Vascular contributions to dementia: A path to prevention

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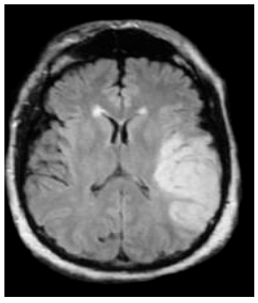
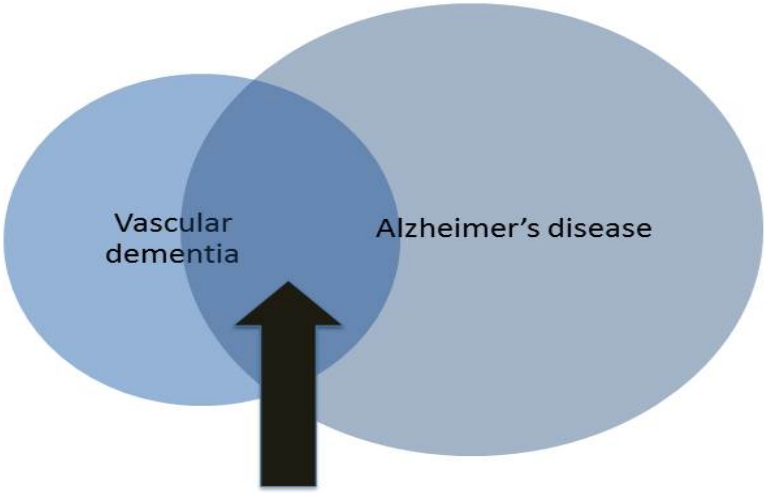
What is Vascular Dementia?

- Also called "Multi-infarct dementia"; other types include subcortical vascular dementia, genetic vascular dementias (CADASIL)
- Classically defined as rapid onset, stepwise progression of symptoms
  - Sometimes occurring after a stroke, but often not
  - Diagnosis requires cognitive disorder AND either clinical stroke or brain vascular disease by neuroimaging (Gorelick et al., 2011)
- Patients often have problems with attention and executive function; memory may not be affected
- Clinically it is the second leading cause of dementia (~20% of dementia cases), occurring in 14.6 per 1000 person-yrs (vs 19.2 for AD) (Fitzpatrick et al., 2004)

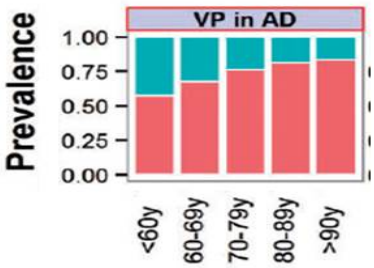


Vascular *contributions* to dementia may be relevant in a much larger percentage of patients with dementia



Vascular and AD overlap: Autopsy evidence

- Between 55-80% of AD patients have coincident vascular changes in the brain (Bangen et al., *Alzheimers & Dementia* 2015; Toledo et al., *Brain* 2013)
- Multiple studies have found less AD neuropathological changes (plaques, tangles) in patients with vascular changes for an equivalent level of cognitive impairment



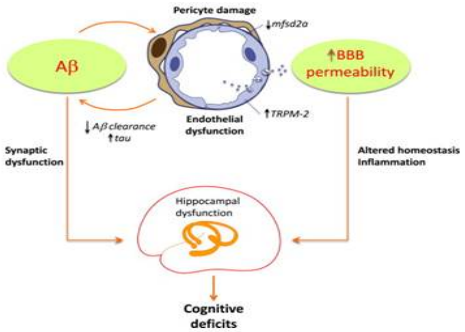
Modified from Toledo et al, *Brain* 2013
(VP: Vascular Pathology; AD: Alzheimer's Disease)

Possible explanations for a vascular/ AD connection

- Vascular disease and Alzheimer's changes are additive, leading to worse cognition when both are present, OR
- Vascular disease directly leads to AD neuropathological changes

