Rebecca Gottesman MD PhD

Modifying risk for dementia: Identifying potential targets for prevention and treatment over the life course

National Institute of Neurological Disorders and Stroke

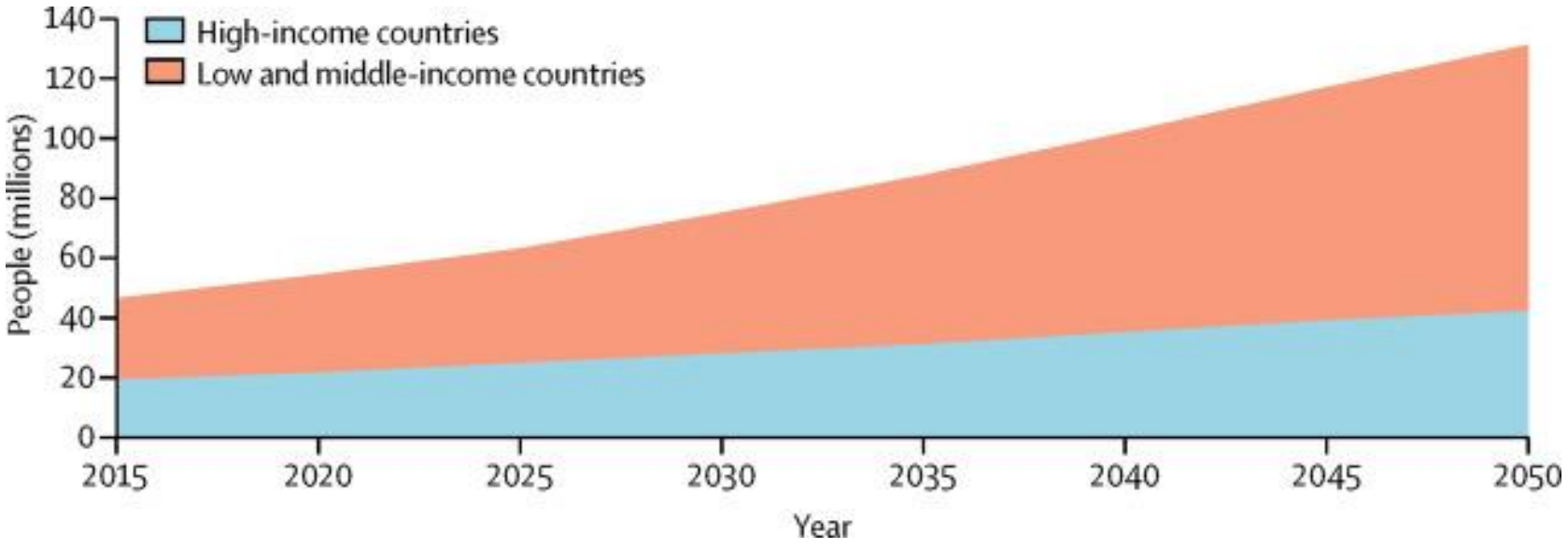
Disclosures

- Current funding: NINDS Intramural research program
- No other disclosures

Dementia as a growing public health epidemic

Alzheimer's disease (AD) is the leading cause of dementia

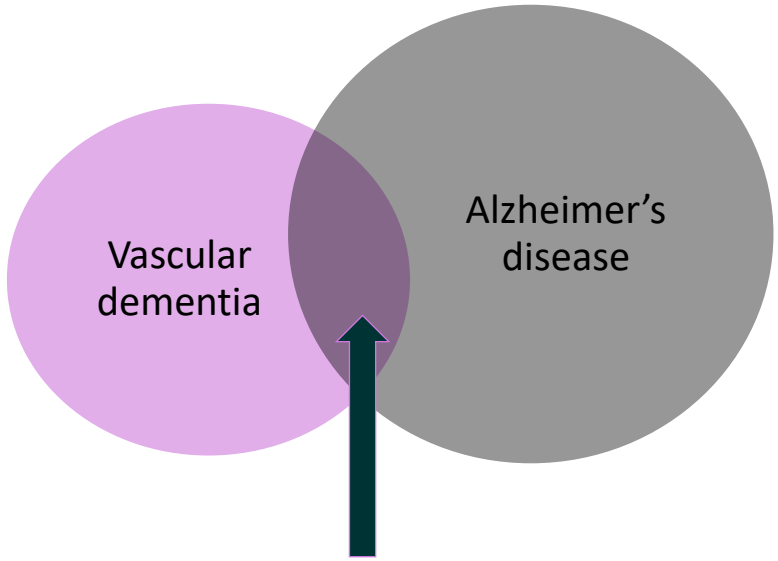
- There are few current treatments, although there are many active clinical trials evaluating possible interventions
  - Most treatments tested to date have been only modestly effective or ineffective, or don't clearly modify disease



Livingston et al., Lancet 2017

Vascular risk and Alzheimer's Disease

- Many patients diagnosed with AD may actually have some vascular contribution, and patients diagnosed with vascular dementia may have some contribution from AD neuropathology
- Vascular risk factors (hypertension, diabetes, smoking, high cholesterol) are known to be present in a subset of individuals with dementia and AD
- This relationship is likely because either:
  - Vascular disease directly causes neuropathologic changes of Alzheimer's dementia, OR
  - Vascular disease of the brain and neuropathologic changes of Alzheimer's together make it more likely that a patient will decline clinically to the point to be labeled with AD



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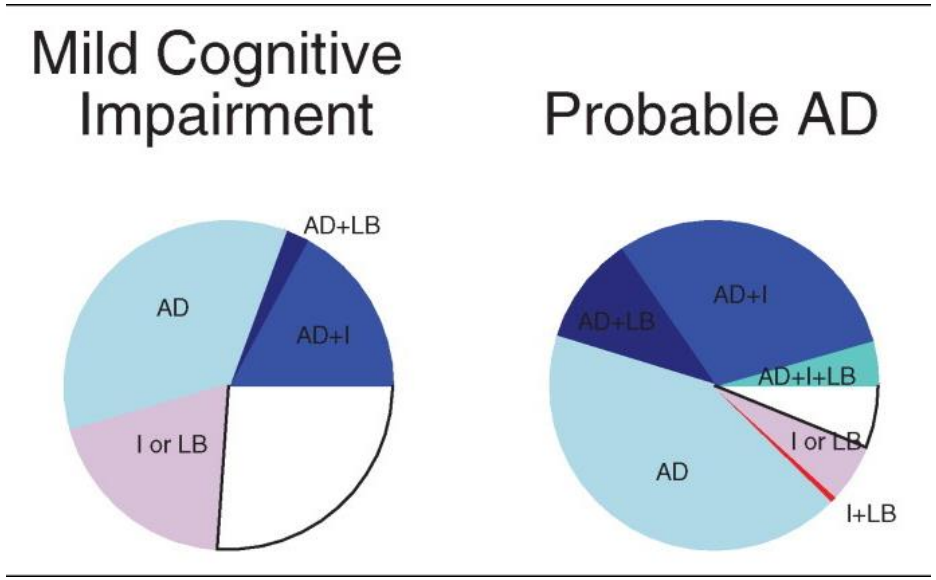
Vascular risk and Alzheimer's Disease

- Many patients diagnosed with AD may actually have some vascular contribution, and patients diagnosed with vascular dementia may have some contribution from AD neuropathology
- 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 fewer AD neuropathological changes (plaques, tangles) in patients with vascular changes for an equivalent level of cognitive impairment



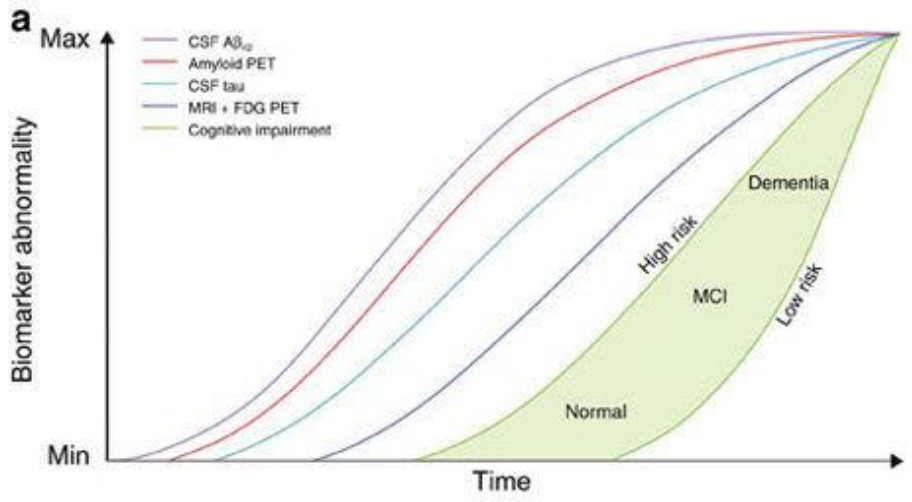
Schneider et al., *Annals of Neurology* 2009

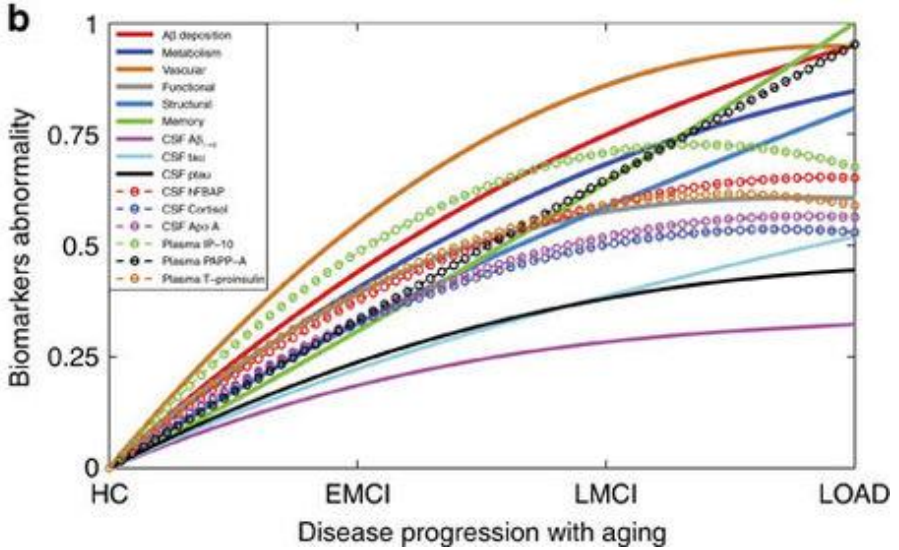
AD=Alzheimer's Disease
I=Infarcts
LB=Lewy Bodies
(White: no AD, no I, no LB)

A window of opportunity for prevention

The long preclinical period of Alzheimer's Disease emphasizes the need to evaluate *early* risk factors

Vascular risk factors from middle age have stronger relationships with cognitive outcomes than from later life





From Iturria-Medina et al., Nat Commun 2016

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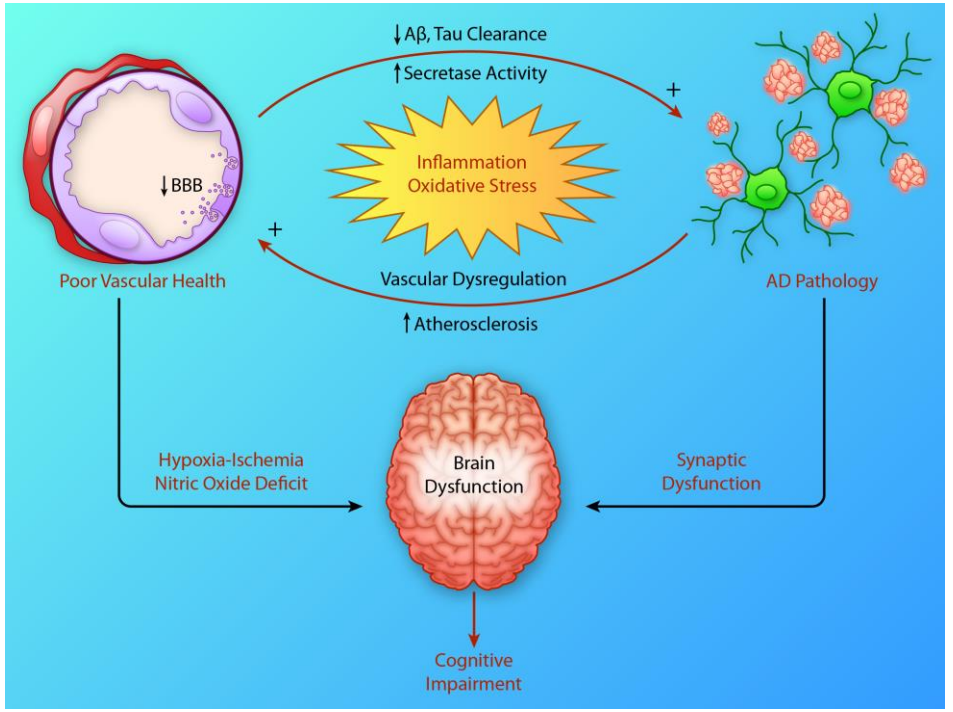
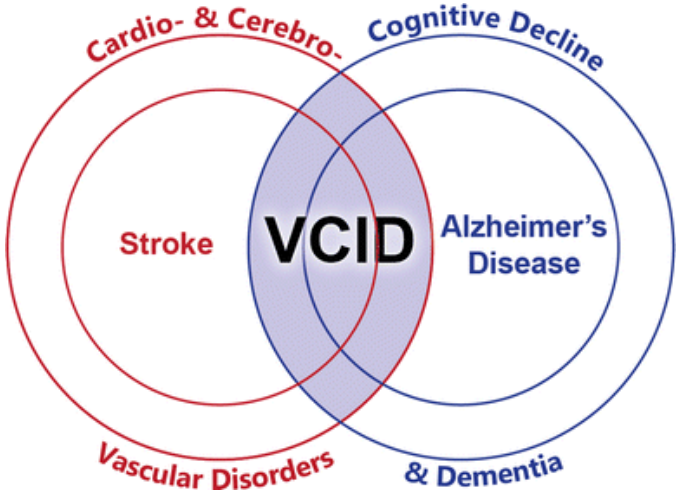
Mechanisms for a vascular/ AD interaction

- 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, with altered neurovascular coupling
- Vascular disease may make clearance of amyloid-β harder; the “glymphatic system” is around blood vessels and helps remove brain waste, and may even lead to more Aβ production

