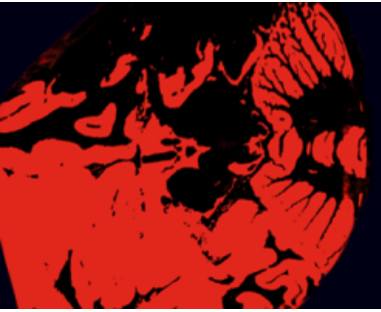

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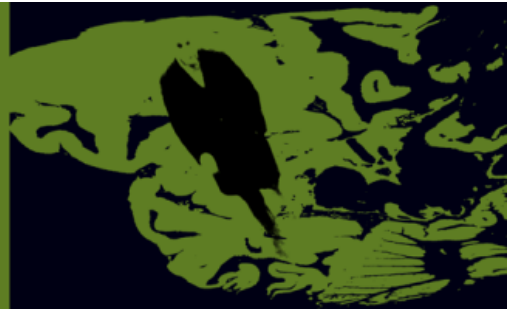

Harnessing the Titans of Vascular Dementia: Hypertension, Diabetes Mellitus, and Obesity

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Financial Disclosure Relevant to This Lecture

- Consulting Fee (eg, Advisory Board): AstraZeneca/ICON, Bayer, Novartis, Evidera, PRA Health Sciences, Takeda, RPharm/IQVIA and AbbVie.

Main Message

- Cognitive impairment and dementias of later life may be prevented by the prevention and treatment of cardiovascular risk factors.

Learning Objectives

In relation to modifiable cardiovascular risk factors and cognitive health, learners will be able to:

- Discuss why the paradigm shifted and cardiovascular risks became associated with both neurodegenerative and vascular forms of cognitive impairment and dementia
- Discuss mechanisms underlying hypertension in the causation of cognitive impairment and dementia
- Discuss mechanisms underlying diabetes mellitus in the causation of cognitive impairment and dementia
- Discuss mechanisms underlying obesity in the causation of cognitive impairment and dementia
- Review lessons learned from clinical trials and studies regarding treatment of cardiovascular risk in patients

The Story Behind the Paradigm Shift to Cardiovascular Risk Factors as Potential Modifiable Risks in Cognitive Impairment and Dementias of Later Life

Brief Historical Note on Alzheimer's Disease

- Discussion at the NIA (1980s): operationally define Alzheimer's disease (AD) as a distinct neurodegenerative disorder vs a more "open-ended" disorder with more data to be collected to establish its definition.
- Clinical Diagnosis of Alzheimer's Disease McKhann et al/NINCDS ADRDA Work Group Criteria: AD as a distinct neurodegenerative entity.

Source: McKhann et al Neurology 1984; 34: 939-944
NIA= US National Institute on Aging

McKhann et al/NINCDS ADRDA Work Group Criteria

Probable AD

- Dementia established by clinical exam and documented by MMSE, Blessed Dementia Scale or similar exam and confirmed by neuropsychological testing
- Deficit in ≥2 areas of cognition
- Progressive worsening of memory and other cognitive functions
- No disturbance of consciousness
- Onset between age 40-90, most after age 65
- Absence of systemic disorders or other brain diseases that in and of themselves could account for the progressive deficits in memory and cognition

Source: Mckhann et al Neurology 1984; 34: 939-944.
MMSE= Mini-Mental State Exam

Hypothesis for Preclinical AD

1st change:
lowering of amyloid beta 42 (AB42) in CSF.

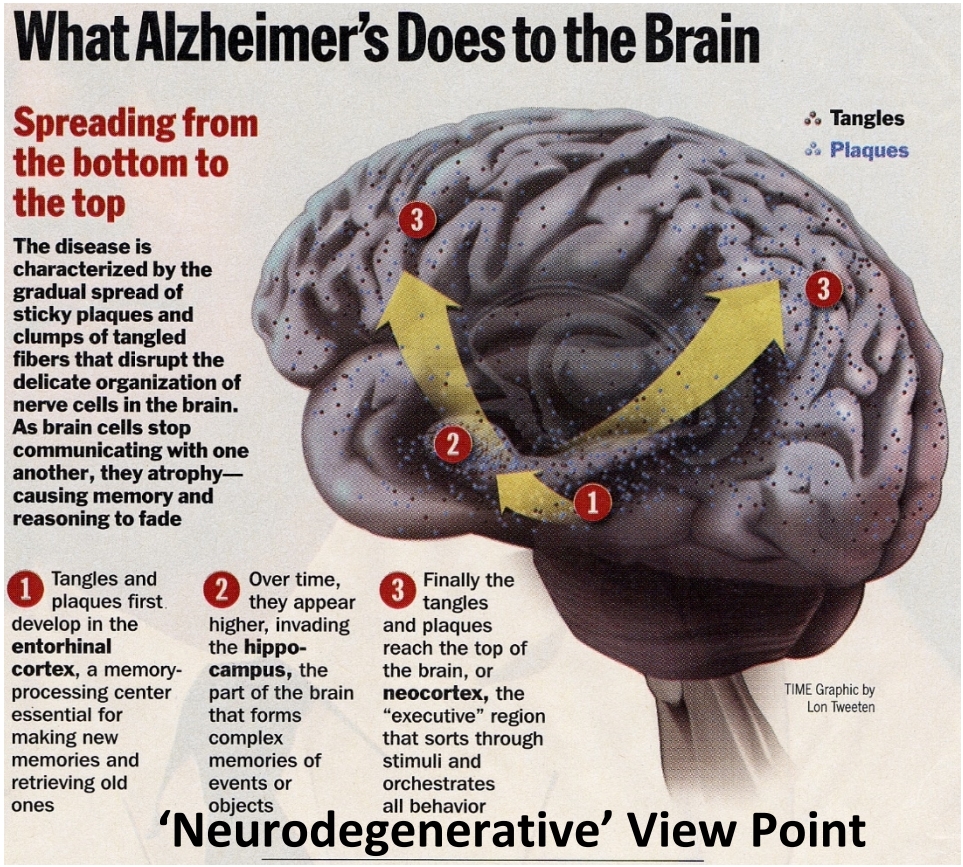
Next change:
amyloid beta observed in brain on PET scan.

Followed by:
phosphorylated tau deposition and then neuro-degeneration.

AD= Alzheimer's disease

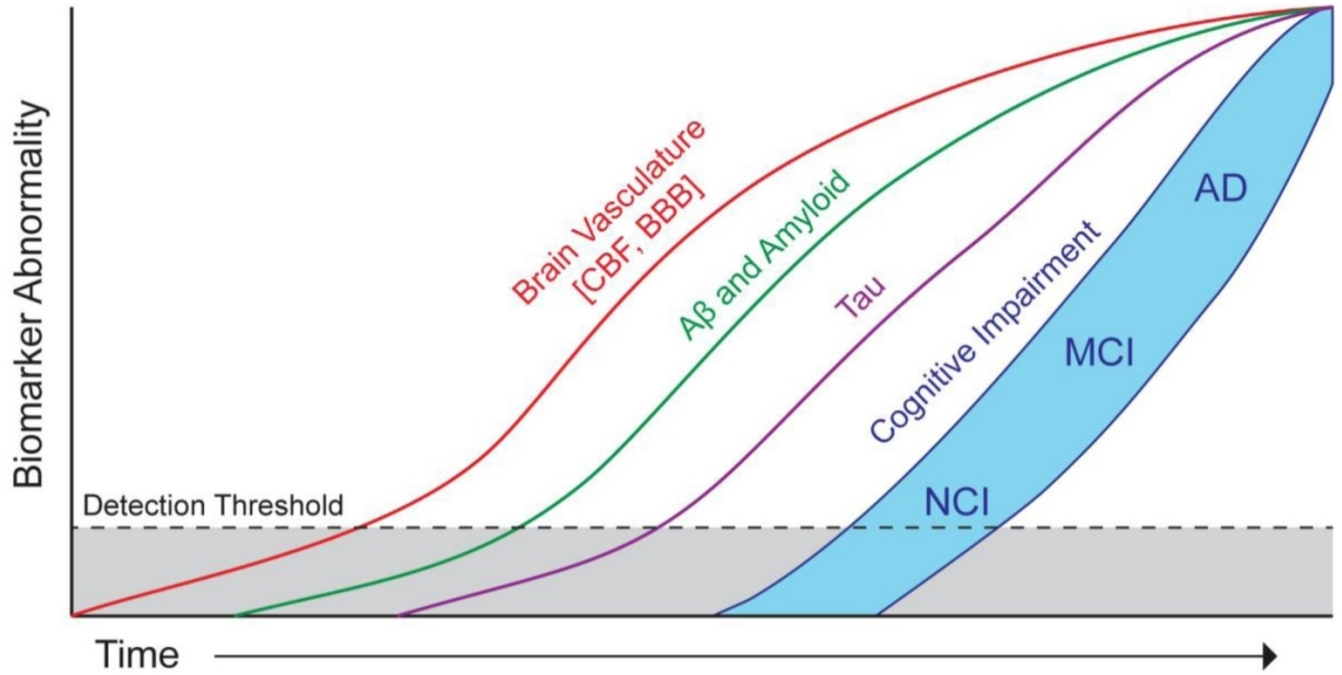
CSF= cerebrospinal fluid

PET= positron emission tomography



Preventing Dementia by Preventing Stroke: The Berlin Manifesto Changes in Blood-Brain Barrier Integrity and Cerebral Blood Flow Deficits May Occur Early in the Alzheimer's Continuum

