

Life Course Progression of Cerebrovascular Disease

Sudha Seshadri, MD

Professor of Neurology,

Boston University School of Medicine and

Senior Investigator, The Framingham Heart Study



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NIDDK, AHA and others

**BOSTON
UNIVERSITY**



No Conflicts of Interest to Disclose

Acknowledgements

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Outline

- The Framingham Brain Study 😊
- Vascular Brain Injury & Stroke
- Vascular Contributions to Cognitive Impairment
 - Impact of lifelong exposures
- Observational Data can Predict Trial Outcomes
- Heterogeneity may be key

Framingham Study



BRITISH MEDICAL JOURNAL

LONDON: SATURDAY, JULY 25, 1964

THE NEWER KNOWLEDGE OF ATHEROSCLEROSIS*

BY

S. S. FURBERG, M.D.

From the Depts. of the University of Medical Research, University of Toronto, Toronto, Canada

In North America and northern Europe the degenerative arterial disease atherosclerosis has become a major cause of death - indeed, possibly the leading cause of death. There may be some controversy as to the fact that the increasing death rate from this disease is due to a reduction of the competing causes like cancer, but the most convincing is the high incidence of death and disability due to atherosclerosis among men in the prime of life. For this is not just a disease of old age. It occurs early in life - about 50% of which is due to arteriosclerotic changes in great vessels - as a cause of sudden death in men aged from 17 to 20 years and 30 to 35 years, and, as it well known, death and disability from coronary disease in men below 40 years of age is increasing.

An attempt will be made to sketch here the main features of our present knowledge of atherosclerosis, the several intriguing problems which have to be solved in order to establish rational prevention.

Terminology and Pathology

The term "arteriosclerosis" is a nonspecific term which is used in various senses. To name it is arteriosclerosis may atherosclerosis; others use it to mean degenerative vascular disease in general. Obviously, certain pathological general diseases are included under the heading. As the term arteriosclerosis has been applied to various diseases which differ pathologically and etiologically, it is probably best, in the interests of clarity, to avoid its application and use a more specific terminology (Baker, 1955).

What atherosclerosis actually means, histologically, is a disease of the arterial wall. It is characterized by the presence of a fibrous plaque in the intima of the vessel. From this plaque an embolus of lipid or cholesterol may arise which causes a fat embolism.

Atherosclerosis is a diffuse hyperplastic disease of the arteries and is usually associated with hypertension.

Atherosclerosis affects mostly the large and small arteries. It progresses by extension - particularly of the coronary, cerebral, and lower-limb vessels - and is characterized, in contrast to the smaller vessels, by the presence of lipid in the arterial intima, by intimal proliferation, and later by medial and intimal degeneration and calcification.

Incidence and Mortality

How common is atherosclerosis? Unfortunately, during the past decades of the disease cannot be detected until lesions are well advanced and some clinical complications occur. Even then, the diagnosis of atherosclerosis is very precarious. Typical pathological arterial disease is not, however, obvious. Cardiovascular abnormalities by radiography may indicate advanced atherosclerosis in only primary arterial disease. The occurrence of myocardial infarction, aortic dissection, stroke, coronary atherosclerosis, fat, lesions of the joints, and irregular abnormalities of the thorax, the full extent of the disease may be assessed only at autopsy.

Fig. 1 shows the incidence of gross atherosclerotic disease in recent studies at the Mount Sinai in the hearts of men and women who died because of age 30 years or younger.

The incidence of atherosclerosis in the hearts of men and women who died because of age 30 years or younger is shown in Table I (Wells et al., 1954; Wells et al., 1955). The hearts of the men and women in each age group were classified into categories according to the extent of atherosclerosis. The incidence in men reached a maximum in the 30 to 39 age group (19%), but, beyond the age of 40, the percentage with atherosclerosis increased progressively. In women, the incidence of atherosclerosis decreased from 19% at 30 to 39 years of age to 11% at 40 to 49 years of age. The incidence in women increases progressively with age.

The incidence of atherosclerosis in the hearts of men and women who died because of age 30 years or younger is shown in Table I (Wells et al., 1954; Wells et al., 1955). The incidence in men reached a maximum in the 30 to 39 age group (19%), but, beyond the age of 40, the percentage with atherosclerosis increased progressively. In women, the incidence of atherosclerosis decreased from 19% at 30 to 39 years of age to 11% at 40 to 49 years of age. The incidence in women increases progressively with age.

How important is atherosclerosis as a cause of death? The disease is not listed as a cause of death in official statistics, but has long been clearly established that about 25% of deaths from coronary disease (Furberg and Wittmann, 1954; about 30% of deaths from stroke, Kawachi, Green, Chung, and Shaver, 1957), and about 50% of deaths attributed to aortic aneurysm (Gardner and Mann, 1959) are due to it. Atherosclerosis is a significant cause of death in men and women below age 35, but its mortality rate increases steadily with age and is not lower outside its main attack zone.

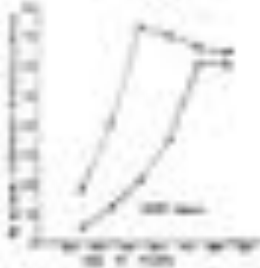


Fig. 1. - The incidence of atherosclerosis in the hearts of men and women who died because of age 30 years or younger.

Accounts for 50% of all deaths from cerebrovascular disease, 95% of deaths from coronary artery disease

Presence of disease cannot be detected in life until well advanced and clinical complications occur

How can we identify causes of atherosclerosis in the population?

*The subject of this review was presented at the International Symposium on Atherosclerosis, St. Louis, Mo., U.S.A., September 1-10, 1963.

Framingham Study: Sampling frame

2/3 of all adults
ages 30-59 years

Men and Women

70% response
~750 volunteers



Framingham Study: the beginnings



Thomas Royal Dawber



William B. Kannel



Framingham Heart Study

Longitudinal Community-Based Family Study

1948

2015

Original cohort N = 5209 men and women (ages 28-62)

31st

1971

2015

Offspring study N = 5124

9th

1995

2015

Omni study N = 506

3rd

2002

2015

Third Gen study N = 4095

3rd

2002

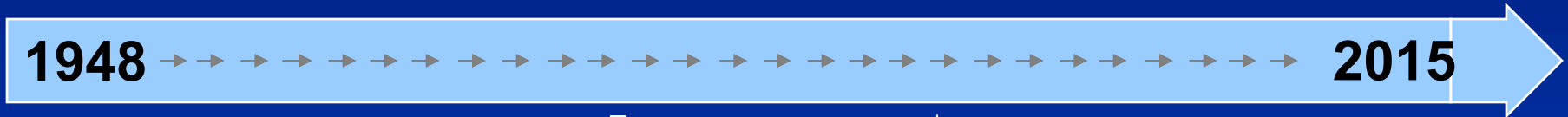
2015

Omni Gen 2 study N = 368

3rd

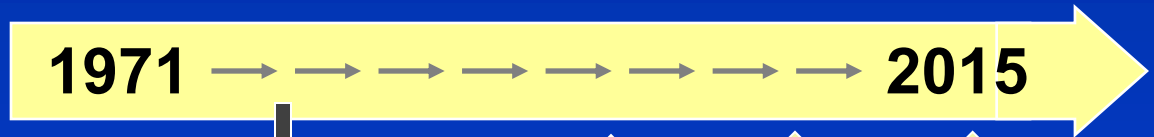


Framingham Heart Study



Gen 1: Dementia Free Persons Identified and Followed Since Exam 14 in 1975; MMSE since Exam 17

1999-2009: 343 Gen 1 survivors MRI/NP



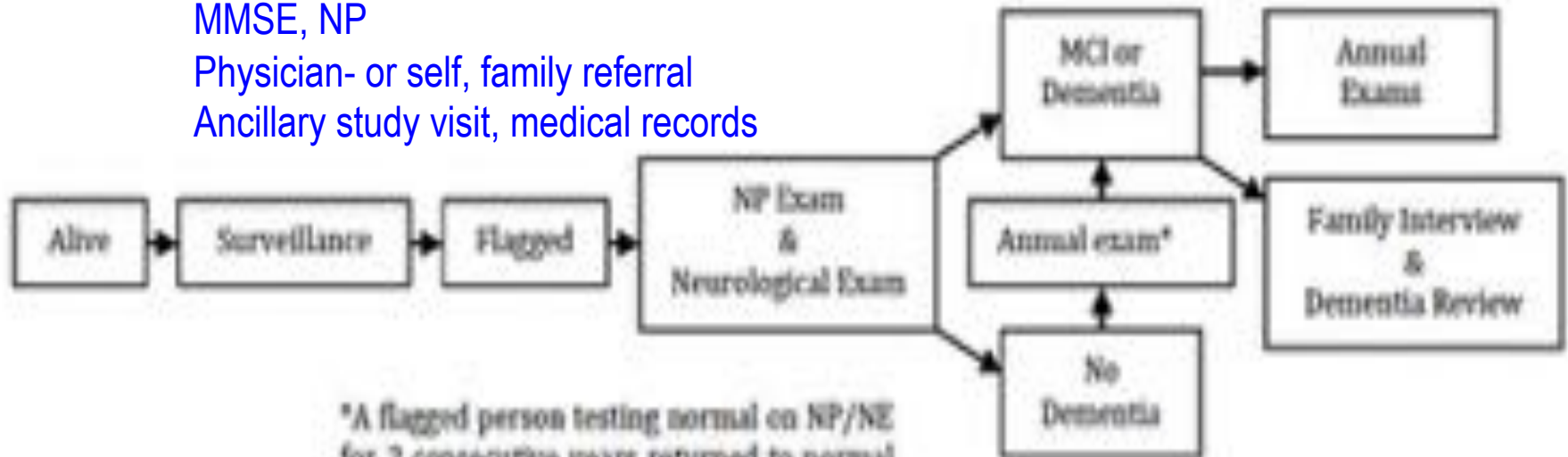
Gen 2: Dementia Surveillance Begins at Exam 2 in 1979

1999-2009: 2900 Gen 2 survivors MRI/NP called back for 2nd, 3rd scans ~6 yr intervals

Brain Bank: 1997

Dementia Tracking

Flagged at FHS exam or health status update
MMSE, NP
Physician- or self, family referral
Ancillary study visit, medical records



*A flagged person testing normal on NP/NE for 2 consecutive years returned to normal surveillance pool

Framingham Heart Study



Gen 1: Dementia Free Persons Identified and Followed
Since Kaplan-Albert Exam 14 in 1975

1999-2009: 343 Gen 1 MRI/NP X3 ~6 yrs apart

More frequent, up to annual, NP/MRI testing in:

- Possible MCI, dementia
- Oldest-old (>85 years)
- Brain Bank Enrollees
- 2 normal NP/Neurology
- Not near one of our MRI centers in New England, FL, AZ etc.

Brain Bank: 1997

Framingham Heart Study

1948



2014

Gen 1 Original cohort;

1971



2014

Gen 2 Offspring cohort

Exam 3: MRI/NP and Novel Imaging

Functional MRI

Amyloid and Tau PET

Tractography, Regional Volumes/shape

Microbleeds

Enlarged Perivascular Spaces

2002

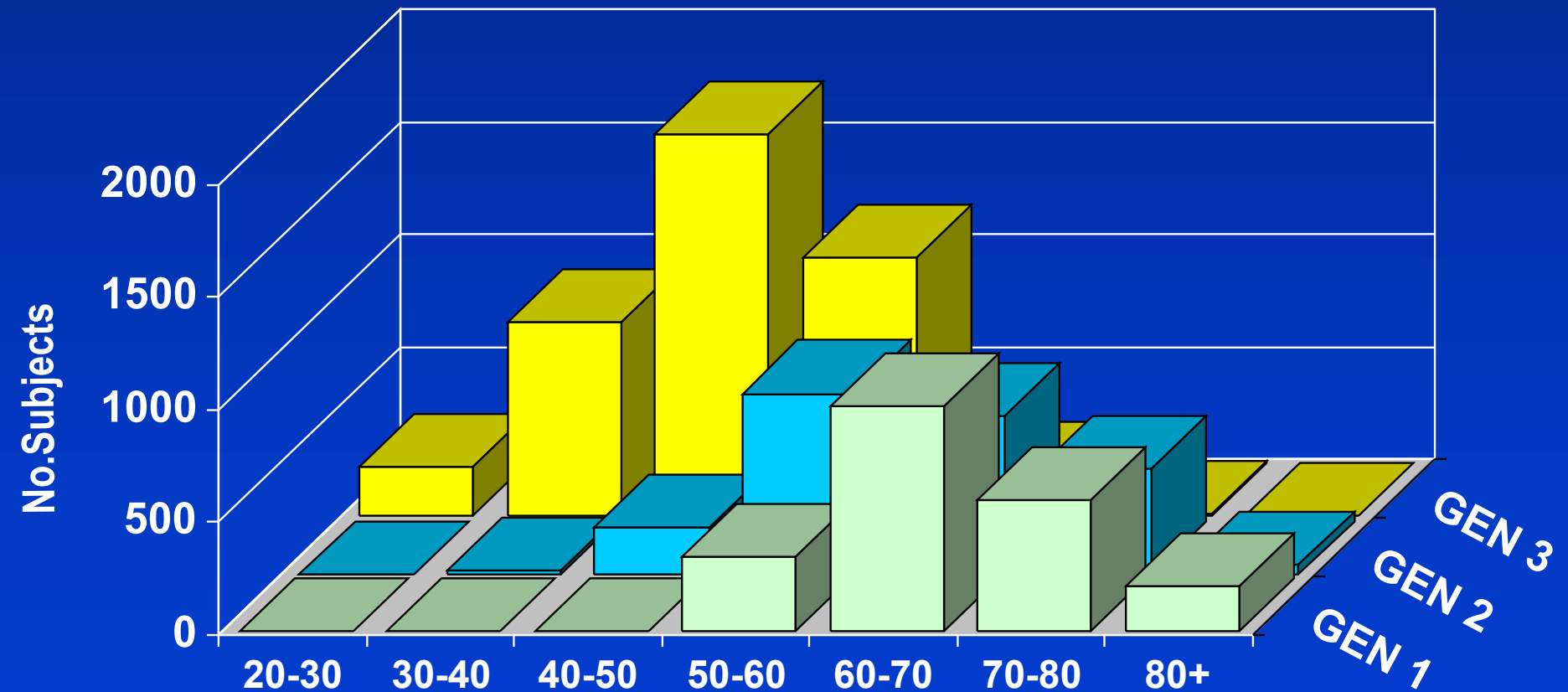
2014

Gen 3 cohort



Exam 2 (2008-12): MRI & NP
mean age 42 yrs

Age Distribution at Initial Brain Aging Evaluation



Cognitive (Neuropsychological) Test Battery

Cognitive Domain	Neuropsychological Test Measures Defined
Verbal Memory	WMS - Logical Memory-Immediate and Delayed Recall
Visual Memory	WMS - Visual Reproductions - Immediate and Delayed Recall
New (Verbal) Learning	WMS - Paired Associates Learning
Attention and Executive Function	Trail-making Test A, Trail-making Test B WMS - Digit Span
Abstract Reasoning	WAIS - Similarities subtest
Naming	Boston Naming Test- 30 item version
Language	Boston Diagnostic Aphasia Cookie Theft
Verbal Fluency	Controlled Word Association Test
Visuospatial Perception and Organization	Hooper Visual Organization Test WAIS: Block Design
Visuoconstruction	Clock Drawing Test
Premorbid Intelligence, Reading	Wide Range Achievement Test (WRAT)-3 Reading Subtest
Premorbid Intelligence, Education	WAIS information
WMS: Wechsler Memory Scale WAIS: Wechsler Adult Intelligence Scale	

Victoria Stroop & CERAD Word List: Gen 3

Video & Audio recordings for QC

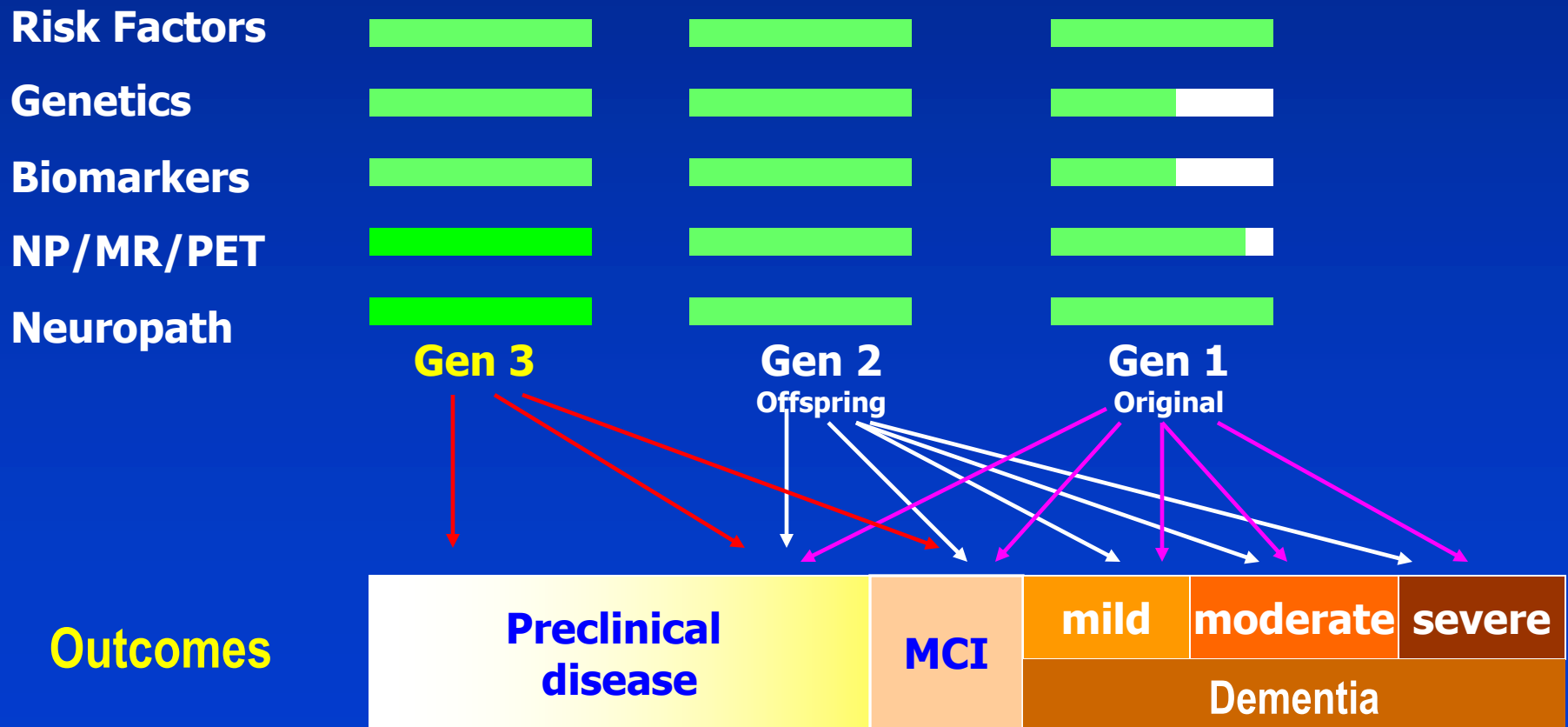
Qualitative Assessment: e.g. intrusions in LM-d

Digital tablet and pen

Neurology at Framingham

- Across 3 Generations
 - Dementia and subtypes (Alzheimer, Vascular etc.)
 - Mild Cognitive Impairment
 - Stroke and subtypes
 - Parkinson's Disease and related disorders
 - Other Neurological Conditions (epilepsy etc.)
 - 'NORMAL' Brain Aging

Spectrum of Preclinical to Clinical AD Studied at FHS



Framingham Study Datasets

Four data sets, each indexed with Dummy IDs

Original cohort

1. Demographic information

- Sex
- Education (four levels)

2. Clinic exam information (Q2 yrs from exams 14-28)

- Exam number
- BMI
- DBP
- Indicator for HTN, Stage I or higher
- Mini Mental State Examination
- Age
- SBP
- Framingham Stroke Risk Profile (FSRP)
- Indicator for current diabetes

Framingham Study Datasets

Data sets indexed with Dummy IDs

Original cohort

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- Indicator for HTN, Stage I or higher
- Indicator for current diabetes
- Mini Mental State Examination

Framingham Study Datasets

3. Cognitive exams & Prevalent Disease

- Age
- Logical Memory, immediate -- delayed
- Visual Reproductions, immediate -- delayed
- Similarities -- Paired Associates
- Digit Span Forward -- Digit Span Backward
- Controlled Oral Word test *Process Variables since 2004*

- Prevalent stroke -- Prevalent dementia

- Prevalent atrial fibrillation -- Prevalent heart failure
- Prevalent coronary disease

MRI Neuropsychological Battery

- Brief, usable across wide age range
- Includes tests used in KA battery in 76-78
 - Logical memory
 - Paired associate learning
 - Visual reproduction
 - Similarities
- Excludes some tests from KA battery
 - Digit span (forwards and backwards)
 - Word Fluency or **C**Ontrolled **W**ord **A**ssociation

Additional tests in MRI battery compared to KA

- Wide Range Achievement Test-3, Reading (WRAT)
- Boston naming
- Trails A and B
- Hooper visual organization
- Finger tapping
- Hand grip, gait measures

Additional tests for dementia surveillance exams

- Digit span
- Controlled word association test (COWA)
- WAIS- Information
- Block design
- Clock drawing
- Cookie theft

Framingham Study Datasets

4. MRI exams

- Age
- Total Cranial Volume
- Total Brain (Parenchymal) Volume
- Hippocampal Volume
- Lateral Ventricular Volume
- White Matter Hyperintensity Volume
- Regional Lobar Volumes

Also have gray, white volumes
Brodmann area (FS +)
Deep Nuclei

Tractography
Infarcts, CMB, ePVS

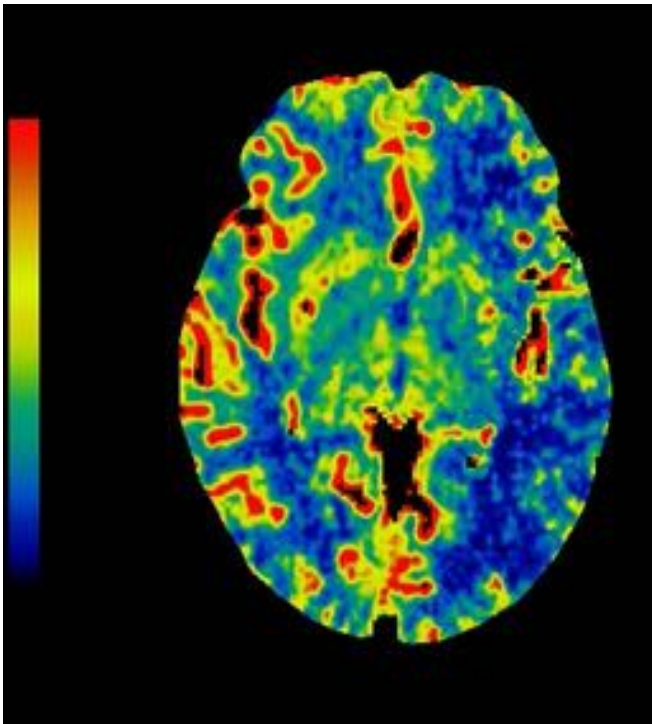


Outline

- The Framingham Brain Study 😊
- Vascular Brain Injury & Stroke
- Vascular Contributions to Cognitive Impairment
 - Framingham Stroke Risk Profile
 - Impact of lifelong exposures
- Observational Data can Predict Trial Outcomes
- Heterogeneity may be key

Vascular Brain Injury

- The Human Brain is.....



