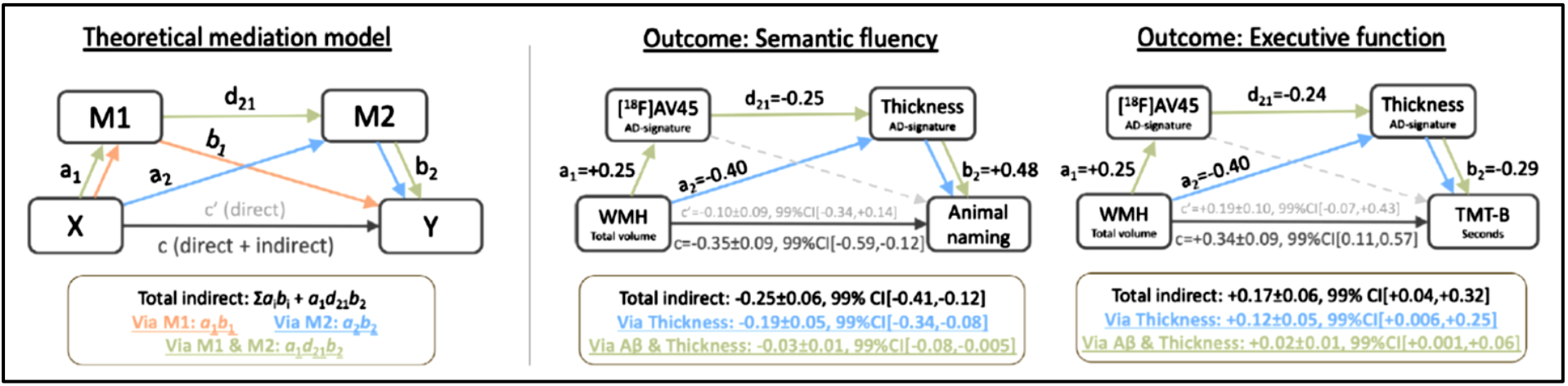
Table 2.—Prevalence of Dementia for Participants Without and Participants With Brain Infarcts Who Met Neuropathologic Criteria for Alzheimer Disease*

Type and Location of Infarct	Proportion Demented (No. Demented/ No. at Risk)	Multivariate-Adjusted Odds Ratio for Dementia (95% CI)
1-2 Lacunar infarcts in basal ganglia, thalamus, or deep white matter	0.93 (14/15)	20.7 (1.5-288.0)
≥1 Large infarcts in lobes of neocortex	0.75 (9/12)	6.7 (0.9-48.3)
No brain infarcts	0.57 (21/37)	. . .

*All 61 participants met the neuropathologic criteria for Alzheimer disease. Variables adjusted were age at the cognitive assessment, number of days between the assessment and death, attained education, and the mean number of neurofibrillary tangles in the neocortex. Lobes

Snowdon Ann Intern Med 2003

Vascular burden and cognition: mediating roles of neurodegeneration and amyloid PET



Il rapporto tra WMH e Funzioni Cognitive è mediato dalla Atrofia Corticale (MRI) nelle regioni temporo-parietali, mentre NON viene evidenziata alcuna associazione con il metabolismo del glucosio (FDG-PET).

WMH → ATROFIA CORTICALE → ↓ FUNZIONI COGNITIVE

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

Ottoy et al. Alzh & Dem 2022

Rotterdam Study

Kungsholmen project

EURODEM

FINMONICA

Honolulu-Asia study

Reported risk factors for AD

Heart-related risk factors

Congestive heart failure
Cardiac arrhythmia
Hypertension
Hypotension
Thrombotic episodes
High concentrations of homocysteine in the serum
Atrial fibrillation
Presence of *APOE* ϵ4 allele
Atherosclerosis

Peripheral risk factors

Smoking
Alcoholism
High serum cholesterol
High intake saturated fat
Diabetes mellitus
Haemorheological abnormalities
High cholesterol concentrations in the plasma

Brain-related risk factors

Ageing
Ischaemic stroke
Silent stroke
Head injury
Transient ischaemic attack
Menopause
Migraine
Lower education
Haemodynamic abnormalities
Depression

"Sono tutti fattori di rischio "vascolari" che compromettono la perfusione cerebrale. Essi supportano fortemente l'ipotesi che una comprimissione della perfusione cerebrale sia il trigger primario nello sviluppo di AD".

THE LANCET Neurology

JC de la Torre Lancet Neurology 2014

ARTICLE

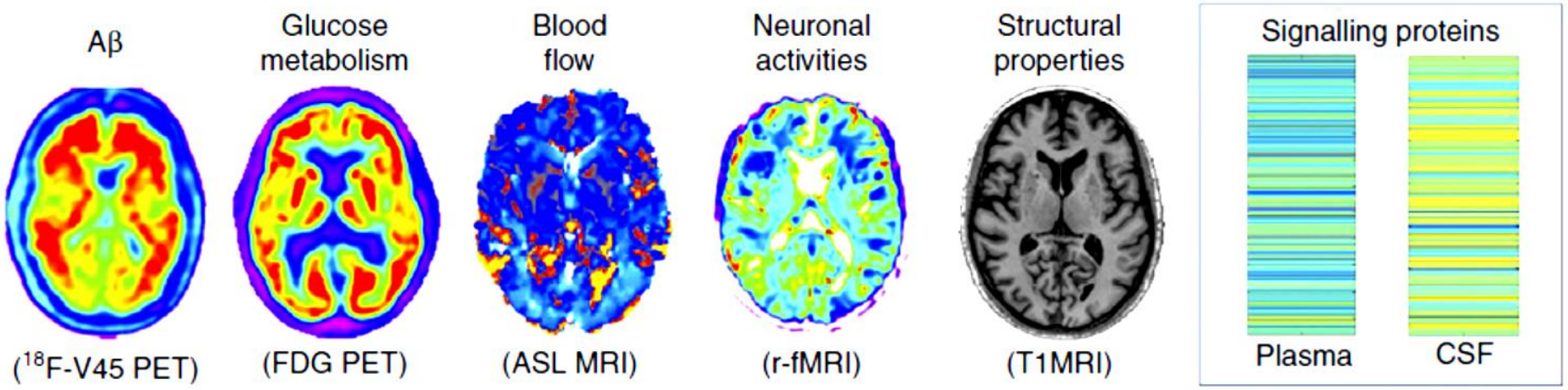
Received 25 Jun 2015 | Accepted 13 May 2016 | Published 21 Jun 2016