Fig. 3



Alzheimer's & Dementia: The Journal of the Alzheimer's Association 2019 15, 961-984DOI: (10.1016/j.jalz.2019.06.001)

My Personal Journey Mid-1980s

Jacob Brody, MD (1931-2014)

Dean UIC School of Public Health

Epidemiology of Dementia

Challenge by the Dean of the University of Illinois School of Public Health

Does Multi-Infarct Dementia Exist or is it all Alzheimer's disease?

Terms Related to Stroke Associated with Dementia

- Arteriosclerotic psychosis (1950s)
- Multi-infarct dementia (1970s)
- Vascular dementia (VaD) (~1990)
- Vascular cognitive impairment (VaD the most severe form) (1990s)
- Vascular cognitive disorders (2014)
- The most common form of VCI: cerebral subcortical small vessel disease
- Focus should be on: mechanism

Source: Gorelick PB, Vascular Cognitive Impairment, In: Lazar RM et al. Neurovascular Neuropsychology, 2nd Edition, Springer, 2020, pp. 121-138.

What is Vascular Cognitive Impairment (VCI)?

- A continuum of cognitive impairment (CI) spanning from *mild* to *moderate* to *severe* cognitive dysfunction.
- Takes into account the underlying mechanism (brain ischemia, hemorrhage, small vessel disease, etc) and prospects for prevention.

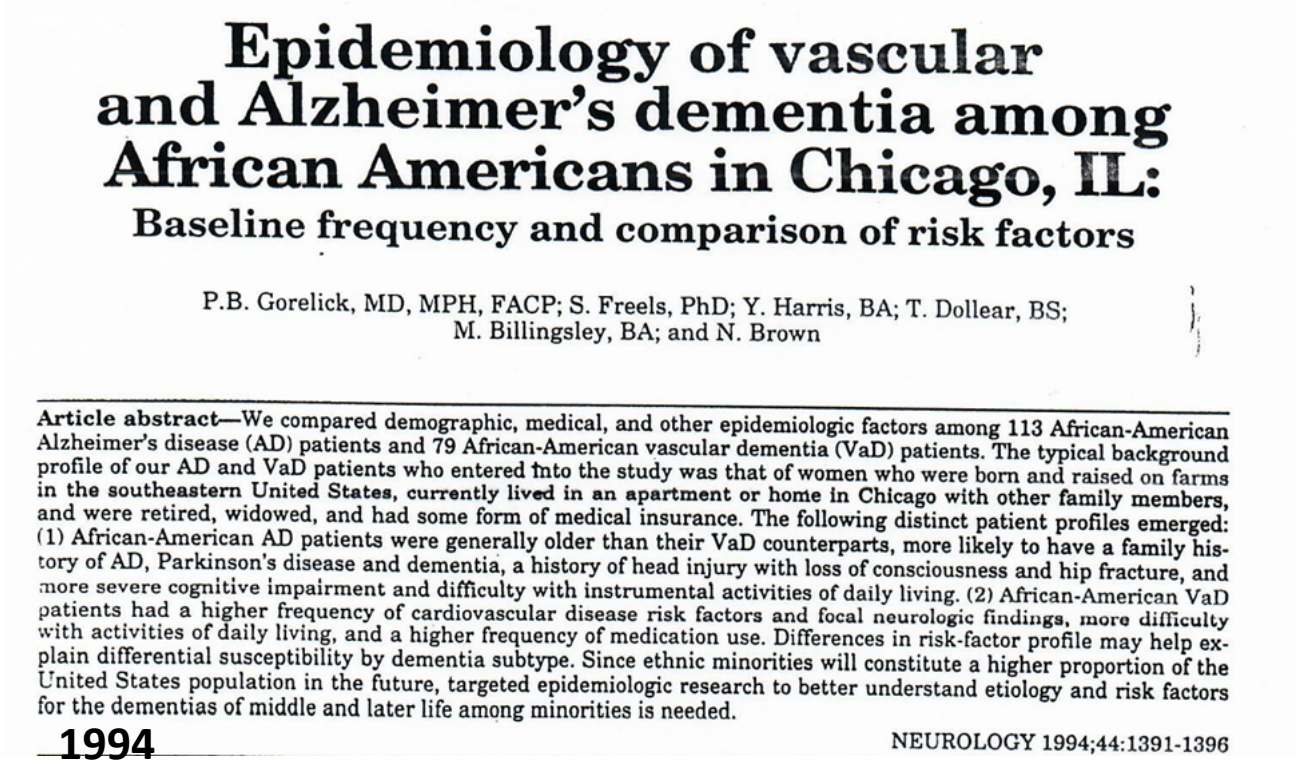
Core Definition of VCI:

1. Occurrence of CI and presence of brain vascular disease;
2. Validation of CI by bedside or formal neuropsychological testing; and
3. History of stroke or evidence on neuroimaging of vascular brain injury thought to explain CI.

- You do NOT need to have memory impairment.
- Dementia: CI with decline in cognition in 2 or more cognitive domains to impair activities of daily living (ADLs).

Source: Gorelick PB et al. Stroke 2011; 42: 2572-2713.

Studies of Dementia in the Black Aged



Epidemiology of vascular and Alzheimer's dementia among African Americans in Chicago, IL:

Baseline frequency and comparison of risk factors

P.B. Gorelick, MD, MPH, FACP; S. Freels, PhD; Y. Harris, BA; T. Dollear, BS; M. Billingsley, BA; and N. Brown

Article abstract—We compared demographic, medical, and other epidemiologic factors among 113 African-American Alzheimer's disease (AD) patients and 79 African-American vascular dementia (VaD) patients. The typical background profile of our AD and VaD patients who entered into the study was that of women who were born and raised on farms in the southeastern United States, currently lived in an apartment or home in Chicago with other family members, and were retired, widowed, and had some form of medical insurance. The following distinct patient profiles emerged: (1) African-American AD patients were generally older than their VaD counterparts, more likely to have a family history of AD, Parkinson's disease and dementia, a history of head injury with loss of consciousness and hip fracture, and more severe cognitive impairment and difficulty with instrumental activities of daily living. (2) African-American VaD patients had a higher frequency of cardiovascular disease risk factors and focal neurologic findings, more difficulty with activities of daily living, and a higher frequency of medication use. Differences in risk-factor profile may help explain differential susceptibility by dementia subtype. Since ethnic minorities will constitute a higher proportion of the United States population in the future, targeted epidemiologic research to better understand etiology and risk factors for the dementias of middle and later life among minorities is needed.

NEUROLOGY 1994;44:1391-1396

1994

<u>Main Findings</u>: Emerging pattern of vascular risks present among African-American Alzheimer patients. Hypertension: 50%, Diabetes Mellitus: 13%, Chest Pain/MI: 15%, & Atrial Fibrillation: 2%.

Prevention of Vascular Dementia: On the Occasion of the Osaka Dementia Harmonization Conference, 1999

"Modifiable cardiovascular risk factors in midlife … may be important targets for prevention of vascular causes of cognitive impairment. These same types of factors may also be associated with AD… and lead to delay or prevention of VaD and AD."

Source: Gorelick PB, Erkinjuntti T, Hofman A, Rocca WA, Skoog I, Winblad B. Alzheimer Disease & Associated Disorders 1999; Suppl 3, pp S131-S139; AD= Alzheimer's disease and VaD= vascular dementia.