Highly Vascular, metabolically very active
1/6th cardiac output, 1/40th body mass

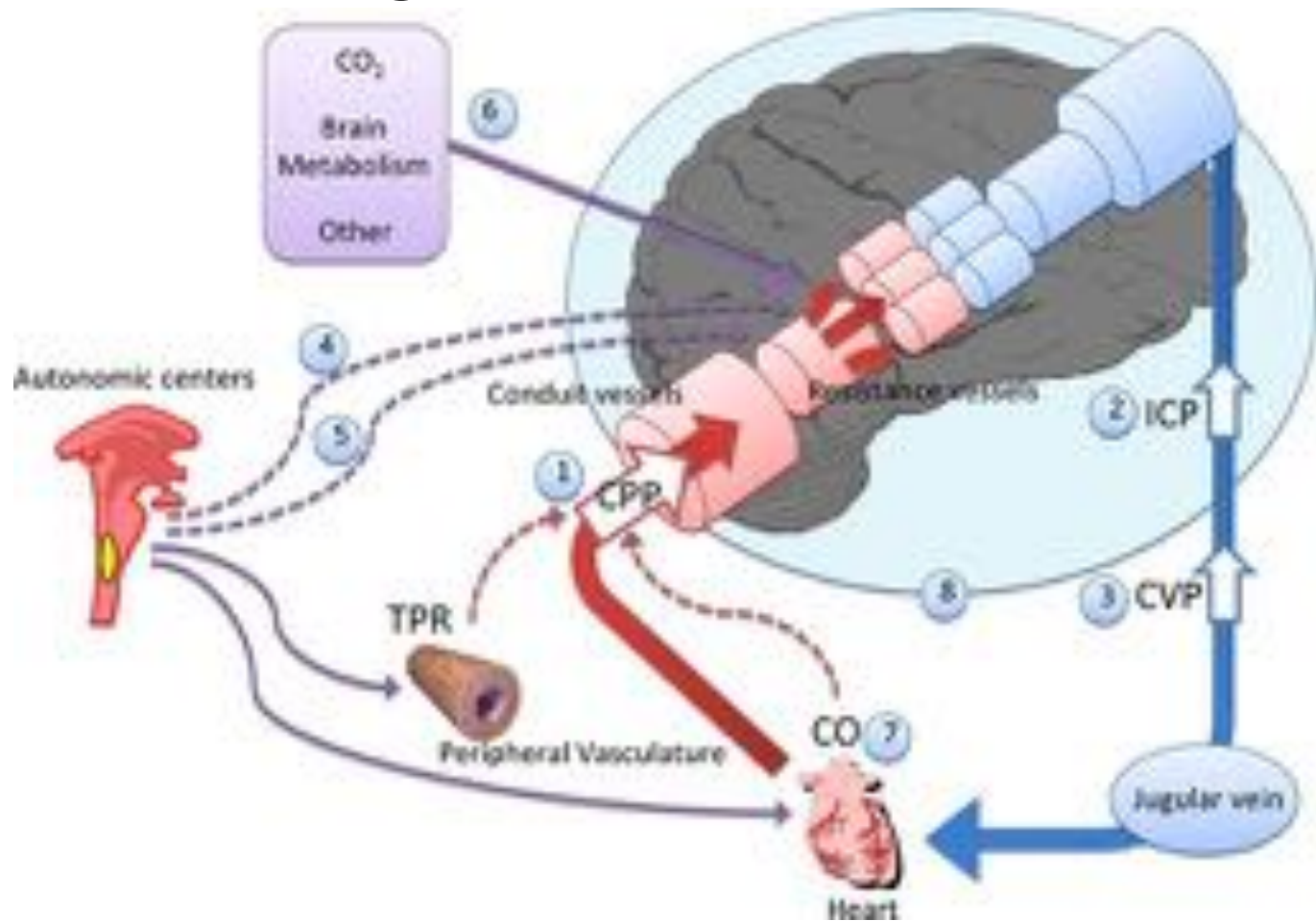
Vulnerable to ischemia
Diseases of 'pump and pipes'

Auto-regulation of blood flow

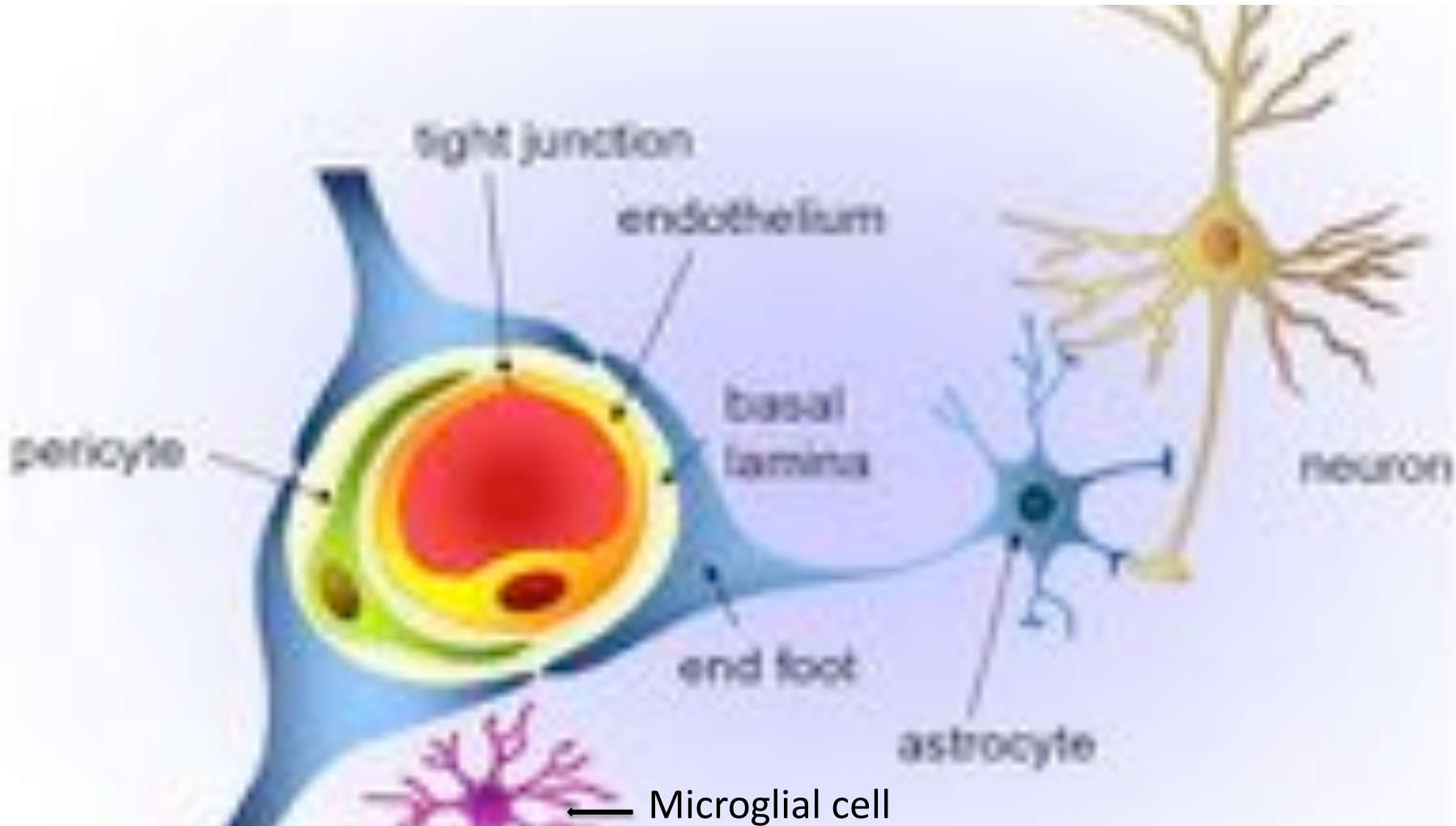
Separated by blood-brain barrier

Vascular Brain Injury

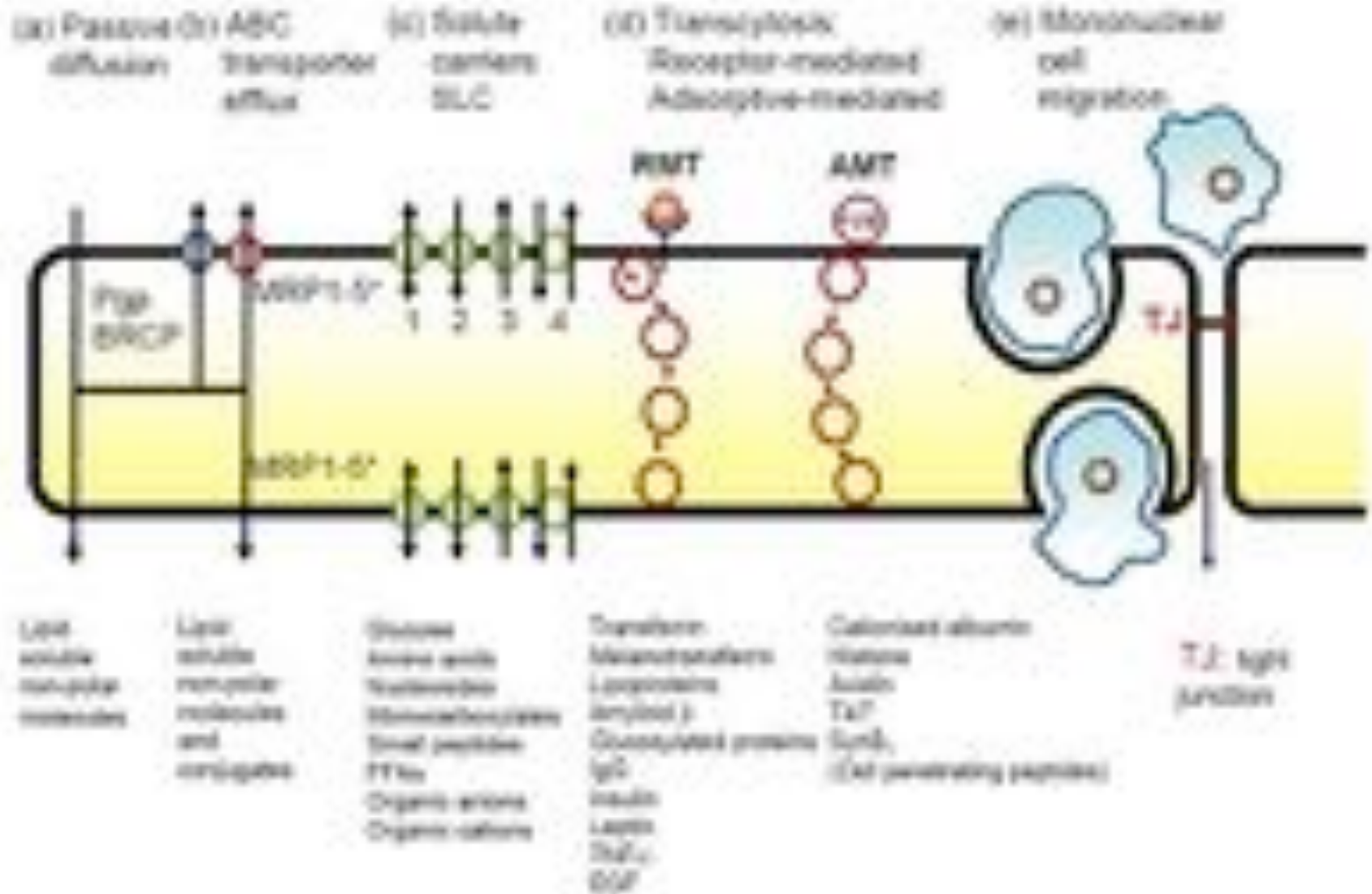
- Cerebral Autoregulation



Neurovascular Unit



Blood-Brain Barrier



Pathobiology of ischaemic stroke

Morphology

Infarction

Inflammation
and
apoptosis

PENUMBRA
CORE

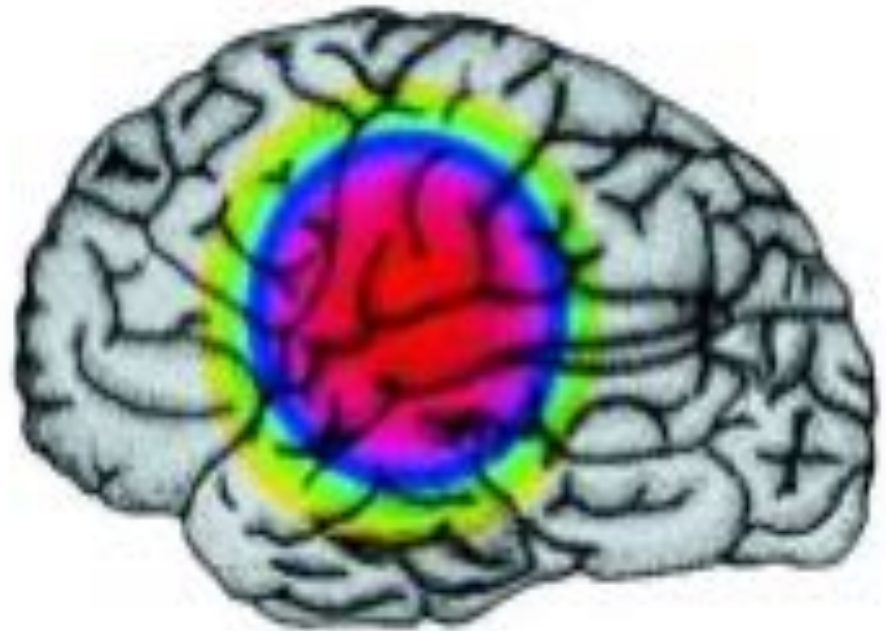
Biochemistry

Ionic failure
Anoxic depolarization
Glucose use ↓

Glutamate release
Glucose use ↑

Protein synthesis ↓
Acidosis
Oxygen extraction ↑

Selective gene expression



Ulrich Dirnagl, Costantino Iadecola, Michael A. Moskowitz, Ulrich Dirnagl, Costantino Iadecola, Michael A. Moskowitz

[http://dx.doi.org/10.1016/S0166-2236\(99\)01401-0](http://dx.doi.org/10.1016/S0166-2236(99)01401-0)



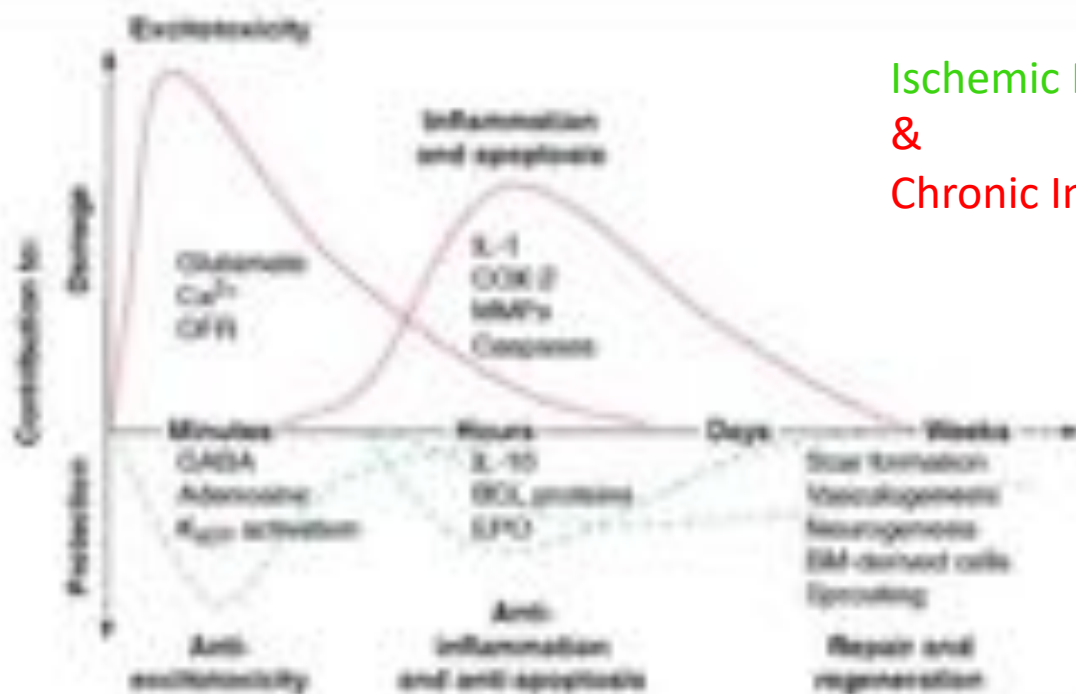
Ischemic tolerance and endogenous neuroprotection

Ulrich Dirnagl¹, Roger P. Simon² and John M. Hallenbeck³

¹Experimental Neurology, Charite Hospital, Humboldt University, 10098 Berlin, Germany

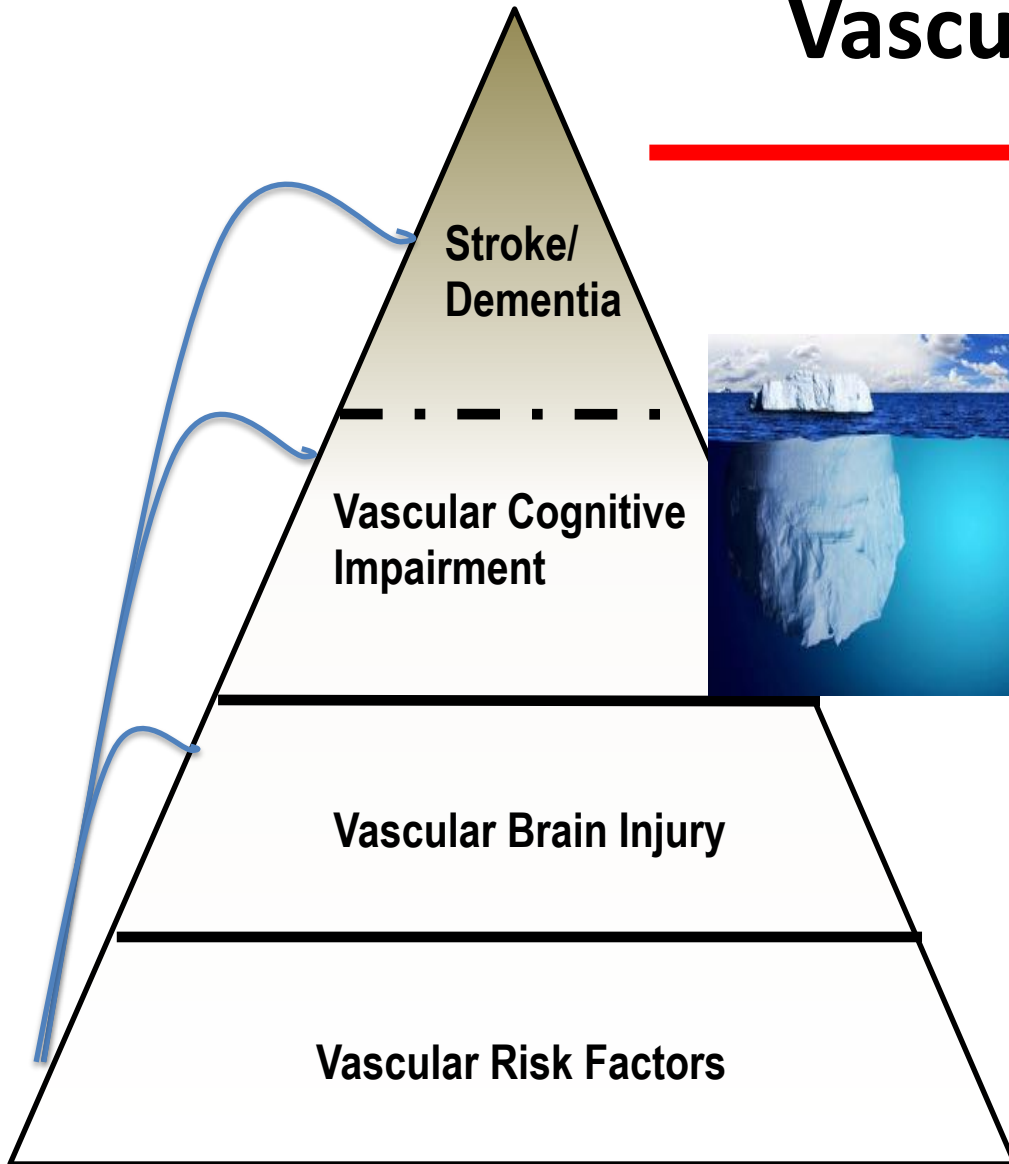
²R.S. Dow Neurobiology Laboratories, 1225 NE 2nd Ave, Portland, OR 97232, USA

³Stroke Branch, NINDS, NIH, Building 36/Room 4A03, 38 Convent Drive MSC 4128, Bethesda, MD 20892-4128, USA



Ischemic Preconditioning
&
Chronic Injury

Vascular 'Iceberg'



Genes
Lifestyle

Inflammation
Neurodegeneration

Definition

- Sudden onset, focal neurological deficit of presumed vascular etiology
- Transient Ischemic Attack (TIA): deficit lasts <24 hrs
 - Typically lasts 5-15 mins
 - **New:** 50% of TIAs show acute ischemic brain injury
- Stroke: clinical deficit lasts > 24 hrs
 - Deficit may be minor or catastrophic
 - May progress, remain static or improve

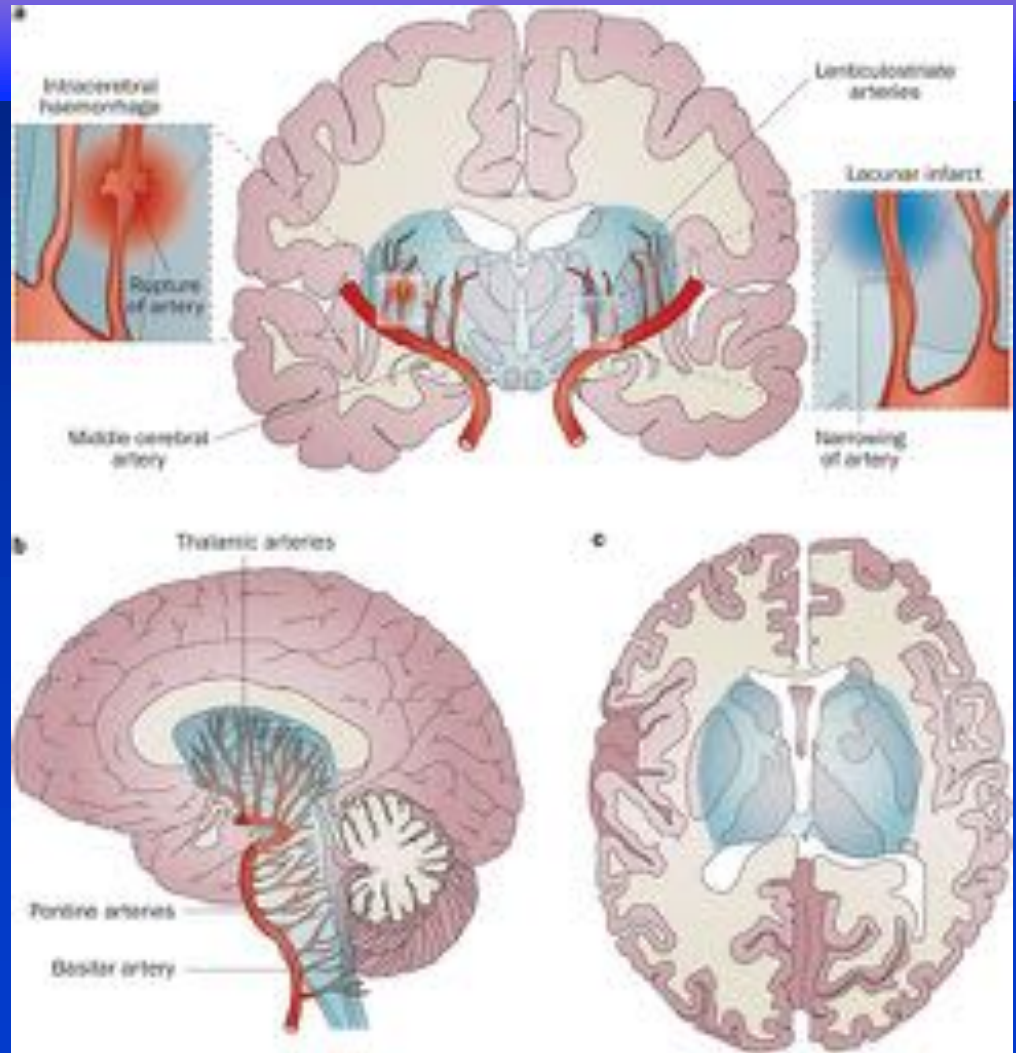
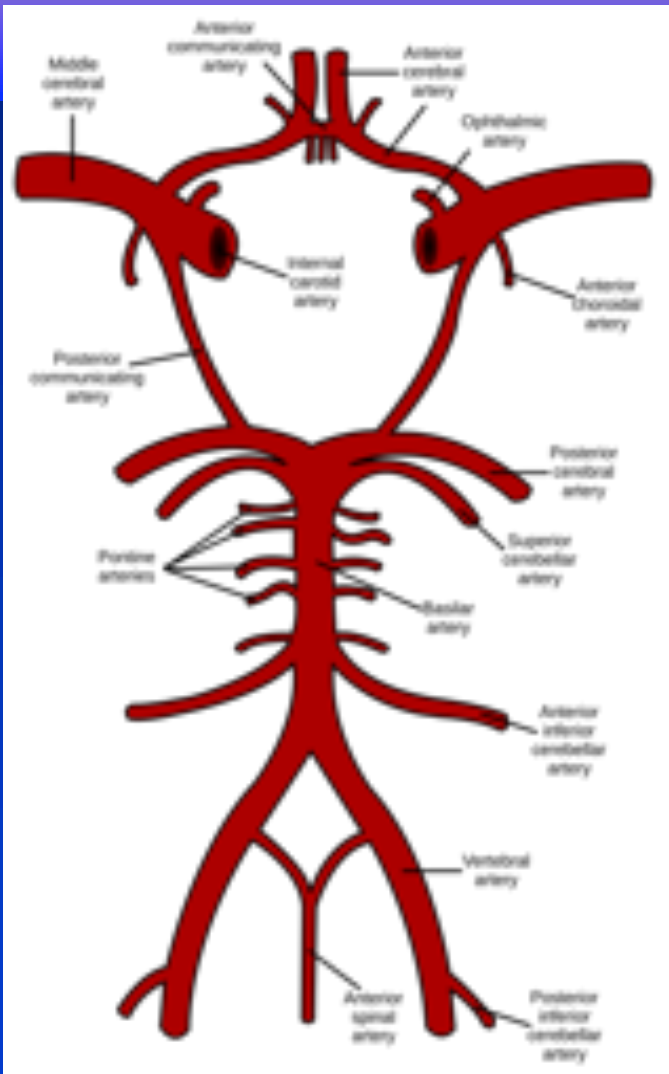
Sacco RL Stroke 2013;44: 2064-2089



Types of Stroke

- Blood flow to brain tissue can be hampered in two ways:
- the vessel clogs within (ischemic stroke)
 - Clot forms at the site of obstruction: thrombosis
 - Clot breaks off and occludes a distal vessel: embolism
- the vessel ruptures, causing blood to leak into the brain (hemorrhagic stroke)
 - Bleeding into brain parenchyma: intracranial hemorrhage
 - Bleeding into CSF space
 - Outside brain: subarachnoid hemorrhage - SAH
 - Inside ventricle: intraventricular hemorrhage - IVH

Pathophysiology of lacunar and haemorrhagic stroke



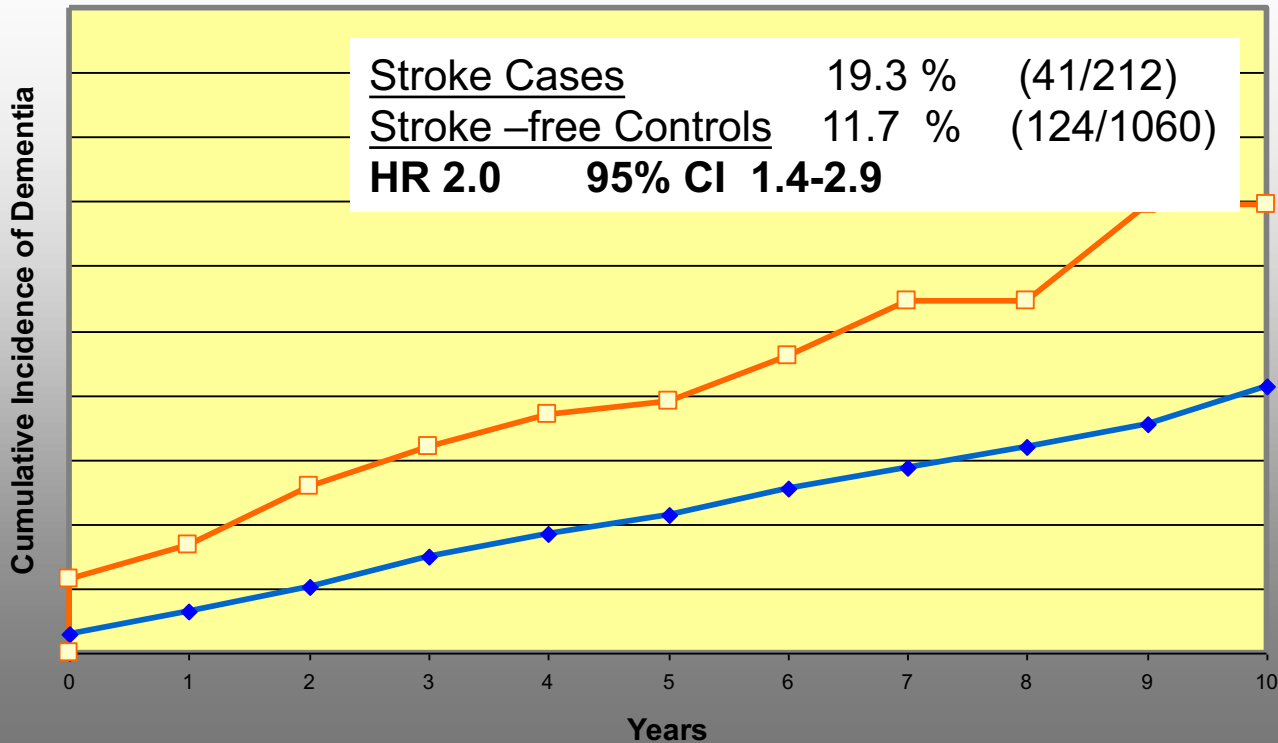
Sörös, P. *et al.* (2012) Antihypertensive treatment can prevent stroke and cognitive decline
Nat. Rev. Neurol. doi:10.1038/nrneuro.2012.255

Dementia After Stroke

The Framingham Study (*Stroke*. 2004;35:1264-1269)

Cristina S. Ivan, MD; Sudha Seshadri, MD; Alexa Beiser, PhD; Rhoda Au, PhD; Carlos S. Kase, MD
Margaret Kelly-Hayes, RN, EdD; Philip A. Wolf, MD

Cumulative Incidence of Dementia
Comparison of Stroke Cases to Controls



FHS data show temporal trend in impact of stroke

400% to 40% increase across 4 epochs

Kaplan-Meier plot showing cumulative incidence of dementia: comparison of stroke cases to controls.

