Life Course Progression of Cerebrovascular Disease

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BOSTON UNIVERSITY

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NIDDK, AHA and others

FRAMINGHAM HEART STUDY
Three Generations of Dedication
1948 1971 2002

No Conflicts of Interest to Disclose

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- The views expressed in written conference materials or publications and by speakers and moderators do not necessarily reflect the official policies of the Department of Health and Human Services; nor does mention by trade names, commercial practices, or organizations imply endorsement by the U.S. Government.

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

THE NEWER KNOWLEDGE OF ATHEROSCLEROSIS*

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?

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

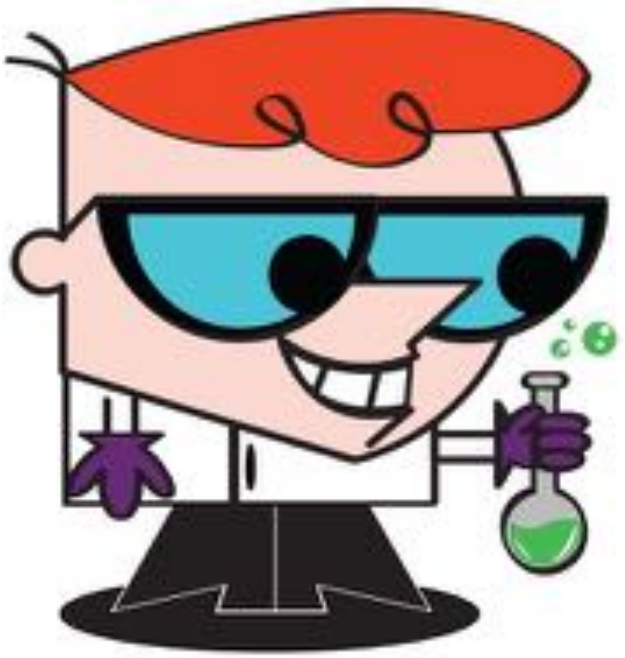
Omni study N = 506 3rd

2002 → 2015

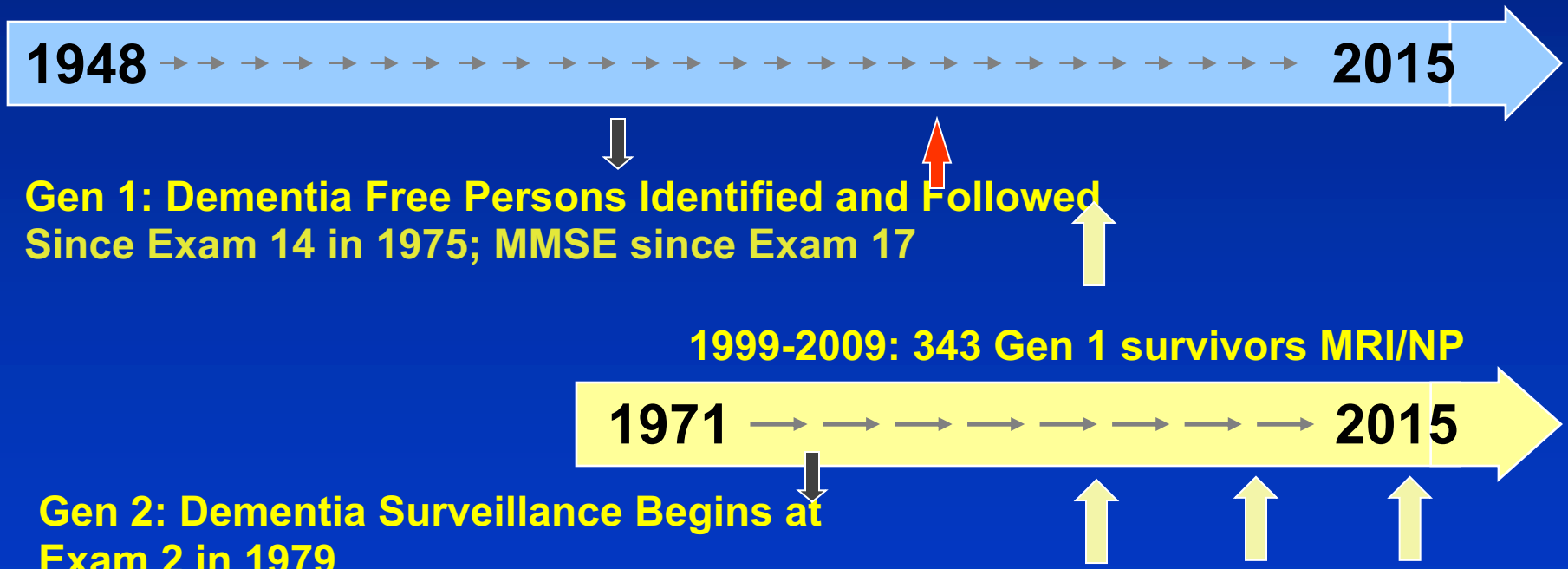
Third Gen study N = 4095 3rd

2002 → 2015

Omni Gen 2 study N = 368 3rd



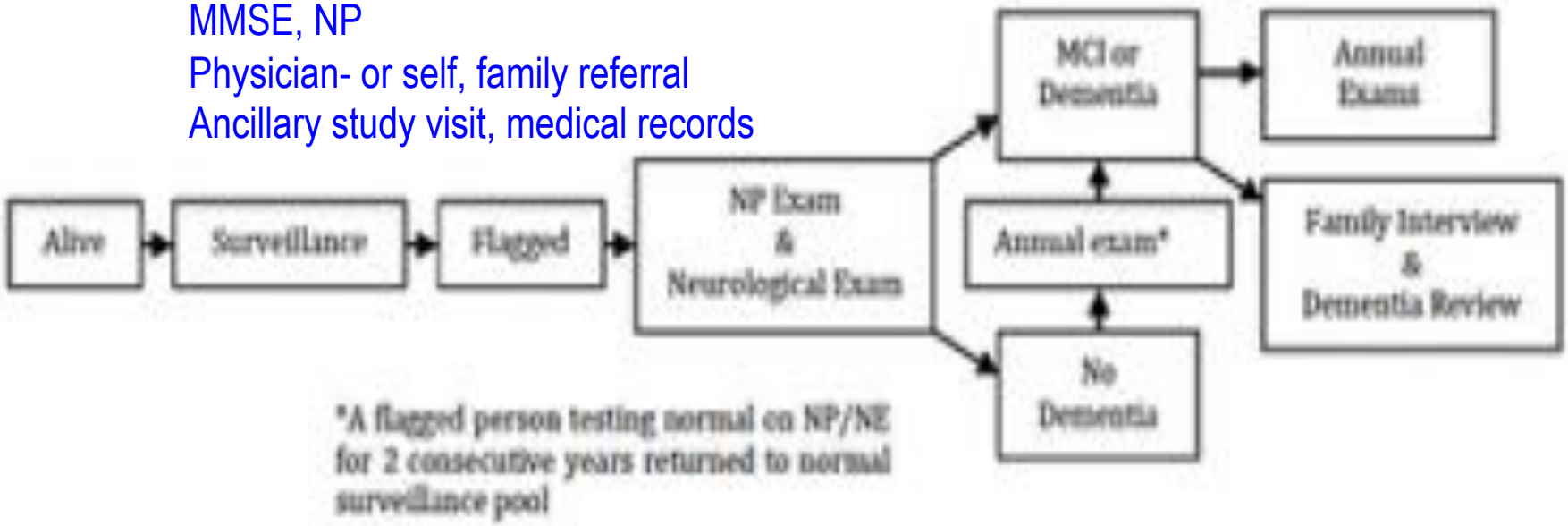
Framingham Heart Study



National Institute on Aging

Dementia Tracking

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



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

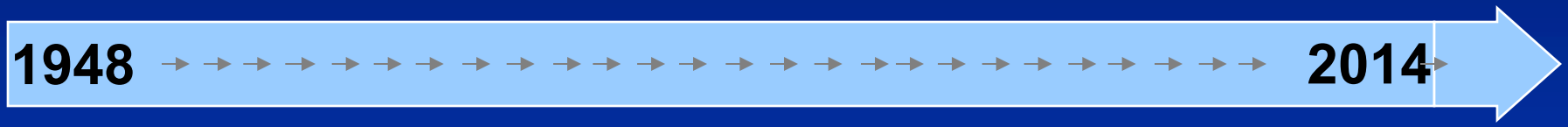
More frequent, up to annual, NP/MRI testing in:

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

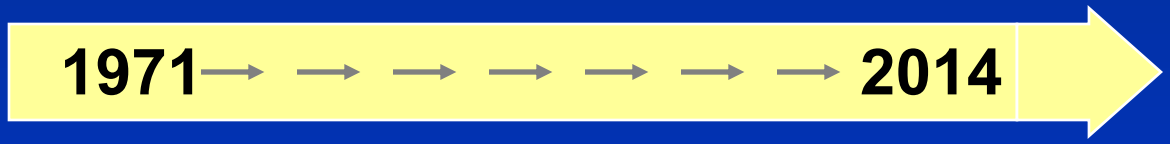
Brain Bank: 1997

National Institute on Aging

Framingham Heart Study



Gen 1 Original cohort;



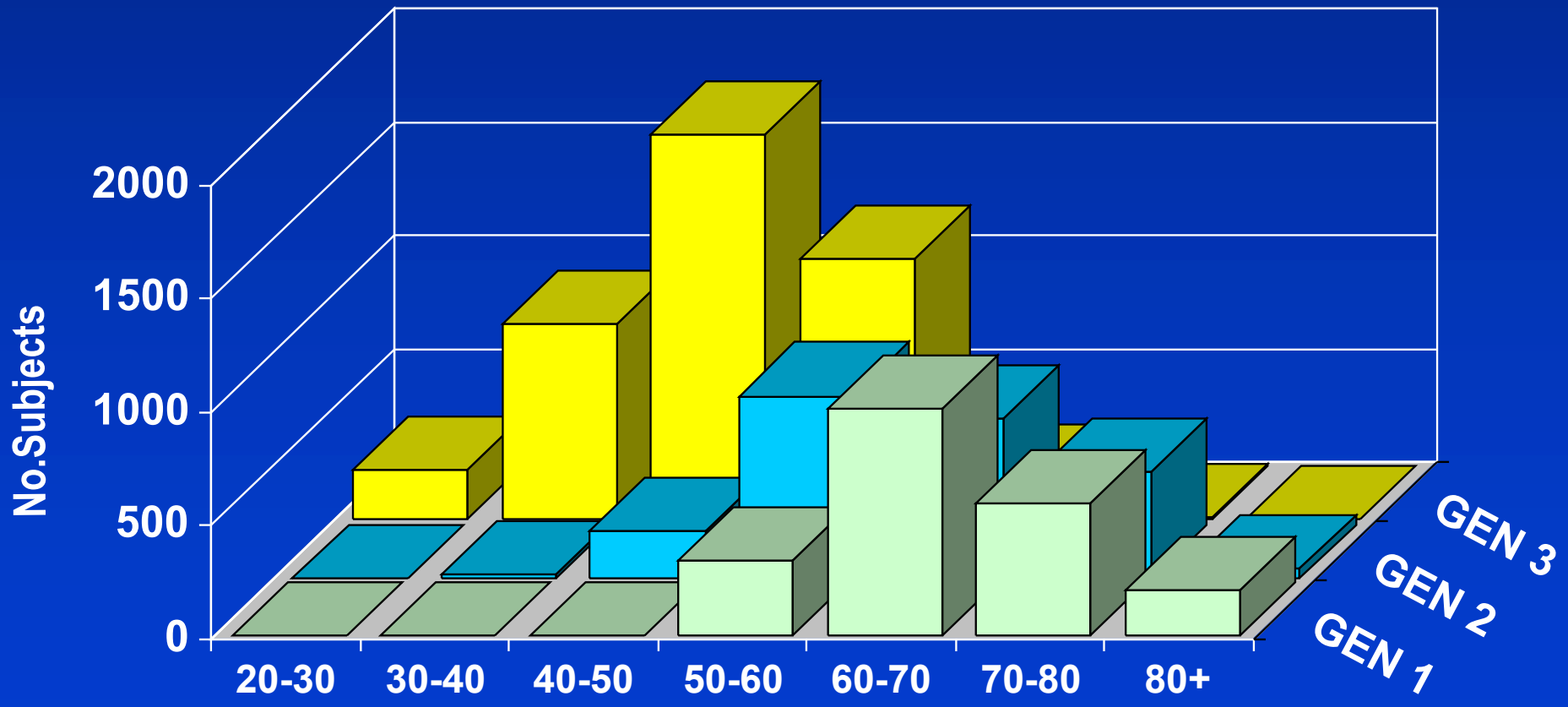
Gen 2 Offspring cohort

Exam 3: MRI/NP and Novel Imaging
Functional MRI
Amyloid and Tau PET
Tractography, Regional Volumes/shape
Microbleeds
Enlarged Perivascular Spaces

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 DrawingTest
Premorbid Intelligence, Reading	Wide Range Achievment Test (WRAT)-3 Reading Subtest
Premorbid Intelligence, Education	WAIS_Information
WMS: Wechsler Memory Scale	WAIS: Wechsler Adult Intelligence Scale

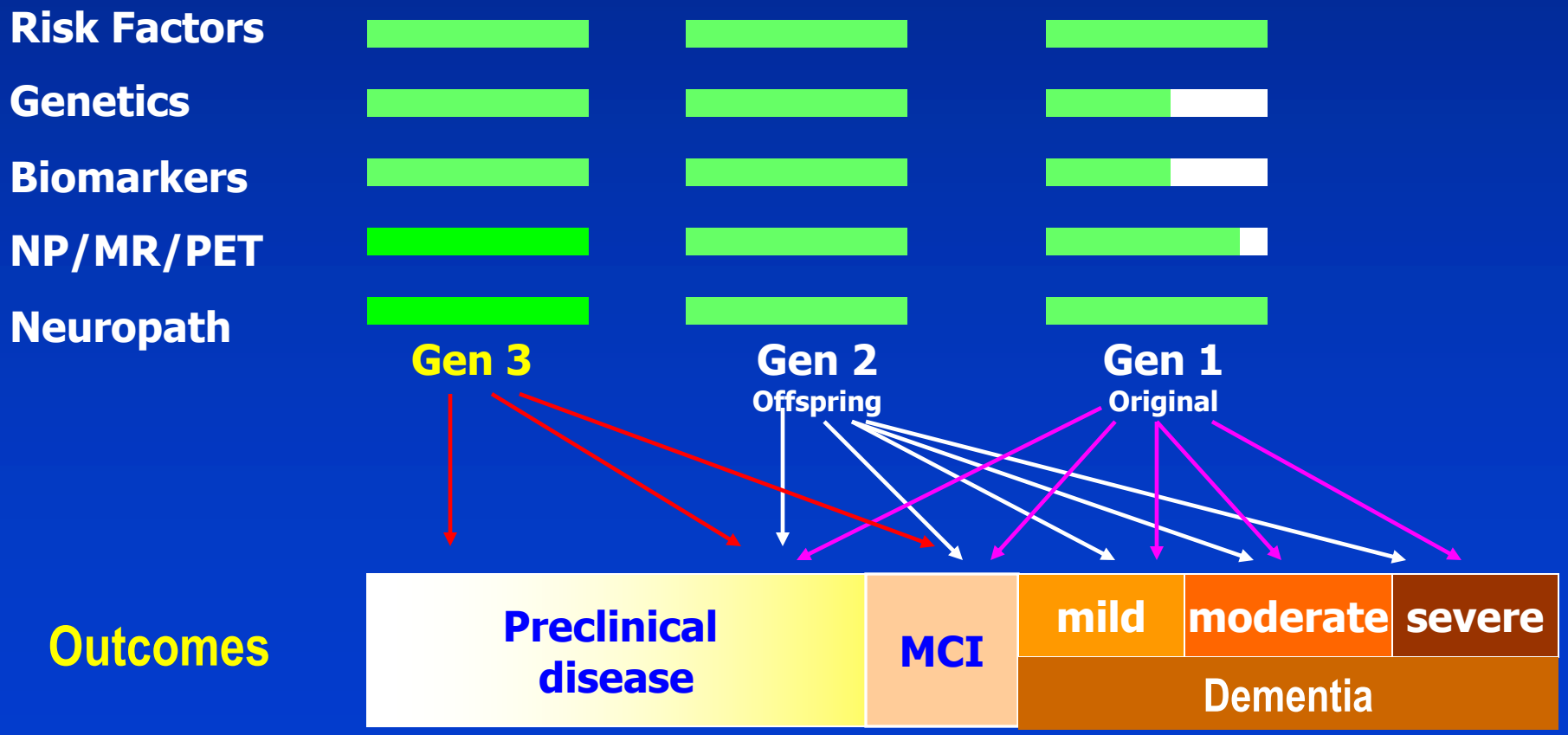
Victoria Stroop & CERAD Word List: Gen 3

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

Framingham Study Datasets

Data sets indexed with Dummy IDs

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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 COntrolled Word Association

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

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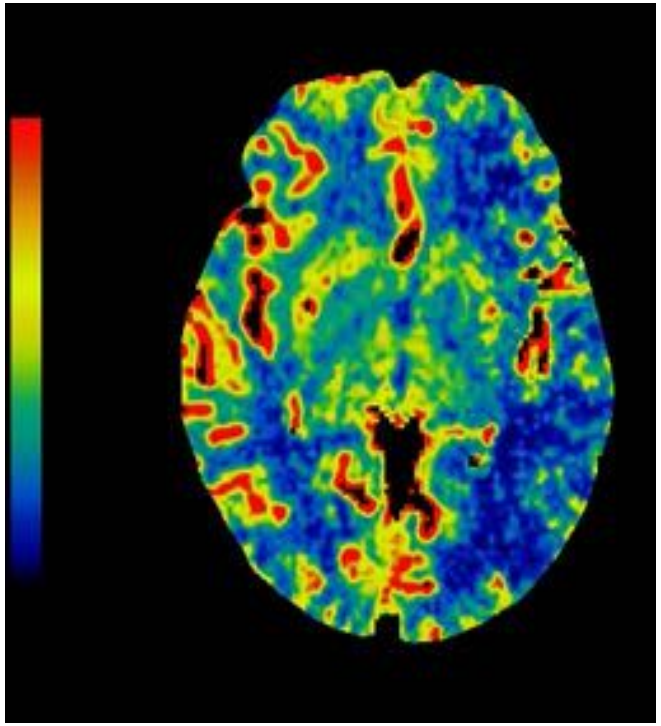
Vascular Brain Injury

- The Human Brain is…..