Mechanisms for a vascular/ AD interaction

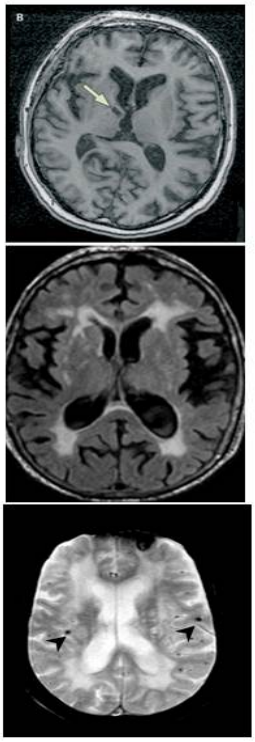
- Vascular risk factors lead to alterations in cerebral blood vessels and can lead to low cerebral blood flow, especially in the white matter of the brain
- The blood brain barrier can be disrupted in the presence of vascular disease
- Role of the neurovascular unit: Amyloid-β itself may directly damage blood vessels, further worsening cerebral blood flow (Iadecola)
- Vascular disease may make clearance of amyloid-β harder; the "glymphatic system" is around blood vessels and helps remove brain waste (Nedergaard)

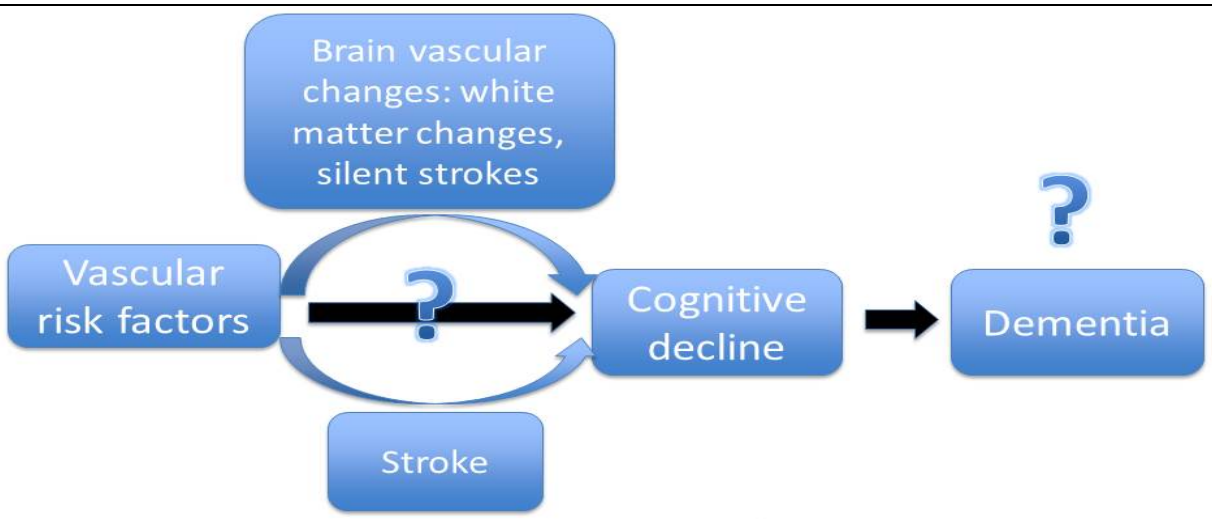


Iadecola, *Neuron* 2015

What do we mean by "vascular disease"?

- Vascular contributions to dementia include:
  - Vascular risk factors (hypertension, diabetes, smoking, high cholesterol)
  - Microvascular markers (retinal microvascular changes)
  - Macrovascular markers (carotid artery disease)
  - Clinical strokes
  - Brain changes on MRI or on autopsy
    - Brain infarcts
    - White matter ischemic changes
    - Microbleeds