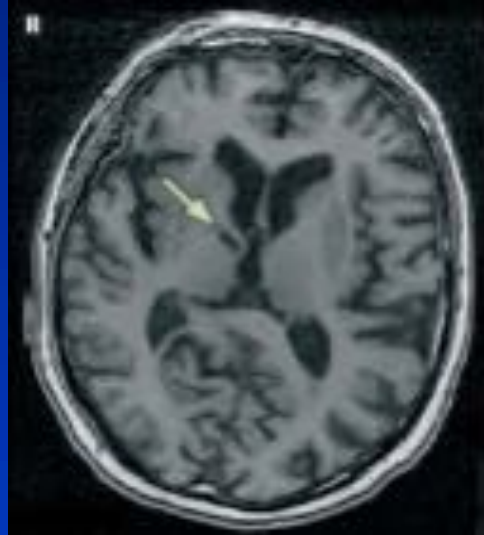
Subclinical Vascular Brain Injury

- 5X prevalence of clinical stroke/TIA
- Increases risk of clinical stroke and dementia, disability, depression and death
- Worse outcome after clinical stroke
- No treatment available; prevention is key

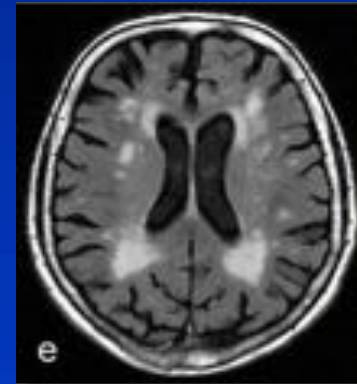
Silent Strokes and Vascular Brain Injury

11-25% prevalence, increases with age & MRI technique used

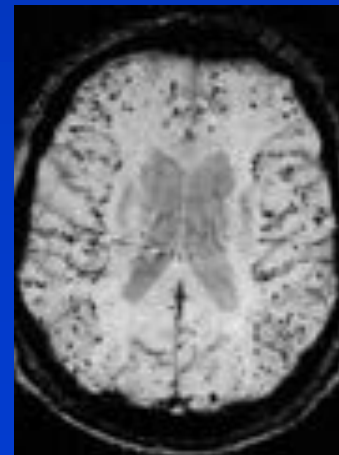
– **Lacunae**



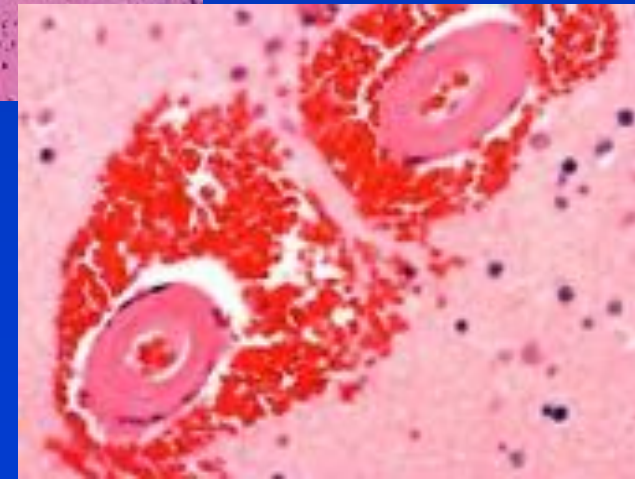
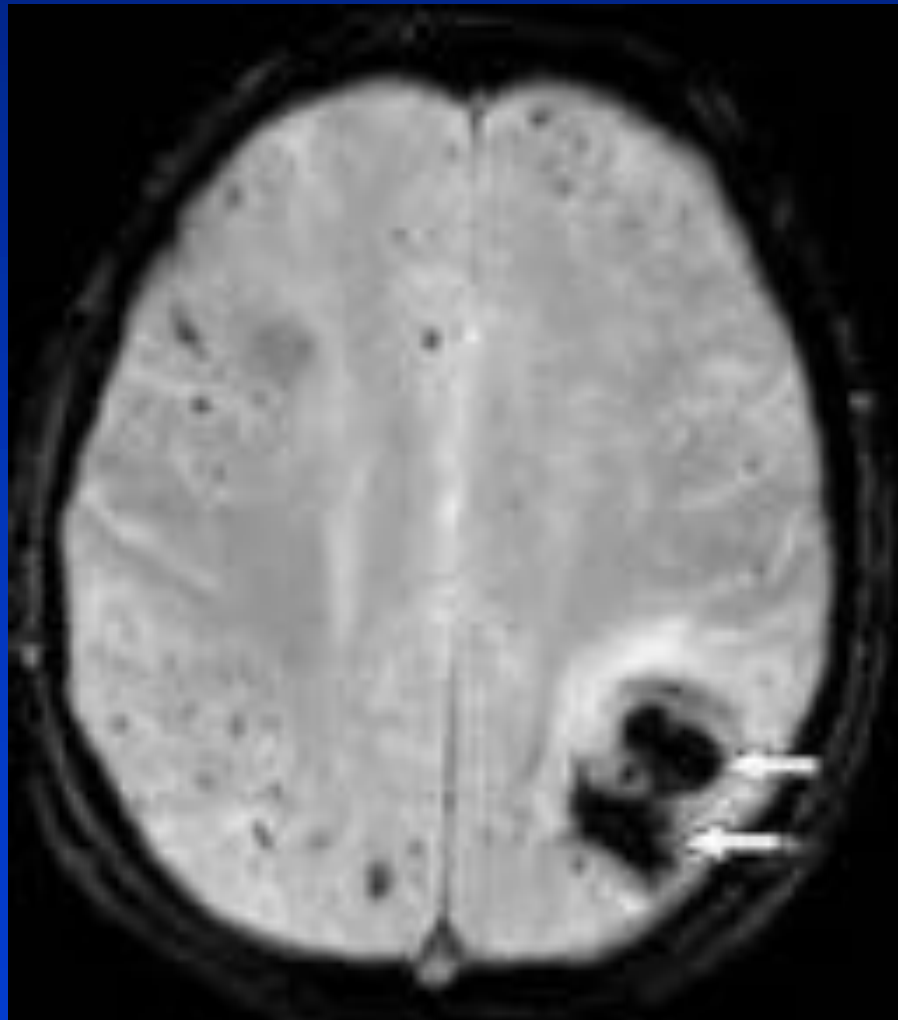
– **White Matter Hyperintensities**



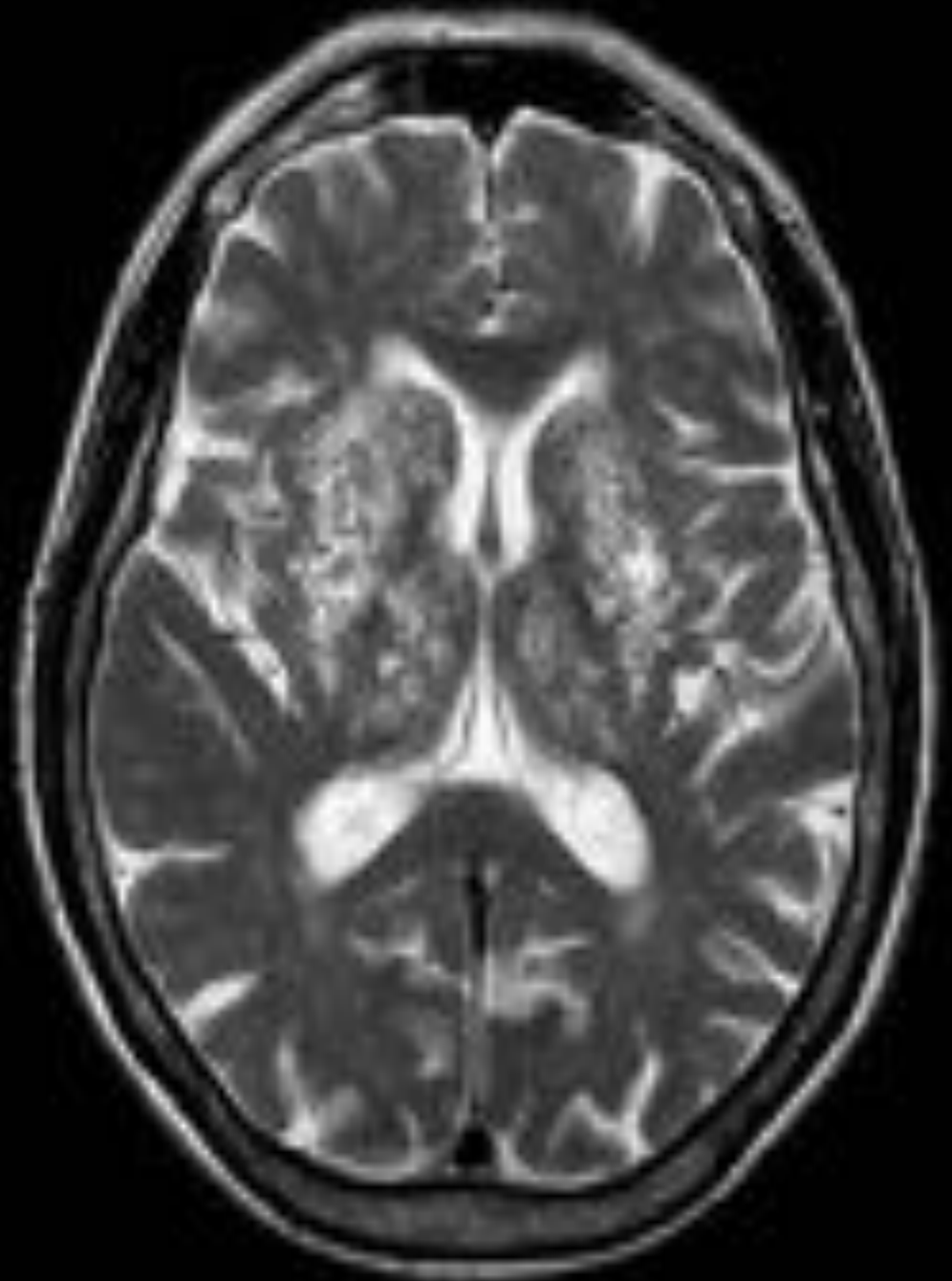
– **Cerebral Microbleeds**

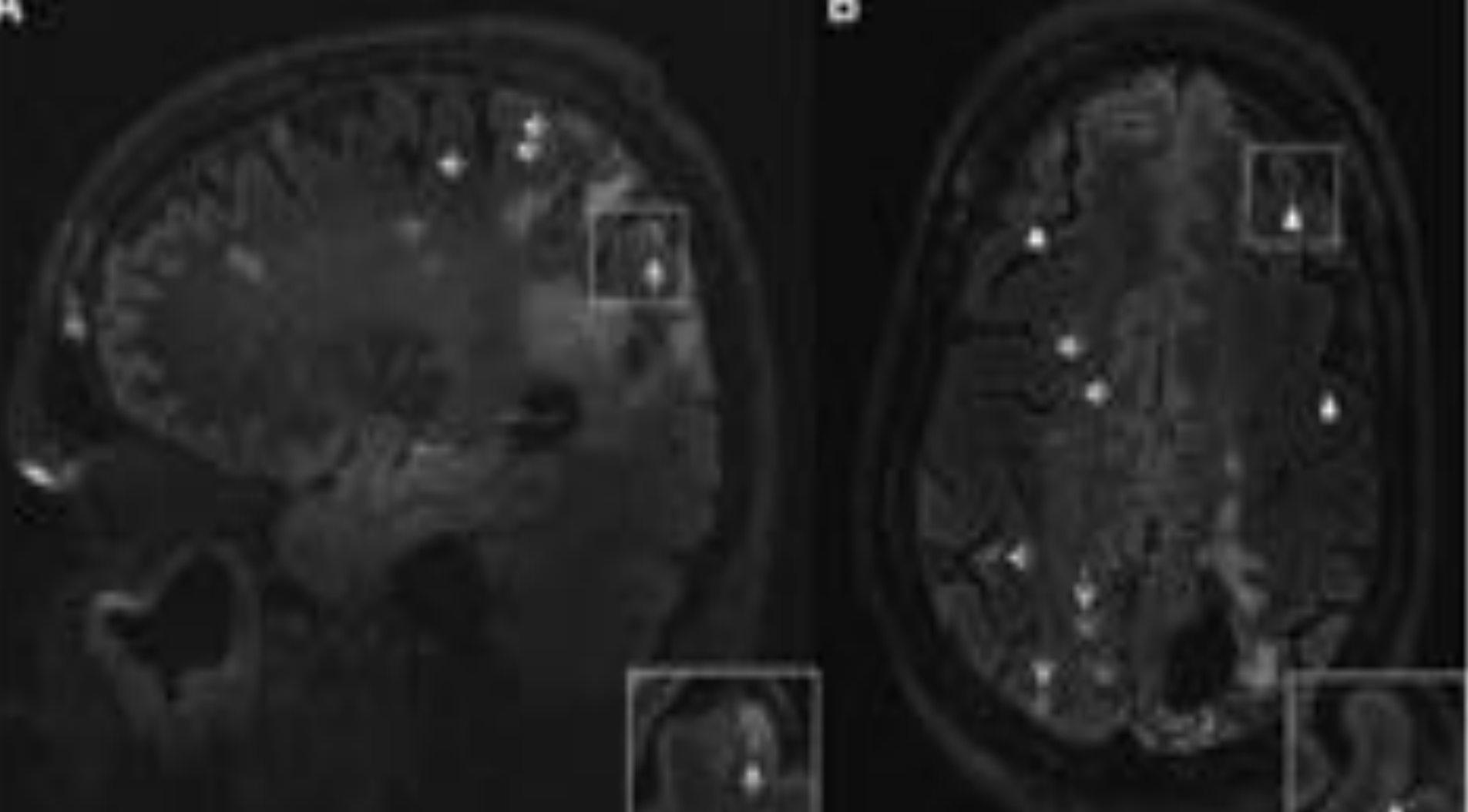


Cerebral Amyloid Angiopathy



Enlarged
Perivascular
Spaces





www.jbfm.com

BRIEF COMMUNICATION

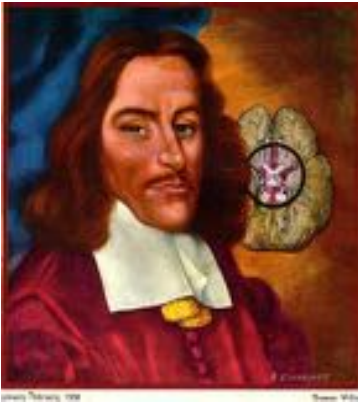
Cortical microinfarcts on 7T MRI in patients with spontaneous intracerebral hemorrhage

Suzanne J van Veluw¹, Wilmar MT Jolink¹, Jeroen Hendrikse², Majam I Geerlings³, Peter R Luijten², Geert Jan Blitsels¹ and Catharina JM Klijn¹

Also now
Detectable
on 3T

History of Vascular Dementia

- 1672 - Willis: Dementia post-apoplexy



“Foolishness may also result from great strokes ...”



- 1894 - Binswanger
 - Encephalitis subchronica progressiva
- 1894 - Alzheimer
 - Arteriosclerotic brain degeneration



History of Vascular Dementia



- 'Hardening of Arteries'
- Blessed, Tomlinson and Roth (1970):
 - Most senile dementia is associated with Alzheimer-type pathology



History of Vascular Dementia

- ‘Hardening of Arteries’
- Blessed, Tomlinson and Roth (1970):
 - Most senile dementia is associated with Alzheimer-type pathology
- Hachinski et al. (1974): ‘multi-infarct dementia’
 - ‘When vascular disease is responsible for dementia it is through the occurrence of multiple small or large cerebral infarcts’



Lancet. 1974;2:207–210

Clinical Criteria to Define VaD

- Hachinski Ischemic Score (HIS)
- Diagnostic and Statistical Manual (DSM- III, IIIR, IV) criteria
- International Classification of Disease (ICD)
- California Alzheimer's Disease Diagnostic and Treatment Centers (ADDC) criteria
- National Institute for Neurological Diseases and Stroke- Association Internationale pour la Recherche et 'Enseignement en Neurosciences (NINDS-AIREN) criteria

K=0.76

Prevalence varies with criteria: 13-50%



Clinicopathological Validation Study of Four Sets of Clinical Criteria for Vascular Dementia

GOLD, BOURAS, CANUTO, ET AL.

(Am J Psychiatry 2002; 159:82–87)

Clinical Criteria for Vascular Dementia	Sensitivity	Specificity
DSM-IV	0.5	0.84
ADDTC-possible	0.7	0.78
NINDS-AIREN-possible	0.55	0.84
ADDTC-probable	0.2	0.91
NINDS-AIREN-probable	0.25	0.93
ICD-10	0.2	0.94

Criteria are insensitive

Vascular Dementia: A Radical Redefinition

Dementia. 1994; 5:130-2.

- 'Vascular' too generic
- 'Dementia' too late
- Vascular Cognitive Impairment
 - Brain at Risk.... to.... Dementia





Vascular Cognitive Impairment (VCI)

The Inclusive Definition

Lancet Neurology, 2003; 2: 89-98

- Cognitive or behavioral problems
- Evidence of damage to brain due to vascular factors

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

Victoria Barkley, MD, PhD, Colette Lathrop, MD, Eric C. Peterson, MD, PhD, Jacques M. Simic, MD, PhD, David L. Dunbar, PhD, Sandra L. Clark, MD, William J. Brown, MD, Charles DeCar, MD, Eric G. Strass, MD, Raj N. Kalaria, PhD, PhD, Hans V. Finsen, MD, David M. Heiserman, MD, Gary A. Ewing, MD, Maria Delgado, MD, John W. Morley, MD, Gabriela G. Lemos, PhD

Background and Purpose: Harmonization of vascular cognitive impairment (VCI) diagnosis is being achieved, but a need for standardization will have negative consequences if not done so. The present study will assess the impact of VCI diagnosis on the early stages of cognitive impairment, but to have a focus on the diagnosis of Alzheimer disease. The present study will assess the impact of VCI diagnosis on the early stages of cognitive impairment, but to have a focus on the diagnosis of Alzheimer disease. The present study will assess the impact of VCI diagnosis on the early stages of cognitive impairment, but to have a focus on the diagnosis of Alzheimer disease.

Methods: The National Institute of Neurological Disorders and Stroke (NINDS) and the Canadian Stroke Network (CSN) convened a meeting to discuss VCI diagnosis, epidemiology, etiology, pathophysiology, and clinical trials in vascular cognitive impairment.

Results: The results of this discussion are reported here.

Conclusions: The development of a common, standard approach to VCI diagnosis is essential if we, as a community, are to have a focus on the diagnosis of Alzheimer disease. The present study will assess the impact of VCI diagnosis on the early stages of cognitive impairment, but to have a focus on the diagnosis of Alzheimer disease.

Key Words: Dementia; stroke; diagnosis; epidemiology; etiology; pathophysiology; clinical trials; vascular cognitive impairment

Recommended
Standardized
Data
Collection

Recognized
'we are at that bewildering stage that
follows discoveries but precedes true understanding'

Stroke

Journal of the American Heart Association

American Stroke
Association

A Division of American
Heart Association



Vascular Contributions to Cognitive Impairment and Dementia: A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association

Philip B. Gorelick, Angelle Stevens, Vanda E. Black, Charles DeCarli, Steven M. Greenberg, Constantine Iadecola, Laura J. Leonar, Stephanie Laurent, Oscar L. Lopez, David Nyengaard, Ronald C. Petersen, Julie A. Schneider, Christophe Tzouras, Dennis K. Aron, David A. Bennett, Helena C. Chui, Randall T. Higazi, Ruth Lindquist, Peter M. Nilsson, Gustavo C. Roman, Frank W. Salfke and Ivánia Verhaegh

Treat HTN in midlife

Prevent Stroke

Stroke 2011; 42:2195-2256 originally published online July 21, 2011

doi: 10.1161/STROKE.0b013e3182290496

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ISSN: 1524-4528

VCI is Heterogenous

- Vascular Dementia
 - Following clinical strokes (single, multiple, strategic)
 - Extensive small vessel disease (silent strokes, WMH)
 - Specific genetic arteriopathies (CADASIL)
 - Amyloid angiopathy & multiple microbleed
- Vascular Mild Cognitive Impairment (VaMCI)
- Contribution of vascular factors to AD

Vascular and Alzheimer pathology co-exist, so both can be diagnosed simultaneously

Emerging Concepts: Vascular Contributions to Cognitive Aging

- Vascular Contribution to Clinical Severity of Dementia
 - Permissive/Additive..... versus....
Synergistic/Multiplicative
- Observational data in humans and experimental data from animal models seem to suggest different answers

'Typical' Clinical Presentation of VaD

- Multifocal rather than global cognitive deficits
- Executive dysfunction more prominent than memory loss
- Recognition better than spontaneous recall
- Depression,
- Involuntary emotional expression (pseudobulbar affect)
- Focal neurological deficits (speech, limb)
- Psychomotor slowing, gait abnormality
- Bladder control problems

Stroke Risk Factors

Non-modifiable

Age, Sex, Race, Ethnicity, Genetics

Modifiable

Medical Conditions

- Hypertension
- Cardiac disease
- Atrial fibrillation
- Diabetes & Met-Syn
- Kidney Disease
- High Homocysteine
- Inflammation
- Subclinical Disease

Behaviors

- Cigarette smoking
- Obesity
- Physical inactivity
- Hormone Replacement Therapy
- Alcohol abuse
- Diet: fruits, vegetable, fish, fat, salt

Probability of Stroke: A Risk Profile From the Framingham Study

Philip A. Wolf, MD; Ralph B. D'Agostino, PhD;
Albert J. Belanger, MA; and William B. Kannel, MD

Stroke 1991;22:312-318

Risk Prediction & Stratification

Education and Motivation

Easy aggregate measure of vascular brain injury

Framingham Stroke Risk Profile

- Framingham Stroke Risk Profile Score based on age, sex & measurements of:
 - Systolic blood pressure
 - Antihypertensive therapy
 - Diabetes
 - Smoking
 - Prior cardiovascular disease
 - Atrial fibrillation
 - EKG- Left ventricular hypertrophy

Lipid and lipoprotein measurements and the risk of ischemic vascular events

Framingham Study

Aleksandra Pilula, MD

ABSTRACT

Neurology 2015

SDU log-HDL	0.77 [0.68-0.87]***	P<0.001
--------------------	---------------------	---------

HDL\leq40	1.59 [1.23-2.05]***	P<0.001
-------------------------------	---------------------	---------

Effect seen in both Men and Women

Not attenuated by adjustment for interim MI

Probability of Stroke in Men in 10 Yrs.