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

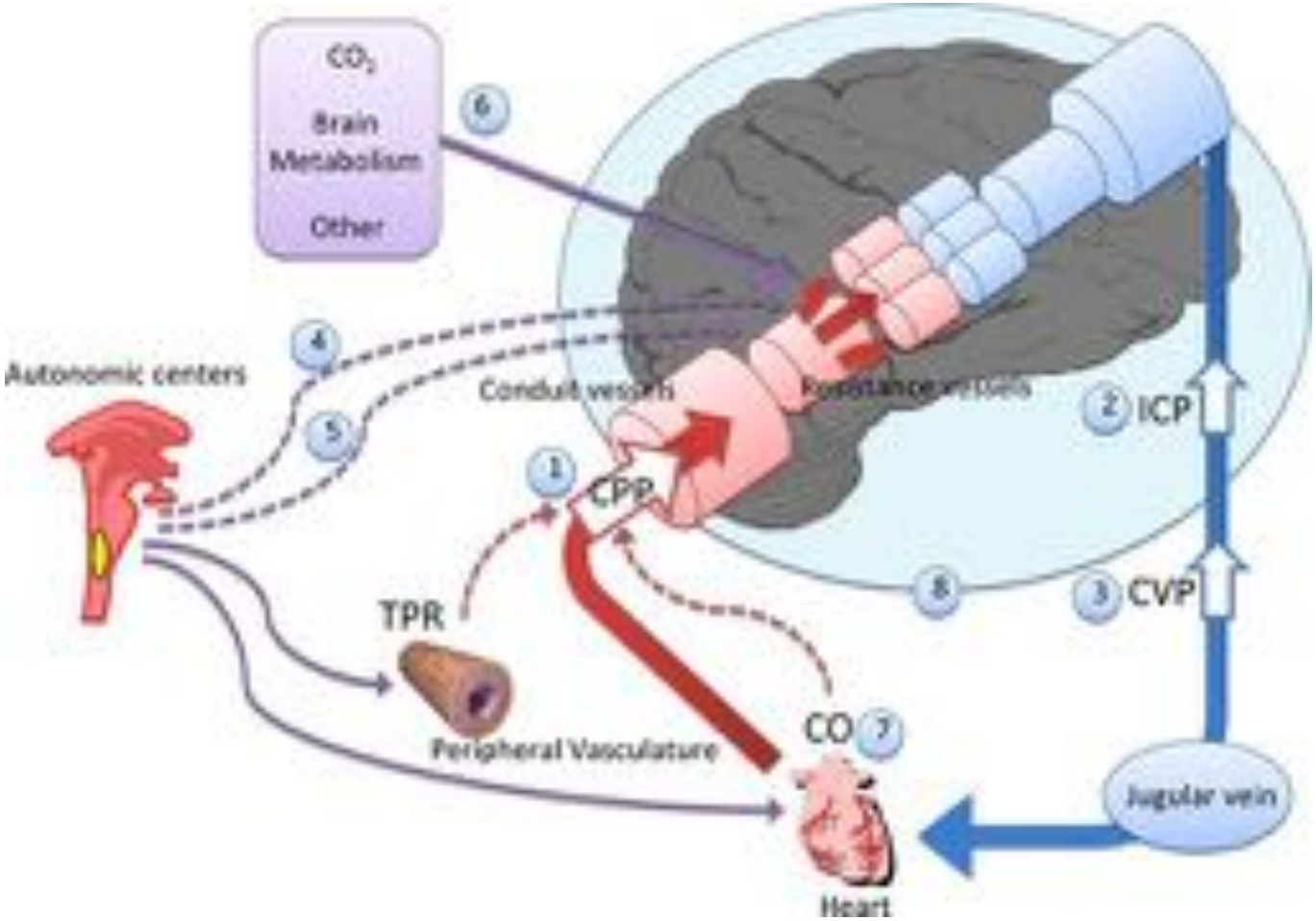
Vulnerable to ischemia
Diseases of ‘pump and pipes’

Auto-regulation of blood flow

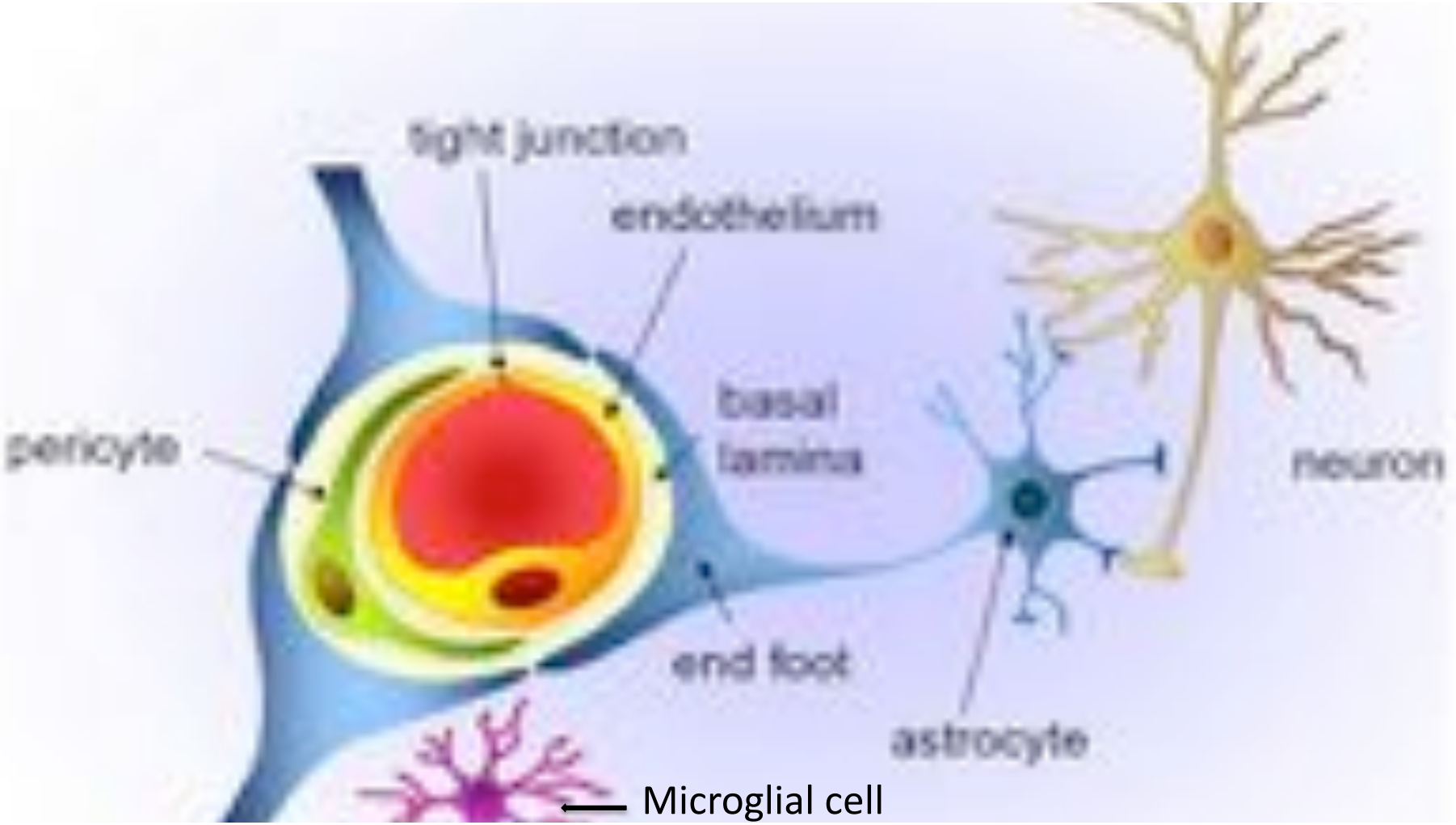
Separated by blood-brain barrier

Vascular Brain Injury

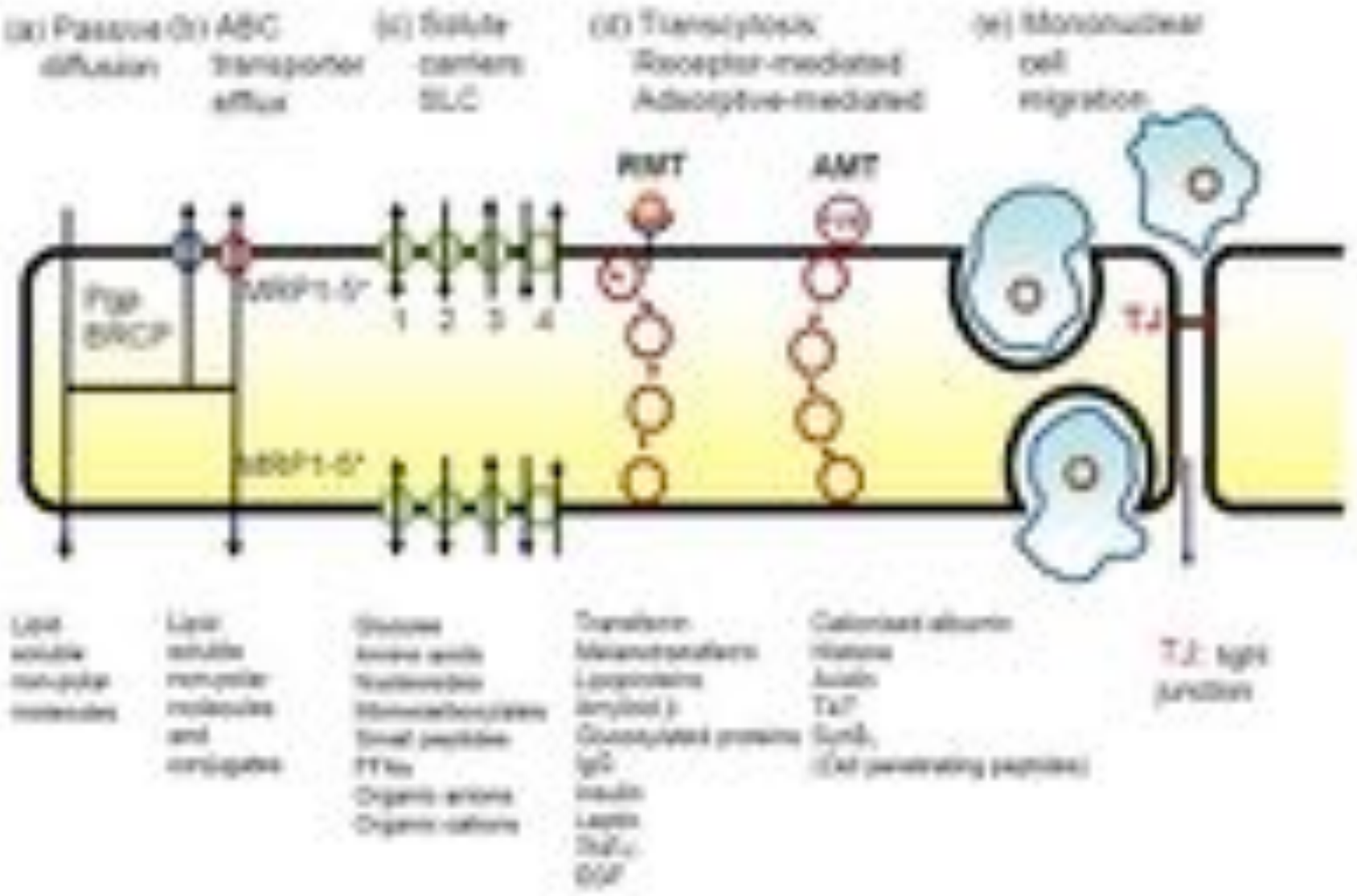
- Cerebral Autoregulation



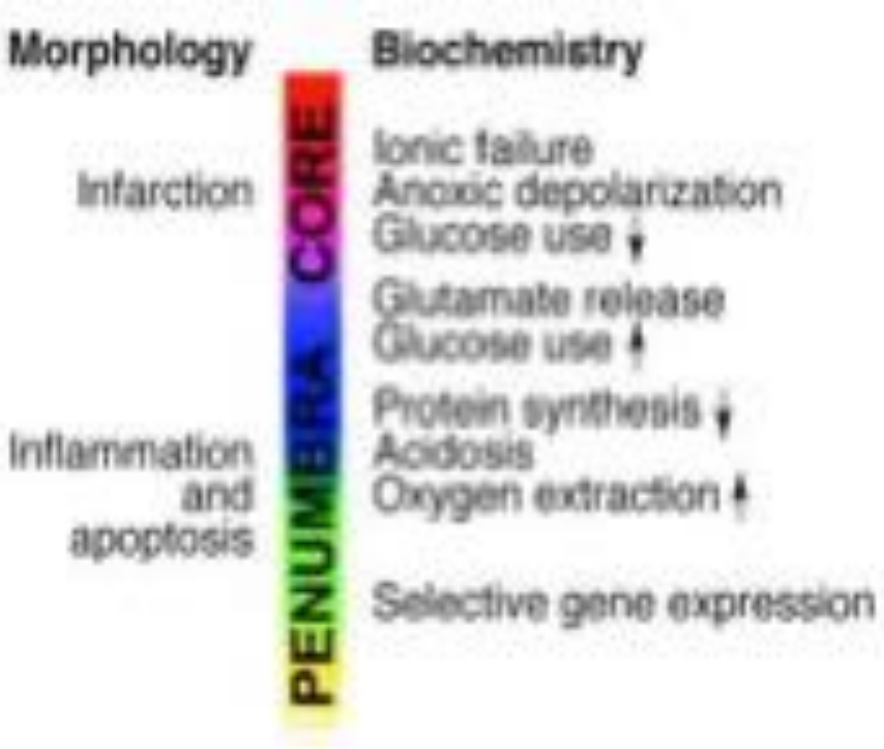
Neurovascular Unit

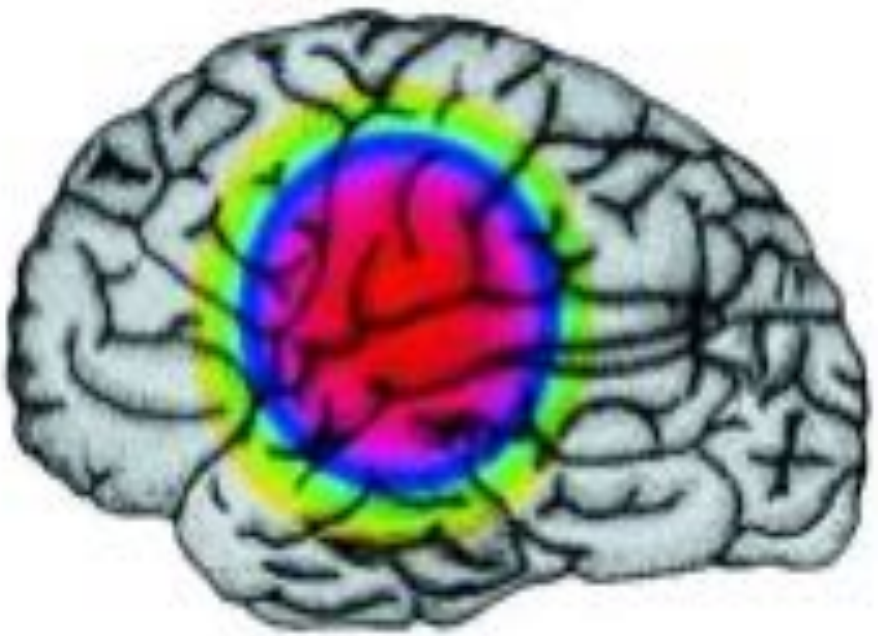


Blood-Brain Barrier



Pathobiology of ischaemic stroke





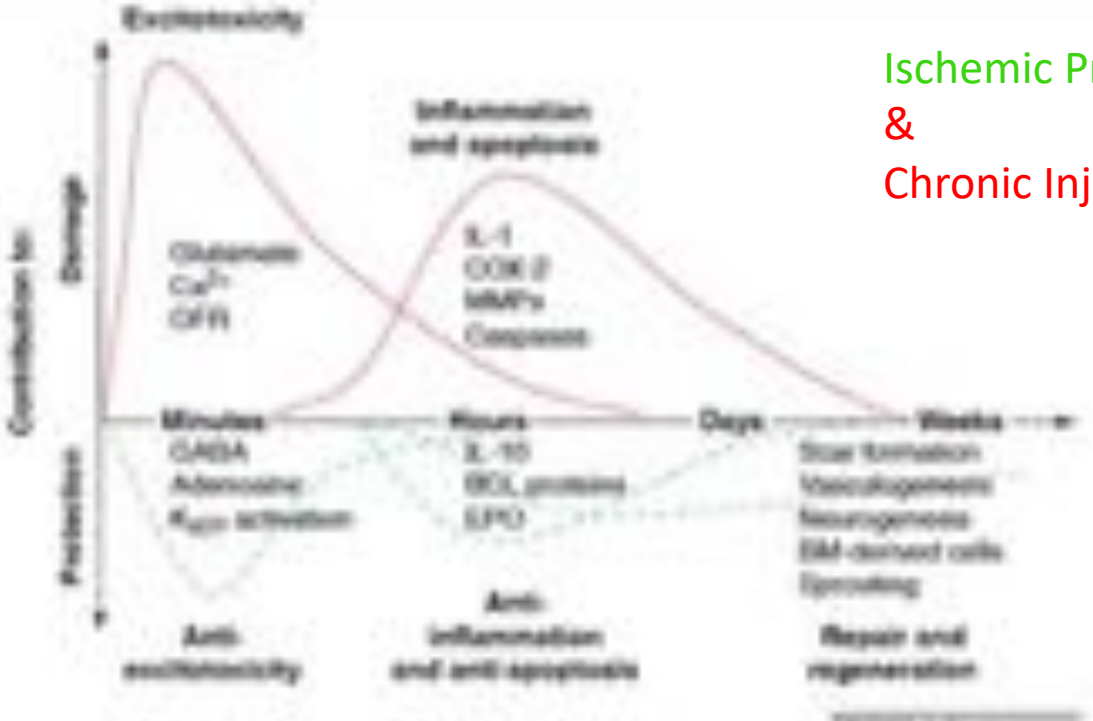
Ulrich Dirnagl, Costantino Iadecola, Michael A. Moskowitz, Ulrich Dirnagl, Costantino Iadecola, Michael A. Moskowitz

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

Ischemic tolerance and endogenous neuroprotection

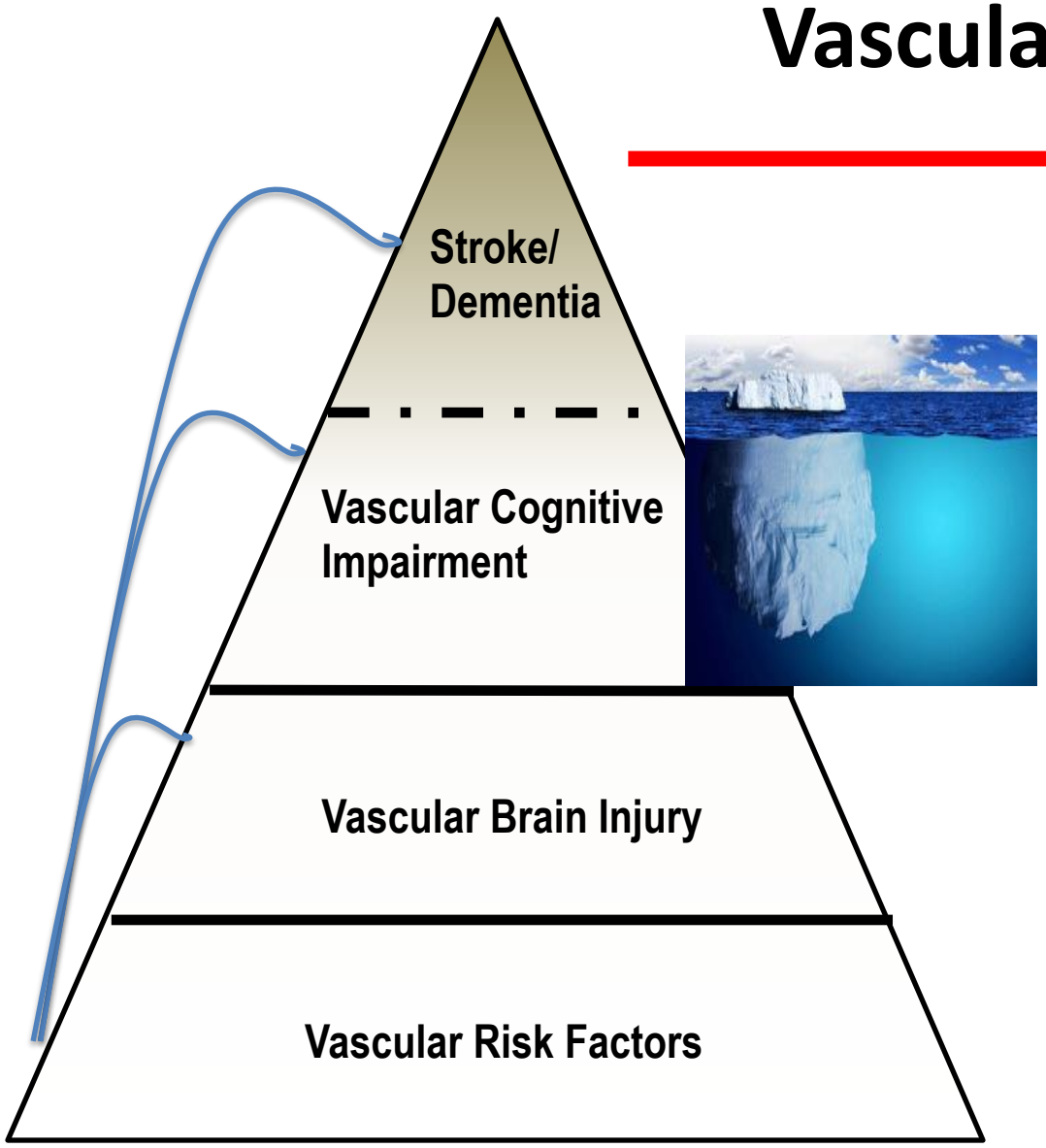
Ulrich Dirnagl[1], Roger P. Simon[2] and John M. Hallenbeck[3]

[1]Experimental Neurology, Charite Hospital, Humboldt University, 10098 Berlin, Germany
[2]R.S. Dow Neurobiology Laboratories, 1225 NE 2nd Ave, Portland, OR 97232, USA
[3]Stroke Branch, NINDS, NIH, Building 36/Room 4A03, 36 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