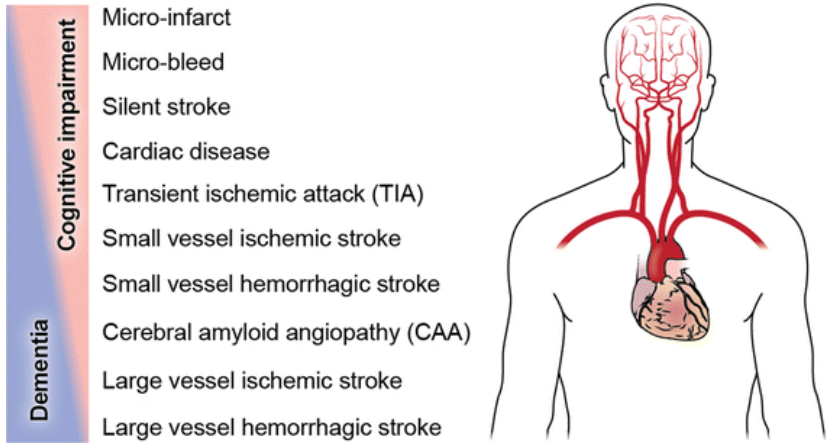


Iadecola & Gottesman, Circulation Research 2019

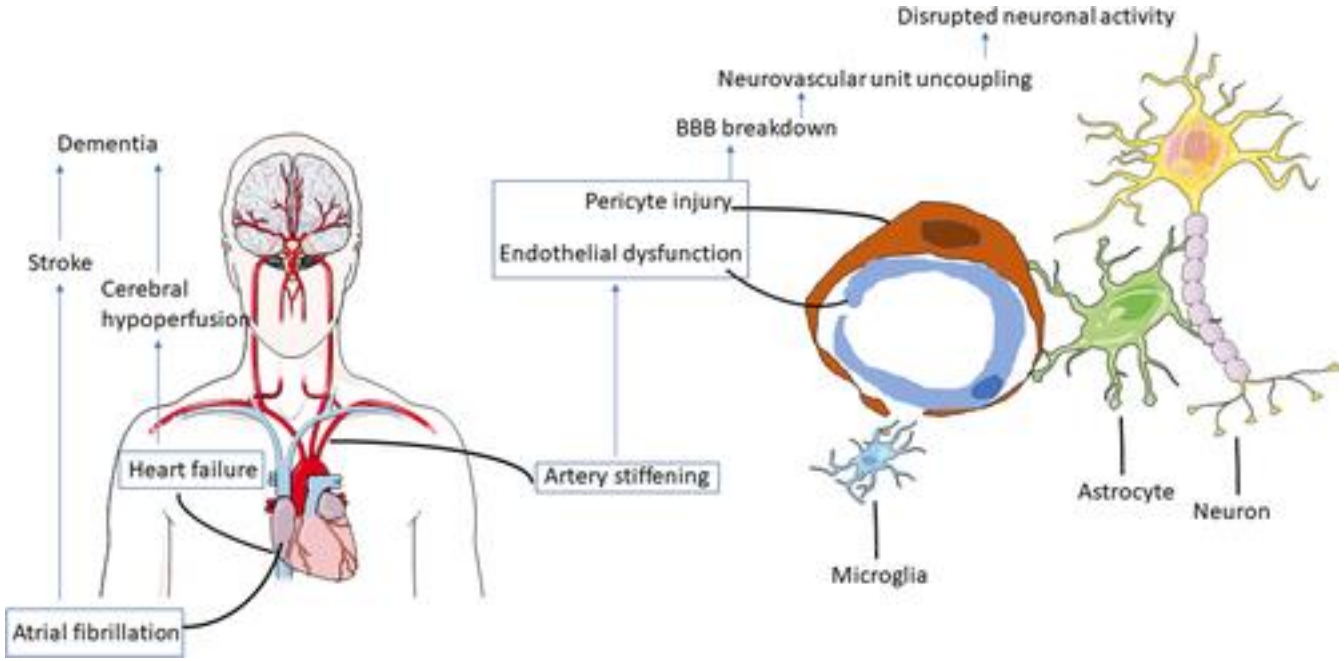
VCID: Vascular Contributions to Cognitive Impairment and Dementia



From Corriveau et al., Cell and Molec Neurobio 2016



- VCID is a broader term, allowing the common mixed pathologies that occur and the different forms that a vascular contribution can take



From Zlokovic, Gottesman et al., Alz & Dem 2018 (NHLBI/ NINDS Workshop report)

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A common form of VCID: Cerebral Small Vessel Disease (SVD)

Neuroimaging standards for research into small vessel disease—advances since 2013

Marco Duering*, Geert Jan Biessels, Amy Brodtmann, Christopher Chen, Charlotte Cordonnier, Frank-Erik de Leeuw, Stéphanie Debette, Richard Frayne, Eric Jouvent, Natalia S Rost, Annemieke ter Telgte, Rustam Al-Shahi Salman, Walter H Backes, Hee-Joon Bae, Rosalind Brown, Hugues Chabriat, Alberto De Luca, Charles deCarli, Anna Dewenter, Fergus N Doubal, Michael Ewers, Thalia S Field, Aravind Ganesh, Steven Greenberg, Karl G Helmer, Saima Hilal, Angela C C Jochems, Hanna Jokinen, Hugo Kuijf, Bonnie Y K Lam, Jessica Lebenberg, Bradley J MacIntosh, Pauline Maillard, Vincent C T Mok, Leonardo Pantoni, Salvatore Rudilosso, Claudia L Satizabal, Markus D Schirmer, Reinhold Schmidt, Colin Smith, Julie Staals, Michael J Thrippleton, Susanne J van Veluw, Prashanthi Vemuri, Yilong Wang, David Werring, Marialuisa Zedde, Rufus O Akinyemi, Oscar H Del Brutto, Hugh S Markus, Yi-Cheng Zhu, Eric E Smith*, Martin Dichgans*, Joanna M Wardlaw*

Lancet Neurology 2023

Published Online
May 23, 2023
https://doi.org/10.1016/
S1474-4422(23)00131-X

STRIVE CONSORTIUM recommended standards for small vessel disease (2013): updated in 2023 with addition of symptomatic vs “covert”, acute vs chronic

Small vessel neuroimaging features:

- Recent small subcortical infarct
- Lacune of presumed vascular origin
- White matter hyperintensity (WMH) of presumed vascular origin
- Perivascular space
- Cerebral microbleed
- Brain atrophy

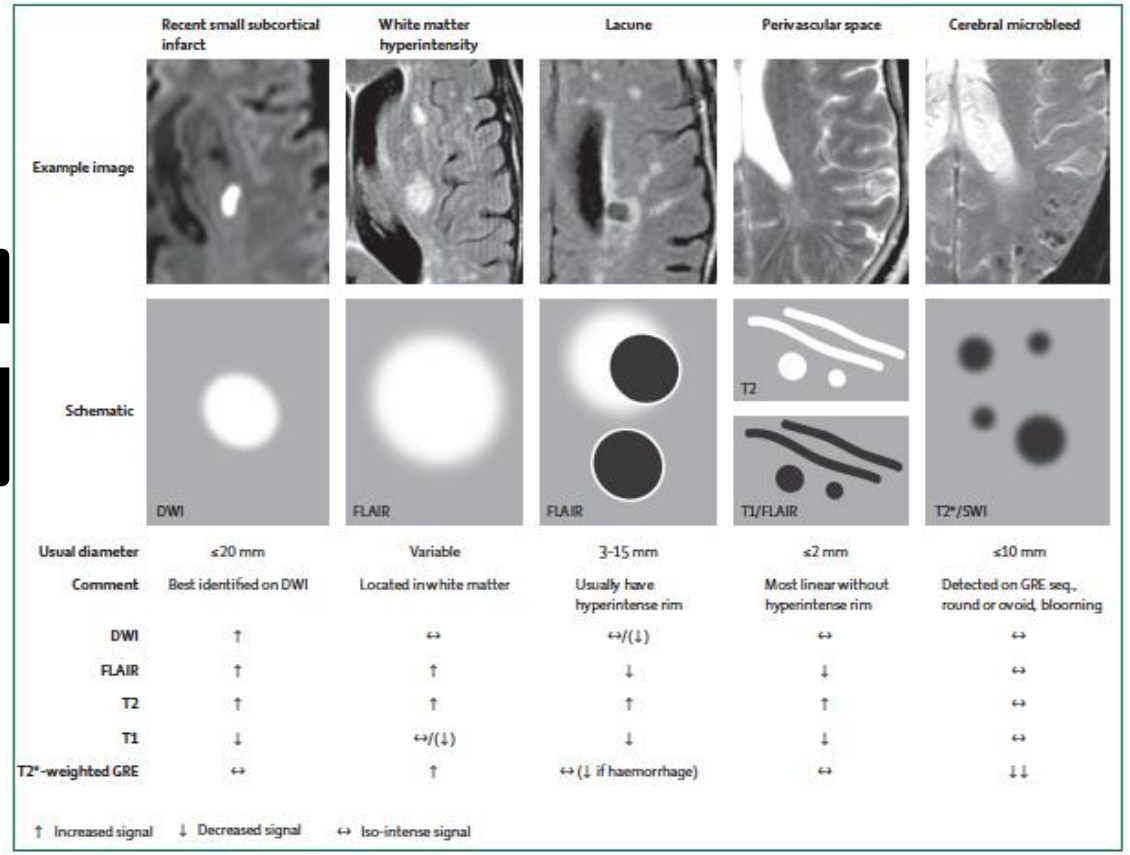

Figure 2: MRI findings for lesions related to small vessel disease
Shows examples (upper) and schematic representation (middle) of MRI features for changes related to small vessel disease, with a summary of imaging characteristics (lower) for individual lesions. DWI=diffusion-weighted imaging. FLAIR=fluid-attenuated inversion recovery. SWI=susceptibility-weighted imaging. GRE=gradient-recalled echo.

Identifying potential targets for prevention and treatment over the life course

- What are modifiable risk factors for cognitive decline and dementia?
- When are modifiable risk factors most important (and thus potentially intervened upon)?
- What are potential mechanisms linking these risk factors to cognitive decline and dementia?
- What other factors (e.g. genetics, other neurodegenerative disease, lifestyle/ social determinants of health) modify how vascular disease may influence cognitive decline and dementia?

Identifying potential targets for prevention and treatment over the life course

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Atherosclerosis Risk in Communities (ARIC)

Community-based prospective cohort of initially 15,792 middle-aged adults

	Visit 1 1987-89	Visit 2 1990-92	Visit 3 1993-95	Visit 4 1996-98	Visit 5 (ARIC-NCS) 2011-13	Visit 6 (ARIC-NCS) 2016-17	Visit 7 (ARIC-NCS) 2018-19	Visit 8 *T (ARIC-NCS) 2020
Age	45-64	48-67	51-70	54-73	68-89	75-94	77-96	79-98
Cognition		N=14,306		N=11,625	N=6,538	N=4,003	N=3,589	N=3,268
Brain MRI			N=1,929		N=1,974			
Florbetapir PET					N=346			

Cognitive analyses consider:
- Change in cognition
- Incident dementia

Methods consider attrition from death and dropout, using inverse probability of attrition weighting and multiple imputation with chained equations

NOTE: Visits ongoing, currently on ARIC visit 11

Original Investigation

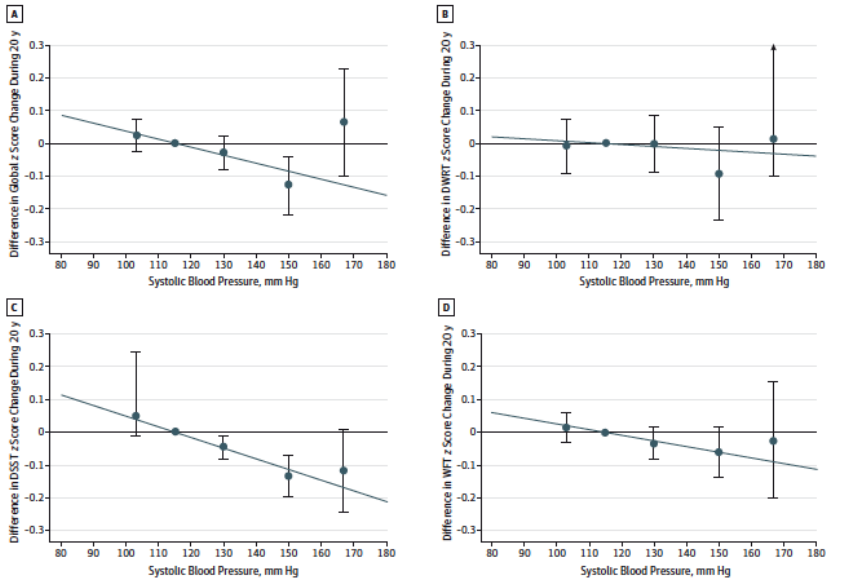
Midlife Hypertension and 20-Year Cognitive Change
The Atherosclerosis Risk in Communities Neurocognitive Study

Rebecca F. Gottesman, MD, PhD; Andrea L. C. Schneider, MD, PhD; Marilyn Albert, PhD; Alvaro Alonso, MD, PhD; Karen Bandeen-Roche, PhD; Laura Coker, PhD; Josef Coresh, MD, PhD; David Knopman, MD; Melinda C. Power, ScD; Andreea Rawlings, MS; A. Richey Sharrett, MD, DrPH; Lisa M. Wruck, PhD; Thomas H. Mosley, PhD

JAMA Neurol. 2014;71(10):1218-1227.

Midlife hypertension is associated with **steeper 20-year cognitive decline**, but *late-life* hypertension is not associated with prior 20 years' worth of change

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



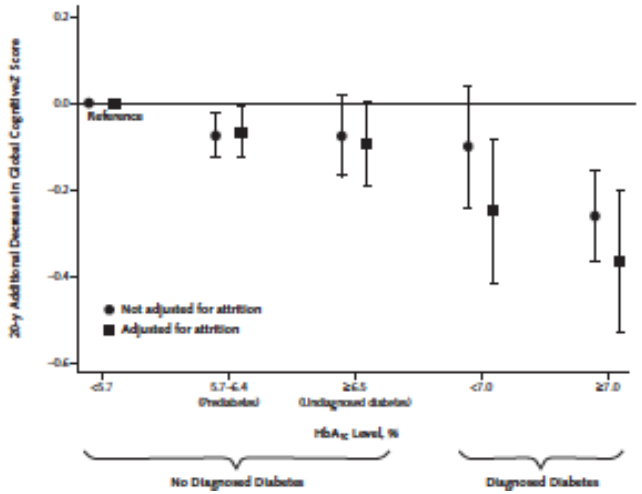
Annals of Internal Medicine | ORIGINAL RESEARCH

Diabetes in Midlife and Cognitive Change Over 20 Years
A Cohort Study

Andrea M. Rawlings, MS; A. Richey Sharrett, MD, DrPH; Andrea L.C. Schneider, PhD; Josef Coresh, MD, PhD, MHS; Marilyn Albert, PhD; David Couper, PhD, MS; Michael Griswold, PhD; Rebecca F. Gottesman, MD, PhD; Lynne E. Wagenknecht, DrPH, MPH; B. Gwen Windham, MD; and Elizabeth Selvin, PhD, MPH

Ann Intern Med. 2014;161:785-793. doi:10.7326/M14-0737

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%.