Points	0	+1	+2	+3	+4	+5	+6	+7	+8	+9	+10	Points
Age	55	58	60	64	66	70	75	78	80	83	85	5
Untreated SBP	100	110	120	130	140	150	160	170	180	190	200	8
Treated SBP	100	108	115	120	126	132	140	146	156	170	190	-
Diab	No		Yes									2
Cigs	No			Yes								3
CVD	No				Yes							0
A-Fib	No				Yes							4
LVH	No					Yes						0
											Total	22

Probability of Stroke in Men in 10 Yrs.

Points	10-Yr Prob	Age	Average 10-Yr Prob
5	5%	55-59	5.9%
10	10%	60-64	7.8%
14	17%	65-69	11%
16	22%	70-74	13.7%
20	37%	75-79	18.0%
22	47%	80-84	22.3%
25	63%		

Risk of Stroke - Increased 3.4 fold

Predicting cognitive decline

A dementia risk score vs the Framingham vascular risk scores

FSRP better than Dementia Risk Score

Greg Kallalides, PhD
Alan Dugmore, MD
Alex Elton, MD, PhD
Marie J. Shipley, MSc
Svenjar Tulba, PhD
Mika Kivimaki, PhD
Arkana Singh-Manoux,
PhD

Correspondence to:
Dr Kallalides,
g.kallalides@hpa.gov.uk

ABSTRACT

Objective: Our aim was to compare 2 Framingham vascular risk scores with a dementia risk score in relation to 10-year cognitive decline in late middle age.

Methods: Participants were men and women with mean age of 55.6 years at baseline, from the Whitehall II study, a longitudinal British cohort study. We compared the Framingham general cardiovascular disease risk score and the Framingham stroke risk score with the Cardiovascular Risk Factors, Aging and Dementia (CAIDE) risk score that uses risk factors in middle to estimate risk of late life dementia. Cognitive tests included reasoning, memory, verbal fluency, vocabulary, and global cognition, assessed 3 times over 10 years.

Results: Higher cardiovascular disease risk and higher stroke risk were associated with greater cognitive decline in all tests except memory; higher dementia risk was associated with greater decline in reasoning, vocabulary, and global cognitive scores. Compared with the dementia risk score, cardiovascular and stroke risk scores showed slightly stronger associations with 10-year cognitive decline; these differences were statistically significant for semantic fluency and global cognitive scores. For example, cardiovascular disease risk was associated with -0.06 (95% confidence interval [CI] = -0.08 , -0.05) decline in the global cognitive scores over 10 years whereas dementia risk was associated with -0.03 (95% CI = -0.04 , -0.02) decline (difference in β coefficients = 0.03 , 95% CI = 0.01 , 0.05).

Conclusions: The CAIDE dementia and Framingham risk scores predict cognitive decline in late middle age but the Framingham risk scores may have an advantage over the dementia risk score for use in primary prevention for assessing risk of cognitive decline and targeting of modifiable risk factors. *Neurology*® 2013;80:1300-1308

From: **Plasma Total Cholesterol Level as a Risk Factor for Alzheimer Disease: The Framingham Study**

Arch Intern Med. 2003;163(9):1053-1057. c

Table 3. Multivariate Adjusted Hazard Ratios of AD in Relation to Cholesterol Measurements*

Variable	AD, No./Study Population	Hazard Ratio (95% Confidence Interval)
Mean TC1-15	60/853	0.95 (0.87-1.04)
TC20	60/853	0.97 (0.90-1.05)
HDL at examination 20	60/849	1.10 (0.93-1.31)
ΔTC15-20†	53/741	1.01 (0.92-1.11)

Abbreviations: AD, Alzheimer disease; TC1-15, total cholesterol levels across examination cycles 1 to 15; TC20, total cholesterol level measured at the 20th examination cycle; ΔTC15-20, change in total cholesterol levels between examination cycles 15 and 20.

*Adjusted for age, sex, apolipoprotein E genotype, coronary heart disease, therapy to lower lipid levels, and body mass index.

†Includes subjects who were not receiving medications to lower lipid levels.

Cholesterol levels were not associated with dementia or AD risk

Table Title:

Multivariate Adjusted Hazard Ratios of AD in Relation to Cholesterol Measurements*



American Journal of EPIDEMIOLOGY

Volume 138

Number 6

September 15, 1993

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School of Hygiene and Public Health

Sponsored by the Society for Epidemiologic Research

ORIGINAL CONTRIBUTIONS

Untreated Blood Pressure Level is Inversely Related to Cognitive Functioning: The Framingham Study

Merit F. Elias,¹ Philip A. Wolf,² Ralph B. D'Agostino,² Janet Cobb,² and Lon R. White⁴

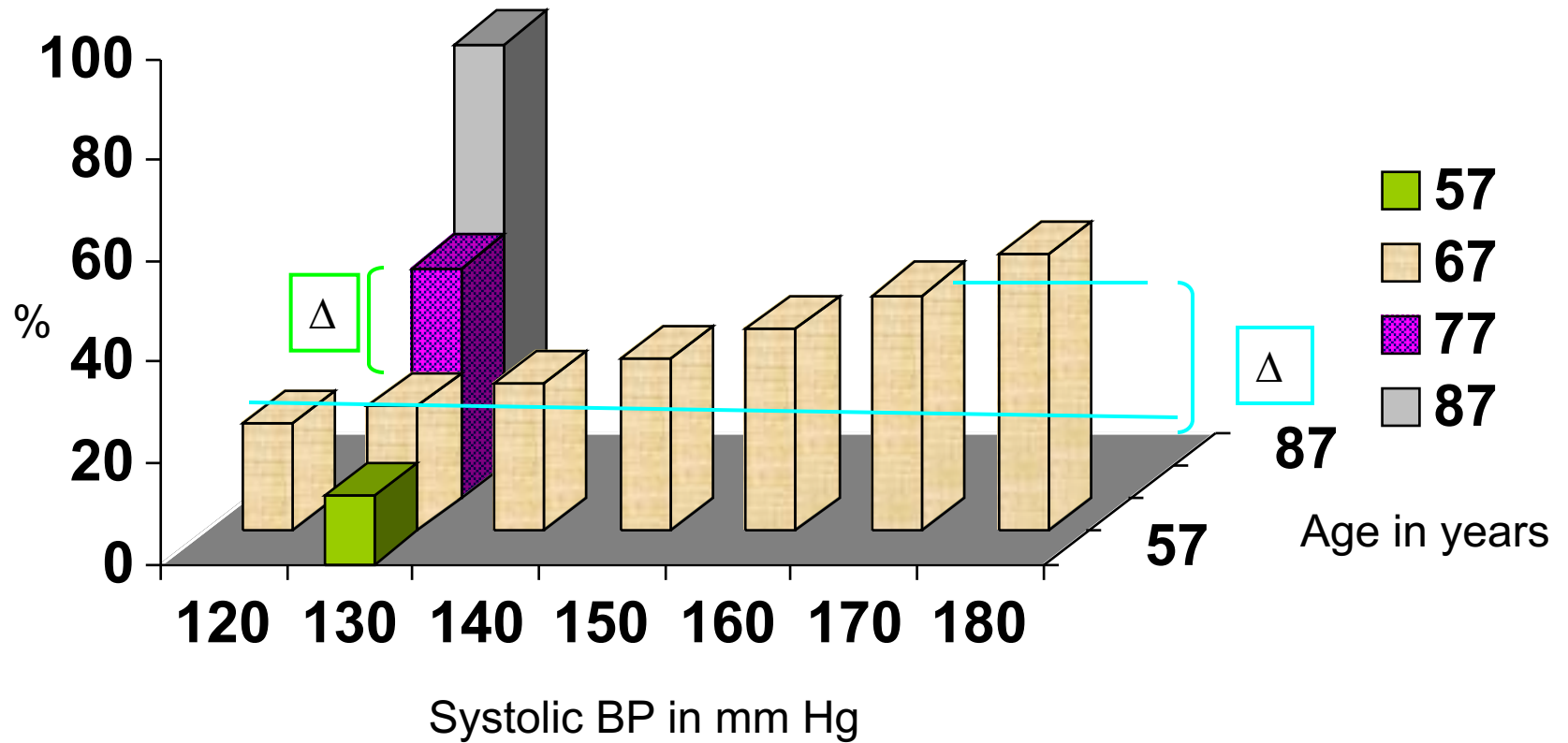
Untreated Blood Pressure Level is Inversely Related to Cognitive Function: The Framingham Study

Elias MF, Wolf PA, D'Agostino RB, Cobb J, White LR.

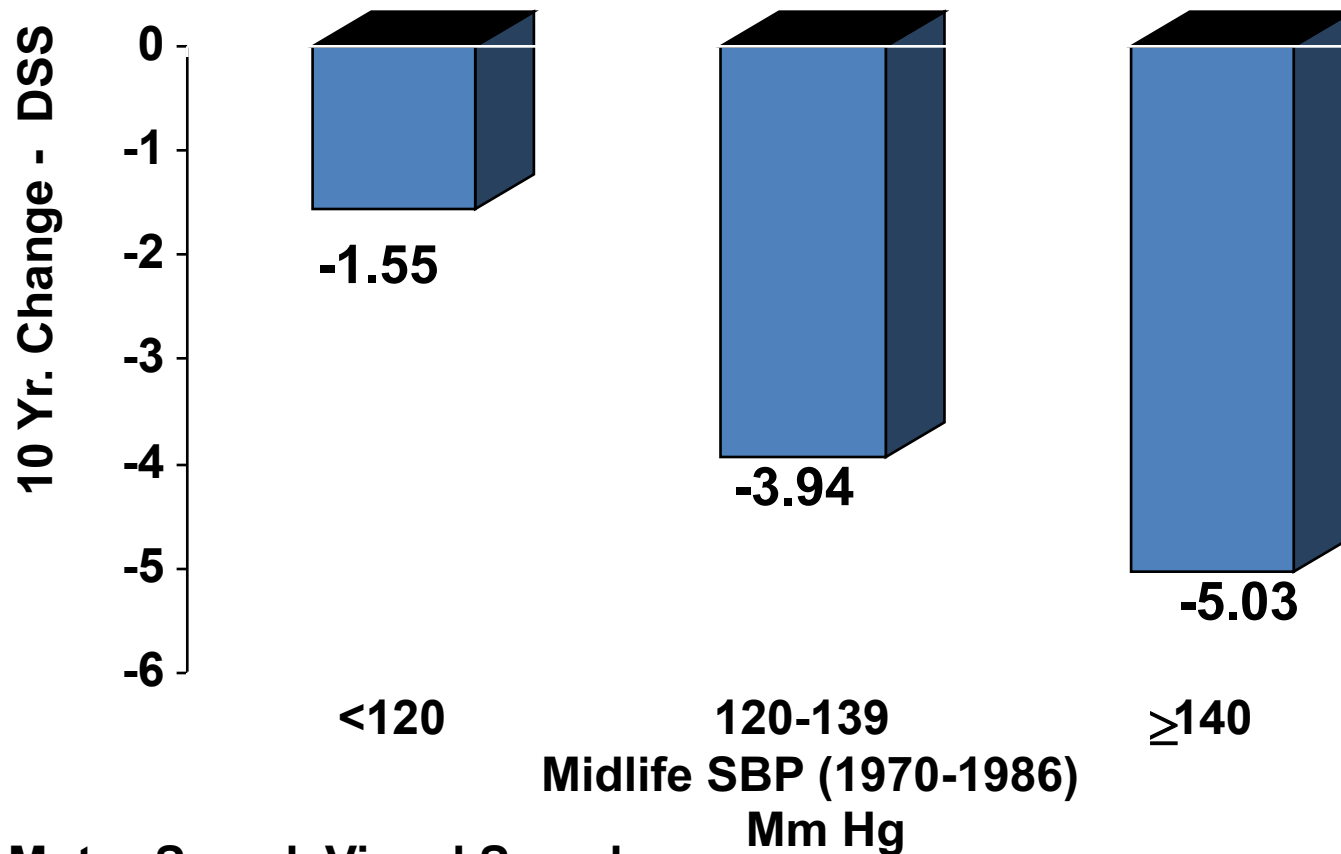
Am J Epidemiol 1993; 138:353-64

- 1702 Framingham subjects aged 55-88
- BP measured over 5 consecutive exams (1956-64) before anti-hypertensive medications were widely used
- On neuropsych evaln in 1976-78, BP was inversely related to performance-

Odds of subject having logical memory (delayed) score in bottom 25% value for sample



Midlife SBP & 10 Yr. Change in Digit Symbol Substitution Test NHLBI Twin Study

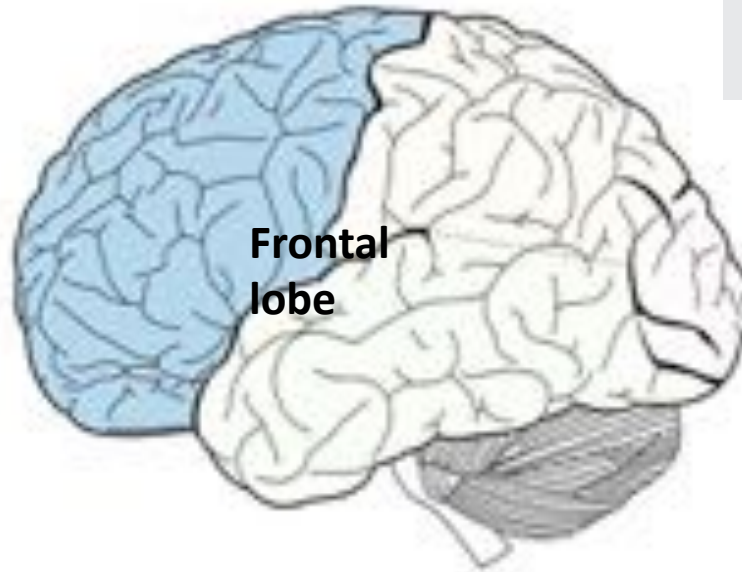


DSS - Motor Speed, Visual Search,
Visuomotor Coordination

Adherence to Ideal CVH slows vascular related brain aging

COHORT 2,750 stroke-, dementia free Framingham Offspring (mean age 61) assessed twice ~6 years apart

RESULTS Higher Ideal CVH predicted a lower risk of incident **stroke** (HR = 0.83, 95% CI 0.71-0.97) and **less cognitive decline** on tasks measuring visual memory ($\beta \pm SE = 0.02 \pm 0.01$, $p=0.012$) and reasoning ($\beta \pm SE = 0.02 \pm 0.01$, $p=0.044$)



A 1-point higher CVH score reduced the rate of decline in frontal brain volume to that of someone 3.4 years younger.

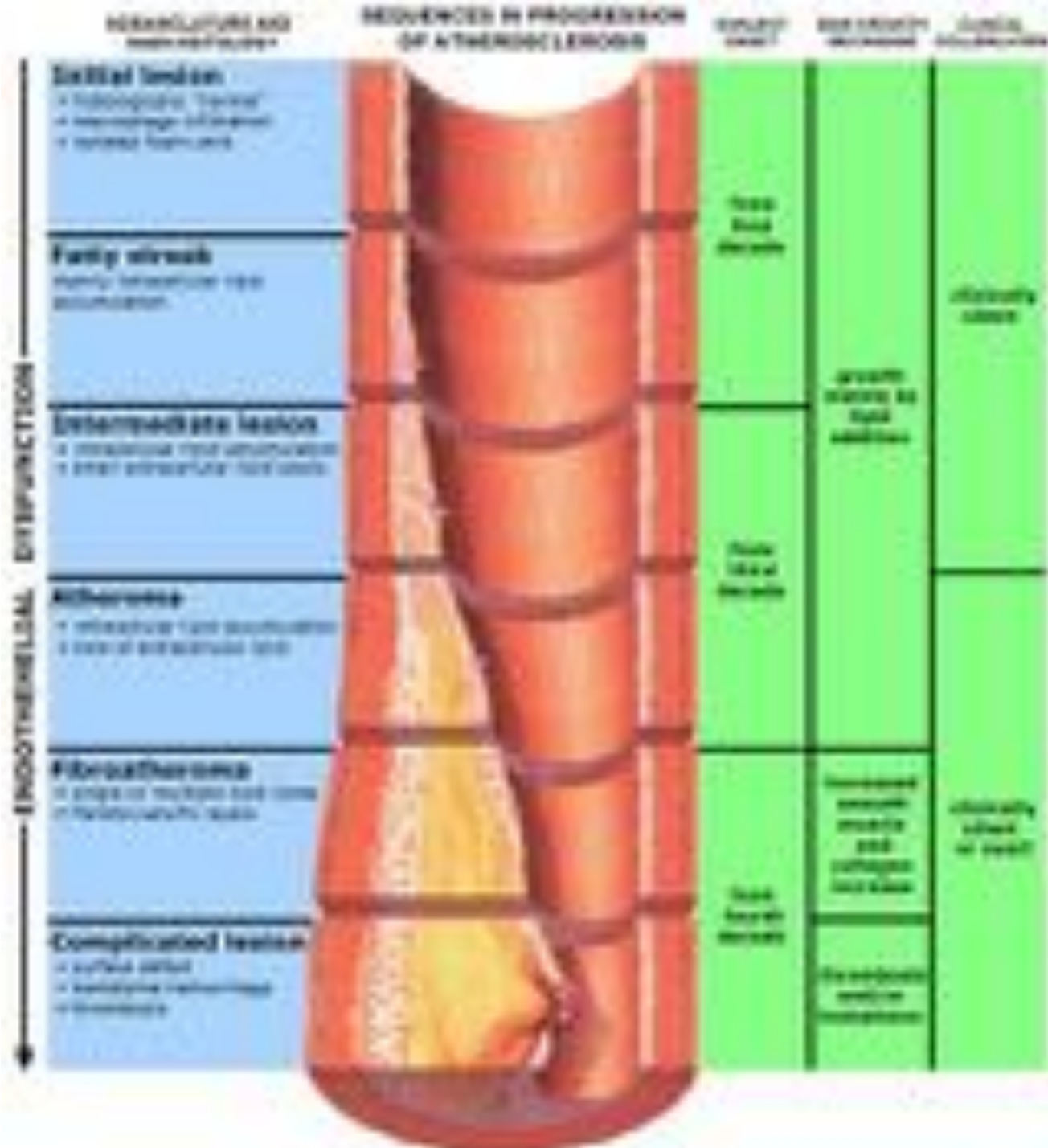
DISCUSSION Adherence to the American Heart Association's Ideal CVH behaviours may protect against vascular related brain injury. The concept of Ideal CVH should be promoted to protect the brain, as well as the heart, from vascular risk factors.

Matthew Pase, Alexa Beiser, Danielle Enserro, Vanessa Xanthakis, Hugo Aparicio, Claudia Satizabal, Jayandra Himali, Carlos Kase, Vasam Ramachandran, Charles DeCarli & Sudha Seshadri.

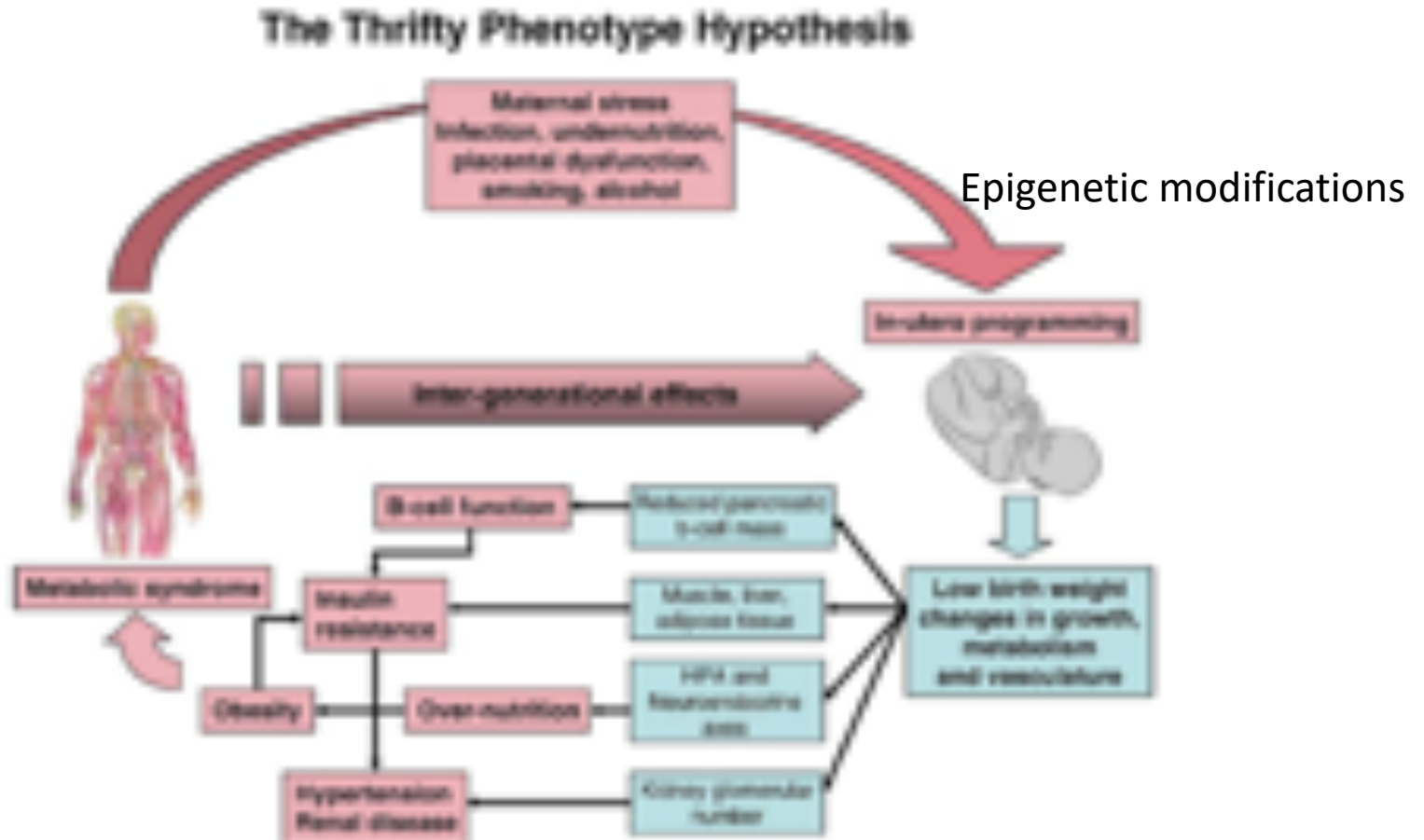


Emerging Concepts: Vascular Contributions to Cognitive Aging

- VCI is a life course 'disease,' but we may need sensitive measures to detect mid-life impact
- Relative Impact Greater in Younger Adults



Barker Hypothesis



Mental Ability in Childhood and Cognitive Aging

Gerontology 2008;54:177-186

Alan J. Gow^a Wendy Johnson^{a,c} Alison Pattie^a Martha C. Whiteman^a
John Starr^b Ian J. Deary^a

Multivariable linear regression suggested IQ at 11 predicted both IQ at 79 and change over next 4 years

LVLGM suggested no association of IQ at 11 with change

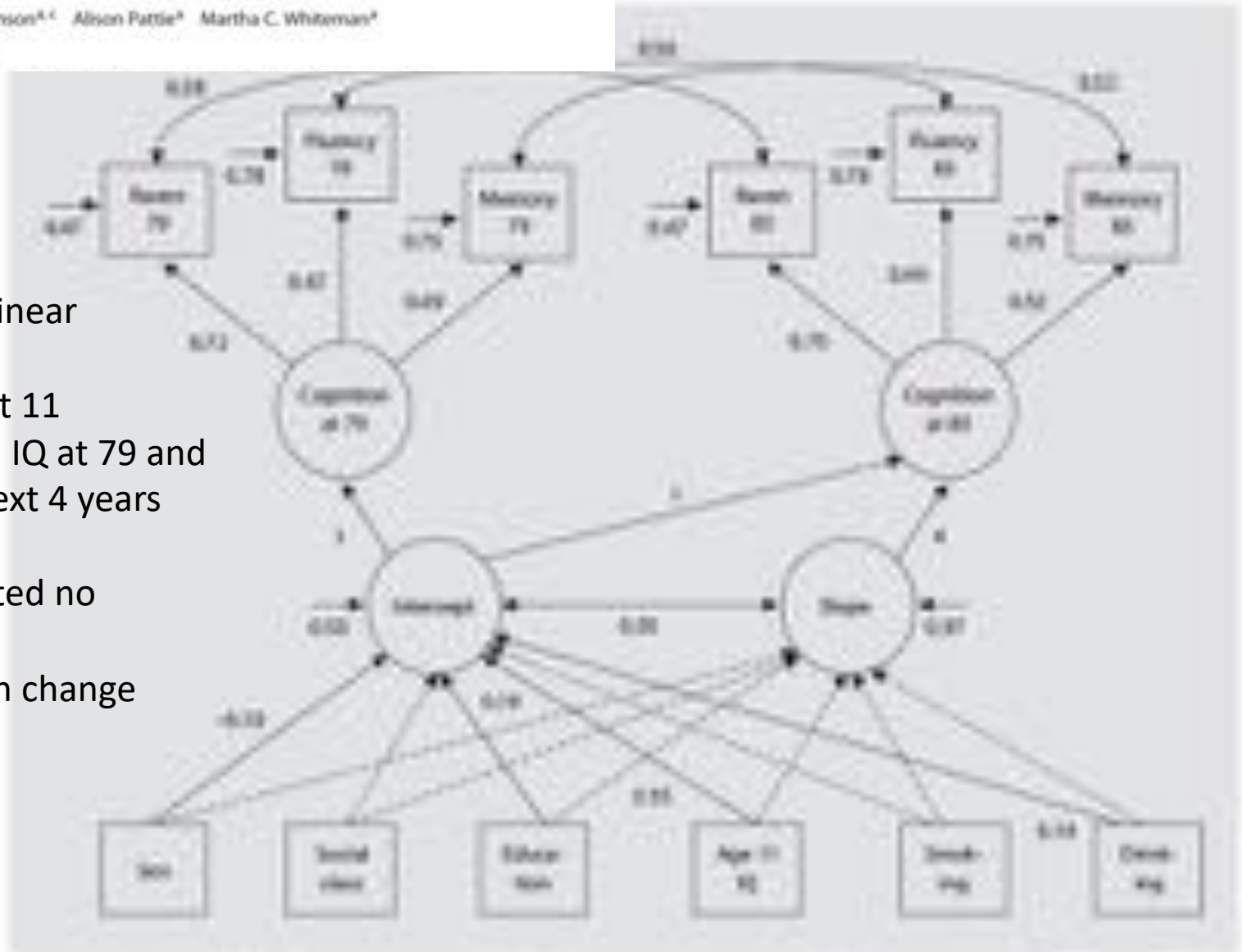


Fig. 3. Latent variable trace growth model with time constant. (a) Results were not measured; they were set by the form of the

