Post-Stroke Cognitive Impairment and Vascular Dementia

10th Regional Teaching Course in Sub-Saharan Africa
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Newcastle Centre for Brain Ageing and Vitality

Newcastle University

Institute of Neuroscience

MRC Medical Research Council

COGFAST Memory After Stroke Study

Newcastle University Campus for Ageing and Vitality

Newcastle Academic Health Partners in partnership with the NHS

- Newcastle Brain Tissue Resource (NBTR)
- NIHR Biomedical Research Centre for Age Related Diseases (NBRB) and NE DenDRoN
- H Wellcome Laboratories for Biogerontology
- Clinical Ageing Research Unit (CARU)
- Newcastle Magnetic Resonance Centre (NMRC)

(old Newcastle General Hospital site)

Newcastle University Institute of Neuroscience

COGFAST Memory After Stroke Study

Lifelong Health & Wellbeing Research for Healthy Ageing

Institute for Ageing Newcastle University

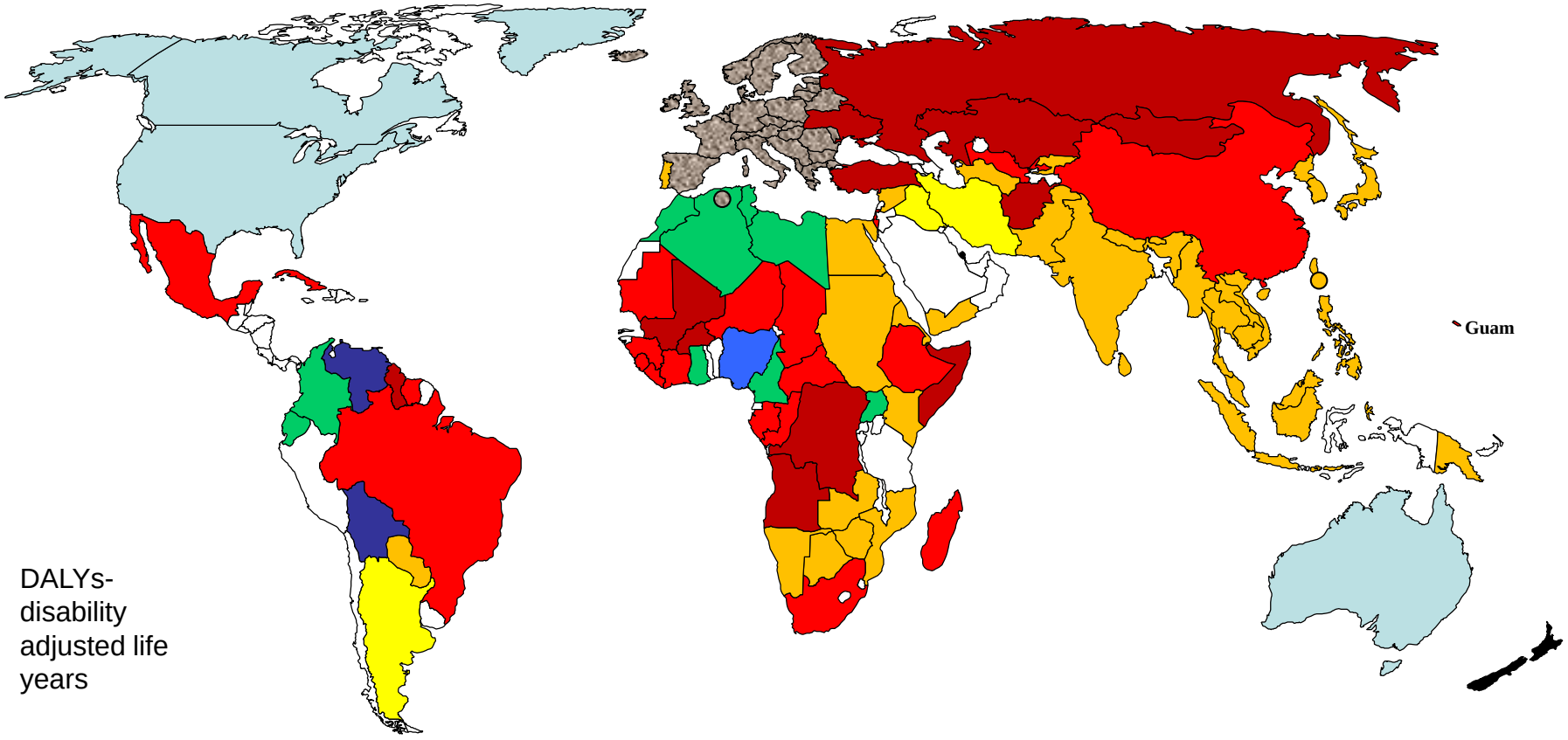
Plan: Cognitive Function after Stroke

Overview

- Introduction: Prevalence, Types and Classification
- Vascular Cognitive Impairment, VaD and SIVD
- Neuropsychometric assessment post-stroke
- **Newcastle and Ibadan (Nigeria) COGFAST studies**
  - Clinical and neuropsychological aspects
  - Pathophysiology of Leukoencephalopathy, White matter changes
  - Post-stroke and VaD in SSA
- Take home message

World-wide Stroke Incidence

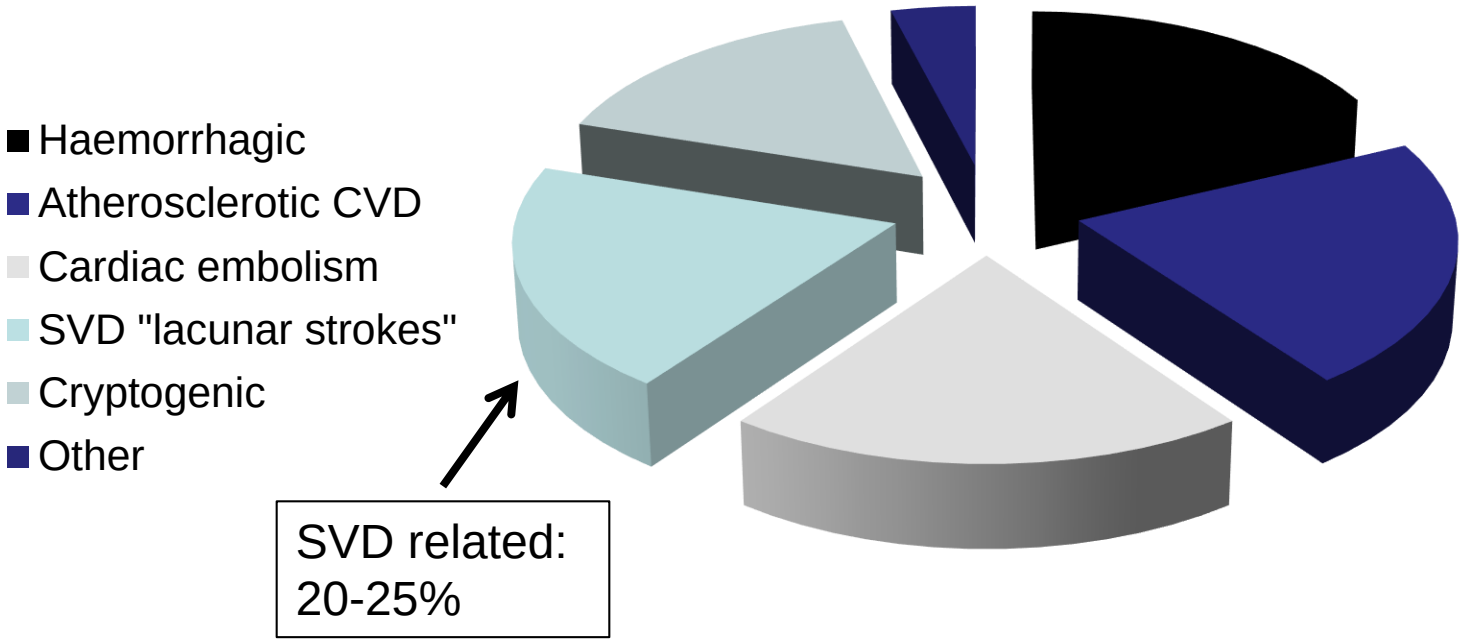
Incidence decreased but total strokes increased worldwide



DALYs-disability adjusted life years

In HIC overall incidence, mortality and DALYs of all stroke types have declined in both younger (<75 years) and older (≥75 years) age groups, in LMIC these have increased (*Krishnamurthi RV et al, 2014; Feigin et al, 2014*)

Types of Stroke



Of all strokes, ~80-82% are ischaemic and 18-20% are haemorrhagic. Of the haemorrhagic strokes, 15% are due to an intracerebral haemorrhage, and 5% are due to a subarachnoid haemorrhage.

Classification of Stroke

(Oxford Community Stroke Project (OSCP); also known as the Bamford or Oxford classification

Relies primarily on the initial symptoms; based on the extent of the symptoms, the stroke episode is classified as:

- **Total anterior circulation stroke (TAC)**
- **Partial anterior circulation stroke (PAC)**
- **Lacunar stroke (LAC)**
- **Posterior circulation stroke (POC)**

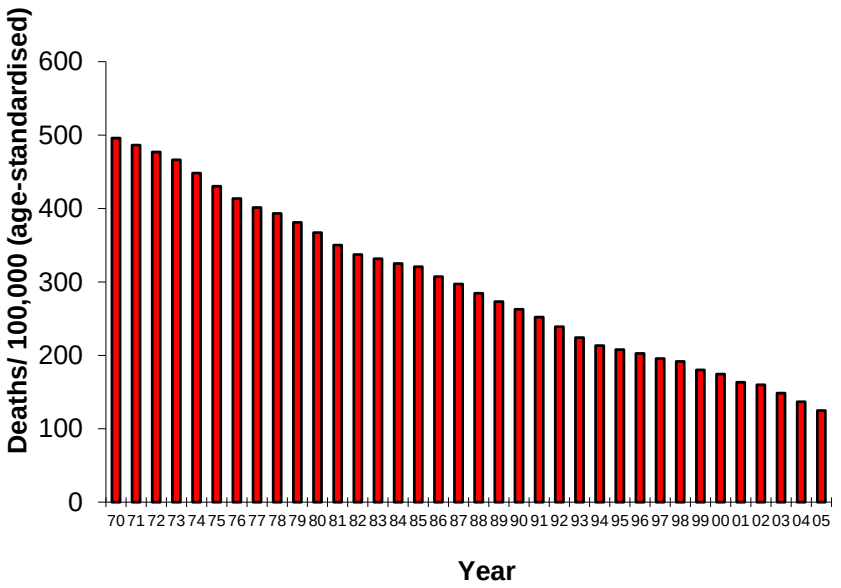
The type of stroke is then coded by adding a final letter to the above:
I – for infarct (e.g. TACI)
H – for haemorrhage (e.g. TACH)
S – for syndrome; intermediate pathogenesis, prior to imaging (e.g. TACS)

Entities predict extent of the stroke, area of brain affected, underlying cause, and the prognosis.

Death rates from stroke and survival

- Risk increases exponentially for both stroke and dementia with age.
- Stroke is the third most common cause of death in developed nations.
- Rate of stroke related deaths has decreased continuously since 1970
- Stroke increases the risk of dementia x5 compared to age match controls (Pendlebury 2009).
- 30% of Stroke survivors develop PSD within 2 years (Leys 2005).

Death rates from stroke, adults aged 65 to 74, 1969 to 2006, England



Data Office of National Statistics UK

Oxfordshire data 2004: age-specific incidence of major stroke fallen by 40% in past 20 yrs (Rothwell et al, 2004)

Stroke and Cerebrovascular Disorders in SSA

Contents lists available at ScienceDirect

Brain Research Bulletin

journal homepage: www.elsevier.com/locate/brainresbull

Review

Stroke, cerebrovascular diseases and vascular cognitive impairment in Africa

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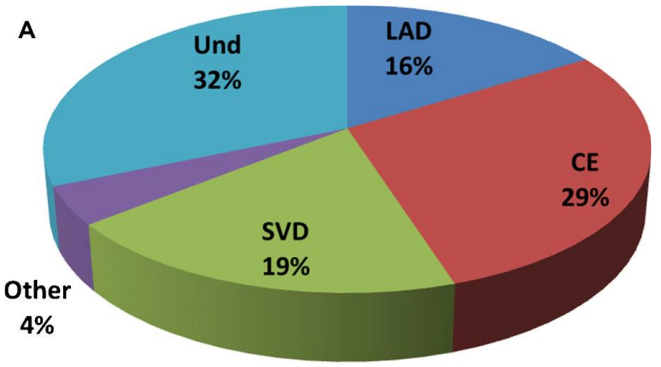
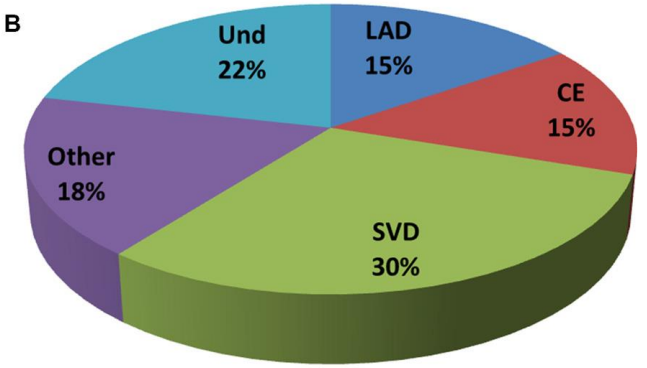


Stroke Subtypes by TOAST criteria- HICs

- Age is the strongest irreversible risk factor
- Hypertension is strongest modifiable risk factor
- Cerebral SVD is higher ≥30% in SSA
- Significant proportions of CVDs ascribed to various forms of infectious disease e.g. HIV
- Prevalence estimates: VaD (2-3%), delayed dementia after stroke (10-20%); VCI (30-40%)



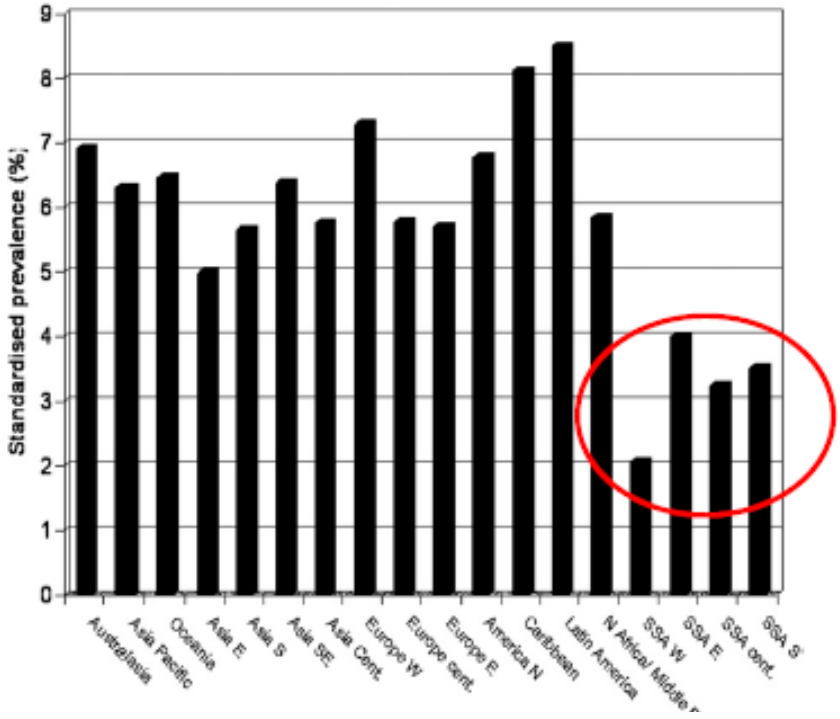
Stroke Subtypes by TOAST criteria- SSA

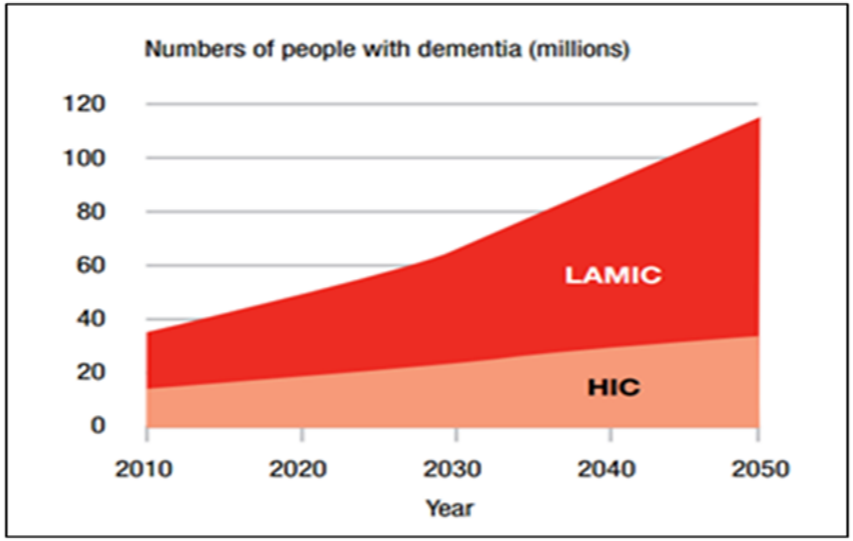
Common and rare causes of stroke pathophysiology in SSA

Primary or 2º Vascular Disorder(s)*	Common conditions	Frequencies (Africa) (low+ to high+++)
Embolic disease	Cardioembolism	+++
Arteriolosclerosis	Cerebral small vessel disease	+++
	Hypertensive vasculopathy	+++
Non-atherosclerotic non-inflammatory vasculopathies	Arterial dissections, fibromuscular dysplasia, dolichoectatic basilar artery, large artery kinking and coiling, radiation induced angiopathy, moyamoya disease	+
	Aneurysms- sacular, berry, fusifom, cerebral	++
	Vascular malformations: cavernous hemiangioma, arteriovenous, capillary	+
	Cerebral venous thrombosis	+
Amyloid angiopathies	Hereditary CAAs (Amyloid β, PrP, cystatin C, transthyretin, gelsolin)	+
Monogenic stroke disorders	CADASIL, CARASIL, retinal vasculopathy with cerebral leukodystrophies (RVCLs), Moyamoya disease, Hereditary angiopathy, nephropathy, HANAC, COL4 disorders	+
Monogenic disorders involving stroke	Fabry disease, FHM, HHT, Vascular Ehlers-Danlos syndrome, Marfan syndrome, Psuedoxanthoma elasticum, Arterial tortuosity syndrome, Loeys-Dietz syndrome, polycystic kidney disease; Neurofibromatosis type 1 (von Ricklinghausen disease), Carney syndrome (Facial lentiginosis and myxoma)	+
Metabolic disorders	MELAS, MERRF, Leigh's disease, MIRAS, Fibromuscular dysplasia, Menkes disease, Homocystinuria, Tangier's disease	++
Haematological disorders	Paraproteinaemia, coagulopathies (antiphospholipid antibodies, SLE, nephrotic syndrome, Sneddon syndrome, protein S, C, Z, antithrombin III, plasminogen)	++
Vasospastic disorders	SAH, Migraine related strokes, paroxysmal hypertension, drug induced vasconstriction	+

Dementia in Africa

- In 2010 there were estimated to be 36 million people who had dementia worldwide
- With demographic transition the prevalence will rise faster in developing countries
- Currently, it is estimated that 58% of people with dementia live in low- and middle-income countries; rising to 71% by 2050
- There are 2.1 million people living with dementia in SSA (2012 estimate)





Source: World Alzheimer Report, 2009

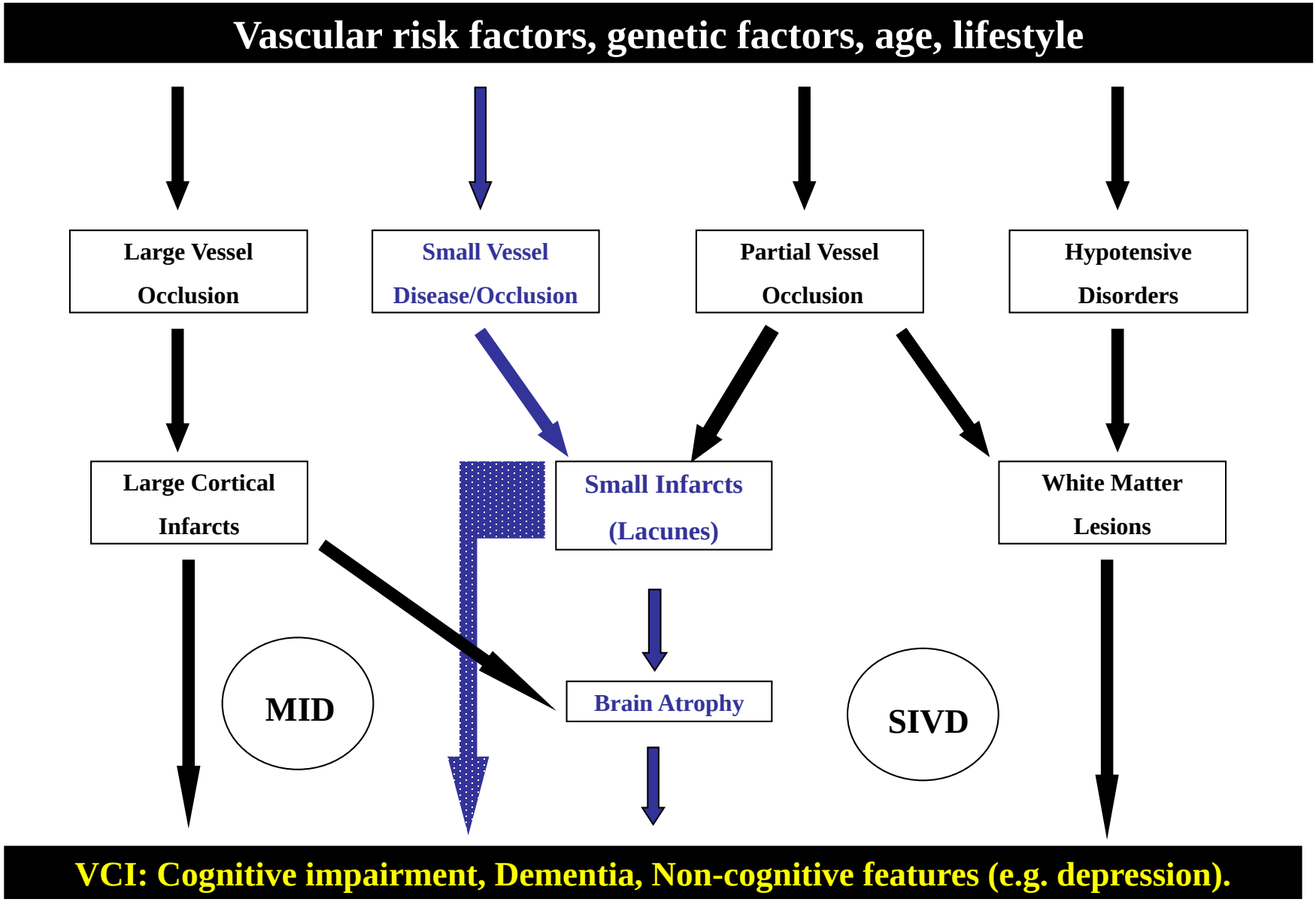
Prevalence of dementia in SSA (~2.2 million people!)

Study	Country	Age range	Screening tool used	Dementia prevalence
Longdon, 2013	Rural Tanzania	70 +	CSI-D	6.4% (age-adjusted)
Paraiso, 2011	Benin, urban	65+	CSI-D, 5WT	3.7%
Guerchet, 2009	Benin, rural	65+	CSI-D, 5WT	2.6%
Guerchet, 2010	CAR Congo	65 +	CSI-D, 5WT	8.1% (CAR) 6.7% (Congo).
Yusuf, 2011	Nigeria, Zaria	75.5 ± 9.4	CSI-D	2.79%
Ochayi & Thacher	Nigeria, Jos	65 +	CSI-D	6.4%
Ogunniyi, 2000	Nigeria	65+	CSI-D	2.29% (age-adjusted)
Gureje, 2006	Nigeria		10 word learning list	'probable dem' 10.1%

Towards Clinicopathological Criteria and Mechanisms of Dementia in after Stroke (VaD)?