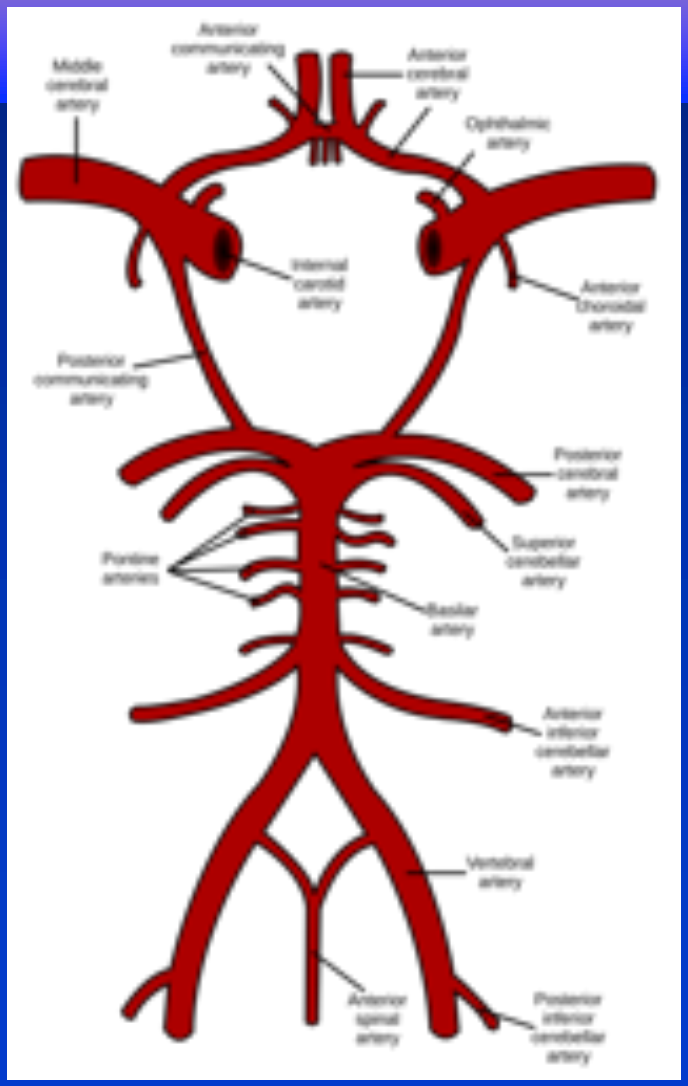
Sacco RL Stroke 2013;44: 2064-2089

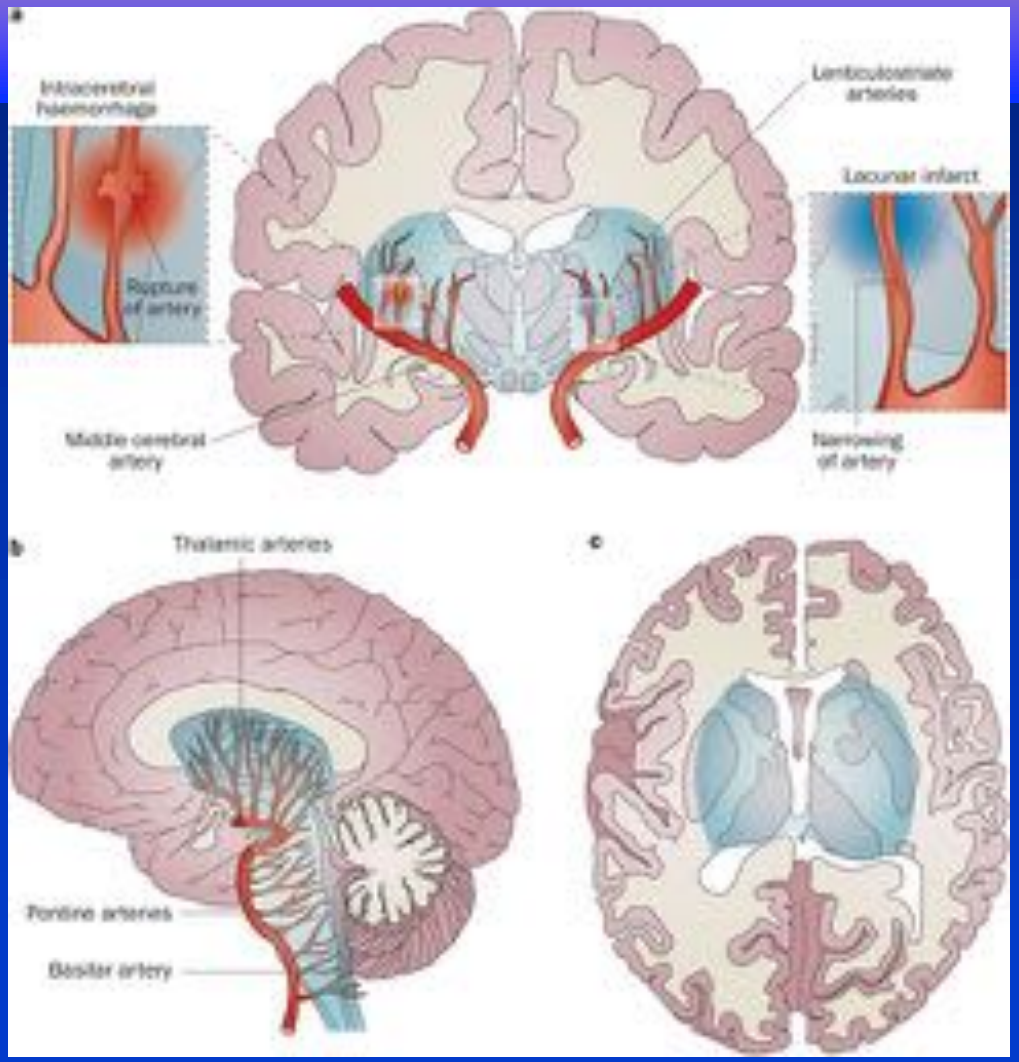
- Stroke: clinical deficit lasts > 24 hrs
  - Deficit may be minor or catastrophic
  - May progress, remain static or improve

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





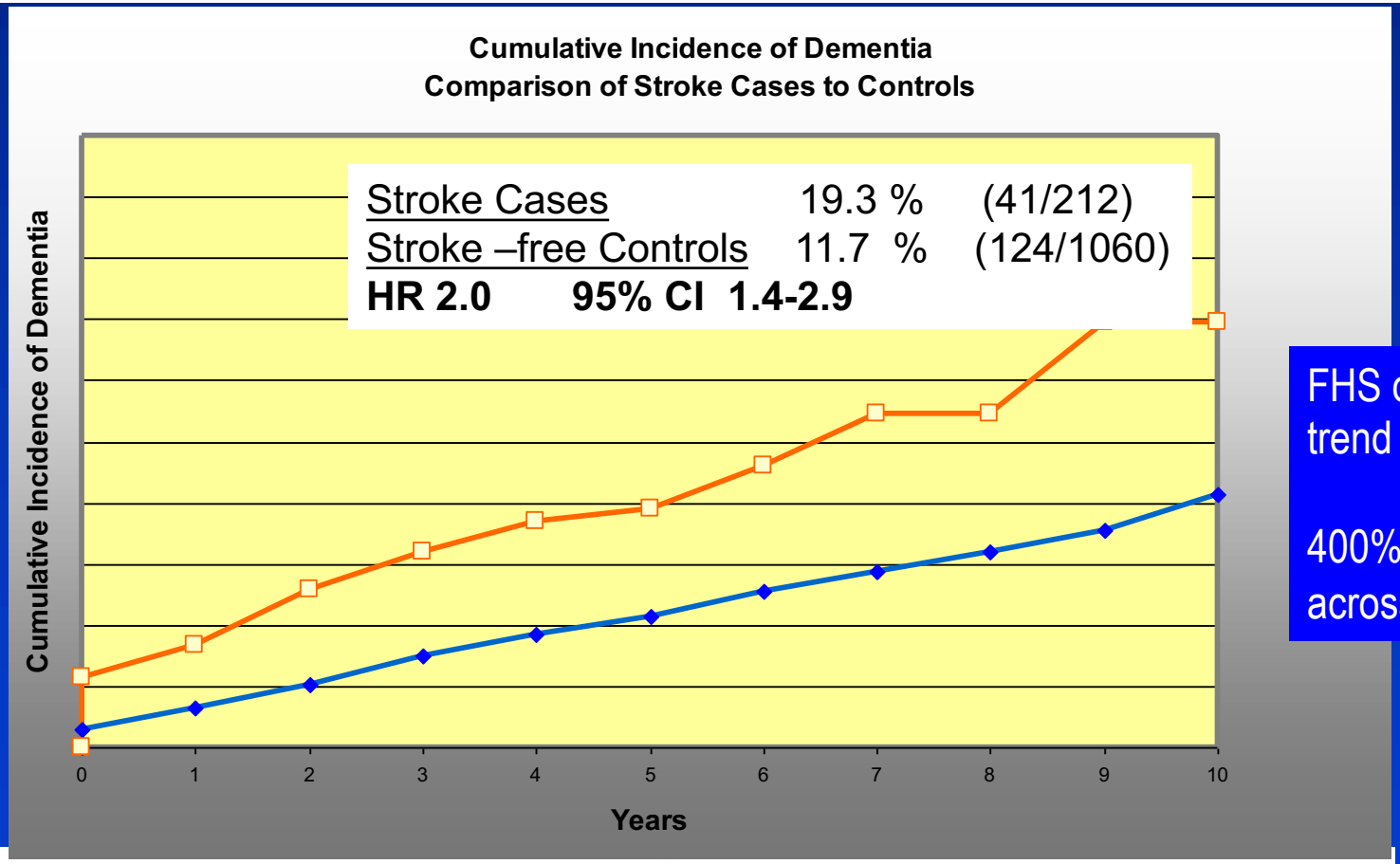
Sörös, P. *et al*. (2012) Antihypertensive treatment can prevent stroke and cognitive decline
Nat. Rev. Neurol. doi:10.1038/nrneurol.2012.255

nature REVIEWS NEUROLOGY

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



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.

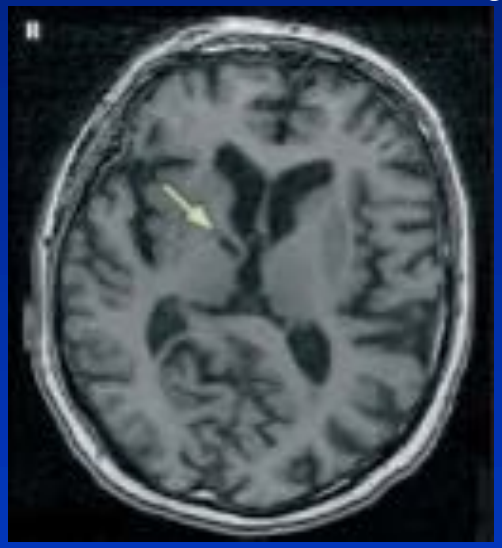
Subclinical Vascular Brain Injury

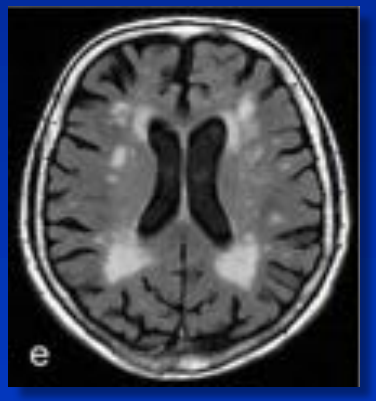
- 5X prevalence of clinical stroke/TIA
- Increases risk of clinical stroke and dementia, disability, depression and death
- Worse outcome after clinical stroke
- No treatment available; prevention is key

Silent Strokes and Vascular Brain Injury

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

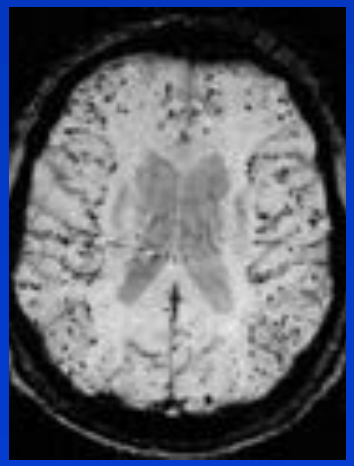
- **Lacunes**



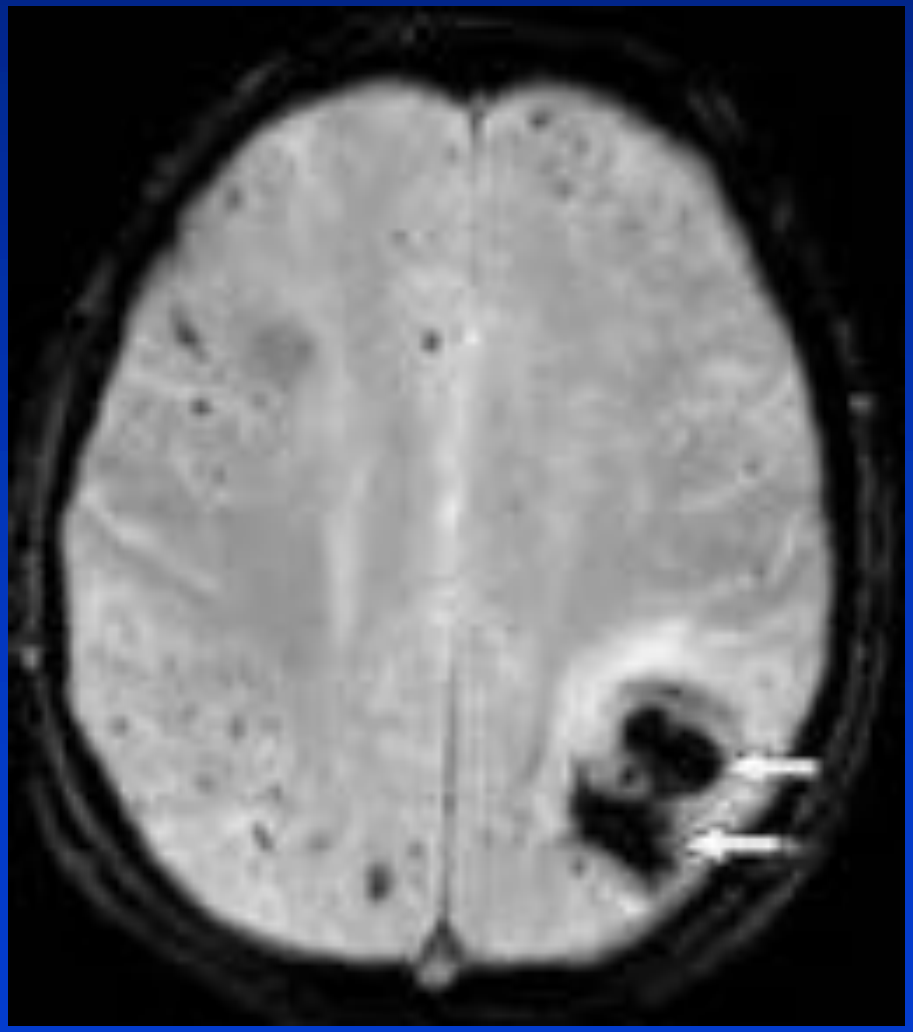


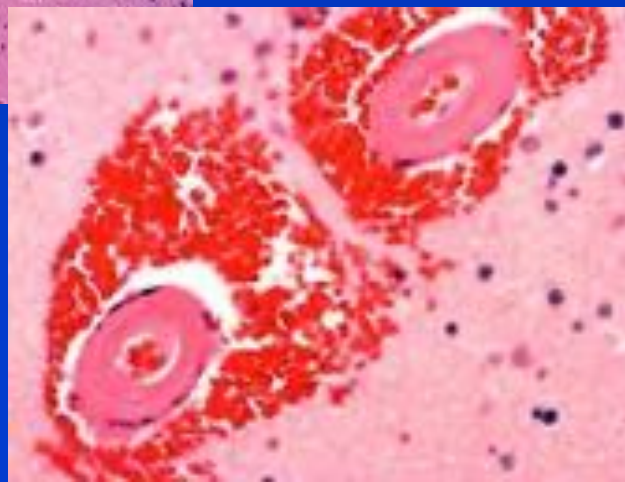
- **White Matter Hyperintensities**

- **Cerebral Microbleeds**

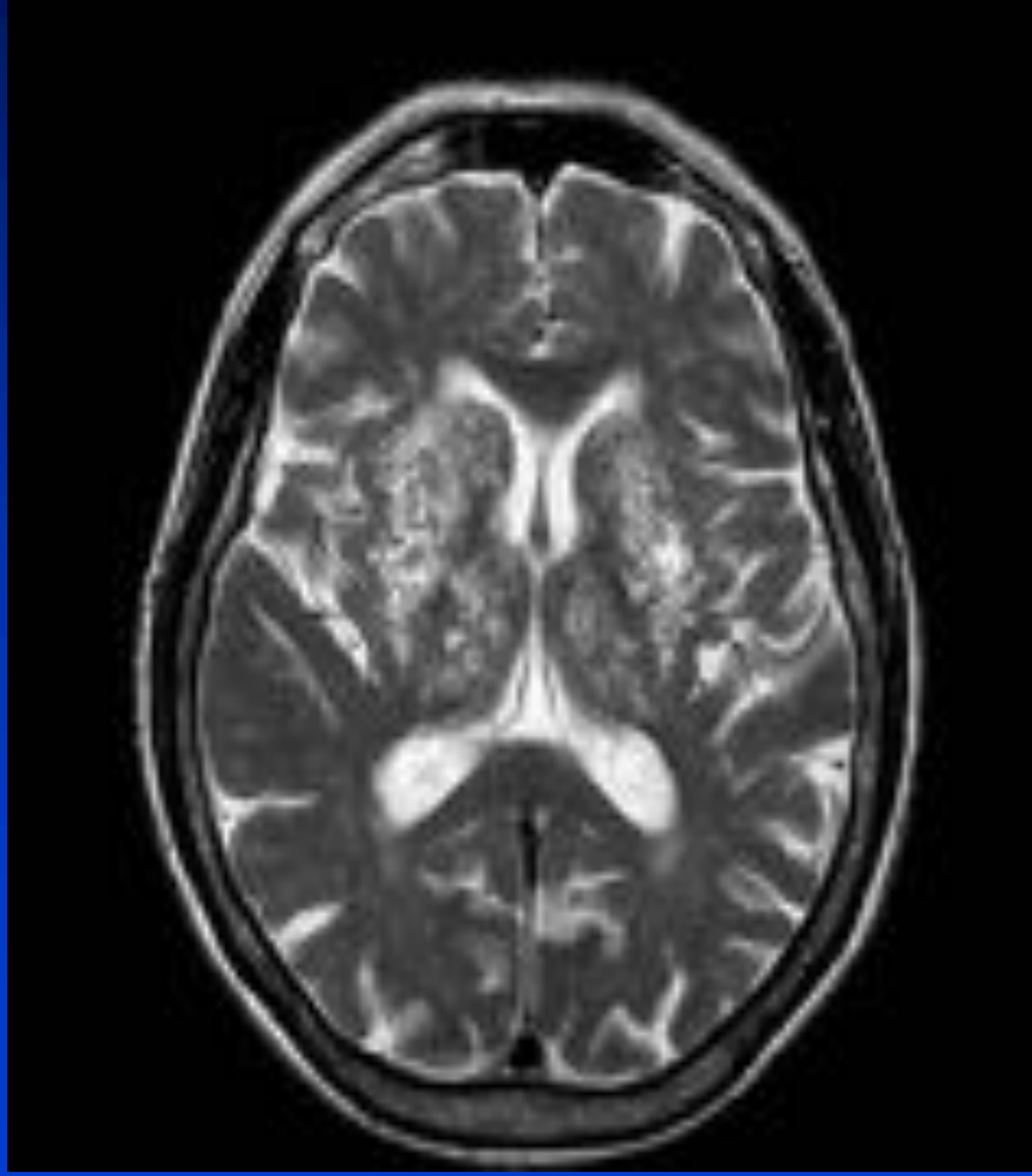


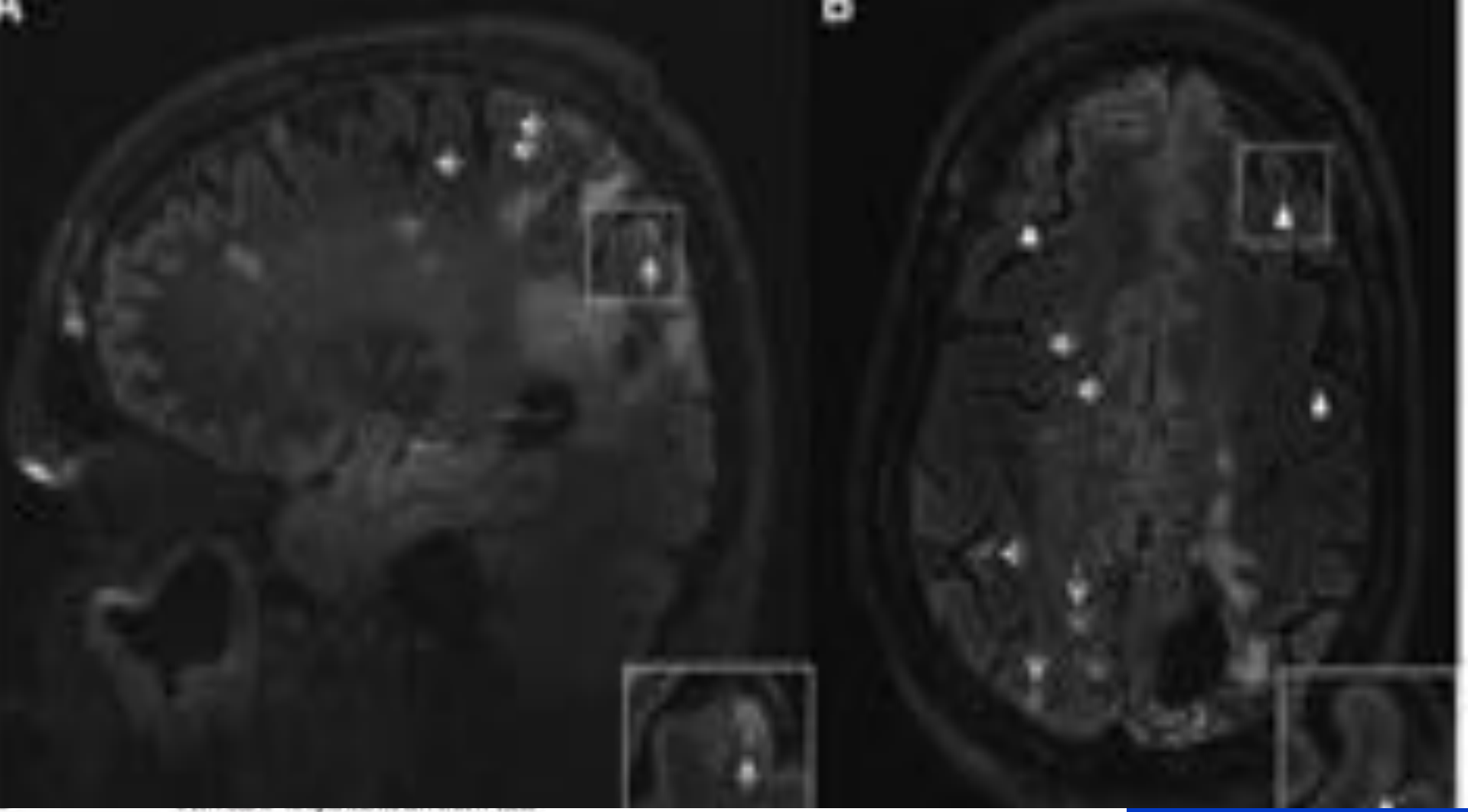
Cerebral Amyloid Angiopathy





Enlarged Perivascular Spaces





www.jcbfm.com

BRIEF COMMUNICATION

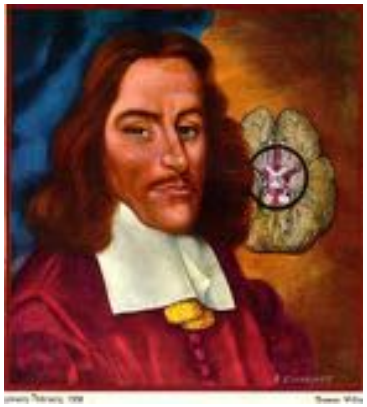
Cortical microinfarcts on 7T MRI in patients with spontaneous intracerebral hemorrhage