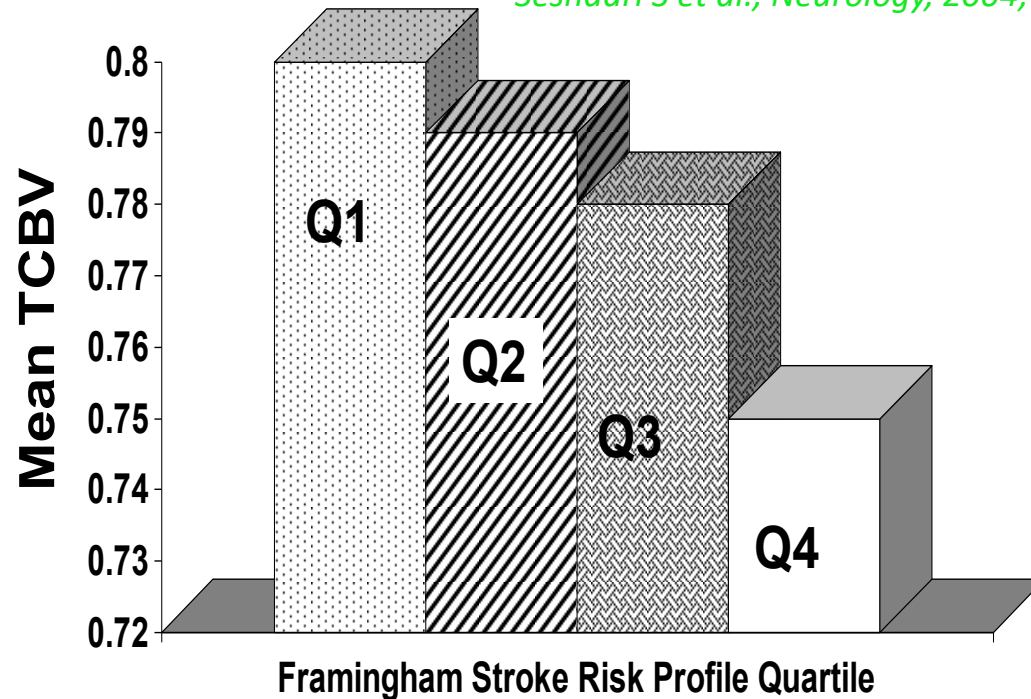
Cohort Studies of Vascular Factors & Cognition/Dementia

- Persons enrolled at ~age 65
 - Cardiovascular Health Study/ Rotterdam 1/ 3C/ FHS Gen 1
- Persons enrolled at ages 45-65
 - Atherosclerosis Risk in Communities
 - FHS Gen 2
- Earlier life information available
 - AGES Reykjavik
 - CARDIA
 - FHS Gen 3

Mean TCBV by Quartile of Framingham Stroke Risk Profile

Seshadri S et al., Neurology, 2004; 63:1590

Lower TCBV was associated with worse performance on Trails, VR-D, Similarities, Hooper



1841 stroke and dementia free adults, Mean age: 62 years

Persons with HTN had a Total Cerebral Brain Volume (TCBV) = that of a person 2 years older

Diabetics had a TCBV = person 6 years older!

Midlife vascular risk factor exposure accelerates structural brain aging and cognitive decline

1. J. L. ...
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Abstract
 Midlife risk factor exposure and progression of dementia have been associated with greater brain atrophy and cognitive decline. However, the extent to which midlife risk factor exposure accelerates structural brain aging and cognitive decline remains unclear.

Objective: A total of 1,100 participants without dementia from the Alzheimer's Disease Memory Clinic Study Study were enrolled. Midlife risk factor and cognitive regression were fitted to assess the association of midlife risk factor exposure with accelerated change in brain volume, hippocampal volume, WMH, executive function, memory, processing speed, and global cognition. Longitudinal mixed-effects models were used to assess the association between midlife risk factor exposure and cognitive decline.

Results: Exposure to midlife risk factor was associated with an increase in brain atrophy ($p < 0.001$) and cognitive decline ($p < 0.001$). Midlife diabetes and smoking were associated with greater cognitive decline in longitudinal models. A stronger pattern of accelerated hippocampal atrophy ($p < 0.001$) and WMH progression ($p < 0.001$) was observed in individuals exposed to midlife risk factor compared to those not exposed ($p < 0.001$) and independent of dementia stage at study enrollment ($p < 0.001$). Midlife risk factor exposure was also associated with greater cognitive decline in individuals with dementia ($p < 0.001$). Midlife risk factor exposure was also associated with greater cognitive decline in individuals with dementia ($p < 0.001$). Cognitive decline in brain atrophy was significantly associated with dementia severity and cognitive decline.

Exposure to midlife risk factor, diabetes, smoking, and dementia were associated with all measures of progression of vascular brain injury, global and hippocampal atrophy, and decline in executive function and memory. *Alzheimer's Dis* 2014;29:1-10

Effects of systolic blood pressure on white-matter integrity in young adults in the Framingham Heart Study: a cross-sectional study



Pauline Maillard, Sudha Seshadri, Alexa Beiser, Jayandra J Himali, Rhoda Au, Evan Fletcher, Owen Carmichael, Philip A Wolf, Charles DeCarli

Summary

Background Previous studies have identified effects of age and vascular risk factors on brain injury in elderly Lancet Neurol 2012; 11: 1039-47



Figure 5 Number of patients with white-matter hyperintensities at a voxel location

Pauline Maillard, Sudha Seshadri, Alexa Beiser, Jayandra J Himali, Rhoda Au, Evan Fletcher, Owen Carmichael...

Effects of systolic blood pressure on white-matter integrity in young adults in the Framingham Heart Study: a cross-sectional study

The Lancet Neurology Volume 11, Issue 12 2012 1039 - 1047

[http://dx.doi.org/10.1016/S1474-4422\(12\)70241-7](http://dx.doi.org/10.1016/S1474-4422(12)70241-7)

Among 579 young middle-aged (45 ± 9) healthy individuals, elevated SBP has a subtle, negative effect on WM microstructural integrity, especially in the corpus callosum. This reinforces the view that vascular brain injury may develop insidiously over several decades.

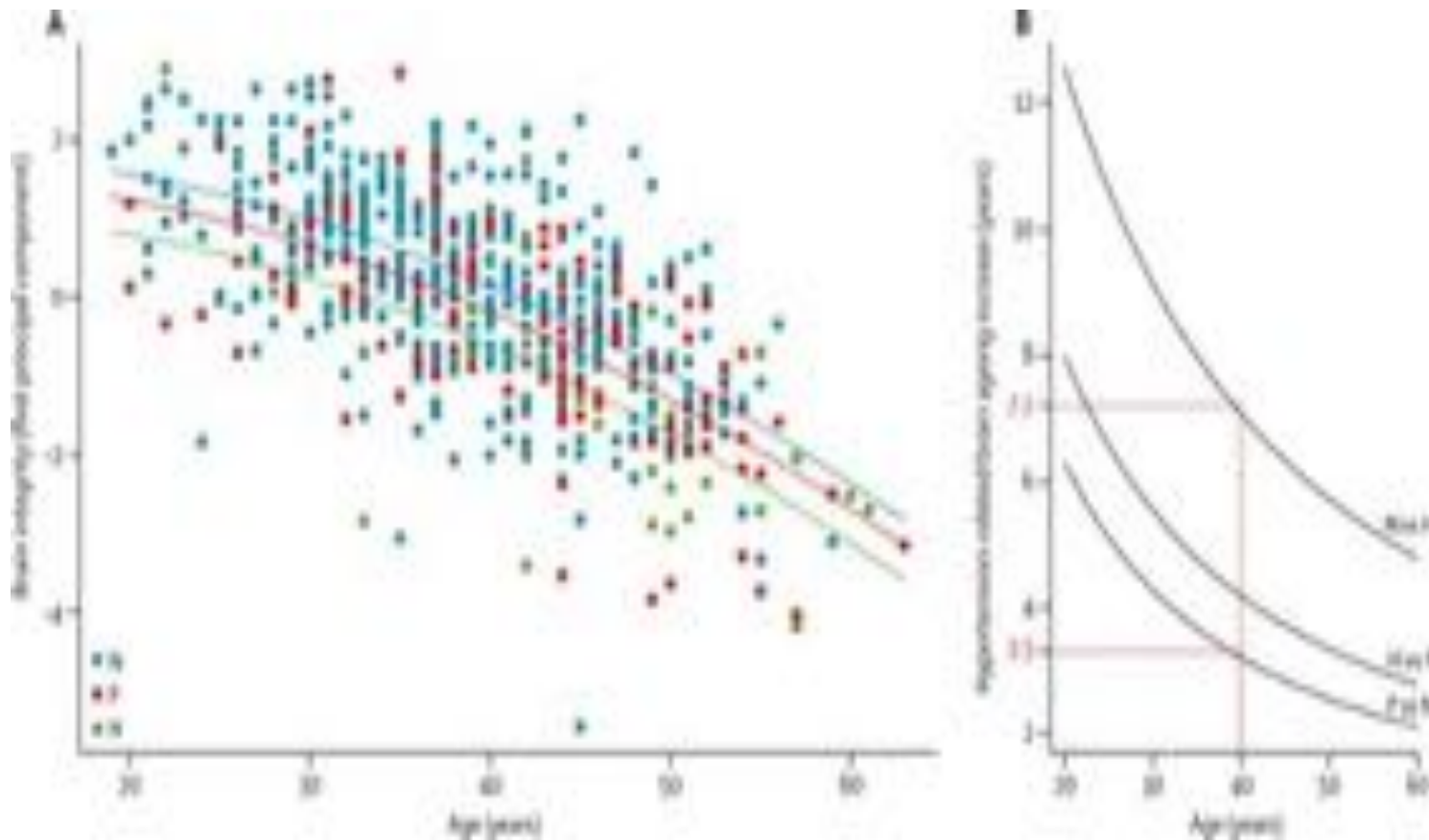


Figure 4 Regression curves relating brain integrity as expressed by the first principal component as a function of the hypertension category and age of the individual (A) and the difference in brain ageing increase between hypertension categories according...

Pauline Maillard , Sudha Seshadri , Alexa Beiser , Jayandra J Himali , Rhoda Au , Evan Fletcher , Owen Carmichael...

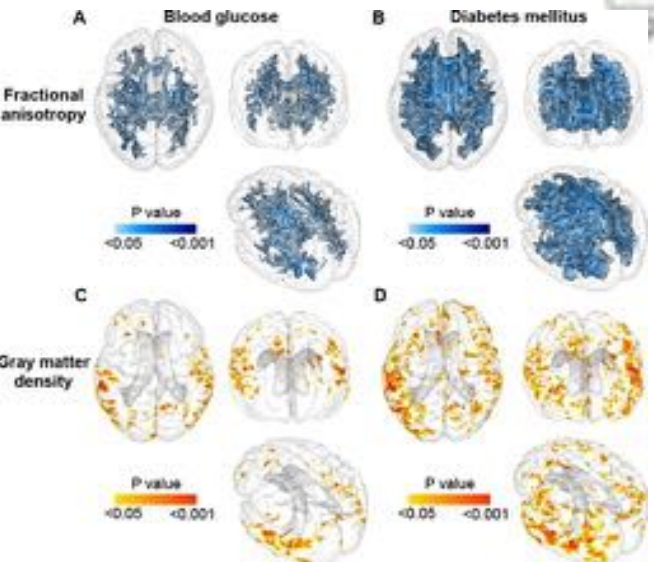
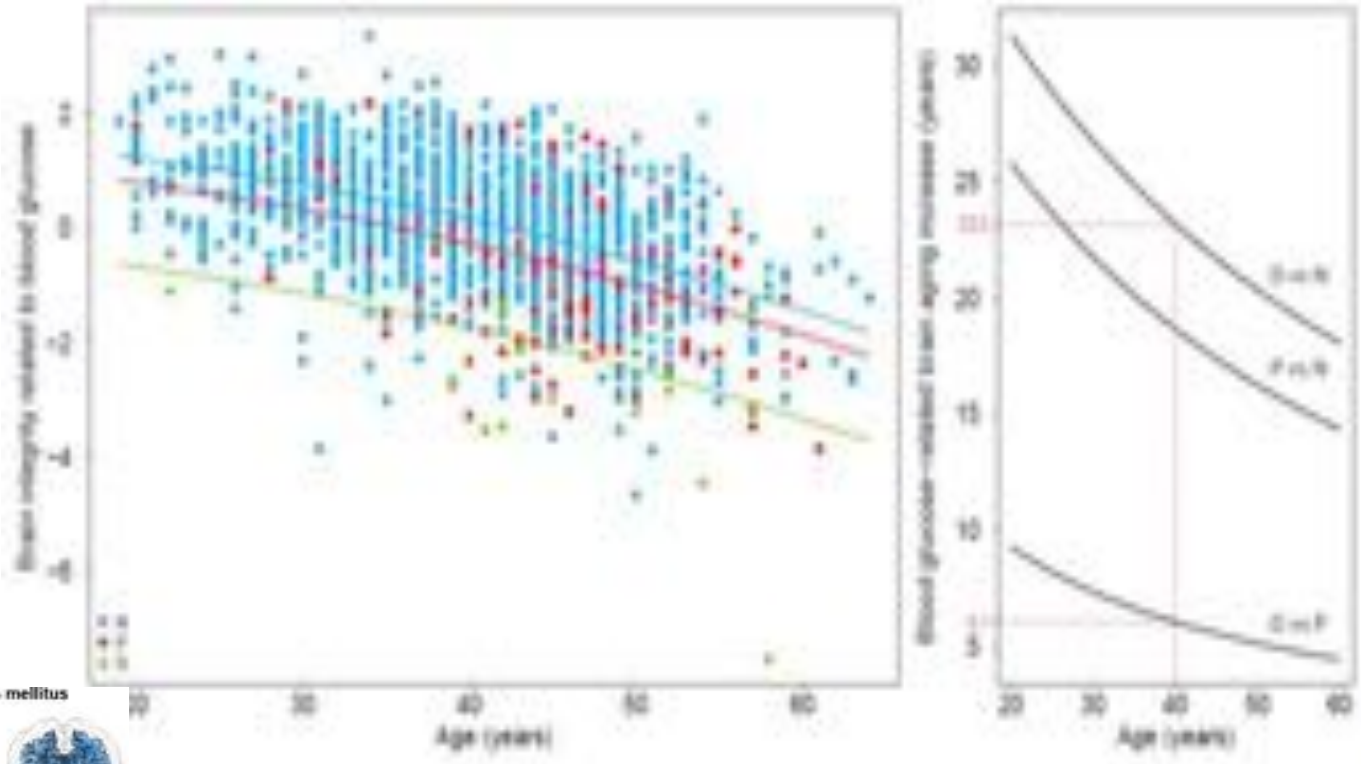
Effects of systolic blood pressure on white-matter integrity in young adults in the Framingham Heart Study: a cross-sectional study

The Lancet Neurology Volume 11, Issue 12 2012 1039 - 1047

Hypertensive 40 year old had loss of brain integrity equivalent to normotensive person aged 47 years

Association of Diabetes, Fasting Blood Glucose and Insulin Resistance with Cognitive and Structural Brain Measures in Young Adults: the Framingham Heart Study *Neurology 2015;84:2329-37*

Weinstein G, Beiser AS, Maillard P, Himali JJ, Au R, Kase CS, Wolf PA, Decarli C, Seshadri S.



1,597 dementia-free Gen 3
age 40±8; 56% women

Diabetic 40 year old had loss of brain integrity
equivalent to non-diabetic aged 63 years

Midlife Physical Fitness Predicts Brain Volume after 20 years

Table 2. Linear regression of TCBV measured in later-life on fitness and exercise hemodynamic variables at baseline and later-life, in Sample 1[#] (n=1094) and Sample 2^{##} (n=1583).

Variable	Model	Sample 1 [#] (n=1094)		Sample 2 ^{##} (n=1583)	
		Beta ± SD	p	Beta ± SD	p
Baseline (cycle 2, mean age 40+9 years; at MRI 58+8 years)					
Exercise Capacity	Model 1	0.02±0.01	0.075	0.05±0.01	<0.0001
	Model 2*	0.03±0.01	0.027	0.05±0.01	<0.0001
Exercise SBP	Model 1	-0.08±0.04	0.040	-0.12±0.04	0.0023
	Model 2†	-0.06±0.05	0.164	-0.10±0.04	0.01
Exercise DBP	Model 1	-0.15±0.06	0.020	-0.18±0.06	0.0034
	Model 2†	-0.14±0.07	0.049	-0.17±0.06	0.008
Exercise HR	Model 1	-0.07±0.04	0.104	-0.09±0.04	0.037
	Model 2†	-0.12±0.05	0.021	-0.11±0.05	0.024

Late-life fitness did not predict brain volume after adjusting for concurrent VRF levels



Outline

- The Framingham Brain Study 😊
- Vascular Brain Injury & Stroke
- Vascular Contributions to Cognitive Impairment
- **Observational Data can Predict Trial Outcomes**
- Heterogeneity may be key

(Reprinted) JAMA, December 3, 2008—Vol 300, No. 21 2545

Framingham Study Insights on the Hazards of Elevated Blood Pressure

SUMMARY OF THE ORIGINAL ARTICLE

Epidemiologic Assessment of the Role of Blood Pressure in Stroke: The Framingham Study

William B. Kannel, MD, Philip A. Wolf, MD, Joel Verter, MS, and Patricia M. McNamara

JAMA. 1970;214(2):201-210

Control of hypertension whether systolic or diastolic, systolic or diastolic, and at any age or in either sex, appears to be central to the prevention of atherosclerotic brain infarction (ABI). Prospectively, hypertension proved to be the most consistent and potent predictor of ABI. Its contribution was direct and

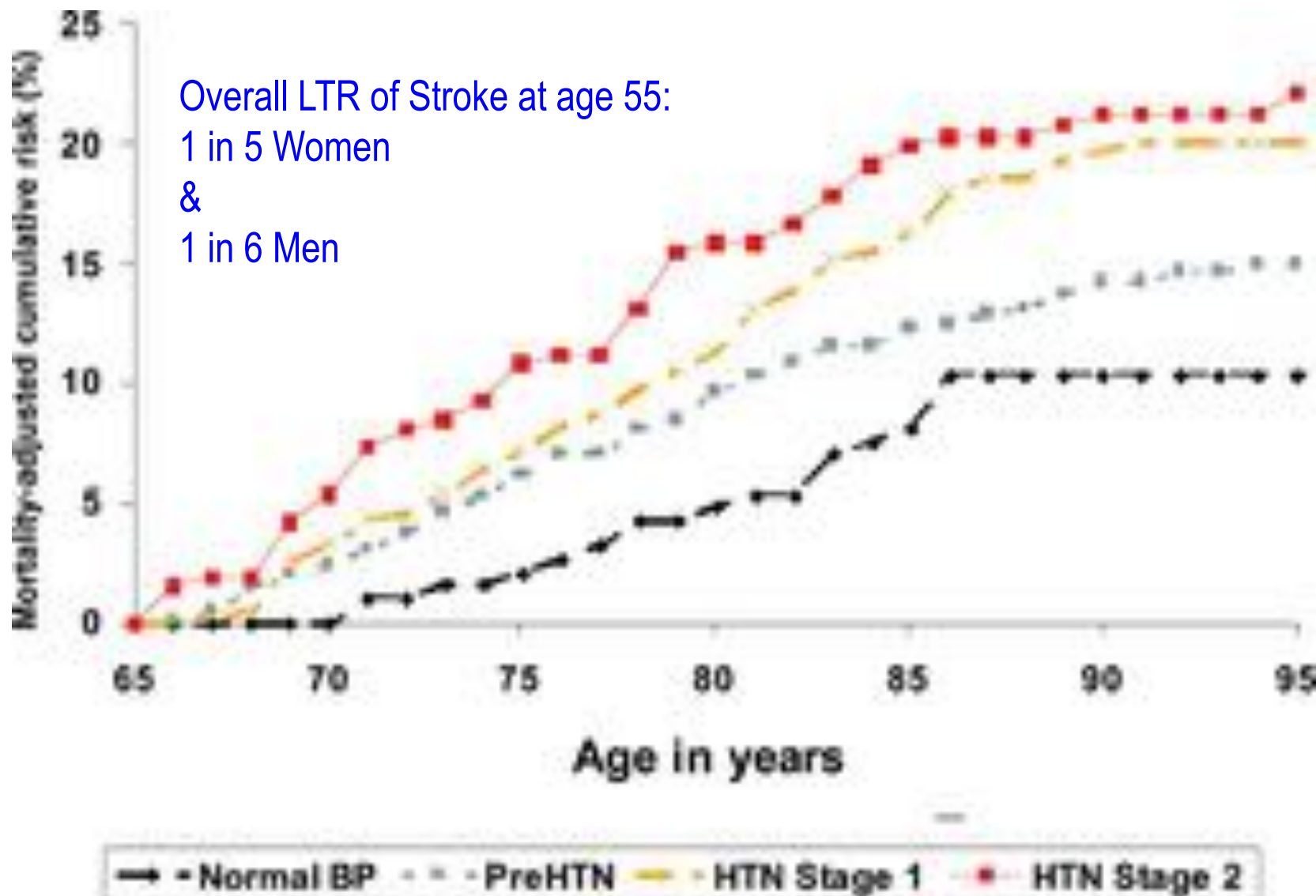
could not be attributed to factors related both to stroke and hypertension. *Asymptomatic, casual hypertension was associated with a risk of ABI about 4 times that of normotensive individuals. The probability of occurrence of an ABI was predicted no better with both blood pressure measurements or the mean arterial pressure than with systolic alone. Since there was no diminishing impact of systolic blood pressure with advancing age, the concept that systolic elevations are, even in the aged, indicative of premature, "white noise" hypertension and hypertensive individuals were compared in each sex, women did not tolerate hypertension better than men.*

See www.jama.com for full text of the original JAMA article.

Commentary by William B. Kannel, MD, MPH,
and Philip A. Wolf, MD

shown to be 1 in 5, with hypertension being a powerful contributor to this hazard.¹ The Framingham Study also

Men, 65 years of age: Lifetime risk of first-ever stroke by baseline BP



SPRINT

Systolic Blood Pressure Intervention Trial

9250 participants;
Half with CKD, half AA, 1/3rd > age 75

Primary outcomes: CVD and Stroke
Sec: Cognitive decline, WMH and dementia.



