Novel brain imaging and functional connectivity changes associated with cerebrovascular disease and cognition

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Largest increases in dementia burden will be in Asia.

How can we prevent cognitive impairment and dementia?
Memory Aging & Cognition Centre (MACC)

• 4 Themes focusing on “Asian” (actually global) phenotype of dementia & cognitive impairment due to neurodegeneration and cerebrovascular disease

• Collaboration of NUHS, NUS, A*STAR and
  – other institutions in Singapore
    • St Luke’s, SERI, Duke-NUS, NNI, NTU
  – and internationally
    • King’s London, Oxford, UCLA, Utrecht, Rotterdam, Melbourne
Memory Aging & Cognition Centre

• **Biomarker Discovery & Mechanisms of Disease**
  – Mitchell Lai, Peter Wong, Sze Siu Kwan

• **Neuroimaging Theme**
  – MRI : Helen Zhou, H Vroomans
  – Retinal : Wong Tien Yin, Carol Cheung
  – PET : Anthonin Reilhac, Mary Stephenson

• **Clinical Theme**
  – Christopher Chen, NV Ramani

• **Epidemiology Theme**
  – NV Ramani, CY Cheng, TY Wong

• Funded by the NMRC 2010-13 (Centre Grant) and
  • renewed for 2013-17 (NUHS Centre Grant)
  • and 2017-2022 (NUHS Centre Grant)
Memory Aging &
Cognition Centre,
NUHS

NUHS Centre for
Translational Medicine
MACC Laboratories and
Neuroimaging (PET)

NUHS Medical Centre
MACC Clinical Research &
Retinal Imaging

Centre for Life Sciences
Neuroimaging (MRI)
2018 National Institute on Aging—Alzheimer’s Association (NIA-AA) Research Framework

NIA-AA Research Framework: Toward a biological definition of Alzheimer’s disease
Neuroimaging, cerebrovascular disease and cognition

Cerebrovascular disease (CeVD) is highly prevalent in elderly people and make important contributions to cognitive impairment and dementia in later life.

Many people with dementia have mixed pathology (commonly AD and CeVD) and CeVD can be additive with AD pathology in impairing cognitive function and increasing the likelihood of dementia.

A substantial proportion of patients after non-disabling stroke are cognitively impaired and remain at an increased risk of incident dementia,

Covert stroke is an under-recognised but important cause of cognitive impairment and dementia.

MRI can be used to demonstrate CeVD burden by use of established and novel imaging markers.

New insights into mechanisms and innovative treatments.
Analysis of over 6000 brains  (Toledo et al, Brain 2013)
Recent Progress in Diagnostic Criteria for Vascular Cognitive Impairment


Alzheimer’s & Dementia 13 (2017) 624-33

The study brought together international researchers and clinicians to agree on a single set of terms and criteria that will be used to help classify different types of VCI. Focus on operationalising these criteria


Diagnostic criteria for vascular cognitive disorders: a VASCOG statement.

Alzheimer Disease & Associated Disorders 28 (2014) 206-218
Post-stroke VCI in Singapore

![Graph showing changes in NCI, CIND, and dementia over time.](image_url)
Post-stroke dementia and outcomes

Poststroke dementia

Higher mortality rates
- More severe vascular disease and complications
- High mortality from dementia
- Higher stroke related mortality
- Less treatment
- Poorer compliance

Higher stroke recurrence

More impaired and more dependent

Didier Leys, Hilde Hénon, Marie-Anne Mackowiak-Cordoli, Florence Pasquier

Lancet Neurol 2005; 4: 752–59
Post stroke CIND and Incident Dementia

Kaplan-Meier survival estimates

Narasimhalu et al, Neurology 2009
Post stroke CIND, Death and Dependency

- CIND was independently predictive of dependency (mRS>=3) with a HR of 3.8 (1.5-9.4)
- CIND was independently predictive of death with a HR of 3.3 (1.1-10.1)
- CIND showed a trend towards being predictive of recurrent vascular events with a HR of 1.7 (0.9-3.0)

Narasimhalu et al, Stroke 2011
Mechanisms of Post Stroke Dementia

• Early-onset PSD results from a complex interplay between stroke lesion features and brain resilience (Yang et al, 2015)
  – Chronic brain changes including WMH, MTLA, and AD pathology are associated with incident dementia after stroke/TIA.

• Delayed-onset PSD is associated mainly with the presence of severe sporadic small vessel disease (WMH), and to a lesser extent with AD pathology or recurrent stroke (Mok et al, 2016)
Prevent, identify, and treat potentially preventable dementias

Subclinical (silent) strokes occur 5 times as often as clinical (obvious) strokes and may affect thinking, mood, and personality.