Midlife diabetes, and higher HbA1c is associated with steeper cognitive change, with strengthening of results with adjustment for attrition

ARIC

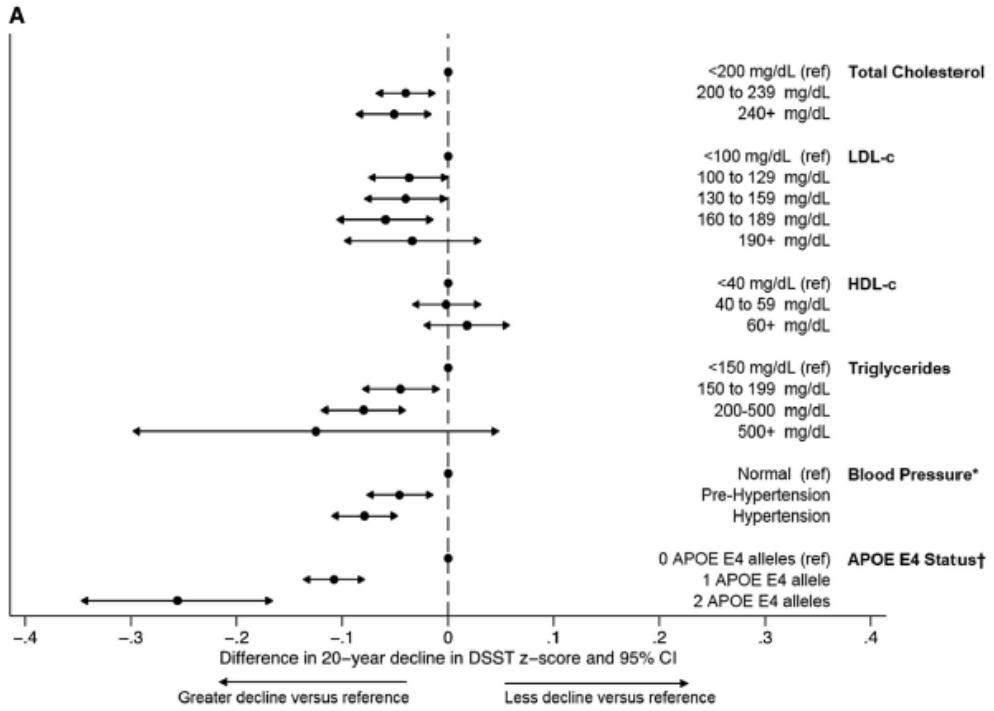
NIH National Institute of Neurological Disorders and Stroke

Featured Article

Association of midlife lipids with 20-year cognitive change: A cohort study

Melinda C. Power[a,b,*], Andreea Rawlings[b], A. Richey Sharrett[b], Karen Bandeen-Roche[c], Josef Coresh[b,c], Christie M. Ballantyne[d], Yashashwi Pokharel[d,e], Erin D. Michos[b,f], Alan Penman[g], Alvaro Alonso[h], David Knopman[i], Thomas H. Mosley[j], Rebecca F. Gottesman[b,k]

Alzheimer's & Dementia ■ (2017) 1-11



Atrial fibrillation and cognitive decline

A longitudinal cohort study

Neurology® 2013;81:119–125

Evan L. Thacker, PhD
Barbara McKnight, PhD
Bruce M. Psaty, MD, PhD
W.T. Longstreth, Jr., MD, MPH
Colleen M. Sitlani, PhD
Sascha Dublin, MD, PhD
Alice M. Arnold, PhD
Annette L. Fitzpatrick, PhD
Rebecca F. Gottesman, MD, PhD
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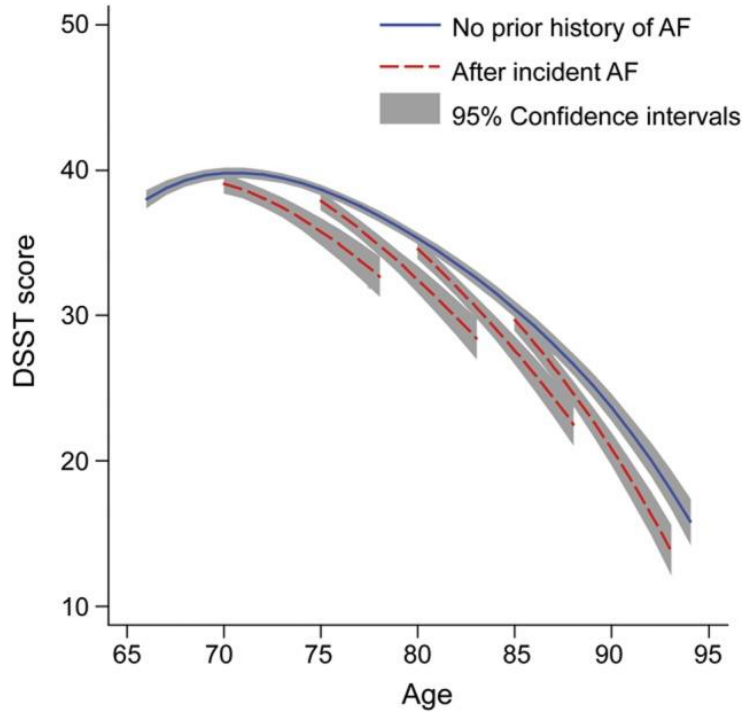


National Institute of Neurological Disorders and Stroke

JAMA Neurology | Original Investigation

Associations Between Midlife Vascular Risk Factors and 25-Year Incident Dementia in the Atherosclerosis Risk in Communities (ARIC) Cohort

JAMA Neurol. doi:10.1001/jamaneurol.2017.1658

Rebecca F. Gottesman, MD, PhD; Marilyn S. Albert, PhD; Alvaro Alonso, MD, PhD; Laura H. Coker, PhD; Josef Coresh, MD, PhD; Sonia M. Davis, DrPH; Jennifer A. Deal, PhD; Guy M. McKhann, MD; Thomas H. Mosley, PhD; A. Richey Sharrett, MD, DrPH; Andrea L. C. Schneider, MD, PhD; B. Gwen Windham, MD, MHS; Lisa M. Wruck, PhD; David S. Knopman, MD

In 15,744 Black and white adults from 4 U.S. communities, the following midlife risk factors were associated with risk of dementia (independent of each other and demographics/ APOE):

Smoking, HR 1.41 (1.23-1.61)

Diabetes, HR 1.77 (1.53-2.04)

Hypertension, HR 1.39 (1.22-1.59)

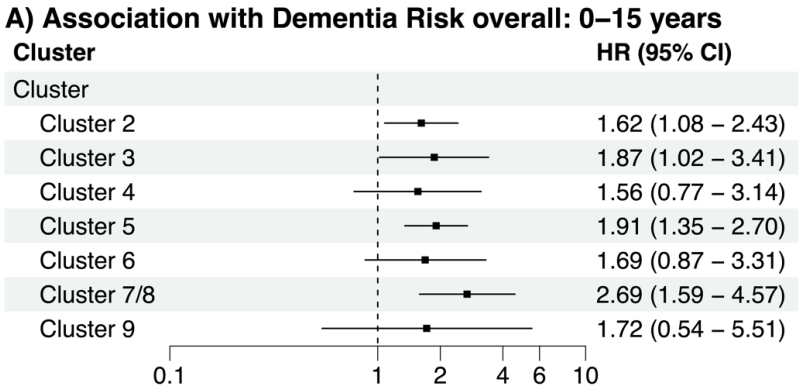
(BMI and total cholesterol were not significantly associated with increased risk)

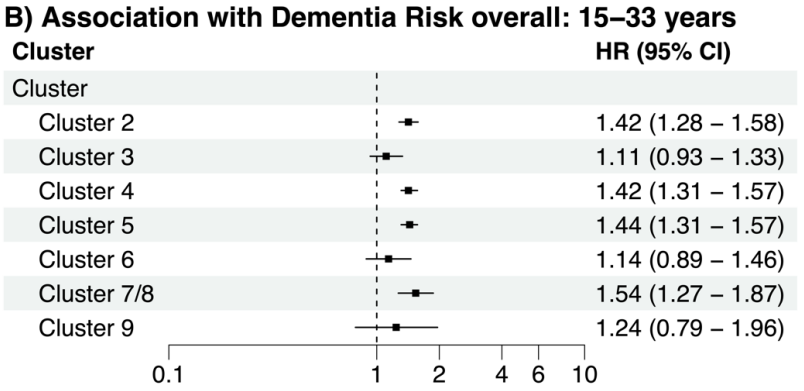
Women were *less* likely to have dementia over follow-up (adjusted HR 0.89, 95 % CI 0.79-0.99), but there was no effect modification of vascular risk factors by sex

Multimorbidity clusters in midlife and late-life dementia risk

Led by Elise Kinyanjui, Marco Egle (in preparation; unpublished)

- Using unsupervised machine-learning cluster analysis, ARIC participants were grouped into clusters based on midlife morbidities/ risk factors:
  - 9 clusters were generated (with 1 having “no defining risk factors”)
  - Cluster 5: obesity, diabetes, hypertension, hypertriglyceridemia; Cluster 7/8: heart disease/ atrial fibrillation, and Cluster 2: smoking were each associated with increased risk of dementia
    - Some clusters were associated more strongly with mortality than dementia, such as renal disease
    - Sex differences in cluster distribution but also in which clusters were associated with dementia: peripheral artery disease (cluster 4) was associated with dementia in men but not women, and heart disease (cluster 7/8) was a stronger risk factor in men than in women (both p-interaction<0.05)



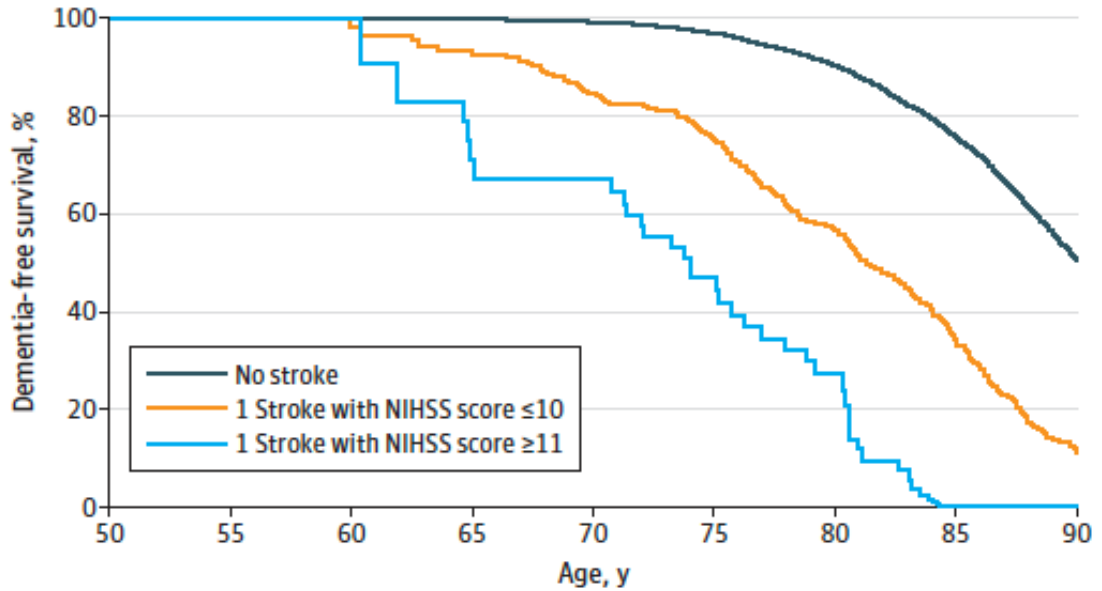


JAMA Neurology | Original Investigation

Association of Ischemic Stroke Incidence, Severity, and Recurrence With Dementia in the Atherosclerosis Risk in Communities Cohort Study

Silvia Koton, PhD, RN; James Russell Pike, MBA; Michelle Johansen, MD, PhD; David S. Knopman, MD; Kamakshi Lakshminarayan, MD, PhD; Thomas Mosley, PhD; Shalom Patole, MD; Wayne D. Rosamond, PhD; Andrea L. C. Schneider, MD, PhD; A. Richey Sharrett, MD, DrPH; Lisa Wruck, PhD; Josef Coresh, MD, PhD; Rebecca F. Gottesman, MD, PhD

Figure 2. Extended Kaplan-Meier Curves of Dementia by National Institutes of Health Stroke Scale (NIHSS) Severity of Incident Ischemic Stroke (N = 15 379)



No. at risk								
No stroke	15 184	14 748	13 907	12 562	10 540	6305	2715	650
1 Stroke with NIHSS score ≤10	14	56	114	195	240	187	108	26
1 Stroke with NIHSS score ≥11	2	10	19	19	19	11	0	0

Dementia risk in ARIC is greater with a larger number and greater severity of strokes (compared to people without stroke)

Event	No. dementia/No. (IR per 100 person-years)	HR (95% CI)		
		Model 1	Model 2	Model 3
Dementia by No. and severity of ischemic stroke events, by NIHSS of most severe stroke event				
1 Stroke, NIHSS ≤10	167/703 (3.28)	1.82 (1.57-2.11)	1.70 (1.46-1.96)	1.73 (1.49-2.00)
1 Stroke, NIHSS ≥11	20/128 (3.30)	3.59 (2.31-5.57)	3.41 (2.19-5.31)	3.47 (2.23-5.40)
≥2 Strokes, all NIHSS ≤10	38/137 (5.73)	3.70 (2.70-5.05)	3.18 (2.32-4.35)	3.48 (2.54-4.76)
≥2 Strokes, at least 1 NIHSS ≥11	12/40 (8.34)	8.44 (4.78-14.88)	7.64 (4.33-13.49)	6.68 (3.77-11.83)

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- What are potential mechanisms linking these risk factors to cognitive decline and dementia?
- What other factors (e.g. genetics, other neurodegenerative disease, lifestyle/ social determinants of health) modify how vascular disease may influence cognitive decline and dementia?

JAMA | Original Investigation

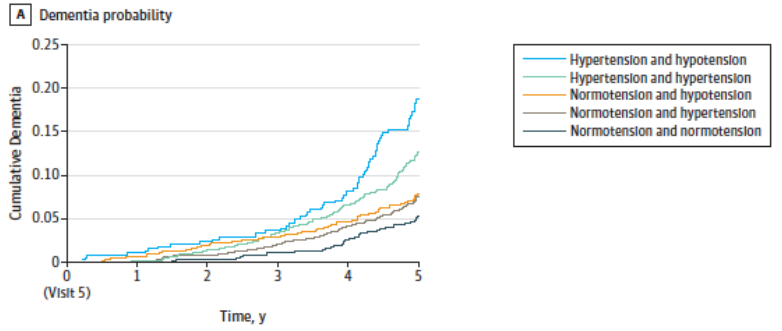
Association of Midlife to Late-Life Blood Pressure Patterns With Incident Dementia

Keenan A. Walker, PhD; A. Richey Sharrett, MD, DrPH; Aozhou Wu, PhD, MHS; Andrea L. C. Schneider, MD, PhD; Marilyn Albert, PhD; Pamela L. Lutsey, PhD, MPH; Karen Bandeen-Roche, PhD; Josef Coresh, MD, PhD; Alden L. Gross, PhD, MHS; B. Gwen Windham, MD, MHS; David S. Knopman, MD; Melinda C. Power, ScD; Andreea M. Rawlings, PhD, MS; Thomas H. Mosley, PhD; Rebecca F. Gottesman, MD, PhD

JAMA. 2019;322(6):535-545. doi:10.1001/jama.2019.10575

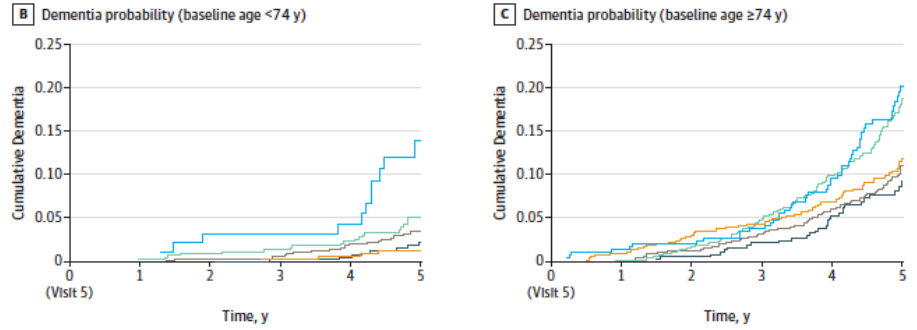
Hypertension followed by hypotension is associated with highest risk of dementia, with most pronounced effect in younger group

Figure 2. Kaplan-Meier Curves for Time to Dementia Onset for Standard Hypertension Definition Blood Pressure Groups



No. at risk, midlife and late life

Normotension and normotension	833	833	831	819	751	377
Normotension and hypertension	1559	1558	1545	1521	1353	709
Normotension and hypotension	927	922	910	892	800	413
Hypertension and hypertension	1030	1028	1015	988	874	439
Hypertension and hypotension	389	385	380	368	320	165

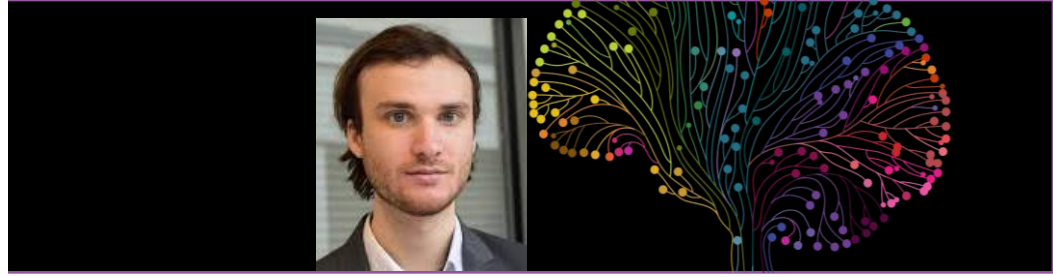


No. at risk, midlife and late life

Normotension and normotension	459	459	459	457	431	227	374	374	372	362	320	150
Normotension and hypertension	715	715	711	708	647	335	844	843	834	813	706	374
Normotension and hypotension	339	339	339	338	315	177	588	583	571	554	485	236
Hypertension and hypertension	446	445	442	439	411	206	584	583	573	549	463	233
Hypertension and hypotension	94	94	91	91	81	40	295	291	289	277	239	125