Susanne J van Veluw[1], Wilmar MT Jolink[1], Jeroen Hendrikse[2], Mirjam I Geerlings[3], Peter R Luijten[2], Geert Jan Biessels[1] and Catharina JM Klijn[1]

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 (ADDTC) 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

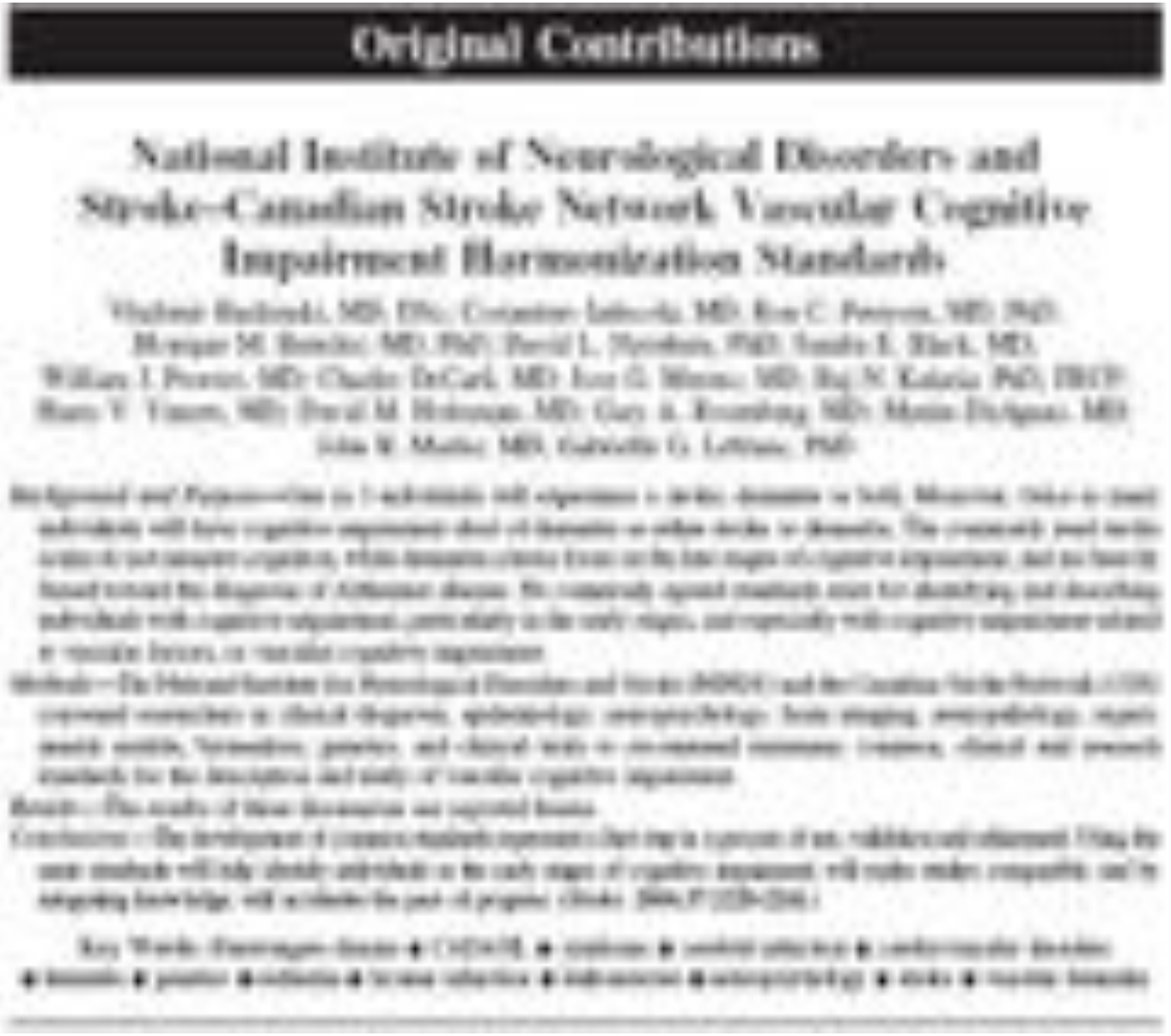
- Vascular Cognitive Impairment
  - Brain at Risk…. to…. Dementia

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



Original Contributions

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

Recommended
Standardized
Data
Collection

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

Treat HTN in midlife

Prevent Stroke

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**

Published Ahead of Print on January 7, 2015 as 10.1212/WNL.0000000000001202

Lipid and lipoprotein measurements and the risk of ischemic vascular events

Framingham Study

Aleksandra Pikula, MD

ABSTRACT

Neurology 2015

SDU log-HDL	0.77 [0.68-0.87]***	P<0.001
HDL≤40	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

Sara Kaffashian, PhD
Aline Dugravot, MSc
Alexis Elbaz, MD, PhD
Marcia J. Shipley, MSc
Séverine Sabia, PhD
Mika Kivimäki, PhD
Archana Singh-Manoux, PhD

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 midlife 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 SD (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 SD (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;80:1300-1306

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

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

Cholesterol levels were not associated with dementia or AD risk

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.

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

American Journal of
EPIDEMIOLOGY

Volume 138
Number 6
September 15, 1993

Sponsored by the Society for Epidemiologic Research

ORIGINAL CONTRIBUTIONS

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

Merrill F. Elias,[1] Philip A. Wolf,[2] Ralph B. D'Agostino,[3] Janet Cobb,[3] and Lon R. White[4]

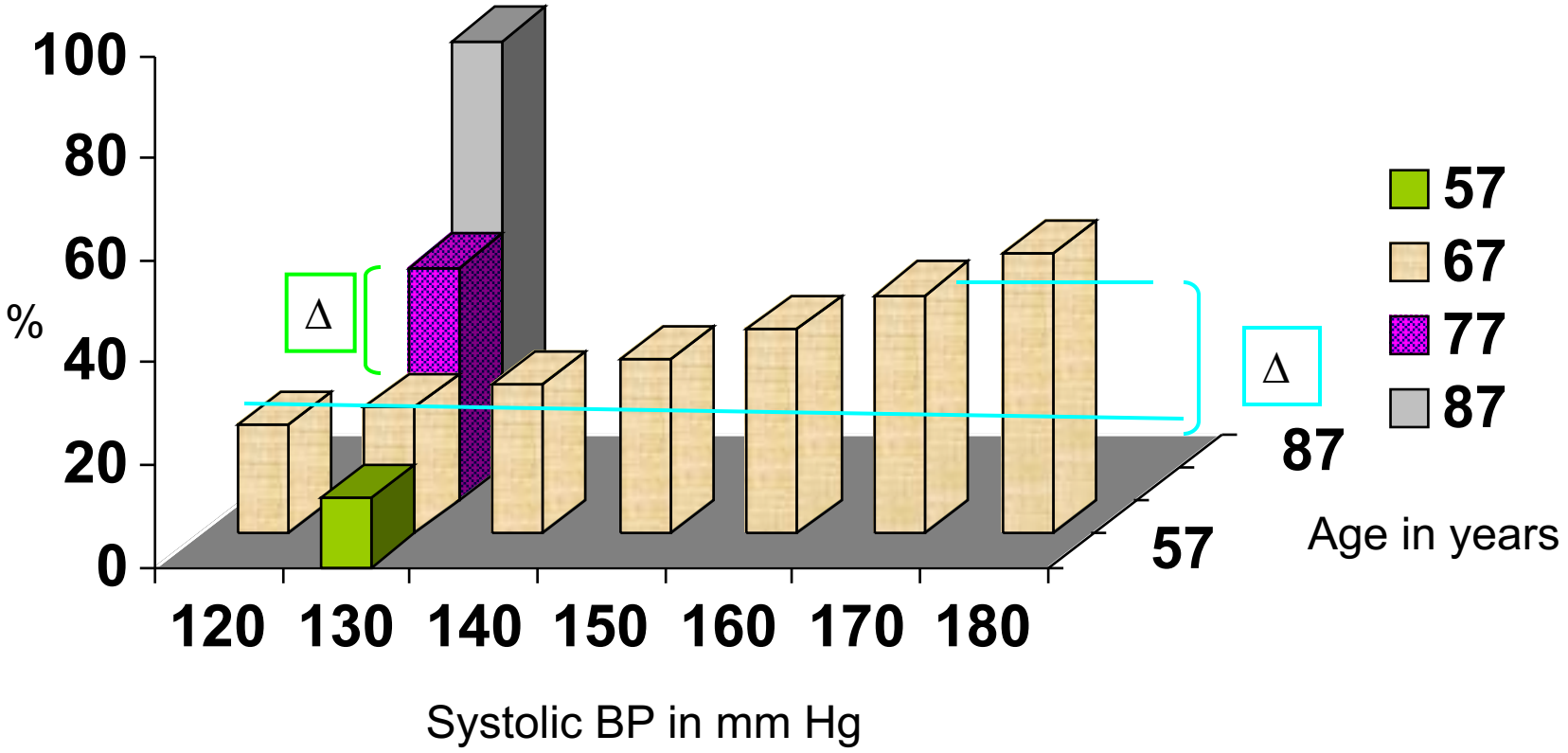
Untreated Blood Pressure Level is Inversely Related to Cognitive Function: The Framingham Study

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

Am J Epidemiol 1993; 138:353-64

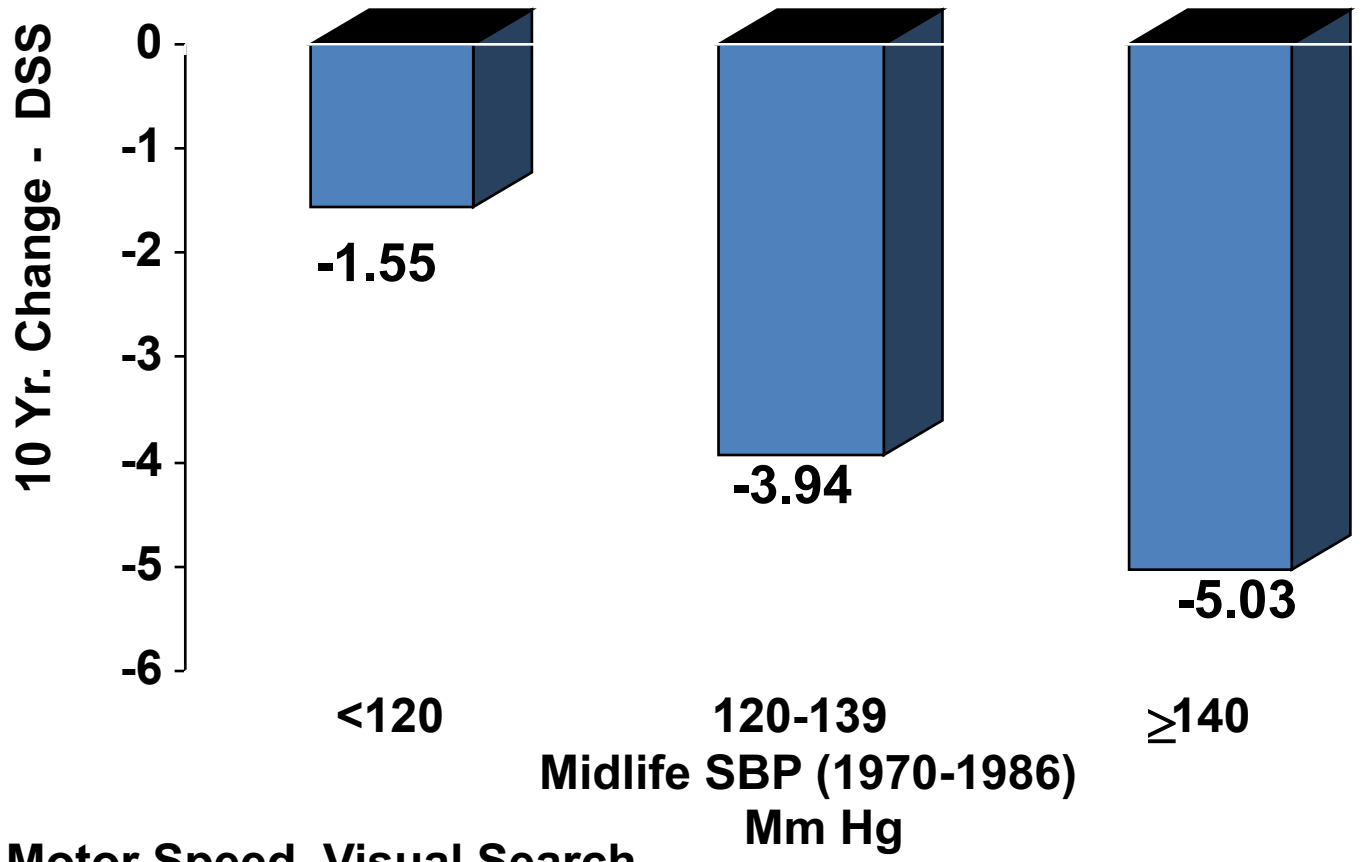
- 1702 Framingham subjects aged 55-88
- BP measured over 5 consecutive exams (1956-64) befor anti-hypertensive medications were widely used
- On neuropsych evaln in 1976-78, BP was inversely related to performance-

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



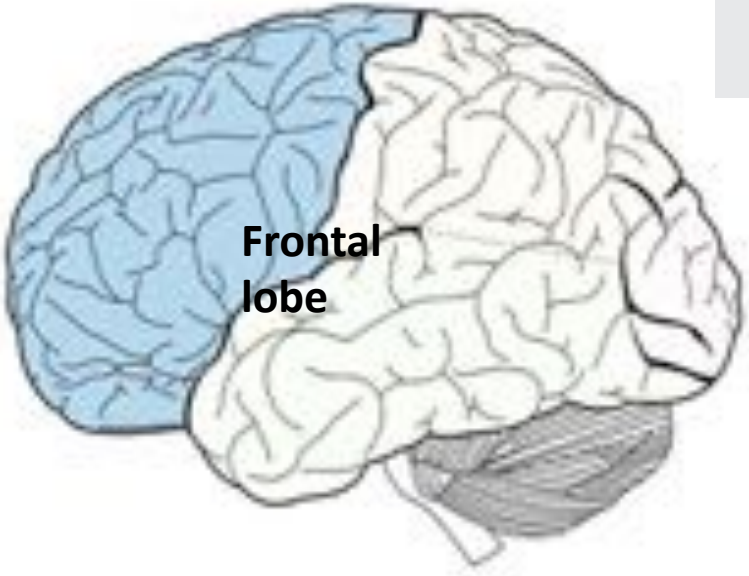
DSS - Motor Speed, Visual Search, Visuomotor Coordination

Swan GS, Neurology, 1998

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 (β±SE =0.02±0.01, p=0.012) and reasoning (β±SE =0.02±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.

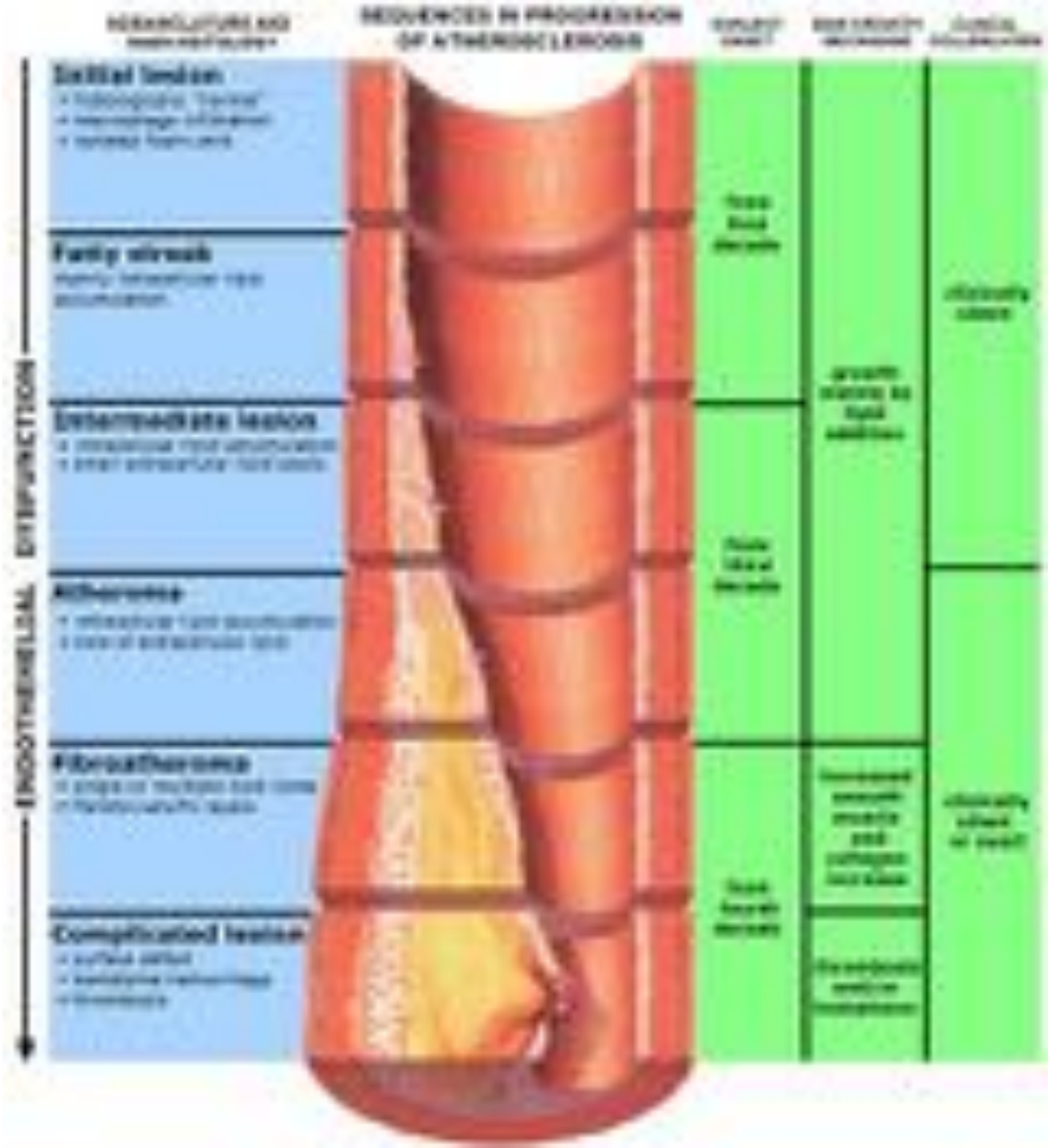
DISCUSSION Adherence to the American Heart Association's Ideal CVH behaviours may protect against vascular related brain injury. The concept of Ideal CVH should be promoted to protect the brain, as well as the heart, from vascular risk factors.