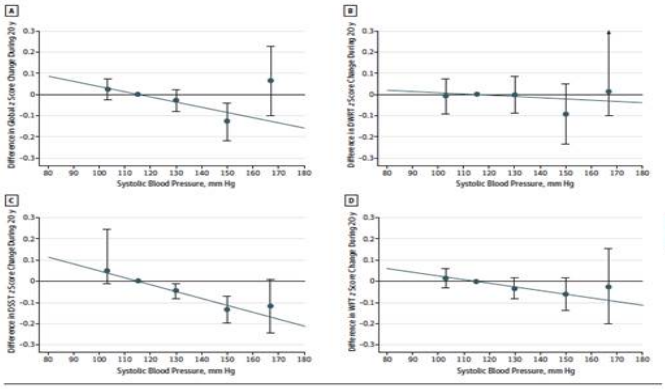
Associations between vascular risk factors and cognitive decline

Associations between stroke and cognitive decline

Associations between vascular risk factors, brain MRI changes and cognitive decline

Hypertension and Diabetes are Each Associated with Steeper Cognitive Decline

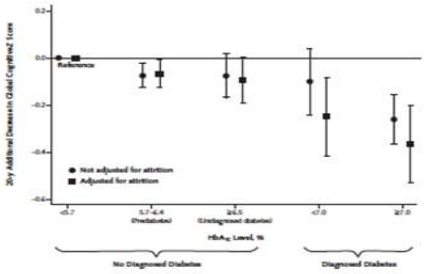
Figure 2. Adjusted Association of Visit 2 (1990-1992) Systolic Blood Pressure Categories and Linear Systolic Blood Pressure With 20-Year Cognitive Change Among Whites



Gottesman et al., *JAMA Neurology* 2014

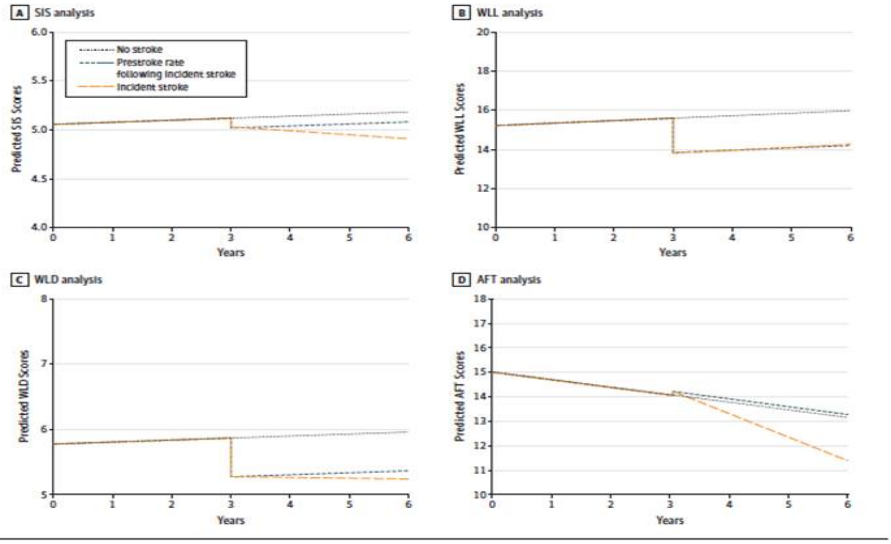
Rawlings et al., *Ann Intern Med* 2014

Figure 2. Difference in global cognitive *Z* score decline by clinical category of HbA_{1c} level compared with decline in persons without diabetes and HbA_{1c} level <5.7%.



Worse cognitive performance noted after stroke (REGARDS study)

Figure 2. Predicted Mean Change in Cognitive Function Test Scores Before and After Acute Stroke at Year 3: REGARDS Study, 2003-2013



