EMEA
2nd workshop on neurodegenerative diseases:*
Focus on Dementia

Overlap between VaD and AD: an epidemiological perspective

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- VaD vs. (?) AD
- Risk & protective factors for dementia
- Dementia Risk Score
- Future directions

Results from the CAIDE study and Kungsholmen Project

Brief historical overview

The beginning

Cerebral arteriosclerosis – the major cause of dementia

Late 1960´s

- AD-type pathology - very common in elderly patients with dementia
- Attempts to make a **sharp distinction** between degenerative and vascular diseases

Nowadays

The relationship between AD and VaD appears to be complex: a considerable overlap in risk factors, clinical features and neuropathology of AD and VaD

Epidemiology of vascular cognitive impairment

- 1/3 of individuals will experience a stroke, dementia or both (Seshadri et al., Stroke 2006)
- After stroke, up to 64% of persons have some degree of cognitive impairment, with up to 30% developing frank dementia (Hachinski et al,. Stroke 2006)

Obscurities in VaD research

- **Definition of dementia** requires memory impairment - often misses the executive dysfunction typical for VCI
- **VaD is a heterogeneous group** (sub-cortical VaD might be more homogeneous)
- Focus on demetia even though **patients with VCI without dementia** might be better candidates for clinical trials (earlier phase of the disease)
- None of the current stroke scales used in clinical trials measure cognition

National Institute of Neurological Disorders and Stroke–Canadian Stroke Network Vascular Cognitive Impairment Harmonization Standards

Vladimir Hachinski, MD, DSc; Costantino Iadecola, MD; Ron C. Petersen, MD, PhD; Monique M. Breteler, MD, PhD; David L. Nyenhuis, PhD; Sandra E. Black, MD; William J. Powers, MD; Charles DeCarli, MD; Jose G. Merino, MD; Raj N. Kalaria, PhD, FRCP; Harry V. Vinters, MD; David M. Holtzman, MD; Gary A. Rosenberg, MD; Martin Dichgans, MD; John R. Marler, MD; Gabrielle G. Leblanc, PhD

Background and Purpose—One in 3 individuals will experience a stroke, dementia or both. Moreover, twice as many individuals will have cognitive impairment short of dementia as either stroke or dementia. The commonly used stroke scales do not measure cognition, while dementia criteria focus on the late stages of cognitive impairment, and are heavily biased toward the diagnosis of Alzheimer disease. No commonly agreed standards exist for identifying and describing individuals with cognitive impairment, particularly in the early stages, and especially with cognitive impairment related to vascular factors, or vascular cognitive impairment.

Methods—The National Institute for Neurological Disorders and Stroke (NINDS) and the Canadian Stroke Network (CSN) convened researchers in clinical diagnosis, epidemiology, neuropsychology, brain imaging, neuropathology, experimental models, biomarkers, genetics, and clinical trials to recommend minimum, common, clinical and research standards for the description and study of vascular cognitive impairment.

Results—The results of these discussions are reported herein.

Conclusions—The development of common standards represents a first step in a process of use, validation and refinement. Using the same standards will help identify individuals in the early stages of cognitive impairment, will make studies comparable, and by integrating knowledge, will accelerate the pace of progress. (*Stroke.* **2006;37:2220-2241.**)

Rethinking the classification of degenerative and vascular cases

‘Pure AD’

AD with severe cerebral amyloid angiopathy

Mild AD with vascular involvement

AD with vascular lesions

AD with cerebrovascular disease

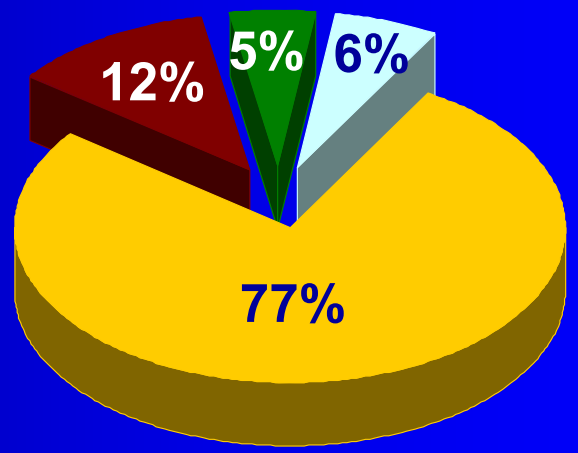
VD with AD changes

VD with small-vessel disease

‘Pure VD’