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

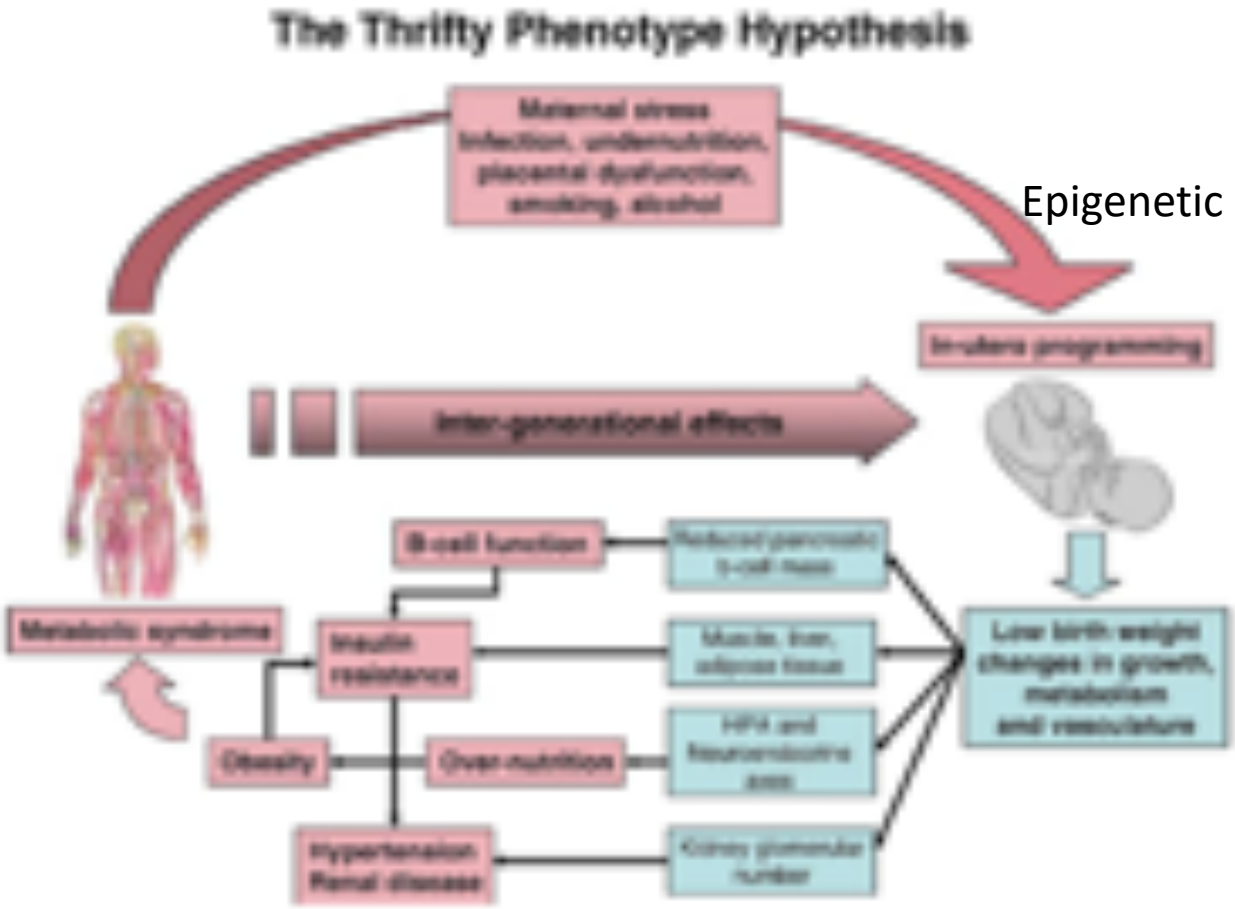
Emerging Concepts: Vascular Contributions to Cognitive Aging

- VCI is a life course ‘disease,’ but we may need sensitive measures to detect mid-life impact

- Relative Impact Greater in Younger Adults


Initial lesion
Fatty streak
Intermediate lesion
Atheroma
Fibroatheroma
Complicated lesion
ENDOTHELIAL DYSFUNCTION

Barker Hypothesis



Epigenetic modifications

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

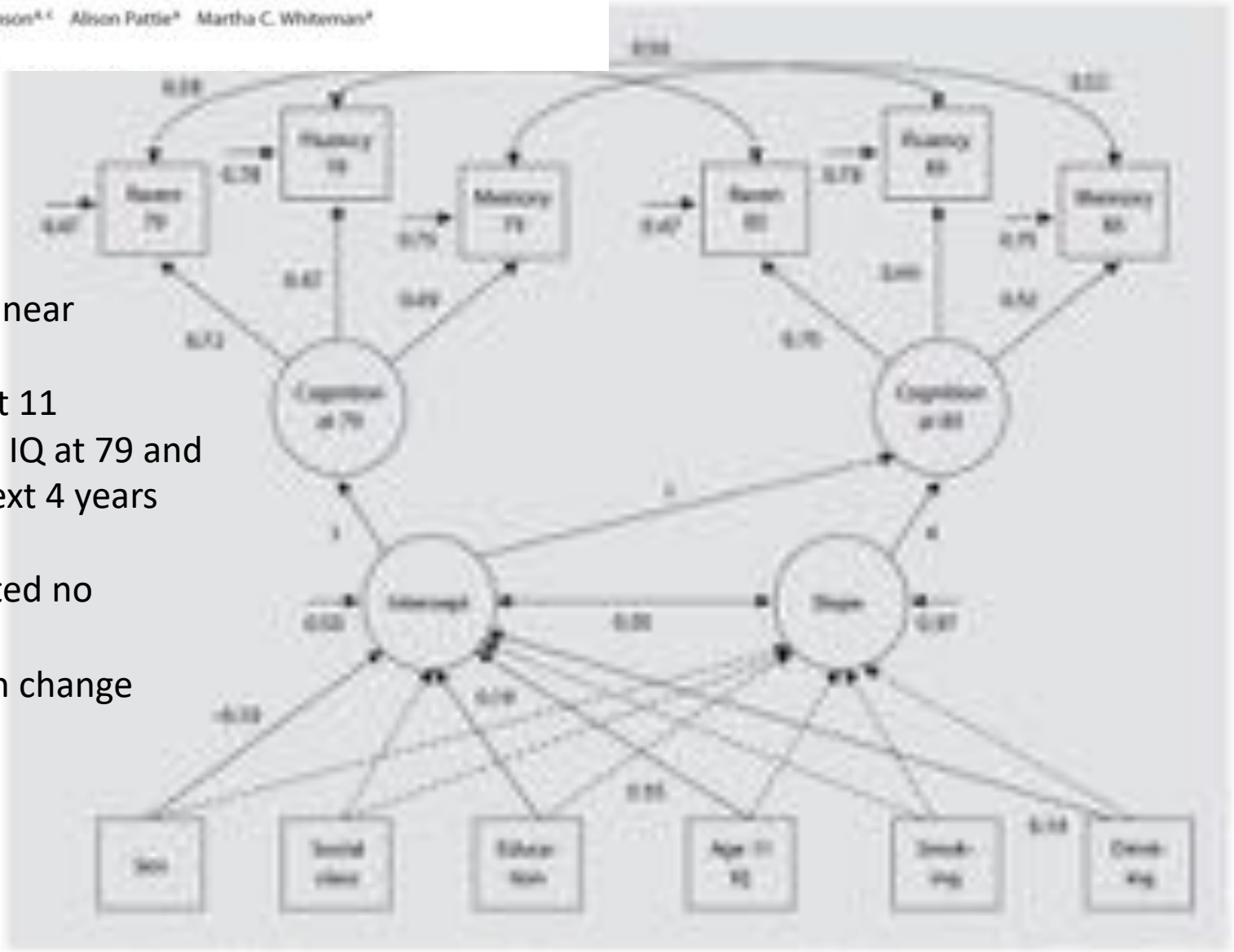


Fig. 1. Latent variable linear growth model with time invariant [illegible] were set by the loads of the

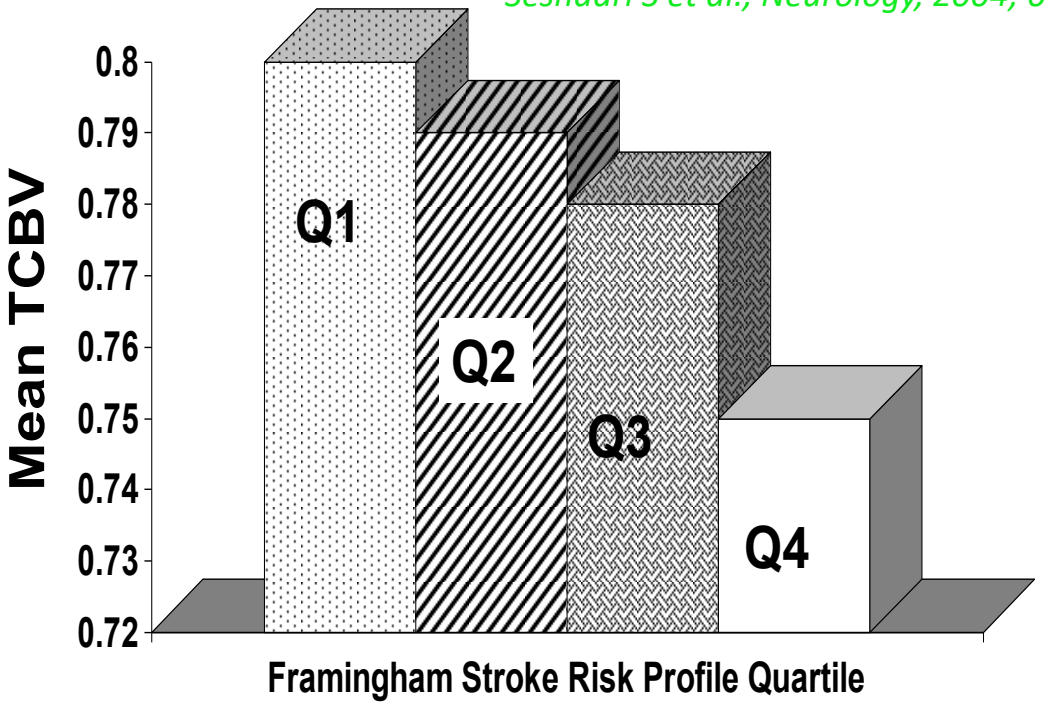
Cohort Studies of Vascular Factors & Cognition/Dementia

- 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

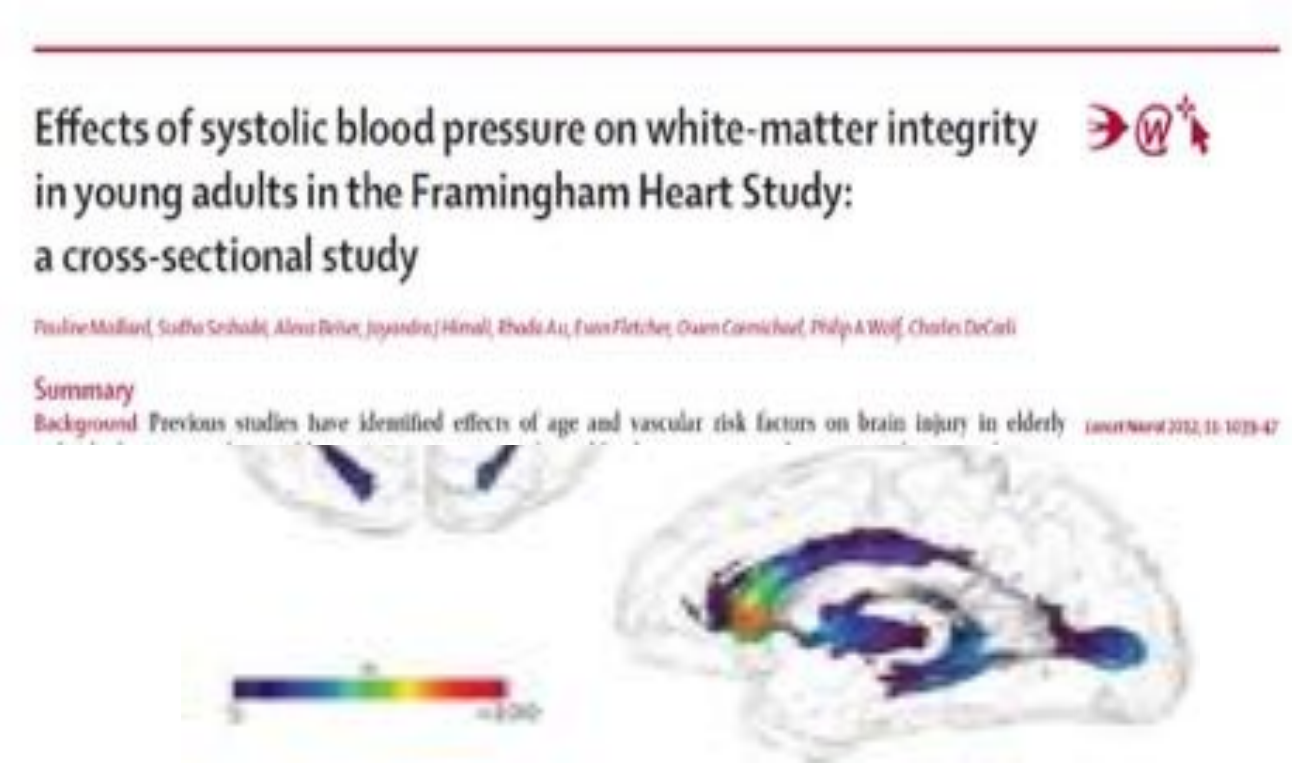
Seshadri S et al., Neurology, 2004; 63:1590

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



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

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

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.

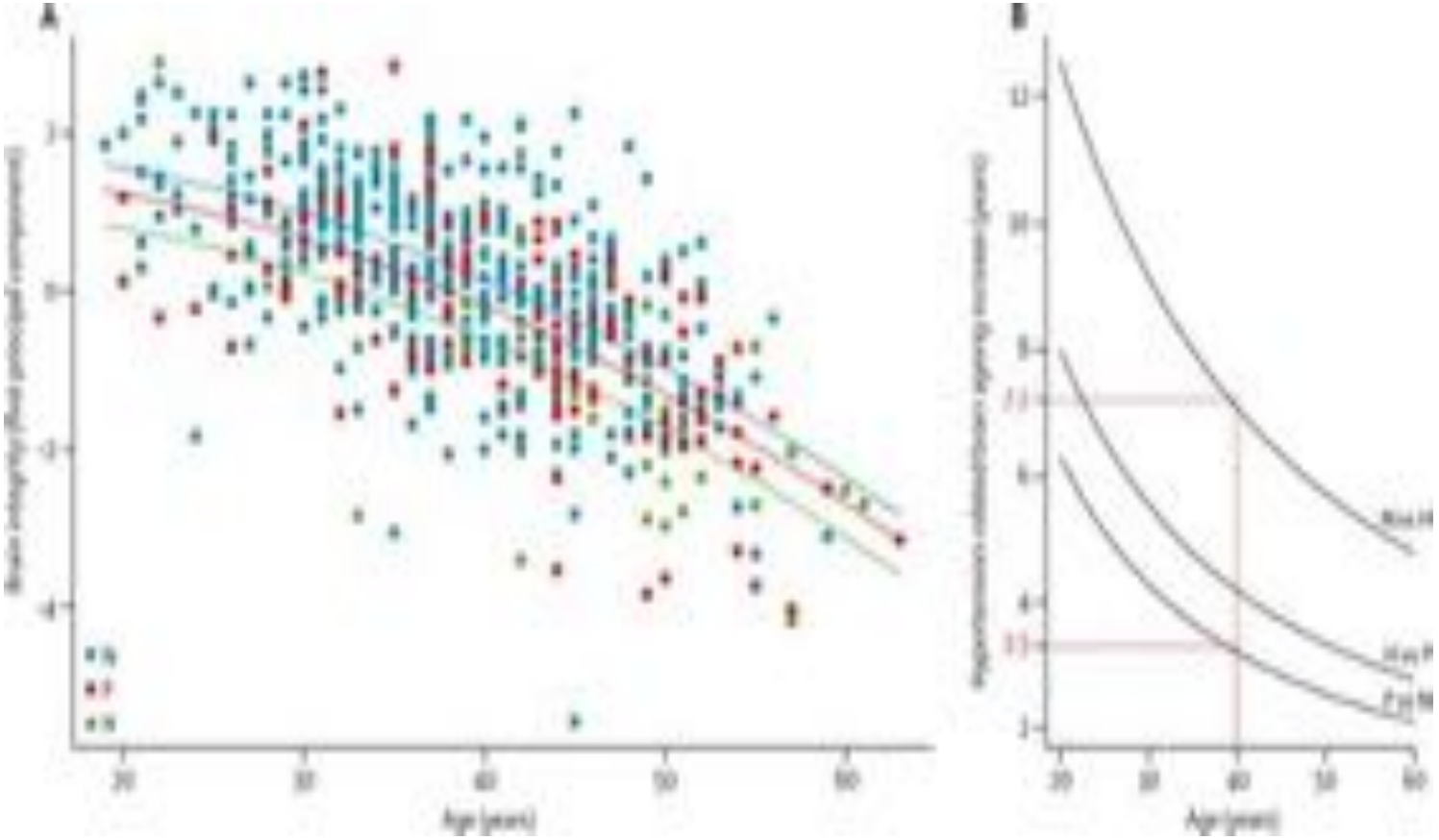


Figure 4 Regression curves relating brain integrity as expressed by the first principal component as a function of the hypertension category and age of the individual (A) and the difference in brain ageing increase between hypertension categories according...

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

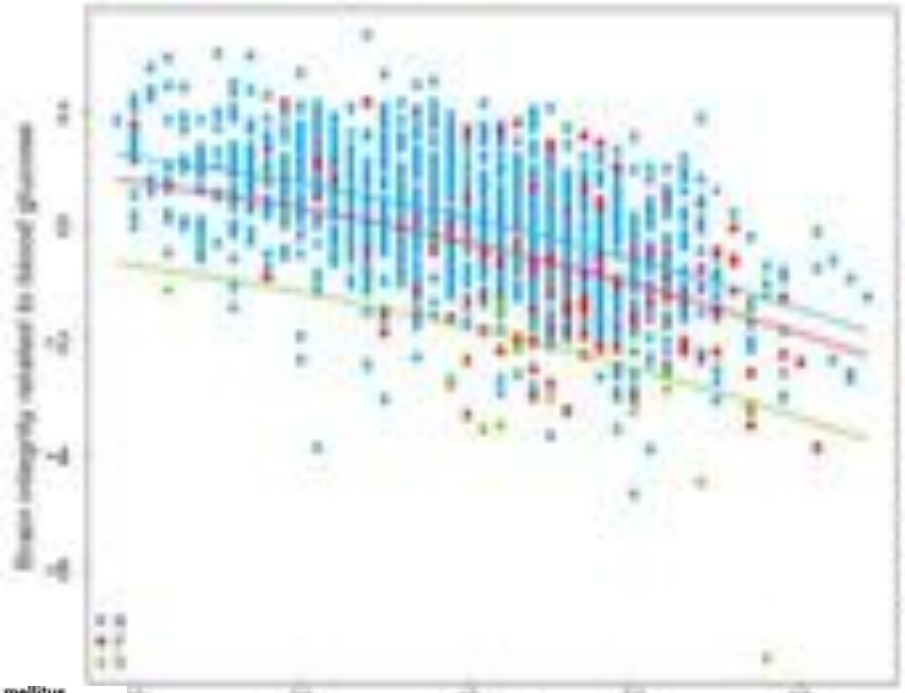
The Lancet Neurology Volume 11, Issue 12 2012 1039 - 1047

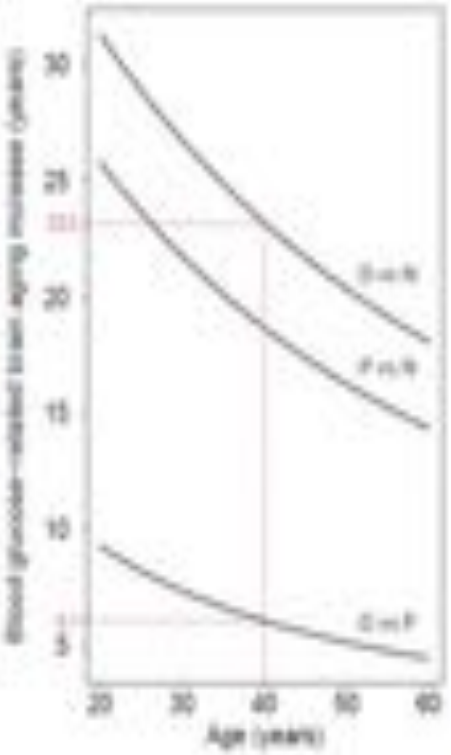
Hypertensive 40 year old had loss of brain integrity equivalent to normotensive person aged 47 years

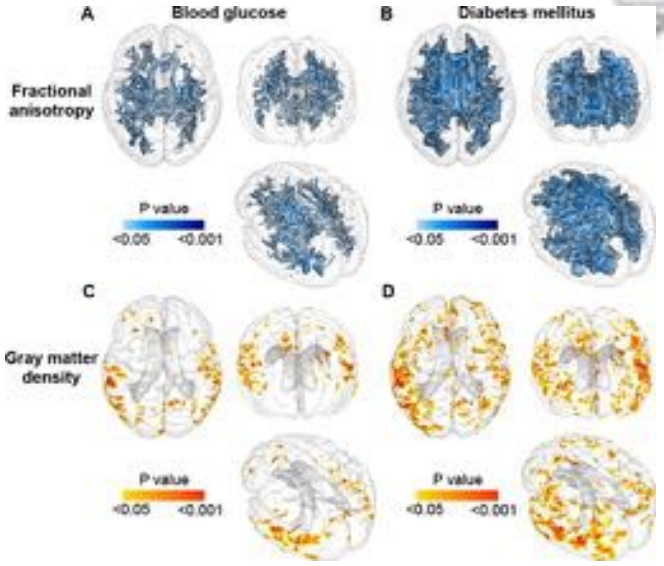
Association of Diabetes, Fasting Blood Glucose and Insulin Resistance with Cognitive and Structural Brain Measures in Young Adults: the Framingham Heart Study

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

Neurology 2015;84:2329-37







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).