**Target SBP of 120 mm Hg
versus 140**

saved lives

POSTMENOPAUSAL ESTROGEN USE, CIGARETTE SMOKING, AND CARDIOVASCULAR MORBIDITY IN WOMEN OVER 50

The Framingham Study

PETER W.F. WILSON, ROBERT J. GARRISON, AND WILLIAM P. CASTELLI

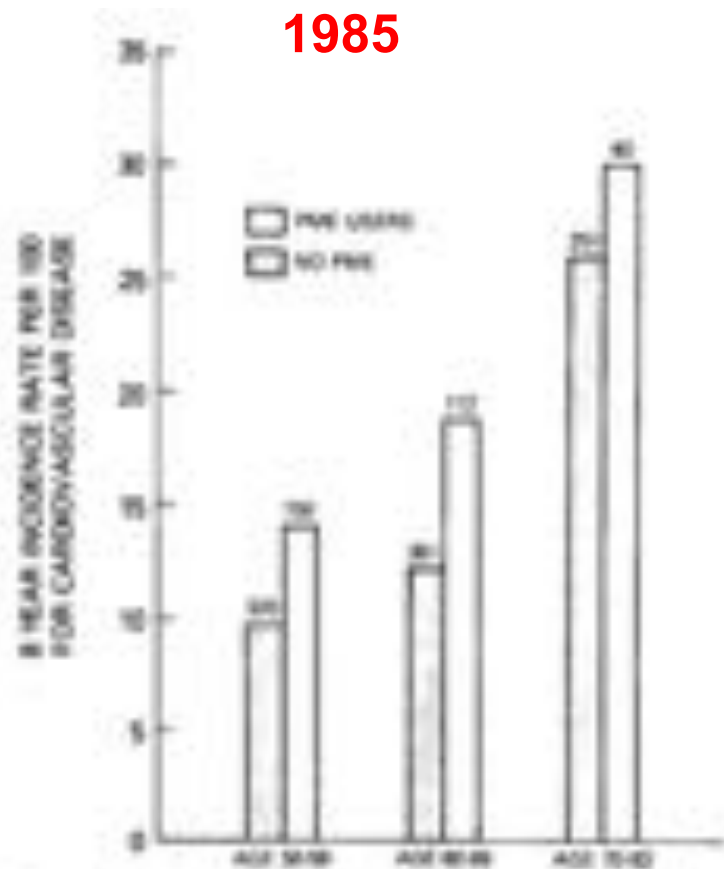


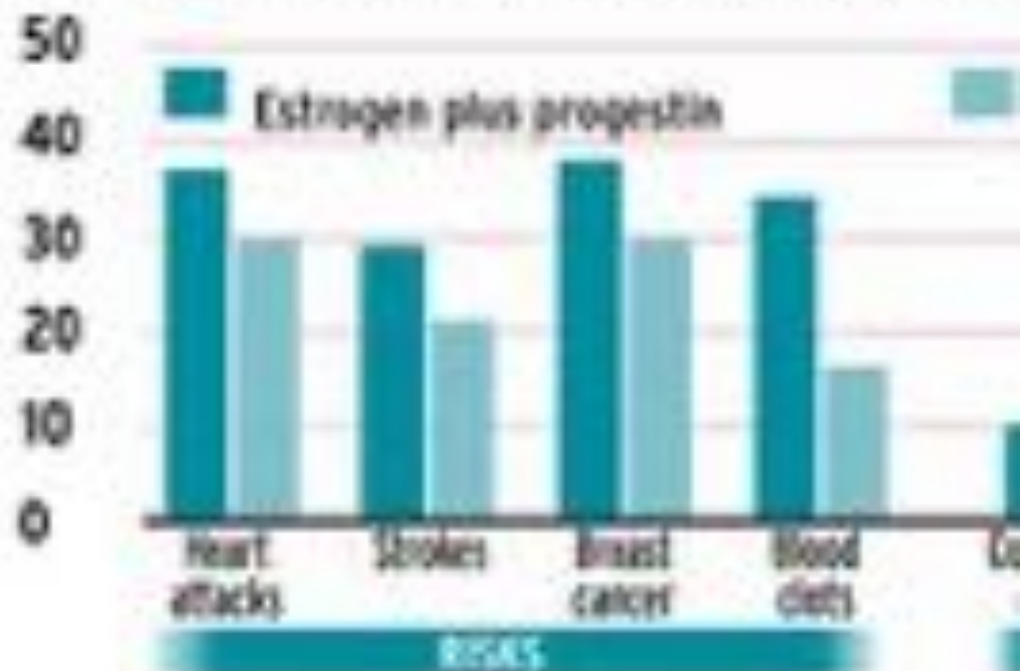
Figure 3. Eight Year Incidence of Cardiovascular Disease among 1234 Women.

The numbers of postmenopausal estrogen (PME) users and non-users are shown above the bars.

2002

HORMONE REPLACEMENT

Disease rates for women on hormone replacement therapy (estrogen plus progestin or placebo). Analysis of the Women's Health Initiative.



Source: Women's Health Initiative



Outline

- The Framingham Brain Study 😊
- Vascular Brain Injury & Stroke
- Vascular Contributions to Cognitive Impairment
- Heterogeneity may be key
 - Persons (Age, Sex, Genes)
 - Risk Factor of interest, duration
 - Concomitant factors, illnesses
 - Measurement (test, interval)

Rates and risk factors for progression to incident dementia vary by age in a population cohort

May Gough, MD,
MPhil
Ching Wan Lee, PhD
Rob E. Isaac, PhD
Tiffany F. Hughes, PhD
Eric McEvie, DO
Chang-Chuan H. Cheng,
PhD

Correspondence to:
Dr Gough
Gough@MNHospitals.edu

ABSTRACT

Objective: To estimate rate of progression from normal cognition or mild impairment to dementia, and to identify potential risk and protective factors for incident dementia, based on age at dementia onset in a prospective study of a population-based cohort (n = 1,962) aged 65 years and older.

Methods: Following the cohort annually for up to 5 years, we estimated incidence of dementia (Clinical Dementia Rating ≤ 1) among individuals previously normal or mildly impaired (Clinical Dementia Rating 0 or 0.5) in the whole cohort, and also stratified by median onset age, we examined several vascular, metabolic, and inflammatory variables as potential risk factors for developing dementia, using interval-censored survival models.

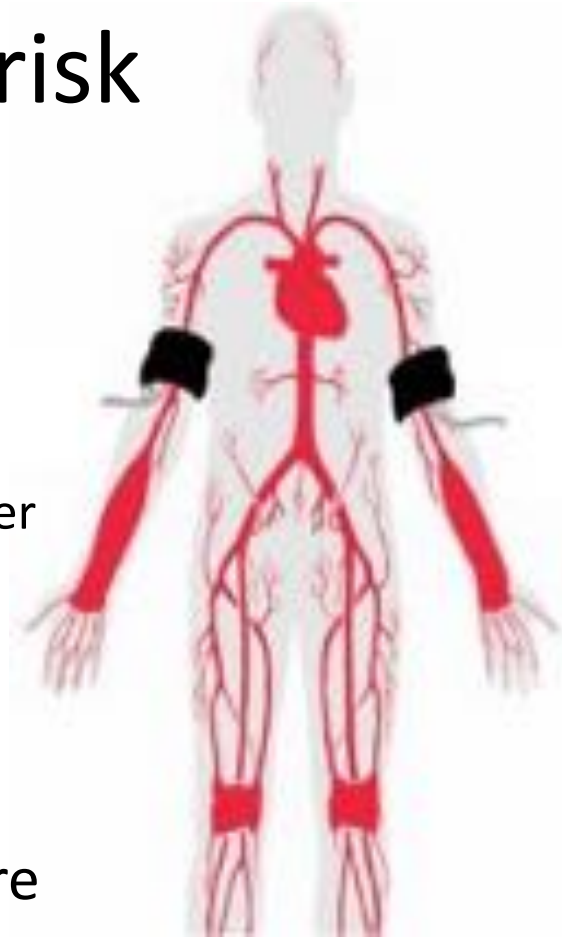
Results: Based on 67 incident cases of dementia, incidence rate (per 1,000 person-years) was 19.0 overall, 5.6 in those with median onset age of 87 years or younger, and 30.5 in those with onset age after 87 years. Adjusting for demographics, the risk of incident dementia with onset age of 87 years or younger (n = 33) was significantly increased by baseline smoking, stroke, low systolic blood pressure, and APOE $\epsilon 4$ genotype, and reduced by current alcohol use. Among those with dementia with onset after 87 years (n = 34), no risk or protective factor was significant.

Conclusions: Risk and protective factors were only found for incident dementia with onset before the median onset age of 87 years, and not for those with later onset. Either unexplored risk factors explain the continued increase in incidence with age, or unknown protective factors are allowing some individuals to delay onset into very old age. *Neurology*[®] 2015;84:72-81

Smoking, stroke,
Low SBP
associated with
dementia, if
onset at <87

Inter-arm differences in systolic BP (IDSBP) predict dementia risk

- Blood pressure (BP) is generally measured from one arm but:
 - 20% of adults have a BP difference between arms ≥ 10 mmHg; a sign of possible vascular disease.
 - Peripheral vascular disease may indicate poorer blood flow and perfusion to the brain meaning that IDSBP could possibly be used as a simple tool to screen for those at risk of cerebrovascular disease and dementia.
- This study examined if IDSBP ≥ 10 mmHg were associated with the risk of incident dementia and subclinical brain injury.



Matthew Pase, Alexa Beiser, Hugo Aparicio, Charles DeCarli, Vasan Ramachandran, Joanne Murabito, & Sudha Seshadri.

Image appropriated from Petznick and Shubrook *Osteopathic Medicine and Primary Care* 2010 4:5 doi:10.1186/1750-4732-4-5



IDSBP and dementia



METHODS 2063 Framingham Heart Study participants underwent assessment of IDSBP with results related to the 10 year risk of incident dementia including clinically characterized Alzheimer’s disease. Secondary outcomes included markers of subclinical brain injury on Magnetic Resonance Imaging.

RESULTS Associations between IDSBP and the 10y risk of all-cause dementia and Alzheimer's disease (AD)

outcome	Whole sample		Apoε4+	
	N cases/ subjects	HR (95% CI)	N cases/ subjects	HR (95% CI)
Any dementia	224/2018	1.05 (0.76, 1.45)	59/416	1.92 (1.09, 3.40)
AD	184/2018	1.07 (0.75, 1.52)	52/416	2.32 (1.29, 4.18)

Adjusts for age, sex, education and systolic blood pressure in the left arm

In APOE ε4 carriers, IDSBP were associated with a greater risk of incident dementia including Alzheimer’s disease (see table), lower total brain volumes ($\beta \pm SE = -1.26 \pm 0.38$, $p < 0.001$) and more prevalent covert brain infarcts (OR = 2.14, 95% CI: 1.10, 4.19)

DISCUSSION These data further underscore the importance of vascular health in the aetiology of clinically characterized AD as well as the convergence of different pathology in the development of dementia.

Matthew Pase, Alexa Beiser, Hugo Aparicio, Charles DeCarli, Vasan Ramachandran, Joanne Murabito, & Sudha Seshadri.

Genetic Overlap of VCI and AD

- Genes determining Brain reserve, response to injury
 - (*APOE, BDNF*)
- Monogenic disorders *may provide a model*
 - *NOTCH3* (CADASIL)
- Stroke genes may directly *affect cognition*

ORIGINAL ARTICLE

Genomewide Association Studies of Stroke

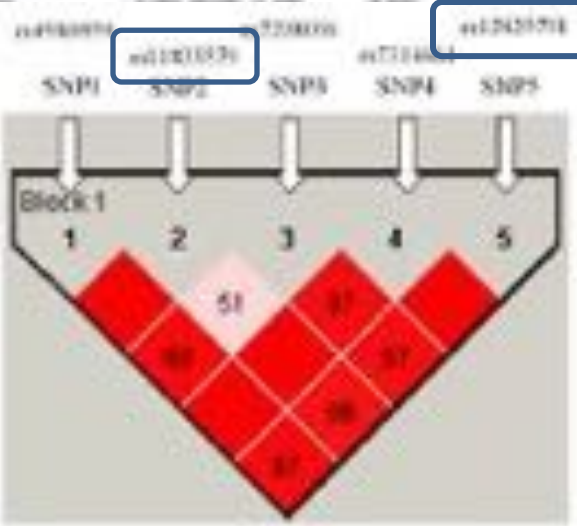
M. Arfan Ikram, M.D., Tessa Srinivasan, M.D., Joshua C. Bis, Ph.D.,
Myriam Fornage, Ph.D., Anita L. DeStefano, Ph.D., Yuri S. Aulchenko, Ph.D.,
Stephanie Debette, M.D., Ph.D., Thomas Lander, Ph.D.,
Agnès E. Gulsjov, M.D., M.P.H., Tessa C. van den Broek, M.D.,
Mehmet J. Bata, M.D., Ph.D., Alexei Zelen, Ph.D., Mary Cushman, M.D., M.Sc.,
Lynette J. Launer, Ph.D., Eyal Shaltiel, M.D., M.P.H., Maysam Jousheghar, M.Sc.,
Yanghua Du, B.S., Nicole L. Glazer, Ph.D., Wayne D. Brooks, Ph.D.,
Fernando Rivadeneira, M.D., Ph.D., Margaret Helmsworth, B.N., D.S.P.,
Ognjen L. Ljubic, M.D., Josef Cernak, M.D., Ph.D., Albert Hofman, M.D., Ph.D.,
Charles DeCarli, M.D., Susan F. Harshbarger, M.D., Ph.D.,
Peter J. Koudryak, M.D., Ph.D., Qing Yang, Ph.D., Nicholas L. Smith, Ph.D.,
Carol S. Kilar, M.D., Kenneth Rice, Ph.D., Taha Harbuzoglu, Ph.D.,
Cecilia Aoki, M.D., Ph.D., Paul L.M. de Kort, M.D., Ph.D., Kent D. Taylor, Ph.D.,
Leonie M. de Lee, M.D., Ph.D., Ben A. Ovwura, Ph.D., Andre G. Uitterlinden, Ph.D.,
Janine I. Smit, M.D., Eda Suterwalla, Ph.D., Bruce M. Psaty, M.D., Ph.D.,
Thomas H. Mosley, Ph.D., Cornelia M. van Duijn, Ph.D.,
Monique M.B. Ervelen, M.D., Ph.D., W.F. Longstreck, Jr., M.D.,
and Philip A. Wolf, M.D.

Genetic Polymorphisms of a Novel Vascular Susceptibility Gene, *Ninjurin2 (NINJ2)*, Are Associated with a Decreased Risk of Alzheimer's Disease

Kun-Pei Lin^{1,2}, Shih-Yuan Chen¹, Liang-Chuan Lai³, Yi-Ling Huang¹, Jen-Hau Chen^{1,2}, Ta-Fu Chen⁴, Yu Sun⁵, Li-Li Wen⁶, Ping-Keung Yip⁷, Yi-Min Chu⁸, Wei J. Chen^{1,9,10}, Yen-Ching Chen^{1,9,10*}

Table 3. *NINJ2* SNP analysis by genotype for dementia patients and controls.

Co-dominant model						Additive model			
SNP	# copies		# copy			# copies			
	Case/control	OR	Case/control	OR (95%CI)	p	Case/control	OR (95%CI)	p	OR (95%CI)
rs1242171 (rs1242171)									
SNP1	98/126	1.00	122/198	1.00 (0.80-1.22)	0.50	10/43	1.23 (0.70-2.17)	0.05	1.12 (0.69-1.42)
SNP2	122/172	1.00	131/194	1.07 (0.87-1.30)	0.49	25/44	0.49 (0.28-0.86)	0.01*	0.78 (0.58-1.04)
SNP3	101/124	1.00	132/12				0.77 (0.46-1.29)	0.25	0.90 (0.70-1.13)
SNP4	129/246	1.00	46/75				1.39 (0.49-3.87)	0.57	1.30 (0.86-1.95)
SNP5	99/220	1.00	166/1				0.33 (0.13-0.80)	0.04*	0.44 (0.33-1.14)
rs1242171									
SNP1	47/158	1.00	20/73				0.83 (0.40-1.69)	0.60	0.87 (0.70-1.04)
SNP2	80/170	1.00	50/73				0.98 (0.49-1.96)	0.97	0.88 (0.67-1.15)
SNP3	28/124	1.00	24/23						
SNP4	88/148	1.00	28/75						
SNP5	98/228	1.00	87/74						

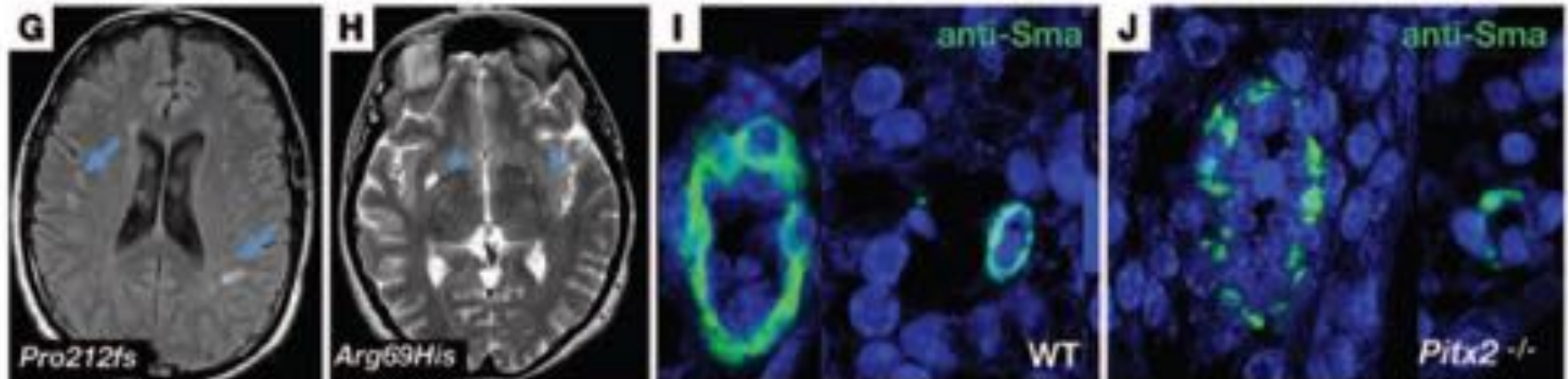


Also worse LM-d performance in FHS and ROS-MAP

*All models were adjusted for age and gender distributions (NA, not applicable).
#Result remains significant after controlling for the rs1242171 (rs1242171) SNP.

Mutation of *FOXC1* and *PITX2* induces cerebral small-vessel disease

Curtis R. French,¹ Sudha Seshadri,² Anita L. Destefano,³ Myriam Fornage,⁴ Corey R. Arnold,¹ Philip J. Gage,⁵ Jonathan M. Skarie,¹ William B. Dobyns,⁶ Kathleen J. Millen,⁶ Ting Liu,⁶ William Dietz,⁷ Tsutomu Kume,⁸ Marten Hofker,¹⁰ Derek J. Emery,¹¹ Sarah J. Childs,⁹ Andrew J. Waskiewicz,¹² and Orfan J. Lehmann¹³



JCI 2014;124:4877-1881.

An atrial fibrillation gene also **directly** causes cerebral small vessel disease
A new gene from same 'neural crest' class of genes also causes stroke- submitted

Genes (SNPs) associated with poorer cognitive function

2493 persons with **no AF** and cognitive testing in the Framingham Study Trails A and B, Visual Reproductions, Hooper, Verbal Fluency

SNPID	chr	Gene	Cognitive Phenotype	p-value
rs2200733	4	<i>PITX2</i>	Trails A	0.02
			Visual memory	0.03
			Verbal Fluency	0.02
rs7193343	16	<i>ZFHX3</i>	Hooper visual organization	0.01
			Verbal Fluency	0.04

Persons without clinical stroke or dementia

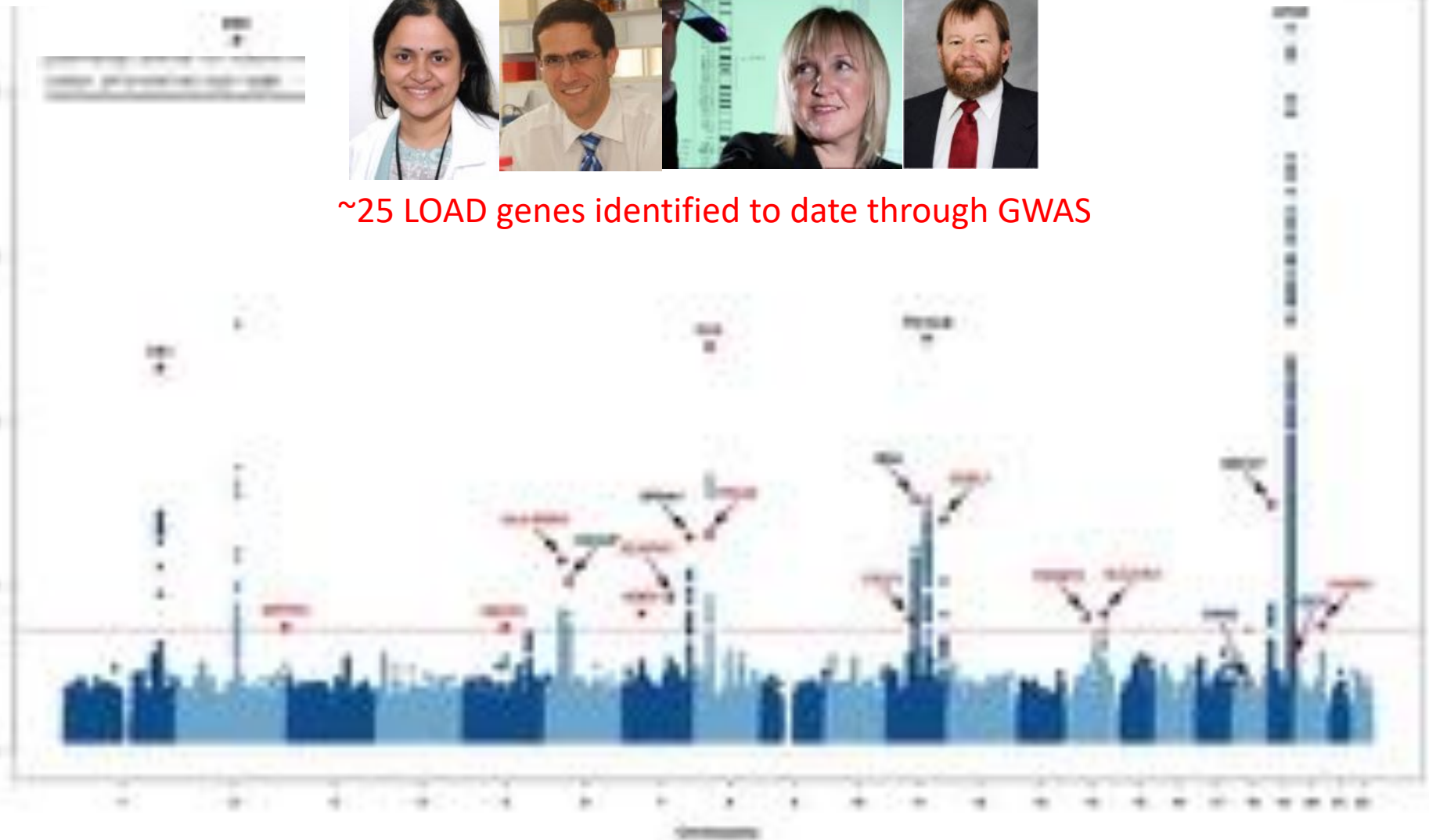
Genetic Overlap of VCI and AD

- Genes determining Brain reserve, response to injury
 - *(APOE, BDNF)*
- Monogenic disorders *may provide a model*
 - *NOTCH3 (CADASIL)*
- Stroke genes may directly *affect cognition*
- AD genes *may act through vascular pathways*

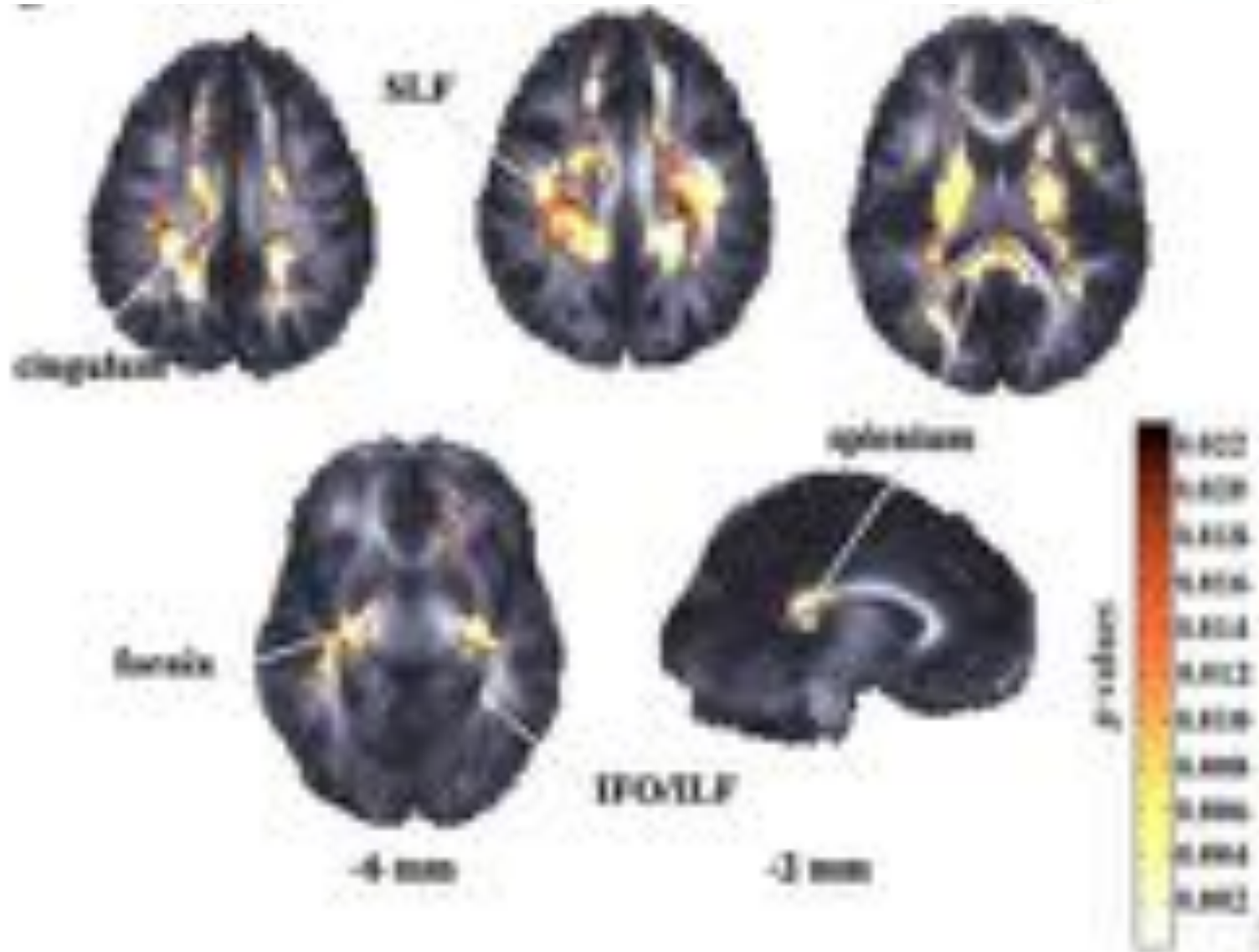
Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease



~25 LOAD genes identified to date through GWAS



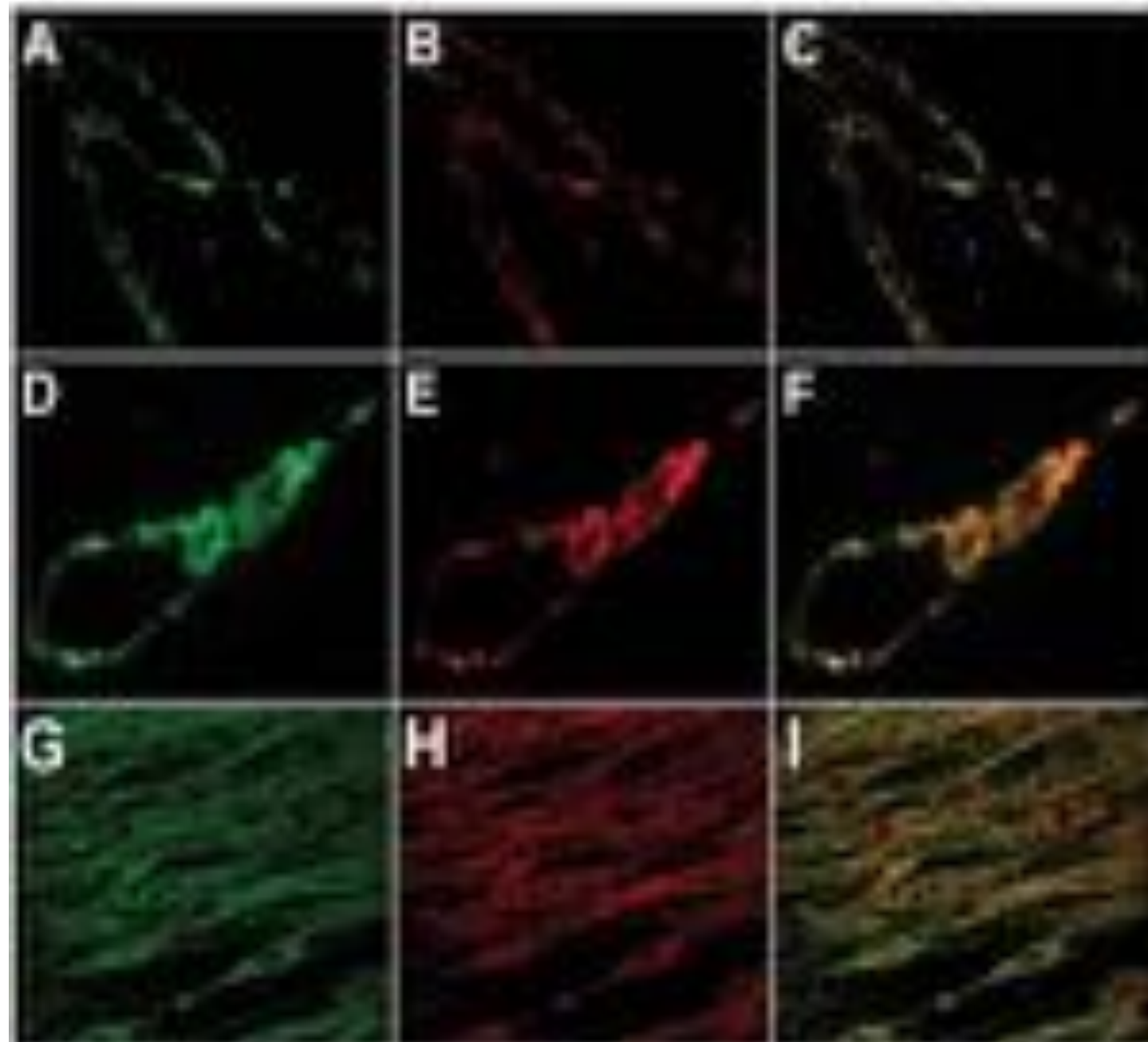
Common Alzheimer's Disease Risk Variant Within the *CLU* Gene Affects White Matter Microstructure in Young Adults



FVIII

Picalm

Merged



Variant of TREM2 Associated with the Risk of Alzheimer's Disease

Hedrik Jonsson, Ph.D., Hironi Dufossean, Ph.D., Stacy Sankberg, Ph.D.,
Inghaf Jarsdottir, Ph.D., Palm V. Jonsson, M.D., Jan Swedin, M.D.,
Egurbain Serrano, M.D., Johannes Wattenhofer B.S., Allen I. Levey, M.D.,
Ph.D., James J. Lee, M.D., Ph.D., Dan Kupfers, M.D., Harold Hampel, M.D.,
Ira Giegling, Ph.D., Ole A. Andreassen, M.D., Ph.D., Enda Ingelbal, M.D., Ph.D.,
Ingun Ulstein, M.D., Ph.D., Sander Djurovic, Ph.D., Carlo Fraboni Verheul, M.D.,
Alban Hofman, M.D., Ph.D., M. Arfan Ikram, M.D., Ph.D.,
Cecelia M van Duijn, Ph.D., Unnur Thorsteinsdottir, Ph.D.,
Agustine Kong, Ph.D., and Karl Blalock, M.D., Ph.D.

N Engl J Med 2013; 368:107-116 & 117-127

IN NEW ENGLAND JOURNAL OF MEDICINE

ORIGINAL ARTICLE

TREM2 Variants in Alzheimer's Disease

Eita Guerreiro, Ph.D., Aleksandra Wojtas, M.S., Jose Bras, Ph.D.,
Mirella Caporquillo, Ph.D., Catarina Ingason, Ph.D., Ulrike Mayeux, Ph.D.,
Carlos Cruchaga, Ph.D., Gelsa Tassi, M.D., John S.K. Kauwe, Ph.D.,
Steven Hyman, M.D., Ph.D., Linaas Hanzel, M.D., Ph.D., John Collins, M.D.,
Jennifer Peacock, Ph.D., Tammara Layton, Ph.D., Julia Williams, Ph.D.,
Jean-Charles Lambert, Ph.D., Philippe Amouyel, M.D., Ph.D., Alison Goate, Ph.D.,
Rosa Rademakers, Ph.D., Kevin Morgan, Ph.D., John Powell, Ph.D.,
Peter St. George-Hyslop, M.D., Andrew Singleton, Ph.D., and John Hardy, Ph.D.,
for the Alzheimer Genetics Analysis Group*

Trigger Receptor
Expressed on
Myeloid Cells 2 protein

May activate microglia
to permit beta-amyloid
oligomer removal

Polycystic lipomembranous
osteodysplasia
with sclerosing
leukoencephalopathy,
(Nasu-Hakola)

TREM2 distribution in patient with AD and TREM2 rare variant

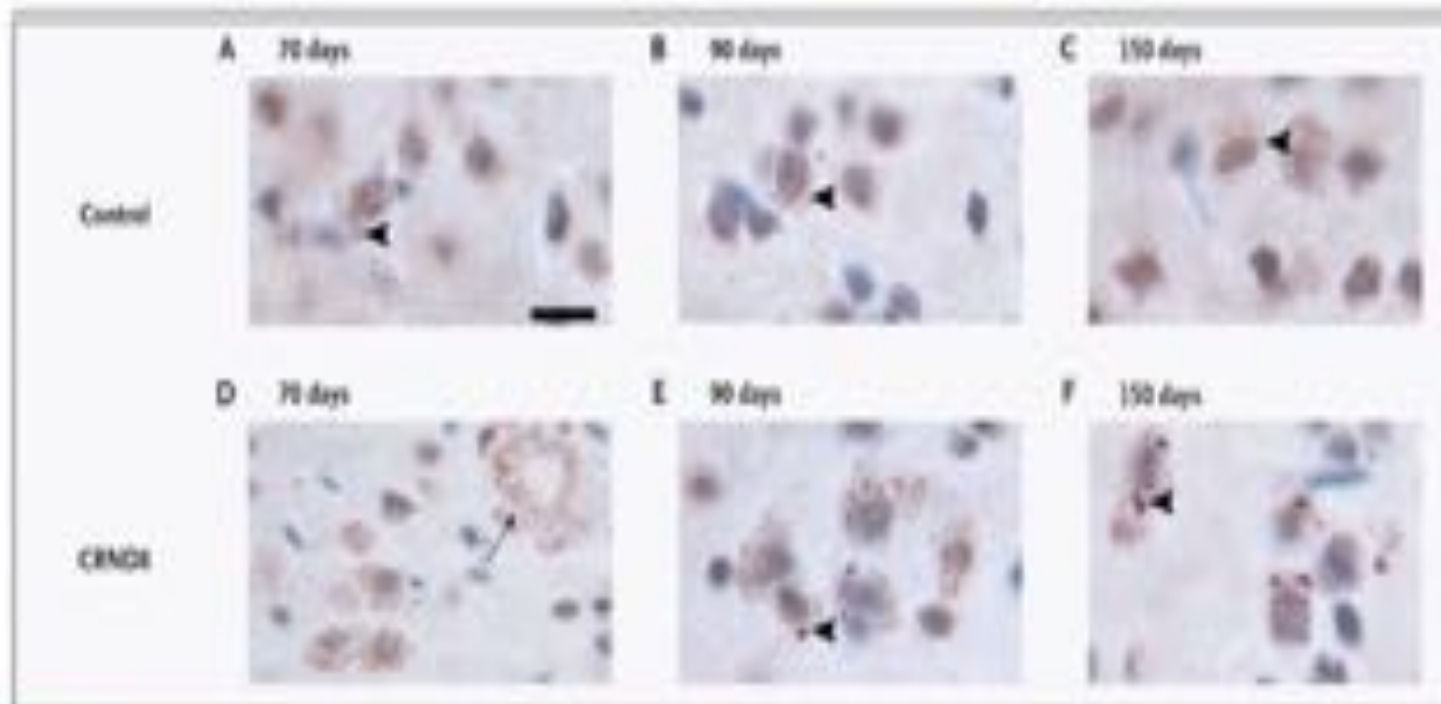
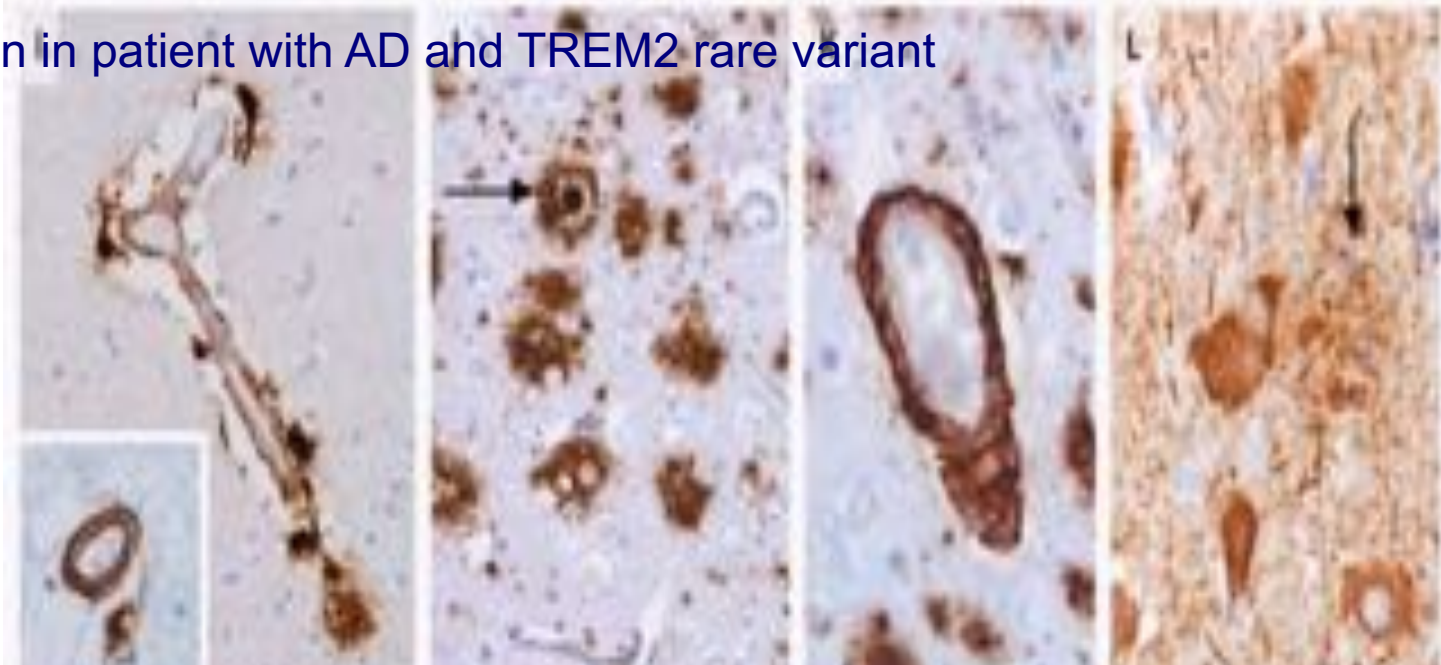


Figure 3. Immunohistochemical Analysis of Trem2 in TgCRND Mice

Vascular Contributions to Cognitive Aging

- Genetic Pathways Overlap, Promise to improve our understanding of VCI

Polygenic Overlap Between C-Reactive Protein, Plasma Lipids, and Alzheimer Disease

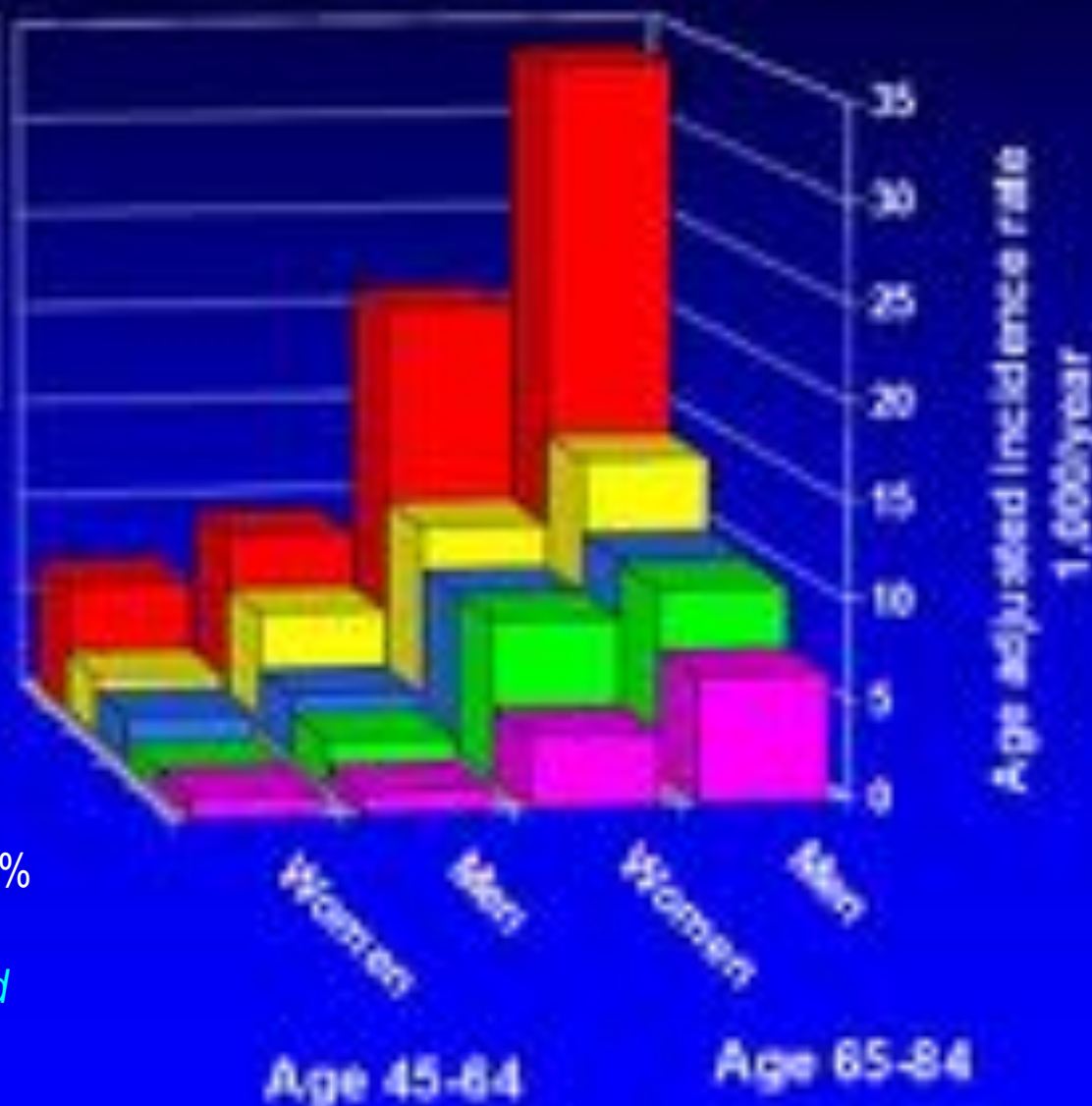
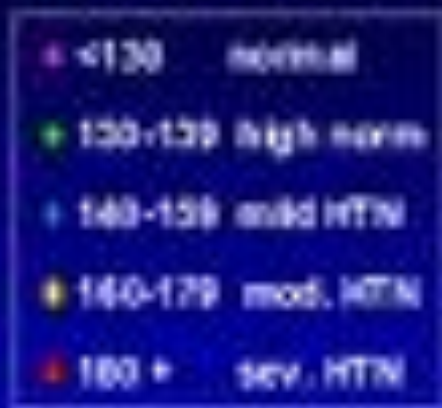
(Circulation. 2015;131:2061-2069)



Outline

- The Framingham Brain Study 😊
- Vascular Brain Injury & Stroke
- Vascular Contributions to Cognitive Impairment
- **Heterogeneity may be key**
 - Persons (Age, Sex, Genes)
 - Risk Factor of interest, duration
 - Concomitant factors, illnesses
 - Measurement (test, interval)

Stroke Incidence by SBP



Antecedent BP:

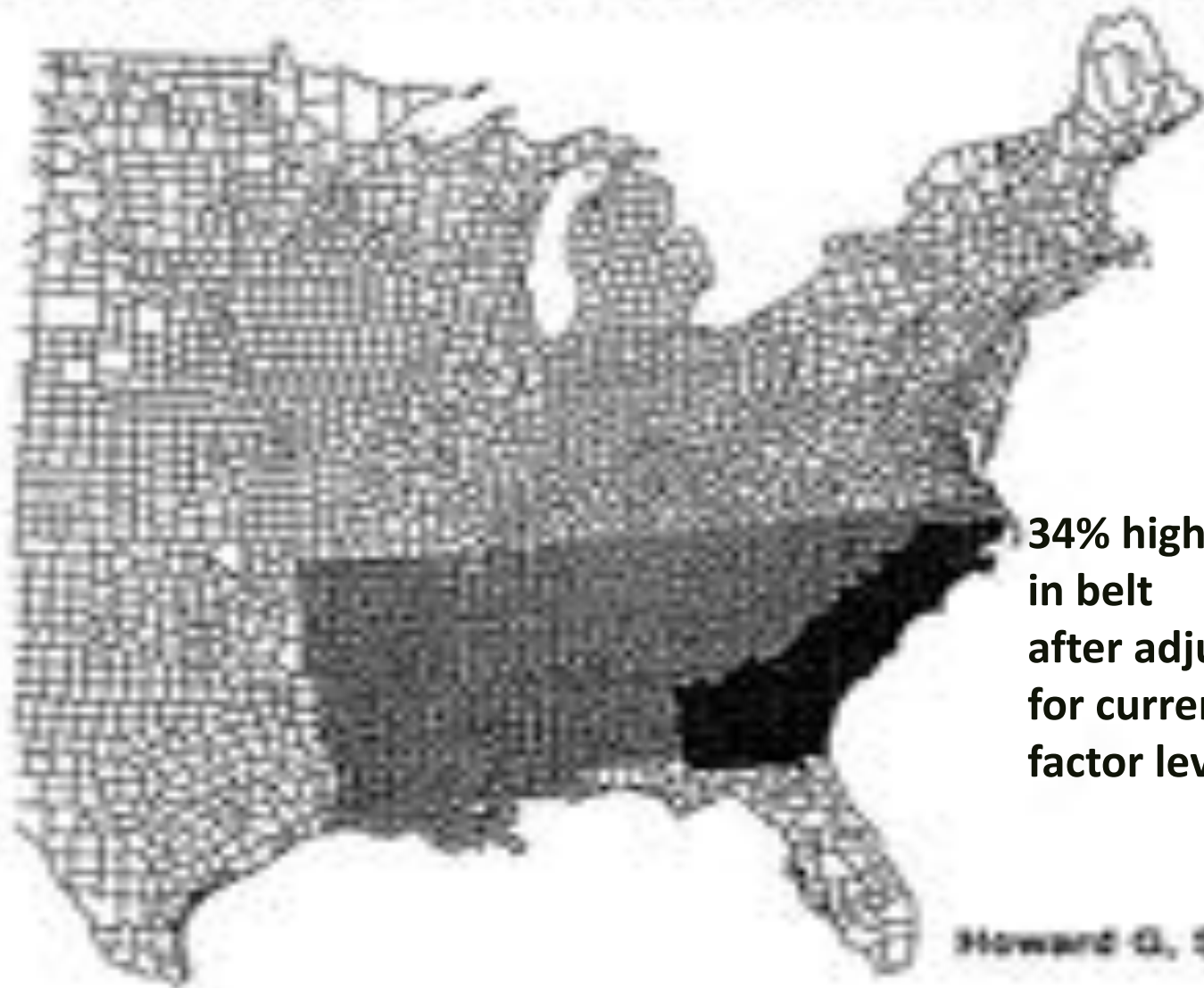
1-9 years earlier and

10-19 years earlier

Also increases risk: 30-100%

Seshadri et al; Arch Int Med
2001;161:2343-2350

Stroke Belt & Buckle



**34% higher risk
in belt
after adjusting
for current risk
factor levels**

Howard G. Stroke, 1997

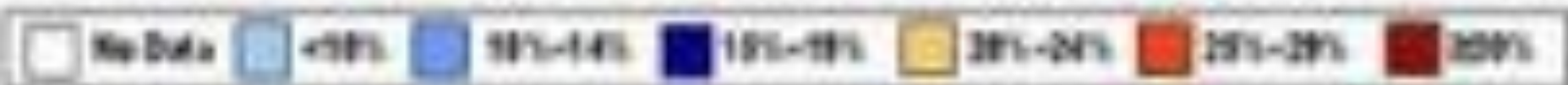
Prevalence of Hypertension, 2011
U.S. Adults Ages 20 and Older (Percentage)



Map based on data from the Behavioral Risk Factor Surveillance System (BRFSS), a national survey of health behaviors and risk factors. The BRFSS is a part of the National Health and Medical Examination Survey (NHANES) conducted by the Centers for Disease Control and Prevention (CDC). The data for this map were obtained from the CDC's National Center for Chronic Disease Prevention and Health Promotion (NCCDPHP).



2010



County-level Estimates of Diagnosed Diabetes among Adults Aged ≥ 20 years
United States 2009



EDITORIAL COMMENT

Indexes of Subclinical Atherosclerosis

Signposts on the Highway to Disease*

Sudha Seshadri, MD



Systemic Vascular Injury Associated with VBI, VCI

- Carotid Imaging: Stenosis, IMT, Plaque
- Cardiac Imaging: ECHO/MRI, Coronary Calcium
- Vascular Imaging: Tonometry, Aortic Plaque

Epidemiology and Prevention

Carotid Artery Atherosclerosis, MRI Indices of Brain Ischemia, Aging, and Cognitive Impairment
The Framingham Study

Relations of arterial stiffness and endothelial function to brain aging in the community

Cardiac Index Is Associated With Brain Aging
The Framingham Heart Study

Visceral Fat Is Associated with Lower Brain Volume in Healthy Middle-Aged Adults

Brain Imaging and Cognitive Predictors of Stroke and Alzheimer Disease in the Framingham Heart Study

Gaël Wainman, PhD; Alexa S. Beiser, PhD; Charles DeCarli, MD; Rhonda Au, PhD; Philip A. Wolf, MD; Sushruth Seshadri, MD, DM

Background and Purpose—Exposure to vascular risk factors has a gradual deleterious effect on brain MRI and cognitive measures. We explored whether a pattern of these measures exists that predicts stroke and Alzheimer disease (AD) risk.

Methods—A cognitive battery was administered to 1179 dementia and stroke-free Framingham offspring (age, ≈ 55 years; mean, 65.7±7.6) between 1990 and 2006; participants were also free of other neurological conditions that could affect cognitive and MRI also had brain MRI examination. We related cognitive and MRI measures to risks of incident stroke and AD 10 years of follow-up. As a secondary analysis, we explored these associations in The Framingham Heart Study original cohort (mean age, 61.3±7.7 and 64.8±7.7 years at the cognitive assessment and MRI examination, respectively).

Results—A total of 19 offspring participants sustained stroke and 7 developed AD offspring who scored ≤ 1.5 SD below predicted mean scores, for age and education, on an executive function test, had a higher risk of future stroke (hazard ratio [HR], 2.25; 95% confidence interval [CI], 1.08–4.65) and AD (HR, 3.66; 95% CI, 1.32–8.32); additional cognitive tests also predicted AD. Participants with low ≤ 25 percentile total brain volume and high ≥ 25 percentile white matter hyperintensity volume had a higher risk of stroke (HR, 1.97; 95% CI, 1.03–3.77) and HR, 2.78; 95% CI, 1.70–4.63, respectively) but not AD. Hippocampal volume in the bottom quartile predicted AD in the offspring and original cohorts (HR, 4.45; 95% CI, 1.06–18.72) and HR, 2.37; 95% CI, 1.12–5.06, respectively). A stepwise increase in stroke risk was apparent with increasing numbers of these cognitive and imaging markers.

Conclusions—Specific patterns of cognitive and brain structural measures observed even in early aging predict stroke risk and may serve as biomarkers for risk prediction. (*Stroke*. 2013;44:2787–2794.)