Dogma, problems, pitfalls

Mechanisms: Cerebral SVDs and Dementia



After O'Brien J et al, 2003

WHO DEFINITION OF DEMENTIA

- '*Dementia is a syndrome that affects memory, thinking, behaviour and ability to perform everyday activities'*
- Currently a WHO priority – 'Dementia a Global Health Priority' report published 2012
- Dementia is NOT part of the normal ageing process

Diagnosis of Dementia

- What is dementia?

- A progressive deterioration in cognitive function
- Causes problems with social interactions, work, relationships
- Need to distinguish dementia from DELIRIUM and PSYCHIATRIC problems

NOT dementia

- **DELIRIUM**: an acute confusional state (causes include infection, malignancy, etc.)

- **PSYCHIATRIC PROBLEMS ("pseudodementia"):** e.g. depression, anxiety. Relatively abrupt onset often with identifiable trigger. Should not progress

How to diagnose dementia?

THE HISTORY

- Try and speak to the patient and also a relative
- Ask about:
  - Symptoms at onset
  - Speed of evolution
  - Impact on work/family life
  - Family history
  - Risk factors (e.g. vascular, alcohol)
  - Past medical history

ICD-10 Dementia criteria

- **G1- Decline in memory** (first, inability to learn new information then loss of previously learned information)
- This should be supported by cognitive testing and interview of a reliable informant
- AND
- **Decline in other cognitive areas** such as judgement and thinking and planning and organising (must be decline from previous level of functioning NB learning disability)
- **G2 - no clouding of consciousness (i.e. no delirium)**
- **G3 Decline** in social functioning, motivation or emotional control (apathy, coarsening of social behaviour, irritability) Essentially evidence of a change in functional ability
- **G4 Present for at least 6 months**
- Mild/Moderate/Severe
- **With additional symptoms** (behavioural and psychological symptoms of dementia (depression, delusions, psychosis) Up to 90% have these

DSM-V Major Neurocognitive Disorder (Dementia)

- 1. Evidence of significant cognitive decline from a previous level of performance in **one or more** cognitive domains – such as complex attention, executive function, learning, memory, language, perceptual-motor or social cognition
- Evidence should consist of history of significant decline (from patient, reliable informant or clinician)

AND

- Impairment in cognitive performance from standardised neuropsychological testing (or another assessment if this is not available

- 2. The cognitive deficits interfere with independence in everyday (functional) activities (at a minimum, assistance with complex activities of daily living such as paying bills)
- 3. Not occurring only in delirium and not better explained by another mental disorder

- Specify subtype (see criteria for subtypes of dementia)

Differences with DSM-V criteria

- NCD – acquired, rather than developmental disorders -represent decline. Due to underlying brain pathology.
- 'Dementia' typically refers to degenerative diseases in older people, whereas NCD expands category to diseases in younger people.
- Allows for one area of deficit only (i.e. amnestic syndrome, cognitive impairment post head injury) except in Alzheimers disease
- **For degenerative dementias, use consensus guidelines for dementia subtype in addition to DSM-V.**

Neuropsychometric Assessment

- Cognitive function tests have been used and developed over several years

- Neuropsychometric batteries may contain several components to test different cognitive abilities, e.g. CANTAB, CAMCOG, ADAS-Cog etc.

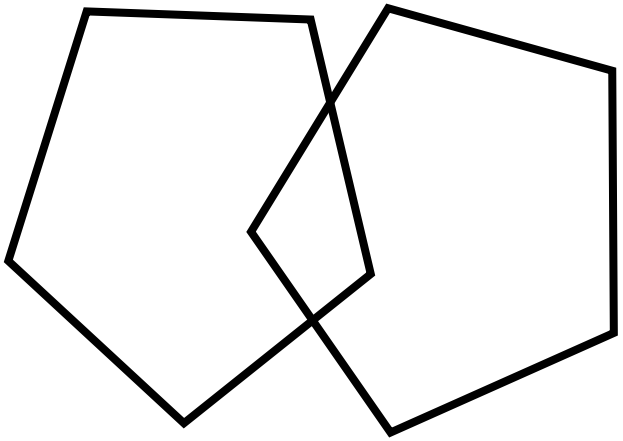
- The Mini-Mental State Examination (MMSE)- widely used. Montreal Cognitive Assessment (MoCA) test.

- Value of informant questionnaires

Mini-Mental State Examination

- MMSE is a short test which measures general cognitive status including short-term memory (Folstein, et al, 1975)

- MMSE includes tests for orientation (e.g. year, season, etc.), registration, attention and calculation, recall, and language



- MMSE is a 30 points score test. Mildly cognitively impaired subjects can have scores 26 to 21

VCI: Definitions and Recent refinements in understanding clinical entity

Difficulties with spectrum of VCI?

Vascular Cognitive Impairment

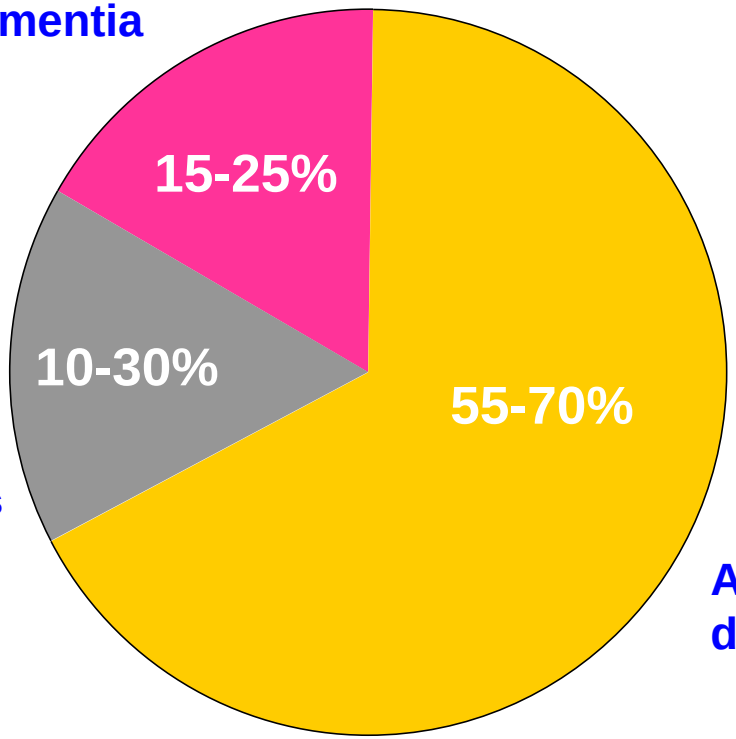
Vascular = all causes of CVD

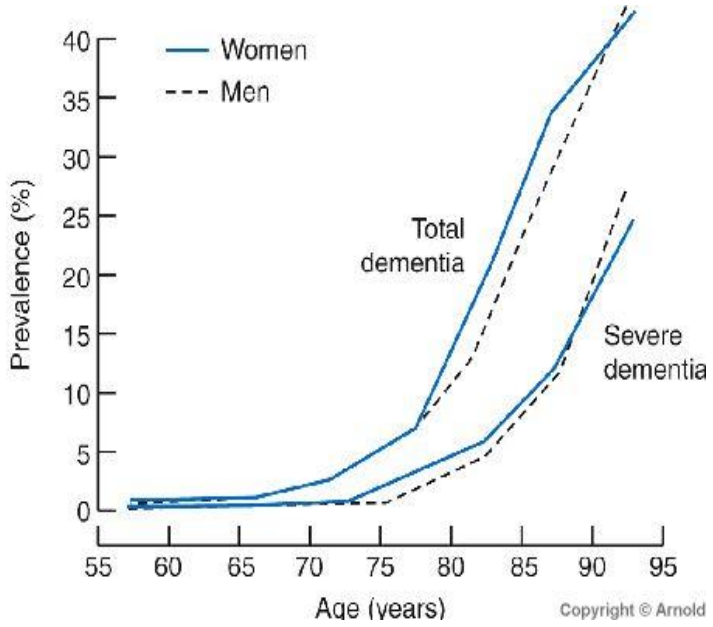
(cardiovascular also)

Cognitive Impairment = early to late and severe forms of dementia syndromes

(VaD and MCI)

Prevalence of VCI: expected to be very high!





- Early-onset VaD (<65 yrs) ranges 3-44 % clinic and population-based studies; Recent US study medicare prevalence ~15%
- Pathologically diagnosed VaD 0.03-60% with an overall mean estimate 18%

Frataglioni L, et al. *Neurology.* 2000;54:S10-15; Vieira et al, 2013; Kalaria, 2016; Goodman et al, 2017: Rarer dementias not shown but do not amount to >15 of total.

VCI: NINDS-CSN Harmonization Guidelines

Stroke
Journal of the American Heart Association

American Stroke Association
A Division of American Heart Association

Original Contributions

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; Anders Wallin; 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.)

VCI: Neuropsychological Tools

Stroke
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Stroke Association
A Division of American Heart Association

National Institute of Neurological Disorders and Stroke-Canadian Stroke Network Vascular Cognitive Impairment Harmonization Standards
Vladimir Hachinski, Costantino Iadecola, Ron C. Petersen, Monique M. Breteler, David L. Nyenhuis, Sandra E. Black, William J. Powers, Charles DeCarli, Jose G. Merino, Raj N. Kalaria, Harry V. Vinters, David M. Holtzman, Gary A. Rosenberg, Anders Wallin, Martin Dichgans, John R. Marler and Gabrielle G. Leblanc
Stroke 2006;37;2220-2241; originally published online Aug 17, 2006;
DOI: 10.1161/01.STR.0000237236.88823.47
Stroke is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514
 Print ISSN: 0039-2499. Online ISSN: 1524-4628

VCI may include all cognitive domains, but there is likely to be a preponderance of so called "executive" dysfunction (i.e. slowed information processing, impairments in the ability to shift from one task to another, and deficits in ability to hold and manipulate information or working memory)

Proposed 30-Minute and 5-Minute Neuropsychological Protocols

30-Minute Test Protocol

- **Semantic Fluency (Animal Naming)**
- **Phonemic Fluency (Oral Word Association Test)**
- **Digit Symbol-Coding from the Wechsler Adult Intelligence Scale, Third Edition**
- **Hopkins Verbal Learning Test**
- **Center for Epidemiologic Studies-Depression Scale**
- **Neuropsych Inventory, Questionnaire Version (NPI-Q)**
- **Supplemental: MMSE, Trail Making Test**

5-Minute Protocol

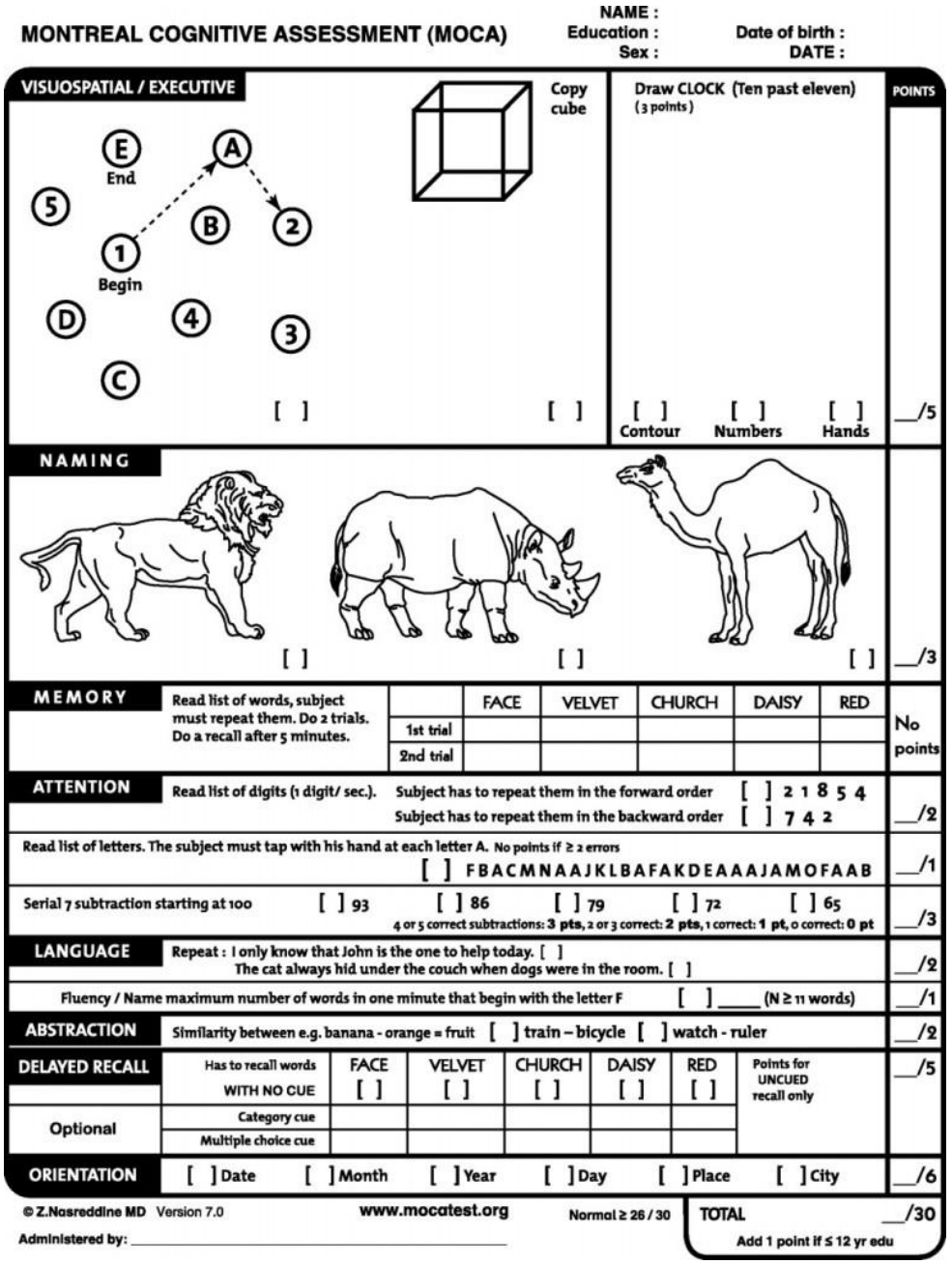
- **MoCA subtests**
- **5-Word Memory Task (registration, recall, recognition)**
- **6-Item Orientation**
- **1-Letter Phonemic Fluency**
- **Supplemental: Remainder of the MoCA, Semantic Fluency (Animal Naming),**
- **Trail Making Test, MMSE (to be administered at least 1 hour before or after the above tests).**

Montreal Cognitive Assessment (MoCA)

MoCA
MONTREAL
COGNITIVE ASSESSMENT

- MoCA also includes tests for orientation (e.g. year, season, etc.), registration, attention and calculation, recall, and language biased towards **Executive Dysfunction**

- MoCA a 30 points score test. Mildly cognitively impaired subjects can have scores 26 to 21



VCI and Cognitive Function after Stroke

Stroke
Journal of the American Heart Association

American Heart Association | American Stroke Association

MoCA, ACE-R, and MMSE Versus the National Institute of Neurological Disorders and Stroke–Canadian Stroke Network Vascular Cognitive Impairment Harmonization Standards Neuropsychological Battery After TIA and Stroke

Sarah T. Pendlebury, Jose Mariz, Linda Bull, Ziyah Mehta and Peter M. Rothwell

Stroke. 2012;43:464-469; originally published online December 8, 2011;
doi: 10.1161/STROKEAHA.111.633586
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

MoCA = Montreal Cognitive Assessment (30 point test)

ACE-R= Addenbrooke's Cognitive Examination– Revised (100 point test)

MoCA and ACE-R had good sensitivity and specificity for MCI defined using the NINDS-CSN Battery (Hachinski et al, 2006) 1 year after TIA and stroke but MMSE showed a ceiling effect

VCI and Cognitive Function after Stroke

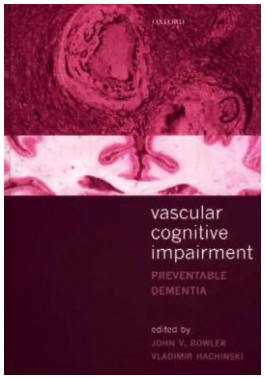
Neuropsychological Test Criteria: General considerations

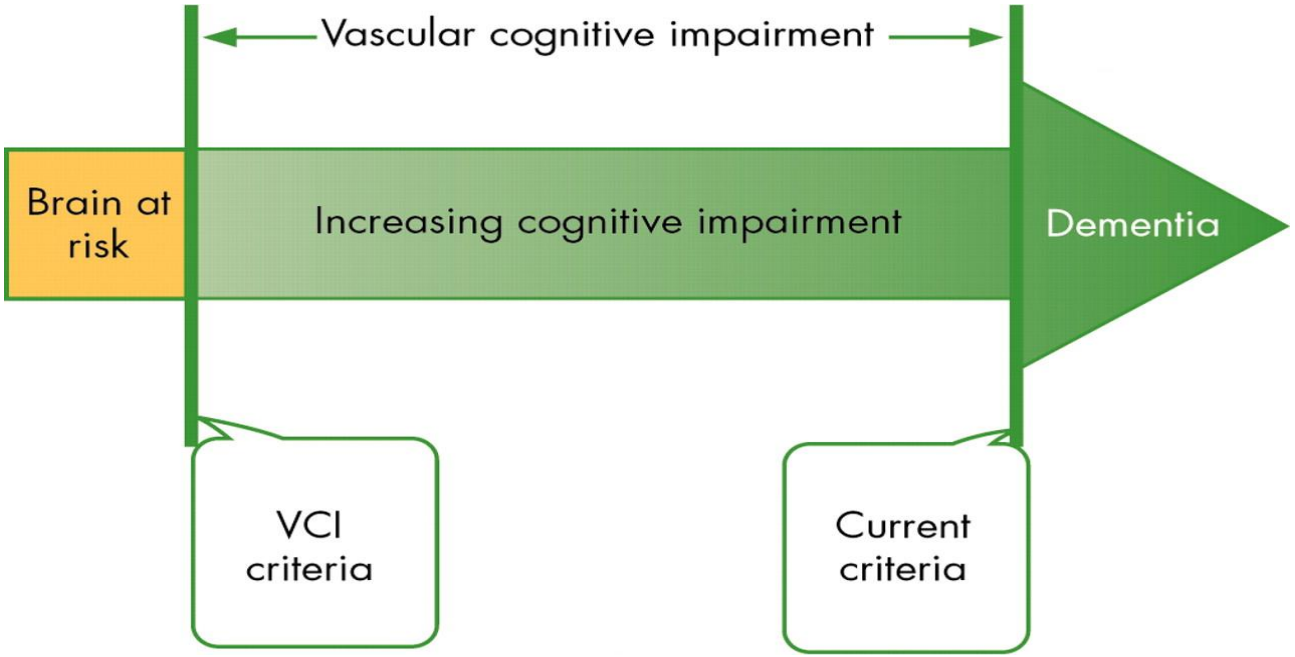
- **Quality of the standardization sample**
- **Psychometric qualities**
- **Portability**
- **Brevity**
- **Cost**
- **Ease of use**
- **Domain specificity (for 1-hour battery)**
- **Availability of multiple forms**
- **International or cross-cultural capability**
- **The lack of ceiling and floor effects**
- **Previous use of the test in VCI samples**

Trialled and Tested in sub-Saharan Africa!

After Hachincki V et al, 2006

The spectrum of VCI





- **O'Brien JT. et al, *Lancet Neurology, 2003*** *-VCI Mechanisms*
- **Bowler JV. *JNNP, 2005*** *–VCI concept refinement*
- **Hachinski V. et al, *Stroke,* 2006** -VCI Harmonization
- **Sachdev P. et al, *ADADJ, 2014* –** Neurocognitive Disorders and VCD
- **Skrobot O. et al, *Alzheimers & Dementia, 2016* -***VICCCS***
- **Skrobot O. et al, *Alzheimers & Dementia, 2017*** *-VICCCS*

Diagnostic criteria for vascular cognitive disorders: a VASCOG statement

- Cognitive disorders of vascular etiology are a heterogeneous group of disorders with diverse pathologies and clinical manifestations as VCD.
- Continuum of VCI recognized by categories of ***Mild Vascular Cognitive Disorder*****, and *Vascular Dementia or Major Vascular Cognitive Disorder***. Diagnostic thresholds, clinical/ ceuroimaging criteria proposed for establishing vascular etiology.
- Subtypes of VCD with frequent co-occurrence of AD pathology emphasized
- Proposed criteria for VCD provide a coherent approach to diagnosis of diverse group of disorders and stimulate clinical-pathological validation studies
- Harmonized with the DSM-5 criteria

From P Sachdev et al, 2014

The Vascular Impairment of Cognition Classification Consensus Study

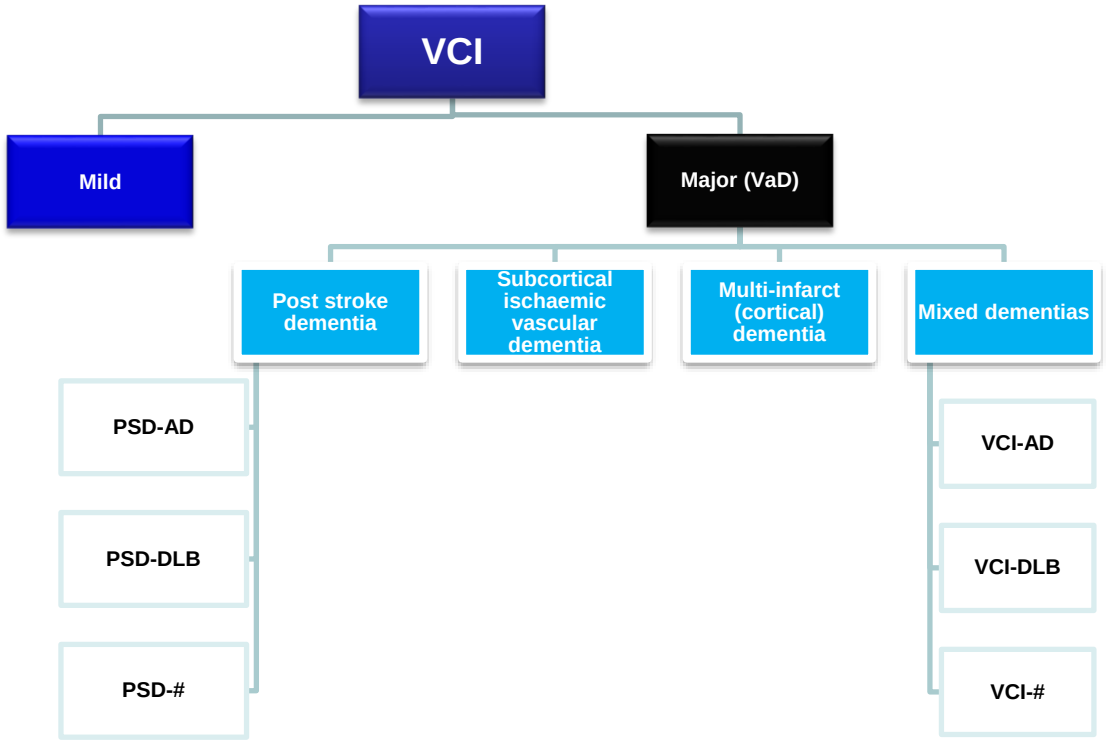
Subtypes in the VICCCS	Descriptive terms in the VICCCS	O'Brien concept classification and causes of sporadic VCI
Post stroke dementia		**Post stroke dementia**
		Vascular dementia
Multi-infarct (cortical)		**Multi-infarct dementia (cortical vascular dementia)**
Subcortical ischaemic		**Subcortical ischaemic vascular dementia**
	Strategic infarct	**Strategic-infarct dementia**
	Hypoperfusion	**Hypoperfusion dementia**
	Haemorrhagic	**Haemorrhagic dementia**
	Specific arteriopathies#	**Dementia caused by specific arteriopathies**
Mixed dementias*		**Mixed AD and vascular dementia**
Mild VCI		**Vascular mild cognitive impairment**
	Vasculitis§	

- **Towards universal acceptance of VCI criteria**

  -impacting on clinical diagnosis rates, prevalence estimates, research and treatment
- VICCCS) consortium by an online Delphi consensus study
- VICCCS redefined VCI including classification of mild and major forms of VCI and subtypes.
- Proposed new standardized VCI-associated terminology and future research priorities to address gaps in current knowledge
- VICCCS proposed a consensus-based updated conceptualization of VCI intended to facilitate standardization in research

From O Skrobot et al, 2016

Progress towards standardised diagnosis of VCI guidelines from VICCCS



Mild VCI: Impairment in at least ONE cognitive domain and mild to no impairment in ADL (independent of motor/sensory sequelae of vascular event)

Major VCI (VaD): Clinically significant deficits of sufficient severity in *at least* ONE cognitive domain (deficits may be present in multiple domains) and severe disruption to ADL (independent of the motor/sensory sequelae of the vascular event)

- Diagnosis of VICCCS-revised *Mild and Major forms of VCI* and endorsed the NINDS-CSN (Hachinski et al, 2006) neuropsychological assessment protocols and recommendations for imaging
- Core domains for assessment should include: executive function, attention and memory as well as language and visuospatial function

From O Skrobot et al, 2017 in press

Diagnosis of VaD: NINDS-AIREN Criteria

Dementia
- Impaired memory
- ≥ 2 other cognitive domains impaired

Cerebrovascular disease
- Neurological exam
- Neuroimaging

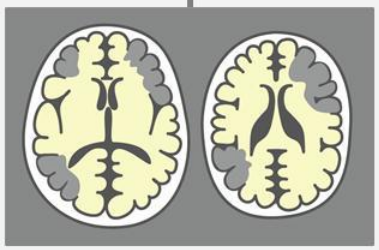
Probable/Possible diagnosis
- Temporal relationship between CVD and dementia
- Abrupt onset / stepwise progression
- Absence of disorders that could account for deficits (eg, AD)

Diagnosis of VaD

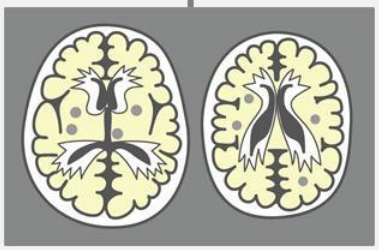
Definitive diagnosis by autopsy?