All major dementias have a vascular component, including 80% in Alzheimer disease. Therefore, we need to:

- Identify and treat the vascular component of all cognitive impairments.
- Understand that the presence of a vascular component doubles the chances that silent neurodegenerative pathology will lead to dementia.

- Manage the common risk factors for stroke, vascular cognitive impairment, dementia (tobacco use, high blood pressure, high cholesterol, physical inactivity, obesity, and diabetes mellitus), and atrial fibrillation. Encourage frequent blood pressure measurements and checking for an irregular heartbeat to detect atrial fibrillation.
- Enhance protective factors, such as education and a socially and physically healthy environment.
- Integrate stroke and dementia prevention strategies because preventing stroke may prevent some dementias.
Silent Brain Infarcts (SBI)

- Infarcts are classified as “silent” when they are detected on brain imaging, but lack temporally correlated stroke-like symptoms.
- The reported prevalence of SBI is 8-28% – increases with age
  - higher in those with previous history of stroke or dementia
    - Vermeer et al Lancet Neurology 2007
- The presence of SBI increases the risk of
  - subsequent stroke
    - Bernick et al, Neurology 2001
  - cognitive impairment
    - Vermeer at al, NEJM 2003
Of 2846 articles identified, 94 studies were eligible, with up to 16012 participants for MRI defined covert brain infarcts (BI) which was associated with higher risk of incident stroke (HR, 2.38; 95% CI, 1.87-3.04; P < .001), ischemic stroke (HR, 2.18; 95% CI, 1.67-2.85; P < .001), intracerebral hemorrhage (HR, 3.81; 95% CI, 1.75-6.52; P = .001), dementia (HR, 1.29; 95% CI, 1.02-1.65; not significant after correction for multiple testing), and death (HR, 1.64; 95% CI, 1.40-1.91; P < .001).
Imaging Biomarkers of Vascular Cognitive Impairment

Cortical Infarcts
Lacunar Infarcts
White Matter Lesions
Atrophy
DTI
Cerebral Microbleeds
Cerebral Micro-Infarcts
Intracranial Stenosis
Retinal Imaging
Amyloid Imaging

and less usual
STRIVE
(STandards for Reporting and Imaging of Small Vessel Disease)
Wardlaw et al 2013

<table>
<thead>
<tr>
<th>Recent small subcortical infarct</th>
<th>White matter hyperintensity</th>
<th>Lacune</th>
<th>Perivascular space</th>
<th>Cerebral microbleeds</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Example image</strong></td>
<td></td>
<td></td>
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<tr>
<td><strong>Schematic</strong></td>
<td></td>
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<tr>
<td><em>DWI</em></td>
<td><em>FLAIR</em></td>
<td><em>FLAIR</em></td>
<td><em>T1/FLAIR</em></td>
<td><em>T2</em>/SWI*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Usual diameter $^1$</th>
<th>≤ 20 mm</th>
<th>variable</th>
<th>3-15 mm</th>
<th>≤ 2 mm</th>
<th>≤ 10 mm</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Comment</strong></td>
<td>best identified on DWI</td>
<td>located in white matter</td>
<td>usually have hyperintense rim</td>
<td>usually linear without hyperintense rim</td>
<td>detected on GRE seq., round or ovoid, blooming</td>
</tr>
<tr>
<td><em>DWI</em></td>
<td>↑</td>
<td>↔</td>
<td>↔/(↓)</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td><em>FLAIR</em></td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
<td>↔</td>
</tr>
<tr>
<td><em>T2</em></td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↔</td>
</tr>
<tr>
<td><em>T1</em></td>
<td>↓</td>
<td>↔/(↓)</td>
<td>↓</td>
<td>↓</td>
<td>↔</td>
</tr>
<tr>
<td>T2$^*$ / GRE</td>
<td>↔</td>
<td>↑</td>
<td>↔(↓ if haemorrhage)</td>
<td>↔</td>
<td>↓↓</td>
</tr>
</tbody>
</table>
White Matter Hyperintensities (WMH)

Elderly Asians have a high burden of SVD which was associated with cognitive dysfunction. The prevalence of confluent WMH was 36.6%, lacunes, 24.6% (Hilal et al, JNPP 2017)

Fazekas scale for WM lesions

On MR, white matter hyperintensities (WMH) and lacunes - both of which are frequently observed in the elderly - are generally viewed as evidence of small vessel disease.