		Sample 1[#] (n=1094)		Sample 2[##] (n=1583)	
Variable	Model	**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

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):301-310

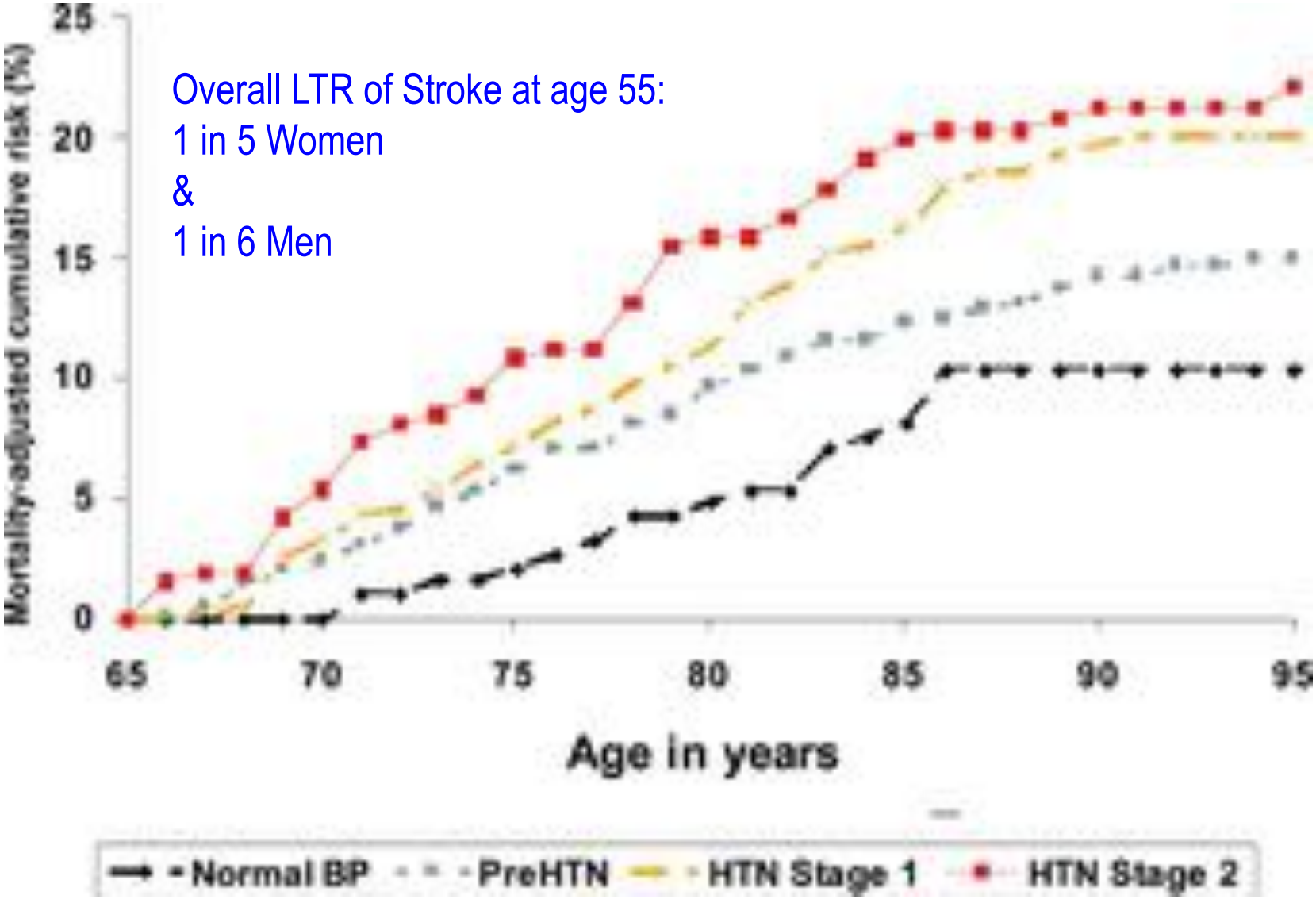
Control of hypertension whether labile or fixed, systolic or diastolic, and at any age or in either sex, appears to be central to the prevention of atherothrombotic brain infarction (ABI). Prospectively, hypertension proved to be the most common and potent precursor of ABIs. Its contribution was direct 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, innocuous is premature. When normotensive 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 so be 1 in 6, with hypertension being a powerful contributor to this hazard.[1] The Framingham Study al

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



Sudha Seshadri et al. Stroke. 2006;37:345-350

SPRINT

Systolic Blood Pressure Intervention Trial

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

Primary outomes: 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

1985

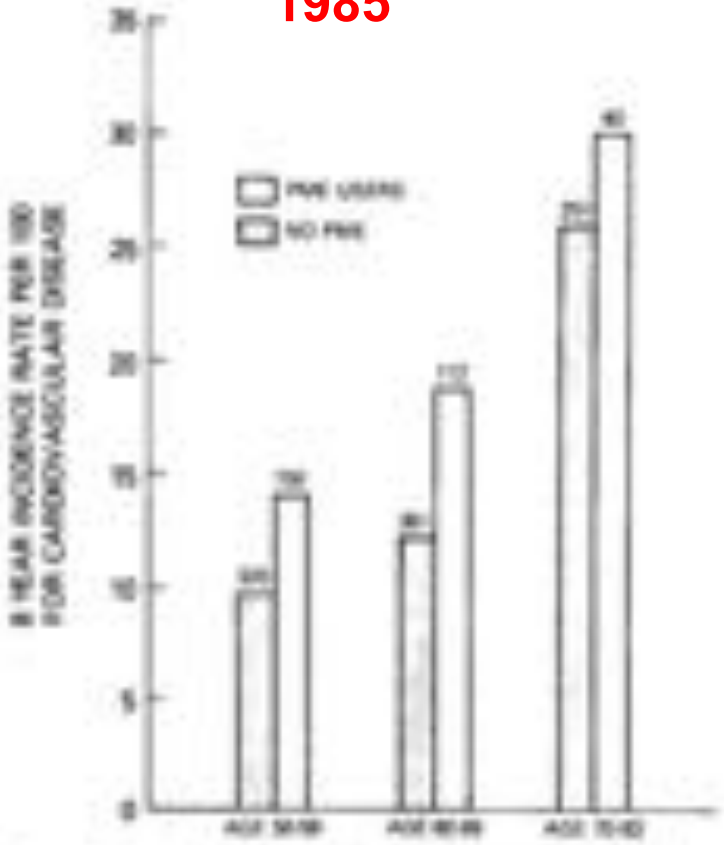
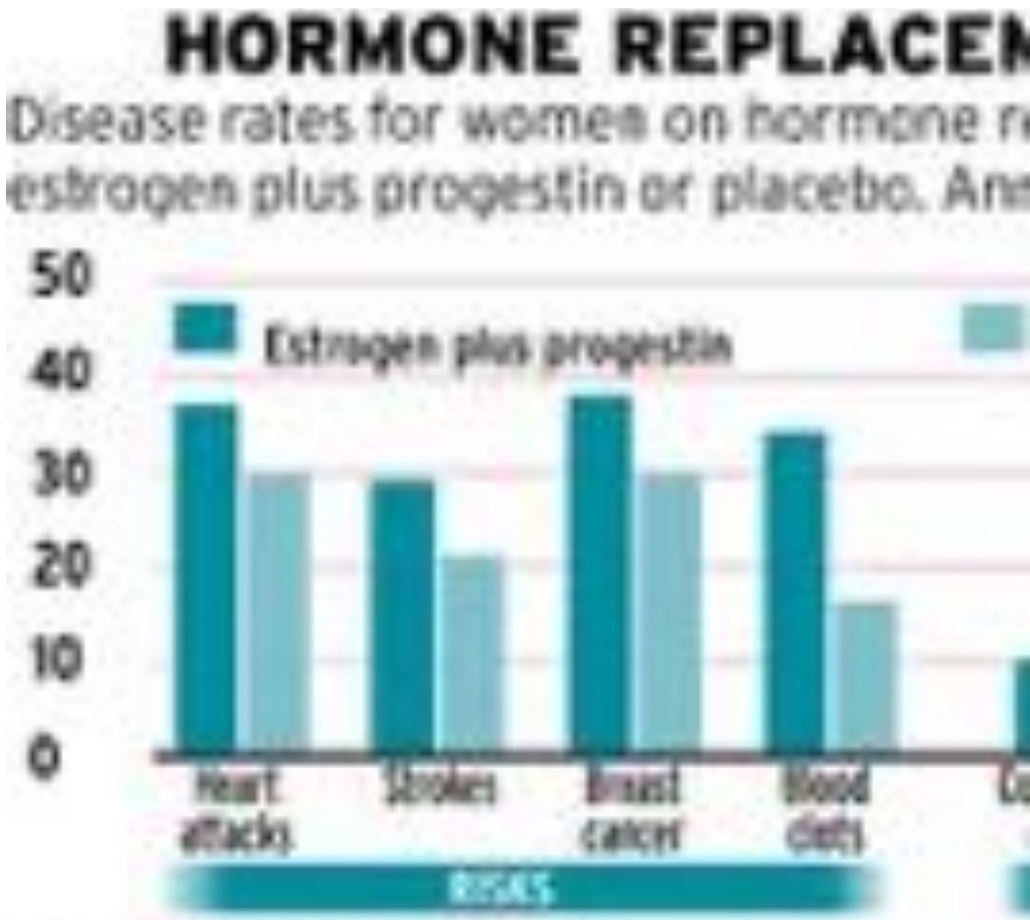


Figure 3. Eight-Year Incidence of Cardiovascular Disease among 1234 Women.

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

2002



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

Mary Ganguli, MD, MPH
Chung-Wen Lee, PhD
Beth E. Snitz, PhD
Tiffany F. Hughes, PhD
Eric McDade, DO
Chung-Chou H. Chang, PhD

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 = 1,982) 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 10.0 overall, 5.8 in those with median onset age of 87 years or younger, and 33.5 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*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.

Conclusion: 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;84:72–83

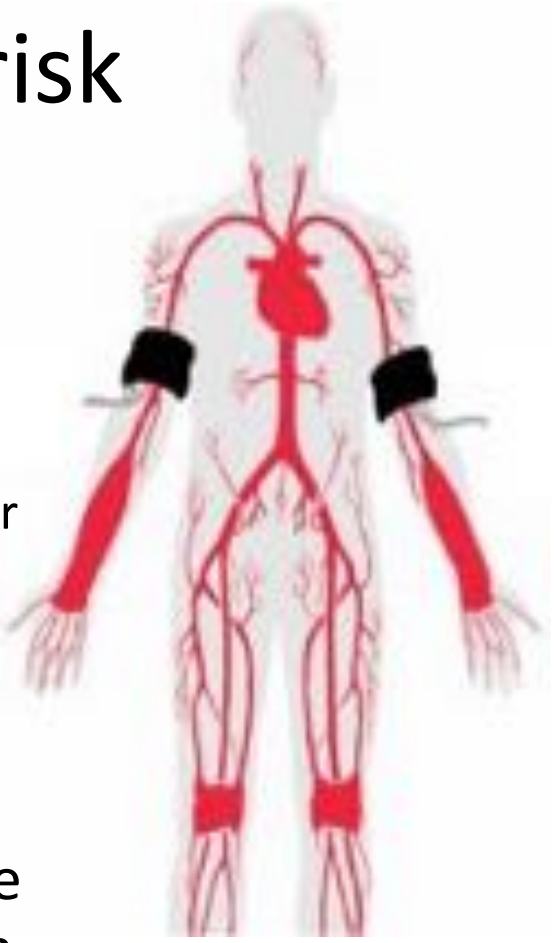
Smoking, stroke, Low SBP associated with dementia, if onset at <87

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 ≥10mmHg; 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 ≥10mmHg 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)**

	Whole sample		Apoe ε4+	
outcome	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

Hugh Watkins, M.D., Sudha Seshadri, M.D., Joshua C. Bis, Ph.D., Myriam Fornage, Ph.D., Anita L. DeStefano, Ph.D., Yurii S. Aulchenko, Ph.D., Stephanie Debette, M.D., Ph.D., Thomas Lumley, Ph.D., Aaron R. Folsom, M.D., M.P.H., Evita G. van den Herik, M.D., Mukhtiar J. Bis, M.D., Ph.D., Alexa Beiser, Ph.D., Mary Cushman, M.D., M.Sc., Lenore J. Launer, Ph.D., Eyal Shahar, M.D., M.P.H., Makiyan Jenkinson, M.Sc., Tangchun Gu, B.E., Nicole L. Glazer, Ph.D., Wayne D. Rosamond, Ph.D., Ramachandra Vasudevan, M.S., Ph.D., Margaret Kelly-Hayes, R.N., D.Ed., Orysia S. Lopez, M.D., Josef Coresh, M.D., Ph.D., Albert Hofman, M.D., Ph.D., Charles DeCarli, M.D., Susan R. Heckbert, M.D., Ph.D., Peter J. Koudstaal, M.D., Ph.D., Qiong Yang, Ph.D., Nicholas L. Smith, Ph.D., Carlos S. Kase, M.D., Kenneth Rice, Ph.D., Talin Haritunians, Ph.D., Corwin Ruiz, M.D., Ph.D., Paul I.M. de Bakker, M.D., Ph.D., Kent D. Taylor, Ph.D., Leonoor M. de Lau, M.D., Ph.D., Ben A. Oostra, Ph.D., André G. Uitterlinden, Ph.D., Jerome I. Rotter, M.D., Eric Boerwinkle, Ph.D., Bruce M. Psaty, M.D., Ph.D., Thomas H. Mosley, Ph.D., Cornelia M. van Duijn, Ph.D., Monique M.B. Breteler, M.D., Ph.D., W.T. Longstreth, Jr., M.D., and Philip A. Wolf, M.D.

N Engl J Med 2009;360:1718-28.

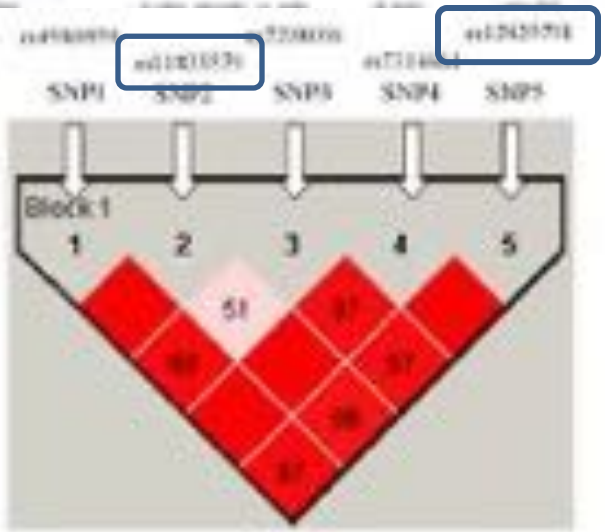
OPEN ACCESS Freely available online

PLoS one

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 Chen[1], Liang-Chuan Lai[3], Yi-Ling Huang[1], Jen-Hau Chen[1,2], Ta-Fu Chen[4], Yu Sun[5], Li-Li Wen[6], Ping-Keung Yip[7], Yi-Min Chu[8], Wei J. Chen[1,9,10], Yen-Ching Chen[1,9,10]*

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

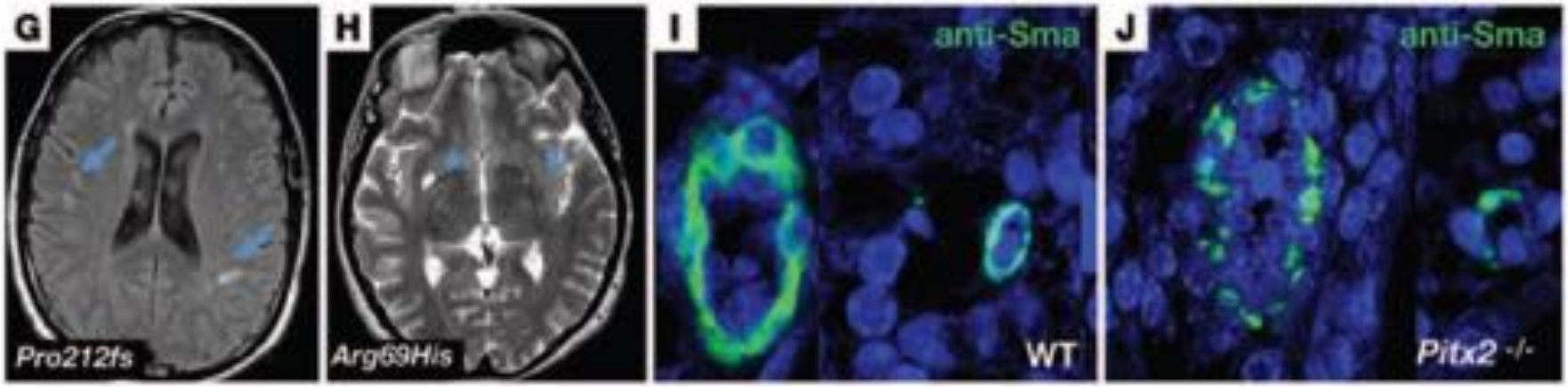


Also worse LM-d performance in FHS and ROS-MAP

The Journal of Clinical Investigation BRIEF REPORT

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,[1] Andrew J. Waskiewicz,[12] and Ordan J. Lehmann[1,13]



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	*PITX2*	Trails A	0.02
			Visual memory	0.03
			Verbal Fluency	0.02
rs7193343	16	*ZFHX3*	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*

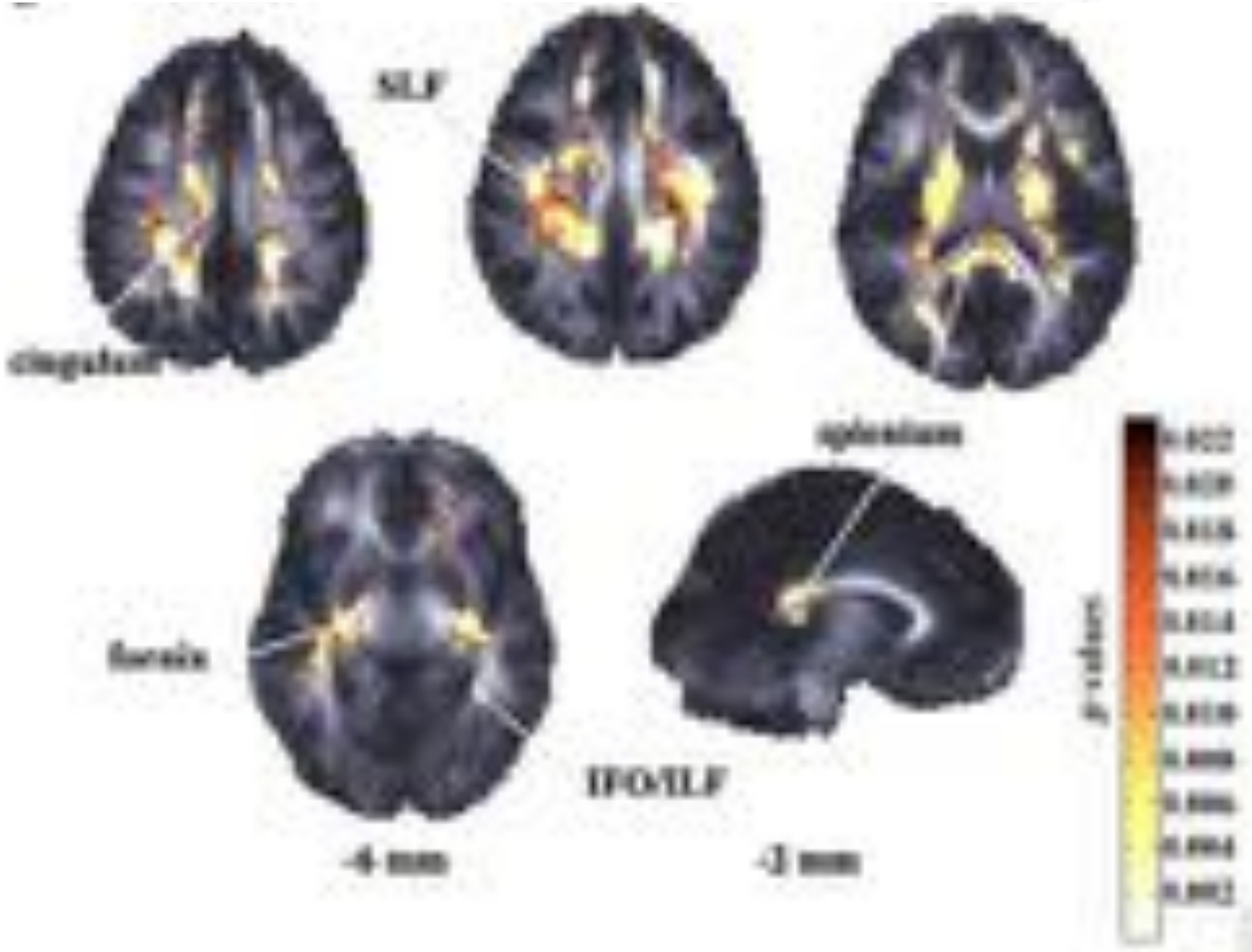
nature genetics

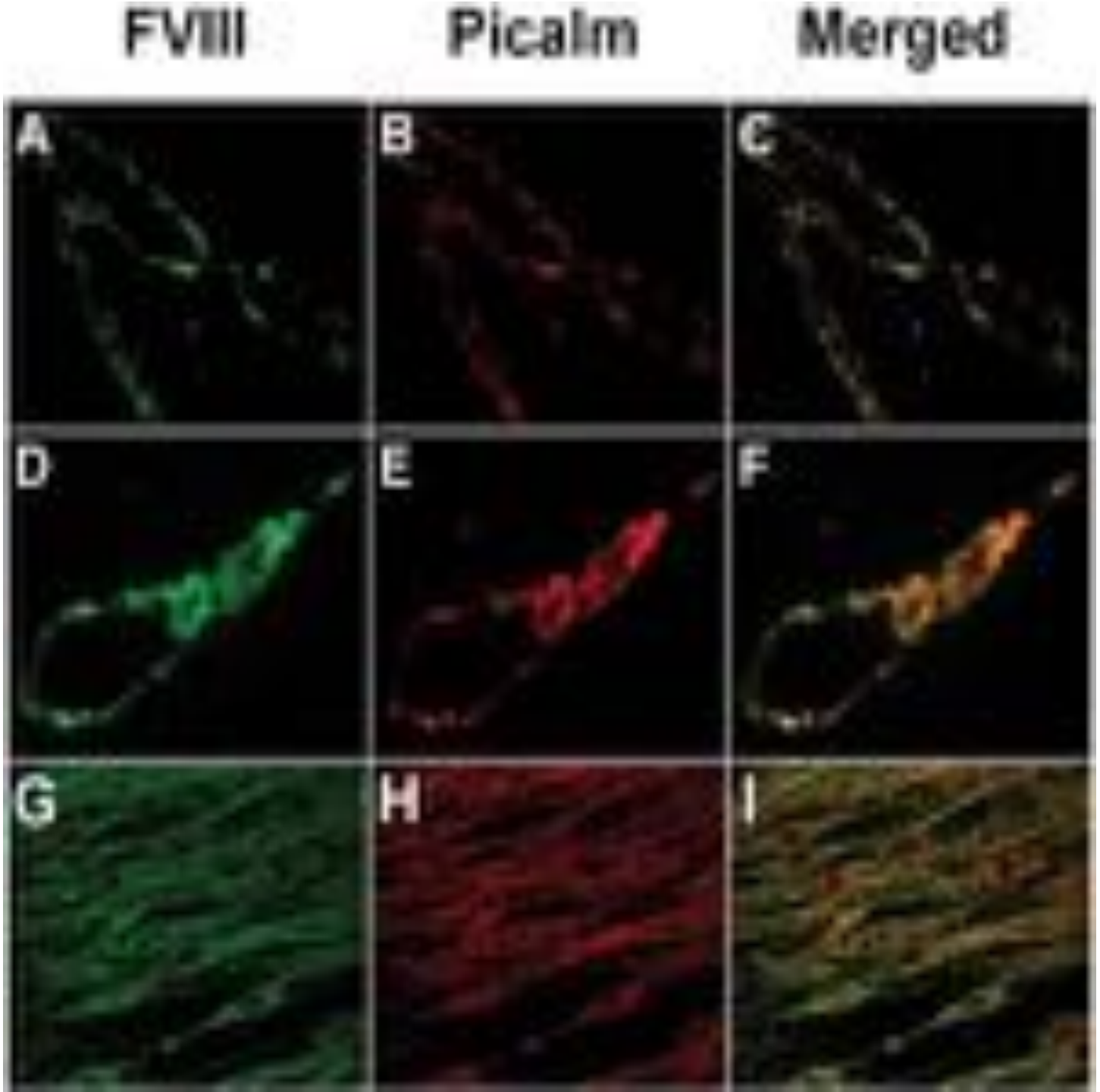
Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease

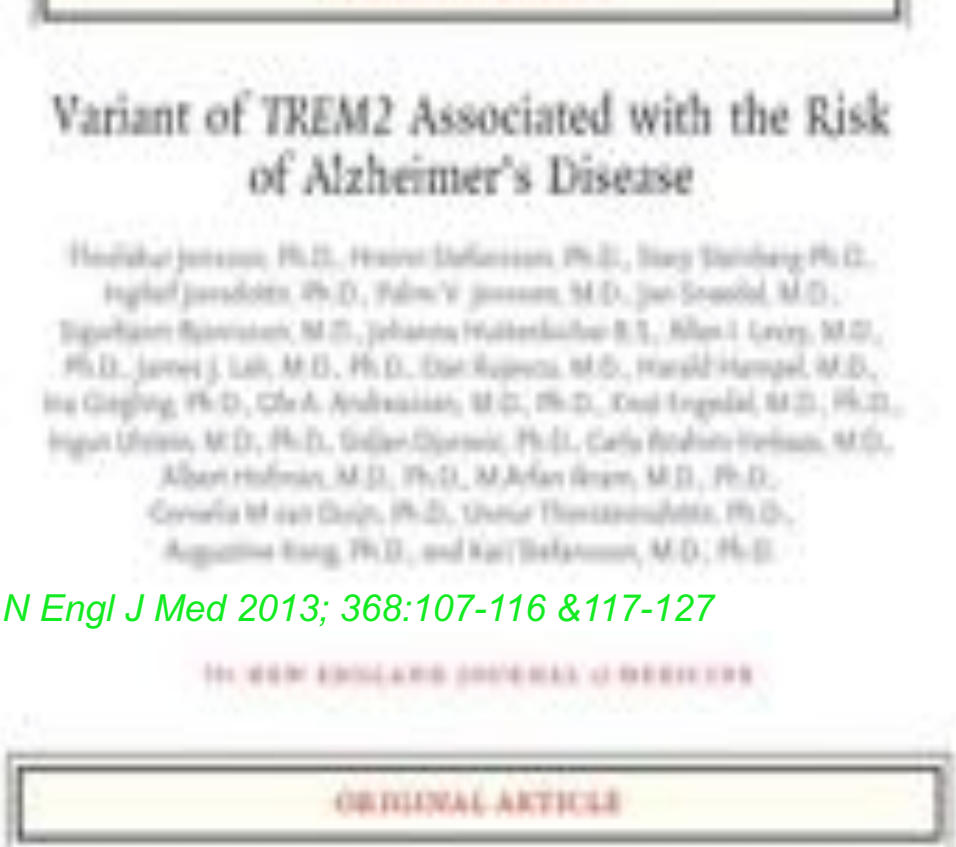
~25 LOAD genes identified to date through GWAS

Braskie et al., 2011

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




FVIII
Picalm
Merged
A
B
C
D
E
F
G
H
I



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

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

ORIGINAL ARTICLE

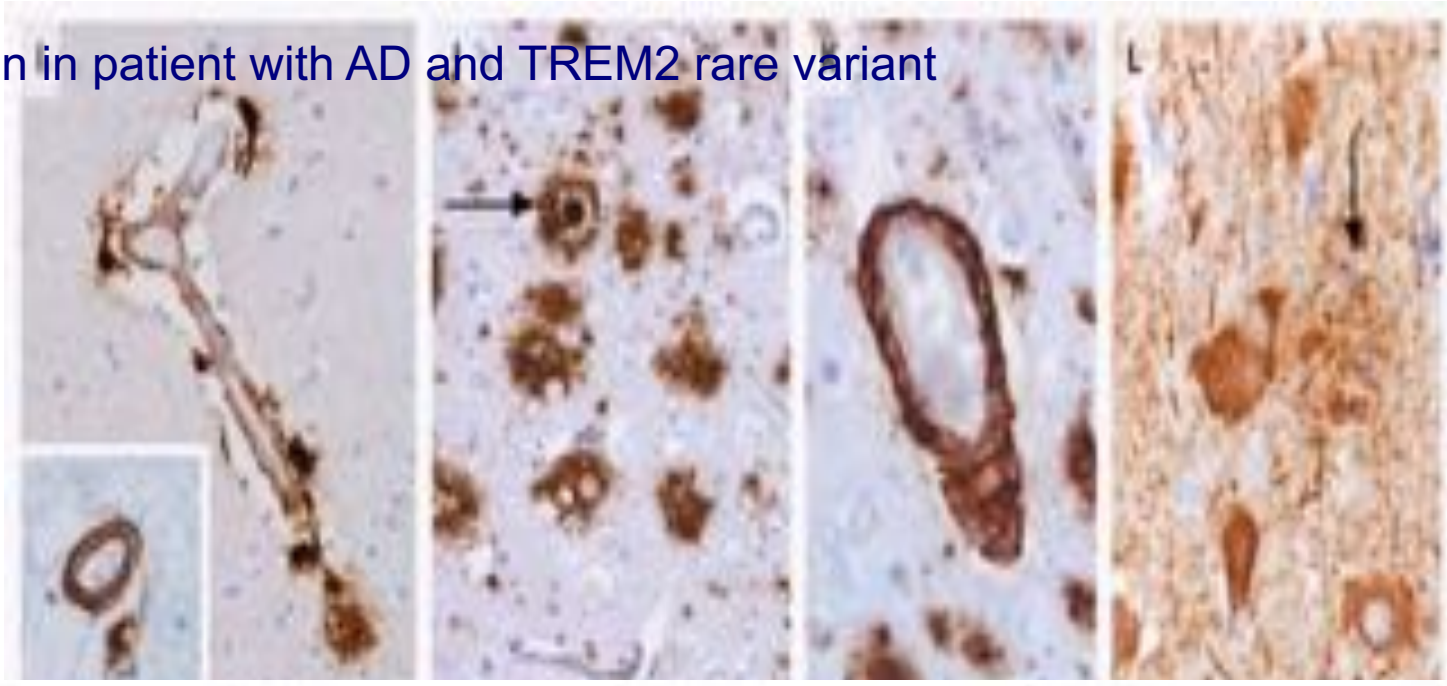
TREM2 Variants in Alzheimer's Disease

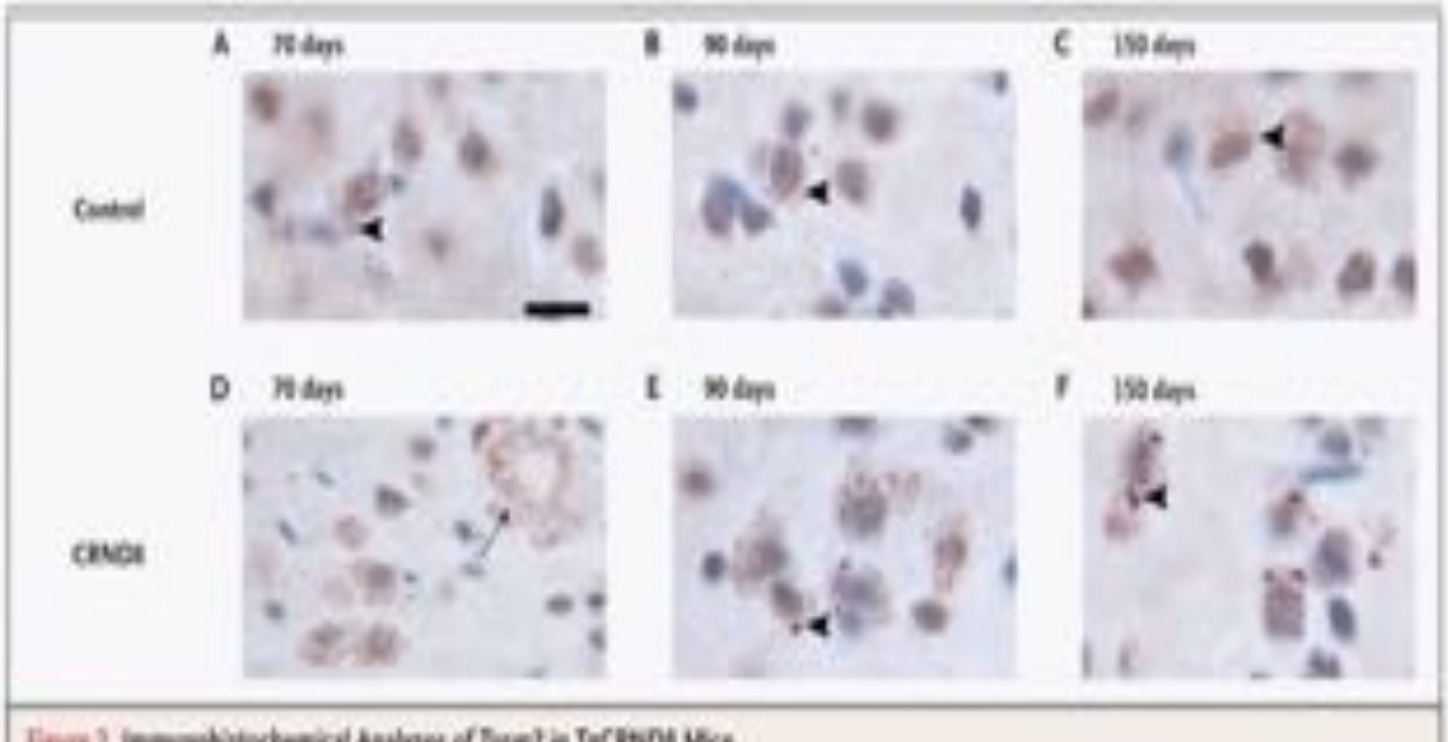
Trigger Receptor Expressed on Myeloid Cells 2 protein

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





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

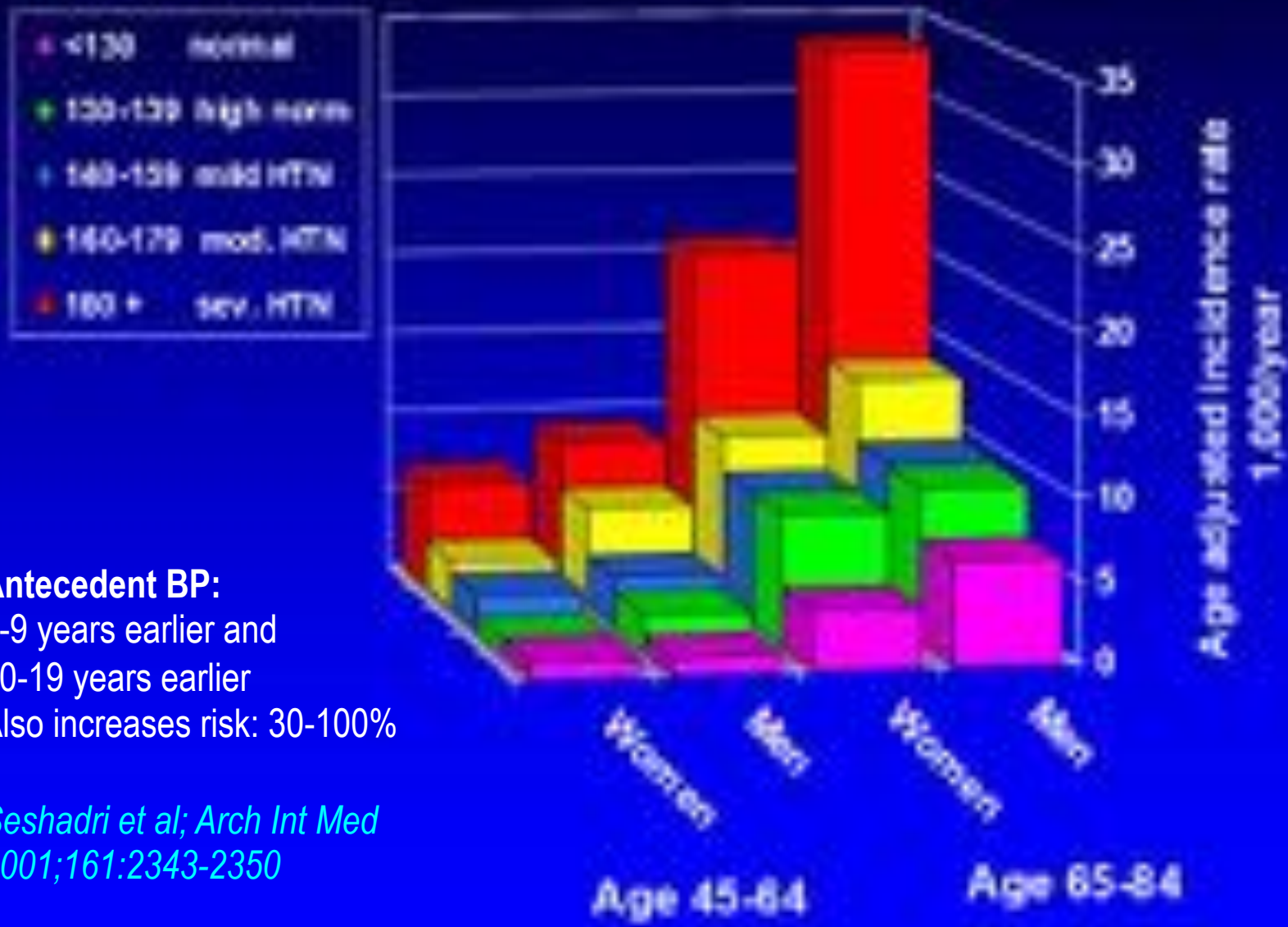
Outline

- 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)

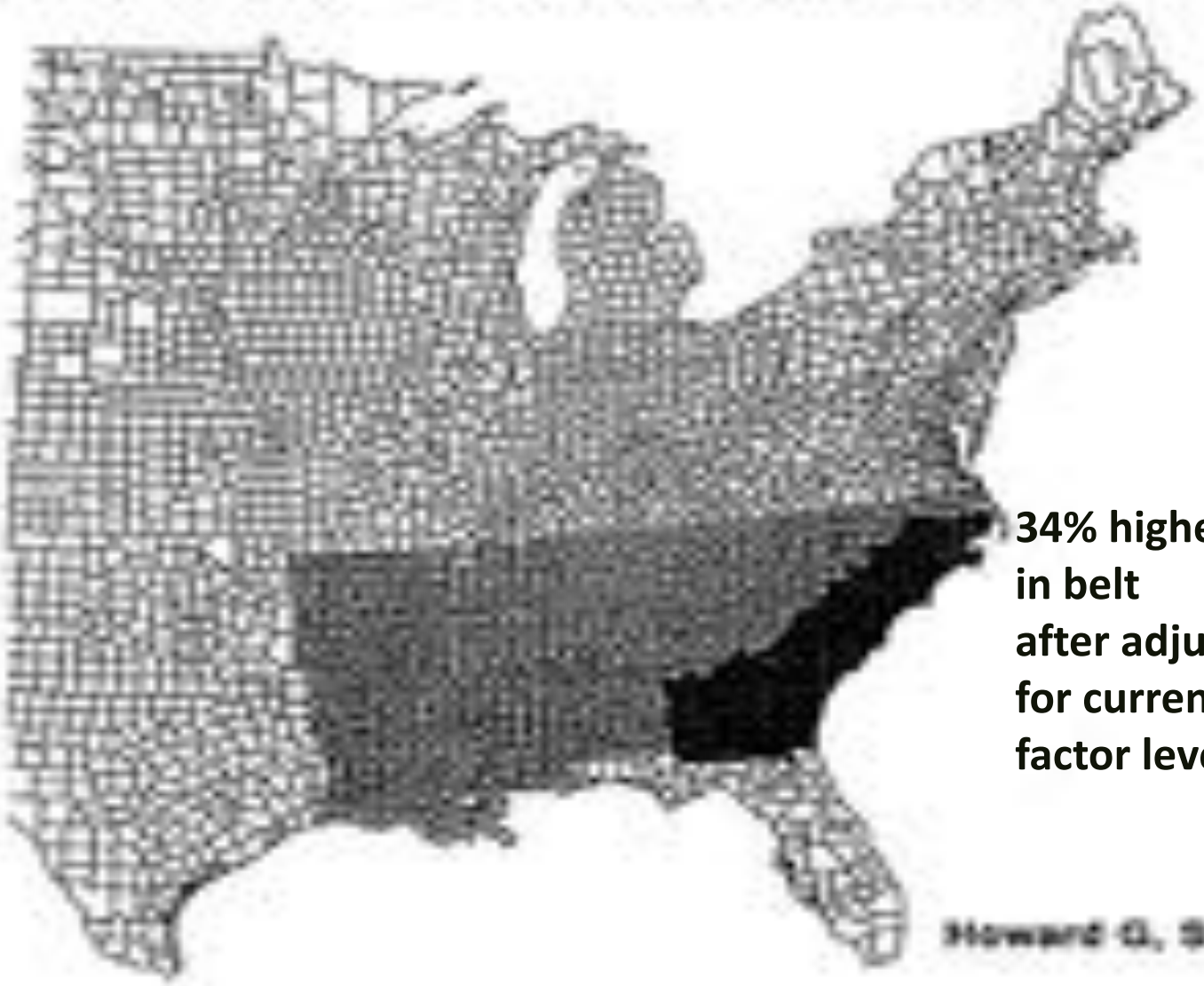
Stroke Incidence by SBP



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)


2010
CDC


County-level Estimates of Diagnosed Diabetes among Adults Aged ≥ 20 years
United States, 2009
www.cdc.gov/diabetes

JACC: CARDIOVASCULAR IMAGING
© 2014 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
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ISSN 1936-8798/$36.00
http://dx.doi.org/10.1016/j.jcmg.2014.09.004

EDITORIAL COMMENT

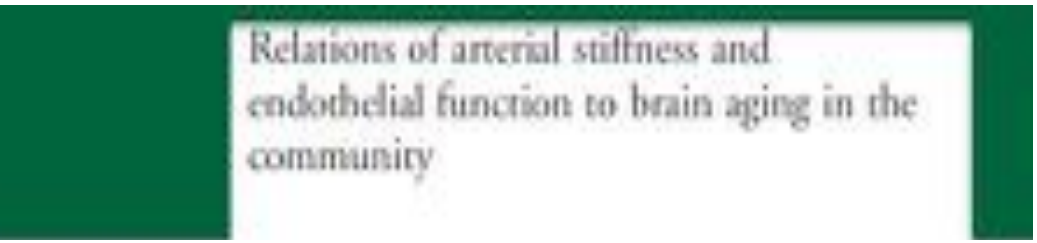
Indexes of Subclinical Atherosclerosis

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



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

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

Galit Weinstein, PhD; Alexa S. Beiser, PhD; Charles DeCarli, MD; Rhoda Au, PhD; Philip A. Wolf, MD; Sudha Seshadri, MD; on behalf of the Framingham Heart Study

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 1679 dementia and stroke free Framingham offspring (age, ≥45 years; mean, 65.7±7.6) between 1999 and 2006; participants were also free of other neurological conditions that could affect cognition and ≈90% 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, 67.3±7.3 and 84.8±3.3 years at the cognitive assessment and MRI examination, respectively).