Román GC, et al. *Neurology.* 1993;43:250-260.

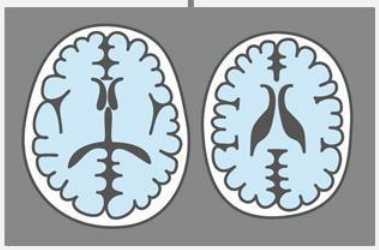
Vascular Dementia



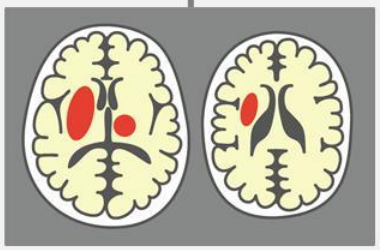
multi-infarct dementia



Small artery lesions

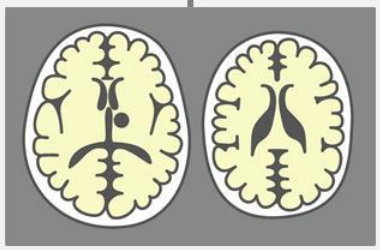


Hypoperfusion

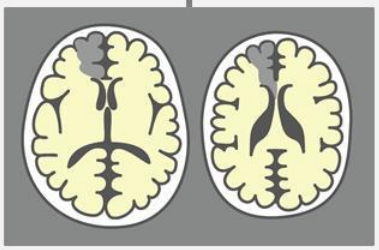


Brain hemorrhage

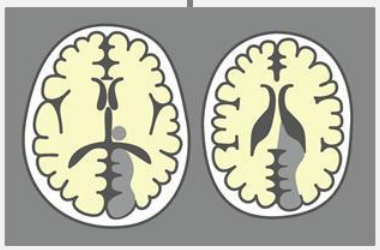
Strategic Lesions



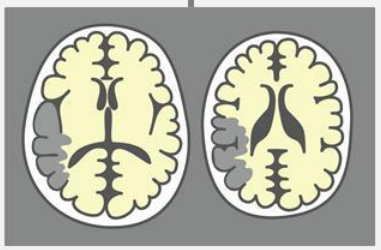
Thalamus



ACA territory



PCA territory



Angular gyrus

NINDS-AIREN criteria Roman et al. Neurology 43:250-260, 1993

THE NINDS-AIREN CRITERIA
Probable Vascular Dementia

1) Dementia

2) Cerebrovascular disease

a) Focal signs consistent with stroke

AND

b) Relevant CVD by brain imaging

- Multiple large-vessel infarcts
- Single strategically placed infarct
- Multiple lacunes
- Extensive periventricular WMLs

3) Relationship between 1) and 2)

a) Dementia onset within 3 months

b) Abrupt deterioration in cognitive functions. Fluctuating stepwise progression

Roman G et al 1993

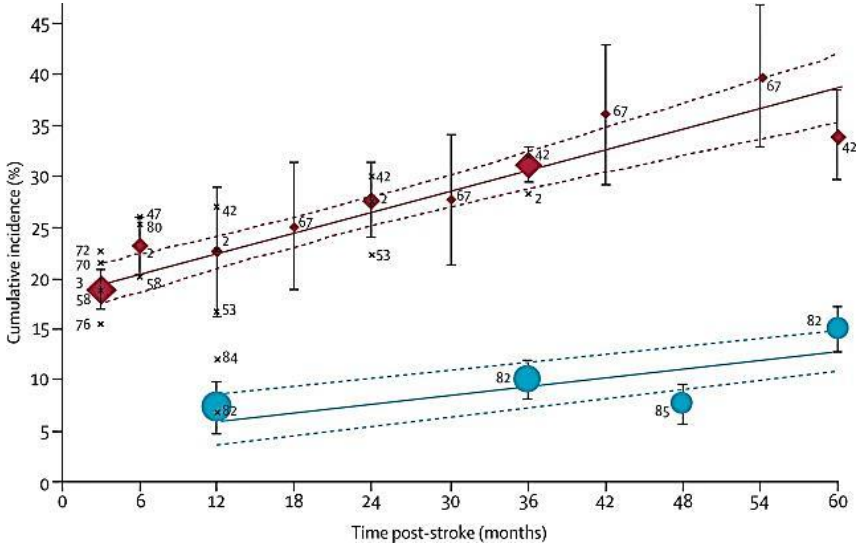
Principles of diagnosis

- Is dementia syndrome present? Refer to DSM/**ICD-10** criteria
- Are two (generally) areas of brain function affected (from cognitive assessment, consider educational level)
- Functional impairment (assess IADLs)
- Always get a collateral history (for functional impairment, timescale (6 months for ICD-10))
- Exclude common differentials,
- DELIRIUM (is attention affected?)
- DEPRESSION (if in doubt, trial of treatment before diagnose dementia)
- Exclude reversible causes of dementia (hypothyroid, B12/folate/anaemia, HIV?, alcohol (thiamine))
- Consider dementia subtype (pattern of cognitive deficit, risk factors, neurological examination

Frequency of Cognitive Impairment and Dementia after Stroke Injury

What type(s) of dementia do stroke survivors develop?

Cognitive Function after Stroke



Pooled cumulative incidence of post-stroke dementia excluding pre-stroke dementia in hospital-based cohorts Pooled cumulative incidence of PSD excluding pre-stroke dementia in hospital-based cohorts of any stroke (first-ever or recurrent stroke)

Causal role of stroke, optimum acute stroke care and secondary prevention important in reducing the burden of cognitive impairment

- Pre-stroke dementia ranged 9-14%
- PSD (≤1 year) rates ranged 7-41% in hospital-based studies of recurrent stroke
- Incidence of dementia >1st year was 3% per yr
- MTLA, female gender, family history of dementia strongly associated with pre-stroke dementia
- Characteristics and complications of stroke and multiple lesions in time and place strongly associated with PSD
- Interpretation: I0% of patients had dementia before first stroke, 10% developed new dementia soon after first stroke, and >third had dementia after recurrent stroke.

Pendlebury ST and Rothwell P, TLN, 2009

Cognitive Impairment in Lacunar Stroke

Cerebrovascular disease

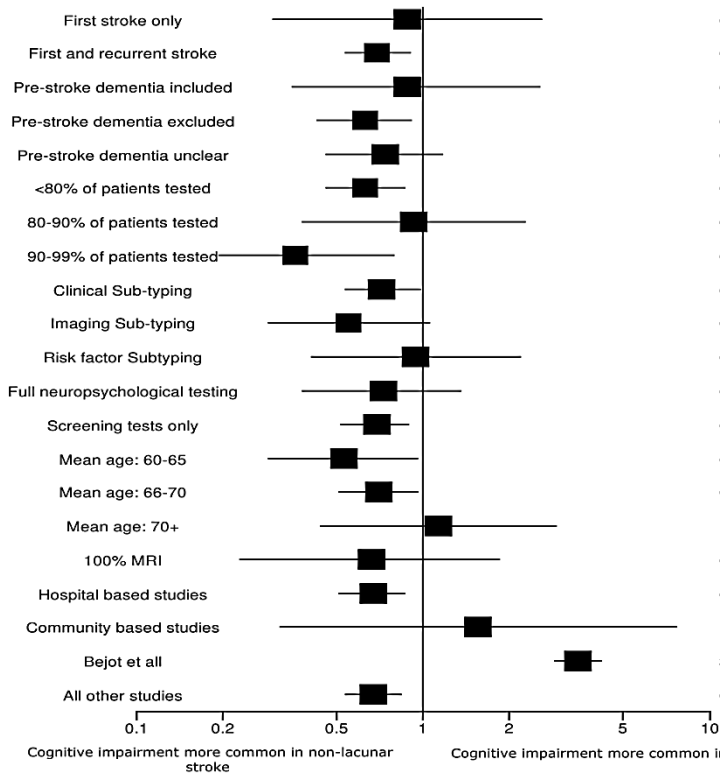
OPEN ACCESS

RESEARCH PAPER

Cognitive impairment after lacunar stroke: systematic review and meta-analysis of incidence, prevalence and comparison with other stroke subtypes

Stephen David James Makin,[1] Sarah Turpin,[2] Martin S Dennis,[1] Joanna M Wardlaw[3]

Makin SDJ, et al. J Neurol Neurosurg Psychiatry 2013;84:893–900.



- **24% had MCI or PSD**
- **Similar proportions: lacunar and non-lacunar strokes had MCI or dementia (1-4 yrs after stroke)**
- **Prevalence: 20% dementia after lacunar stroke**
- **Incidence: 37% MCI or dementia**
- **Limitations: short follow-up, subtype classification methods and confounding factors**
- **Conclusions: cognitive impairment common after lacunar strokes.**
- **New prospective studies required with accurate stroke subtyping to assess long term outcomes while accounting for co-factors**

OR of cognitive impairment in lacunar against cortical stroke for studies with particular characteristics

Neuroimaging Correlates of Cognitive Impairment and Dementia

SVD type(s) of VCI most common

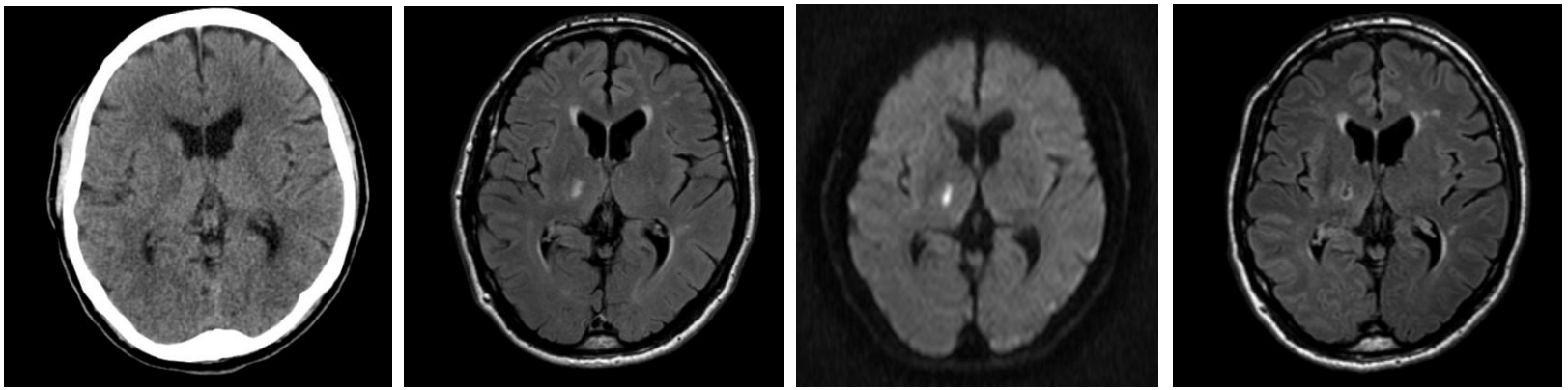
Cerebral Small Vessel Disease: Clinical Features

Varied manifestations

- Much of SVD can be clinically silent
- Sudden-onset stroke symptoms or syndromes e.g. lacunar syndrome
- Mostly covert neurological symptoms and signs
- Motor slowing, dysarthria, short-stepped gait
- *Cognitive: Self-reported cognitive difficulties e.g. executive slowing, processing speed, forgetfulness, dementia*
- *Behavioural: apathy (20-25%), depression (20-30%)*

Neuroimaging of SVD: lacunar infarction

Male 61 yr old, lacunar infarct



CT 3 hours

MR-FLAIR 3 days

MR-DWI 3 days : ADC-low signal

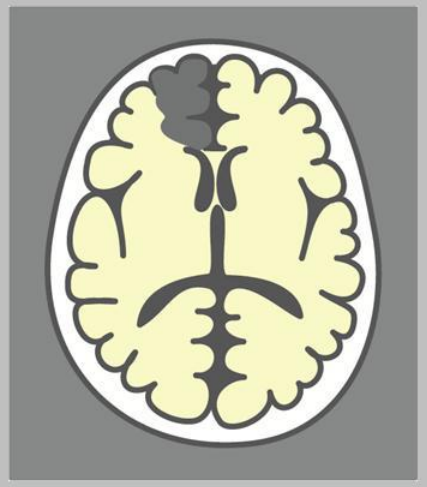
MR-FLAIR 2 years central caviatation of the infacrt → lacune

Symptoms: left side hemiparesis, dysarthria. Reported as normal, but with information later MRI a faint hypodensity discerned at lateral border of right thalamus

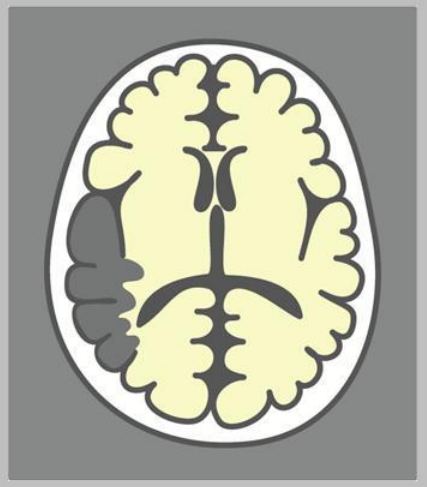
What Neuropsychometric changes can you predict?

Rather than amnestic type memory impairment features associated with frontal lobe function i.e. Executive Function tasks, processing speed, working memory are more eveident.

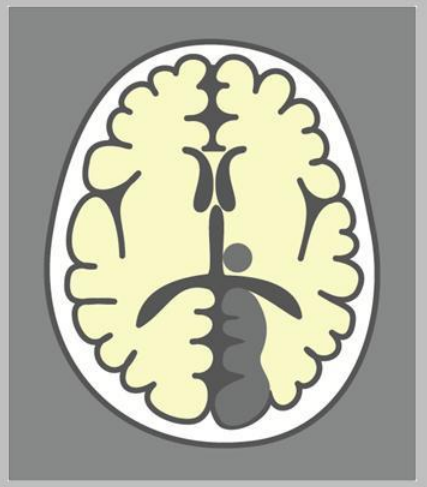
Large-vessel Disease



ACA territory

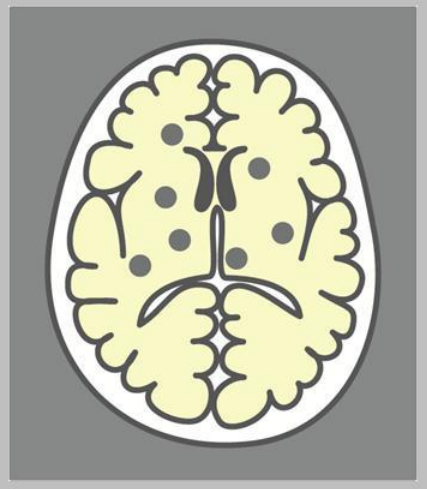


MCA territory

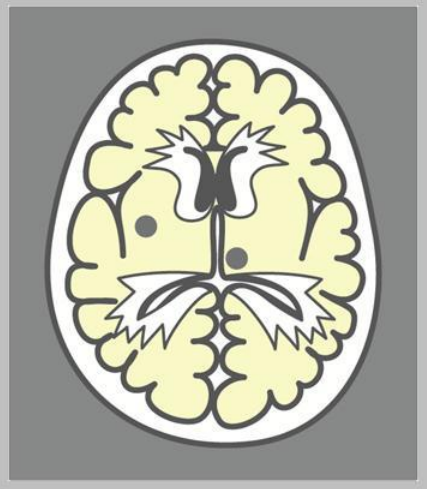


PCA territory

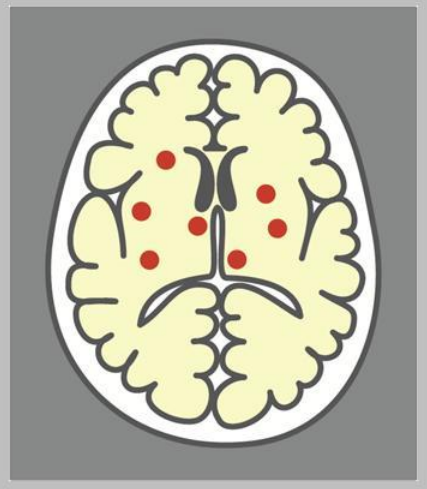
Small-vessel Disease



Lacunes

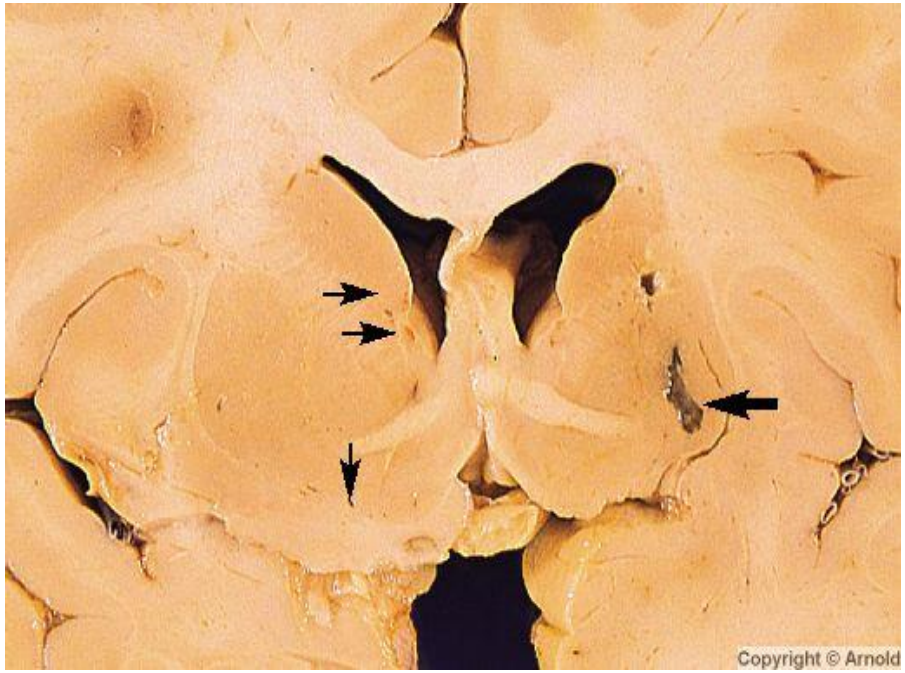


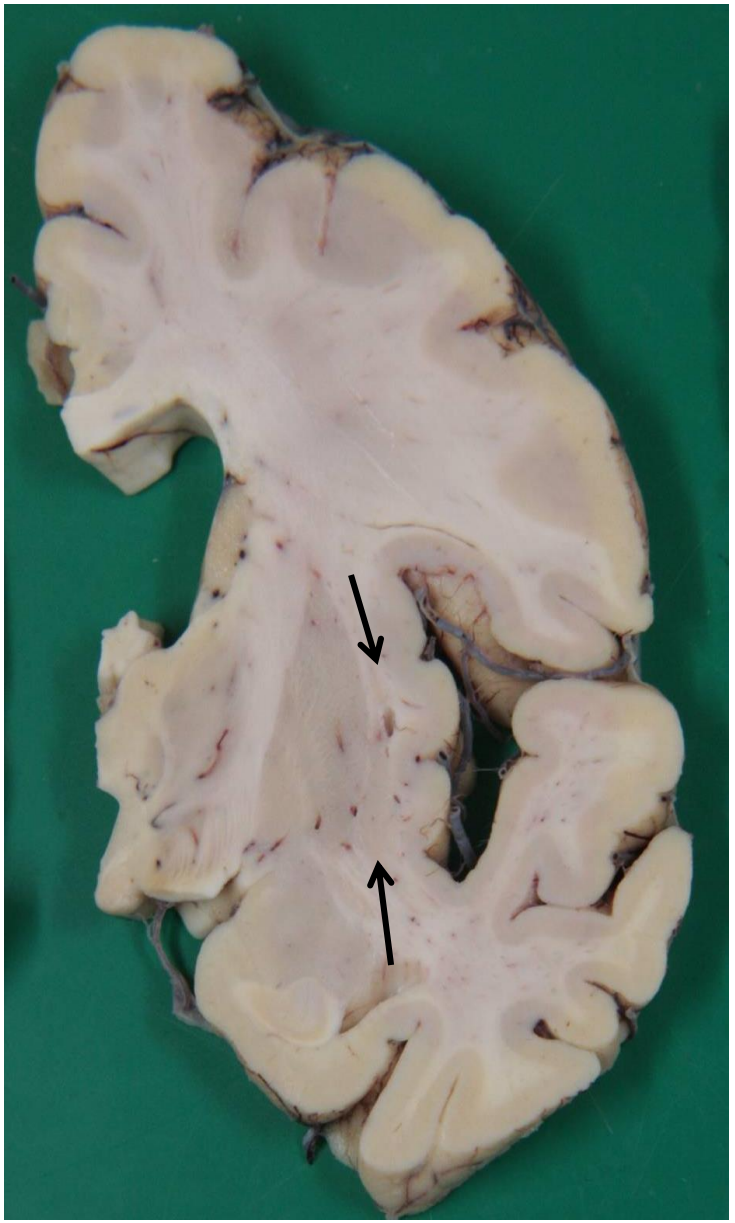
Leuko-araiosis



microbleeds

Lacunes and Lacunar infarcts





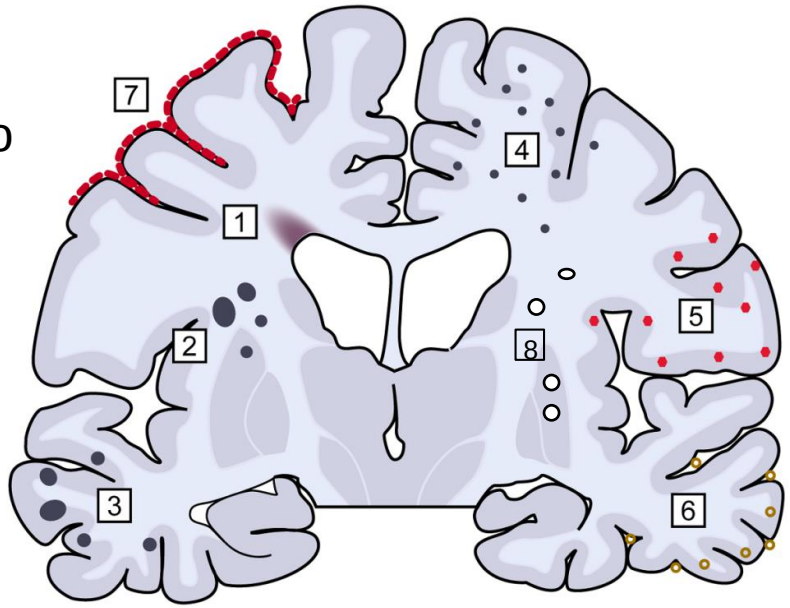
Lacunes

• complete or cavitating infarcts; up to 15 mm; common in subcortical structures

SVD Pathophysiology

Neuroimaging (MR)