DOI: 10.1038/ncomms11934 OPEN

Early role of vascular dysregulation on late-onset Alzheimer's disease based on multifactorial data-driven analysis

Y. Iturria-Medina[1,2], R.C. Sotero[3], P.J. Toussaint[1,2], J.M. Mateos-Pérez[1,2], A.C. Evans[1,2] & The Alzheimer's Disease Neuroimaging Initiative[†]

1171 subjects - 7700 brain images - 10 plasma/cerebrospinal fluid biomarkers from the Alzheimer's Disease Neuroimaging Initiative (ADNI)



nature COMMUNICATIONS

Iturria Medina et al. NATURE COMMUNICATIONS 2016

Received 25 Jun 2015 | Accepted 13 May 2016 | Published 21 Jun 2016
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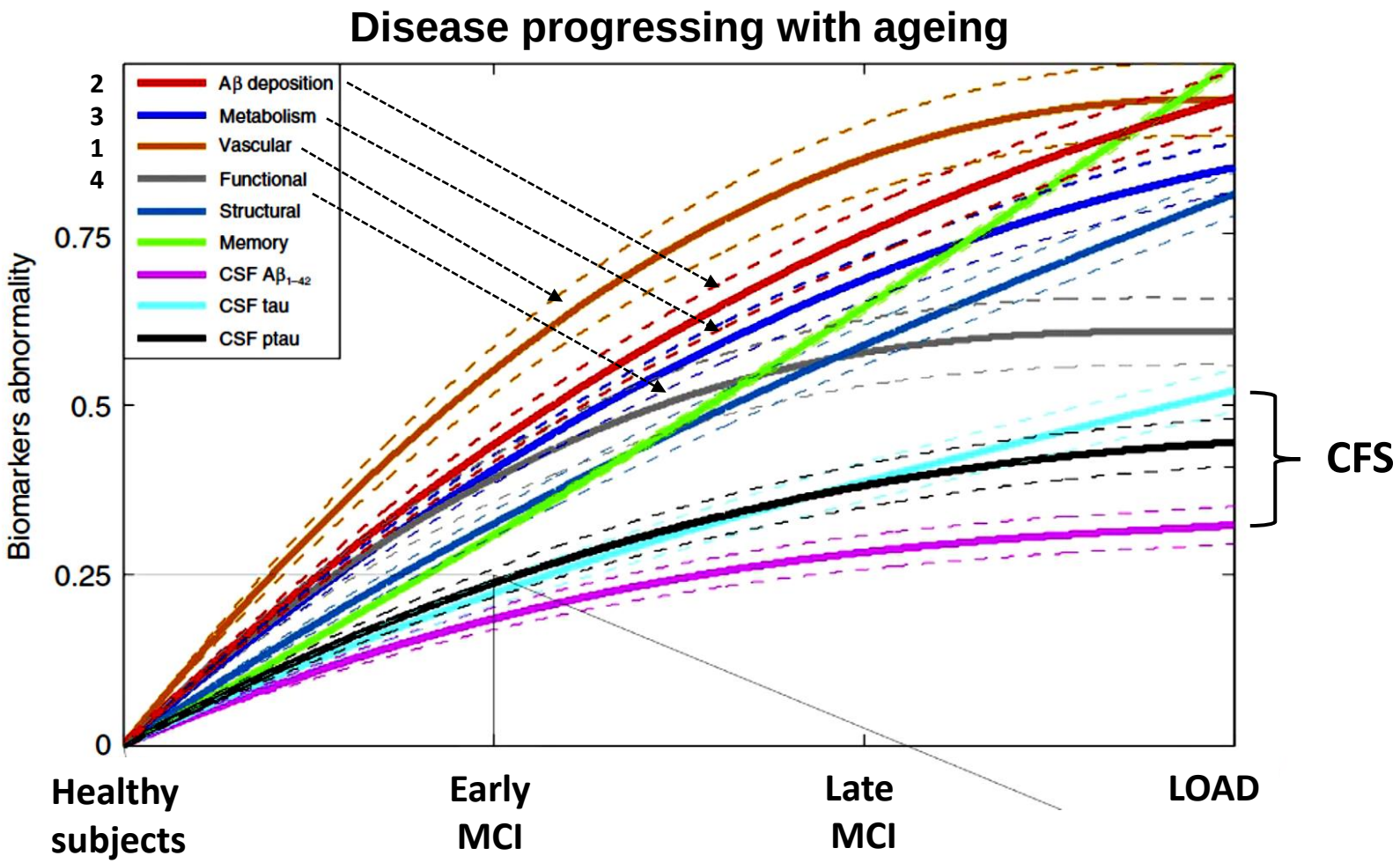