Kalaria R *et al.* Alzheimer Dis Assoc Disord 1999

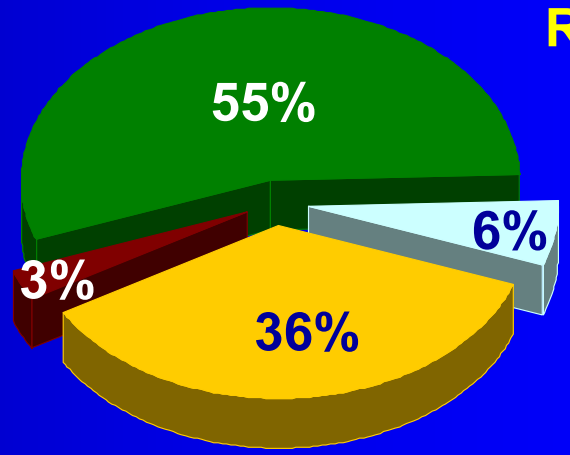
Kungsholmen Project



DSM III-R criteria

AD VaD Mixed Other

Reclassified



SILENT BRAIN INFARCTS AND RISK OF DEMENTIA

	Risk of dementia HR (95% CI)	Risk of Alzheimer's disease HR (95% CI)
Silent brain infarct†	2.3 (1.1-4.7)	2.6 (1.2-5.7)
Silent brain infarct‡	2.0 (0.9-4.4)	2.6 (1.1-6.0)

†Adjusted for age, sex, and education.
‡Additionally adjusted for subcortical atrophy, and periventricular white matter lesions.

Vermeer S et al. NEJM 2003;348:1215-22

The Nun Study

Dementia in individuals with AD neuropathology

No infarcts	57%
1-2 lacunar	**93%**
Large infarcts	75%

Snowdon et al JAMA 1997

Vascular related risk/protective factors for dementia/AD/VaD

Risk factors

- Cerebrovascular disorders
- Hypertension
- Hypercholesterolemia
- Obesity
- Diabetes mellitus
- Homocysteine
- Smoking
- Depression

Protective factors

- High education
- Physical activity
- Active lifestyle
- Alcohol consumption
- Antioxidants
- Fish oils
- Antihypertensives
- Statins
- NSAIDs?
- Estrogen?

Midlife risk factors for dementia/AD later in life

Main findings from the CAIDE study

Vascular:

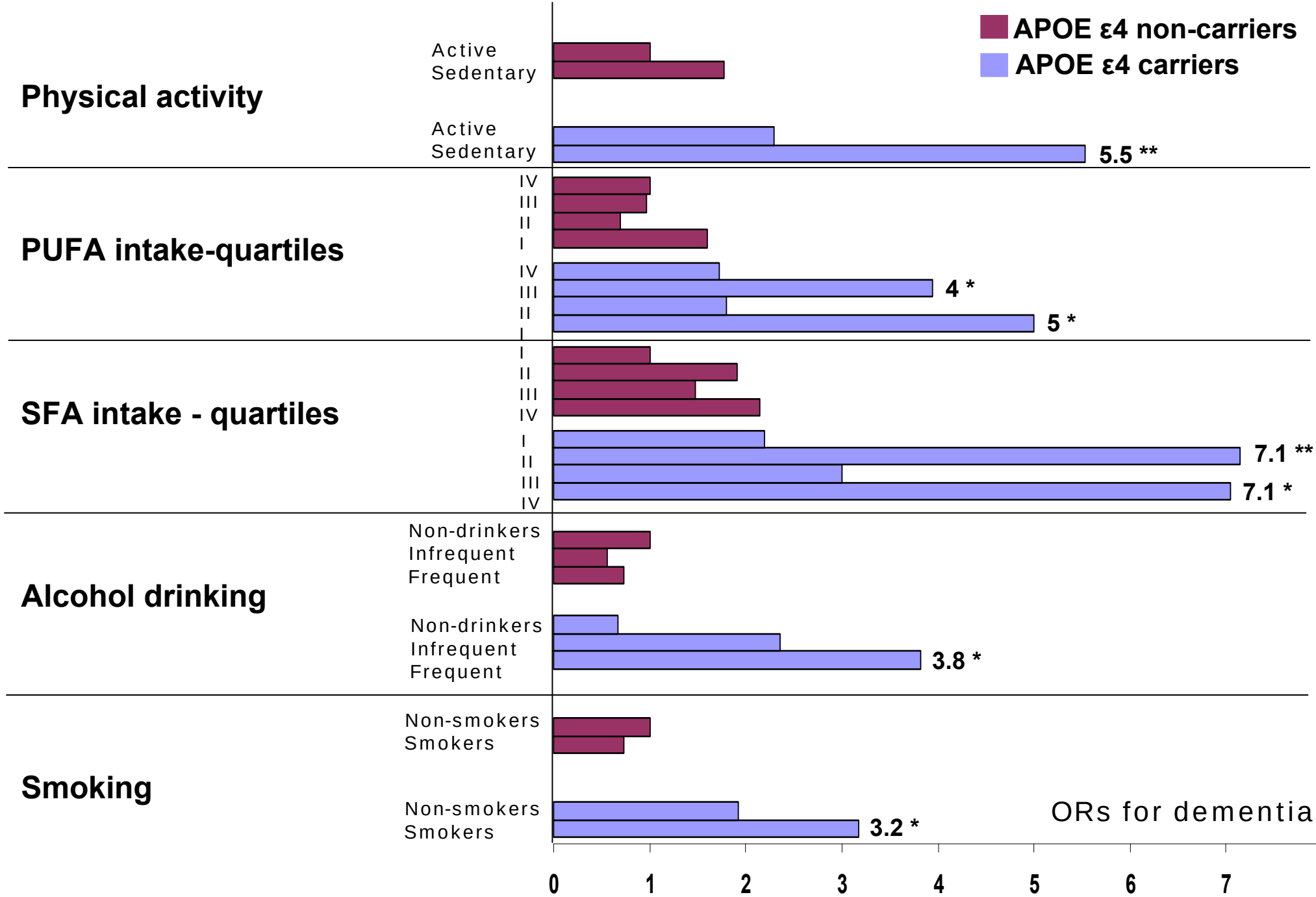
- High midlife cholesterol
- High midlife systolic BP