1. Periventricular and Deep WMH
2. Lacunes and macro infarcts
3. Cortical: small infarcts
4. Subcortical: macroinfarcts
5. Cerebral Microbleeds
6. Amyloid deposition (PET)
7. Superficial siderosis
8. Perivascular spaces

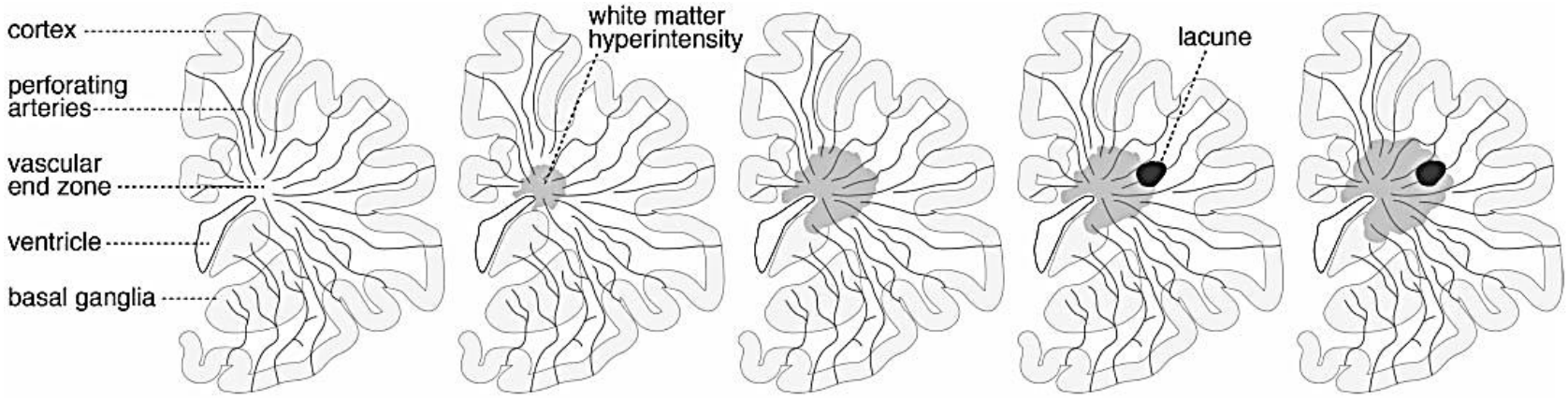


Neuropathology

1. Periventricular WM changes (myelin loss)
2. Subcortical infarcts: Lacunes and macro infarcts
3. Cortical: small infarcts
4. Subcortical and cortical: microinfarcts
5. Microhaemorrhage/ haemosiderin
6. Superficial haemosiderin (some)
7. Cerebral Amyloid Angiopathy
8. Perivascular spaces

Arteriolosclerosis

Lacunar Infarcts in relation to WMH in SVD

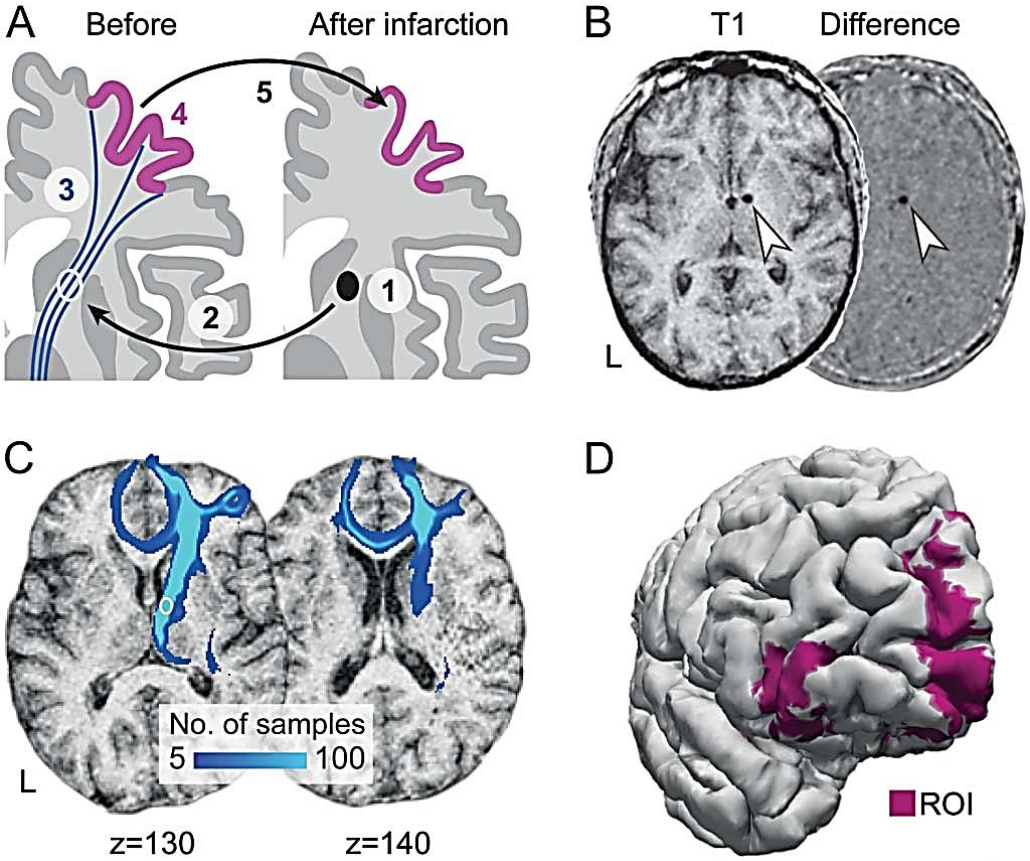


Proposed model for a typical evolution of WMH and lacunes in SVD

- Spread of changes towards subcortical regions in SVD (ASPS and CADASIL cohorts)
- Majority (>90%) of lacunes were found at the edge (proximal predilection) of WMH
- Pathophysiology of lacunes and WMH is intimately connected

Modified after M Duering et al, 2011

Secondary cortical neurodegeneration after subcortical ischemia (SVD) as a mechanism for brain atrophy



A causal relationship between incident subcortical infarcts and morphologic alterations in connected cortical regions

Implies a role for 2^{o} neurodegeneration within cortical GM (focal cortical thinning) after axonal damage e.g. infarct in WM

From M Duering et al, 2012

Subtypes of VaD/VCI: Vascular Mechanisms and Brain Changes

Vascular mechanisms	Cortical VaD	Strategic infarct VaD	Subcortical ischemicVaD SVD
Large-vessel disease	✓	✓	×
Cardiac embolic events	✓	✓	×
Hypoperfusion (focal or global)	✓	✓	✓
Small-vessel disease	×	✓	✓
Clinical and Cognitive Features			
Focal neurological signs	✓	✓ / ×	×
Stepwise progression	✓	×	×
Cognition (memory/executive)	✓	✓	✓
Changes in the brain			
Large cortico-subcortical	✓	×	×
Arterial territorial infarct	✓	✓	×
Distal field (watershed) infarct	✓	✓	×
Lacunar infarcts	×	✓	✓
Focal, diffuse WMLs	×	✓	✓
Incomplete ischaemic injury	×	×	✓
Heterogeneity	++	+++	+

WMLs- white matter lesions

T Erinkinjuntti and R Kalaria, 2005

Accumulation of Focal Cortical Symptoms

Large-vessel disease

↓

Cortical infarcts in strategic locations

Frontal lobe	Hippocampus, basal forebrain	Gyrus angularis	Parietal lobe
↓	↓	↓	↓
Aphasia, apraxia, disinhibition, apathy	Amnesia	Constructional problems	Alexia, agraphia

Cortical type of dementia

Non-Specific Disconnection of the Cortex

Small-vessel disease

↓

Diffuse white matter lesions

↓

Disruption of cortico-cortical pathways

↓

Frontal, temporal and parietal cortical deficits

Mixed cortical / subcortical type of dementia

Disruptions of Subcortico-cortical Circuits

Small-vessel disease

↓

Subcortical infarcts in strategic locations

Thalamus, caudate nucleus, internal capsule

↓

Disruption of specific fronto-subcortical circuits or non-specific thalamo-cortical projections

↓

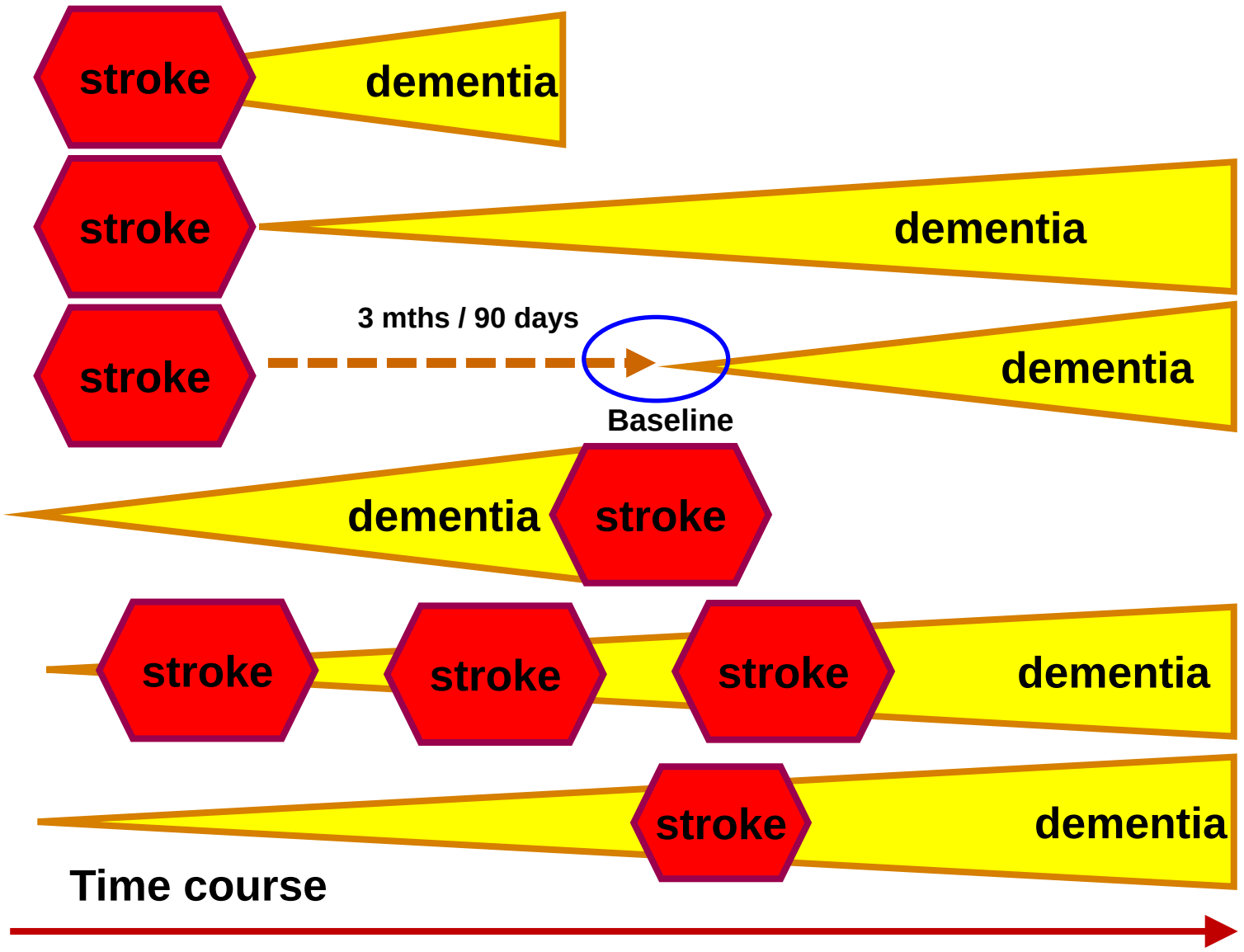
Executive dysfunction Apathy Attentional deficit Personality change

Subcortical type of dementia

Vascular Basis for Dementia and Neurodegeneration in Stroke Survivors

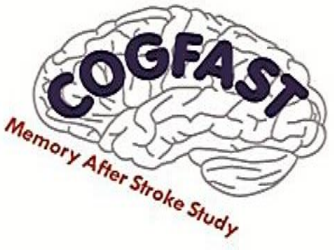
What type(s) of dementia do stroke survivors develop?

Stroke and Dementia are risks for each other



Modified from K Nagata, 2007

COGnitive Function After STroke (COGFAST – Newcastle Study)



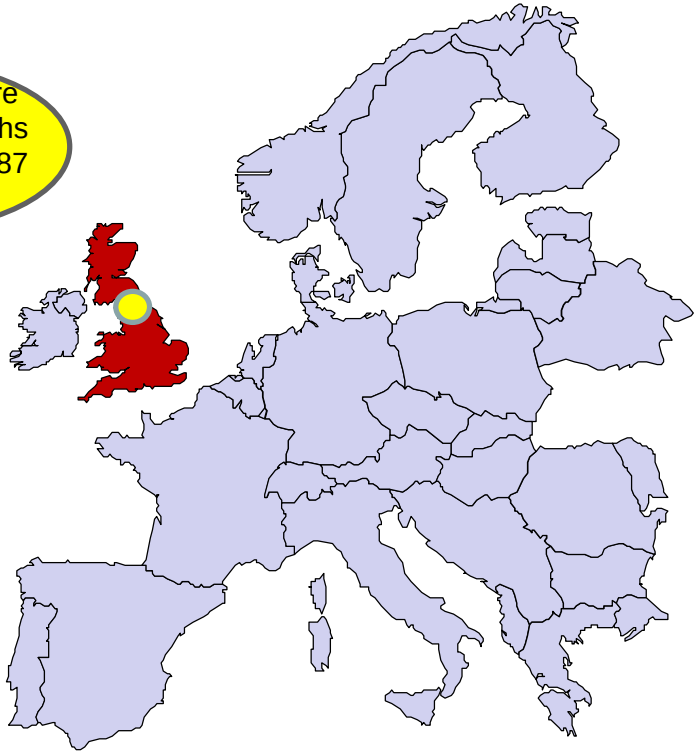
415 participants

Demented/severe disability 3 months post stroke: n=287 removed

356 stroke survivors (dementia free)

59 Vascular Dementia cases

103 sub study (MRI and Cardiovascular Assessment)



Baseline Recruitment at 3 months: COGFAST- first ever (overt) stroke

Original screen ~702 Non- demented elderly (>70 years) stroke survivors

COGFAST study: Overall Clinical and Neuropsychometric Findings

- Elderly group
- After 5 years, nearly half will have died.
- Only 1 third will be alive without dementia
- Greater decline to death or dementia if >2 vascular risk factors or baseline cognitive impairment but no dementia
- Incident depression 36.9 episodes per 100 person years

- Already lived to 80
- Improvement in cognitive function (CAMCOG) in ~25% post stroke
- Approx. 50% chance of another 5 years
- Better outcomes if no other risk factors (to CI or death)
- >60% free of depressive illness

MRC 15-year Longitudinal study of post-stroke survivors: Lead PI R Kalaria

Kalaria and Ballard, 2001; Ballard C et al, Stroke, 2003; Ballard C et al, Dementia 2003 ;Ballard et al, Neurology 2004; Stephens S et al, J Am Geriatr Soc, 2003; Kalaria RN et al, 2004; Allan LM et al, 2011; Kalaria RN 2012; Allan L et al, 2013

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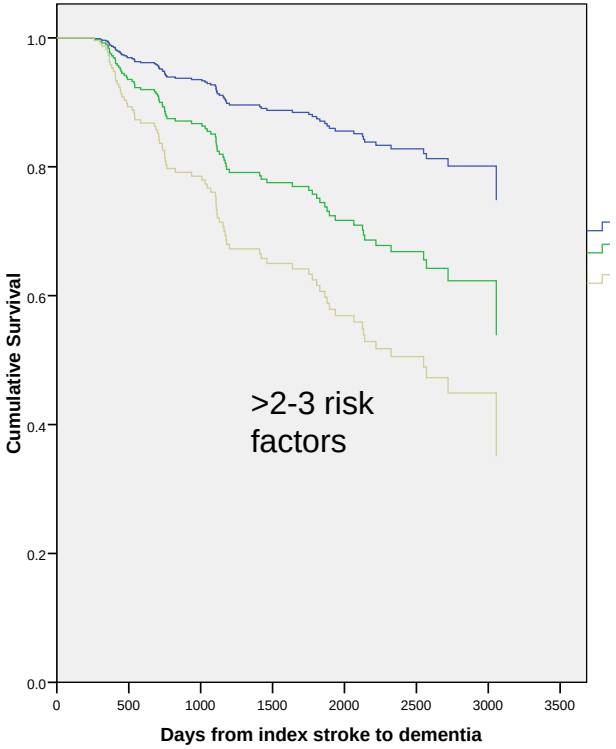
- Incident depression 36.9 episodes per 100 person years

Time to dementia by number of cardiovascular risk factors



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COGFAST study: Dementia, Vascular Risk Factors and Pathological Diagnosis of VaD

doi:10.1093/brain/awr273 Brain 2011: 134; 3713–3724 | 3713

BRAIN
A JOURNAL OF NEUROLOGY

Long term incidence of dementia, predictors of mortality and pathological diagnosis in older stroke survivors

Louise M. Allan, Elise N. Rowan, Michael J. Firbank, Alan J. Thomas, Stephen W. Parry, Tuomo M. Polvikoski, John T. O'Brien and Raj N. Kalaria

Institute for Ageing and Health, Newcastle University, Wolfson Research Centre, Campus for Ageing and Vitality, Newcastle upon Tyne, NE4 5PL, UK

Correspondence to: Prof. Raj N. Kalaria

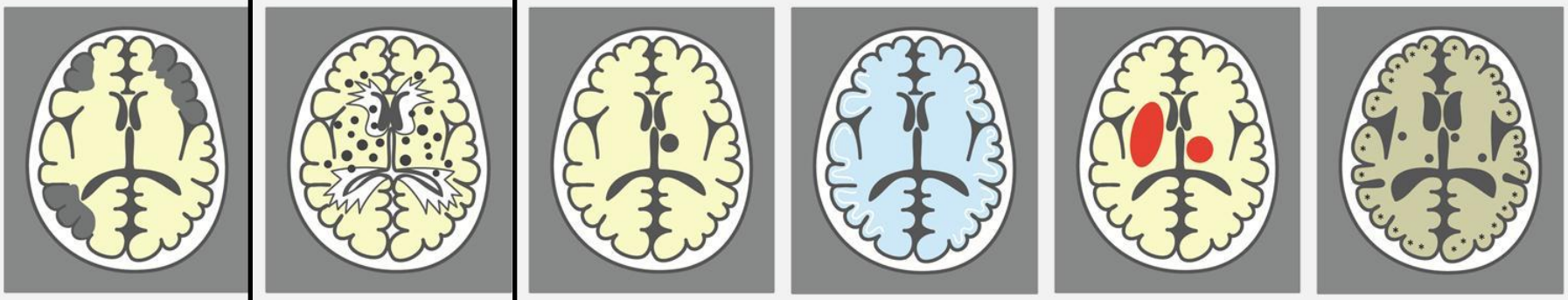
- During mean follow-up of 3.8 years, ~25% developed PSD
- Duration of survival (days from baseline stroke to death) or overall burden of vascular and minimal neurodegenerative pathology (Braak <2.5) similar between PSD and PSND
- Elderly stroke survivors in this age group likely to develop VaD: Pathological diagnosis indicated ~75% VaD, rest Mixed (AD type pathology with vascular lesions) and frontotemporal dementia (1)
- Microinfarction differentiated PSD from non-demented PS survivors

Ballard C et al, 2003; Kalaria RN et al, 2004; Firbank M et al, 2007, 2011, 2012; Allan L et al, 2012; 2013, Deramecourt V et al, 2012; Polvikoski T et al , in preparation

Neuropathology in Elderly Stroke Survivors

What are the pathological substrates of PSD?