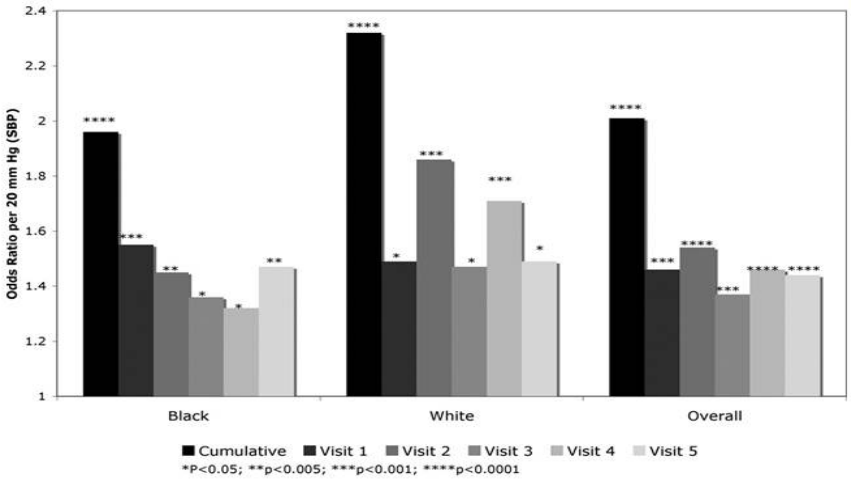
From Levine et al., *JAMA* 2015

Blood Pressure and White-Matter Disease Progression in a Biethnic Cohort

Atherosclerosis Risk in Communities (ARIC) Study

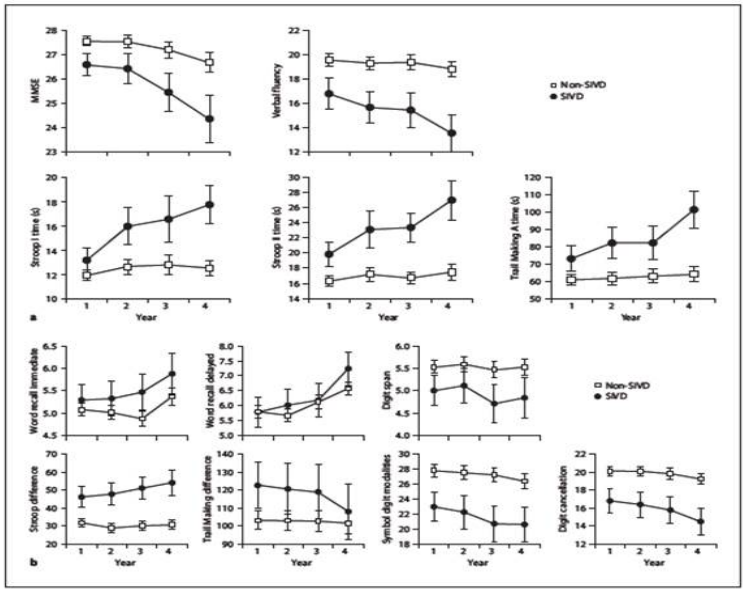
Rebecca F. Gottesman, MD, PhD; Josef Coresh, MD, PhD; Diane J. Catellier, DrPH; A. Richey Sharrett, MD, DrPH; Kathryn M. Rose, PhD; Laura H. Coker, PhD; Dean K. Shibata, MD; David S. Knopman, MD; Clifford R. Jack, MD; Thomas H. Mosley, Jr, PhD

(*Stroke*. 2010;41:3-8.)