} Kivipelto et al, BMJ 2001, Ann Intern Med 2002

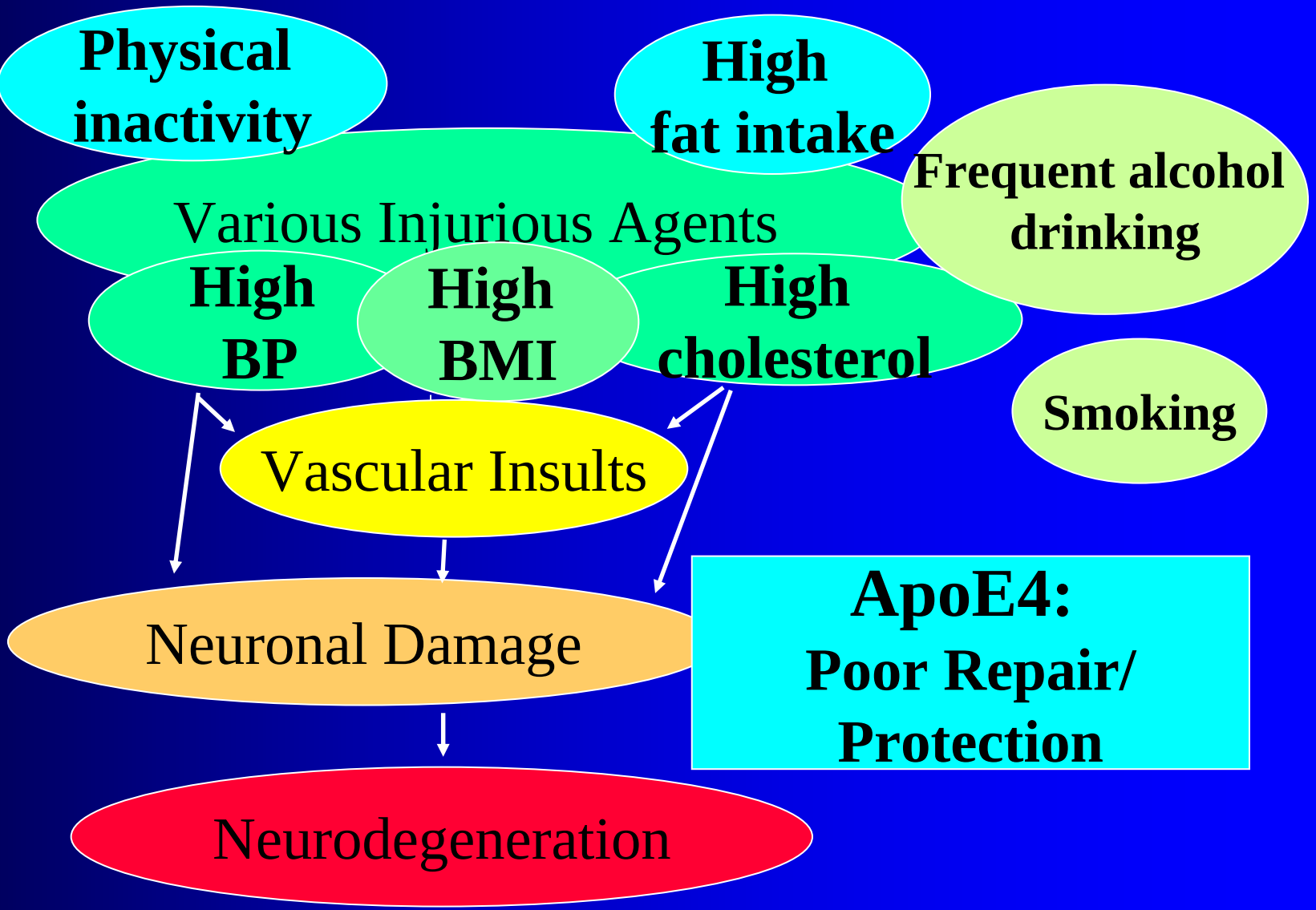
- Obesity - Kivipelto et al., Arch Neurol 2005

Lifestyle-related (especially among the ApoE4 carriers)

- Use of saturated / lack of polyunsaturated fatty acids - Laitinen et al, 2005
- Frequent alcohol drinking - Anttila et al, BMJ 2004
- Physical inactivity - Rovio et al, Lancet Neurology 2005


APOE ε4 non-carriers
APOE ε4 carriers
Physical activity
Active
Sedentary
Active
Sedentary
5.5 **
PUFA intake-quartiles
IV
III
II
I
IV
III
II
I
4 *
5 *
SFA intake - quartiles
I
II
III
IV
I
II
III
IV
7.1 **
7.1 *
Alcohol drinking
Non-drinkers
Infrequent
Frequent
Non-drinkers
Infrequent
Frequent
3.8 *
Smoking
Non-smokers
Smokers
Non-smokers
Smokers
3.2 *
ORs for dementia
0
1
2
3
4
5
6
7
8

Possible processes for the development of AD



CAIDE Dementia Risk Score		
Age	< 47 years 47-53 years >53 years	0 3 4
Formal education	≥10 years 7-9 years 0-6 years	0 2 3
Sex	Women Men	0 1
Systolic BP	≤ 140 mm Hg > 140 mm Hg	0 2
BMI	≤ 30 kg/m2 > 30 kg/m2	0 2
Total cholesterol	≤ 6.5 mmol/l > 6.5 mmol/l	0 2
Physical activity	Active Inactive	0 1