nature COMMUNICATIONS

Iturria Medina et al. NATURE COMMUNICATIONS 2016

CONTROLLI

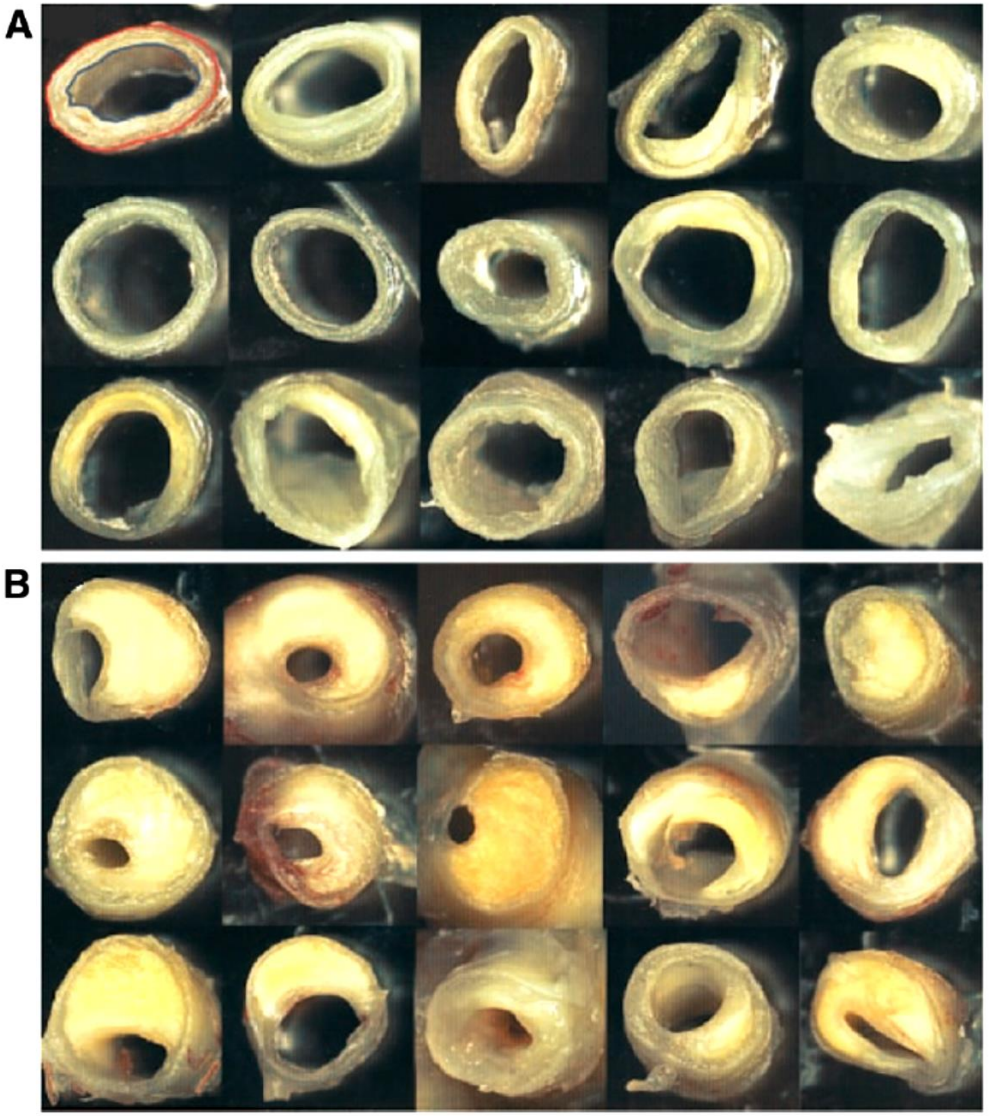
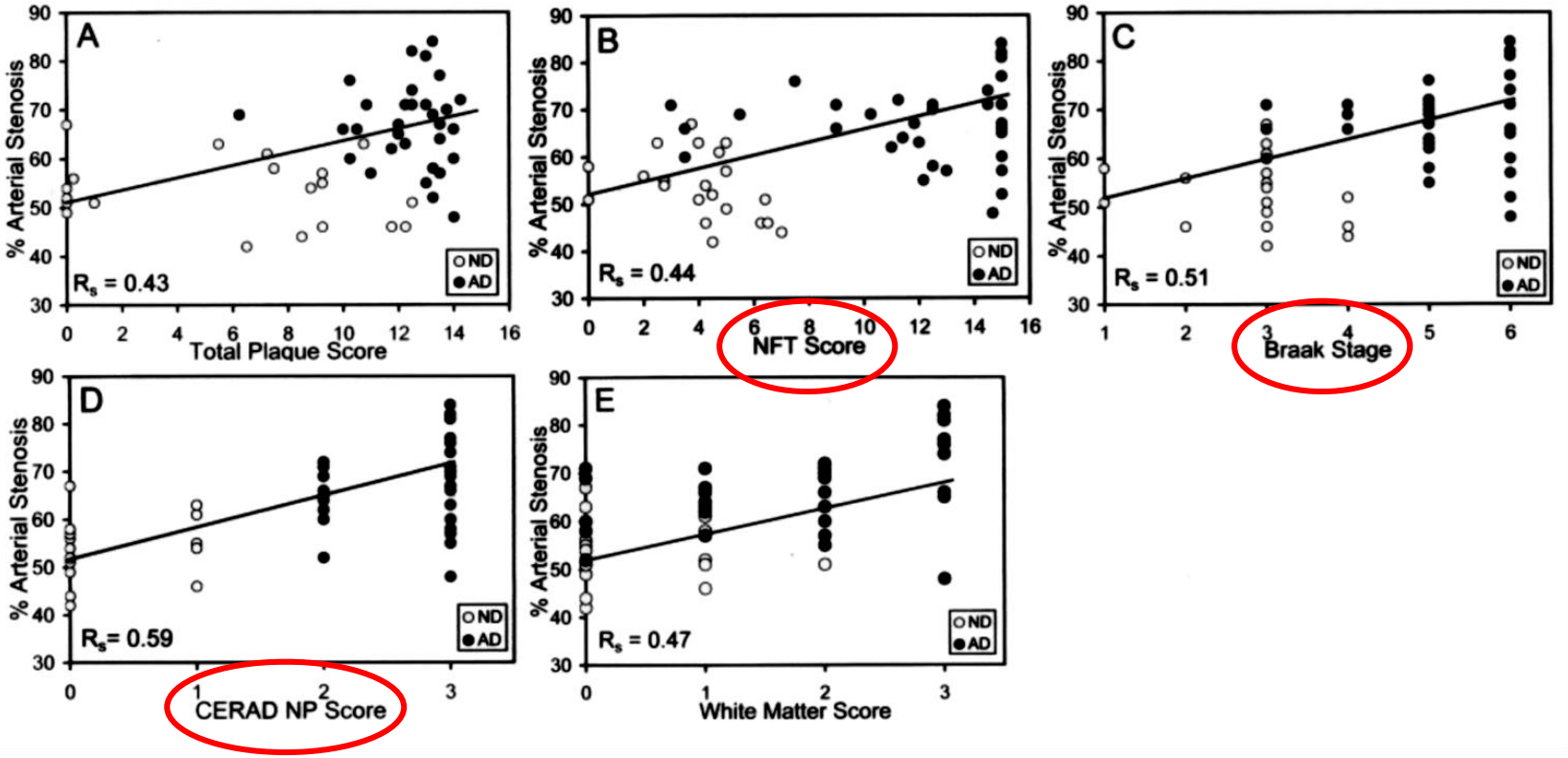


Figure 2 Occlusions of brain blood vessels ('circle of Willis') in controls and AD. Panel **(A)** shows cerebral arteries from non-demented elderly individuals, whereas Panel **(B)** shows arteries from AD patients showing atheromatous plaque deposition.