Common Genetic and Environmental Risk Factors for Alzheimer Disease and Atherosclerosis

Epidemiological factor
ApoEe4 polymorphism
Hypercholesterolemia
Hypertension
Hyperhomocysteinemia
Diabetes mellitus
Metabolic syndrome
Smoking
Systemic inflammation
Increased fat intake and obesity

Source: Casserly I, Topol E. Lancet 2004; 363: 1139-46

Midlife Risks and Healthy Survival in Men Honolulu-Asia Aging Program

Predictors of Healthy Survival (Brain Health)

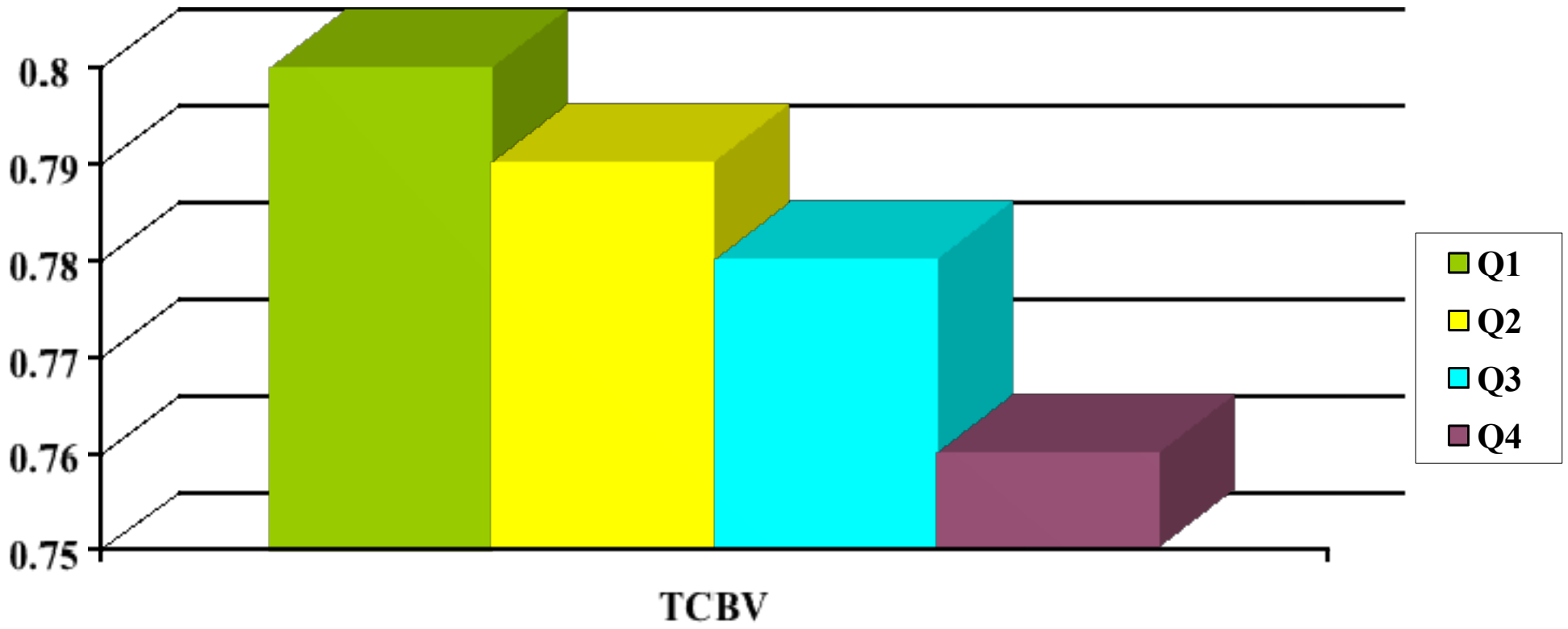
High grip strength

Avoidance of overweight, hyperglycemia, hypertension, smoking, and excessive alcohol consumption (high education and avoidance of hypertriglyceridemia)

Predictor of mortality: lack of a marital partner

Source: Wilcox BJ et al. JAMA **2006**; 296: 2343-50

Mean TCBV by FSRP Quartile



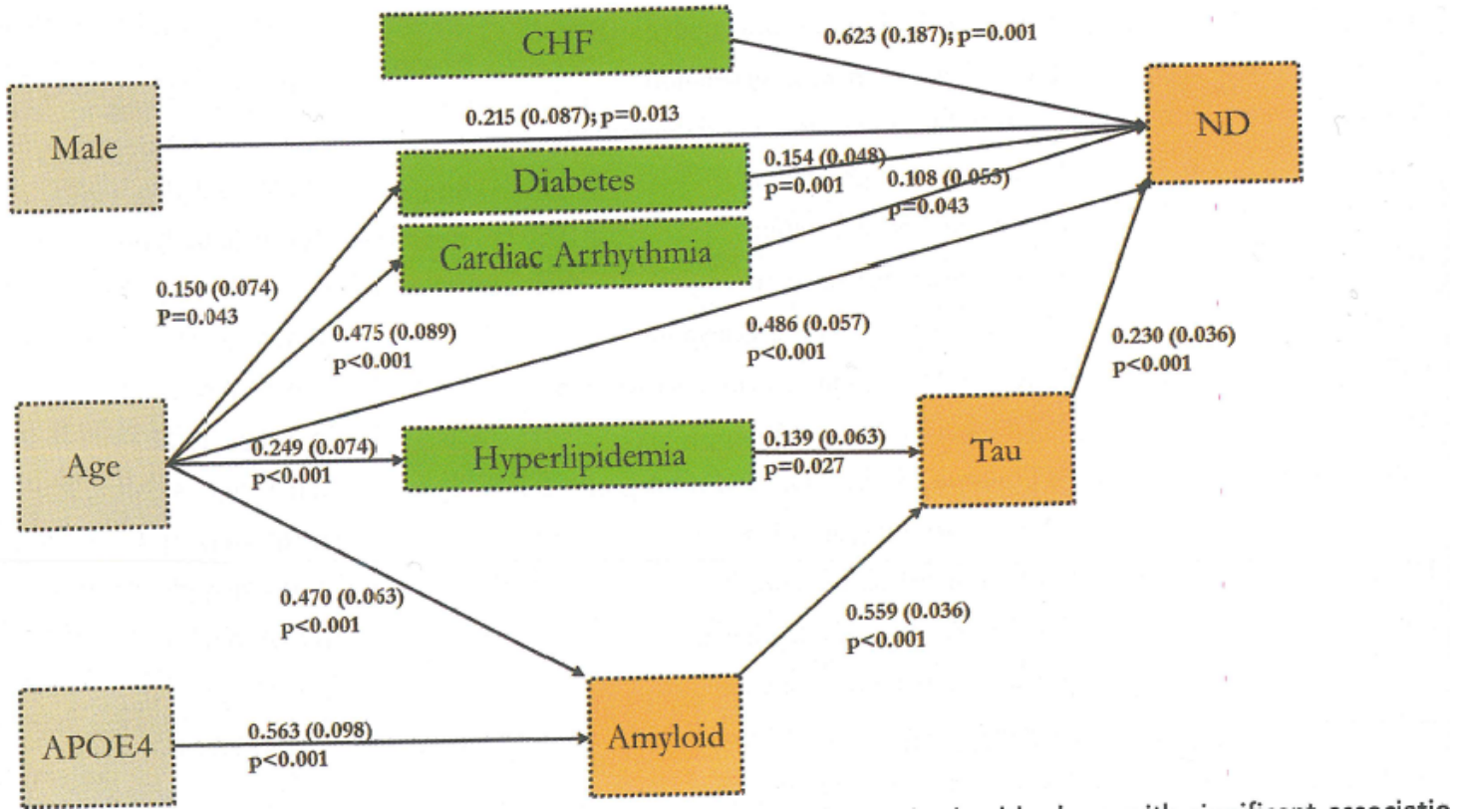
TCBV= Total Cerebral Brain Volume FSRP= Framingham Stroke Risk Profile
Courtesy of Philip A. Wolf, MD; Elias (Stroke 2004) and Seshadri (Stroke 2004)

Framingham Stroke Risk Profile and Lowered Cognitive Performance

(Elias et al, Stroke 2004)

Psychometric Domain (composites)*	**P-Value for 10% Increment in 10-yr Stroke Risk**
Visual-Spatial Memory and Organization*	**<0.0001**
Concentration, Visual Scanning and Tracking*	**<0.0001**
Abstract Reasoning	**0.0005**

Mayo Clinic Study of Aging
Predictors of Neurodegeneration (ND), Tau, & Amyloid (older adults: age 70s)



Source: Vemuri P et al. Ann Neurol 2017; 82: 706-718

Atherosclerosis Risk in Communities (ARIC) Study PET Amyloid Imaging Study: Association of Midlife Vascular Risk Factors & Estimated Brain Amyloid Deposition

- Risk factors: BMI ≥30, current smoking, HTN, DM, and total cholesterol (≥200 mg/dL)

Results:

1. Late life risk factors NOT associated with late life brain amyloid deposition
2. Odds ratio for elevated SUVR based on # of risks (vs 0 factors):
   A. 1 = 1.88 (95% CI: 0.95, 3.72)
   B. ≥2 = 2.88 (95% CI: 1.46, 5.69)

Conclusion: midlife but not later life effect

Source: Gottesman RF et al. JAMA 2017; 317: 1443-50.
SUVR= Standardized Uptake Value Ratio for amyloid

JAMA Network™

From: **Association of Midlife Cardiovascular Risk Profiles With Cerebral Perfusion at Older Ages**
→Negative relationship of Framingham Risk Score in Midlife with Cerebral Perfusion over 20 Years

Suri et al. JAMA Netw Open. 2019;2(6):e195776. doi:10.1001/jamanetworkopen.2019.5776

Longitudinal cohort study, individuals from the Whitehall II Imaging Sub-study. No clinical diagnosis of dementia, no gross brain structural abnormalities on magnetic resonance imaging scans, and had received arterial spin labeling MRI. Mean ages: 1st exam: 47.1 vs last exam: 67.4 yrs.