Kivipelto et al., Lancet Neurology 2006

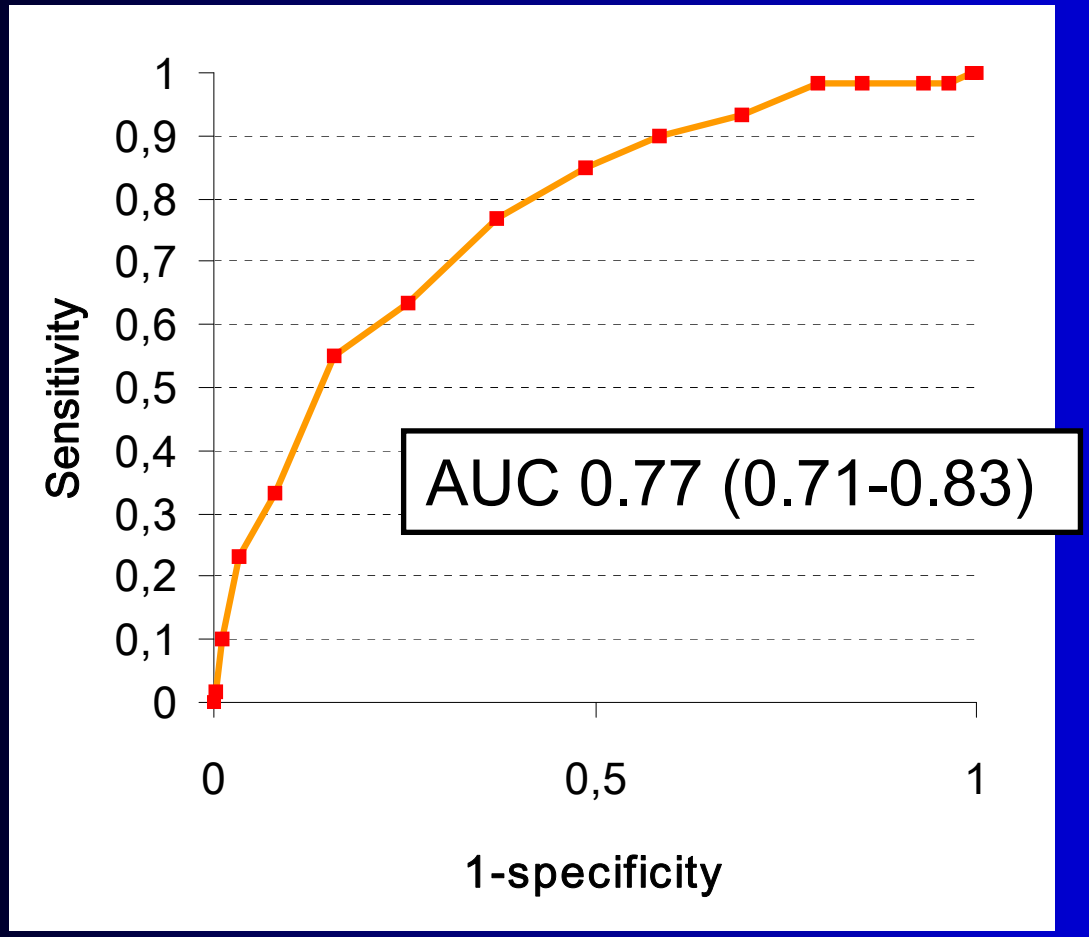
Probability of dementia in late-life according to the risk score category in middle age

The overall occurrence of dementia 4.4%

SCORE	All /Demented, n	% Risk (95% CI)
0-5	401 / 4	1.0 (0.0-2.0)
6-7	270 / 5	1.9 (0.2-3.5)
8-9	312 / 13	4.2 (1.9-6.4)
10-11	245 / 18	7.4 (4.1-10.6)
12-15	122 / 20	16.4 (9.7-23.1)