MALATTIA DI ALZHEIMER

Roher et al. ATVB 2003

Circle of Willis atherosclerosis is a risk factor for sporadic Alzheimer's disease



Correlazione significativa tra ATS del circolo di Willis (% stenosi) e lesioni neuropatologiche della AD.

Roher et al. ATVB 2003

Atherosclerosis and AD: analysis of data from the US National Alzheimer's Coordinating Center - NACC

1.054 individuals: 921 AD and 133 neuropathologically normal

Results: There was NO association between neuritic plaques or neurofibrillary tangles, with either clinical history of stroke or presence of cerebral infarcts, SVD or arteriosclerosis …

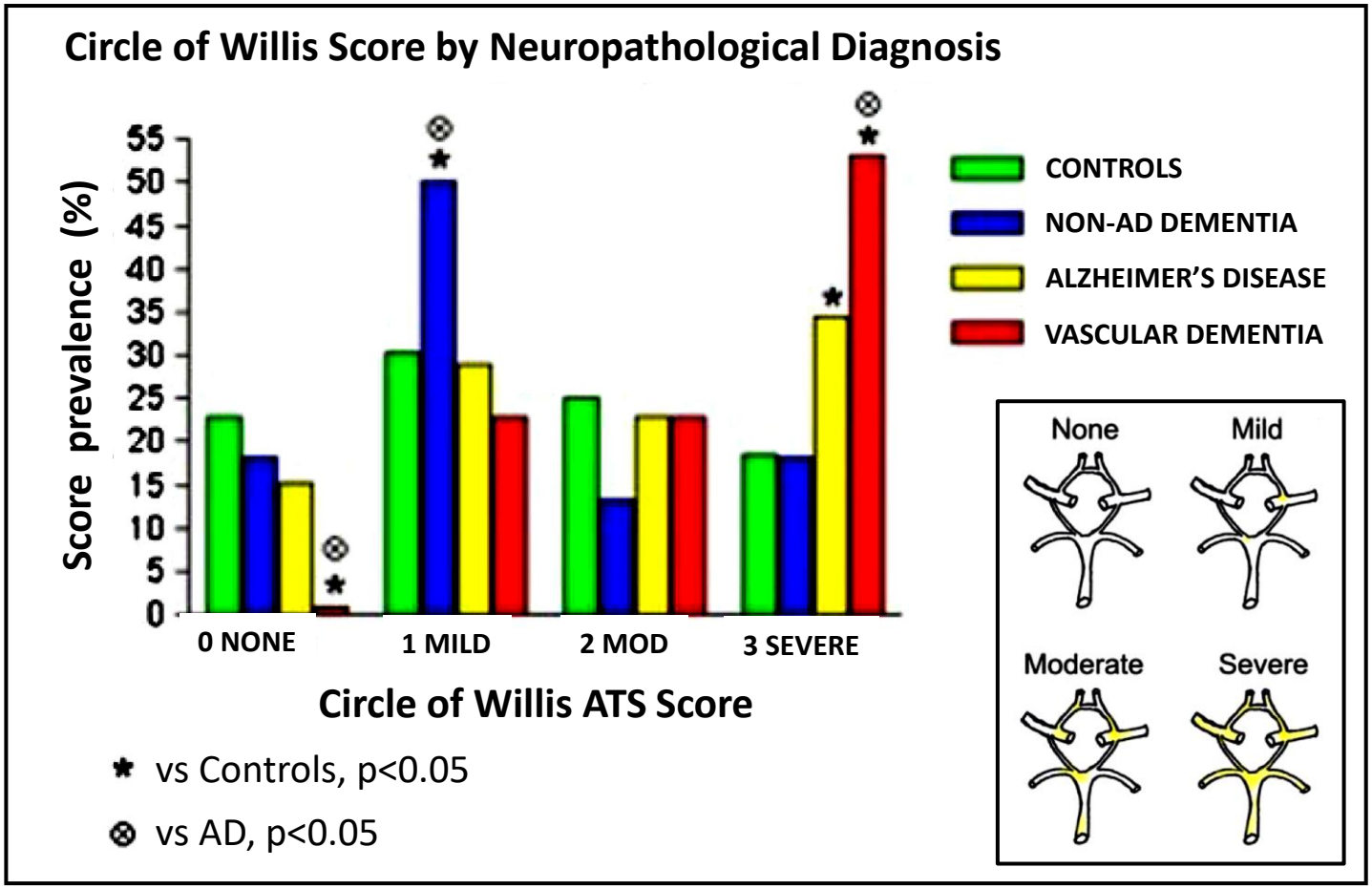
However, the presence of large-vessel disease or atherosclerosis was strongly associated with an increased frequency of neuritic plaques.

Conclusions: Atherosclerotic cerebrovascular disease may have a role in the pathogenesis of Alzheimer's disease because of a strong association with frequent neuritic plaques.

NACC
National Alzheimer's Coordinating Center

Honig et al. Neurology 2005

Circle of Willis atherosclerosis: association with Alzheimer's disease, neuritic plaques and neurofibrillary tangles



Sun Health Research Institute Brain Donation Program, AR, USA

Beach et al. Acta Neuropathol 2007

Circle of Willis atherosclerosis: association with Alzheimer's disease, neuritic plaques and neurofibrillary tangles

0: none - 1: mild - 2: moderate - 3: severe

Table 2 Odds ratios for disease diagnosis with each unit increase in circle of Willis atherosclerosis grade, using the control group as reference

Non-AD versus control	AD versus control	VaD versus control
1.02 ($P = 0.92$; 0.72–1.40)	1.31 ($P = 0.02$; 1.04–1.69)	2.50 ($P < 0.001$; 1.52–4.10)

All results are adjusted for age, gender and presence of the apolipoprotein E-ε4 allele. Probability and 95% confidence intervals are shown in parentheses.