Newcastle Categorization of the Major CV lesions Associated with Cognitive Impairment



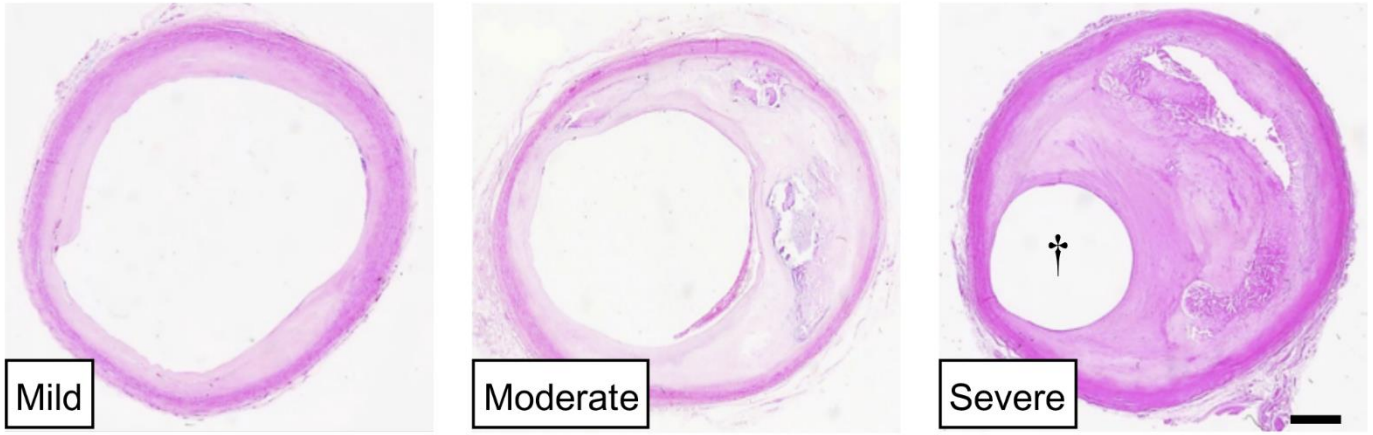
I	II	III	IV	V	VI
large infarct or several infarcts	multiple small or microinfarcts	strategic infarcts	cerebral hypoperfusion	cerebral hemorrhage	CV lesions with AD pathology
multi-infarct dementia	white matter lesions	thalamus hippocampus basal forebrain	hippocampal sclerosis	lobar ICH SAH	mixed dementia

Slide courtesy of Dr Ken Nagata

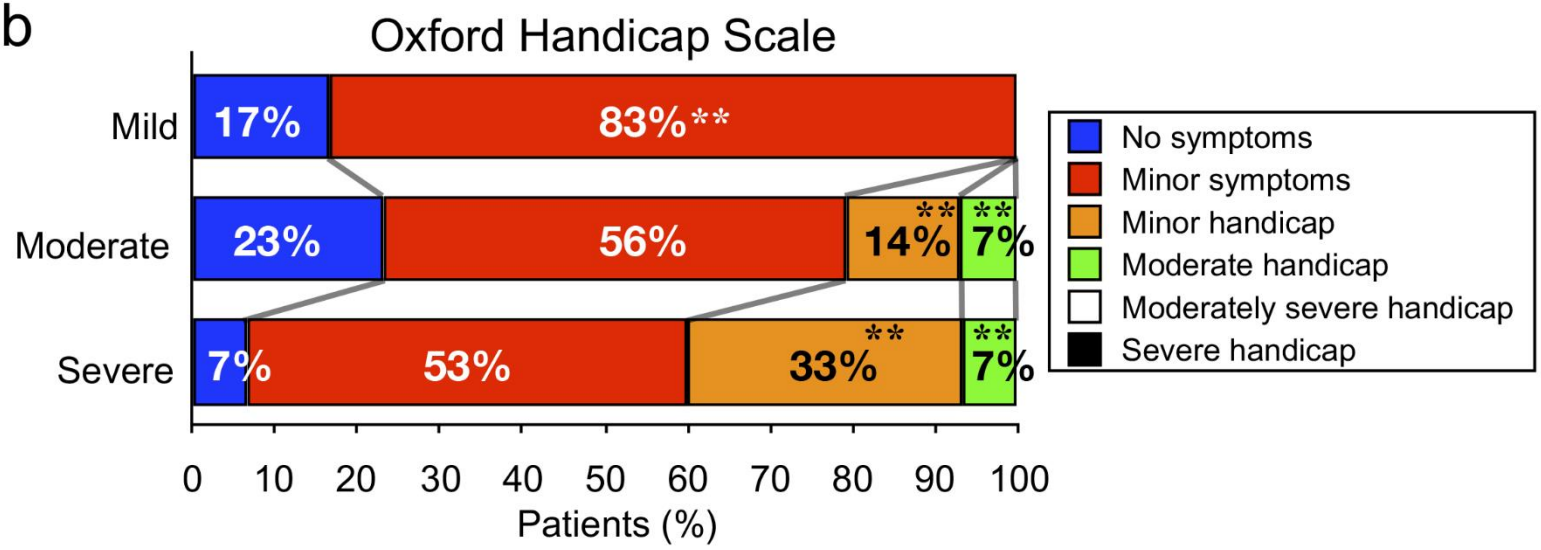
Kalaria, RN, et al. J Neuro Sci 226: 75-80, 2004

COGFAST study: Carotid Artery Disease (CAD) and Stroke Injury

a

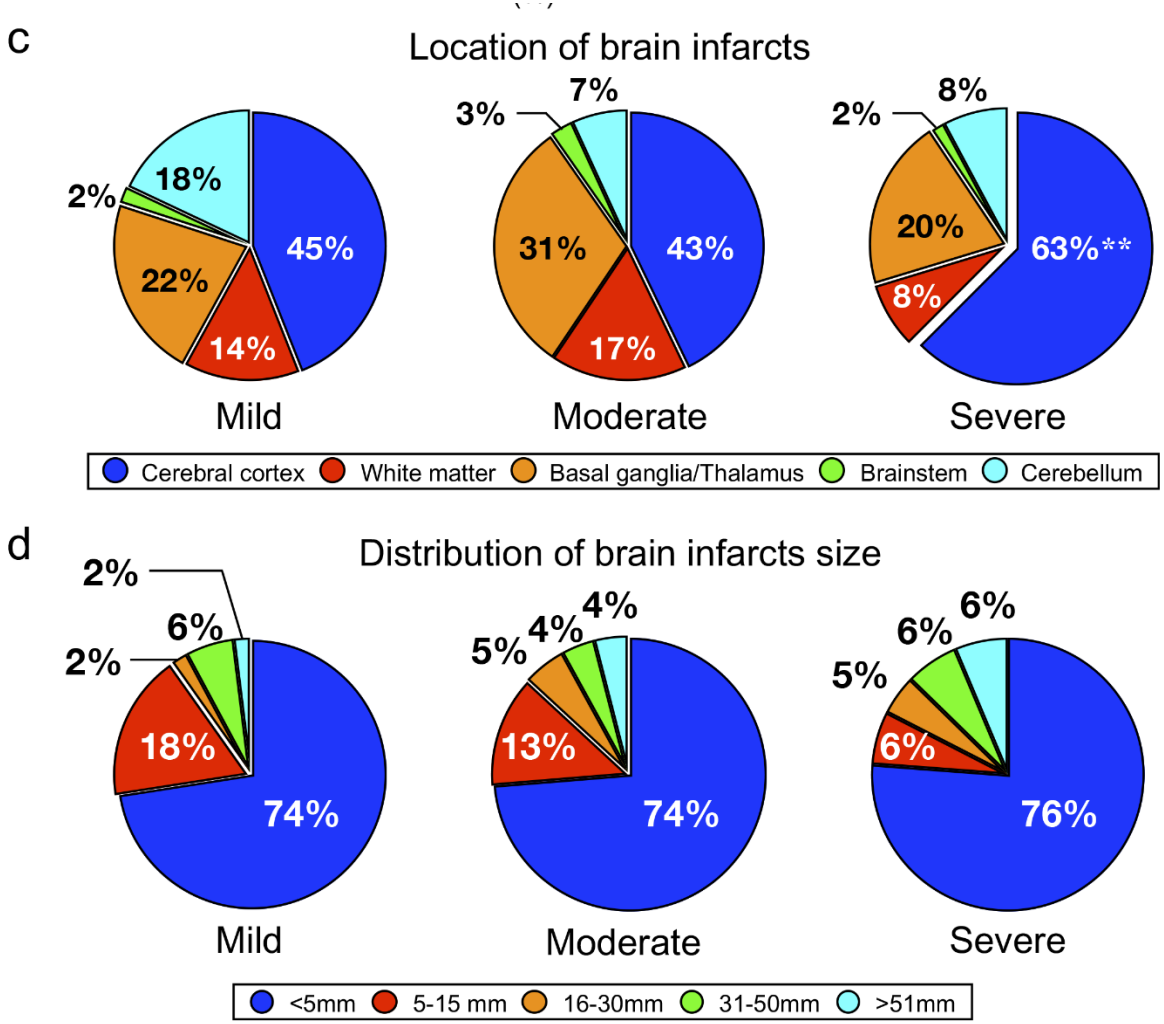


b



Hase Y et al, Submitted 2018

COGFAST study: Carotid Artery Disease (CAD) and Stroke Injury



Hase Y et al, Submitted 2018

Staging and natural history of cerebrovascular pathology in dementia

V. Deramecourt, MD, PhD
J.Y. Slade, BSc
A.E. Oakley, MBiol
R.H. Perry, FRCPath
P.G. Ince, FRCPath
C.-A. Maurage, MD, PhD
R.N. Kalaria, FRCPath

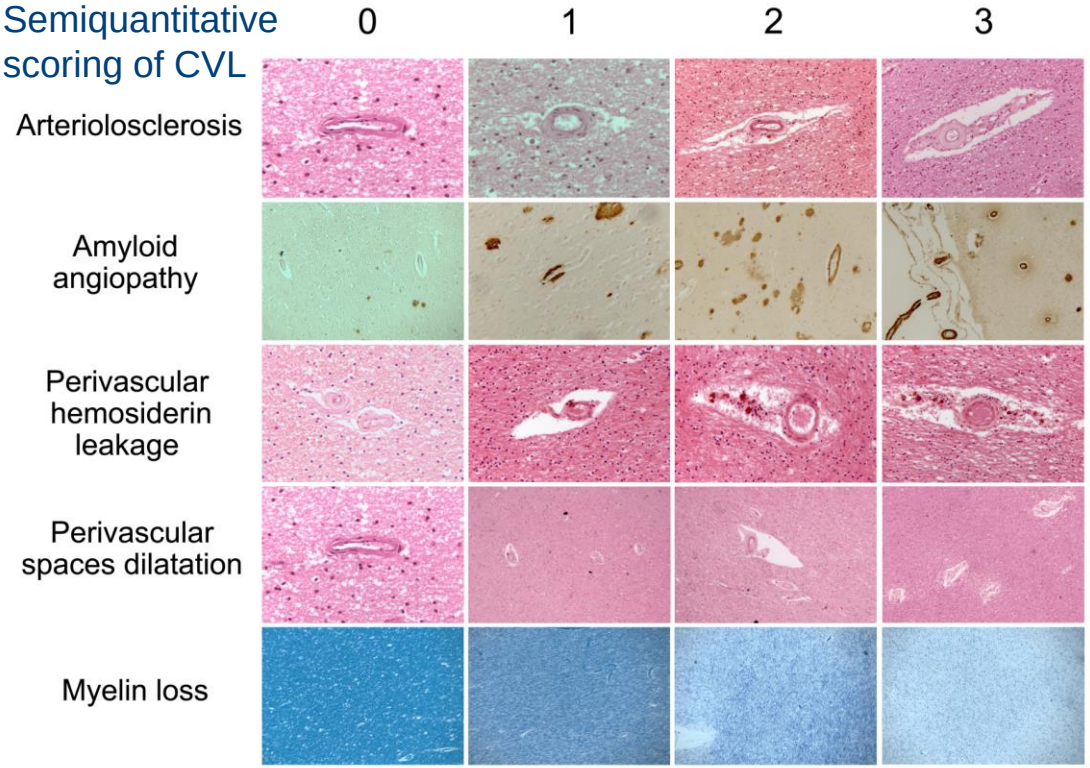
Deramecourt V et al, 2012

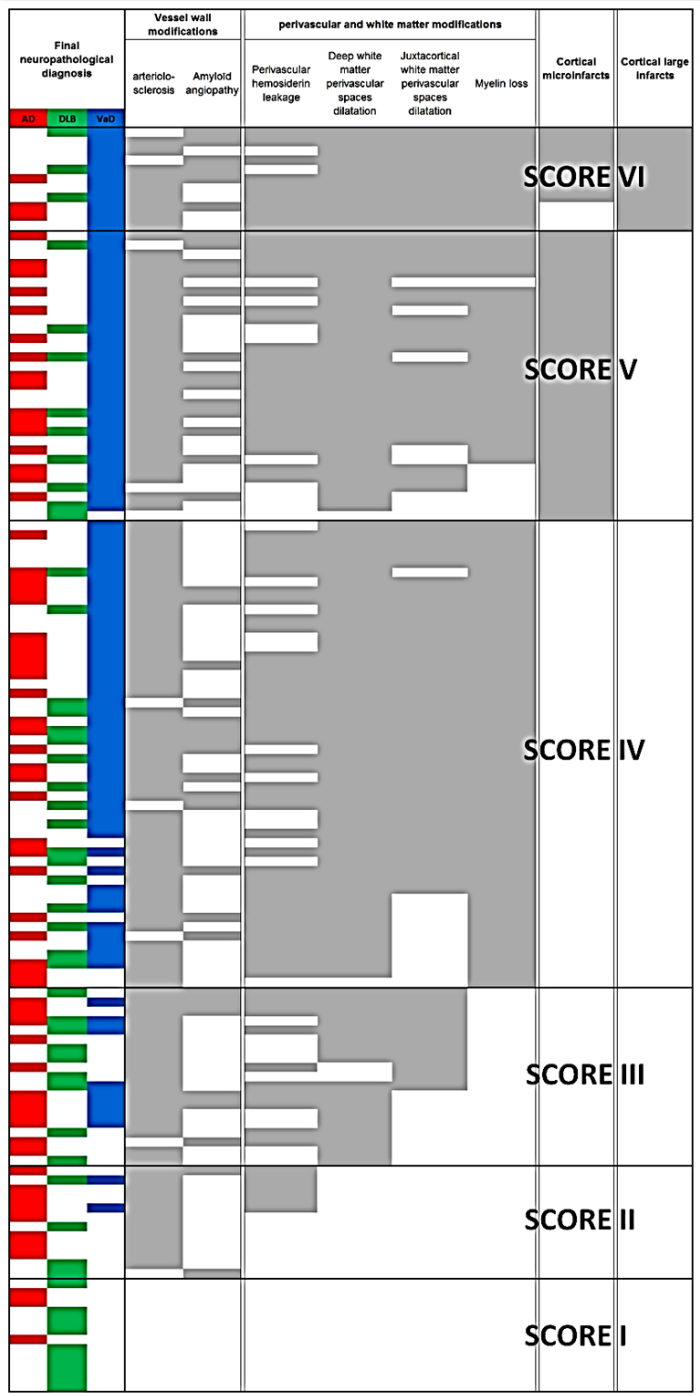
ABSTRACT

Objective: Most pathologic studies indicate that significant vascular changes are found in the majority of elderly persons, either alone or in association with neurodegenerative processes such as Alzheimer disease (AD) or dementia with Lewy bodies (DLB). Cumulative burden of cerebrovascular lesions can explain cognitive decline described as vascular cognitive impairment, but because there is a lack of consensus in the best way to quantify vascular pathology, the relationship between cognitive decline and cerebrovascular disease remains uncertain. We developed a rating scheme for cerebrovascular lesions using postmortem brains from patients with dementia from 2 European tertiary care memory clinics.

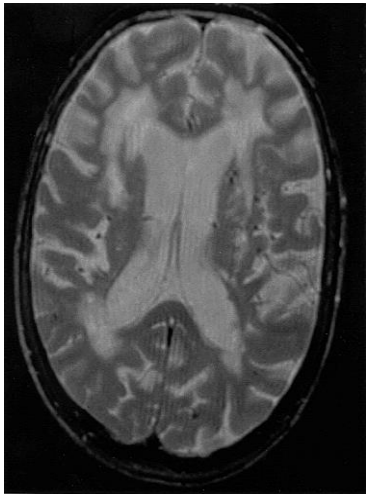
Staging and Natural history of cerebrovascular pathology

Semiquantitative scoring of CVL





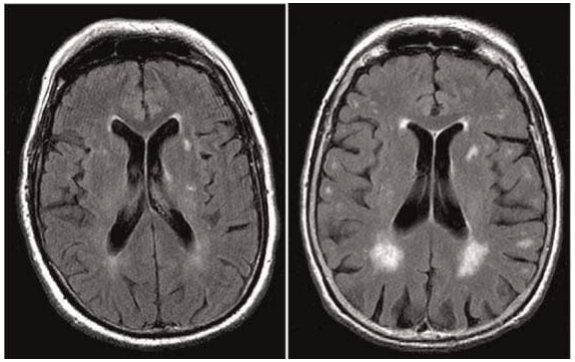
White Matter Changes: do they matter?



Leukoencephalopathy

1) periventricular versus deep WM
2) anterior versus posterior deep WM

WMHs, Stroke and VCI/Dementia



BMJ

RESEARCH

The clinical importance of white matter hyperintensities on brain magnetic resonance imaging: systematic review and meta-analysis

Stéphanie Debette, neurologist and research fellow,[1,2,3] H S Markus, professor of neurology[1]

White matter hyperintensities (WMHs) associated with an increased risk of

- Stroke (HR 3.3)
- Dementia (1.9)
- Death (2.0)

Association of WMH with a faster decline in global cognitive performance, executive function, and processing speed.

WMH indicate an increased risk of CBV events when identified as part of diagnostic investigations

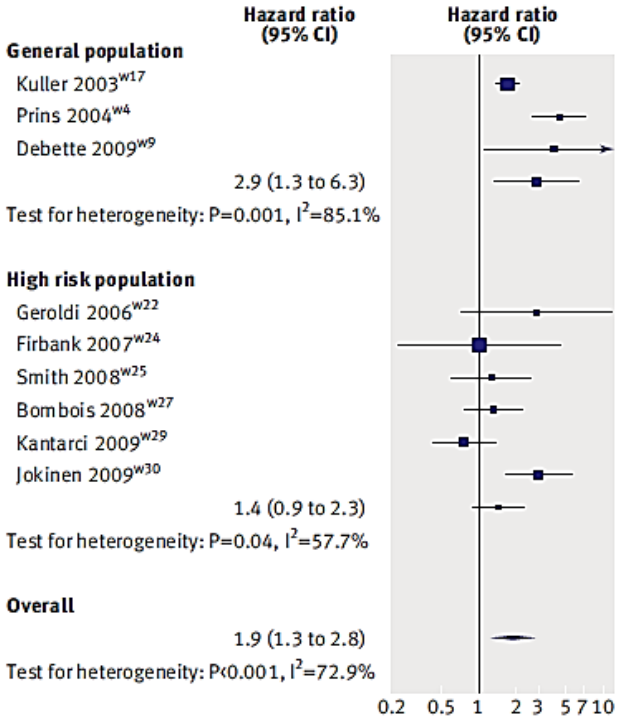
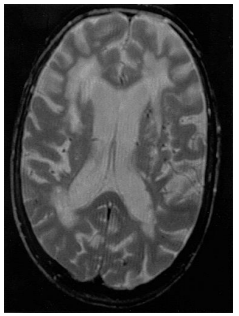
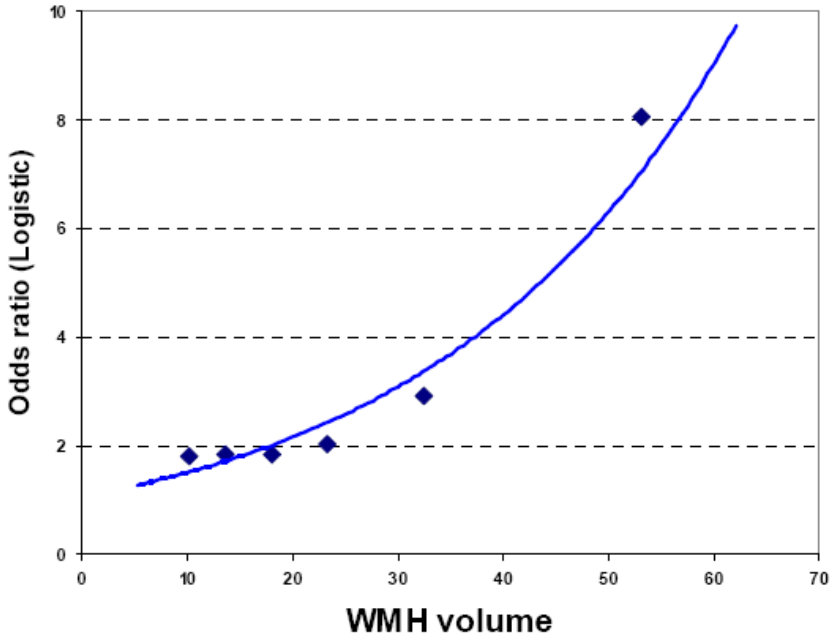


Fig 3| Inverse variance meta-analysis of studies testing association of white matter hyperintensities with incident dementia

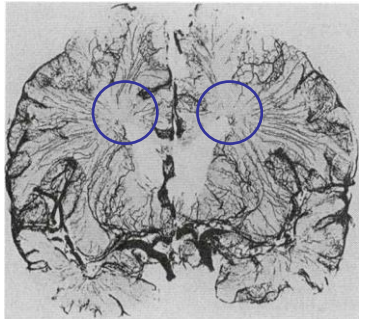
Leukoencephalopathy



WMLs predict functional decline over a 3 yr period in elderly without disability at baseline (LADIS study)



3-year probability of disability transition or death according to baseline WMH volume [volume deciles, with the first 4 taken as reference]

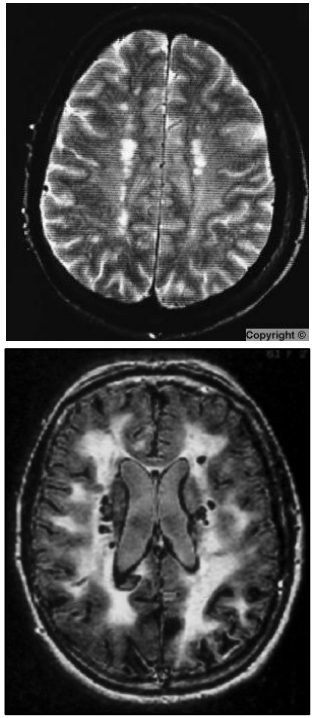


- Annual rates of transition to disability or death were 29.5% in those with severe vs. 10.5% in mild WMLs

Inzitari D et al, 2009

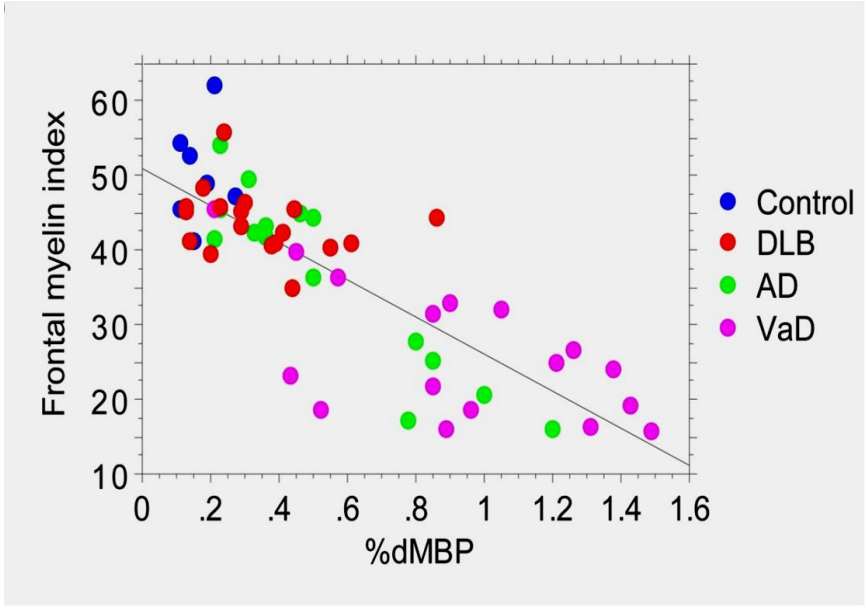
Neuroimaging defined SVD: What are the substrates of dementia?