Kivipelto et al., Lancet Neurology 2006

Performance of the Dementia Risk Score in predicting the risk of dementia in 20 years

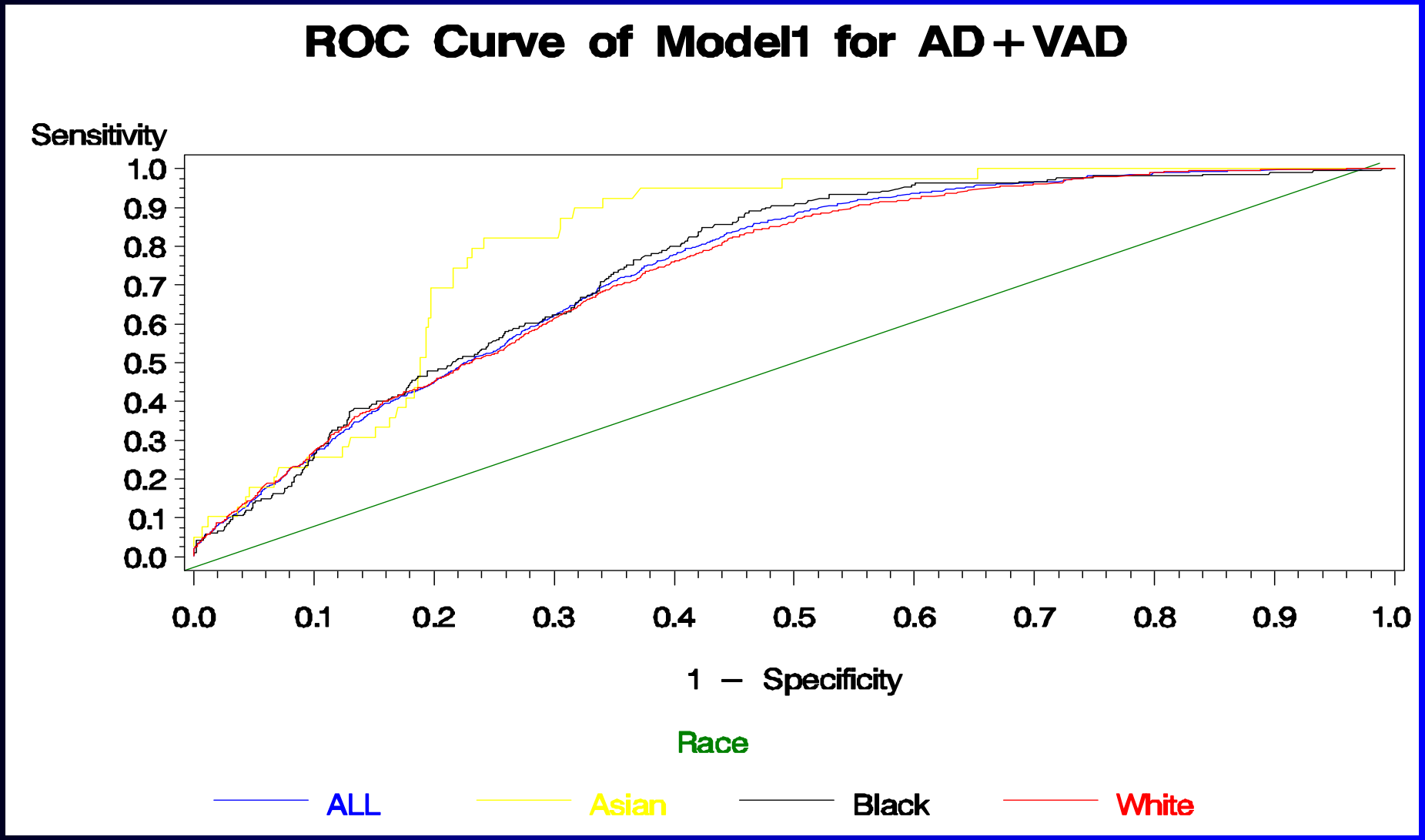


Cutpoint: score ≥9

(39 % of population)