Higher midlife FRS→ lower blood flow (yellow); effect attenuates over time (blue).

FRS= Framingham Risk Score

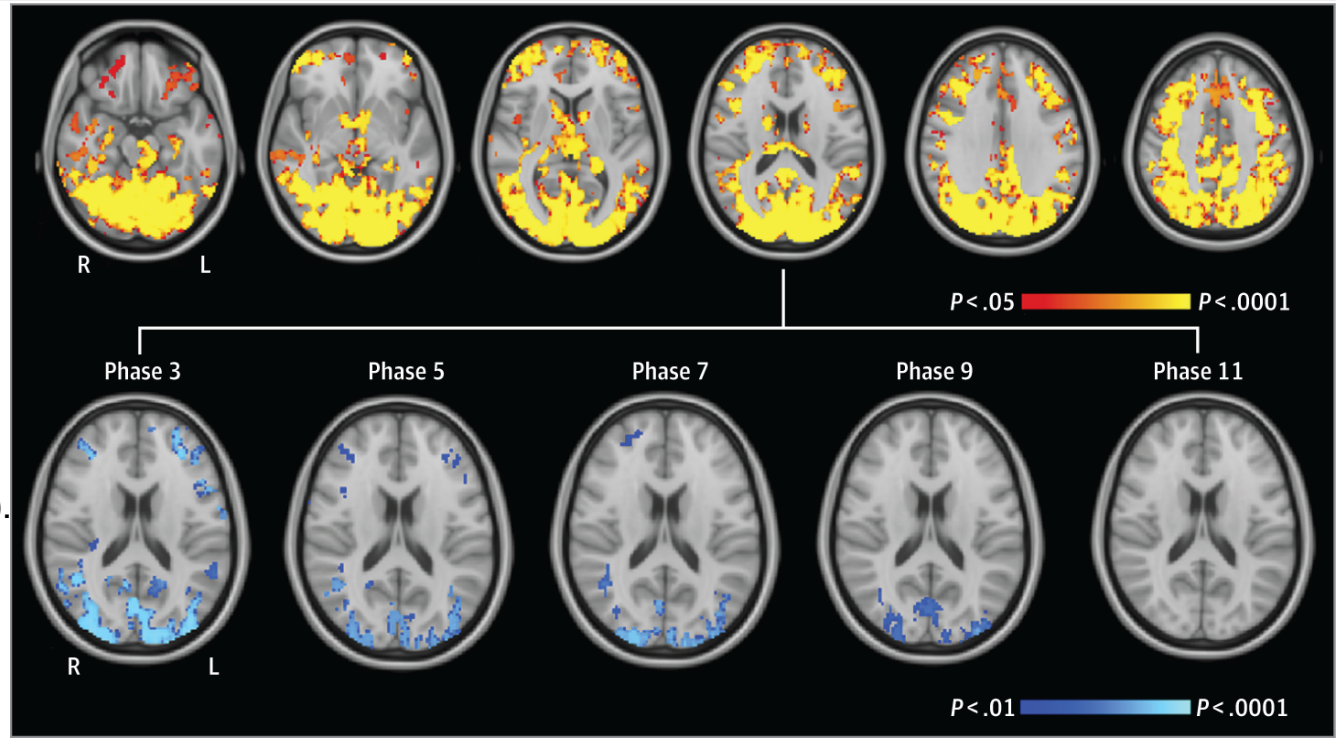


Figure Legend:

Voxelwise Association of Framingham Risk Scores With Cerebral Blood Flow. Top, red-yellow clusters denote regions showing a significant negative association of cumulative Framingham Risk Score with gray matter cerebral blood flow during 20 years (thresholded at familywise error–corrected P < .05). From left to right, horizontal slices are displayed at z = −24, z = −12, z = 0, z = 12, z = 24, and z = 36 in coordinate space (millimeters). Bottom, blue clusters denote regions showing a significant negative association of Framingham Risk Score with gray matter cerebral blood flow at 5 study phases (thresholded at familywise error–corrected and Bonferroni-corrected P < .01). The association of Framingham Risk Score with cerebral blood flow became progressively less widespread from phase 3 to phase 9 and was not statistically significant for phase 11 risk scores. L indicates left; R, right.

2017

TBD 2017

AHA/ASA Presidential Advisory

Defining Optimal Brain Health in Adults

A Presidential Advisory From the American Heart Association/American Stroke Association

Philip B. Gorelick, MD, MPH, FAHA, Chair*; Karen L. Furie, MD, MPH, FAHA, Co-Chair†; Costantino Iadecola, MD, FAHA, Co-Chair†; Eric E. Smith, MD, MPH, FAHA‡; Salina P. Waddy, MD§; Donald M. Lloyd-Jones, MD, ScM, FAHA‖; Hee-Joon Bae, MD, PhD, FAHA; Mary Ann Bauman, MD, FAHA; Martin Dichgans, MD; Pamela W. Duncan, PhD, PT, FAHA; Meighan Girgus; Virginia J. Howard, PhD, FAHA; Ronald M. Lazar, PhD, FAHA; Sudha Seshadri, MD, FAHA; Fernando D. Testai, MD, PhD, MS, FAHA; Stephen van Gaal, MD; Kristine Yaffe, MD, FAHA; Hank Wasiak, MBA; Charlotte Zerna, MD, MSc; on behalf of the American Heart Association/American Stroke Association

AQ3

Released ahead of publication: September 7, 2017.
Source: Gorelick Stroke 2017; 48: e284-e303. DOI: 10.1161/STR.0000000000000148.

BRAINWEEK™

7 Metrics for Optimal Brain Health Originating from AHA's Life's Simple 7
(3Ms: easy to measure, monitor, & modify)

Factor
4 Ideal Health Behaviors
1. Nonsmoking
2. Physical activity at goal levels
3. Healthy diet consistent with current guideline levels
4. Body mass index <25 kg/m2
3 Ideal Health Factors
5. Untreated blood pressure <120/<80 mm Hg
6. Untreated total cholesterol <200 mg/dL
7. Fasting blood glucose <100 mg/dL

Source: Gorelick PB et al. Stroke 2017; 48: e284-e303

What Have We Just Learned?

Cardiovascular risks as measured by the Framingham Risk Score are associated with:

1. Lower total brain volume
2. Lower cerebral blood flow
3. More amyloid deposition in the brain

Mechanisms

How Might Hypertension, Diabetes Mellitus, and Obesity Injure the Brain?