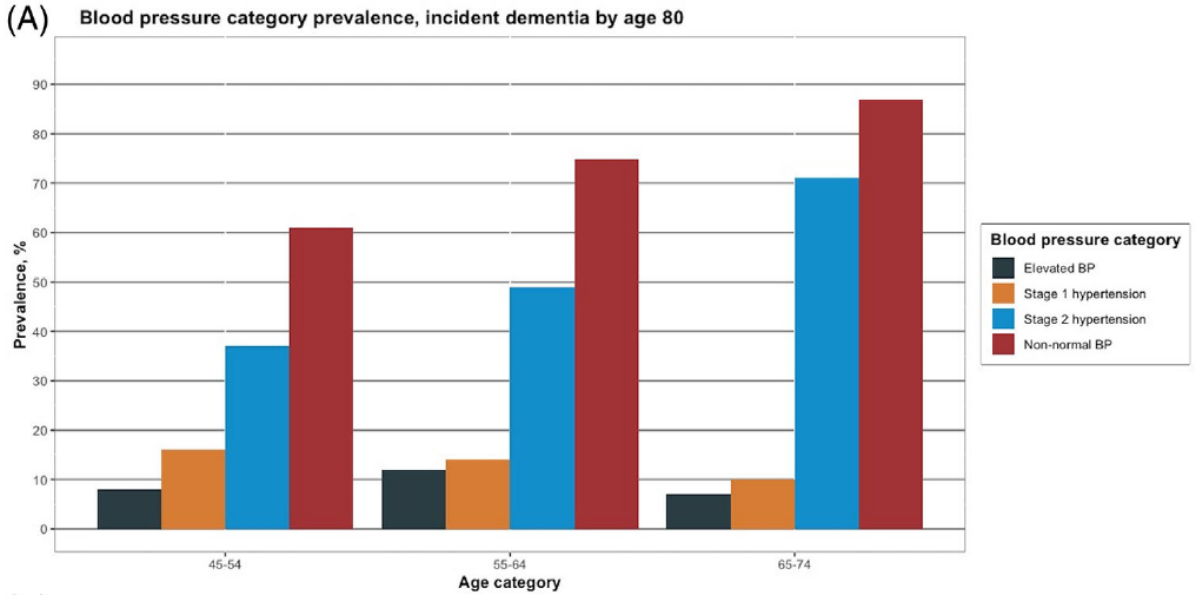
National Institute of Neurological Disorders and Stroke

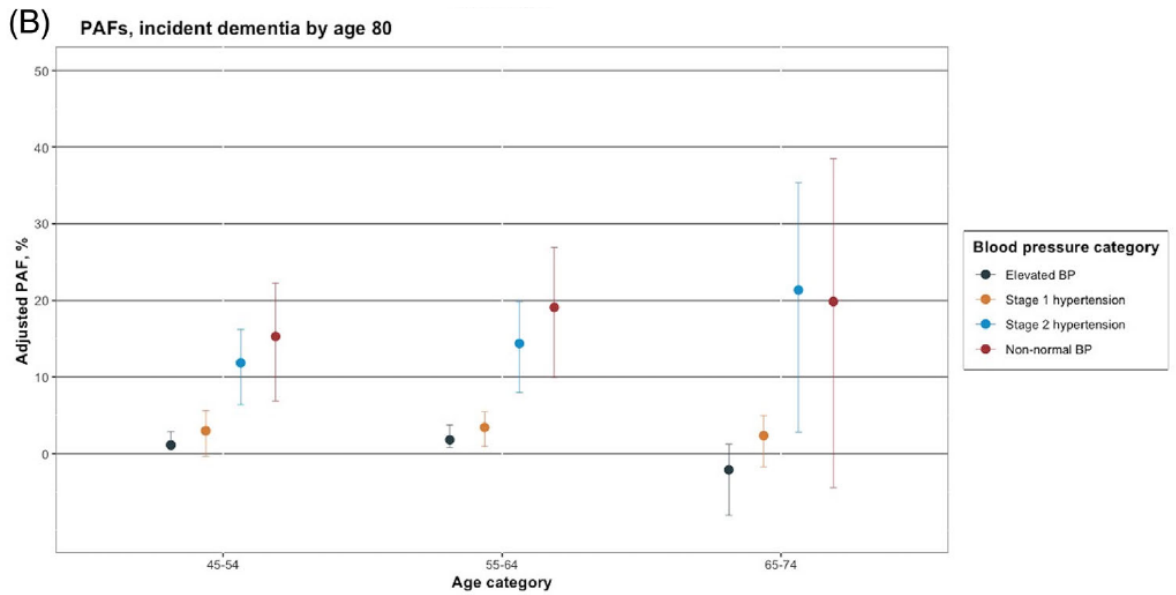
Dementia occurring over a 32-year follow-up attributable to hypertension observed at different ages: Implications for dementia prevention



Alzheimer's Dement. 2023;19:3435–3447.

Jason R. Smith[1,2] | A. Richey Sharrett[1] | James Russel Pike[3] | Rebecca F. Gottesman[4] | David S. Knopman[5] | Mark Lee[6] | Pamela L. Lutsey[7] | Priya Palta[8] | B. Gwen Windham[9] | Josef Coresh[1] | Jennifer A. Deal[1,2]





PAF of dementia by age 80 is:

15.3% for non-normal BP at ages 45-54

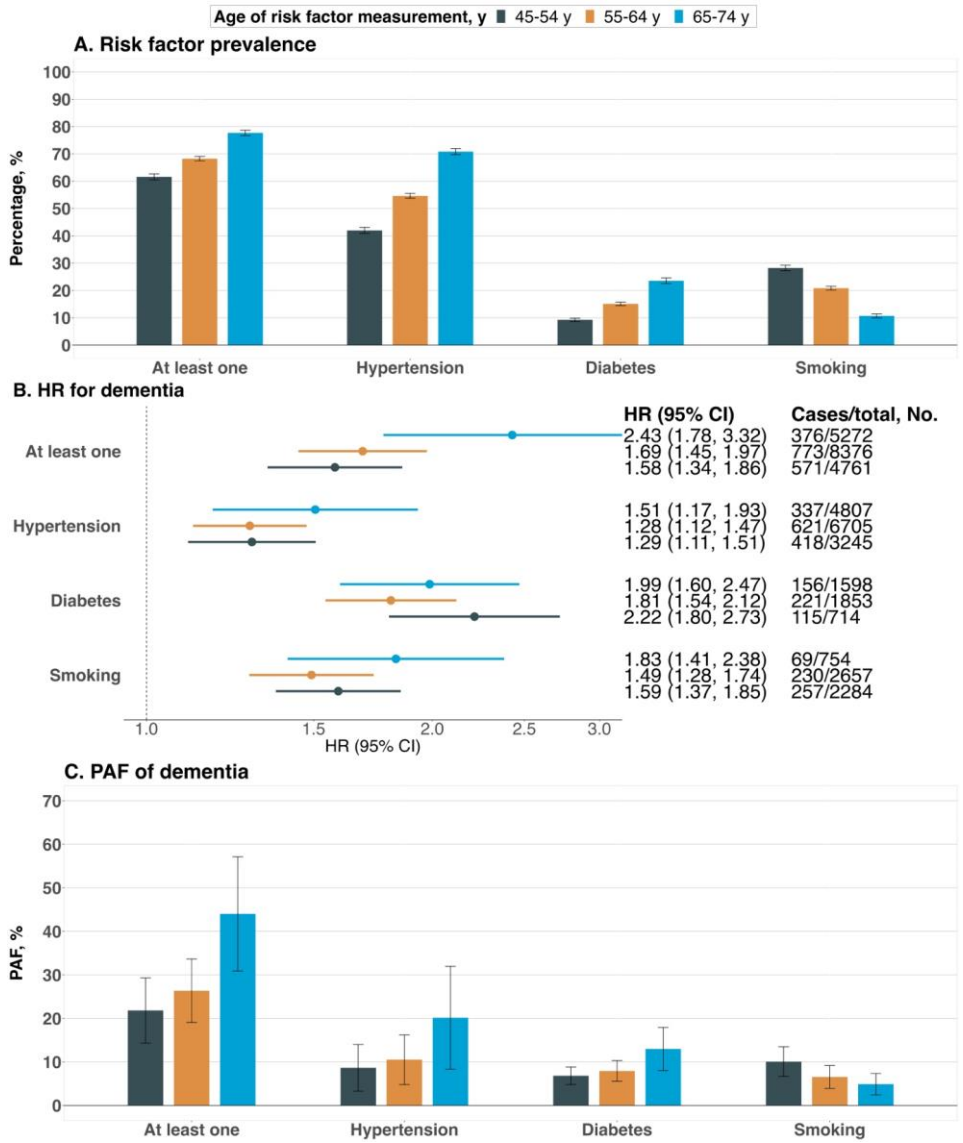
19.1% for non-normal BP at ages 55-64

19.9% for non-normal BP at ages 65-74

Not significant PAF of dementia by age 90 for age 75+

National Institute of Neurological Disorders and Stroke

Population attributable risks for midlife through late life RF's (Jason Smith, Hopkins): *Unpublished*



- Using ARIC data, population attributable risks for incident dementia *by age 80* were calculated for vascular risk factors occurring in midlife/ late midlife/ early late-life
  - Higher PAF for later life RF's because of higher prevalence of those risk factors generally
  - 22-44% of incident dementia by age 80 explained by having at least one vascular risk factor by age 74

The contributions of having at least one vascular risk factor in midlife or late-life on incident dementia by age 80, stratified by sex

	At least one vascular risk factor[a], age of measurement					
	45-54 years		55-64 years		65-74 years	
	Male	Female	Male	Female	Male	Female
Dementia cases/total exposed, No.	261/2097	310/2664	323/3839	450/4537	162/2353	214/2919
Risk factor prevalence, % (95% CI)	64.8 (63.1, 66.4)	59.3 (57.8, 60.7)	68.8 (67.6, 70.1)	67.7 (66.6, 68.9)	77.8 (76.4, 79.3)	77.6 (76.2, 78.9)
HR for dementia (95% CI)[b]	1.81 (1.40, 2.34)	1.44 (1.16, 1.78)	1.53 (1.21, 1.92)	1.80 (1.46, 2.22)	2.03 (1.31, 3.13)	2.82 (1.80, 4.43)
PAF of dementia, % (95% CI)[c]	28.0 (16.5, 39.5)	17.2 (7.4, 27.0)	21.2 (10.2, 32.3)	29.2 (19.6, 38.9)	34.8 (15.5, 54.0)	51.3 (33.7, 69.0)

Age of Diabetes Diagnosis and Lifetime Risk of Dementia: The Atherosclerosis Risk in Communities (ARIC) Study

Jiaqi Hu,[1,2] James R. Pike,[3] Pamela L. Lutsey,[4] A. Richey Sharrett,[1,2] Lynne E. Wagenknecht,[5] Timothy M. Hughes,[6] Jesse C. Seegmiller,[7] Rebecca F. Gottesman,[8] Thomas H. Mosley,[9] Elizabeth Selvin,[1,2] Michael Fang,[1,2] and Josef Coresh[3,10]

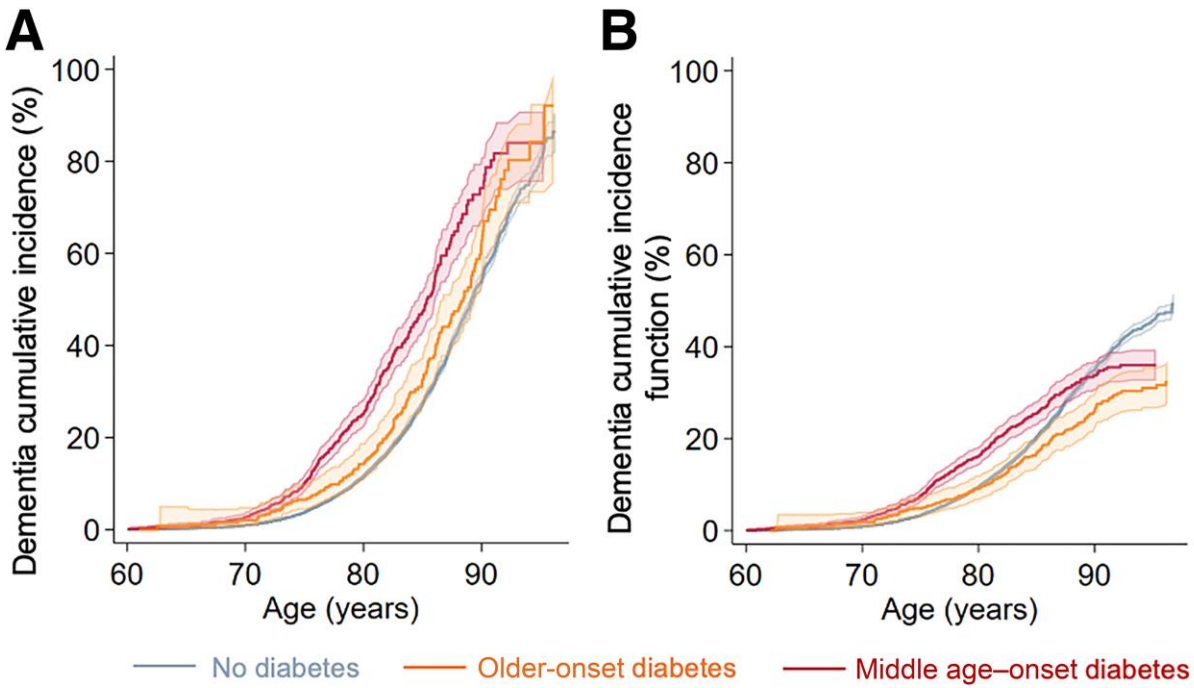
Diabetes Care 2024;47:1576–1583 | https://doi.org/10.2337/dc24-0203

In ARIC, individuals diagnosed with diabetes in midlife:

-had a higher lifetime risk of dementia than those with late-life diabetes onset

-developed dementia 4 years earlier than those without diabetes and 1 year earlier than those with older-onset diabetes

-had higher cumulative incidence of dementia by age 80 but lower lifetime risk than those with no diabetes due to shorter survival



Dementia cumulative incidence from Kaplan-Meier (A) and CIF (B) from competing risk analysis, by age of diabetes diagnosis. Shaded areas indicate the 95% CI.