The Fazekas scale provides an overall impression of the presence of WMH in the entire brain. It is best scored on transverse FLAIR or T2-weighted images.

Score:

- Fazekas 0: None or a single punctate WMH lesion
- Fazekas 1: Multiple punctate lesions
- Fazekas 2: Beginning confluency of lesions (bridging)
- Fazekas 3: Large confluent lesions
Of 2846 articles identified, 94 studies were eligible, with up to 14,529 participants for WMH. Extensive WMH burden was associated with higher risk of incident stroke (HR, 2.45; 95% CI, 1.93-3.12; P < .001), ischemic stroke (HR, 2.39; 95% CI, 1.65-3.47; P < .001), intracerebral hemorrhage (HR, 3.17; 95% CI, 1.54-6.52; P = .002), dementia (HR, 1.84; 95% CI, 1.40-2.43; P < .001), Alzheimer disease (HR, 1.50; 95% CI, 1.22-1.84; P < .001), and death (HR, 2.00; 95% CI, 1.69-2.36; P < .001).
Prevalence, risk factors and consequences of cerebral small vessel diseases: data from three Asian countries

Saima Hila,1,2 Vincent Mok,3 Young Chul Youn,4 Adrian Wong,3 Mohammad Kamran Ikram,5 Christopher Li-Hsian Chen1,2

Table 1  Baseline characteristics of the study participants

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Overall (n=1797)</th>
<th>Singapore (n=832)</th>
<th>Hong Kong (n=850)</th>
<th>Korea (n=115)</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Small vessel disease markers (SVD)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presence of lacunes, n (%)</td>
<td>442 (24.6)</td>
<td>143 (17.2)</td>
<td>277 (32.6)</td>
<td>22 (19.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Presence of cerebral microbleeds, n (%)</td>
<td>480 (26.9)</td>
<td>286 (34.4)</td>
<td>179 (21.1)</td>
<td>15 (13)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Presence of confluent WMH, n (%)</td>
<td>657 (36.6)</td>
<td>395 (47.5)</td>
<td>243 (28.6)</td>
<td>19 (16.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Number of SVD markers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presence of one SVD marker, n (%)</td>
<td>619 (45.2)</td>
<td>296 (49.3)</td>
<td>297 (44.6)</td>
<td>26 (25.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Presence of two SVD markers, n (%)</td>
<td>324 (30.2)</td>
<td>165 (35.1)</td>
<td>150 (28.9)</td>
<td>7.8 (10.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Presence of three SVD markers, n (%)</td>
<td>104 (12.2)</td>
<td>66 (17.8)</td>
<td>34 (8.4)</td>
<td>4 (5)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Table 3  Association of number of small vessel disease markers with cognition

<table>
<thead>
<tr>
<th>Number of small vessel disease markers</th>
<th>MMSE*</th>
<th>MoCA*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β (95% CI), † p value</td>
<td>β (95% CI), † p value</td>
</tr>
<tr>
<td>Presence of one marker</td>
<td>-0.00 (-0.01 to 0.00), 0.205</td>
<td>-0.01 (-0.02 to -0.00), 0.035</td>
</tr>
<tr>
<td>Presence of two markers</td>
<td>-0.01 (-0.02 to -0.01), 0.001</td>
<td>-0.02 (-0.04 to -0.01), 0.002</td>
</tr>
<tr>
<td>Presence of three markers</td>
<td>-0.03 (-0.04 to -0.02), &lt;0.001</td>
<td>-0.04 (-0.05 to -0.02), &lt;0.001</td>
</tr>
</tbody>
</table>
**Bi-tensor model**

**Free-water and tissue compartments**

- **Tissue (FA\(_T\))** compartment (axon bundles)
- **Free water (FW)** compartment (extracellular water)

**Pasternak et al., J. Neurosci., 2012**
WMH is not sensitive to detect mild water increases in normal-appearing WM

Duering et al., Alzheimer's & Dementia, 2018
FW is more strongly associated with cognition than WMH

Duering et al., Alzheimer's & Dementia, 2018

Results from simple linear regression analyses between FW and processing speed scores

Random forest regressions for estimating the importance of independent variables with regard to processing speed (dependent variable) while accounting for all other variables
FW detected mild water increases in AD. WMH did not.