Cerebral Small Vessel Disease

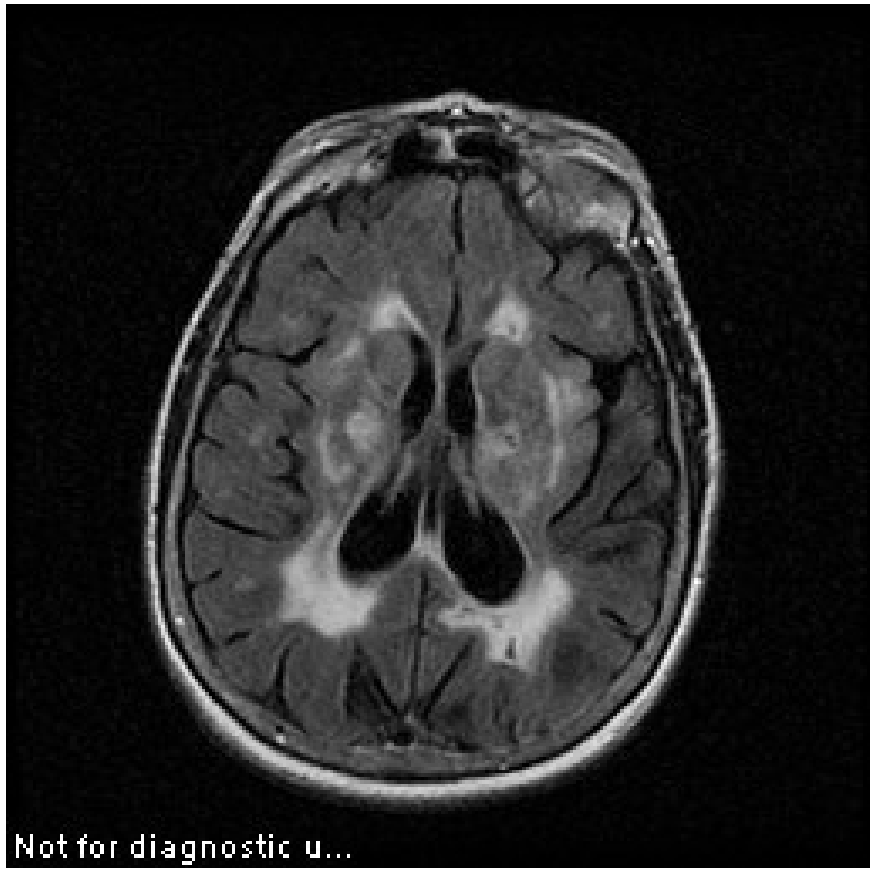
1. Believed to be the most common cause of VCI
2. Refers to all of the pathologies that may affect small vessels of the brain:
   A. Small subcortical infarcts
   B. Lacunes
   C. White matter hyperintensities
   D. Enlarged perivascular spaces
   E. Cerebral microbleeds
   F. Atrophy

(venous structures of the brain also are included; eg, venous collagenosis)

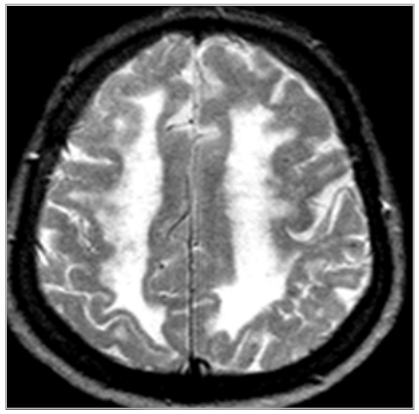
Source: Pantoni L. Lancet Neurol 2010; 9: 689-701.
VCI= vascular cognitive impairment.

PROGRESS MRI Substudy: Presence and Volume of Incident WMH by Treatment (Dufouil et al, 2005)

(White matter lesions disconnect cortex from subcortex)



Active BP-Lowering stopped or delayed progression of WMHs



Small-Vessel Disease Subcortical VCI

Small-vessel disease

Subcortical infarcts in strategic locations
Thalamus, caudate nucleus, internal capsule

↓

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

↓

Executive dysfunction **Apathy** **Attentional deficit** **Personality change**

Subcortical type of VCI

Source: A. Kurz, München, Germany.

VCI= vascular cognitive impairment.

HYPERTENSION→ Lipohyalinosis

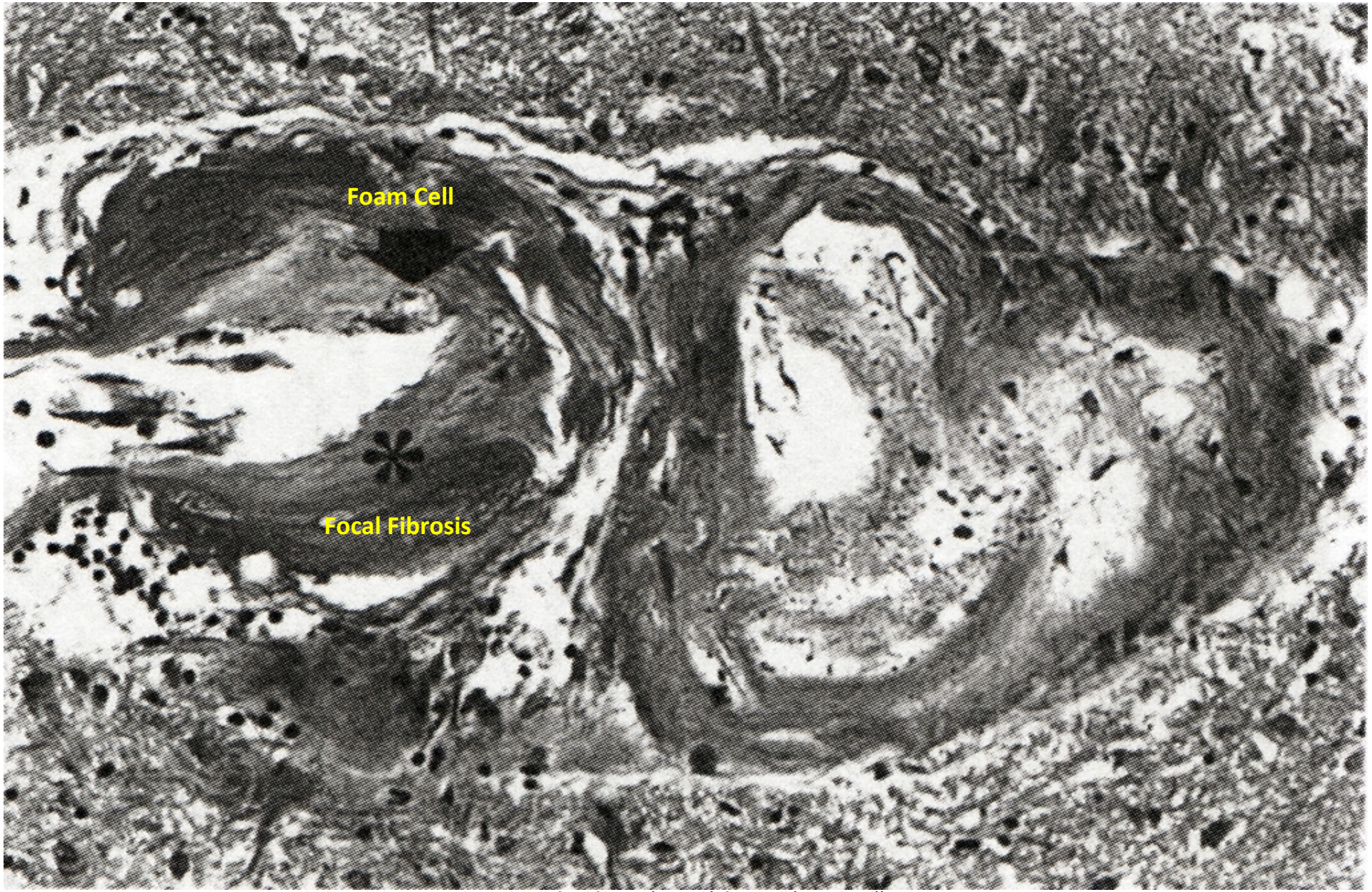


Fig 2: Thickened, disorganized vessel wall; focal fibrosis (asterisk), foam cell (arrowhead))
Source: Han J et al. In: Aiyagari V, Gorelick PB. Hypertension & Stroke 2011; pp. 77-94.