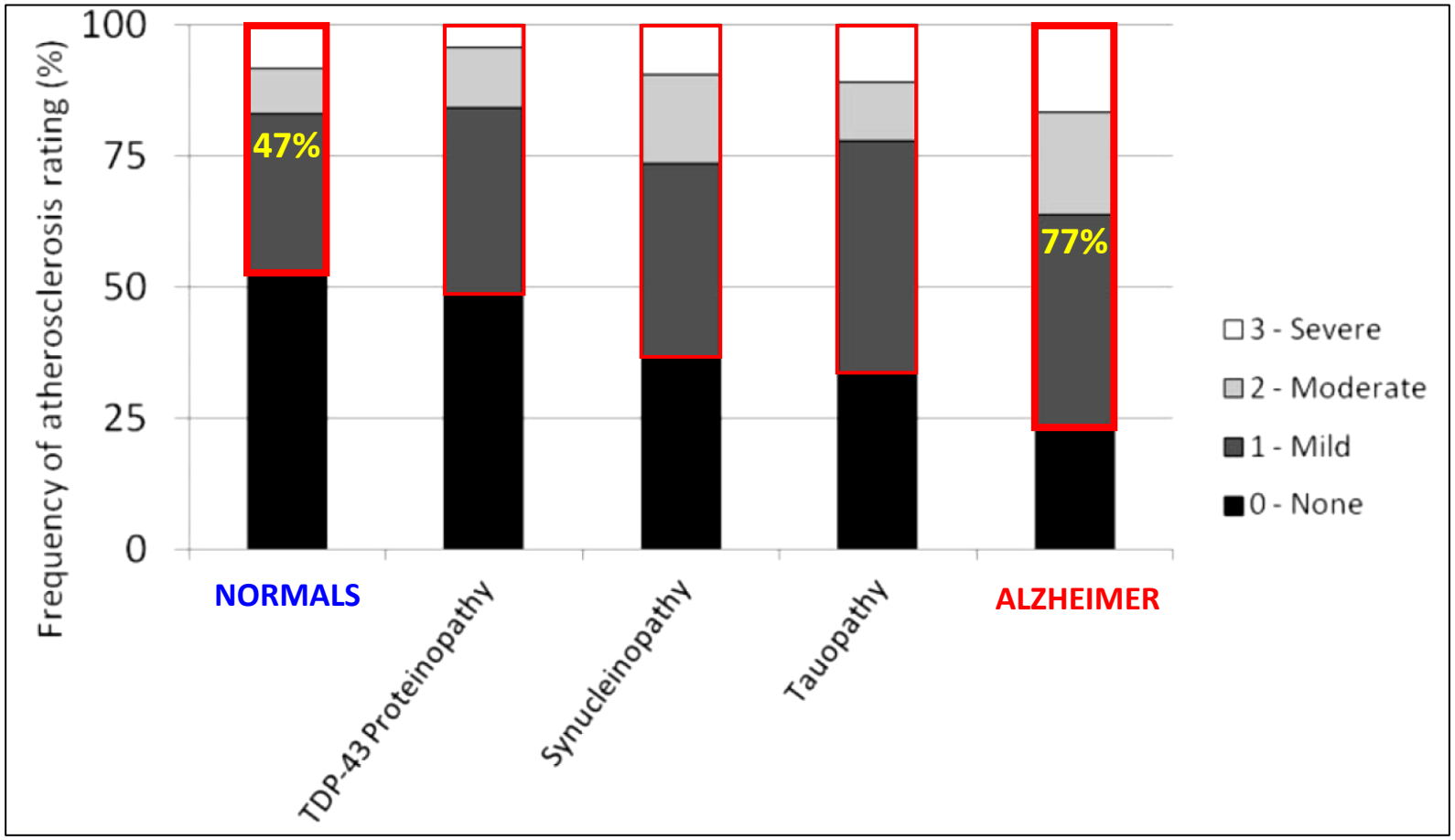
Table 3 Odds ratios for the diagnosis of Alzheimer's disease versus control, comparing each of the groups having atherosclerosis scores of 1, 2 or 3 with the group with atherosclerosis score 0

Atherosclerosis score 1 versus 0		Atherosclerosis score 2 versus 0		Atherosclerosis score 3 versus 0
1.36 ($P = 0.20$; 0.66–2.79)) $N = 138$	➡	1.43 ($P = 0.17$; 0.67–3.05) $N = 132$	➡	2.30 ($P = 0.02$; 1.02–5.20) $N = 134$

Associazione significativa tra ATS intracranica e AD.
L'ATS del circolo di Willis NON è aumentata nei pazienti con demenze non-AD: questo dimostra che l'associazione NON è spuria.