- Silent Infarcts increase with age and are a risk for dementia (increases risk for AD by >2.5-fold)
- White matter changes (WMHs on T2w MRI) increase risk for dementia (and AD)
- Greater baseline CVD risks or WMHs are associated with cognitive impairment (and AD)
- Vascular risk factors contribute to dementia (even AD) through additive effects but not necessarily independent of amyloid (PiB tracer studies) pathway

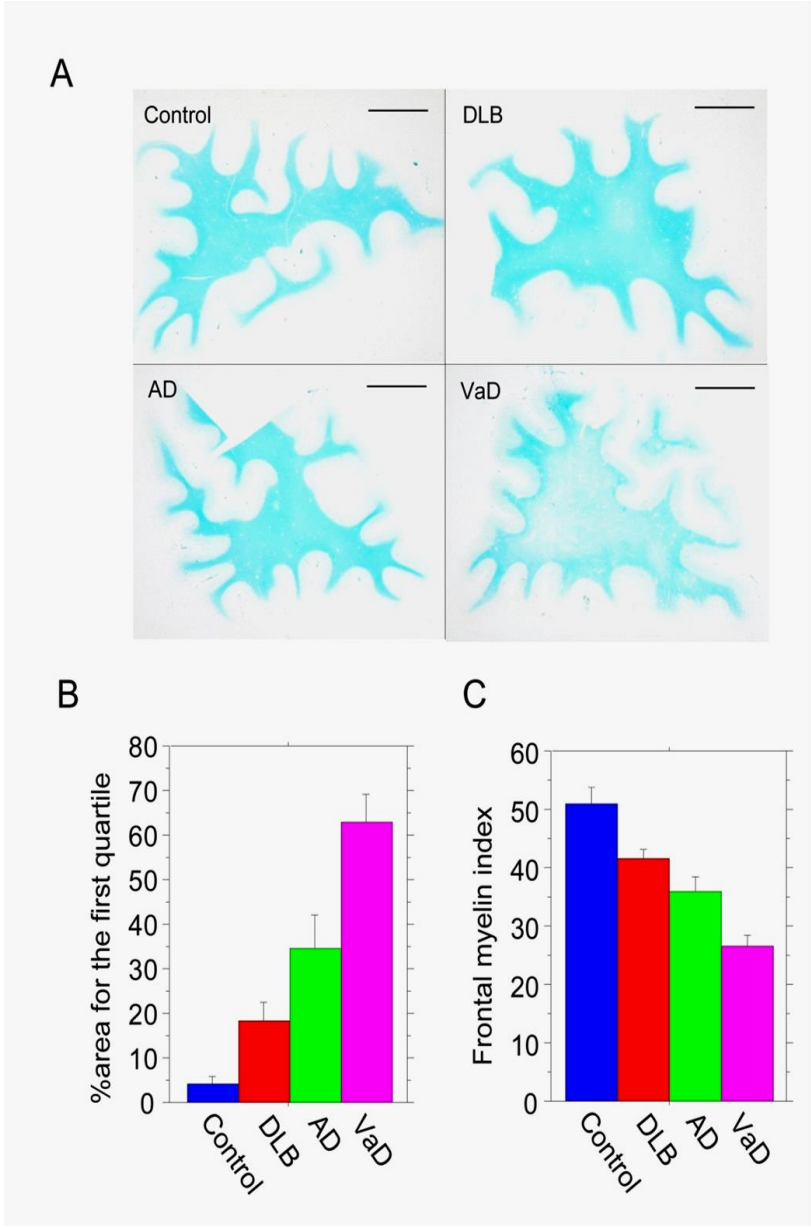


Vermeer SE et al. NEJM 2003; Lee DY et al, Neurology 2009; Debette S and Markus HS BMJ 2010; Lo RY et al, Neurology 2012; Jagust W, Neuron 2012

Severe Frontal WM Myelin Loss in VaD

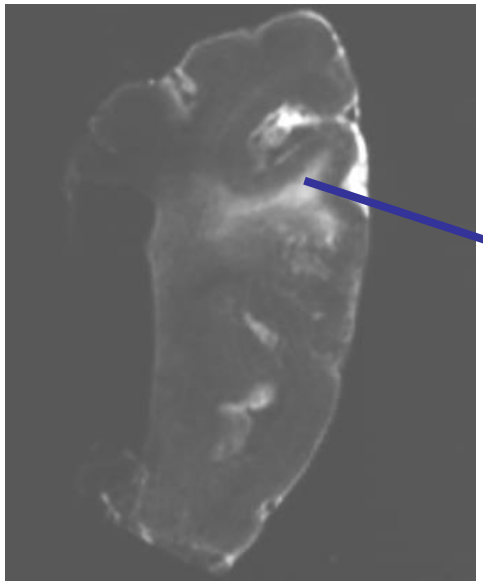


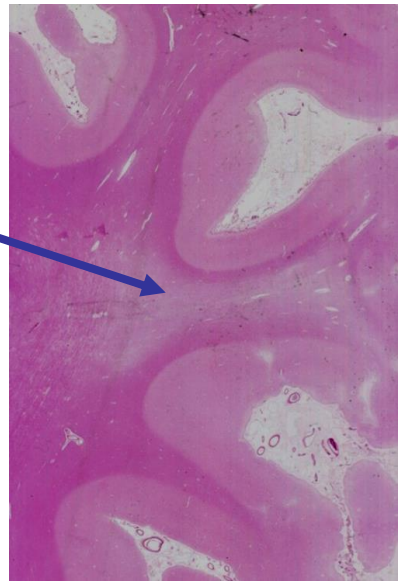
- Degree of myelin loss in related to greater %dMBP
- %dMBP inversely correlated with the mean size of oligodendrocytes
- Greatest degrees of myelin loss in VaD versus other dementias

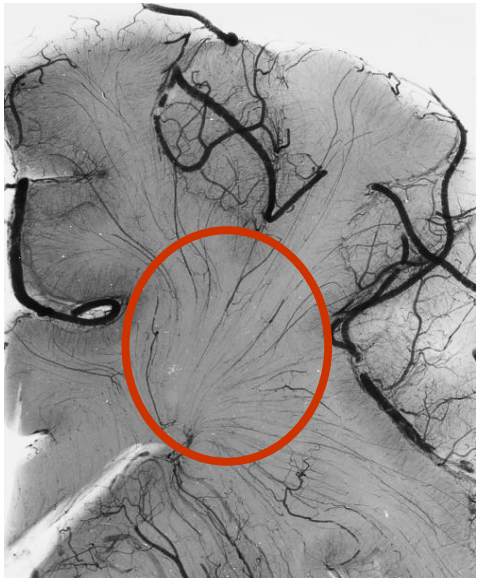


Ihara M et al, 2010

Chronic hypoxic state in deep WM: a common finding

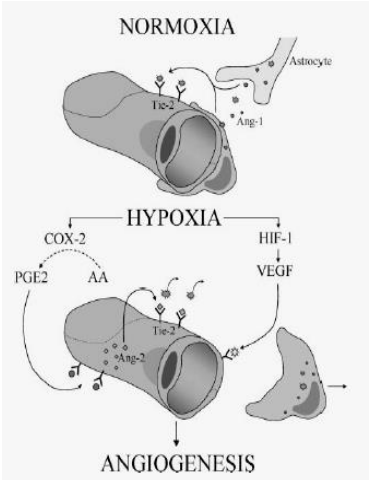






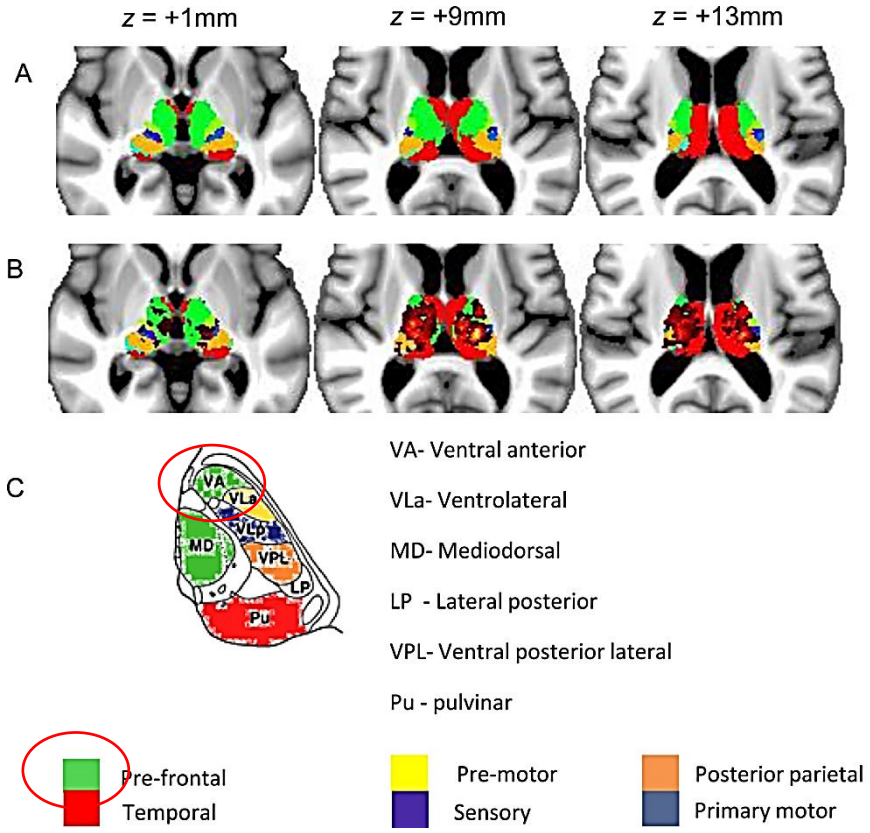
- Long perforators
- End arteries
- Watershead areas

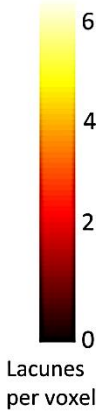
- Dementia related to deep WM rather than periventricular WMLs
- Arteriolar changes restricted to Deep WM; ↑WM rarefaction (lesional) correlated with severity in degree of (cortical) CAA
- ↑ ICAM/Collagen IV ratio for lesional deep WM vs normal WM
- ↑ CD68 +ve cells in lesional deep WM (VCI) vs normal WM
- ↑ HIF1α +ve cells in lesional deep WM vs normal WM



Fernando M et al, 2003; Simpson S et al, 2007; 2008; Ihara M et al 2010

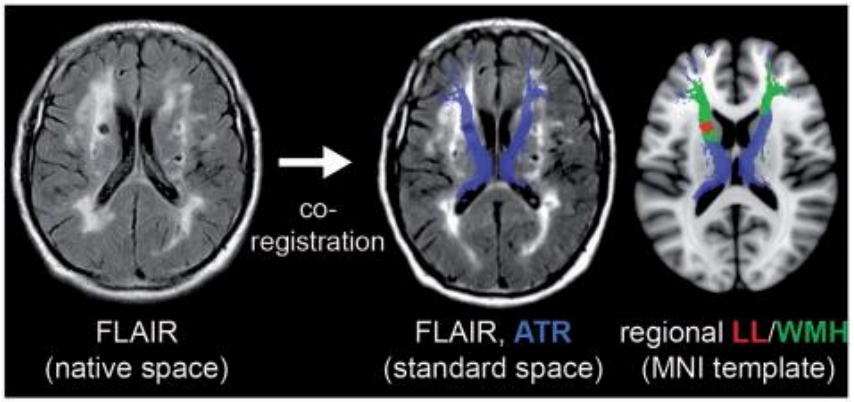
Strategic role of frontal white matter tracts in vascular cognitive impairment





- Most prominent feature: processing speed
- Predominantly affected cognitive domain in lacunar stroke SVD and CADASIL
- Strategic locations included ***anterior parts of thalamus***, the genu and anterior limb of the internal capsule, anterior corona radiata and genu of the corpus callosum
- Interpretation: anterior thalamic radiation as a major anatomical structure impacting on processing speed.
- Strong support for a central role of frontal-subcortical circuits in SVD and VCI

Duering M et al, Brain, 2011; Benjamin et al, 2014



What factors in WM Pathology are important in Elderly Stroke Survivors who develop Dementia?

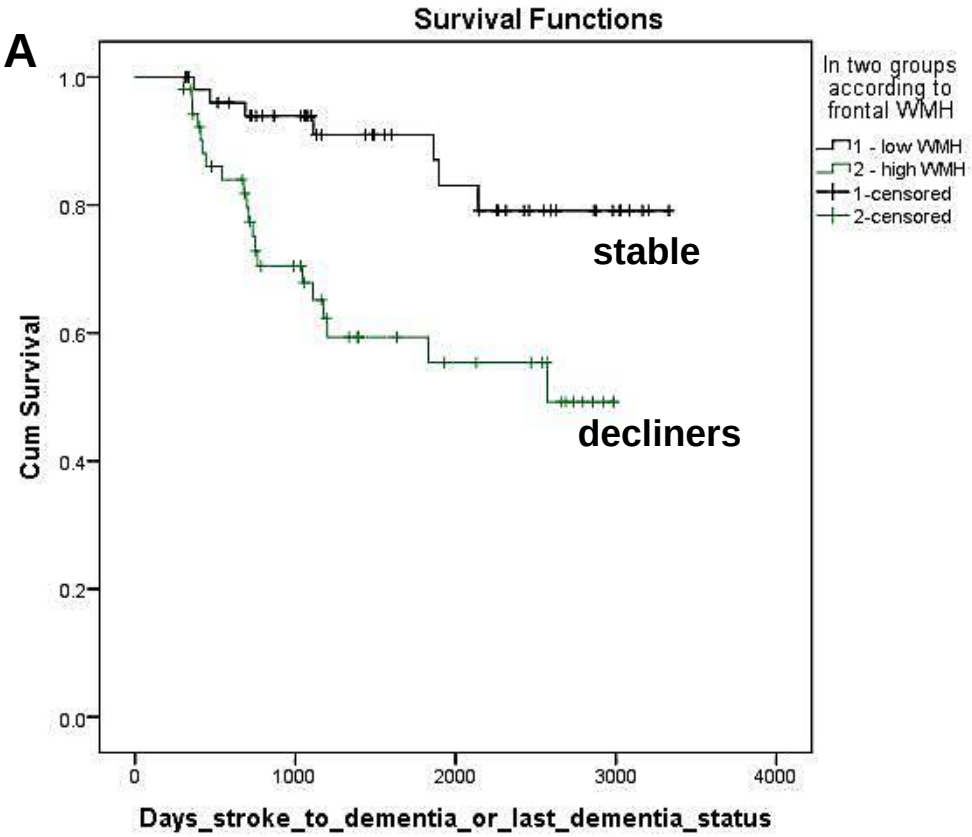
WM Marker	PSND† (Stable)	PSD† (Decliners)	Significance
Leukoaraiosis (WMH on MRI)	+	++	SD↑
Total Vascular pathology score	+++	+++	nsd
Microinfarction	++	+++	SD↑
Myelin Index	++	+++	trend↑
Degenerated MBP	+	++	trend↑
Axons: SMI32/SMI31	++	+++	trend↑
Sclerotic Index / PVS	+++	+++	nsd
Astrocyte degeneration/ BBB damage	++	+++	SD↑
Pericyte degeneration/ Capillary coverage	++	+++	SD↑
Microglial Activation/ Perivscular	++	+++	SD↑

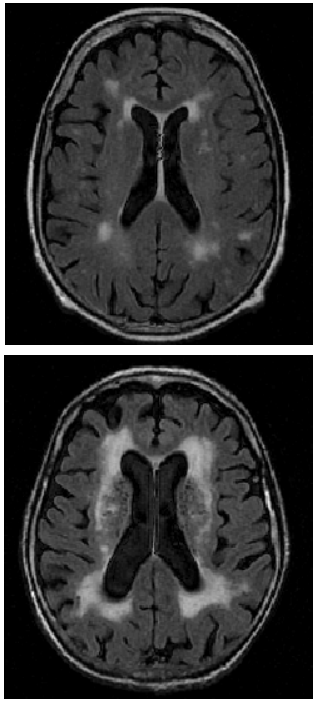
† Mean Braak stage = 2.6 in PSND and PSD

References: Firbank M et al, 2012; Deramecourt V et al, 2012; Ihara M et al, 2010; Allan LM et al, 2012; Foster V et al, 2014; Chen A et al, 2015

Which markers of WM pathology differentiate demented (PSD) and non-demented (PSND) survivors?

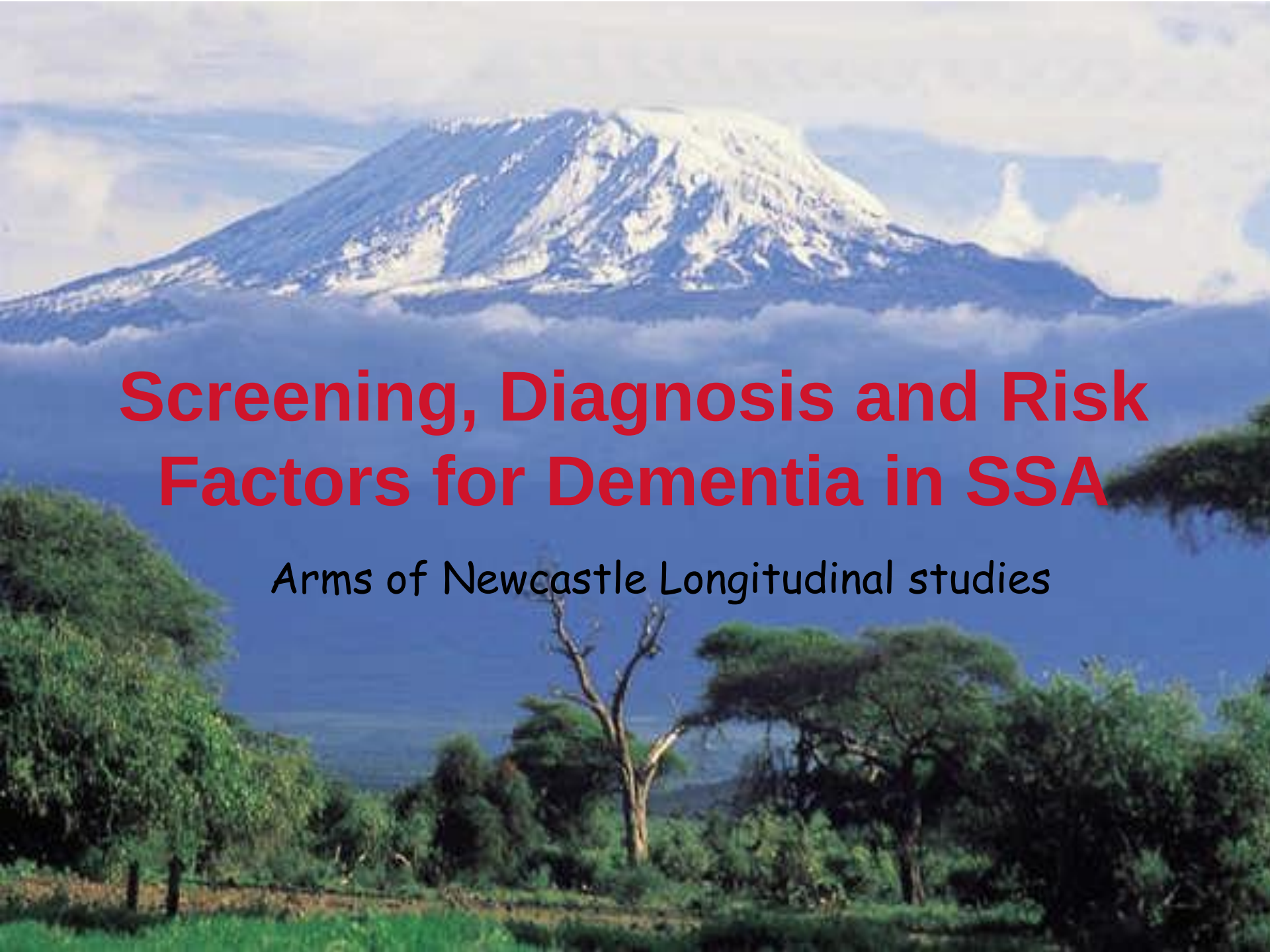
A





MRI T2-FLAIR scans

Frontal WMH volume was an independent predictor of survival to dementia Data analysis: n=106 subjects; Cox multivariate models; p=0.037, HR 95%1.90 (1.04 to 3.48)



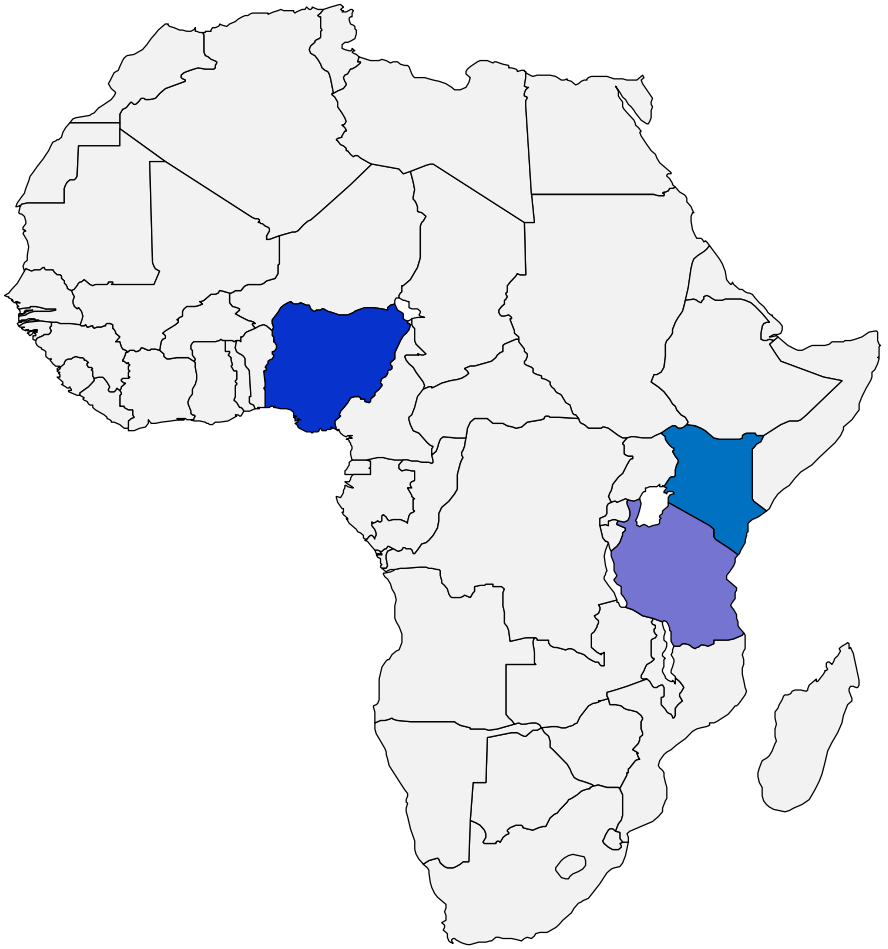
Screening, Diagnosis and Risk Factors for Dementia in SSA

