Amyloid Deposition in Healthy Aging, Vascular and Neurodegenerative Disease and Genetic Effects

MCI Symposium

Presented by: Rebecca Gottesman, MD PhD

January 19, 2019

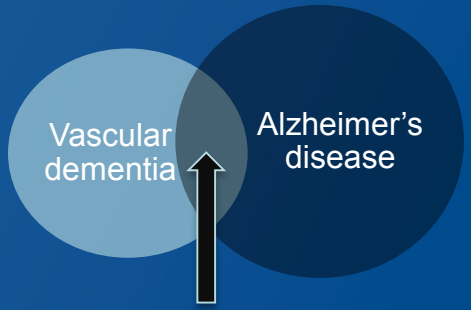
Disclosures

- I am an Associate Editor for the journal *Neurology*.

Vascular risk and Alzheimer's Disease

JOHNS HOPKINS MEDICINE

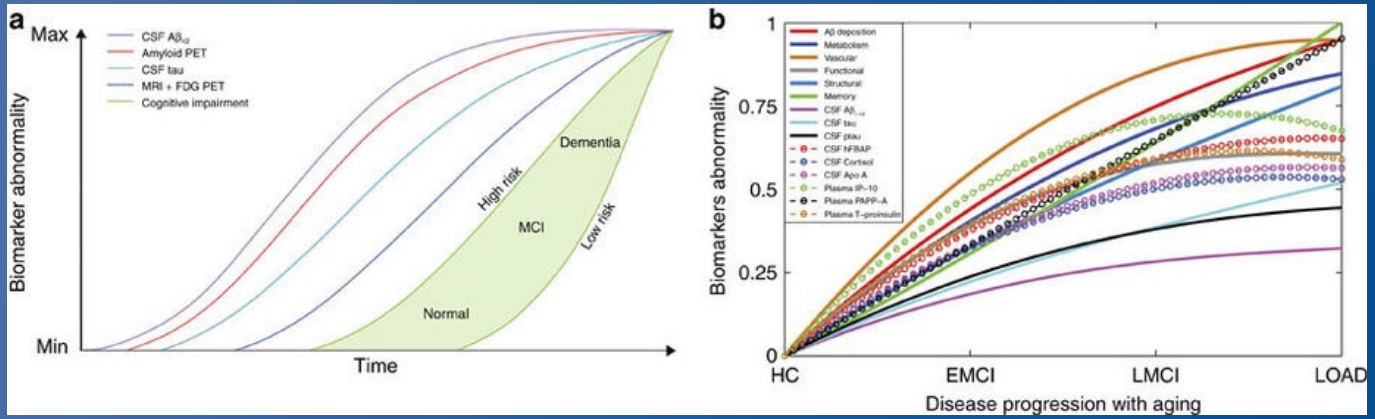
- Many patients diagnosed with AD may actually have some vascular contribution, and patients diagnosed with vascular dementia may have some contribution from AD neuropathology
- Vascular risk factors (hypertension, diabetes, smoking, high cholesterol) are known to be present in a subset of individuals 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



Mixed dementia

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

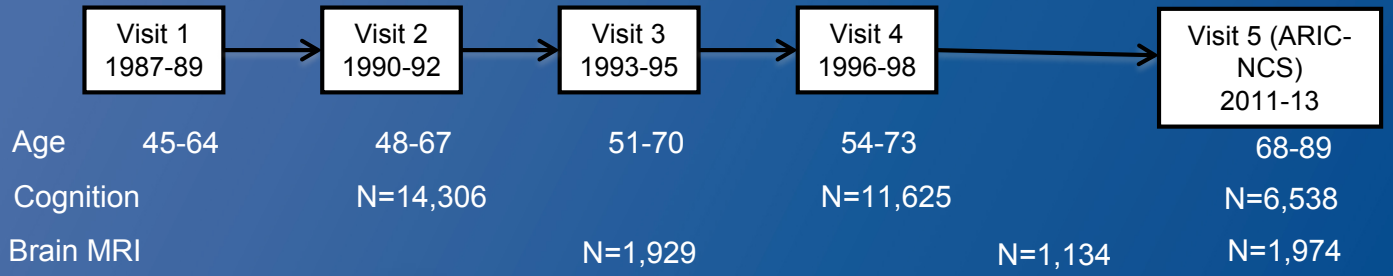


From Iturria-Medina et al., Nat Commun 2016

Atherosclerosis Risk in Communities (ARIC)