nature medicine

Brief Communication

https://doi.org/10.1038/s41591-024-03340-9

Lifetime risk and projected burden of dementia

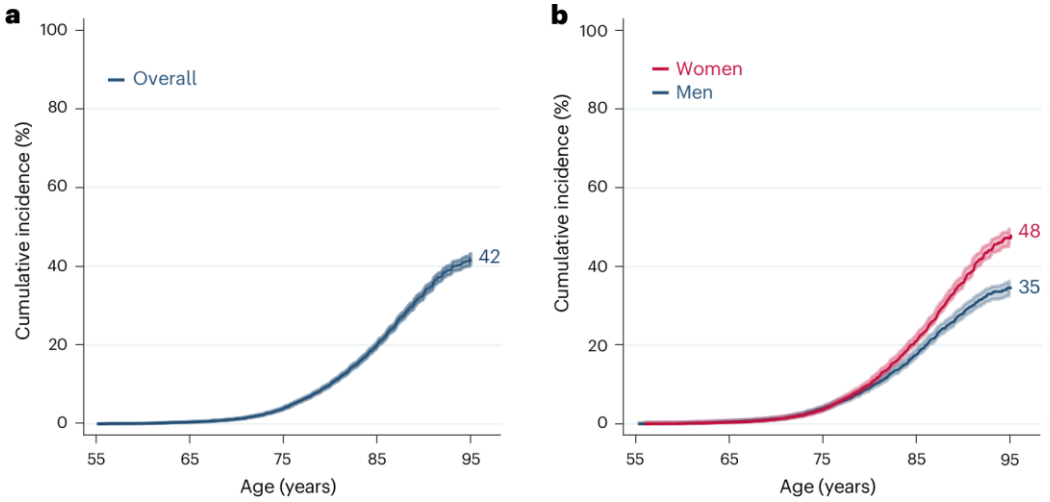
Received: 15 May 2024

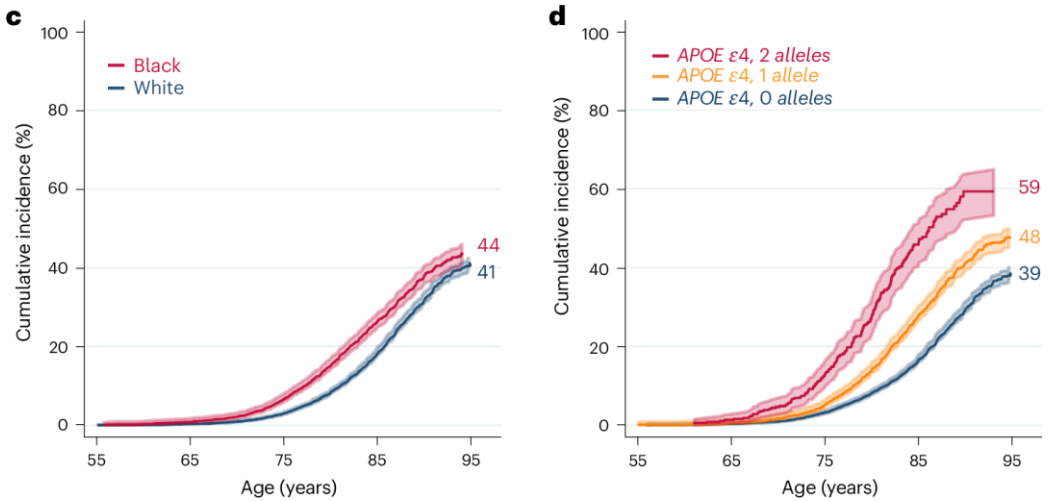
Accepted: 3 October 2024

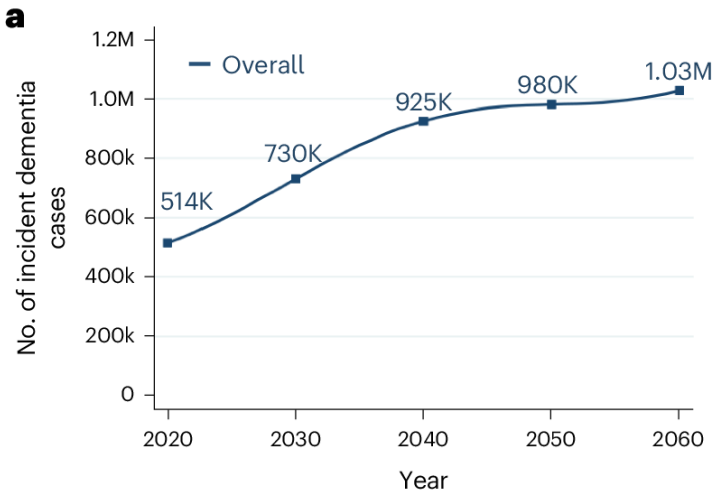
Published online: 13 January 2025

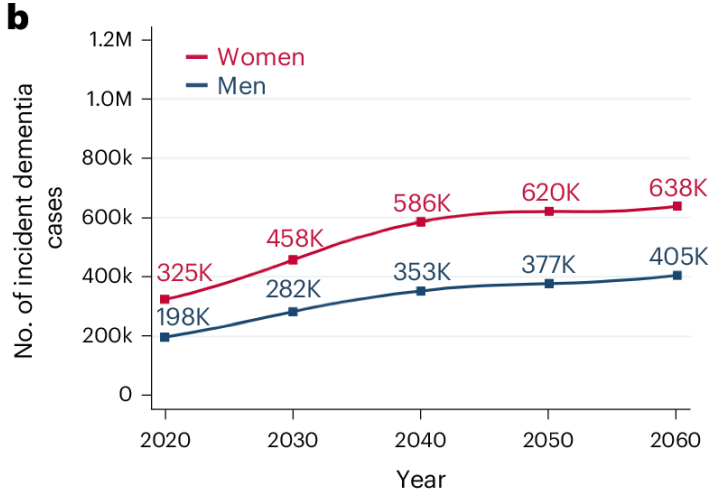
Michael Fang[1], Jiaqi Hu[1,2], Jordan Weiss[3], David S. Knopman[4], Marilyn Albert[5], B. Gwen Windham[6], Keenan A. Walker[7], A. Richey Sharrett[1], Rebecca F. Gottesman[8], Pamela L. Lutsey[9], Thomas Mosley[6], Elizabeth Selvin[1] & Josef Coresh[3,10]

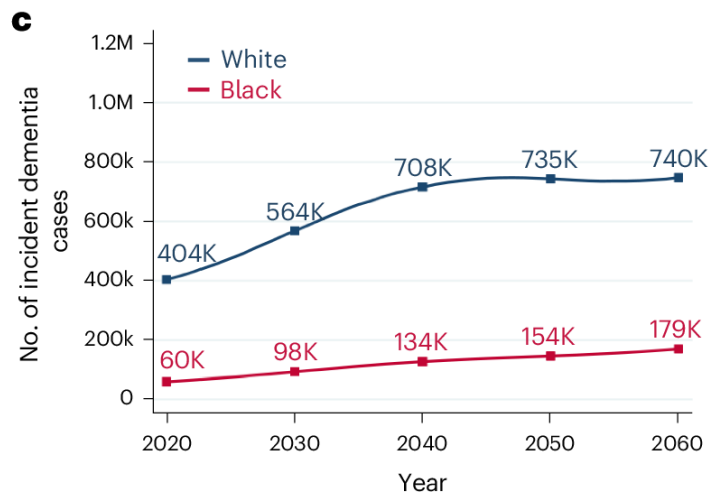
Used data from ARIC to estimate lifetime risk of dementia from age 55 to 95, with mortality as competing event; then applied these to US census projections.

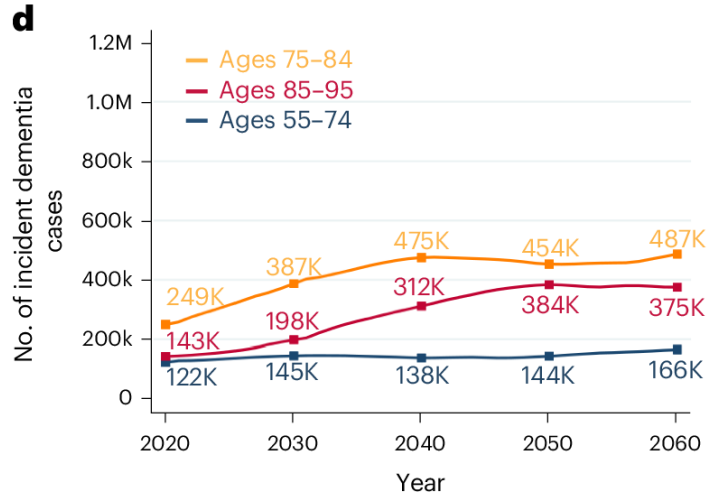












Identifying potential targets for prevention and treatment over the life course

- What are modifiable risk factors for cognitive decline and dementia?
- When are modifiable risk factors most important (and thus potentially intervened upon)?
- **What are potential mechanisms linking these risk factors to cognitive decline and dementia?**
- What other factors (e.g. genetics, other neurodegenerative disease, lifestyle/ social determinants of health) modify how vascular disease may influence cognitive decline and dementia?

Possible mechanisms of a vascular impact on cognitive impairment and dementia

- Vascular risk factors, especially in midlife, lead to vascular changes in the brain (clinical *or* subclinical)
- Midlife vascular risk factors lead to other brain structural changes, which may or may not be via vascular brain changes
- Midlife vascular risk factors might directly impact Alzheimer's neuropathologic changes, which themselves (or in combination with brain vascular changes) can impact cognition

Risk factors

Hypertension

Diabetes

Smoking

Hyperlipidemia

Obesity

Poor diet

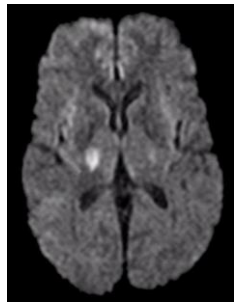
Inactivity

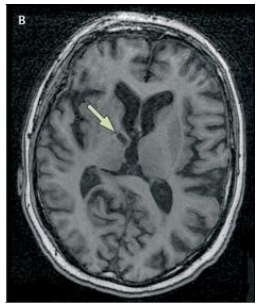
Inflammation

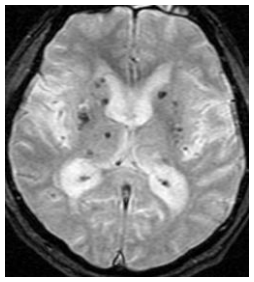
Genetic risk

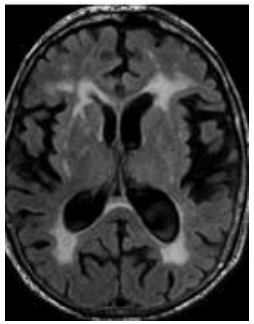
Other factors

Small vessel disease

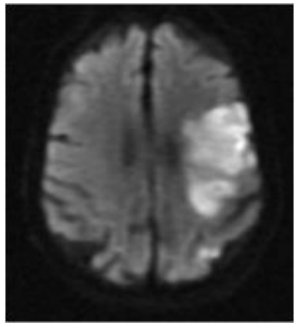




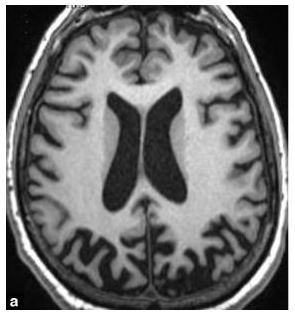




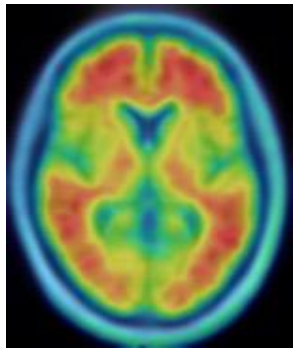
stroke



atrophy

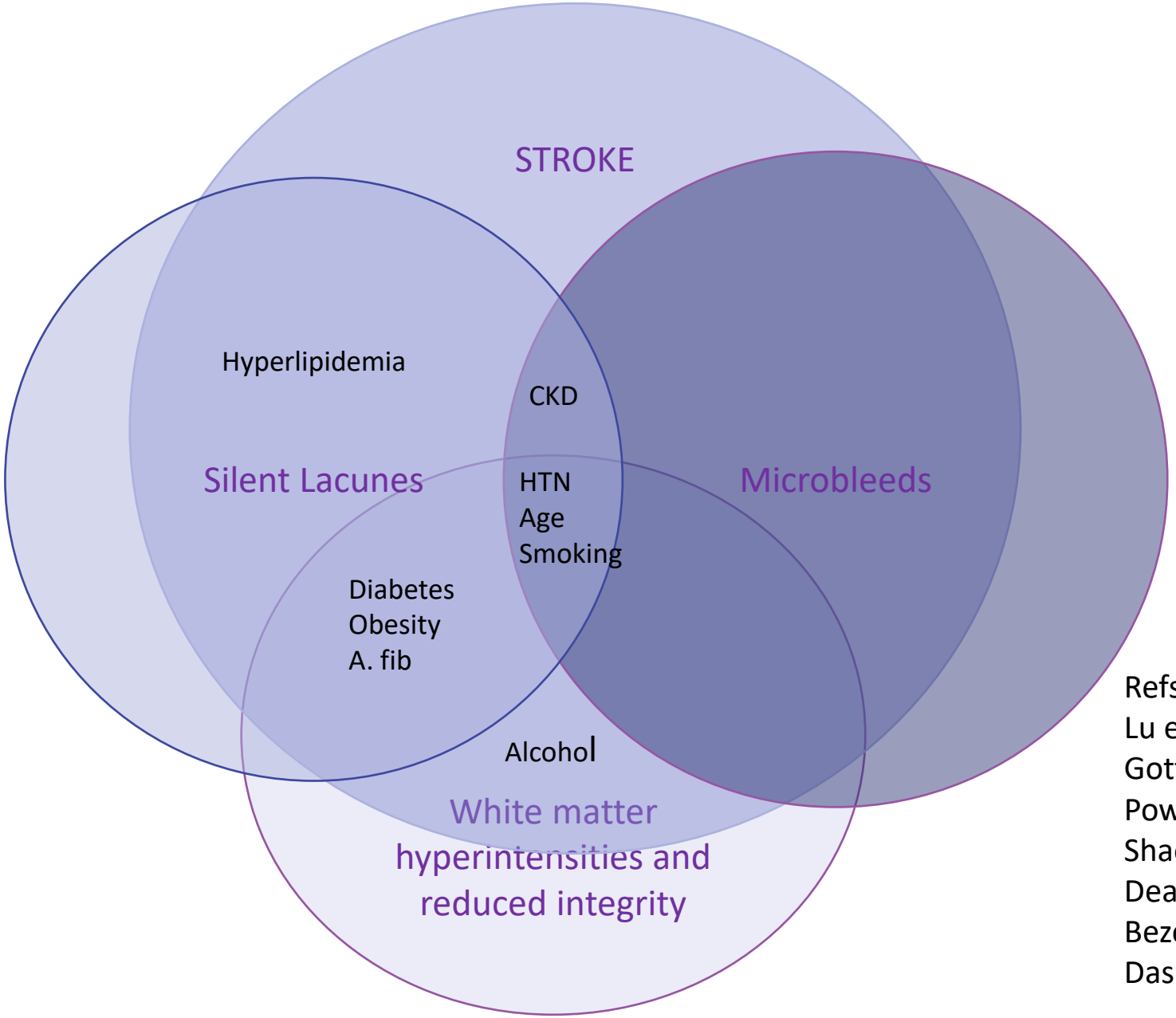


changes in AD biomarkers (amyloid)



Dementia

Stroke and small vessel disease: shared risk factors



Note: this is NOT comprehensive!