Hyaline Arteriosclerosis

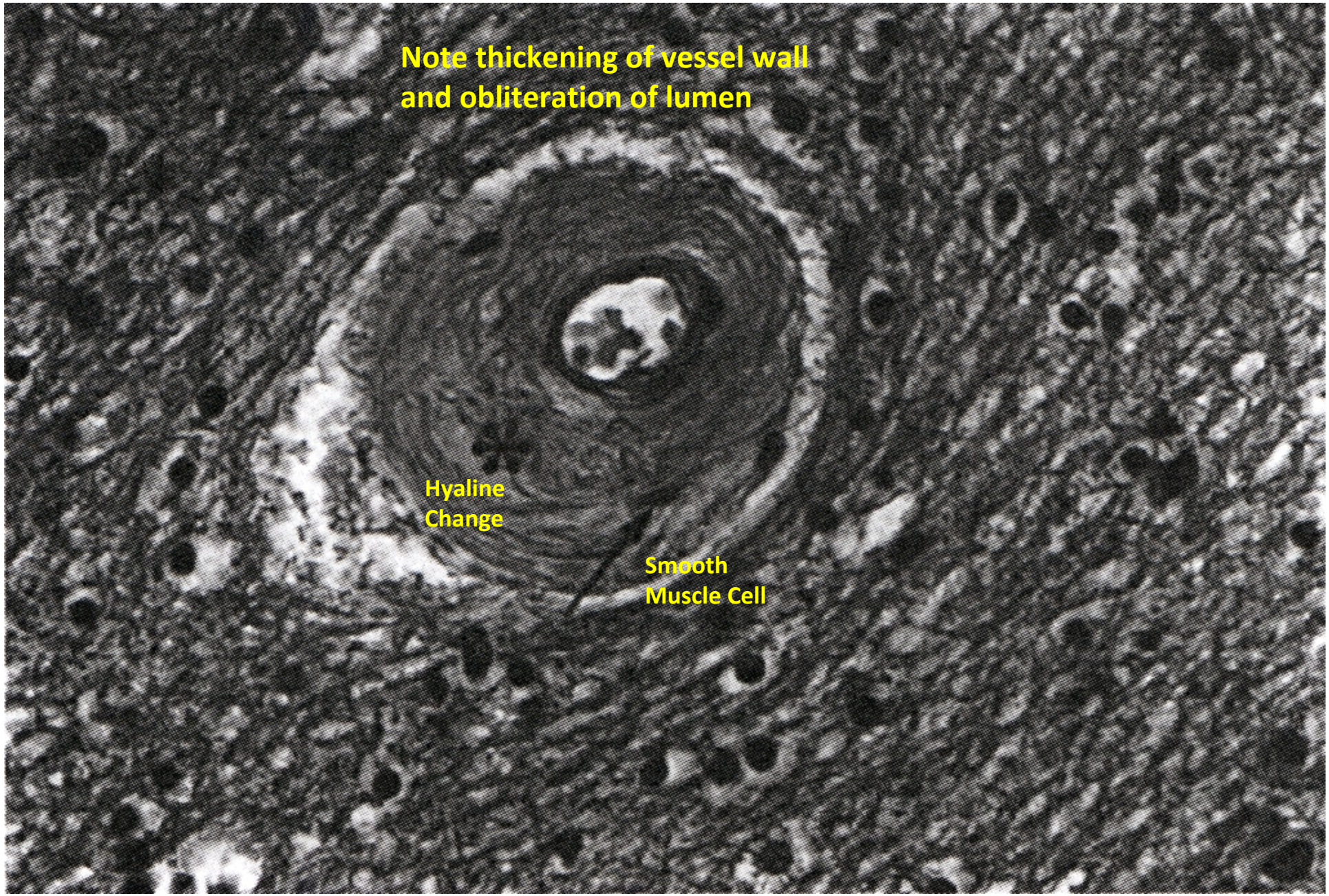


Fig. 1: Concentric vessel wall thickening; hyaline collagenous material (asterisk), occasional surviving smooth muscle cell (arrow)
Source: Han J et al. In: Aiyagari V, Gorelick PB. Hypertension & Stroke 2011; pp. 77-94.

Shared Mechanisms for All Cardiovascular Risk Factors Associated with Stroke

1. Brain Infarcts: large vessel, small vessel, and cardioembolic (eg, atrial fibrillation): disconnects key fiber tracts from brain areas and critical loss of brain tissue
2. Increase in white matter disease: disconnects key fiber tracts from brain areas
3. Strategic infarcts (eg, thalamus, hippocampus) and results in cognitive signs

Hypertension: Other Potential Mechanisms Associated with Cognitive Impairment

1. More brain atrophy (eg, temporal regions) and lower brain weight: an accelerator of neurodegenerative change
2. More neurofibrillary tangles/amyloid plaques
3. Imbalance of angiotensin I and II system

Source: Testai FD, Gorelick PB. Cerebro-Vascular Disease/Cognitive Function. In: Bakris G, Baliga RR (eds.): Hypertension 2012

Diabetes Mellitus: Potential Mechanisms Associated with Cognitive Impairment

1. Type 3 or brain diabetes (decreased production of insulin, peripheral insulin resistance) → endothelial dysfunction, impaired NO activity, atherosclerosis, and more stroke and brain volume loss (gray matter)
2. Hyperinsulinemia → decreased insulin transport across brain and reduced insulin in brain and insulin signaling
3. Insulin resistance → more beta amyloid generation or reduced clearance and poor insulin signaling
4. Decreased insulin signaling → more tau → neuronal cell death
5. Advanced glycation end products (AGE) → may play a role in pathogenesis of AD (plaques/tangles)
6. Brain inflammation

Source: Hooshmand B et al. Am J Med 2019; 132: 467473 & Testai FD, Gorelick PB. Cerebro-Vascular Disease/Cognitive Function. In: Bakris G, Baliga RR (eds.): Hypertension 2012.
NO= nitric oxide.

Obesity: Potential Mechanisms Associated with Cognitive Impairment

1. Association with hypertension +/or diabetes, metabolic syndrome, other cardiovascular risks (eg, low physical activity, hypercortisolemia, adipose-related hormones, adiponectin/leptin)
2. Risk for stroke (large, small vessel, etc)
3. Inflammation of brain (eg, white matter) and hippocampal shrinkage, more white matter disease

Source: Lampe L et al. Ann Neurol 2019; 85: 194-203, Fotuhi M, Lubinski B. Practical Neurology July/August 2013, & Pedditizi E et al. Age and Ageing 2016; 45: 14-21.

Clinical Trials & Lessons Learned

High Blood Pressure

RCTs, Blood Pressure Lowering, and Preservation of Cognition

HOPE-3 Cognition Study (2016): negative with cognitive decline as primary endpoint.

Of these clinical hypertension trials (SPS3, PROGRESS, SCOPE, PROFESS, ONTARGET, TRANSCEND, SHEP, SYST-EUR, HYVET, ACCORD MIND):

1. SYST-EUR: *marginally significant* result for reduction of dementia; and
2. PROGRESS: reduction of dementia or cognitive decline *if a recurrent stroke and* in perindopril treatment group

Source: Iadecola C et al. Impact of Hypertension on Cognitive Function. Scientific Statement from AHA. Hypertension 2016 (available online); RCTs= randomized controlled trials.

Is It the Degree of Blood Pressure Lowering?

Is intensive blood pressure lowering better?

SPRINT Research Question

Examine effect of more intensive high blood pressure treatment than is currently recommended

Randomized Controlled Trial Target Systolic BP

SPRINT design details available at:

- ***ClinicalTrials.gov (NCT01206062)***
- ***Ambrosius WT et al. Clin. Trials. 2014;11:532-546.***

Source: Whelton P et al
AHA presentation Nov. 2015

SPRINT: Eligibility Criteria

Inclusion Criteria	Exclusion Criteria
1. ≥50 years of age	1. Stroke
2. SBP 130-180 mm Hg (treated or untreated)	2. Diabetes mellitus
3. ≥1 *additional cardiovascular disease risk:*	3. Polycystic kidney disease
A. Clinical or subclinical CVD (excluding stroke) B. Chronic kidney disease (CKD), defined as eGFR 20 – <60 ml/min/1.73m^2	4. Congestive heart failure (symptoms or EF < 35%) 5. Proteinuria >1g/d
C. Framingham Risk Score for 10-year CVD risk ≥15% D. Age ≥75 years	6. CKD with eGFR < 20 mL/min/1.73m^2 (MDRD) 7. Adherence concerns
Source: Whelton P et al. AHA presentation Nov. 2015	

From: **Effect of Intensive vs Standard Blood Pressure Control on Probable Dementia: A Randomized Clinical Trial**

JAMA. 2019;321(6):553-561. doi:10.1001/jama.2018.21442

Table 2. Incidence of Probable Dementia and Mild Cognitive Impairment by Treatment Group

Outcomes	Treatment Group: Intensive — No. With Outcome/Person-Years	Intensive — Cases per 1000 Person-Years	Standard — No. With Outcome/Person-Years	Standard — Cases per 1000 Person-Years	Hazard Ratio (95% CI)[a]	*P* Value
Probable dementia	149/20 569	7.2	176/20 378	8.6	0.83 (0.67-1.04)	.10
Mild cognitive impairment[b]	287/19 690	14.6	353/19 281	18.3	0.81 (0.69-0.95)	.007
Composite of mild cognitive impairment or probable dementia	402/19 873	20.2	469/19 488	24.1	0.85 (0.74-0.97)	.01

[a] Intensive treatment group vs standard treatment group based on Cox proportional hazards regression.

[b] Participants adjudicated as having probable dementia at the first follow-up visit (year 2) do not contribute to the analyses of mild cognitive impairment.