**FW in total WM**

**FW in normal-appearing WM**

**WMH**

FW in total WM

FW in normal-appearing WM

WMH

Ji et al, 2017
FW metric related to dementia severity

WMH does not

FW metric is superior to WMH in measuring water content increase

Ji et al, 2017
FW increases and tissue compartment deterioration correlated with cognitive deficits

A Attention: free water

B Language: free water

C Attention: FA_T

D Executive function: FA_T

FW: free water
Tissue: Tissue
WM skeleton: WM skeleton

Ji et al, 2017
White Matter Hyperintensities (WMH)

- Considerable debate as to the causes of WMH
- Diverse (demyelinating, infectious, toxic or metabolic processes) but include ischemia and neurodegeneration
- Nevertheless, WMH have become an integral part of our concepts of vascular cognitive impairment
Lacunes may form at the edge or in the middle of WMH.

Duering et al
Brain 2013

Gouw et al
Stroke 2008
Are Acute Infarcts the Cause of Leukoaraiosis? 
Brain Mapping for 16 Consecutive Weeks

John Conklin, MD, MSc,1
Frank L. Silver, MD,2
David J. Mikulis, MD,1,3 and
Daniel M. Mandell, MD, PhD1,3

Neuroimaging of older adults commonly reveals abnormality (leukoaraiosis) in the cerebral white matter. Studies have established that extensive leukoaraiosis predicts dementia and disability, but the pathogenesis of leukoaraiosis remains unclear. We recruited 5 patients with leukoaraiosis and performed magnetic resonance mapping of the brain for 16 consecutive weeks. We observed tiny lesions arising de novo in the cerebral white matter. These lesions were clinically silent. They had the signature features of acute ischemic stroke. With time, the characteristics of these lesions approached those of pre-existing leukoaraiosis. Together, these findings suggest that tiny silent acute infarcts are a cause of leukoaraiosis.

ANN NEUROL 2014;76:899–904
To conclude, this prospective study suggests that the accumulation of tiny, clinically silent acute infarcts is a cause of leukoaraiosis, and possibly the primary cause.
Acute Incidental Infarcts

- In 2 Singaporean cohorts, AII were seen in
  - 7 (1.2%) of 623 subjects in a community based study (mean age 70.9 ± 6.8 yrs, 45% males)
  - 12 (3.2%) of 389 subjects (mean age 72.1 ± 8.3 yrs, 46% males) in a clinic based study

- All were present in
  - 0.8% of subjects with no cognitive impairment,
  - 1.9% of those with Cognitive Impairment Not Dementia and
  - 4.2% of subjects with dementia
  - Associated with chronic lacunes and microbleeds

Saini et al, Stroke 2015
Acute Incidental Infarcts

• Assuming that a hyperintense DWI lesion is detectable for 10 days, the incidence of AII in the community based cohort was 0.45 AII per person-year \([(7/562) \times (365/10)]\).

• The incidence of AII in the clinic based population ranged from 0.68 (baseline) to 1.28 (year two) per person-year
  • increasing over time
  • Some subjects may have none
  • Others many

• Follow up imaging may be useful to understand the eventual fate of such lesions.

Saini et al, Stroke 2015
Among 221 DWI scans (79 patients with 2 DWI scans; 40 with ≥3), 60 DWI lesions were found in 28 patients. DWI lesions were associated with chronic cortical cerebral microinfarcts (CMI) and cortical superficial siderosis, but not with other markers. For 39/60 DWI lesions, >1 MRI sequence was available at follow-up to determine lesion evolution. Twenty-four (62%) were demarcated as chronic lesions on follow-up MRI. Five appeared as cavitations, 18 as noncavitated infarcts, and 1 underwent hemorrhagic transformation.
Acute Incidental Infarcts

“acute” DWI lesion: estimate of annual microinfarct rate

Auriel et al Stroke 2015
Microinfarcts: Important but previously invisible during life

**systematic review autopsy studies**
- cystic or gliotic
- 100-200 μm to a few mm

prevalence:
- Alzheimer’s - 43%
- vascular dementia – 62%
- non-demented elderly – 24%
ADDITIVE EFFECT OF MICROINFARENTS AND AD PATHOLOGY

Religious Orders Study

Probability dementia: AD + vascular pathology

Arvanitakis et al Stroke 2011
Until the advent of high field strength 7T MRI
Cortical Microinfaracts are Visible on 7T MRI
Cortical Microinfarcts also Visible on 3T MRI

- 27% CMI 7T visible on 3T
- 87% CMI 3T also CMI 7T

van Veluw et al JCBFM 2013, Alz&Dem 2015
Clinical Significance of Cortical Microinfarcts

- 238 consecutive patients (72.5±9.1 years, 49% men) from a memory clinic in Singapore between December 2010 and September 2013.
- All patients underwent extensive neurological and neuropsychological testing and 3T MRI on the same day.
- Cortical CMI rating criteria were adapted from a previous study at 7T MRI.