Refs:

Lu et al., Neurology 2021;
Gottesman et al., Stroke 2010;
Power et al., Neurology 2015;
Shao et al., Stroke 2019;
Dearborn et al., Stroke 2015;
Bezerra et al., Neurology 2012;
Das et al., J Stroke 2019

Annals of Internal Medicine ORIGINAL RESEARCH

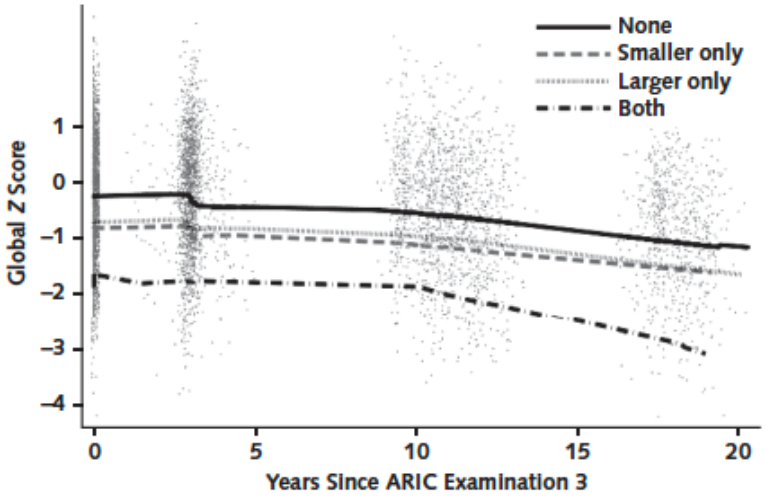
Midlife Smaller and Larger Infarctions, White Matter Hyperintensities, and 20-Year Cognitive Decline

A Cohort Study

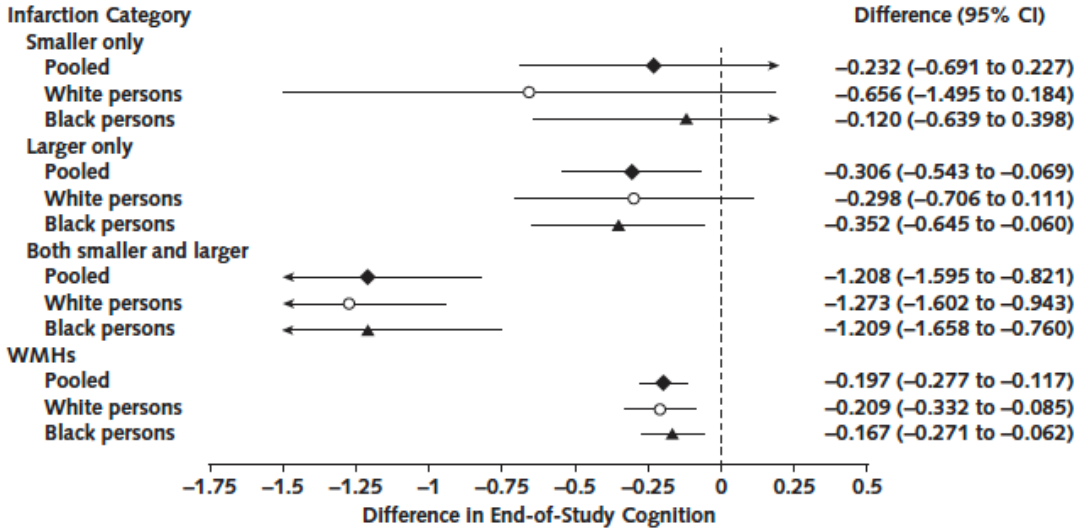
B. Gwen Windham, MD, MHS; Michael E. Griswold, PhD; Steven R. Wilkening, MD, MS; Dan Su, MS; Jonathan Tingle, BS; Laura H. Coker, PhD; David Knopman, MD; Rebecca F. Gottesman, MD, PhD; Dean Shibata, MD; and Thomas H. Mosley, PhD

Ann Intern Med. 2019;171:389-396. doi:10.7326/M18-0295

Figure 1. Twenty-year global cognitive change, by infarction category.



ARIC = Atherosclerosis Risk in Communities.



Silent lacunar infarcts, “small” infarcts (enlarged perivascular spaces) and WMH were associated with steeper cognitive decline over 20 years

NIH National Institute of Neurological Disorders and Stroke

Small vessel disease's effect on cognition is partially mediated through atrophy

Vascular Imaging Abnormalities and Cognition

Mediation by Cortical Volume in Nondemented Individuals: Atherosclerosis Risk in Communities-Neurocognitive Study

David S. Knopman, MD; Michael E. Griswold, PhD; Seth T. Lirette, MS; Rebecca F. Gottesman, MD, PhD; Kejal Kantarci, MD; A. Richey Sharrett, MD, DrPH; Clifford R. Jack Jr, MD; Jonathan Graff-Radford, MD; Andrea L.C. Schneider, PhD, MD; B. Gwen Windham, MD; Laura H. Coker, PhD; Marilyn S. Albert, PhD; Thomas H. Mosley Jr, PhD; the ARIC Neurocognitive Investigators*

Stroke. 2015;46:433-440.

WMH and infarcts were associated with psychomotor speed/ executive function *BUT these associations were attenuated by inclusion of posterior cortical volumes in the models*, suggesting some mediation by atrophy/ volume loss

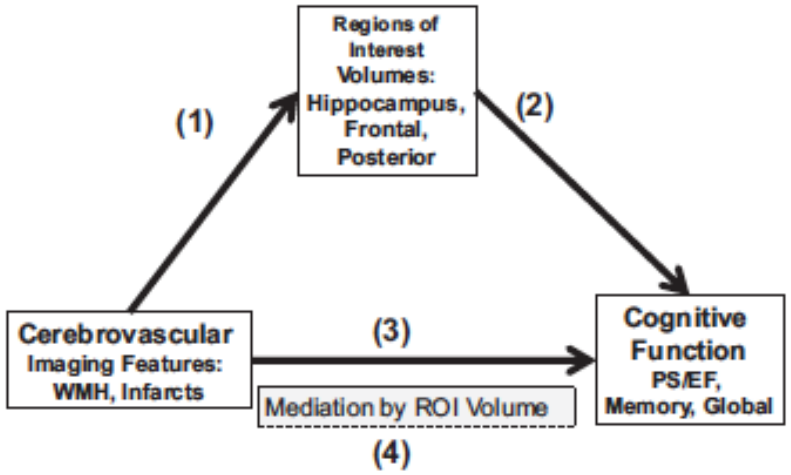


Figure 2. Analysis model for mediation in Atherosclerosis Risk in Communities neurocognitive study. With strong mediating influences, pathways (1) and (2) should be present, and the apparent pathway (3) should be attenuated when additionally adjusting for the potential mediator, as in pathway (4). PS/EF indicates psychomotor speed/executive function; ROI, region of interest; and WMH, white matter hyperintensities.

JAMA | Original Investigation

Association Between Midlife Vascular Risk Factors and Estimated Brain Amyloid Deposition

JAMA. 2017;317(14):1443-1450.

Rebecca F. Gottesman, MD, PhD; Andrea L. C. Schneider, MD, PhD; Yun Zhou, PhD; Josef Coresh, MD, PhD; Edward Green, MD; Naresh Gupta, MD; David S. Knopman, MD; Akiva Mintz, MD; Arman Rahmim, PhD; A. Richey Sharrett, MD, DrPH; Lynne E. Wagenknecht, DrPH; Dean F. Wong, MD, PhD; Thomas H. Mosley, PhD

Table 2. Adjusted Odds Ratios for the Association of Midlife and Late-Life Vascular Risk Factors With Global Cortex SUVR >1.2 (N = 322)

	Midlife (Study Visit 1, 1987-1989)			Late Life (Study Visit 5, 2011-2013)		
Risk Factors	No. With Vascular Risk Factor and SUVR >1.2/Total No. With Vascular Risk Factor (%)	No. Without Vascular Risk Factor and SUVR >1.2/Total No. Without Vascular Risk Factor (%)	Adjusted OR (95% CI)[a]	No. With Vascular Risk Factor and SUVR >1.2/Total No. With Vascular Risk Factor (%)	No. Without Vascular Risk Factor and SUVR >1.2/Total No. Without Vascular Risk Factor (%)	Adjusted OR (95% CI)[a]
Body mass index ≥30[b]	54/83 (65.1)	110/239 (46.0)	2.06 (1.16-3.65)	66/121 (54.6)	98/201 (48.8)	1.44 (0.85-2.44)
Current smoking	30/55 (54.6)	134/267 (50.2)	1.15 (0.61-2.19)	9/16 (56.3)	155/306 (50.7)	1.53 (0.50-4.62)
Hypertension	55/95 (57.9)	109/227 (48.0)	1.30 (0.75-2.28)	125/230 (54.4)	39/92 (42.4)	1.29 (0.74-2.26)
Diabetes	10/20 (50.0)	154/302 (51.0)	1.06 (0.39-2.86)	68/130 (52.3)	96/192 (50.0)	1.06 (0.65-1.74)
Total cholesterol ≥200 mg/dL	101/180 (56.1)	63/142 (44.4)	1.33 (0.82-2.19)	54/94 (57.5)	110/228 (48.3)	1.17 (0.67-2.05)

Relationships between number of risk factors and brain amyloid were strongest from midlife

Figure 1. Adjusted Odds Ratios for Global Cortex Florbetapir SUVRs >1.2 by Number of Vascular Risk Factors, Midlife Through Late Life

No. of Risk Factors by Study Visit	No. With Elevated SUVR/Total No. (%)	Adjusted Odds Ratio (95% CI)
Visit 1 (1987-1989)		
≥2	82/134 (61.2)	2.88 (1.46-5.69)
1	62/123 (50.4)	1.88 (0.95-3.73)
0	20/65 (30.8)	1 [Reference]
Visit 2 (1990-1992)		
≥2	80/137 (58.4)	2.24 (1.19-4.23)
1	57/108 (52.8)	1.88 (0.97-3.62)
0	27/77 (35.1)	1 [Reference]
Visit 3 (1993-1995)		
≥2	83/146 (56.9)	2.18 (1.12-4.26)
1	60/111 (54.1)	1.98 (1.00-3.92)
0	21/65 (32.3)	1 [Reference]
Visit 4 (1996-1998)		
≥2	93/153 (60.8)	1.98 (1.01-3.89)
1	47/111 (42.3)	1.07 (0.53-2.14)
0	24/58 (41.4)	1 [Reference]
Visit 5 (2011-2013)		
≥2	114/205 (55.6)	1.66 (0.75-3.69)
1	37/82 (45.1)	1.02 (0.43-2.43)
0	13/35 (37.1)	1 [Reference]

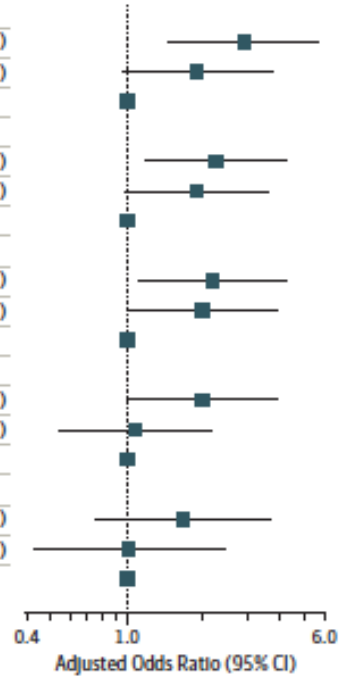


Table 3. Adjusted Odds Ratios for the Association of Midlife and Late-Life Number of Vascular Risk Factors With Global Cortex SUVR >1.2 Overall and Stratified by *APOE* ε4 Genotype (N = 322)

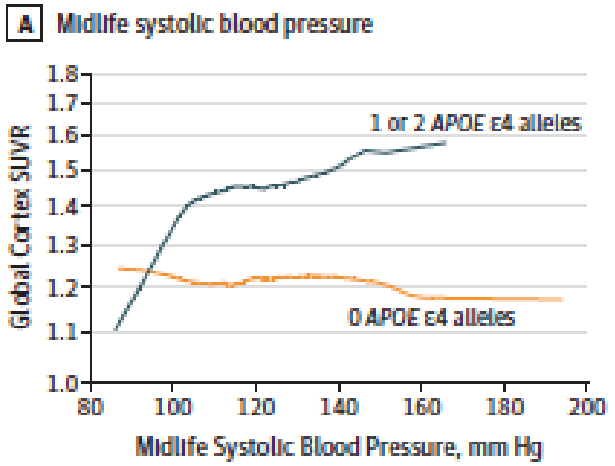
	Overall (n = 322)		0 *APOE* ε4 Alleles (n = 220)		1 or 2 *APOE* ε4 Alleles (n = 100)	
Risk Factors[a]	No. With SUVR >1.2/Total No. (%)	Adjusted OR (95% CI)[b]	No. With SUVR >1.2/Total No. (%)	Adjusted OR (95% CI)[b]	No. With SUVR >1.2/Total No. (%)	Adjusted OR (95% CI)[b]
Midlife (Study Visit 1, 1987-1989)						
Vascular risk factors						
0	20/65 (30.8)	1 [Reference]	14/47 (29.8)	1 [Reference]	6/18 (33.3)	1 [Reference]
1	62/123 (50.4)	1.88 (0.95-3.73)	37/85 (43.5)	1.36 (0.61-3.05)	25/38 (65.8)	3.10 (0.84-11.50)
≥2	82/134 (61.2)	2.88 (1.46-5.69)	45/90 (50.0)	1.86 (0.83-4.14)	37/44 (84.1)	9.15 (2.27-36.89)
Late life (Study Visit 5, 2011-2013)						
Vascular risk factors						
0	13/35 (37.1)	1 [Reference]	6/23 (26.1)	1 [Reference]	7/12 (58.3)	1 [Reference]
1	37/82 (45.1)	1.02 (0.43-2.43)	16/50 (32.0)	1.38 (0.43-4.39)	21/32 (65.6)	0.56 (0.12-2.67)
≥2	114/205 (55.6)	1.66 (0.75-3.69)	74/149 (49.7)	2.21 (0.78-6.26)	40/56 (71.4)	1.03 (0.25-4.29)

Abbreviations: OR, odd ratio; SUVR, standardized uptake value ratio.

[a] Vascular risk factors included body mass index ≥30, current smoking, hypertension, diabetes, and total cholesterol ≥200 mg/dL.

[b] Models are adjusted for age (at visit 5, 2011-2013), sex, race, education level, and *APOE* ε4 genotype.

Adjusted odds ratios (with 95% CIs as error bars) are shown for number of vascular risk factors for visits 1 through 5 for standardized uptake value ratios (SUVRs) >1.2. Models are adjusted for age (at visit 5, 2011-2013), sex, race, education level, and *APOE* ε4 genotype. Vascular risk factors include body mass index ≥30, current smoking, hypertension, diabetes, and total cholesterol level ≥200 mg/dL.



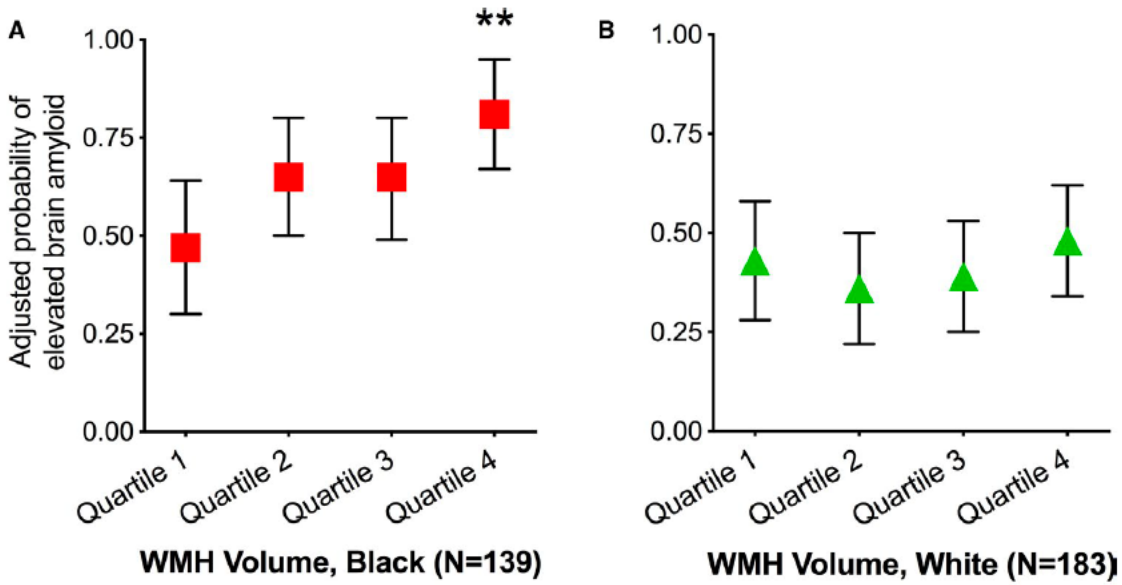
WMH and Alzheimer's disease-specific neuropathology

Journal of the American Heart Association

BRIEF COMMUNICATION

Brain White Matter Structure and Amyloid Deposition in Black and White Older Adults: The ARIC-PET Study

Keenan A. Walker, PhD; Noah Silverstein, MD; Yun Zhou, PhD; Timothy M. Hughes, PhD; Clifford R. Jack Jr, MD; David S. Knopman, MD; A. Richey Sharrett, MD, DrPH; Dean F. Wong, MD; Thomas H. Mosley, PhD; Rebecca F. Gottesman, MD, PhD



Cross-sectionally, elevated white matter hyperintensities were associated with elevated odds of PET-detected amyloid (adjusted OR 1.37, 95% CI 1.03-1.83, per SD increase in WMH volume); there was a suggestion of a stronger association in Black participants.