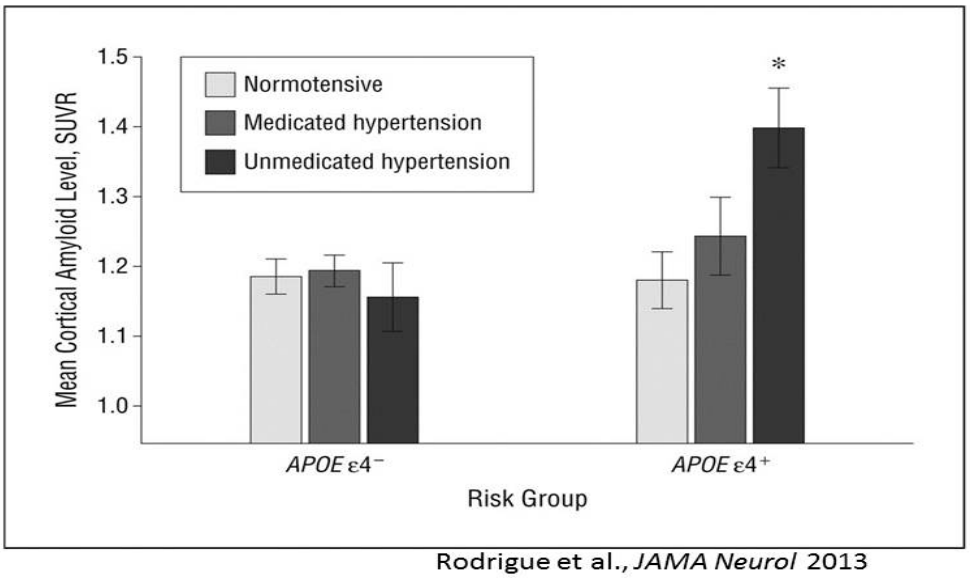
ARIC

Worse cognitive performance is found in people with brain vascular changes



Jokinen et al., *Cerebrovasc Dis* 2009 (LADIS Study)

ApoE and vascular disease: A synergistic effect?



Rodrigue et al., *JAMA Neurol* 2013

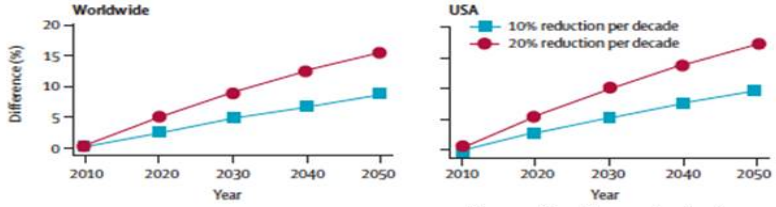
Why is the vascular contribution to dementia and AD so important?

- Vascular disease is preventable
- Vascular disease is very common
- Therefore, this may be a way to prevent AD and other dementia cases

Prevention of vascular disease and AD

USA	Prevalence*	PAR (95% CI)	Number of attributable cases in 2010 (95% CI)† †In thousands
Diabetes mellitus	10·3%	4·5% (2·0–7·3)	240 (107–389)
Midlife hypertension	14·3%	8·0% (2·2–15·1)	425 (119–798)
Midlife obesity	13·1%	7·3% (4·3–10·8)	386 (226–570)
Physical inactivity	32·5%	21·0% (5·8–36·6)	1115 (308–1942)
Depression	19·2%	11·1% (7·5–15·0)	588 (395–796)
Smoking	20·6%	10·8% (3·0–19·8)	574 (159–1050)
Low educational attainment	13·3%	7·3% (4·4–10·3)	386 (236–544)
Combined‡	--	52·7% (25·9–72·8)	2796 (1374–3858)
Adjusted combined§	--	30·6% (14·5–45·3)	1622 (771–2401)

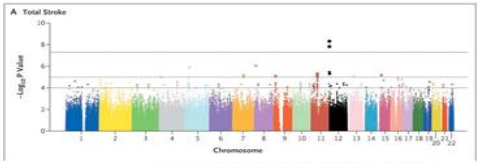
Combined vascular risk factors account for 9.6 million additional cases of AD *worldwide*



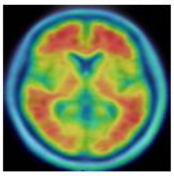
From Norton et al., *Lancet Neurology* 2014

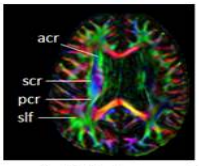
Future directions in the study of vascular contributors to Alzheimer's Disease

- Evaluation of shared genetic risks, or differences in genetic factors that effect an individual's susceptibility to vascular disease and/or AD
- Study of racial disparities in AD prevalence, which may be partially attributable to differences in vascular disease
- Use of neuroimaging, animal models to further explore mechanism of an additive versus synergistic effect of vascular disease and AD



NEJM 2009;360(17):1718-28.





Gottesman & Hillis, Lancet Neurology, 2010

Thanks for your attention.