Arms of Newcastle Longitudinal studies

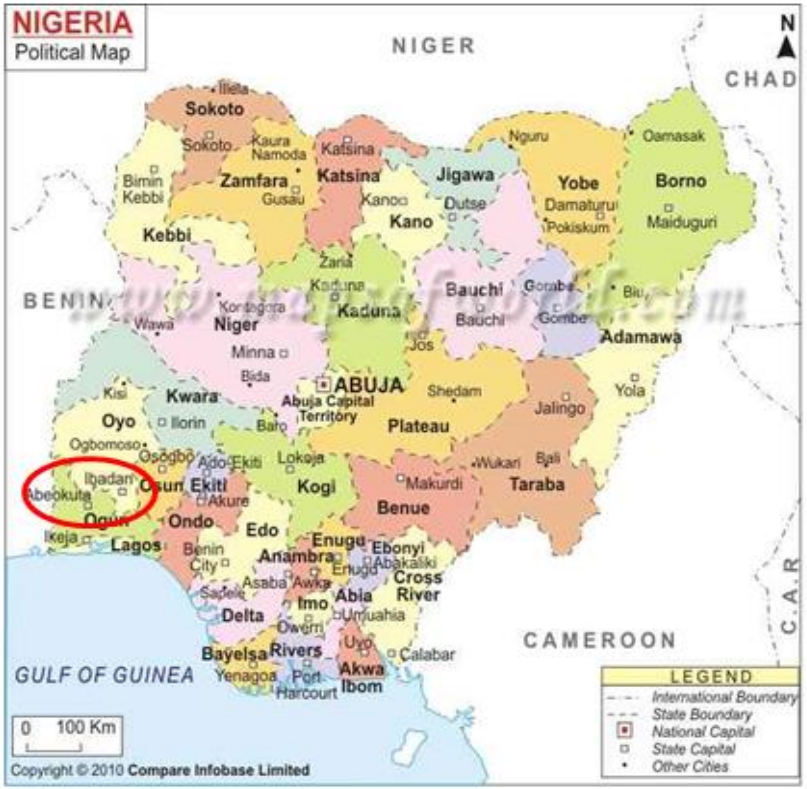
COGFAST

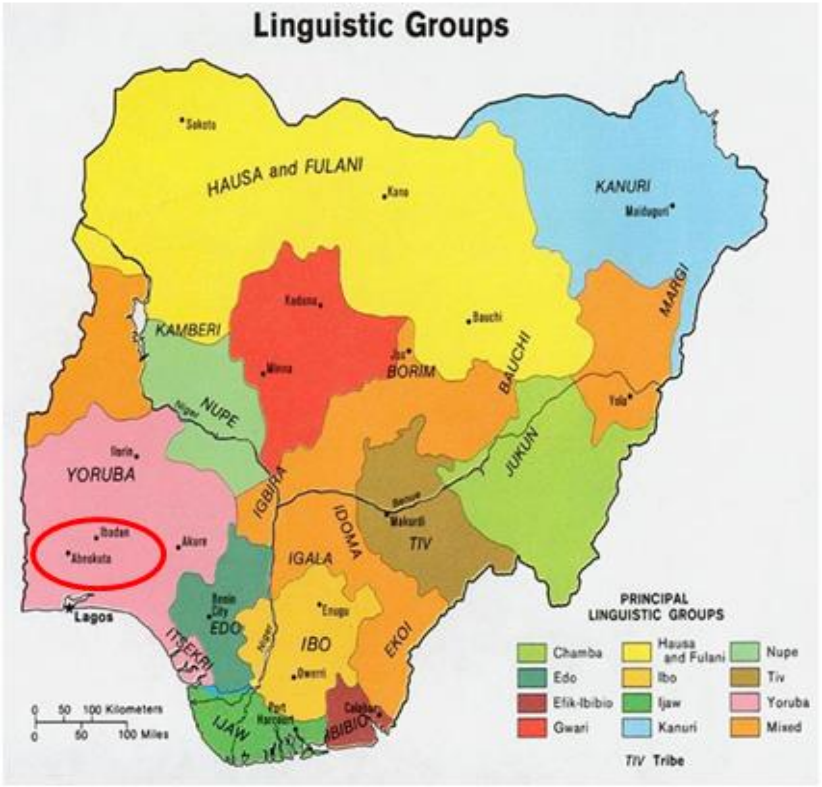
Memory After Stroke Study

COGnitive Function After STroke (COGFAST – Nigeria Study)



Longitudinal study of post-stroke survivors in Africa (Ibadan, Nigeria, Nairobi, Kenya and Hai District Tanzania: PIs R Kalaria, A Ogunniyi, M Owolabi, R Akinyemi, R Walker





Map of Nigeria showing the study area in Southwestern part of the country [A] Political map of Nigeria showing Abeokuta and Ibadan north of Lagos [B] An ethno-linguistic map showing the Yoruba speaking Southwestern region of the country with location of study centres

CogFAST –Nigeria: Vascular Neuropsychological Battery

Cognitive Domain	Test
Executive Function	Category (Animal) Fluency Test
/Activation	
	Phonemic (Letter) Fluency Test
	Verbal Reasoning (Similarities Test)
	Ideational Fluency Test
Language/	Boston Naming Test (2nd version)
Lexical Retrieval	
Memory/ Learning	Word List Test (Learning, Recall,
	Recognition)
	Delayed Recall of Stick Design
Visuospatial/	Stick Design Test
Visuoconstruction	Modified Tokens Test
	(IU Token Test)
General Cognitive	Community Screening Instrument
Functioning	for Dementia (CSID
	Minimental State Examination
	(MMSE)

- Based on the 60 min VCI Harmonization Standards – Neuropsychological Protocol proposed by the NINDS – CSN (Hachinski et al, 2006).
- Multiple test items assessing each cognitive domain were selected in consonance with the recommendations of the Harmonization standards
- Utility of tests in previous cognitive evaluations in environment of study population

Refs: Folstein, 1995; Hall et al, 1993; 2000; Gureje et al., 1995; Blessed et al, 1991; Unverzagt et al., 1999; Ballard et al, 2002; Baiyewu et al., 2005; Akinyemi et al., 2008

CogFast- Nigeria: Stroke and Cognition

Journal of the Neurological Sciences 346 (2014) 241–249

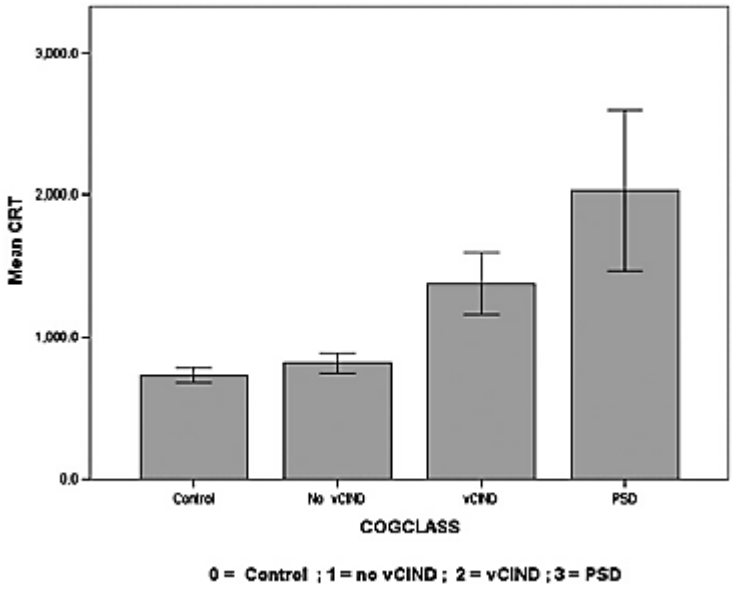
Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Profile and determinants of vascular cognitive impairment in African stroke survivors: The CogFAST Nigeria Study

Rufus O. Akinyemi [a,b,*,1], Louise Allan [b], Mayowa O. Owolabi [c], Joshua O. Akinyemi [d], Godwin Ogbole [e], Akinlolu Ajani [a], Michael Firbank [b], Adesola Ogunniyi [c], Raj N. Kalaria [b,*,1]



pattern of performance on Choice Reaction Time (CRT) in controls and impaired subjects.

- First ever stroke survivors mean age = 61 yrs
- 80% Ischaemic stroke; 41% lacunar stroke
- Median modified Rankin score=2)
- 8.4% demented at baseline and 30% cognitive impairment no dementia (CIND)
- Pre-stroke cognitive decline
- Medial temporal lobe atrophy (MTA) [OR = 2.25 (1.16–4.35)] was independently associated with cognitive dysfunction
- High frequency of early VCI

Akinyemi R et al, 204; 2015

Predictors of Post-stroke VCI - COGFAST Nigeria

Variable	Univariate analysis OR (95%CI)	Multivariate analysis: OR (95%CI)
Baseline Age (years)	**1.06 (1.02 – 1.10)**	**1.05 (1.00 – 1.09)**
Female Gender	**2.27 (1.15 -4.45)**	1.87 (0.80 – 4.40)
< 6 years of education	**4.84 (2.36 – 9.92)**	**5.09 (2.17 – 11.95)**
Hypertension	1.18 (0.30 4.58)	
DM	1.29 (0.59 -2.79)	
Previous stroke	1.38 (0.51 -3.10)	
Smoking	1.253 (0.51 – 3.10)	
Alcohol use	**2.01 (1.01 – 4.00)**	1.19 (0.47 -3.00)
Daily fish intake pre-stroke	**0.42 (0.20 – 0.88)**	**0.37 (0.15 -0.89)**
Moderate to strenuous physical activity pre - stroke	**0.17 (0.04 – 0.84)**	1.00 (0.99 -1.02)
Modified Rankin Score	1. 03 (0.53 – 1.98)	
Barthel Index	0.98 (0.90 -1.06)	
CESD score	1.04 (0.96 – 1.12)	

Significant results are shown in bold (p <0.01)

Factors associated with PS VCI include **older age at baseline, female gender and lower educational attainment**

While pre-stroke moderate- heavy physical activity and **daily fish intake were protective**

Akinyemi R et al, JNS, 2014; BMC Res Notes 2015

Neuroimaging in Nigerian Older Stroke Survivors

Medial temporal lobe atrophy (MTLA) was independently associated with VCI/VaD in PS survivors at 12 months

MTLA correlated significantly with cognitive performance and **white matter hyperintensities (WMH**s) on T2W MRI

Akinyemi et al. BMC Res Notes (2015) 8:625
DOI 10.1186/s13104-015-1552-7

BMC Research Notes

RESEARCH ARTICLE Open Access

Medial temporal lobe atrophy, white matter hyperintensities and cognitive impairment among Nigerian African stroke survivors

Rufus O. Akinyemi[1,2], Michael Firbank[2], Godwin I. Ogbole[3], Louise M. Allan[2], Mayowa O. Owolabi[4], Joshua O. Akinyemi[5], Bolutife P. Yusuf[3], Oluremi Ogunseyinde[3], Adesola Ogunniyi[4†] and Raj N. Kalaria[2*†]

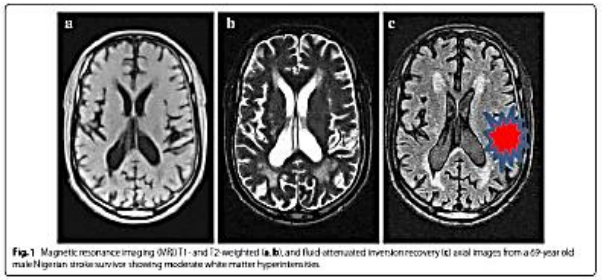


Fig. 1 Magnetic resonance imaging (MRI) T1- and T2-weighted (a, b) and fluid attenuated inversion recovery (c) axial images from a 69-year old male Nigerian stroke survivor showing moderate white matter hyperintensities.

**MTLA vs WMH score showed positive correlation (r =0.461, p = 0.002) supporting a vascular basis for MTLA.

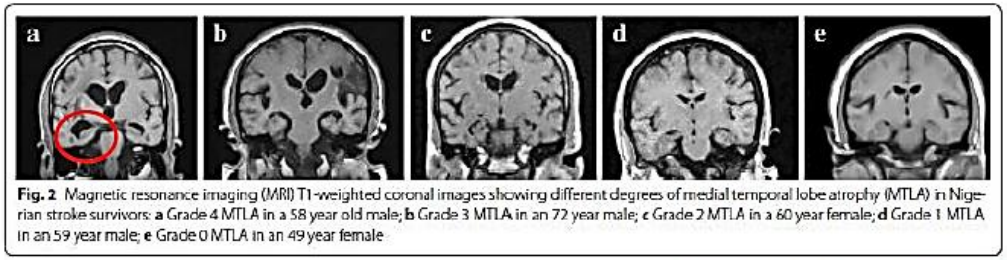


Fig. 2 Magnetic resonance imaging (MRI) T1-weighted coronal images showing different degrees of medial temporal lobe atrophy (MTLA) in Nigerian stroke survivors: **a** Grade 4 MTLA in a 58 year old male; **b** Grade 3 MTLA in an 72 year male; **c** Grade 2 MTLA in a 60 year female; **d** Grade 1 MTLA in an 59 year male; **e** Grade 0 MTLA in an 49 year female

Akinyemi et al, BMC Res Notes. 2015 ;8:625

	Normal vs vCIND			vCIND vs PSD			Normal vs (vCIND + PSD)		
Variable	**OR**	**95%CI**	***p value**	**OR**	**95%CI**	**p value**	**OR**	**95%CI**	***p value**
MTLA rating	2.02	1.05 – 3.87	**0.035**				2.25	1.16 – 4.35	**0.016**
Log _ TBV							0.01	0- 1996.50	0.260

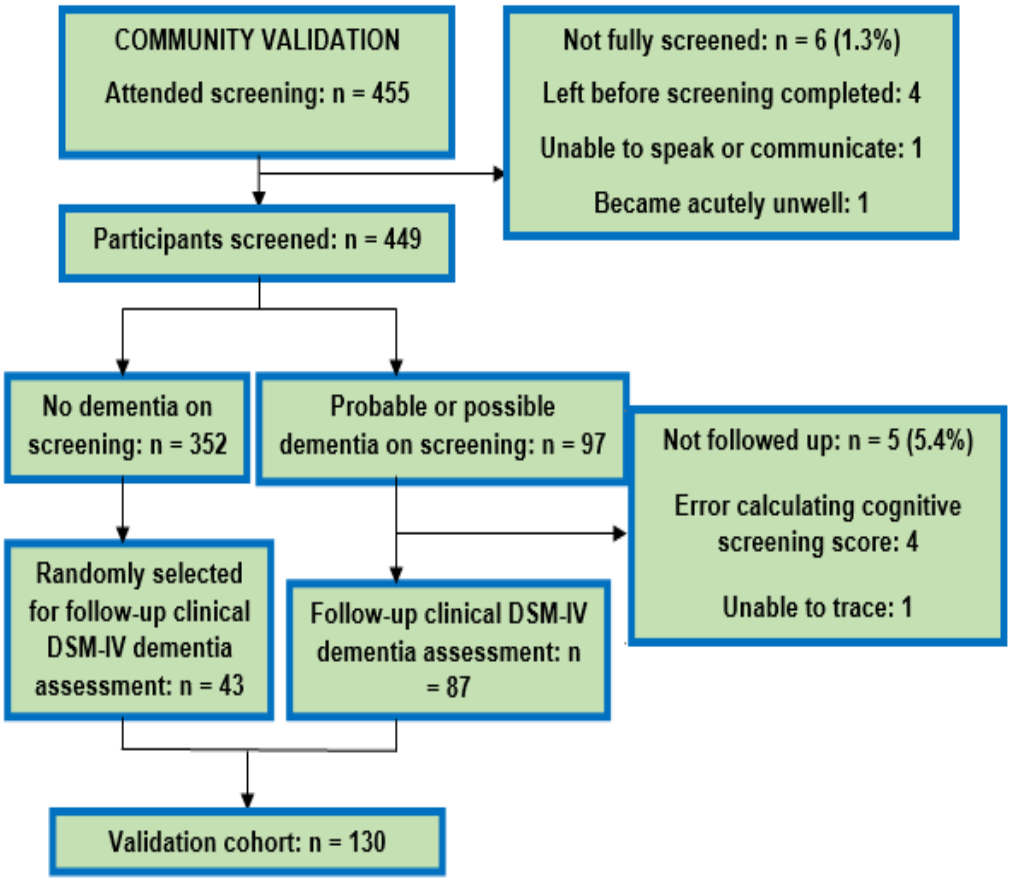
Hypertension and Incident dementia risk

Effect	Odds Ratio	95% CI
Hypertension	1.52	1.01- 2.30
Systolic BP, X 10 mm Hg	1.09	1.03 – 1.16
Diastolic BP, X 10 mm Hg	1.22	1.07 – 1.38
Pulse Pressure, X 10 mm Hg	1.10	1.01 – 1.21

Ogunniyi A et al. Acta Neurol Scand 2011

Screening Cognitve Function and Diagnosis of Dementia in Hai, Tanzania

Community Validation, Hai Dementia screening Study



Cut-off of ≤ 7	
Sensitivity	60.0%
Specificity	84.2%
LR	3.80
Cut-off of ≤ 8	
Sensitivity	88.6%
Specificity	64.2%
AUROC curve	0.846 (95%CI 0.776 - 0.915)
	Educational level no association

Difficulties with cognitive assessment Pilot MMSE used in Hai, 2011

*=missing	Dementia n=17	MCI N=29	Normal cognition N=14
Age (med, IQR)	81.0 (16.50) *=1	85.0 (10.0)	80.00 (14.0)
Female (n, %)	11 (64.71)	19 65.52	11 (78.57)
Ever attended formal school (n, %)	4 (23.53)	10 34.48	7 (50.0)
Years of education (med, IQR)	0.00 (1.00)	0.00 (3.00)	0.50 (4.0)
Self-reported basic literacy (n, %)	4 (23.53)	7 (24.14)	7 (50.0)
Minimally adapted MMSE total score (med, IQR)	12.00 (4.50)	15.0 (5.0)	19.50 (3.75)
MMSE total disregarding literacy and numeracy based items /22	12.00 (4.50)	14.0 (4.0)	19.00 (2.5)

Screening and diagnosis of Dementia in LMICs

10/66 Dementia Research Group

THE LANCET
Volume 361, Issue 9361, 15 March 2003, Pages 909–917

Articles

Dementia diagnosis in developing countries: a cross-cultural validation study *

Prof Martin Prince, MD[a], Daisy Acosta, MD[b], Prof Helen Chiu, FRCPsych[c], Marcia Scazufca, PhD[d], Mathew Varghese, MD[e], for the 10/66 Dementia Research Group

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[b] Department of Psychiatry, Universidad Nacional Pedro Henriqueuz Ureña, Santo Domingo, Dominican Republic
[c] Department of Psychiatry, The Chinese University of Hong Kong, Shatin, Hong Kong
[d] Institute of Psychiatry, University of Sao Paulo, Sao Paulo, Brazil
[e] National Institute of Mental Health and Neurosciences, Bangalore, India

Available online 14 March 2003

Epidemiological Studies

Population-based epidemiological studies (prevalence phase) in eight Latin American countries (Cuba, Brazil, Dominican Republic, Venezuela, Peru, Mexico, Argentina and Puerto Rico), India, China, Nigeria and South Africa.

A three year follow up of all prevalence phase participants (incidence phase) in Cuba, Dominican Republic, Venezuela, Peru, Mexico, Argentina and China, with a more limited follow-up in India.

Screening tools for dementia designed for use in SSA?

- **MMSE is still the most widely used test – but almost useless in those with low education**

Test	Questions	Sensitivity	AUROC
CSI-D	**30 + 30**	**92**	**0.9191 (90–92)**
TEST OF SENEGAL	**39**		**0.967**

- CSI-D validated in >2000 older people in LMICs (but only 20 from SSA)
- False positive rate still 25% in low edu.
- Both tests take over 30-40 min to complete – too long for screening

The IDEA six-item cognitive screen

- Developed for low-literacy settings in sub-Saharan Africa
- Takes 5-10 minutes to administer
- Validated for dementia screening in community and geriatric OPD (Tanzania)
- Validated for major cognitive impairment (dementia or delirium) in older inpatients (Tanzania, Nigeria and Zambia)

The IDEA study brief screening test

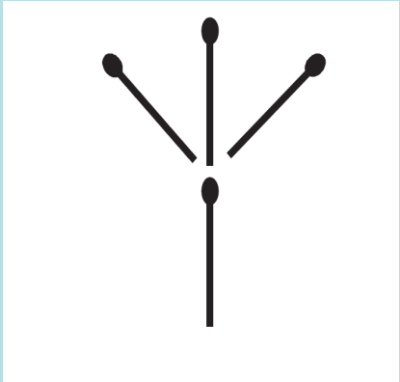
- 6 item screening test
- Designed for non specialists and low literacy population
- Designed to cover all lobes of the brain
- Most discriminating questions from CSI-D (used in Hai dementia prevalence study)
- CERAD 10 word learning list
- Baiyewu matchstick test

	First attempt	Second attempt	Third attempt
Siagi			
Mkono			
Barua			
Mfalme			
Tikiti			
Nyasi			
Kona			
Jiwe			
Kitabu			
Fimbo			

IDEA Screening tool -2

I will tell you the name of something and I want you to describe what it is. What is a bridge? (correct answer: something that goes across a river, canyon or road)	0 if incorrect 2 if correct	Score:____/2
I want you to name as many different animals as you can in one minute.	Number of animals named:____ 0 for 0-3 animals named 1 for 4-7 animals named 2 for 8 or more animals	Score: ____/2
Who is the chief/head/leader of this village?	0 if incorrect 1 if correct	Score:____/1
What day of the week is it?	0 if incorrect 2 if correct	Score:____/2
Can you tell me any of the words you learned earlier?	1 one word 2 two words 3 three words 4 four words 5 5 or more words	Score:____/5

IDEA screening tool - 3

6	**Can you make the design shown below using these four matchsticks. I will show you once and then you have to copy exactly)** **.** 	**Score 1 for each part of the design that is performed correctly** **1 Middle two matchstick heads pointing same way** **1 Outside two matchsticks pointing at an angle** **1 Matchstick heads are orientated correctly**	**Totalpoints:__ /3**
			Total Score: ____/15

Comparison with other cognitive screening tools commonly used in high income countries

TEST	Sensitivity	Specificity	Area under ROC
MMSE – specialist clinic (meta-analysis 34 studies)	79.8	81.3	
MMSE - mixed hospital (meta-analysis)	71.1	96.6	
RUDAS	89	98	0.95
Addenbrookes (meta-analysis 5 studies	96.7	77.4	
Six-item screener (for ER)	63	81	0.77
IDEA inpatients Tanzania	90.9	87.5	0.917
IDEA outpatients Tanzania > 8	84.6	89.1	0.919
IDEA inpatients Nigeria	100	96.3	0.990

Instrumental Activities of Daily Living in high-income countries

Instrumental Activities of Daily Living (IADL)

Instructions: Circle the scoring point for the statement that most closely corresponds to the patient's current functional ability for each task. The examiner should complete the scale based on information about the patient from the patient him-/herself, informants (such as the patient's family member or other caregiver), and recent records.

A. Ability to use telephone	Score
1. Operates telephone on own initiative; looks up and dials numbers, etc.	1
2. Dials a few well-known numbers	1
3. Answers telephone but does not dial	1
4. Does not use telephone at all	0

B. Shopping	
1. Takes care of all shopping needs independently	1
2. Shops independently for small purchases	0
3. Needs to be accompanied on any shopping trip	0
4. Completely unable to shop	0

C. Food preparation	
1. Plans, prepares, and serves adequate meals independently	1
2. Prepares adequate meals if supplied with ingredients	0
3. Heats and serves prepared meals, or prepares meals but does not maintain adequate diet	0
4. Needs to have meals prepared and served	0

D. Housekeeping	
1. Maintains house alone or with occasional assistance (e.g., "heavy work domestic help")	1
2. Performs light daily tasks such as dishwashing, bed making	1
3. Performs light daily tasks but cannot maintain acceptable level of cleanliness	1
4. Needs help with all home maintenance tasks	1
5. Does not participate in any housekeeping tasks	0

E. Laundry	Score
1. Does personal laundry completely	1
2. Launders small items; rinses stockings, etc.	1
3. All laundry must be done by others	0

F. Mode of transportation	
1. Travels independently on public transportation or drives own car	1
2. Arranges own travel via taxi, but does not otherwise use public transportation	1
3. Travels on public transportation when assisted or accompanied by another	1
4. Travel limited to taxi or automobile with assistance of another	0
5. Does not travel at all	0

G. Responsibility for own medications	
1. Is responsible for taking medication in correct dosages at correct time	1
2. Takes responsibility if medication is prepared in advance in separate dosages	0
3. Is not capable of dispensing own medication	0

H. Ability to handle finances	
1. Manages financial matters independently (budgets, writes checks, pays rent and bills, goes to bank), collects and keeps track of income	1
2. Manages day-to-day purchases, but needs help with banking, major purchases, etc.	1
3. Incapable of handling money	0

(Lawton & Brody, 1969)

Scoring: The patient receives a score of 1 for each item labeled A – H if his or her competence is rated at some minimal level or higher. Add the total points circled for A – H. The total score may range from 0 – 8. A lower score indicates a higher level of dependence.

Sources:

- Cromwell DA, Eagar K, Poulos RG. The performance of instrumental activities of daily living scale in screening for cognitive impairment in elderly community residents. *J Clin Epidemiol.* 2003;56(2):131-137.
- Lawton MP. The functional assessment of elderly people. *J Am Geriatr Soc.* 1971;19(6):465-481.
- Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. *Gerontologist.* 1969;9(3):179-186.
- Polisher Research Institute. Instrumental Activities of Daily Living Scale (IADL). Available at: http://www.abramsoncenter.org/PRI/documents/IADL.pdf. Accessed February 15, 2005.