JAMA | Original Investigation

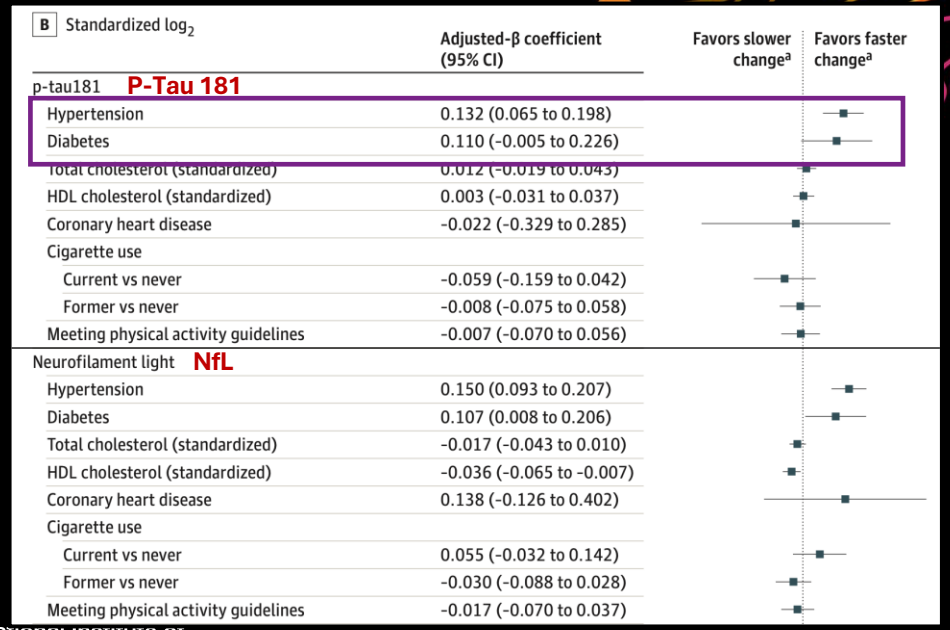
Changes in Alzheimer Disease Blood Biomarkers and Associations With Incident All-Cause Dementia

The Atherosclerosis Risk in Communities Study

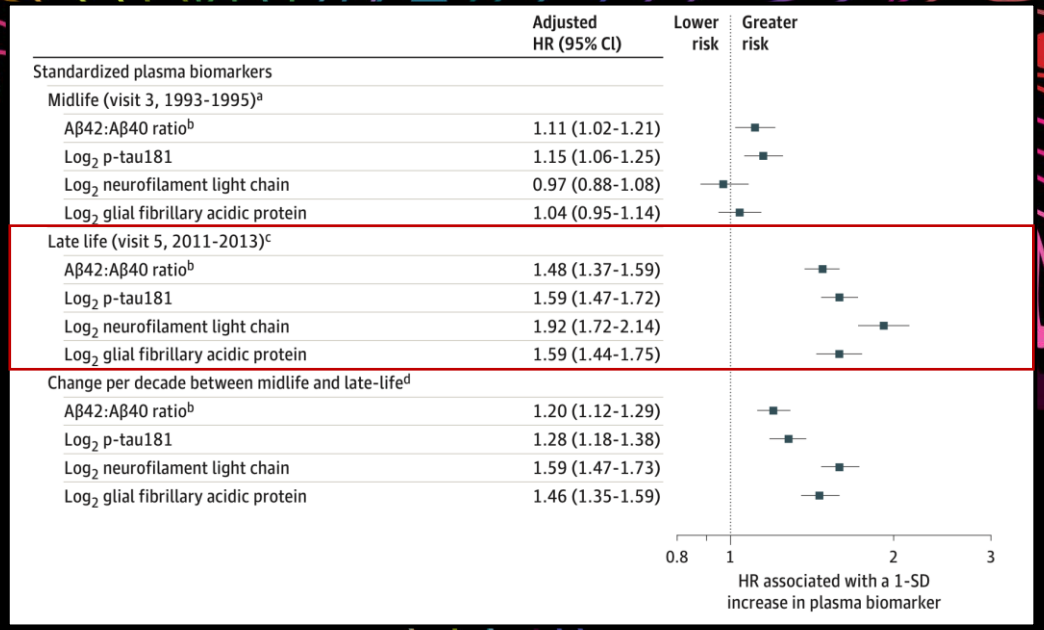
Yifei Lu, PhD; James Russell Pike, MBA; Jinyu Chen, MS; Keenan A. Walker, PhD; Kevin J. Sullivan, PhD; Bharat Thyagarajan, MD, PhD; Michelle M. Mielke, PhD; Pamela L. Lutsey, PhD, MPH; David Knopman, MD; Rebecca F. Gottesman, MD, PhD; A. Richey Sharrett, MD, DrPH; Josef Coresh, MD, PhD; Thomas H. Mosley, PhD; Priya Palta, PhD

Yifei Lu James Pike Priya Palta

Differences in Biomarker Rate of Change from Midlife to Late-Life



B Standardized log_2	Adjusted-β coefficient (95% CI)	Favors slower change[a]	Favors faster change[a]
p-tau181 **P-Tau 181**			
Hypertension	0.132 (0.065 to 0.198)		
Diabetes	0.110 (-0.005 to 0.226)		
Total cholesterol (standardized)	0.012 (-0.019 to 0.043)		
HDL cholesterol (standardized)	0.003 (-0.031 to 0.037)		
Coronary heart disease	-0.022 (-0.329 to 0.285)		
Cigarette use			
Current vs never	-0.059 (-0.159 to 0.042)		
Former vs never	-0.008 (-0.075 to 0.058)		
Meeting physical activity guidelines	-0.007 (-0.070 to 0.056)		
Neurofilament light **NfL**			
Hypertension	0.150 (0.093 to 0.207)		
Diabetes	0.107 (0.008 to 0.206)		
Total cholesterol (standardized)	-0.017 (-0.043 to 0.010)		
HDL cholesterol (standardized)	-0.036 (-0.065 to -0.007)		
Coronary heart disease	0.138 (-0.126 to 0.402)		
Cigarette use			
Current vs never	0.055 (-0.032 to 0.142)		
Former vs never	-0.030 (-0.088 to 0.028)		
Meeting physical activity guidelines	-0.017 (-0.070 to 0.037)		



	Adjusted HR (95% CI)	Lower risk	Greater risk
Standardized plasma biomarkers			
Midlife (visit 3, 1993-1995)[a]			
Aβ42:Aβ40 ratio[b]	1.11 (1.02-1.21)		
Log_2 p-tau181	1.15 (1.06-1.25)		
Log_2 neurofilament light chain	0.97 (0.88-1.08)		
Log_2 glial fibrillary acidic protein	1.04 (0.95-1.14)		
Late life (visit 5, 2011-2013)[c]			
Aβ42:Aβ40 ratio[b]	1.48 (1.37-1.59)		
Log_2 p-tau181	1.59 (1.47-1.72)		
Log_2 neurofilament light chain	1.92 (1.72-2.14)		
Log_2 glial fibrillary acidic protein	1.59 (1.44-1.75)		
Change per decade between midlife and late-life[d]			
Aβ42:Aβ40 ratio[b]	1.20 (1.12-1.29)		
Log_2 p-tau181	1.28 (1.18-1.38)		
Log_2 neurofilament light chain	1.59 (1.47-1.73)		
Log_2 glial fibrillary acidic protein	1.46 (1.35-1.59)		

NIH National Institute of Neurological Disorders and Stroke

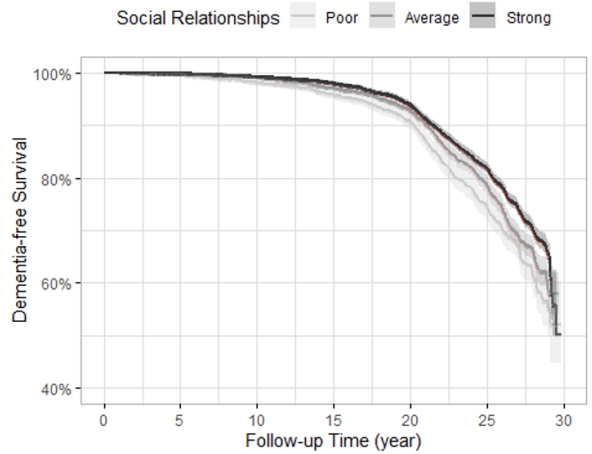
Plasma Biomarkers and Incident Dementia in Late-Life

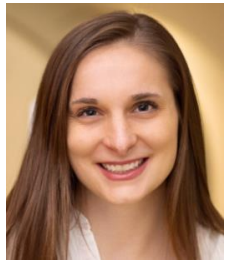
Identifying potential targets for prevention and treatment over the life course

- What are modifiable risk factors for cognitive decline and dementia?
- When are modifiable risk factors most important (and thus potentially intervened upon)?
- What are potential mechanisms linking these risk factors to cognitive decline and dementia?
- **What other factors (e.g. genetics, other neurodegenerative disease, lifestyle/ social determinants of health) modify how vascular disease may influence cognitive decline and dementia?**

Social factors as modifiers of risk

- Social support: In ARIC, **better social engagement in midlife** (*less social isolation and more social support*) associated with **lower dementia rates** (**HR 0.76**, 95% CI 0.67-0.85 for strong social relationships, **HR 0.84**, 95% CI 0.74-0.95 for average (vs poor social relationships), independent of genetics and not modified by genetic risk (under revision, Renee Groechel et al)
- Jobs with higher "information processing" are associated with lower dementia rates (Then et al., Alzheimers Dement 2017)





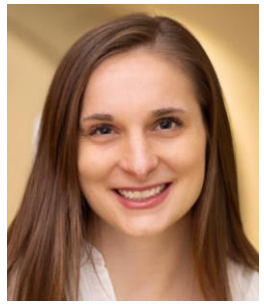
National Institute of Neurological Disorders and Stroke

Stroke

CLINICAL AND POPULATION SCIENCES

Psychosocial Health and the Association Between Cerebral Small Vessel Disease Markers With Dementia: The ARIC Study

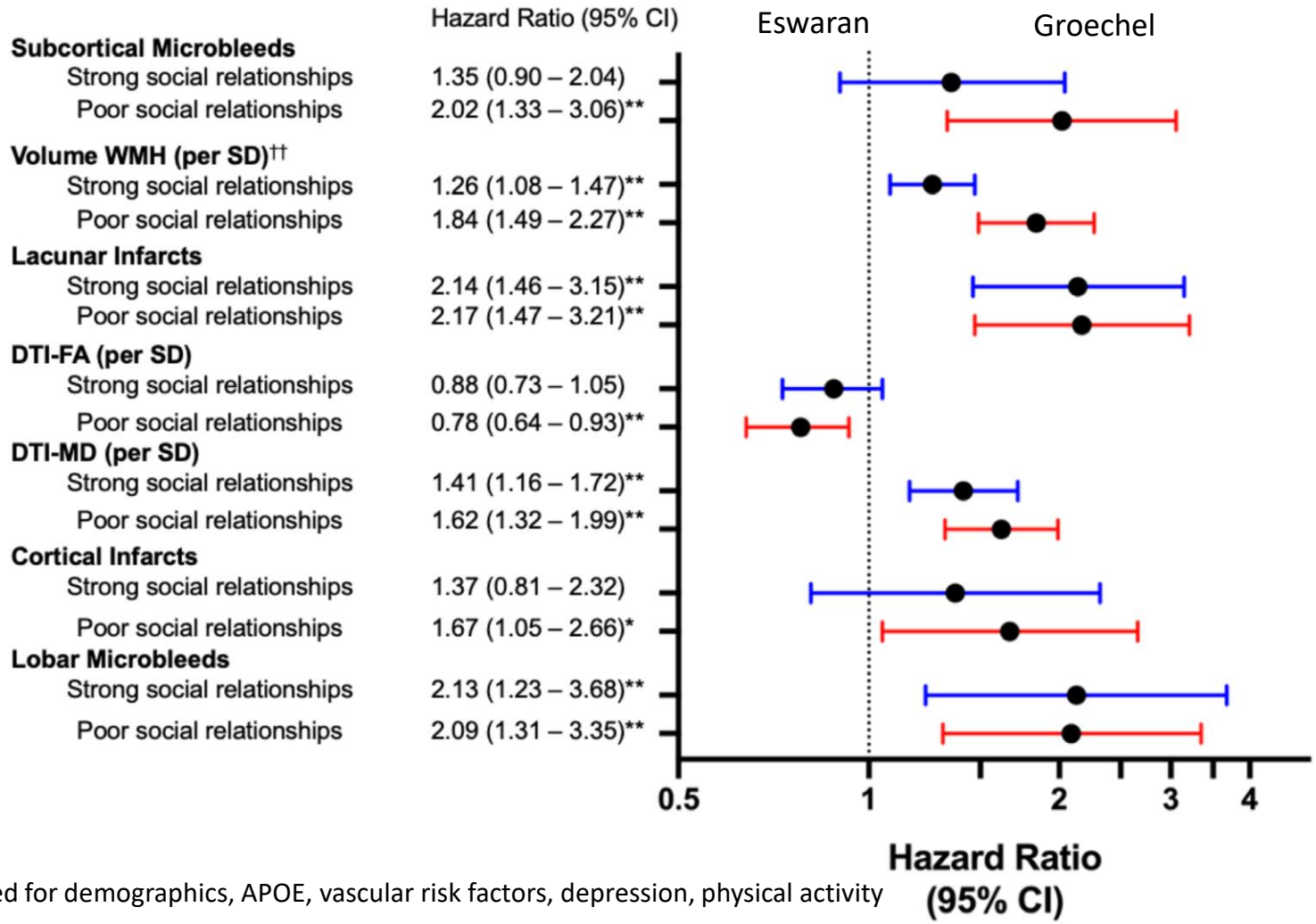
Surabhee Eswaran; David S. Knopman, MD; Silvia Koton, RN, PhD; Anna M. Kucharska-Newton, PhD; Albert C. Liu, MD, MPH; Chelsea Liu, PhD; Pamela L. Lutsey, PhD, MPH; Thomas H. Mosley, Jr, PhD; Priya Palta, PhD, MHS; A. Richey Sharrett, MD, DrPH; Kevin J. Sullivan, PhD; Keenan A. Walker, PhD; Rebecca F. Gottesman, MD, PhD; Renee C. Groechel, PhD



Surabhee Eswaran

Renee Groechel

- ARIC participants underwent two social engagement measures in late midlife (ARIC visit 2)
  - Lubben Social Network Scale (social isolation), Interpersonal support evaluation list short form (social support)
- The association between V5 small vessel disease imaging markers (infarcts, microbleeds, WMH, and DTI (FA/ MD) and dementia was evaluated using Cox proportional hazards models, with effect modification by social engagement category evaluated