Cortical Microinfarcts : Cognition

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>without CMIs (N=163)</th>
<th>with CMIs (N=75)</th>
<th>B [95% CI]</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive profile</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mini-mental state examination</td>
<td>21.0 ± 6.2</td>
<td>19.5 ± 5.9</td>
<td>-1.49 [-2.89; -0.08]</td>
<td>0.038</td>
</tr>
<tr>
<td>Montreal Cognitive Assessment</td>
<td>16.5 ± 7.2</td>
<td>15.2 ± 6.9</td>
<td>-1.38 [-2.96; 0.20]</td>
<td>0.086</td>
</tr>
<tr>
<td>Composite z-score</td>
<td>0.08 ± 1.05</td>
<td>-0.17 ± 0.10</td>
<td>-0.20 [-0.42; 0.01]</td>
<td>0.067</td>
</tr>
<tr>
<td>Executive function</td>
<td>0.06 ± 1.00</td>
<td>-0.13 ± 1.00</td>
<td>-0.18 [-0.41; 0.05]</td>
<td>0.133</td>
</tr>
<tr>
<td>Attention</td>
<td>0.03 ± 1.00</td>
<td>-0.07 ± 1.02</td>
<td>-0.11 [-0.34; 0.13]</td>
<td>0.375</td>
</tr>
<tr>
<td>Language</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verbal memory</td>
<td>0.09 ± 1.04</td>
<td>-0.21 ± 0.89</td>
<td>-0.28 [-0.53; -0.04]</td>
<td>0.023</td>
</tr>
<tr>
<td>Visual memory</td>
<td>0.05 ± 1.05</td>
<td>-0.11 ± 0.88</td>
<td>-0.13 [-0.37; 0.10]</td>
<td>0.268</td>
</tr>
<tr>
<td>Visuoconstruction</td>
<td>0.07 ± 1.06</td>
<td>-0.15 ± 0.84</td>
<td>-0.21 [-0.45; 0.03]</td>
<td>0.086</td>
</tr>
<tr>
<td>Visuomotor speed</td>
<td>0.07 ± 1.06</td>
<td>-0.15 ± 0.83</td>
<td>-0.19 [-0.40; 0.01]</td>
<td>0.067</td>
</tr>
</tbody>
</table>

Prevalence of 32% in Memory Clinic patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Without CMIs (N=163)</th>
<th>With CMIs (N=75)</th>
<th>OR [95%CI]</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Referral diagnosis</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>No cognitive impairment</td>
<td>26 (16)</td>
<td>4 (5)</td>
<td>0.27 [0.09 ; 0.85]</td>
<td>0.025</td>
</tr>
<tr>
<td>CIND, without stroke</td>
<td>29 (18)</td>
<td>5 (7)</td>
<td>0.34 [0.12 ; 0.92]</td>
<td>0.033</td>
</tr>
<tr>
<td>CIND with stroke</td>
<td>32 (20)</td>
<td>23 (31)</td>
<td>1.80 [0.94 ; 3.47]</td>
<td>0.078</td>
</tr>
<tr>
<td>Alzheimer's disease</td>
<td>66 (40)</td>
<td>31 (41)</td>
<td>1.13 [0.60 ; 2.12]</td>
<td>0.708</td>
</tr>
<tr>
<td>Vascular dementia</td>
<td>10 (6)</td>
<td>12 (16)</td>
<td>2.86 [1.17 ; 6.99]</td>
<td>0.021</td>
</tr>
</tbody>
</table>

van Veluw, Hilal S et al. 2015, Alz and Dem
Detection, risk factors, and functional consequences of cerebral microinfarcts

Susanne J van Veluw, Andy Y Shih, Eric E Smith, Christopher Chen, Julie A Schneider, Joanna M Wardlaw, Steven M Greenberg, Geert Jan Biessels

Cerebral microinfarcts are small lesions that are presumed to be ischaemic. Despite the small size of these lesions, affected individuals can have hundreds to thousands of cerebral microinfarcts, which cause measurable disruption to structural brain connections, and are associated with dementia that is independent of Alzheimer’s disease pathology or larger infarcts (ie, lacunar infarcts, and large cortical and non-lacunar subcortical infarcts). Substantial progress has been made with regard to understanding risk factors and functional consequences of cerebral microinfarcts, partly driven by new in-vivo detection methods and the development of animal models that closely mimic multiple aspects of cerebral microinfarcts in human beings. Evidence from these advances suggests that cerebral microinfarcts can be manifestations of both small vessel and large vessel disease, that cerebral microinfarcts are independently associated with cognitive impairment, and that these lesions are likely to cause damage to brain structure and function that extends beyond their actual lesion boundaries. Criteria for the identification of cerebral microinfarcts with in-vivo MRI are provided to support further studies of the association between these lesions and cerebrovascular disease and dementia.
CMI may impair white-matter pathways and affect brain function that extends beyond lesion boundaries.