Table Title: **Incidence of Probable Dementia and Mild Cognitive Impairment by Treatment Group**

SPRINT MIND:
Results of MRI Volumetric Subset Study

- 27 sites in the US, 670 subjects and 4 years of follow-up (n=449) for intensive treatment (n=355) vs standard treatment (n=315).
- Baseline MRI and follow-up MRI (median: 3.97 years) with a median intervention period of 3.40 years.

	Intensive Treatment	vs	Standard Treatment
1.	Mean WML volume increase: 4.57 → 5.49 cm3 (0.92 cm3 difference)		4.40 → 5.85 cm3 (1.45 cm3)
	Between-Group WML difference in change: -0.54 cm3 (95% CI: -0.87, -0.20; P<0.001)		
2.	Mean total brain volume decrease: 1134.5 → 1104.0 cm3 (-30.6 cm3 difference)		1134.0 → 1107.1 cm3 (-26.9 cm3)
	Between-Group brain volume difference in change: -3.7 cm3 (95% CI: -6.3, -1.1; P=0.006)		

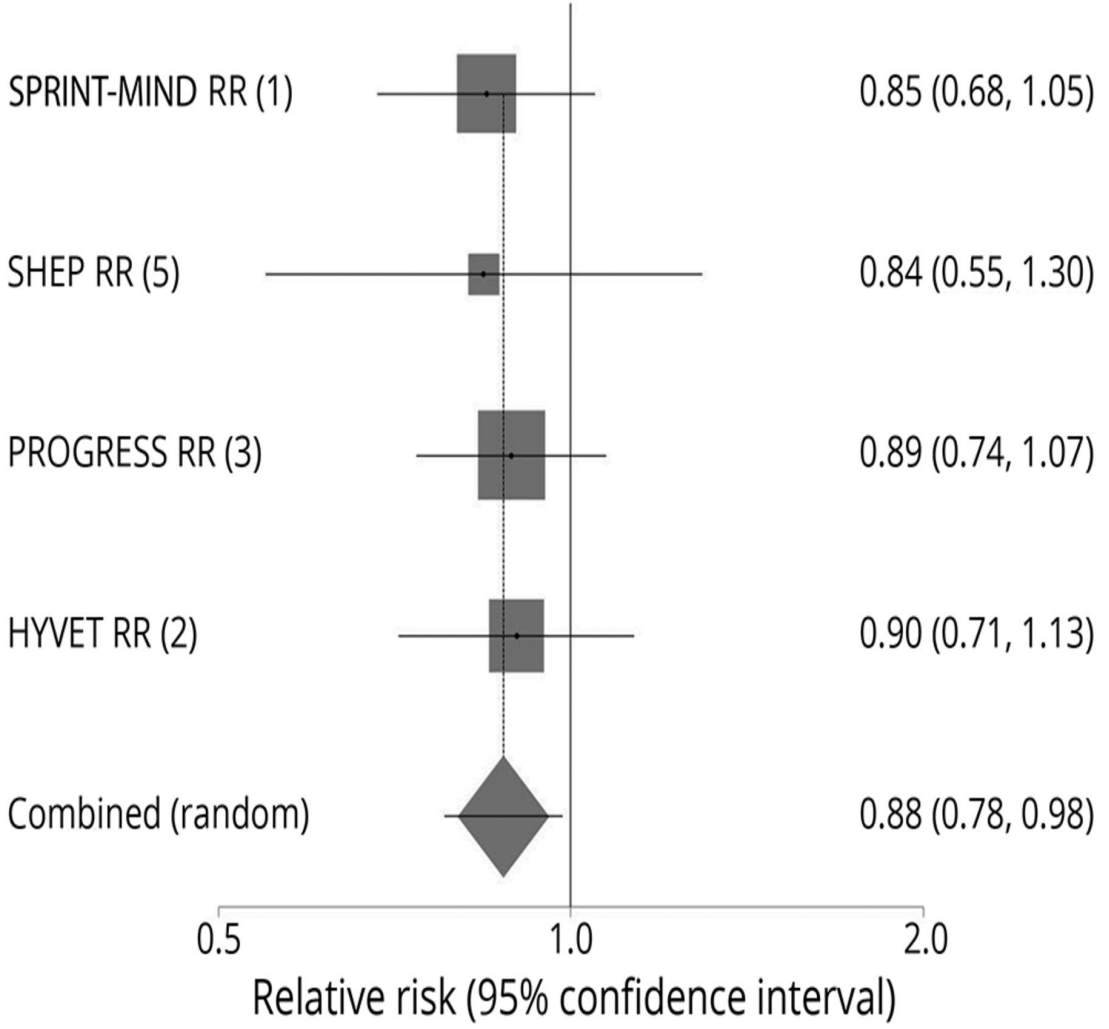
- Conclusion: Intensive blood pressure treatment was associated with a smaller increase in cerebral white matter volume and a greater decrease in total brain volume, but the differences were small.

Source: SPRINT MIND Investigators. JAMA 2019; 322: 524-534. WML= white matter lesion.

Figure: Meta-analysis of trials of blood pressure (BP)–lowering on dementia outcomes, according to having ≥10 mm Hg systolic BP difference

The totality of the evidence is moderately strong in the absence of important harms.

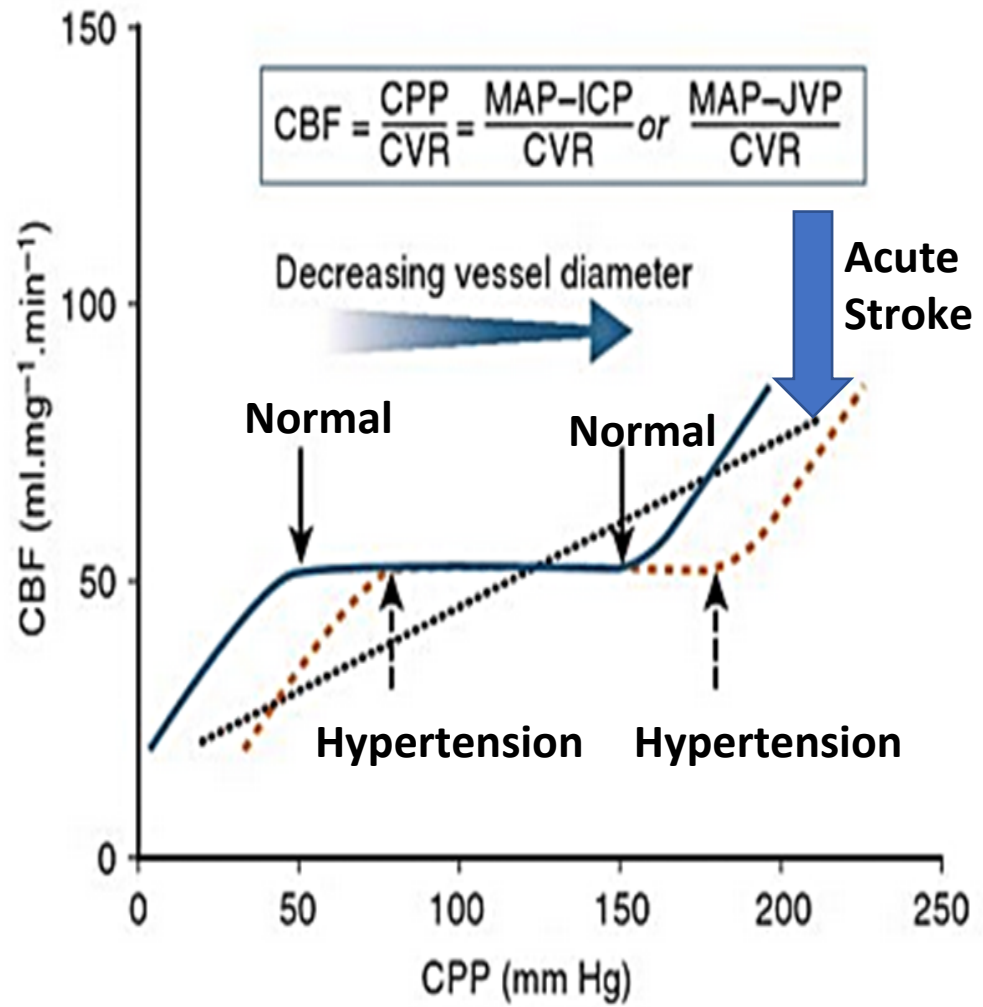
<u>In observational studies</u>, no evidence that a specific BP lowering drug class more effective than another (Ding J et al. Lancet Neurology, online Nov. 6, 2019).]