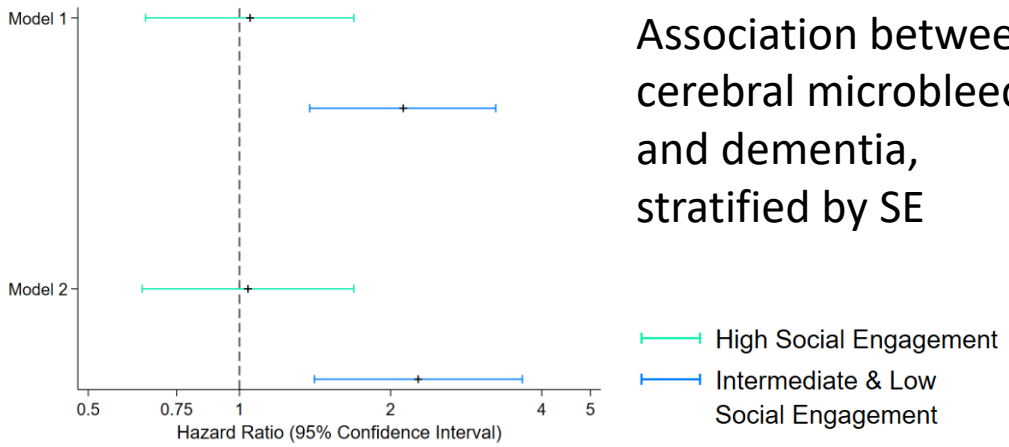


*adjusted for demographics, APOE, vascular risk factors, depression, physical activity

Midlife Social engagement (SE) modifies the association between some SVD forms and dementia

	Adjusted* hazard ratios (95% CI)			
	Overall (n=1,668)	High social engagement (n=1,048)	Intermediate/ Low social engagement (n=620)	P-interaction
Subcortical microbleeds	**1.40 (1.01-1.94)**	1.06 (0.66-1.70)	**2.11 (1.35-3.32)**	**0.025**
WMH volume (per SD)	**1.42 (1.22-1.64)**	**1.26 (1.04-1.50)**	**1.78 (1.38-2.30)**	**0.003**
Lacunar infarcts	**2.16 (1.60-2.93)**	**2.10 (1.40-3.15)**	**2.06 (1.26-3.38)**	0.98
DTI: Fractional anisotropy (FA; per SD)	**0.77 (0.67-0.89)**	**0.82 (0.68-1.00)**	**0.73 (0.60-0.89)**	0.78
DTI: Mean diffusivity (MD; per SD)	**1.63 (1.41-1.89)**	**1.52 (1.25-1.85)**	**1.81 (1.45-2.26)**	0.88

*adjusted for demographics, APOE, vascular risk factors, depression, physical



Association between cerebral microbleeds and dementia, stratified by SE

Race modifies the SE X DTI 2-way interaction:

		FA (per SD)	MD (per SD)
Black participants *, **	Overall	0.89 (0.68 – 1.16)	1.30 (0.98 – 1.72)
	Strong SE	1.25 (0.84 – 1.86)	0.93 (0.63 – 1.38)
	Poor SE	0.73 (0.50 – 1.05)	**1.74 (1.16 – 2.60)**
White participants	**Overall**	**0.73 (0.62 – 0.86)**	**1.70 (1.46 – 1.98)**
	Strong SE	**0.72 (0.58 – 0.89)**	**1.73 (1.43 – 2.10)**
	Poor SE	**0.76 (0.59 – 0.99)**	**1.68 (1.27 – 2.23)**

*2-way interaction SE X DTI marker $p<0.05$

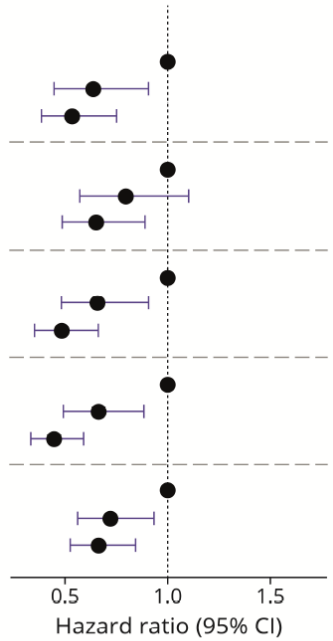
** 3-way interaction (race X SE X DTI marker) $p<0.05$

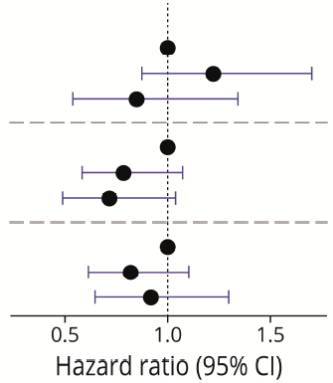
Genetic risk, Midlife Life's simple 7, and Incident Dementia in the Atherosclerosis Risk in Communities Study

Life's simple 7 score (ideal cardiovascular health) was associated with risk of dementia, in all (Alzheimer's disease polygenic) genetic risk strata, in white and Black adults

A Tin, J Bressler, J Simino, KJ Sullivan, H Mei, BG Windham, M Griswold, RF Gottesman, E Boerwinkle, M Fornage, TH Mosley. Neurology 2022

Genetic risk score	Life's Simple 7 category	Hazard ratio (95% CI)	*p* value
EA participants			
Quintile 1	Low, 0–6	Reference	
	Intermediate, 7–8	0.64 (0.45, 0.91)	0.010
	High, 9–14	0.54 (0.39, 0.75)	<0.001
Quintile 2	Low, 0–6	Reference	
	Intermediate, 7–8	0.79 (0.57, 1.10)	0.170
	High, 9–14	0.65 (0.48, 0.88)	0.006
Quintile 3	Low, 0–6	Reference	
	Intermediate, 7–8	0.66 (0.48, 0.91)	0.010
	High, 9–14	0.48 (0.35, 0.66)	<0.001
Quintile 4	Low, 0-6	Reference	
	Intermediate, 7–8	0.66 (0.49, 0.88)	0.005
	High, 9–14	0.44 (0.33, 0.59)	<0.001
Quintile 5	Low, 0–6	Reference	
	Intermediate, 7–8	0.72 (0.56, 0.94)	0.010
	High, 9–14	0.66 (0.52, 0.84)	<0.001
AA participants			
Tertile 1	Low, 0–6	Reference	
	Intermediate, 7–8	1.22 (0.87, 1.70)	0.24
	High, 9–14	0.85 (0.54, 1.34)	0.48
Tertile 2	Low, 0–6	Reference	
	Intermediate, 7–8	0.79 (0.58, 1.07)	0.13
	High, 9–14	0.71 (0.49, 1.04)	0.08
Tertile 3	Low, 0–6	Reference	
	Intermediate, 7–8	0.82 (0.61, 1.10)	0.19
	High, 9–14	0.92 (0.65, 1.30)	0.63





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Associations of Vascular Risk and Amyloid Burden with Subsequent Dementia

Rebecca F. Gottesman, MD PhD,[1] Aozhou Wu, PhD,[2] Josef Coresh, MD PhD,[2] David S. Knopman, MD,[3] Clifford R. Jack Jr MD,[3] Arman Rahmim, PhD,[4] A. Richey Sharrett, MD DrPH,[2] Adam P. Spira, PhD,[5] Dean F. Wong, MD PhD,[6] Lynne E. Wagenknecht, PhD,[7] Timothy M. Hughes, PhD,[8] Keenan A. Walker, PhD,[9] and Thomas H. Mosley, PhD[10]

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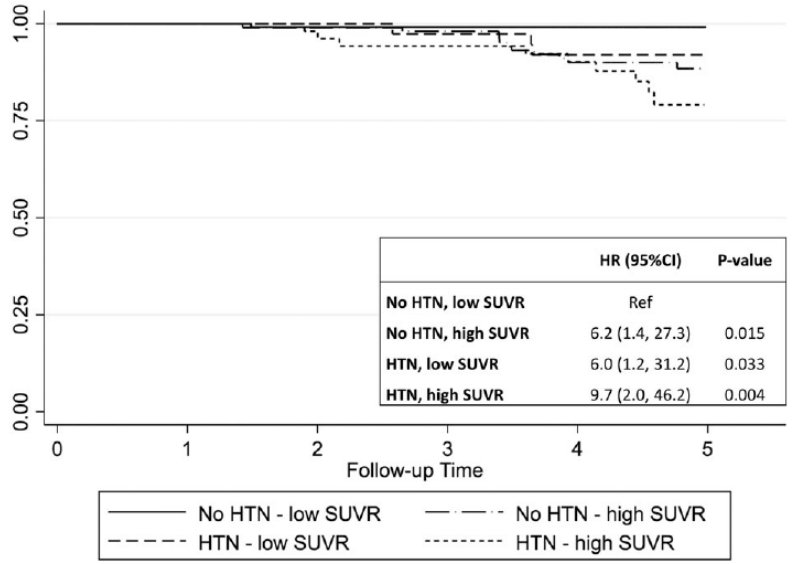

		Incident dementia HR (95% CI): Model 1	Incident dementia HR (95% CI): Model 2
Late-life (at visit 5)	Log WMH	1.51 (1.03, 2.20)	1.21 (0.77, 1.89)
	Log SUVR (amyloid)	2.52 (1.83, 3.47)	2.58 (1.72, 3.89)
Midlife (at visit 1)	Hypertension		2.58 (1.13, 5.85)
	Smoking		1.29 (0.44, 3.77)
	Diabetes		1.04 (0.31, 3.55)
	BMI>30		1.83 (0.88, 3.78)
	↑ total chol.		0.61 (0.29, 1.30)

Midlife HTN and amyloid independently contributed to dementia risk, but did not interact on a multiplicative scale

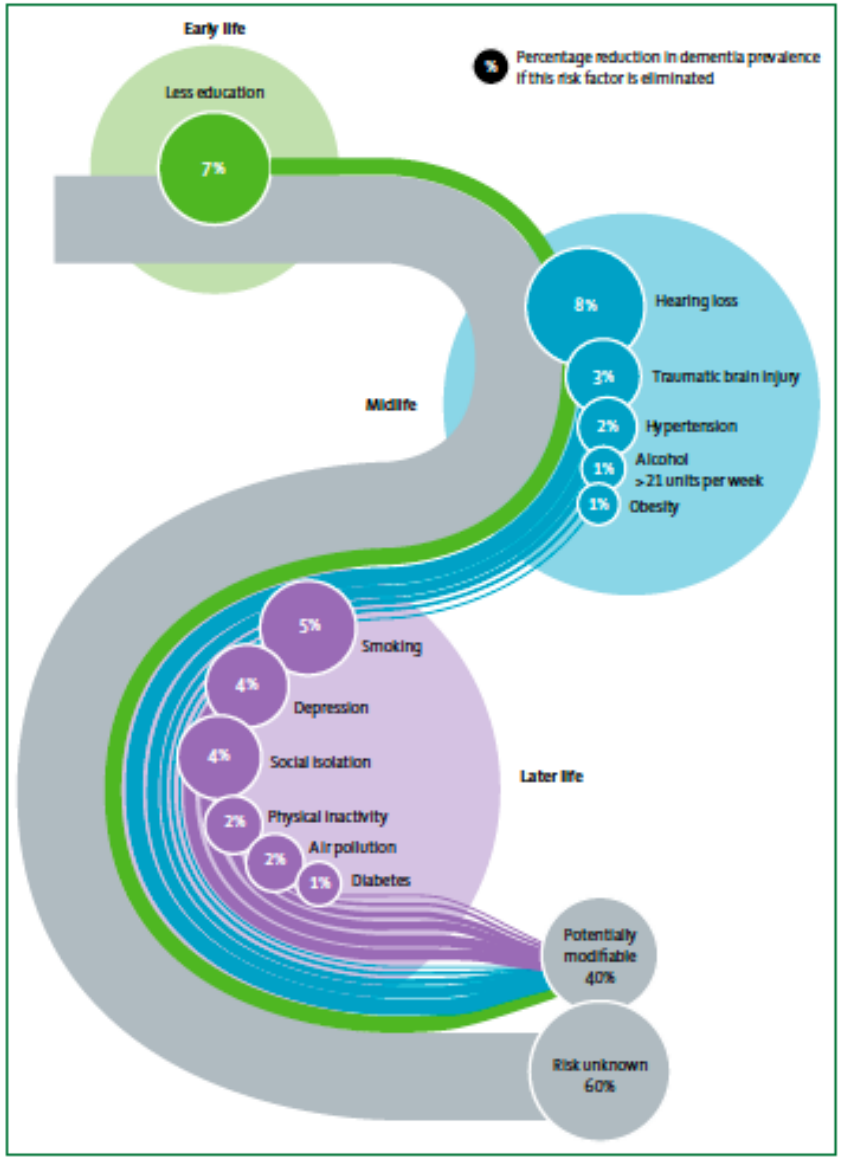

Figure 7: Population attributable fraction of potentially modifiable risk factors for dementia

From Livingston et al., Lancet 2020

JAMA Network | Open

Original Investigation | Neurology

Variation in Population Attributable Fraction of Dementia Associated With Potentially Modifiable Risk Factors by Race and Ethnicity in the US

Mark Lee, MA; Eric Whitsel, MD, MPH; Christy Avery, PhD; Timothy M. Hughes, PhD; Michael E. Griswold, PhD; Sanaz Sedaghat, PhD; Rebecca F. Gottesman, MD, PhD; Thomas H. Mosley, PhD; Gerardo Heiss, PhD; Pamela L. Lutsey, PhD, MPH

- 41% of US dementia cases are attributable to 12 *modifiable* risk factors, *especially* hypertension, obesity, and physical inactivity
  - A 15% reduction in each RF would reduce dementia by 7%
  - PAR up to 46% for Black Americans, 47% for Latinx

NIH National Institute of Neurological Disorders and Stroke

Conclusions

- Most dementia is due to mixed pathology
- Vascular risk factors represent an important modifiable target for dementia prevention, although interventional trials have shown mixed results
- Vascular contributions to dementia may act on dementia risk via alterations in brain structure, function, and possibly deposition of brain amyloid
- Modifiable risk may even have a role in individuals with increased genetic risk, and could also include social factors as well as vascular risk factors
- As improvements in treatment options advance for underlying dementia pathologies, they should continue to consider vascular contributions as these are likely impacting risk in parallel, as well as other modifiers of risk including factors contributing to cognitive reserve

Conclusions:
Sex differences in VCID over the life course

- Women have a lower risk of dementia in ARIC, but the lifetime risk of dementia over the life course is greater in women than in men
- Risk factors have differential prevalence by sex, so may further impact dementia attributable risks
- Brain amyloid levels appear to be higher in women than in men, although not after adjustment for cognitive status
- Social engagement, although generally stronger in women than in men, is associated with similar decrease in dementia risk in women and in men
- Consideration of sex-specific risk factors not discussed in detail here, but in our prior work we found a U-shaped association between parity with dementia risk in ARIC (for women with 0-1 births, HR 0.82, 95% CI 0.69-0.99; women with 5+ births HR 0.85, 95% CI 0.72-0.99, compared to 2 births; DiBiase et al., J Womens Health, 2023)

NIH National Institute of Neurological Disorders and Stroke

Acknowledgements

NIH:

- Keenan Walker (NIA)
- Derrick Okine
- Marco Egle
- Renee Groechel
- Sylee Kanetkar
- Mohini Johri
- Valerie Morrill
- Olivia Emanuel
- Nicole Williams

Johns Hopkins:

- A.Richey Sharrett
- Andreea Rawlings
- Marilyn Albert
- Michelle Johansen
- Jason Smith
- Jennifer Deal
- Jiaqi Hu

NYU:

- Josef Coresh
- James Pike

Wake Forest University:

- Lynne Wagenknecht
- Timothy Hughes

University of North Carolina, Chapel Hill:

- David Couper
- Priya Palta

University of Mississippi Medical Center

- Thomas Mosley
- Kevin Sullivan
- Gwen Windham

Mayo Clinic:

- David Knopman
- Cliff Jack

University of Minnesota

- Pam Lutsey
- Wendy Wang
- Lin-Yee Chen
- Mark Lee
- Sanaz Sedaghat

ARIC participants and staff

University of Pennsylvania: Andrea Schneider

Tel Aviv University: Silvia Koton

Washington University in St. Louis: Dean Wong

George Washington University: Melinda Power

Previous Funding Sources:

NIH/ NIA (R01: ARIC-PET, K24)
NIH: NHLBI, NINDS, NIA (U01: ARIC)
McKhann Scholar Fund/ Dana Foundation
Avid Radiopharmaceuticals: provided Isotope for ARIC-PET study

NINDS Intramural Research Program

Acknowledgements

Thank you!

Questions?

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