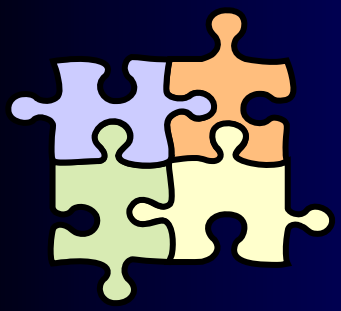
Sensitivity	**= 0.77**
Specificity	**= 0.63**
PPV	**= 0.09**
NPV	**= 0.98**

The CAIDE Risk Score in the Kaiser Study



Overall AUC .74

Asian: 0.813
Black: 0.751
White: 0.737



Minding heart health protects the brain

Dementia Risk Score highlights the role of vascular factors in the development of dementia (AD, VaD and mixed), and may help to identify high risk individuals who might benefit from intensive lifestyle consultations and pharmacological interventions

Multi-domain intervention study as a next step?

- For persons at an increased risk of dementia
- Several outcomes measures:
  - Sensitive measures for executive functions
  - Depression, ADL and IADL functions, disability

Target population in VaD/VCI trials?

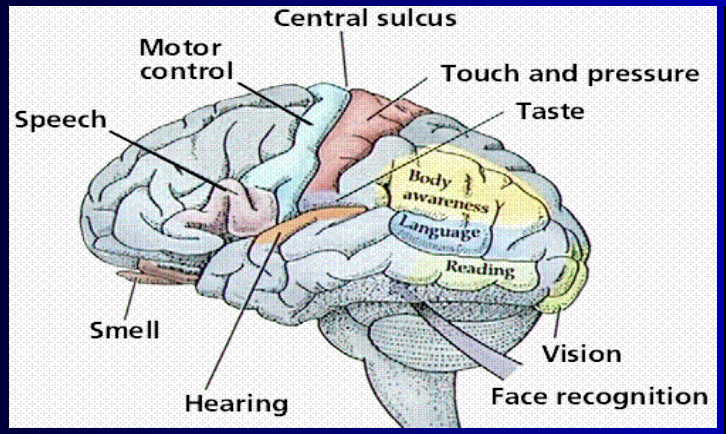
- Sub-cortical VaD?
- VCI (VCI Harmonization criteria)?
  - Neurpsychological tests
  - Neuroimaging
  - Biomarkers (e.g. CSF albumin index, sulfatide, neurofilament, metalloproteases)

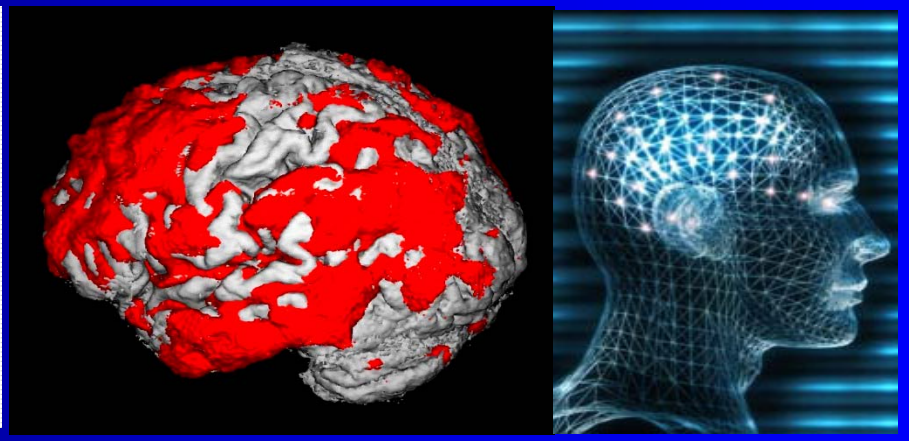
New Pre-AD criteria
Lancet Neurology 2007

Pushing our research to the limits of our disciplines…and beyond: integrated approach to stroke and dementia

Thinking and remembering brain as an end-organ:

Moving from ”stroke brain” to ”network brain”