Ruth Peters et al. Neurology 2019;92:1017-1018

AMERICAN ACADEMY OF NEUROLOGY

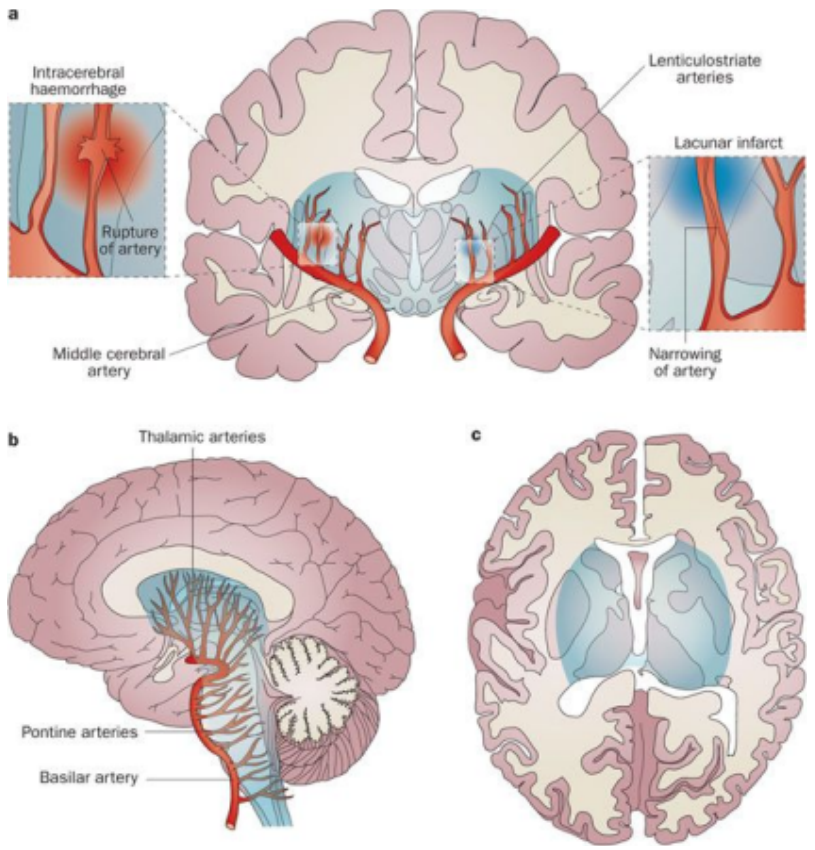
Cerebral Autoregulation Curve



Source: Aiyagari V, Ruland S, Gorelick PB. In: Johnson RJ et al (eds.): Comprehensive Clinical Nephrology, Chapter 42, 2015, pp. 488-495

End arteries from the anterior and posterior circulation w/o substantial collaterals, vulnerable to hypertension (fibrinoid degeneration, microaneurysms), and supply phylogenetically older parts of the brain or centrencephalic and adjacent white matter (blue).

Source: Soros P et al. Nat Rev Neurol 2013; 9(3): 174-178.



Diabetes Mellitus (Type 2)

Diabetes and Recent Clinical Trials to Preserve Cognition

Study	Intervention	Result
1. ACCORD MIND	Intensive BP control, fibrate, LDL <100 mg/dL	No measureable effect on cognitive decline at 40 m
2. Finnish Diabetes Prevention Study	Lifestyle intervention	No benefit on cognition
3. FINGER	Multi-domain diet, exercise, cog. exercise, vascular risk control	Improved overall cognition, executive function & processing speed, and lifestyle habits, but not memory
4. LIFE	Moderate intensity physical activity	No improvement in global or domain-specific cognitive function
5. AREDS2	Long-chain PUFAs +/or lutein	No statistically significant effect on cognition

Novel Antidiabetic Drugs

1. Glucagon-like peptide-1 receptor agonists (GLP-1RAs) (REWIND)
2. Sodium-glucose cotransporter-2 inhibitors (SGLT-2 inhibitors)

Proven valuable to reduce stroke risk, heart failure, ESRD, cardiovascular death, and all-cause mortality.

Source: Tsapas A et al. Ann Intern Med 2020; 173: 278-286.

Promising Antidiabetic Agents of Interest for Preservation of Cognition

- *Intranasal Insulin*
- *Glucagon-like peptide-1 (GLP-1) receptor agonist, dulaglutide* (REWIND):

A. Exploratory primary outcome: Montreal Cognitive Assessment or Digit Symbol Substitution Test ≥1.5 SDs below baseline.

B. Intervention: dulaglutide 1.5 mg sub-q weekly vs matching placebo.

- Main result in subanalysis:
  substantial cognitive impairment reduced by 14% (p=0.0018)

REWIND=Researching Cardiovascular Events With a Weekly Incretin in Diabetes.
Source: Cukierman-Yaffe T et al. Lancet Neurol 2020; 19: 582-90.

Obesity

1. Time windows
2. Inflammation

Time Windows

- Systematic review and meta-analyses: positive association with being overweight/obese below the age of 65 years and the later development of dementia, with the opposite for aged 65 and over.
- Obesity paradox: overweight and high cardiovascular risk in mid-life and subsequent weight decrease → worst outcome in late life.

Source: Pedditizi E et al. Age and Ageing 2016; 45: 14-21

Colchicine as an Ameliorator of Inflammation in Atherosclerosis

- Colchicine Cardiovascular Outcomes Trial (COLCOT): reduction of cardiovascular outcome events (colchicine 0.5mg/d) vs placebo & 74% relative stroke risk reduction.
- Colchicine for Prevention of Vascular Inflammation in Non-cardioembolic Stroke (CONVINCE): ongoing in patients with noncardioembolic minor ischemic stroke or TIA (colchicine 0.5 mg/d).

Source: Katsanos A, Hart R. JAMA Neurol 2020; 77: 1308-17..

National and International Guidance Recommendations on Maintenance of Brain Health

Institute of Medicine Report (April 2015, www.iom.edu/cognitiveaging): Be physically active, reduce and manage cardiovascular risk factors (including hypertension, diabetes, smoking).

Report of the National Academies of Sciences, Engineering, Medicine (2017 [Leshner AI et al]): Encouraging but INCONCLUSIVE evidence for: cognitive training, physical activity, BP management, diet, statins.

Population Attributable Fraction of 12 Potentially Modifiable Risk Factors for Dementia

Potential modifiability:
40% higher attributable fraction

1. Early life: education: 7%
2. Mid life: hearing loss: 8%
3. Later life: smoking: 5%

New factors:

1. Air pollution: 2%
2. Alcohol: 1%
3. Traumatic brain injury: 3%

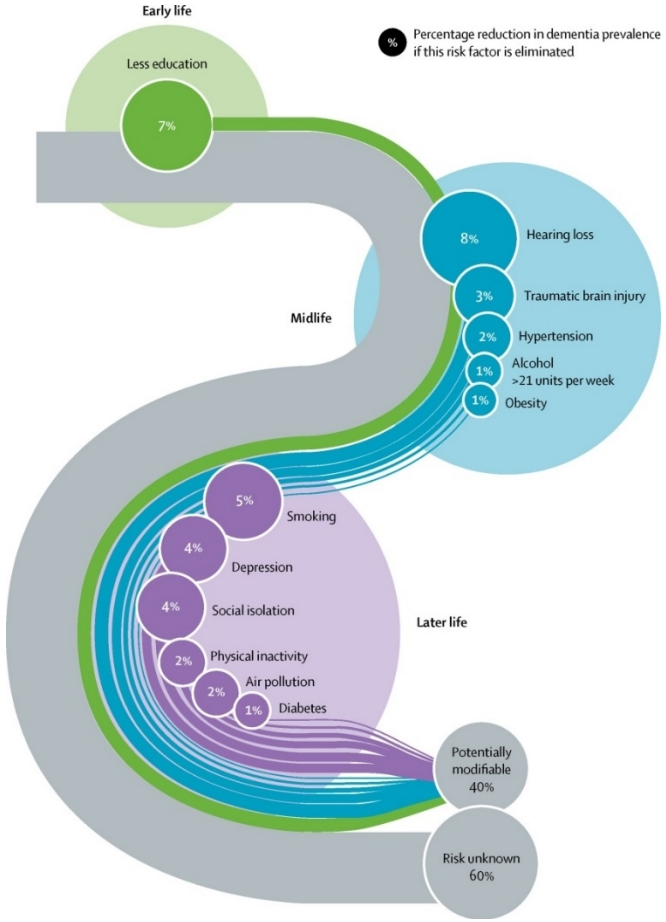


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Figure 7

Main Message

1. Cognitive impairment and dementias of later life may be prevented by the prevention and treatment of cardiovascular risk factors.
2. Control of cardiovascular risks will reduce the risk of heart disease and stroke.

Thank You

Q & A