(Adapted from Van Veluw et al. 2017)
Interethnic Differences in Dementia Epidemiology: Global and Asia-Pacific Perspectives

N. Venketasubramanian\textsuperscript{a} S. Sahadevan\textsuperscript{d} E.H. Kua\textsuperscript{b} C.P.L. Chen\textsuperscript{c} T.-P. Ng\textsuperscript{b}

\textsuperscript{a}Division of Neurology, University Medicine Cluster, and Department of Epidemiology and Public Health, 
\textsuperscript{b}Department of Psychological Medicine, and \textsuperscript{c}Department of Pharmacology, National University Health System, National University of Singapore, and \textsuperscript{d}Department of General Medicine, Tan Tock Seng Hospital, Singapore

Intercountry and intracountry variations in the rates of dementia exist that are not simply due to differences in ascertainment protocols and lack of statistical standardisation. Importance of studying genetic, environmental risk and protective factors, ethnic factors in the aetiology and progression of dementia to determine preventative approaches in reducing dementia burden.
Review article

Epidemiology of dementia in Asia: Insights on prevalence, trends and novel risk factors

Joseree-Ann S. Catindig a,1, N. Venketasubramanian a, Mohammad Kamram Ikram a,b,c, Christopher Chen d,*

a Department of Medicine, 5 Lower Kent Ridge Road, National University Hospital, Singapore 119074, Singapore
b Singapore Eye Research Institute, Saw Swee Hock School of Public Health, Centre for Quantitative Medicine, Duke-NUS, Singapore
c Department of Epidemiology, Erasmus Medical Center, Rotterdam, The Netherlands
d Department of Pharmacology, Yong Loo Lin School of Medicine, National University of Singapore, Block MD11, Clinical Research Center, #05-0910 Medical Drive, Singapore 117597, Singapore

Earlier Asian studies reported a lower prevalence of Alzheimer's disease (AD) and a higher prevalence of vascular dementia (VaD). Recent studies, however, show a reversal of this ratio that now parallels that of Western countries. This change may be attributed to an altered demographic profile, urbanization, environmental reactions, ethnicity and advances in the use of neuroimaging modalities. Several factors may influence the results of epidemiological studies including changes in societal perception of aging, family attitudes, validity of assessment tools due to language and literacy, and medical practitioners' expertise in recognizing dementia. Nevertheless, epidemiological studies in Asia may reveal factors contributory to inter-ethnic differences in dementia. Potentially modifiable risk factors apparent only in low and middle-income countries and gene–environment interactions may underlie these disparities and identification of such factors may lead to effective treatments.
Factors contributing to interethnic differences occurring in the same geographic area:

- prevalence of environmental risk factors
- prevalence of traditional and novel risk factors
- genetic factors
- cultural and socioeconomic factors
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Study 1 [26]</th>
<th>Study 2 [27]</th>
<th>Study 3 [28]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Publication year</td>
<td>1995</td>
<td>2008</td>
<td>2010</td>
</tr>
<tr>
<td>Sample size</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>349</td>
<td>14,817</td>
<td>995</td>
</tr>
<tr>
<td>Chinese</td>
<td>200</td>
<td>8,849</td>
<td>479</td>
</tr>
<tr>
<td>Malay</td>
<td>149</td>
<td>3,053</td>
<td>300</td>
</tr>
<tr>
<td>Indian</td>
<td></td>
<td>2,915</td>
<td>216</td>
</tr>
<tr>
<td>Age group, years</td>
<td>&gt;65</td>
<td>&gt;50</td>
<td>&gt;60</td>
</tr>
<tr>
<td>Prevalence, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>3.2</td>
<td>1.26</td>
<td>5.2</td>
</tr>
<tr>
<td>Chinese</td>
<td>2.5</td>
<td>1.19</td>
<td>4.2</td>
</tr>
<tr>
<td>Malay</td>
<td>4.0</td>
<td>1.56</td>
<td>9.4</td>
</tr>
<tr>
<td>Indian</td>
<td>ND</td>
<td>1.93</td>
<td>8.8</td>
</tr>
<tr>
<td>Subtype</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chinese F</td>
<td>1.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chinese M</td>
<td>1.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malay F</td>
<td>1.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malay M</td>
<td>1.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MID</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chinese F</td>
<td>0.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chinese M</td>
<td>1.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malay F</td>
<td>4.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malay M</td>
<td>1.2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Pie Chart
- Chinese: 76.2%
- Malay: 7.4%
- Indians: 15%
- Others: 1.4%