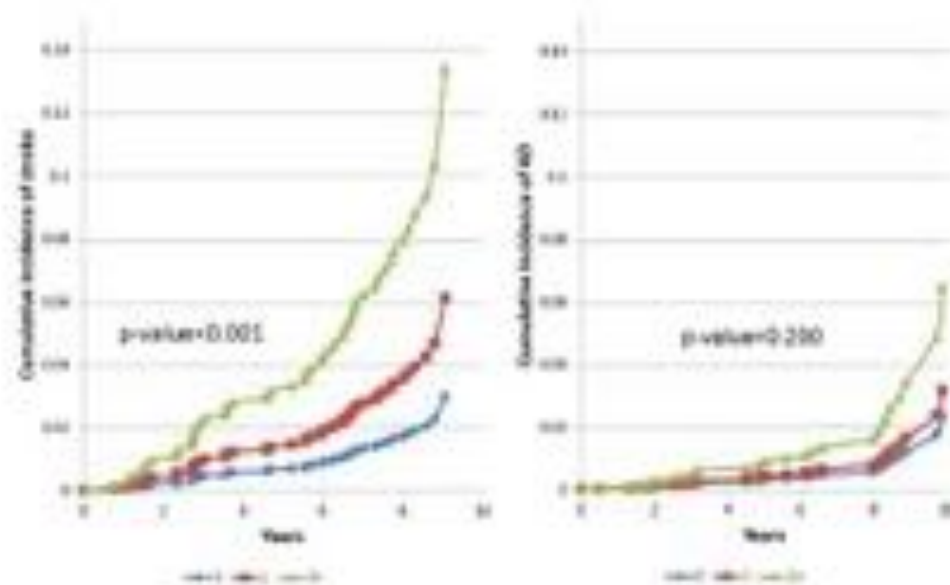


Figure 2. Cumulative incidence of stroke (left) and Alzheimer disease (AD) (right) in the offspring cohort based on age- and sex-adjusted Cox models by number of cognitive imaging biomarkers. Top WMHV quintile and bottom WMHV quintile.

RESEARCH ARTICLE

Vascular Factors and Multiple Measures of Early Brain Health: CARDIA Brain MRI Study

Lenore J. Launer^{1*}, Cora E. Lewis², Pamela J. Schreiner², Steve Sidney³, Harsha Battapady³, David R. Jacobs², Kelvin O. Lim⁵, Mark D'Esposito¹, Qian Zhang¹, Jared Reis⁶, Christos Davatzikos⁵, R. Nick Bryan²

ORIGINAL ARTICLE

Nocturnal Blood Pressure in Young Adults and Cognitive Function in Midlife: The Coronary Artery Risk Development in Young Adults (CARDIA) Study

Yuichiro Yano,¹ Hongyan Ning,¹ Paul Muntner,² Jared P. Reis,³ David A. Calhoun,⁴ Anthony J. Viera,⁵ Deborah A. Levine,⁴ David R. Jacobs Jr.,⁷ Daichi Shimbo,⁸ Kiang Liu,¹ Philip Greenland,¹ and Donald Lloyd-Jones¹



Outline

- The Framingham Brain Study 😊
- Vascular Brain Injury & Stroke
- Vascular Contributions to Cognitive Impairment
- **Heterogeneity may be key**
 - Persons (Age, Sex, Genes)
 - Risk Factor of interest, duration
 - **Concomitant risk factors, illnesses**
 - Measurement (test, interval)

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

Debbie S, *BMJ* 2010;341:c3666

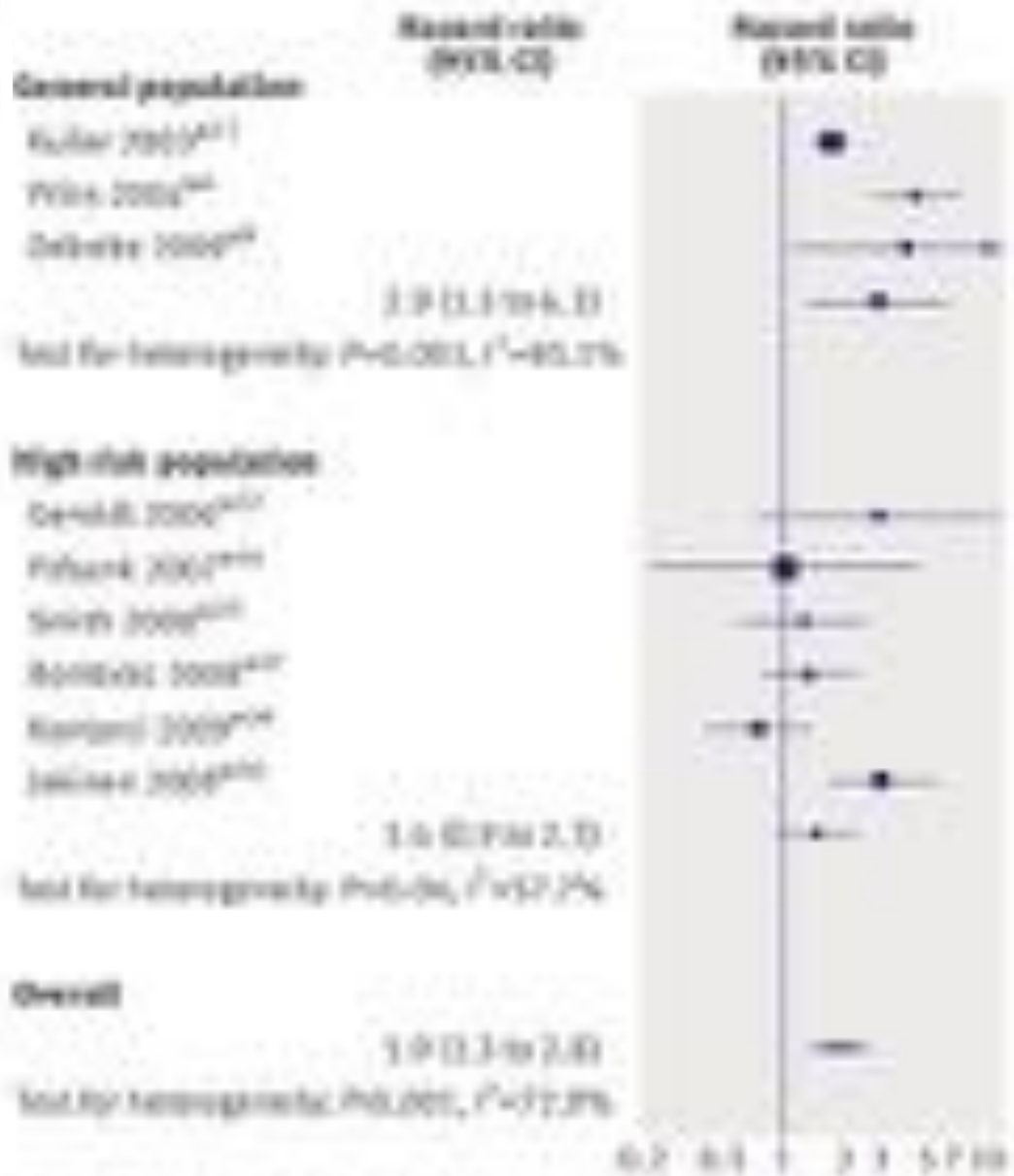


Fig 3 | Inverse variance meta-analysis of studies testing association of white matter hyperintensities with incident dementia

WMH is a risk factor for developing dementia only in persons who are not already cognitively impaired

Central obesity and increased risk of dementia more than three decades later



Qin Qian, PhD
Yue Chen, PhD
Changchun Tang, PhD
Wen Wang, PhD
Yanping Zhang, PhD
Li Han, PhD

Department of Psychiatry
and Behavioral Sciences
Stanford University
Stanford, CA
USA
yanping.zhang@stanford.edu

Abstract

Background: Numerous reports show that a centralized distribution of adiposity is more dangerous for the brain than peripheral fat. However, few studies that used brain imaging to measure body adiposity evaluated whether the same pattern works with dementia. The objective was to evaluate the association between body adiposity (measured as waist and hip circumference) and dementia.

Methods: A longitudinal analysis was conducted of 9,222 members of Framingham Offspring who had their weight, abdominal diameter (AD), waist-hip ratio (WHR), hip diameter, and systolic blood pressure measured at average of three visits (January 5, 1988, to June 10, 2016). Longitudinal dementia incidence was defined by age-specific incident clinical diagnosis, hospitalization, prescriptions of drugs, hospitalizations, and verbal ability scores.

Results: A total of 1,210 participants (13.1%) were diagnosed with dementia. Compared with those in the lowest quartile of AD, those in the highest had nearly 3-fold higher risk of dementia (hazard ratio: 1.13, 95% CI: 1.04 to 1.24), and this was only weakly attenuated after adjusting for age, sex, education, systolic blood pressure, AD, WHR, and hip circumference. However, age, AD, WHR, and hip circumference were not associated with dementia (1.01, 95% CI: 0.96 to 1.06; 1.01, 95% CI: 0.96 to 1.06; 1.01, 95% CI: 0.96 to 1.06; 1.01, 95% CI: 0.96 to 1.06, respectively). Moreover, those with both AD and WHR in the highest quartile had a 2.5-fold higher risk of dementia (2.50, 95% CI: 1.99 to 3.20).

Conclusions: Having obesity is a better predictor of dementia independent of age, sex, and cardiovascular comorbidity. The pattern of body fat (central obesity) matters, independent from central obesity, in determining the dementia risk. [https://doi.org/10.1186/s12916-020-01976-9](#)



Original Contribution

Overweight and Obesity in Midlife and Brain Structure and Dementia 26 Years Later

The AGES-Reykjavik Study

No association of midlife (age 50) obesity (BMI) with MRI measures or dementia

Erlendur Kibviksson, Benjamin Davis, Páll V. Jónsson, Wilen Chang, Thor Aspelund, Melissa Garcia, Tamara Harris, Vilhundur Gudnason, and Larsore J. Launer*

*Correspondence to: Larsore J. Launer, Laboratory of Epidemiology and Population Sciences, Neuroimaging in Aging, National Institute of Health, 301 Wisconsin Avenue, Suite 3C104, Bethesda, MD 20892 (email: launer@nih.gov)

initially submitted May 12, 2014; accepted for publication October 27, 2014

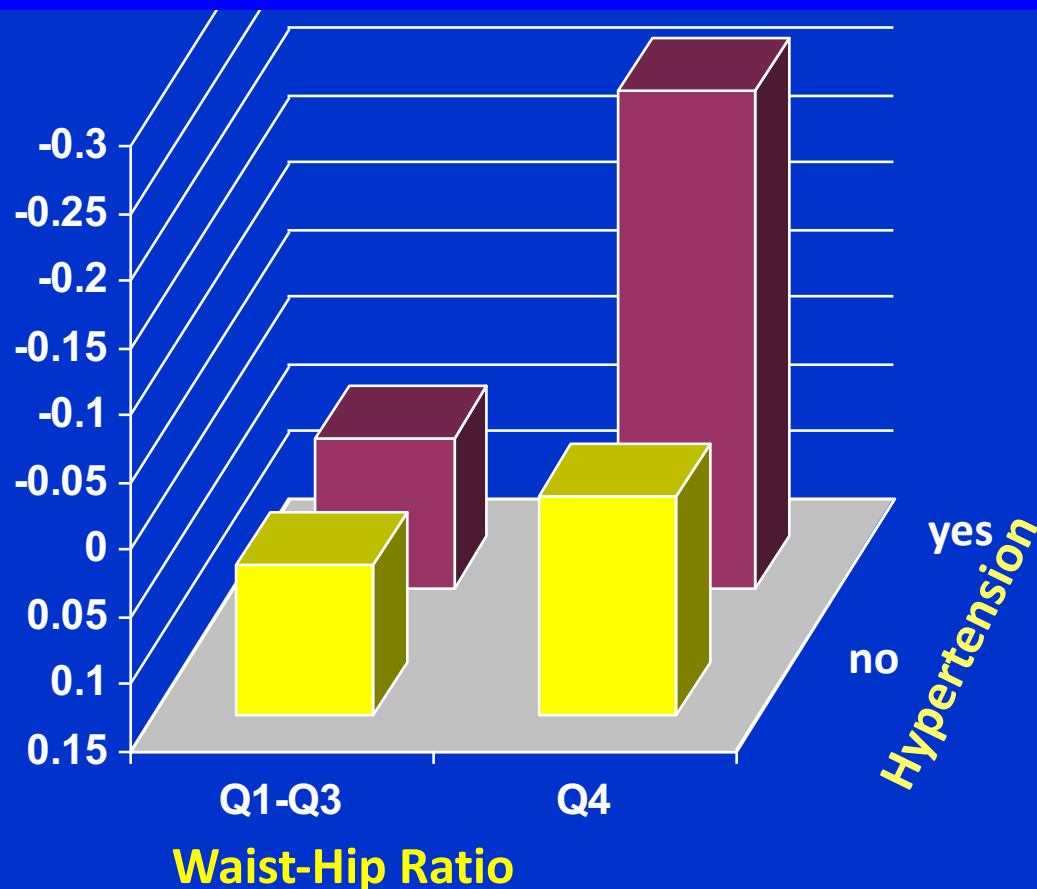
High adiposity in midlife might increase risk for late-life brain pathology, including dementia. Using data from the prospective Age, Gene/Environment Susceptibility Reykjavik Study of men and women (born 1907–1926), we studied the associations of overweight and obesity of midlife (mean age, 50 [standard deviation, 4.7] years) with 1.5-T brain magnetic resonance imaging measures of infarct-like brain lesions, cerebral microbleeds, total brain volume, and white matter volume, as well as dementia, in late-life (mean age, 76 [standard deviation, 5.7] years). We used linear and logistic models to estimate associations in 3,884 persons after adjustment for sociodemographic, health, and lifestyle characteristics. In midlife, the prevalence of overweight was 30% and that of obesity was 10%. Many men follow-up of 26.2 (standard deviation, 4.3) years, midlife overweight and obesity were not associated with infarct-like brain lesions (odds ratio [OR] = 1.02, 95% confidence interval [CI] 0.69, 1.50), cerebral microbleeds (OR = 1.08, 95% CI 0.37, 3.20), total brain volume (β = 0.06, 95% CI: -0.26, 0.46), white matter volume (volume β = -0.15, 95% CI: -0.26, -0.03), or dementia (OR = 0.98, 95% CI 0.48, 1.72) compared with normal weight. These findings do not support the hypothesis that high body mass index in midlife increases the risk for dementia.

Relation of Obesity to Cognitive Function: Importance of Central Obesity and Synergistic Influence of Concomitant Hypertension. The Framingham Heart Study

P.A. Wolf*, A. Beiser, M.F. Elias, R. Au, R.S. Vasan and S. Seshadri

Combined Impact of Waist-Hip Ratio & HTN on Visual Reproductions – Delayed Recall

Z-scores



1814 persons
WHR in 1988-90
at age 50

Cognitive tests 12
yrs later



Outline

- The Framingham Brain Study 😊
- Vascular Brain Injury & Stroke
- Vascular Contributions to Cognitive Impairment
- **Heterogeneity may be key**
 - Persons (Age, Sex, Genes)
 - Risk Factor of interest, duration
 - Concomitant factors, illnesses
 - **Measurement (test, interval)**

Hypertension, Executive Dysfunction, and Progression to Dementia

The Canadian Study of Health and Aging

Shahram Oveisgharan, MD; Vladimir Hachinski, MD, FRCPC, DSc(Lond)

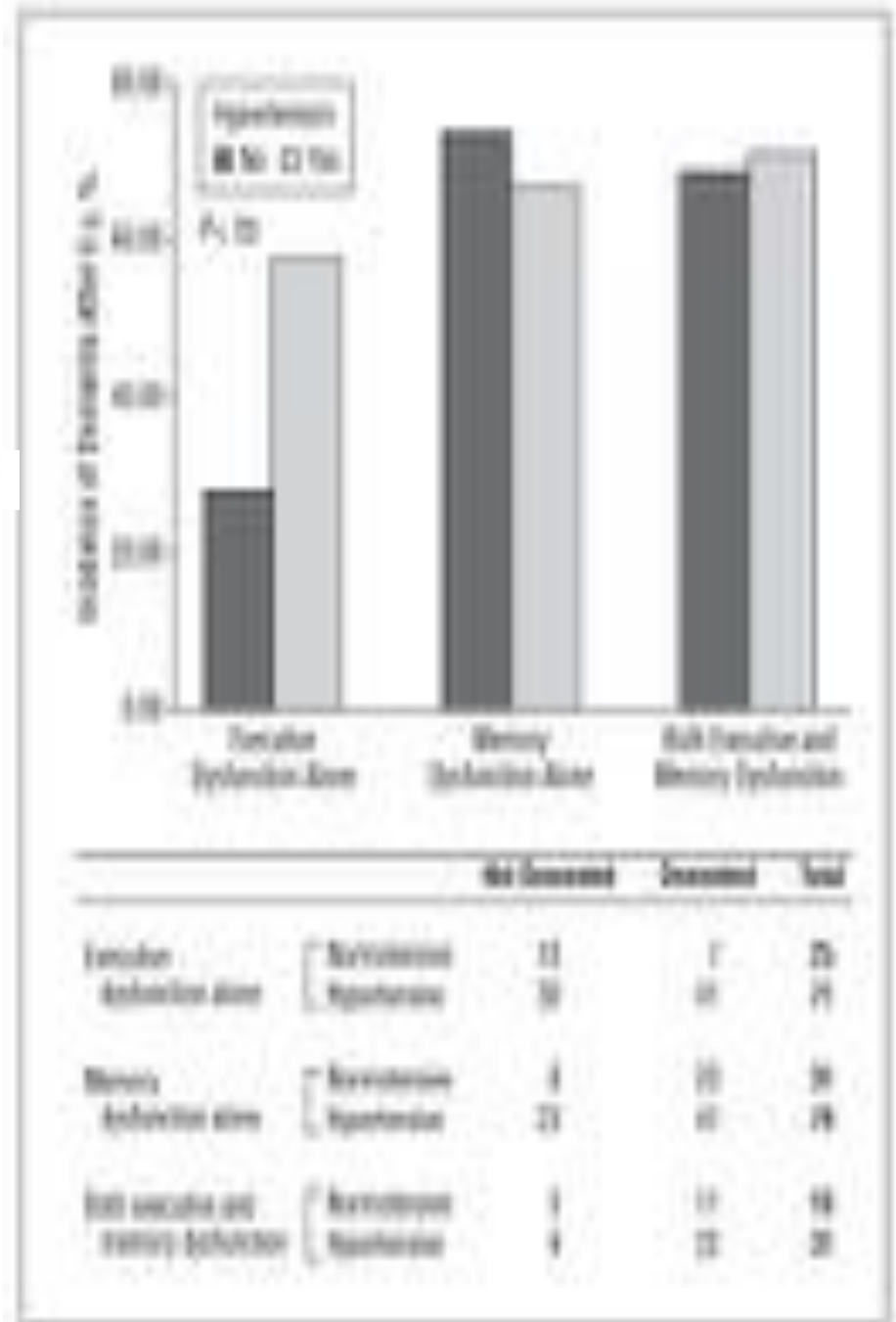
Arch Neurol. 2010;67(2):187-192

Patterns in Cognitive Impairment

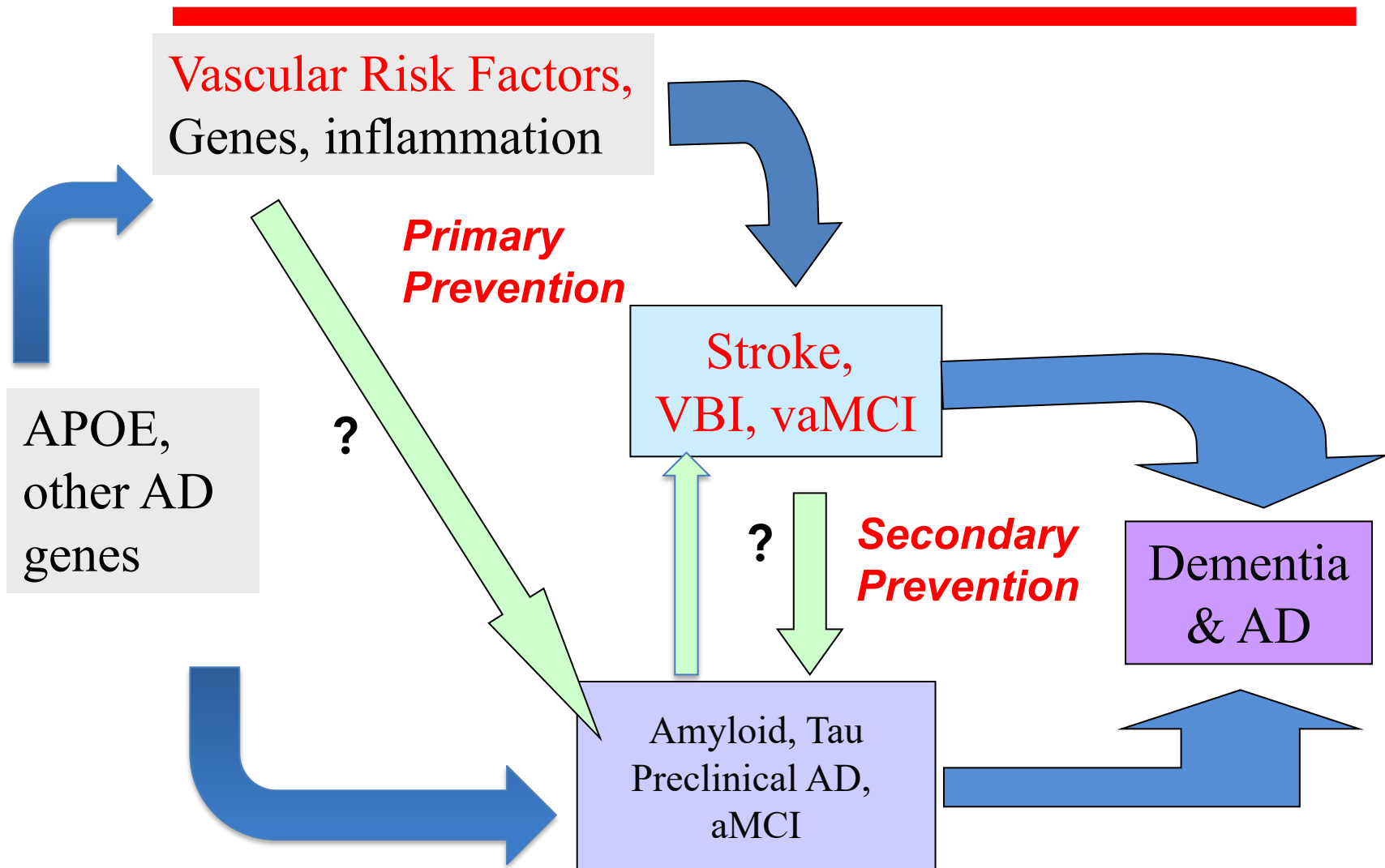
Domain assessed, test used
matter

In FHS

Post processing for
Latency of response
Error patterns
Process Used to answer



Pathways to Cognitive Impairment, Dementia, including Alzheimer Disease Dementia



Some Questions

- A Healthy Cerebral Vasculature Likely Postpones *Clinical* Dementia-
 - Addressing which vascular risk factors would be most effective? When and How? In Whom?
- Will cerebral vascular health prevent or postpone *amyloid and tau pathology*?
 - Addressing which vascular risk factors would be most effective? When and How? In Whom?



Research Article

Development and validation of a brief dementia screening indicator for primary care

Deborah E. Barnes^{1,2,3,4,5,6,7,8,9}, Alexa S. Beiser^{1,2}, Anne Lee¹, Kenneth M. Langa^{10,11}, Alan Kaye¹², Sarah R. Perin¹, John Newham¹, Ryan F. McCarron¹, Kristine Yaffe^{13,14,15}, Sudha Seshadri¹⁶, Mary N. Haan¹, David R. Weir¹

¹Department of Psychiatry, University of California, San Francisco, CA, USA

²Department of Neurology, University of California, San Francisco, CA, USA

³Department of Epidemiology & Biostatistics, University of California, San Francisco, CA, USA

⁴San Francisco Medical Center, San Francisco, CA, USA

⁵Samueli California Institute for Research and Education, San Francisco, CA, USA

⁶Department of Neurology, Mount Holyoke, South Africa, 1994

⁷Department of Neurology, Boston University, Boston, MA, USA

⁸Section for Health Research, University of Michigan, Ann Arbor, MI, USA

⁹Department of Health Care, University of Michigan, Ann Arbor, MI, USA

¹⁰Survey of Health, Aging and Retirement in America, Washington, DC, USA

Abstract

Background: Presence of “any cognitive impairment” is considered a part of the Medicare annual wellness visit, but screening of patients was limited to standard tests (e.g., Folstein).

Methods: We developed and validated a brief dementia screening indicator using data from four large, ongoing cohort studies: the Cardiovascular Health Study (CHS), the Honolulu Heart Study (HHS), the Health and Retirement Study (HRS), the Sacramento Area Latino Study on Aging (SALA). We fully identified a subgroup of high-risk patients eligible for cognitive screening.

Results: The brief dementia screening indicator included age of onset (year), age, 65–74 years; less than 12 years of education (yes/no); stroke (yes/no); diabetes mellitus (yes/no); body mass index less than 18.5 kg/m² of patients requiring assistance with walking or medication (0/1 points).

Dementia Risk Prediction

- Congress has passed an act requiring cognitive screening at Medicare Annual Wellness visit
- But there is concern about high % of false +ves
- **Dementia Risk Assessment**
 - Framingham Study
 - Sacramento Area Latino Study of Aging
 - Cardiovascular Health Study
 - Health & Retirement Study
- <http://campuslifeservices.ucsf.edu/clsforms/documentsmedia/dementiarisk/>

Age, Education, BMI, DM, Stroke, Money/Meds, Depression

Thanks to