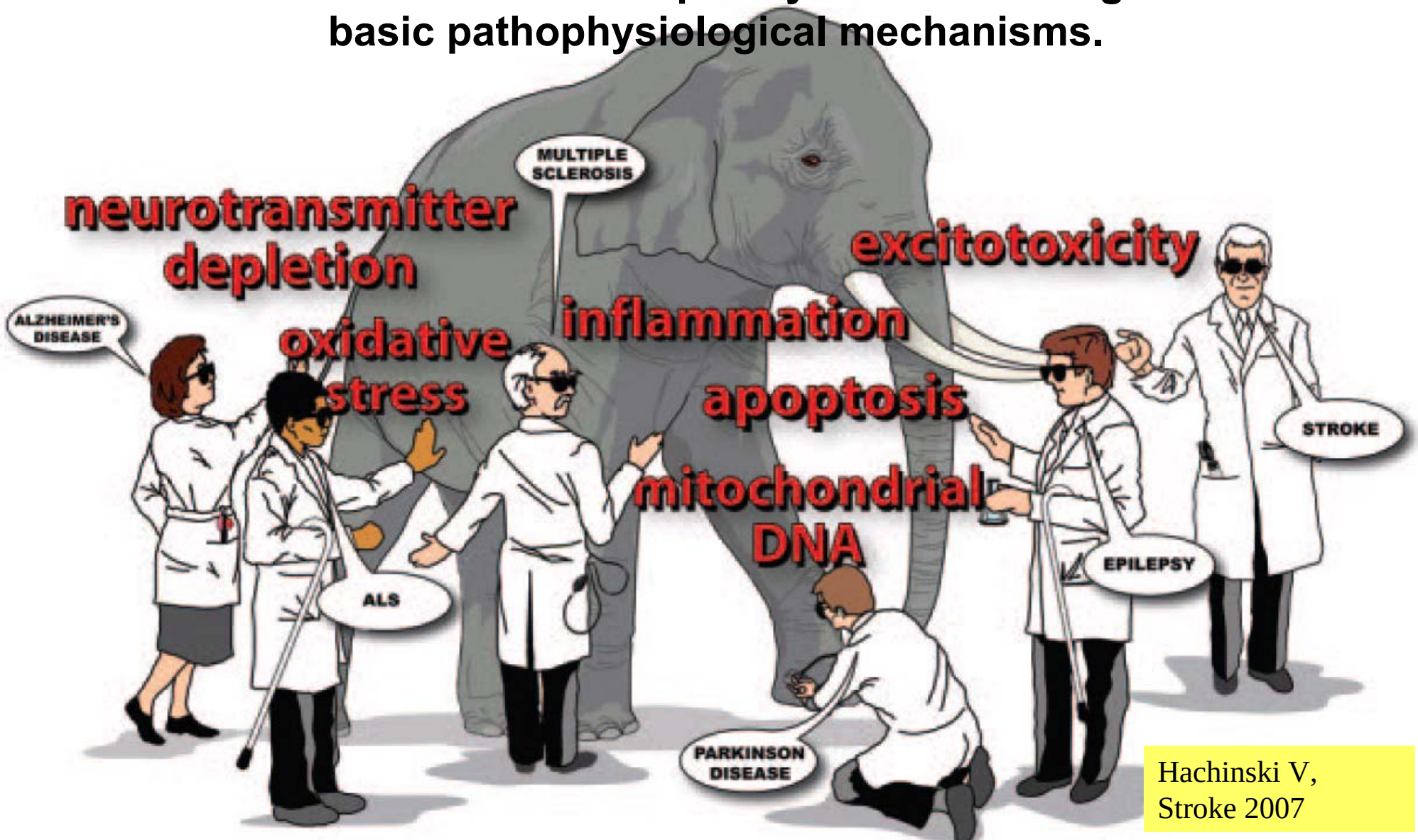




Erkinjuntti, Alhainen, Kivipelto

The Pathogenesis Pachyderm

The brain functions with complexity but fails through common basic pathophysiological mechanisms.



Hachinski V,
Stroke 2007

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