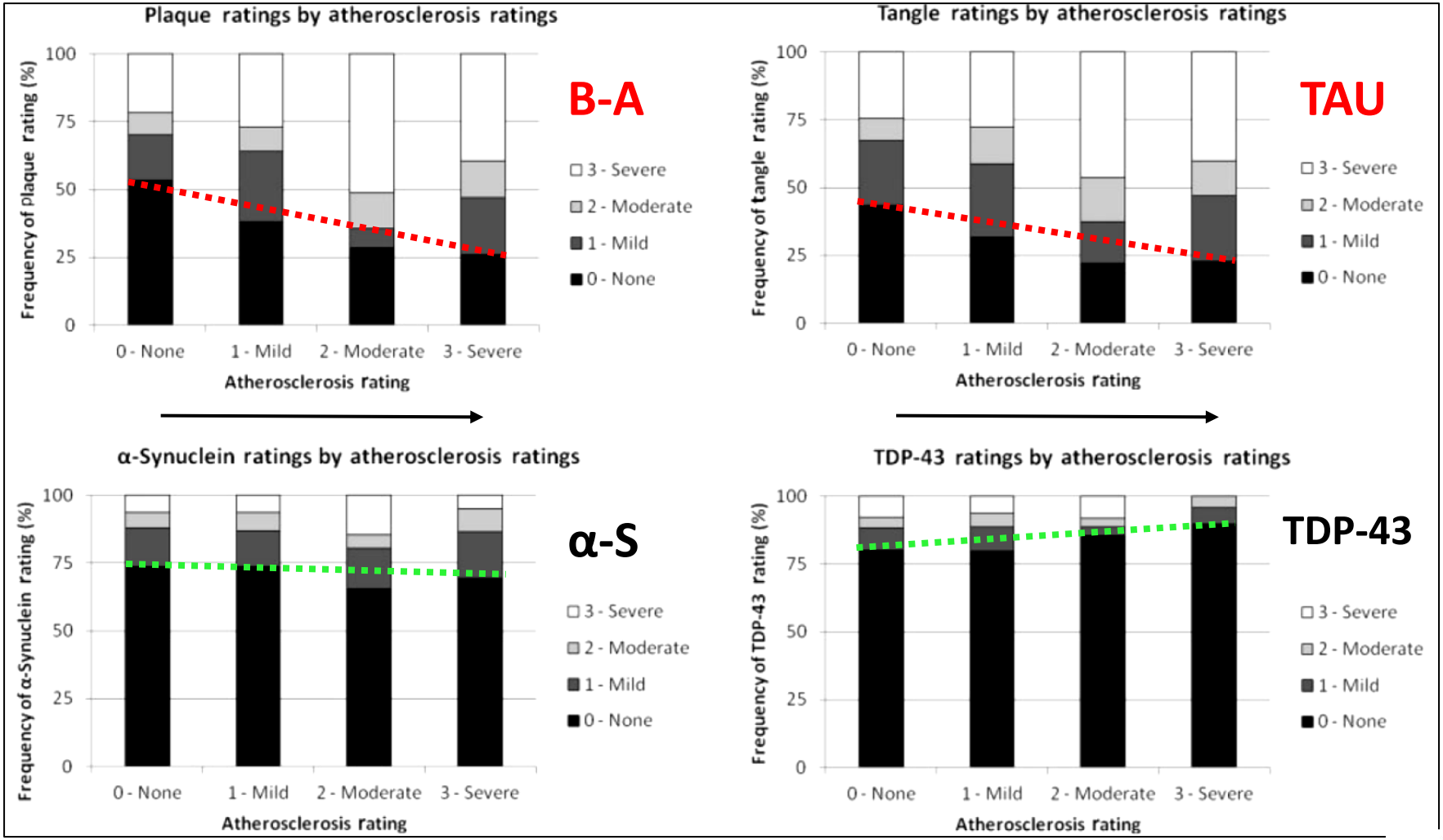
Beach et al. Acta Neuropathol 2007

Cerebrovascular atherosclerosis correlates with Alzheimer pathology in neurodegenerative dementias



Yarchoan et al. BRAIN 2012

Cerebrovascular atherosclerosis correlates with Alzheimer pathology in neurodegenerative dementias



Yarchoan et al. BRAIN 2012

Cerebrovascular atherosclerosis correlates with Alzheimer pathology in neurodegenerative dementias

" … These results provide further confirmation and specificity that vascular disease and Alzheimer's disease are interrelated and suggest that common aetiologic or reciprocally synergistic pathophysiological mechanisms promote both vascular pathology and plaque and tangle pathology".

BRAIN
A JOURNAL OF NEUROLOGY

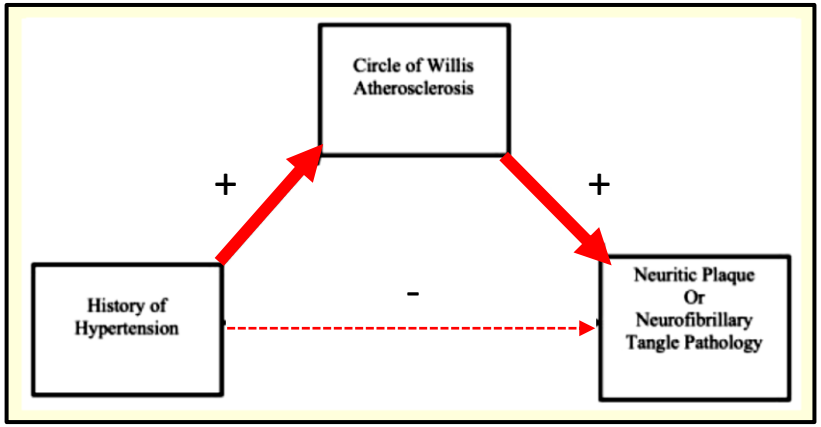
Yarchoan et al. BRAIN 2012

Hypertension and Alzheimer's disease: indirect effects through circle of Willis atherosclerosis

BRAIN COMMUNICATIONS

	HTN → atherosclerosis	Atherosclerosis → ADNP	HTN → ADNP	HTN → atherosclerosis → ADNP
Overall sample ($N = 2198$)				
Neuritic plaques	1.29 (1.07–1.54)**	1.20 (1.09–1.32)***	0.73 (0.59–0.89)**	1.01 (1.004–1.03)*
Neurofibrillary tangles	1.29 (1.07–1.54)**	1.13 (1.02–1.24)*	0.82 (0.62–0.97)*	1.01 (1.001–1.02)*
Alzheimer's dementia sample ($N = 1587$)				
Neuritic plaques	1.29 (1.05–1.58)*	1.31 (1.15–1.47)***	0.85 (0.67–1.04)	1.01 (1.003–1.03)*
Neurofibrillary tangles	1.29 (1.05–1.58)*	1.18 (1.03–1.35)*	0.94 (0.71–1.22)	1.01 (1.001–1.02)*
MCI sample ($N = 239$)				
Neuritic plaques	1.15 (0.54–2.50)	0.97 (0.69–1.36)	0.98 (0.45–2.18)	1.00 (0.95–1.03)
Neurofibrillary tangles	1.15 (0.54–2.50)	1.13 (0.76–1.58)	1.53 (0.66–3.27)	1.00 (0.98–1.05)
Normal cognition sample ($N = 372$)				
Neuritic plaques	1.63 (0.95–2.75)	1.00 (0.80–1.26)	0.70 (0.40–1.25)	1.00 (0.94–1.04)
Neurofibrillary tangles	1.63 (0.95–2.75)	0.85 (0.67–1.08)	0.98 (0.54–1.73)	0.99 (0.94–1.003)