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Epidemiology of Dementia in Singapore (EDIS) Study: Design

- **2009-2012**: Singapore Chinese Eye Study (SCEES)
- **2011-2013**: Singapore Malay Eye Study (SiMES)
- **2013-2015**: Singapore Indian Eye Study (SINDI)

*Note: The total sample size is approximately 10,000.*
The prevalence of cognitive impairment and dementia in Singaporean Chinese was 15.2%.

By comparison, with a similar protocol of recruitment and assessment, Malays were more likely to have any cognitive impairment (OR adjusted for age, demographic and CVD risk factors, and ApoEε4 : 2.03, 95% CI: 1.48-2.77). Further research is needed to unravel other factors that may underlie ethnic differences in the occurrence of cognitive impairment.
Epidemiology of Dementia in Singapore (EDIS) Study: Neuroimaging

Neuroepidemiologic studies have traditionally focused on studying associations between determinants and neurologic outcomes, while treating the pathway in between both as a "black box." With the rise of noninvasive, advanced neuroimaging techniques, it has become possible to directly study brain changes occurring in this "black box." This importantly aids to unravel disease pathways, find new markers of disease, or identify subjects at risk of disease. Imaging in neuroepidemiologic studies is also called population neuroimaging.

Vernooij MW et al, 2016
Discussion

- Increased burden of cerebrovascular burden in Malays compared to Chinese and Indians

- May possibly be implicated in the higher rates of cognitive impairment in these ethnicities

- Possibly a combination of genetic and lifestyle factors
  ➢ ApoE4, vascular risk factors, diet, exercise etc.

- Further research is required to identify the possible risk factors and their mechanism of action
VASCULAR COGNITIVE IMPAIRMENT: TREATMENT

Prevention by treating risk factors for stroke

- hypertension
- diabetes
- cardiac arrhythmia
- hyperlipedemia
- vascular disease
- hyperhomocysteinemia
Blood pressure lowering clinical trials with dementia endpoints

MRC trial substudy (BMJ 1996 312 : 801-805)
2584 subjects
no difference in learning tests over time

4736 subjects
no effect
37 (1.6%) active vs 44 (1.9%) placebo cases

Syst-Eur substudy (Lancet 1998 352 : 1347-51)
2418 subjects
50% dementia risk reduction (21 vs 11 events)
wide confidence intervals; methodological problems
## PROGRESS : EFFECT OF ADDITIONAL BP LOWERING

<table>
<thead>
<tr>
<th></th>
<th>Events</th>
<th>Favors</th>
<th>RRR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Active</td>
<td>Placebo</td>
<td>active</td>
</tr>
<tr>
<td><strong>Dementia</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With stroke</td>
<td>43</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>Without stroke</td>
<td>150</td>
<td>152</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>193</td>
<td>217</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>34% (3,55)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1% (-24,22)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>12% (-8, 28)</td>
</tr>
<tr>
<td><strong>Severe Cognitive Decline</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With stroke</td>
<td>48</td>
<td>86</td>
<td></td>
</tr>
<tr>
<td>Without stroke</td>
<td>228</td>
<td>248</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>276</td>
<td>334</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>45% (22,62)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>10% (-9,25)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>19% (4,32)</td>
</tr>
</tbody>
</table>

In patients with lower cognitive function (MMSE ≤ 28), the MMSE score declined less in the candesartan than in the control group (mean difference 0.49, 95% confidence interval 0.02 to 0.97, P = .04).