Results—A total of 55 (4.0%) offspring participants sustained strokes and 31 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], 2.27; 95% confidence interval [CI], 1.06–4.85) and AD (HR, 3.60; 95% CI, 1.32–9.82); additional cognitive tests also predicted AD. Participants with low (<20 percentile) total brain volume and high (>20 percentile) white matter hyperintensity volume had a higher risk of stroke (HR, 3.97; 95% CI, 1.83–8.77 and HR, 2.74; 95% CI, 1.31–5.68, respectively) but not AD. Hippocampal volume in the bottom quintile predicted AD in the offspring and original cohorts (HR, 4.41; 95% CI, 2.06–9.72 and HR, 2.37; 95% CI, 1.12–5.00, 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.)

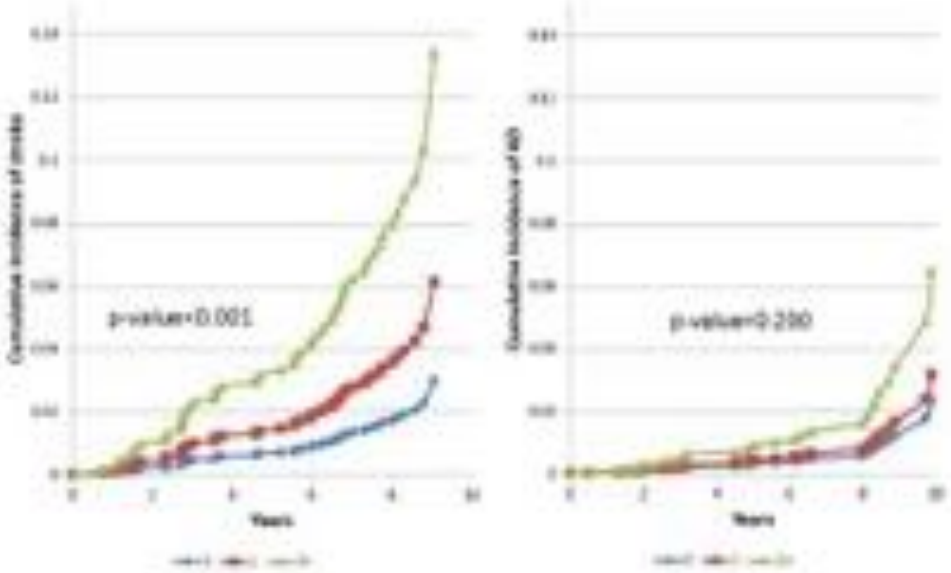


Figure 2. Cumulative incidence of stroke (**left**) and Alzheimer disease (AD; **right**) in the offspring cohort based on age- and sex-adjusted Cox models by number of [illegible] among poor performance on Trail making B test, top WMHV quintile and bottom TCBV quintile.

PLOS | ONE

RESEARCH ARTICLE

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

Lenore J. Launer[1]*, Cora E. Lewis[2], Pamela J. Schreiner[3], Steve Sidney[4], Harsha Battapady[5], David R. Jacobs[3], Kelvin O. Lim[6], Mark D'Esposito[7], Qian Zhang[1], Jared Reis[8], Christos Davatzikos[5], R. Nick Bryan[5]

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,[6] David R. Jacobs Jr,[7] Daichi Shimbo,[8] Kiang Liu,[1] Philip Greenland,[1] and Donald Lloyd-Jones[1]

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)

BMJ

RESEARCH

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

*Debette S, BMJ 2010;341:*c3666

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

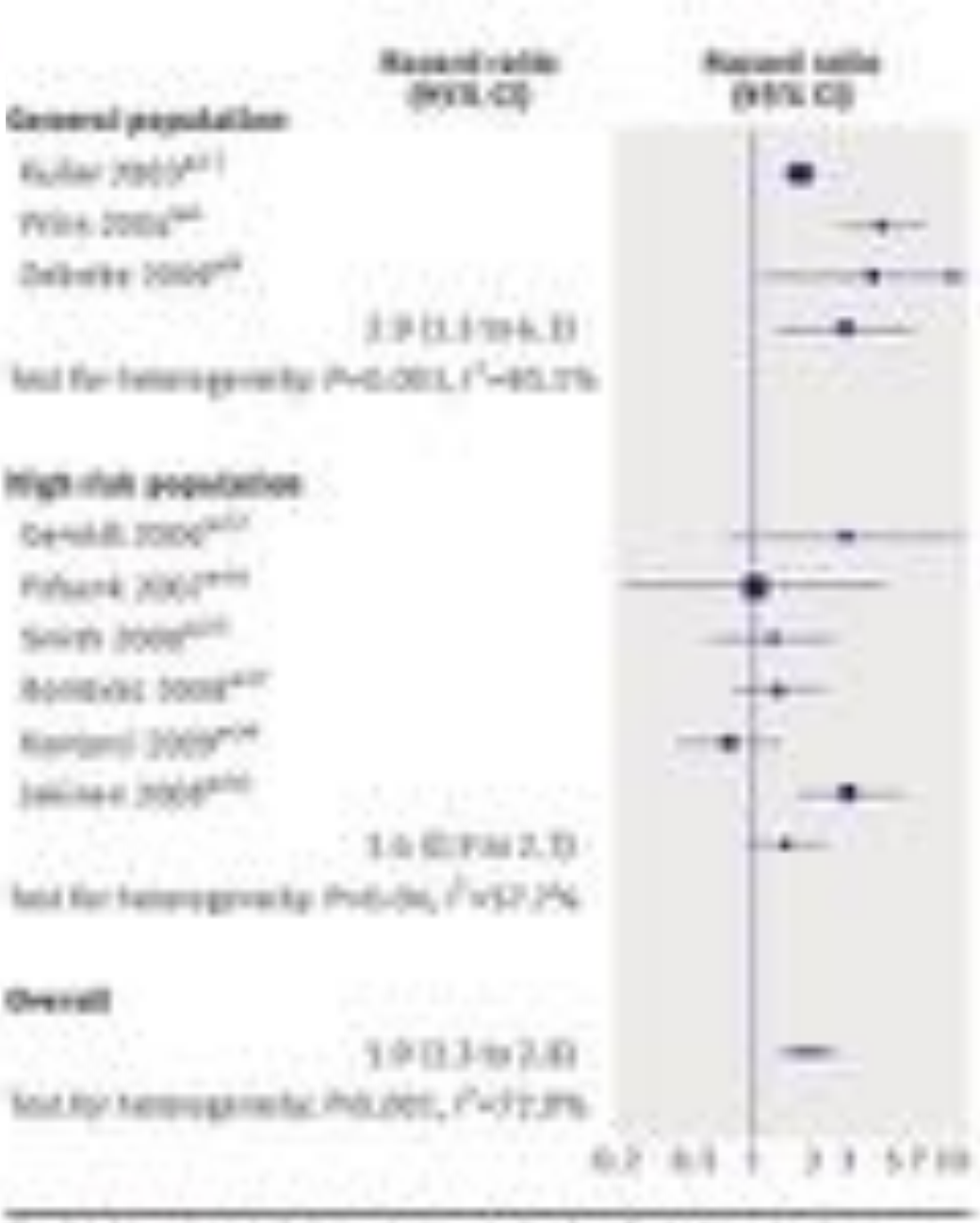


Fig 3 | Inverse variance meta-analysis of studies testing association of white matter hyperintensities with incident dementia

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

[redacted]

[redacted]

Background: [redacted]

Methods: [redacted]

Results: [redacted]

Conclusions: [redacted]

Original Contribution

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

The AGES-Reykjavik Study

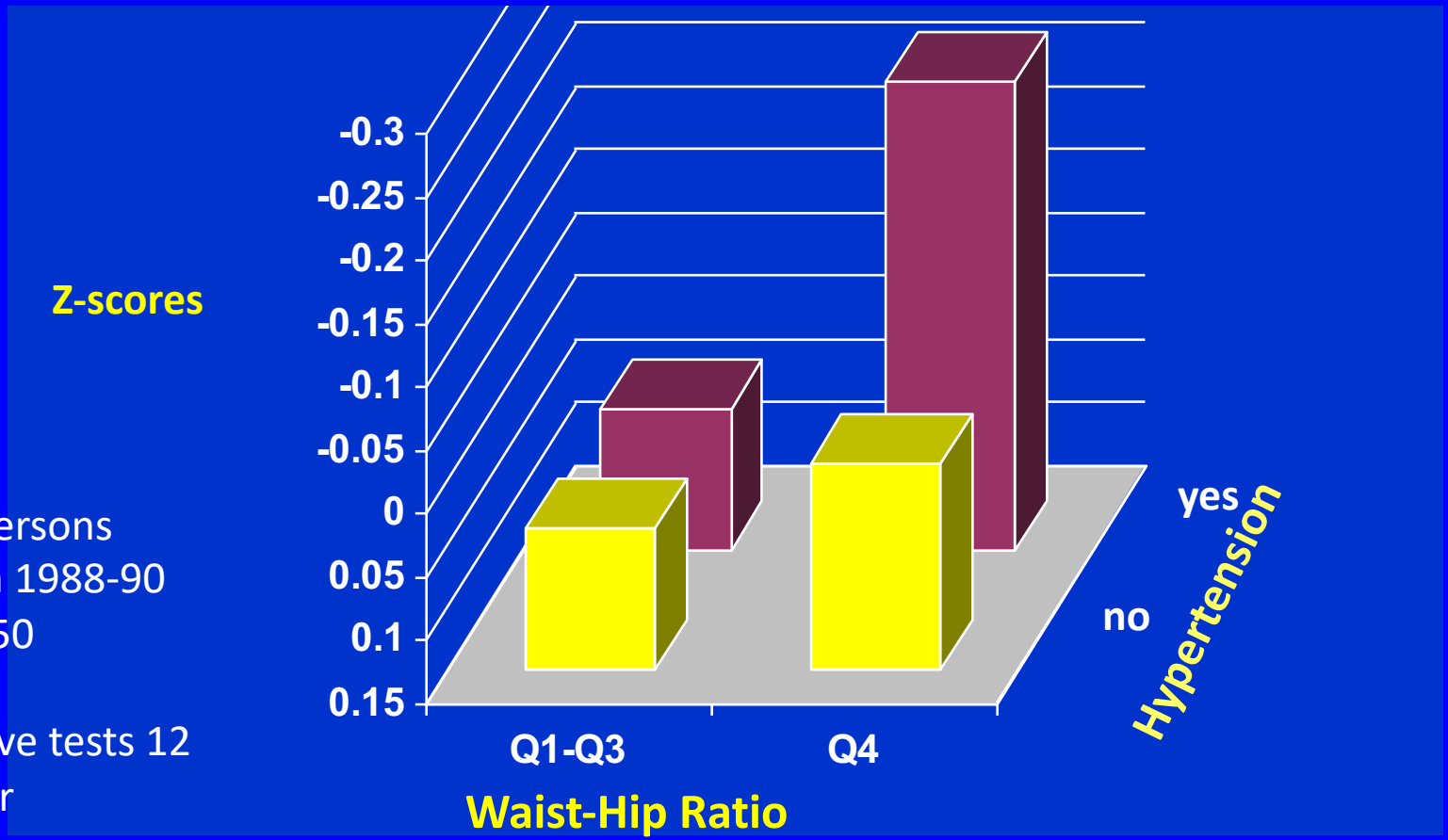
No association of midlife (age 50) obesity (BMI) with MRI measures or dementia

Current Alzheimer Research, 2007, *4*, 000-000

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



1814 persons
WHR in 1988-90
at age 50

Cognitive tests 12 yrs later

Obesity phenotypes in midlife and cognition in early old age

The Whitehall II cohort study

[redacted]

[redacted]

Outline

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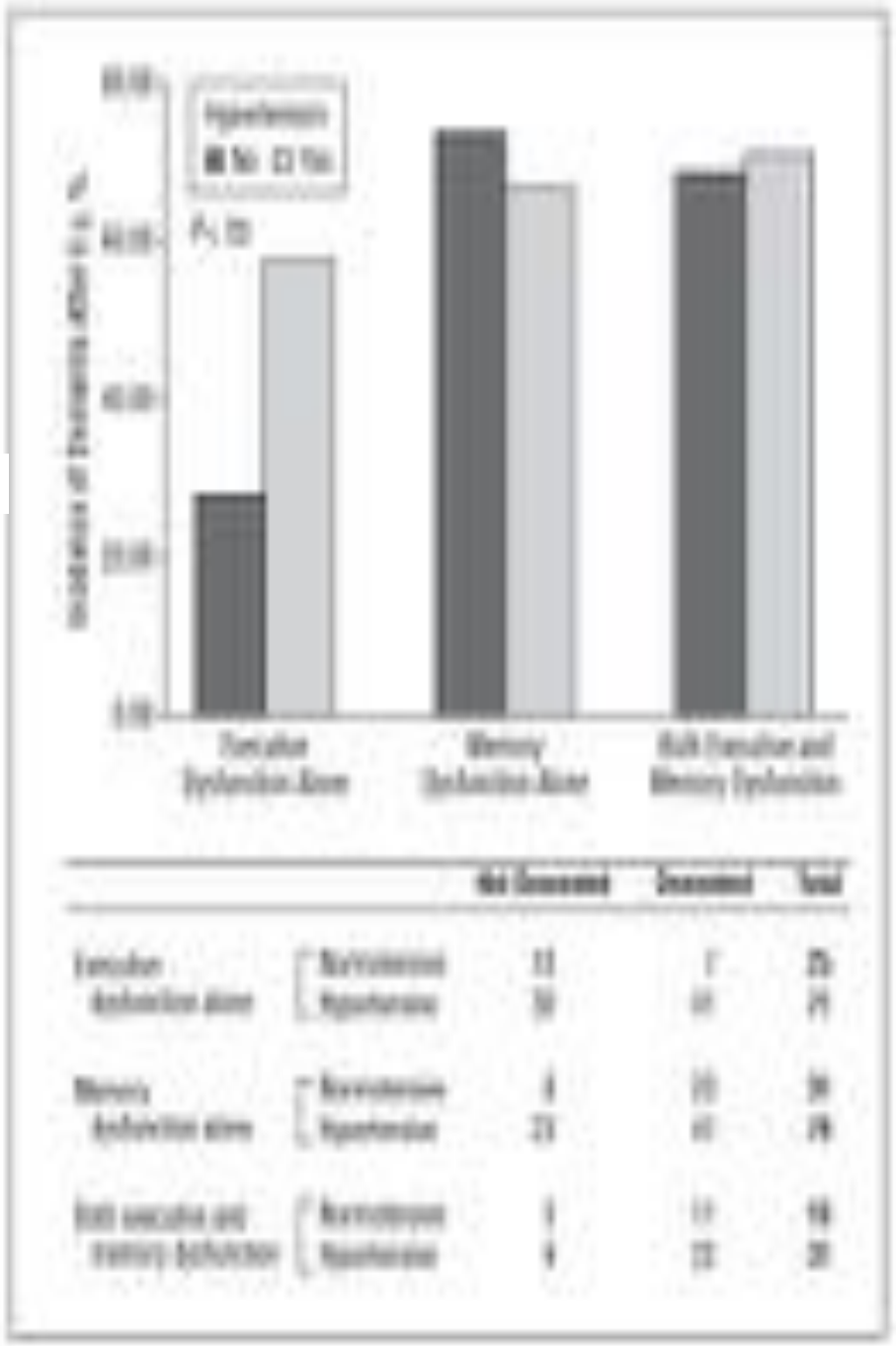
Hypertension, Executive Dysfunction, and Progression to Dementia

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

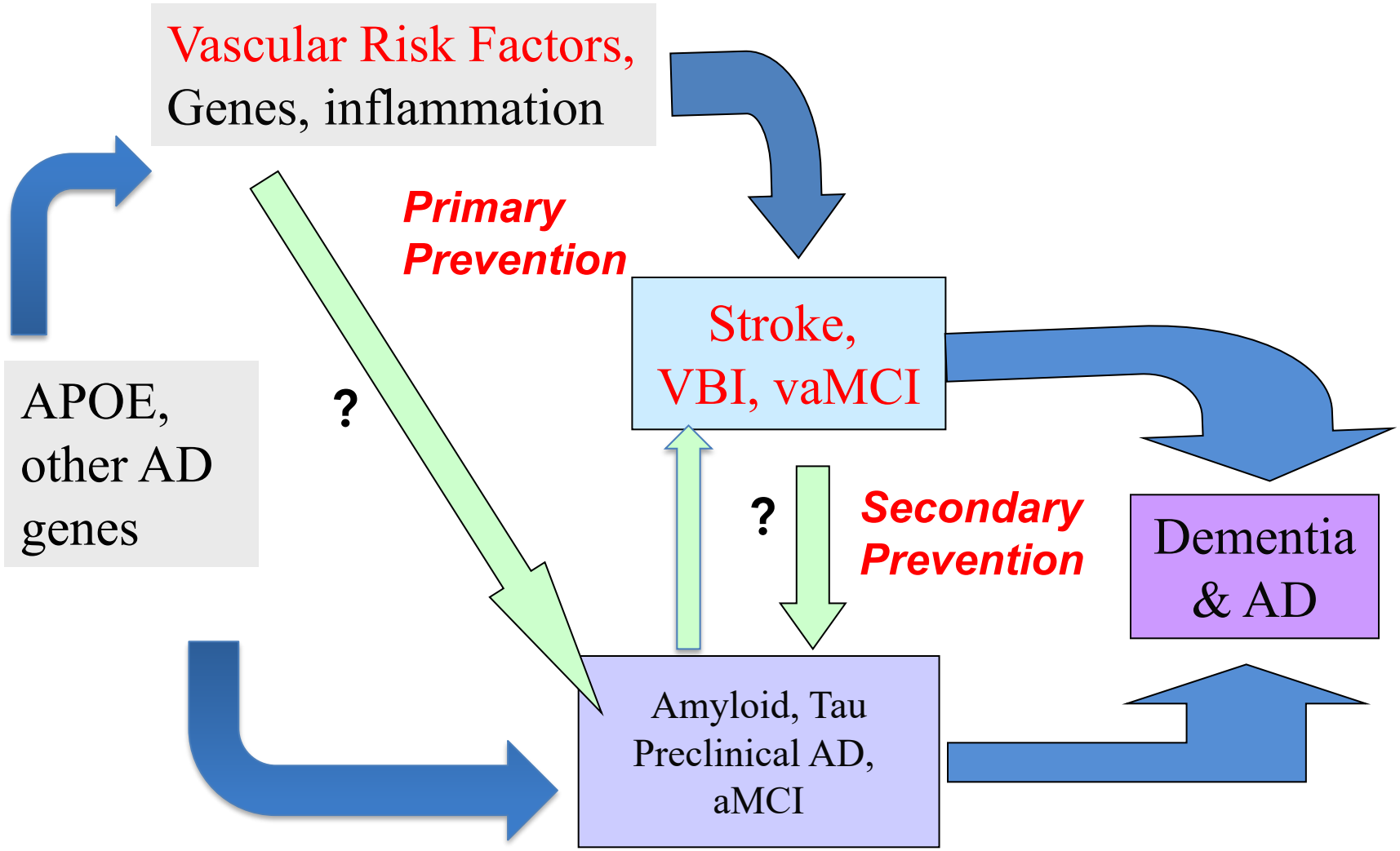
Domain assessed, test used matter

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?

Alzheimer's & Dementia

Research Article

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

Deborah E. Barnes[1,2,3,4,*], Alexa S. Beiser[5,6], Annie Lee[1], Kenneth M. Langa[7,8,9], Alain Koyama[1], Sarah R. Preis[5], John Neuhaus[10], Ryan J. McCammon[7], Kristine Yaffe[1,2,3,11], Sudha Seshadri[5,6], Mary N. Haan[7], David R. Weir[7]

[1]Department of Psychiatry, University of California, San Francisco CA, USA
[2]Department of Neurology, University of California, San Francisco CA, USA
[3]Department of Epidemiology & Biostatistics, University of California, San Francisco CA, USA
[4]Veterans Affairs Medical Center, San Francisco, CA, USA
[5]Framingham Heart Study, Framingham, MA, USA
[6]Department of Neurology, Boston University School of Medicine, Boston, MA, USA
[7]Institute for Social Research, University of Michigan, Ann Arbor, MI, USA
[8]Department of Medicine, University of Michigan, Ann Arbor, MI, USA
[9]Veterans Affairs Center for Practice Management and Outcomes Research, Ann Arbor, MI, USA

Background: Inclusion of "any cognitive impairment" as measures as part of the Medicare annual wellness visit, but screening all patients may result in excessive false positives.

Methods: We developed and validated a brief Dementia Screening Indicator using data from four large, ongoing cohort studies (the Cardiovascular Health Study (CHS), the Framingham Heart Study (FHS), the Health and Retirement Study (HRS), the Sacramento Area Latino Study on Aging (SALSA)) to help clinicians identify a subgroup of high-risk patients to target for cognitive screening.

Results: The final Dementia Screening Indicator included age (if enrolled over age 65–75 years), less than 12 years of education (if present), stroke (if present), diabetes and blood pressure (if present). Study participants less than 80.5 kg/m^2 (if patients reporting assistance with memory or medications (if present).

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 -Cardiovascular Health Study
  - Sacramento Area Latino Study of Aging -Health & Retirement Study
- http://campuslifeservices.ucsf.edu/clsforms/documentsmedia/dementiarisk/

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

Thanks to

BOSTON UNIVERSITY

FRAMINGHAM HEART STUDY
Three Generations of Dedication
1948 1971 2002