- 2198 soggetti - NACC
- Età media ultima visita: 80 anni
- 47% donne



NACC National Alzheimer's Coordinating Center

Eglit et al. Brain Communications 2020

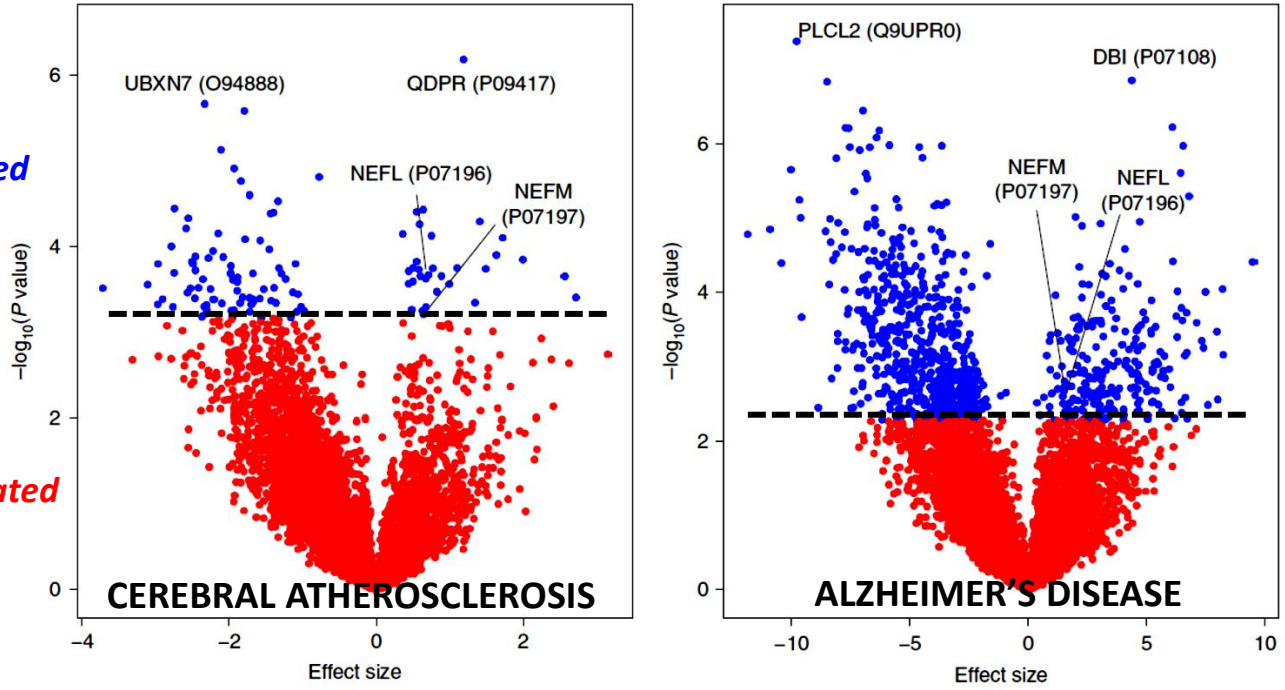
Shared proteomic effects of cerebral atherosclerosis and Alzheimer's disease on the human brain

Proteome-wide association study (PWAS)
438 older subjects

nature neuroscience

Blue: associated

Red : not associated



More abundant in greater CA and AD	Less abundant in greater CA and AD
ANLN (Q9NQW6)*, ATG4C (Q96DT6), CBR1;SETD4 (P16152)*, CPM (P14384)*, CYB5R2 (Q6BCY4)*, ENDOD1 (O94919)*, NEFL (P07196)*, NEFM (P07197)*, NPEPPS (P55786), QDPR (P09417), TUBB4A (P04350)	AKAP5 (P24588), ARHGEF9 (O43307), BABAM1 (Q9NWV8), DAB2IP (Q5VWQ8), HMGB3 (O15347), IGSF9B (Q9UPX0), LZTS3 (O60299), PROSAPIP1 (O60299), MAGI2 (Q86UL8), PCSK1 (P29120), RASAL2 (Q9UJF2), TBC1D24 (Q9ULP9), TLN2 (Q9Y4G6)

Wingo et al. NATURE NEUROSCIENCES 2020

23 proteine sono associate sia alla ATS cerebrale che alla M. di Alzheimer suggerendo meccanismi patogenetici comuni

Cerebral atherosclerosis contributes to Alzheimer's dementia independently of its hallmark amyloid and tau pathologies

- **La ATS (circolo di Willis e arterie prossimali) è legata a AD attraverso modificazioni proteomiche della corteccia pre-frontale** (NB: independentemente da βA, Tau, TDP-43, corpi di Lewy, angiopatia amiloide, macro-microinfarti e sclerosi ippocampale).
- **Anche Tau è legata alla AD in modo indipendente, attraverso modificazioni proteomiche in parte sovrapposte alla ATS.**
- **ATS, Tau e βA sembrano contribuire a AD in modo indipendente (<u>non vi è interazione statistica</u>)**