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Last visit</th>
<th>Change (adj)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cand</td>
<td>Con</td>
<td>Cand</td>
</tr>
<tr>
<td>n=2417</td>
<td>n=2409</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMSE score</td>
<td>28.5</td>
<td>28.5</td>
<td>27.9</td>
</tr>
</tbody>
</table>

Difference between treatments in MMSE change (adjusted)

<table>
<thead>
<tr>
<th>mean</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.15</td>
<td>-0.08 ; 0.38</td>
<td>0.20</td>
</tr>
</tbody>
</table>
Patients with recent (<6 months) lacunar stroke were randomised to
- 130-149 mmHg vs
- <130 mmHg target levels of systolic bp

2916 patients mean age 63+/−11
Mean follow up 3 years
No significant change in CASI z scores between bp target groups (p=0.52)
Cognitive function is not affected by short term blood pressure reduction in young patients with lacunar stroke at low risk of cognitive decline

Pearce et al, Lancet Neurology 2014
DOES ANTIHYPERTENSIVE TREATMENT PREVENT DEMENTIA?

Does it depend on:
- Patient risk for dementia
  - Age
  - Previous stroke
  - Severity of cognitive impairment
  - White Matter Disease (LEOPOLD)
- Degree of blood pressure reduction (SCOPE-MIND)
- Other outcomes
  - Stroke
- Drug used
TARGETING WHITE MATTER DISEASE

• The presence and progression of WMH is associated with cognitive decline.
• In the PROGRESS MRI sub-study, blood pressure lowering was associated with less progression in WMH, with effects greatest among those with severe WMH at baseline
• In the ROCAS (Regression Of Cerebral Artery Stenosis) study, statins use was associated with less WMH progression only among those with severe WMH at baseline
B Vitamins and Magnetic Resonance Imaging–Detected Ischemic Brain Lesions in Patients With Recent Transient Ischemic Attack or Stroke

The VITAmins TO Prevent Stroke (VITATOPS) MRI-Substudy

Margherita Cavalieri, MD; Reinhold Schmidt, MD; Christopher Chen, MD; Vincent Mok, MD; Gabriel R. de Freitas; Swithin Song, MBBS; Qilong Yi, MSc, PhD; Stefan Ropele, PhD; Anja Grazer, MD; Nina Homayoon, MD; Christian Enzinger, MD; Katherine Loh; Ka Sing Lawrence Wong, MD; Adrian Wong, PhD; Yunyun Xiong, MD; PhD; Hui Meng Chang, MD; Meng Cheong Wong, MBBS; Franz Fazekas, MD; John W. Eikelboom, MBBS; Graeme J. Hankey, MD; on behalf of the VITATOPS Trial Study Group.

471 patients (5 centres)

8 contraindications to MRI
10 deaths
54 withdrawn
10 refused 2nd MRI
6 lost to follow up

383 follow-up MRI

24 MRI exams excluded because of low quality

359 follow-up MRI
Table 3. MRI Changes in Relation to 2-Year Treatment With B Vitamins or Placebo in a Subset of 100 Patients With Severe SVD (Deep WMH Score ≥2 AND Lacunes)

<table>
<thead>
<tr>
<th></th>
<th>B vitamins (n=54)</th>
<th>Placebo (n=46)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>WMH volume change, cm³, median (range)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total†</td>
<td>50</td>
<td>44</td>
<td></td>
</tr>
<tr>
<td>Value</td>
<td>0.3 (0–13.6)</td>
<td>1.7 (0–13.6)</td>
<td>0.039</td>
</tr>
<tr>
<td>Incident lacunes, n (%)</td>
<td>54</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td>Value</td>
<td>9 (16.6)</td>
<td>5 (10.8)</td>
<td>0.405</td>
</tr>
<tr>
<td>Incident infarcts, n (%)</td>
<td>54</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td>Value</td>
<td>6 (11.1)</td>
<td>0</td>
<td>1.000</td>
</tr>
<tr>
<td>Type of infarct, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Territorial</td>
<td>54</td>
<td>46</td>
<td>1.000</td>
</tr>
<tr>
<td>Watershed</td>
<td>54</td>
<td>46</td>
<td></td>
</tr>
</tbody>
</table>
COGNITIVE IMPAIRMENT & DEMENTIA
THE CHALLENGES AHEAD

• Identification of high risk groups
  – Biomarkers
  – Neuroimaging

• Development of effective treatments
  – Understanding pathophysiology
    • molecular biology
    • Vascular function

• Performing well designed trials

• Balancing between prevention and treatment strategies
  – Primary (risk reduction / increasing cognitive reserve)
  – Secondary (early detection and screening)
  – Tertiary (treatment of dementia / stroke)
Important to assess the burden of “silent” and not so silent cerebrovascular disease

Under-recognized
Ignored
Preventable
Important
Detecting and intervening in prodromal dementia is important.

An early or premonitory symptom or sign (Neuroimaging / Blood biomarkers) that indicates the onset or development of disease.