Instrumental Activities of daily living (IADL) Scale

- 1. **Wanatoa Historia**/They give histories of the family, their life, past events
- 2. **Wana suluhisha**/They settle conflicts
- 3. **Wanasaidia shughuli ndogo ndog**o/They assist in small works in the home
- 4. **Wanatoa ushauri**/They give advice
- 5. **Wanadumisha na kufundisha mila/unyago**/They teach traditions of society
- 6. **Ni walinzi wa nyumban**i/They watch over the house when others are out.
- 7. **Wanatunza wajukuu/**they look after the grandchildren
- 8. **Wanatoa ushawishi**/Persuasion, or changing people's ideas for the better.
- 9. **Wanasaidia katika maswala mazito kama sherehe**/They preside over feasts and ceremonies
- 10. **Wanapangia watu majukumu**/Delegation of responsibilities to others.
- 11. **Wanasimamia haki**/They ensure fairness.

Results of combined screening, Hai Dementia screening programme

Assessment	Auroc
IDEA 6 item screen, used alone	0.846 (0.776-0.915)
IADL –SSA scale, used alone	0.896 (0.842-0.951)
IDEA 6 item screen and IADL-SSA used together	0.937 (0.896-0.979)

- Conclusions
  - The IDEA brief dementia screening tool performed well in hospital inpatient, outpatient and community settings
  - This screening test should prove useful in screening for dementia in SSA
  - Less educationally biased than existing tools
  - Performance in the community was improved by addition of a functional assessment tool
  - Further testing in of this system of dementia screening in other low-resource and community settings is required

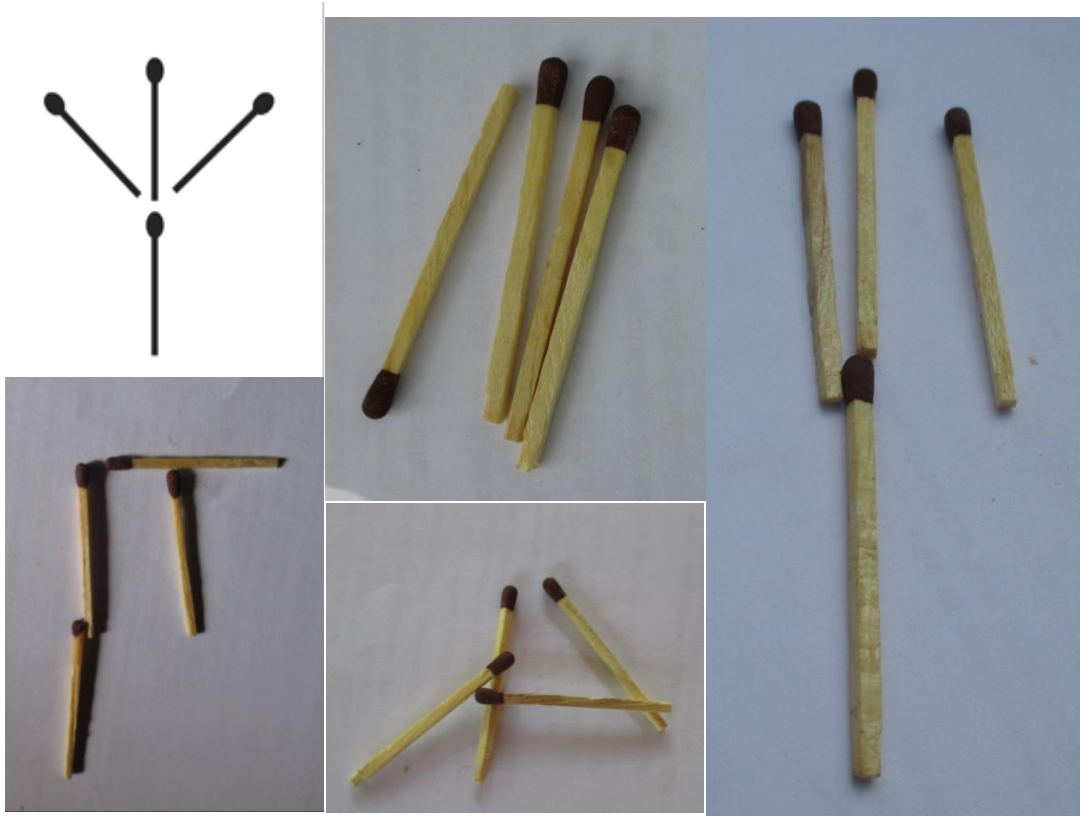
IDEA Study Screening Tools

Matchsticks (Orientation) Test

(Baiyewu et al 2003)

Subject asked to make the design shown above using four matchsticks. He/She is shown once and then they have **to** copy exactly

Score 1 for each part of the design that is performed correctly



2010 Dementia Prevalence in Hai

- Six villages -Total population 34,078
- 1260 eligible >70 yr on census (56% female)
- 1198 screened -184 Probable dementia, 108 possible dementia and rest no dementia
- 78 cases (22 male) ; DSM-IV
- Age-adjusted prevalence of dementia was 6.4% (95% CI: 4.9-7.9)
- Age-adjusted “10/66 dementia” prevalence 21.6% (95% CI 17.5-25.7%)
- Dementia Subtypes: 48.7% AD; 41.0% VaD; prevalence 3.9% AD and 2.9% VaD
- Vascular Risk Factors: *Diabetes; Cholesterol and Hypertension*

Longdon AR et al, 2013

Treatment of VaD/PSD

- There is no known treatment
- Medications to treat symptoms
  - Depression
  - Agitation
- Cholinesterase Inhibitors – no good evidence
- Behavioral strategies

- Potential Agents: several e.g. Cilostazol
  (PDE Inhibition)

Risk factors for stroke

Risk factor	Ischaemic Injury	Intracerebral haemorrhage	Subarachnoid haemorrhage
Greater age	++	++	+
Hypertension	++	++	+
Ischaemic Heart Disease	++	0	0
Atrial fibrillation	++	0	0
Diabetes mellitus	++	0	0
Peripheral Vascular Disease	++	0	0
Raised haematocrit	+	0	0
High cholesterol	+	0	0
Low cholesterol	0	+	0
High plasma fibrinogen	+	0	0
Smoking	++	+	++
Alcohol	–	++	+
Obesity	+	+	?
Transient ischaemic attack	++	0	0

Hypertension

- Main modifiable risk factor for stroke
- Stroke risk doubles with each 7.5mmHg increase in usual diastolic BP[1]
- Similar, and probably stronger, relationship with systolic BP
- Treatment of hypertension reduces stroke risk[2]- an average BP reduction of 8.5mmHg results in a 42% reduction in stroke incidence

*1) MacMahon et al. 1990 Lancet **335** 765-774*

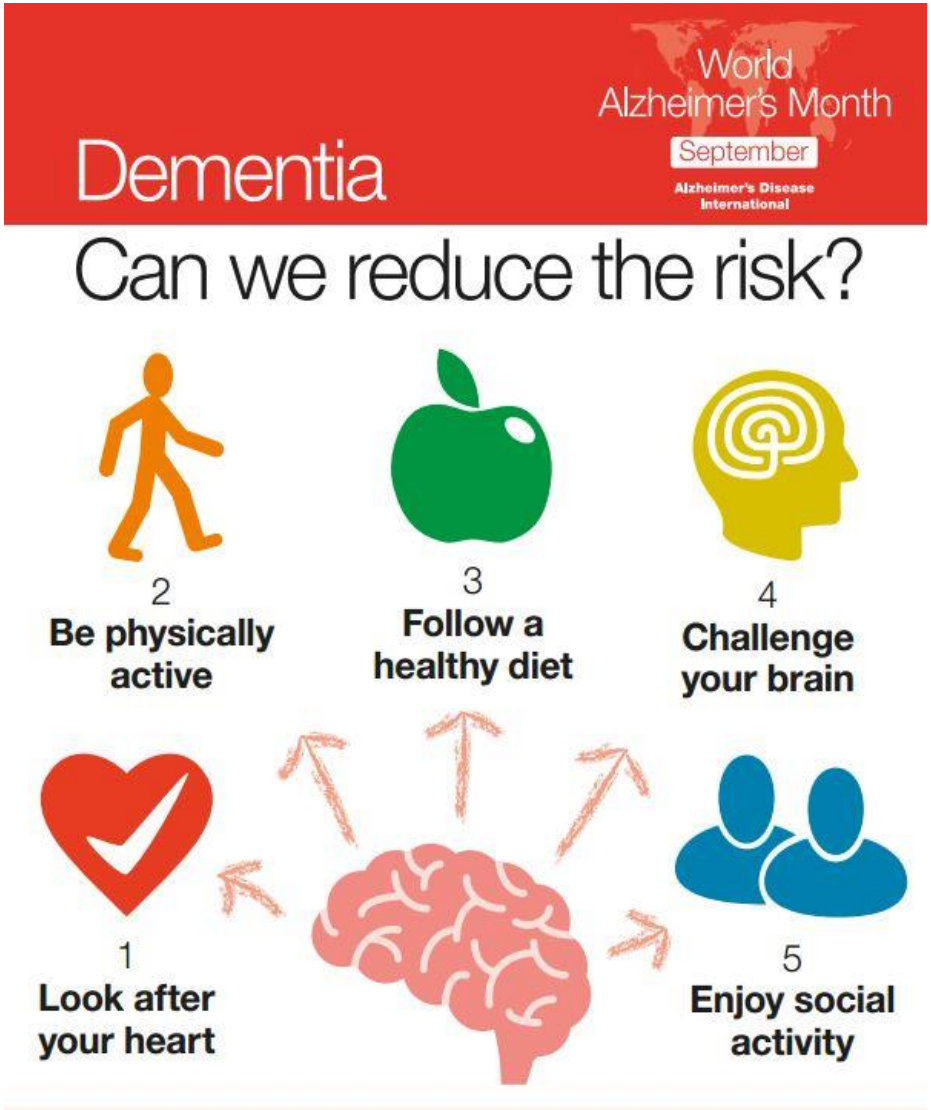
*2) Collins et al. 1990 Lancet **335** 827-838*

Hypertension management

- Population or opportunistic screening
- Three separate blood pressure measurements
- Non-pharmacological treatment, e.g. low salt diet, weight loss, exercise
- Drug treatment - costs, monitoring, compliance - high default rates

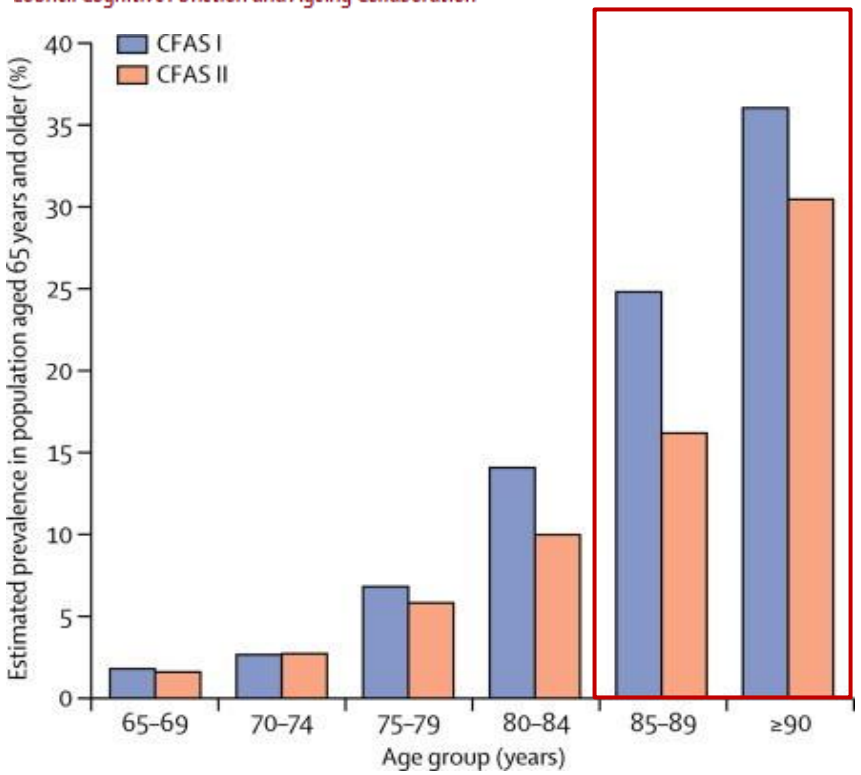
Advice for Patients and Carers

- Treatment of VRFs is likely to reduce risk of both VaD and AD
- Cholinesterase inhibitors may help DLB/AD and mixed VaD/AD but only if supervision/follow up available
- Cognitive stimulation therapy (psychosocial treatment likely to be beneficial (trialed in Tanzania and Nigeria) but not widely available
- Avoid antipsychotics if possible (stroke and mortality risk in dementia – especially in DLB)
- Carer support and assessment of psychiatric symptoms/difficulties such as refusing to eat usually most distressing for carers



A two-decade comparison of prevalence of dementia in individuals aged 65 years and older from three geographical areas of England: results of the Cognitive Function and Ageing Study I and II

Fiona E Matthews, Antony Arthur, Linda E Barnes, John Bond, Carol Jagger, Louise Robinson, Carol Brayne, on behalf of the Medical Research Council Cognitive Function and Ageing Collaboration



Dementia prevalence can be modified by societal changes…..many factors increase dementia prevalence at specific ages (e.g. those associated with diabetes, survival after stroke, and vascular incidents),

Factors, which could decrease prevalence, such as improved prevention of vascular morbidity, higher levels of education, seem to have had a greater effect

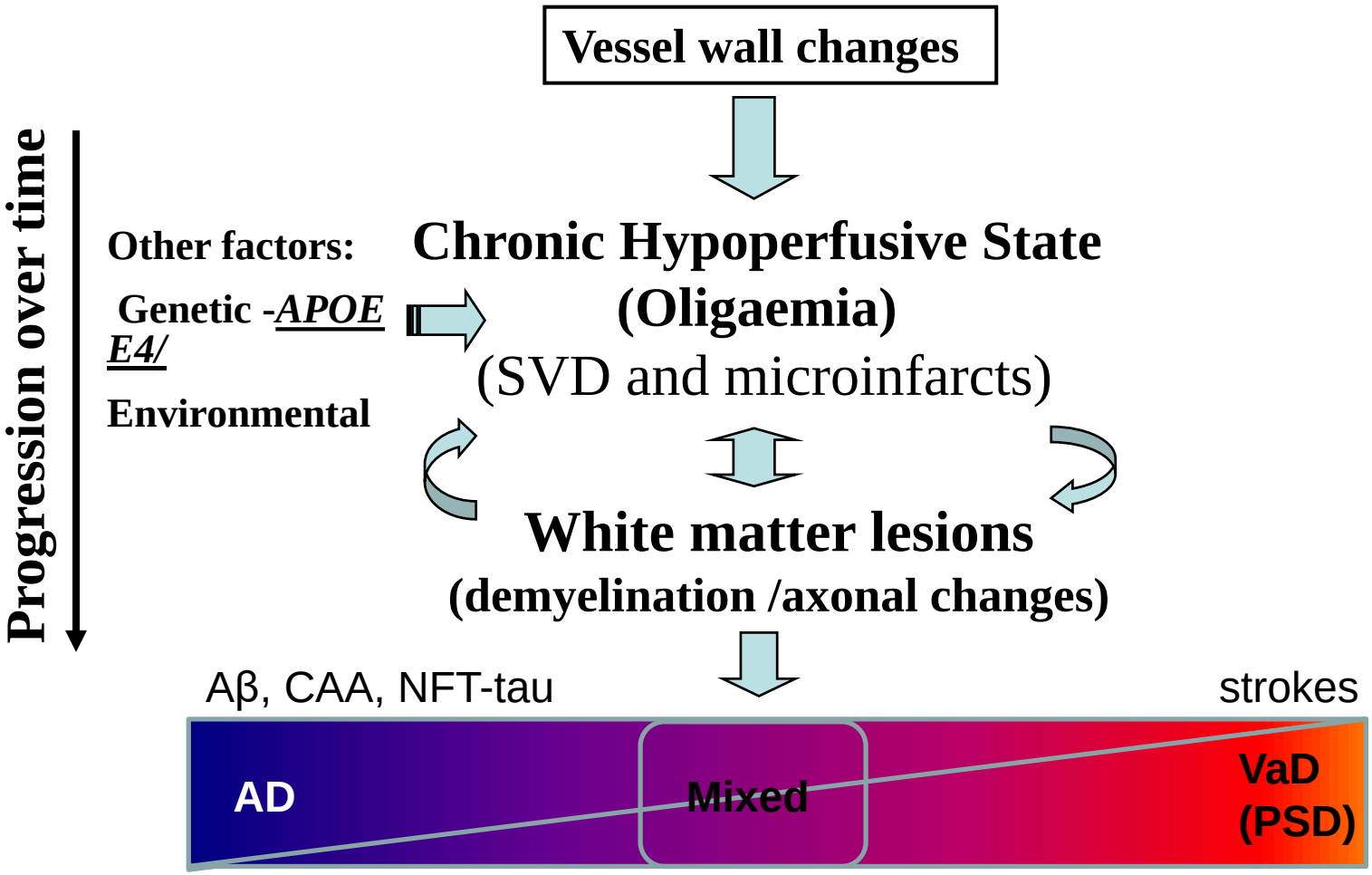
Matthews FE, Arthur A, Barnes LE, MRC CFA S Collaboration. *Lancet* 2013; 382: 1405-1412.

"CFAS results suggest that prevention is possible and that we can have agency in this most complex of disorders." Sube Banerjee, Editorial Lancet, 2013

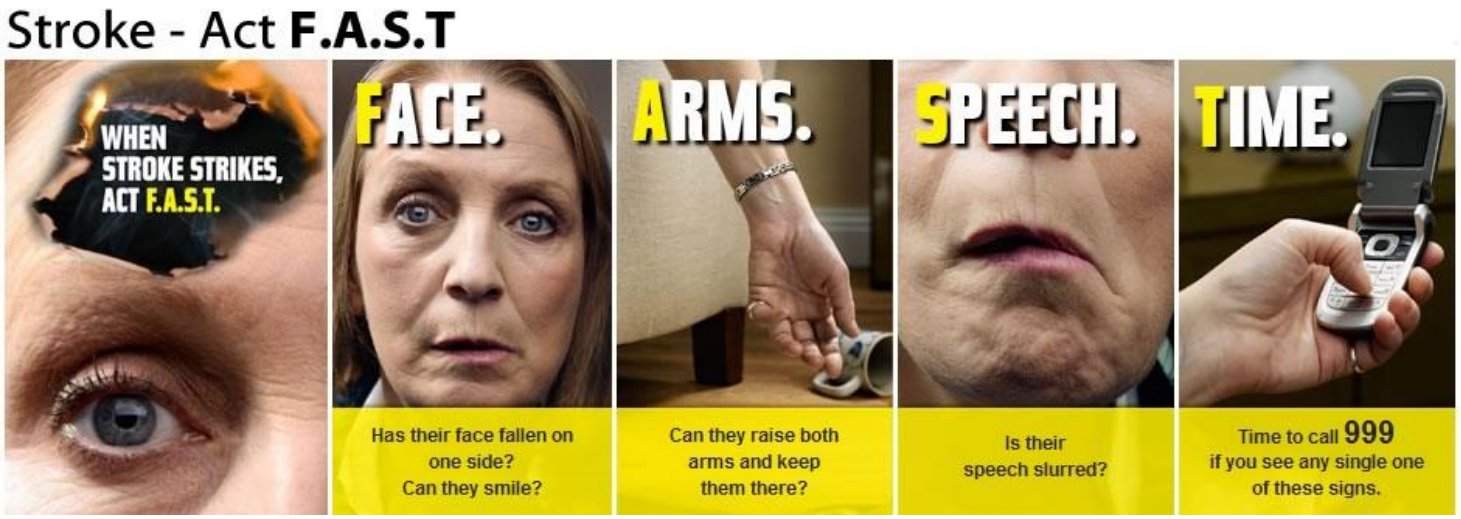
Vascular Factors and Neurodegeneration

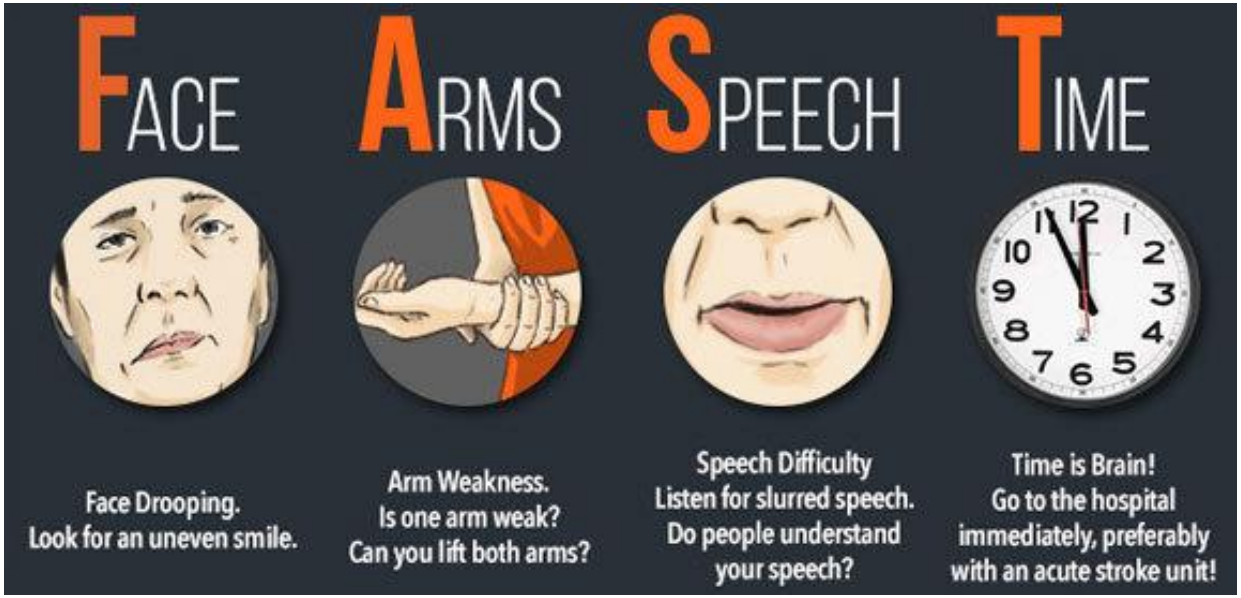
Vascular disease risk factors

Stroke, hypertension, diabetes, dyslipidemia, obesity, atherosclerosis,



Stroke: Time is Brain





Rufus Akinyemi et al, (2005): Dementing disorders in west Africa

Vascular Dementia in Africa

Knowledge and perception of stroke amongst hospital workers in an African community

Rufus O Akinyemi, OS Ogah, RF Ogundipe, OA Oyesola, AA Oyadoke, MO Ogunlan, FM Otubogun, TF. Odeyink, BS Alabi, JO Akinyemi, JK Osinfade & Raj N Kalaria *Eur J Neurology*, 2009

"This study demonstrates gaps in the knowledge of hospital workers about stroke, and treatment choice is influenced by cultural and religious beliefs"

"Health education is still important, even, amongst health workers and stroke awareness campaigns may need to involve faith-based organizations."

And Finally…

The Learning Objectives?

Summary: Post-stroke Cognitive Impairment and Dementia

- In tandem with ageing, stroke and dementia increased in LMICs
- Vascular risk factors associated with Dementia and Neurodegeneration; ***Hypertension is foremost in most studies; control VRFs***
- **Neuropsychometric assessement: MMSE, MoCA, CSI-D, IDEA**
- ~30% Stroke survivors develop dementia (PSD): ~75% in form of VaD; similar trends in SSA; in SSA VaD prevalence is 2-3%
- Demographic transition suggests changing dementia trends in SSA: higher estimates of VCI and VaD than 10 years ago

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Asante Sana!

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