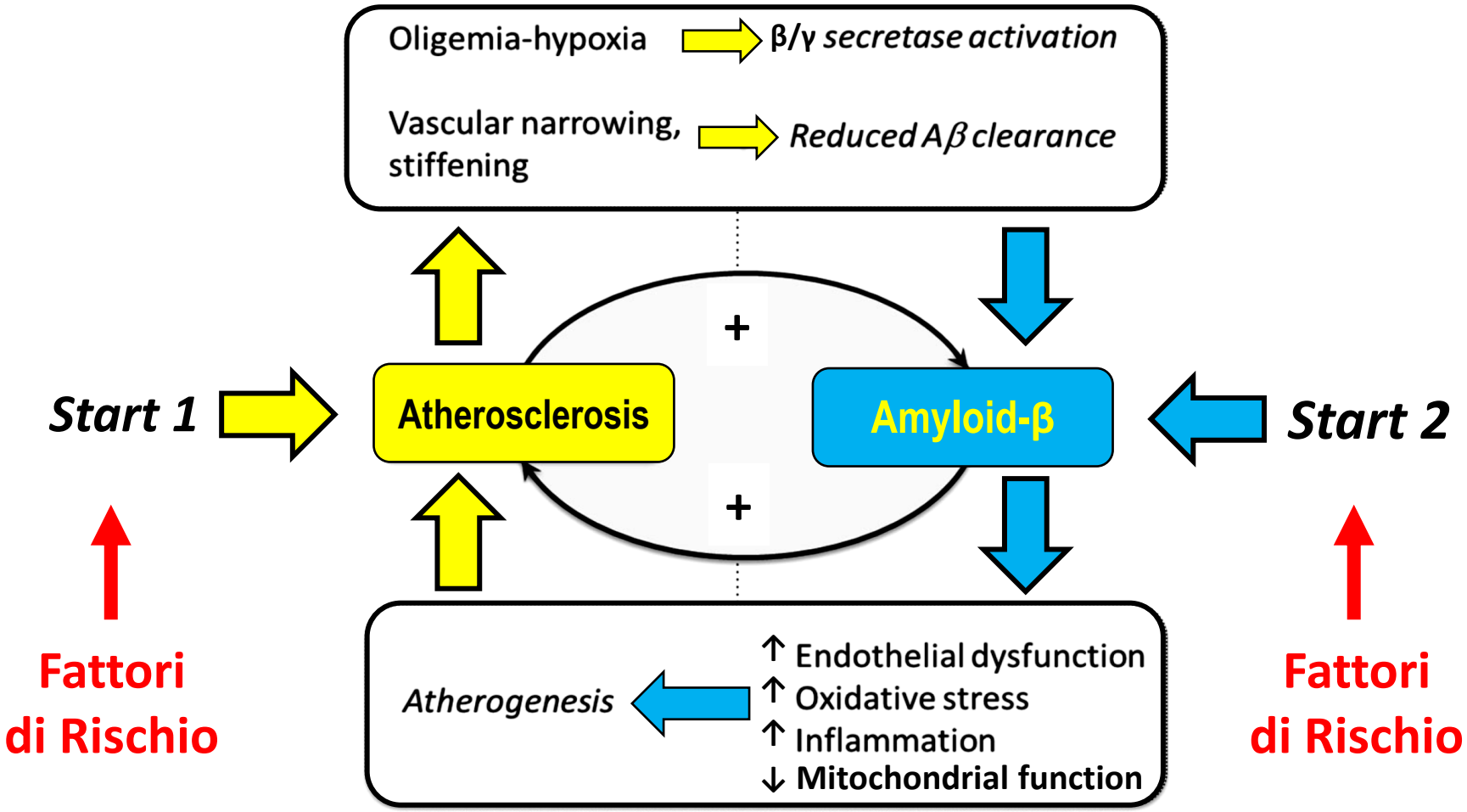
nature neuroscience

Iadecola et al. NATURE NEUROSCIENCES 2020

Come spiegare l'associazione tra Aterosclerosi e malattia di Alzheimer ?

1. *Fattori di rischio vascolare comuni = patogenesi comune?*
2. *Amiloide & disfunzione endotelio ↓ Metabolismo cerebrale*
3. *ATS → Ipossia ↑ Attività BACE1 ↑ Amiloide*
4. *↓ NOCTH → alterazione microcircolo ↔ ↑ Amiloide*
5. *↓ Flusso cerebrale & ↑rigidità arteriosa ↑ Amiloide & tau*
6. *ATS & Ipossia ↓ Clearance della Amiloide*

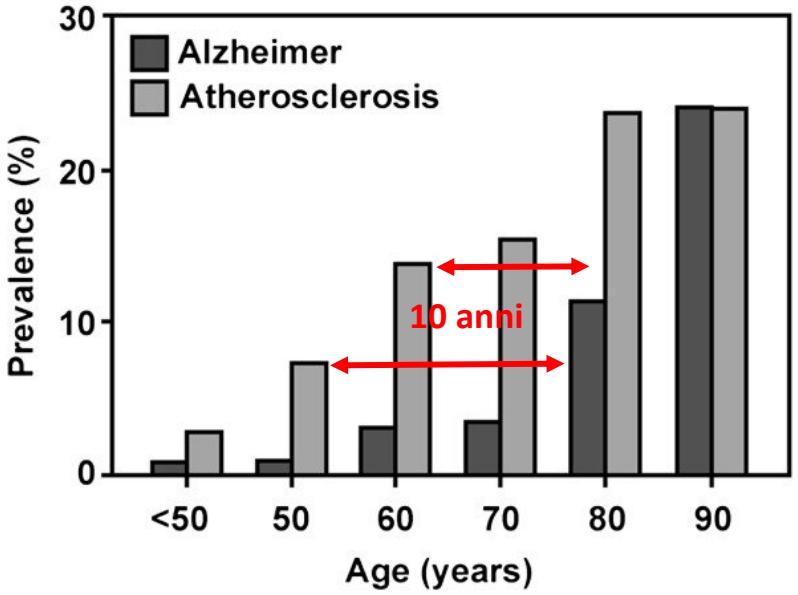
Potenziale e pericoloso circolo vizioso tra arterio/aterosclerosi e malattia di Alzheimer



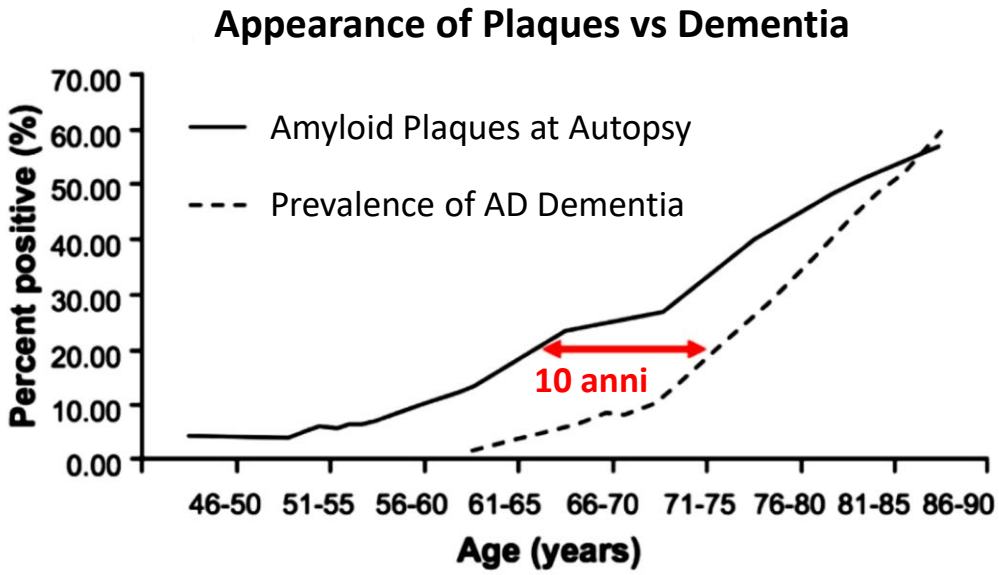
MODIFICATA DA: Gupta & Iadecola Front Aging Neurosc 2015

ATS → NEUROPATOLOGIA AD → LOAD

50-60 anni *60-70 anni* *70-80 anni*



Lathe et al. BMC Geriatrics 2014



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