JOHNS HOPKINS MEDICINE

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



Cognitive analyses through visit 5 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

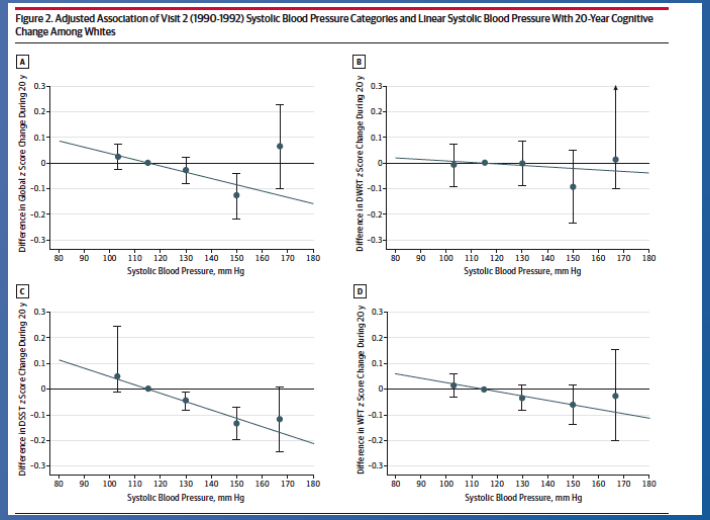
Original Investigation

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.

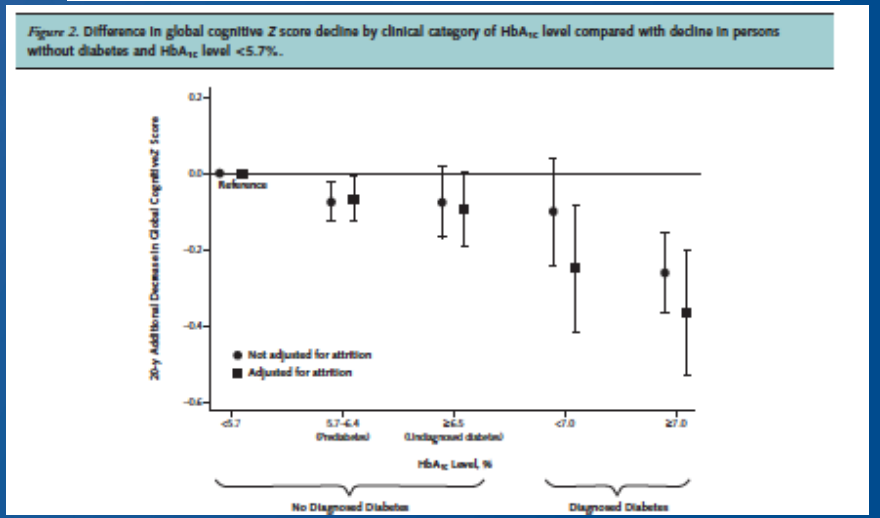
Midlife hypertension is associated with **steeper 20-year cognitive decline**, but *late-life* hypertension is not associated with prior 20 years' worth of change



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



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

JAMA Neurology | Original Investigation

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

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

JAMA Neurol. doi:10.1001/jamaneurol.2017.1658

- *Participants*: ARIC participants of black or white race (N=15,744)
- Vascular risk factors from ARIC visit 1 (midlife)
- Dementia: (through visit 5) defined using:
  - adjudicated dementia cases from complete ARIC-NCS evaluation
  - Telephone Interview for Cognitive Status, Informant interviews
  - Prior ICD-9 hospitalization codes for dementia
- Level 1 dementia used data from three repeated cognitive tests, informant CDR/ FAQ interviews, and larger neurocognitive battery given at ARIC visit 5, with algorithmic diagnosis and expert review and classification
- Statistical analysis: Cox proportional hazards model
  - Also: discrete time analysis with complimentary log-log link; logistic regression; competing risk proportional hazards model

JOHNS HOPKINS MEDICINE

Table 2. Cox Proportional Hazards Regression Model of Time to Incident Dementia Overall and Stratified by Race

Variable	Hazard Ratio (95% CI)		
	Full Eligible Cohort (n = 15 407)[a]	Black (n = 4004)	White (n = 11 403)
Female	0.89 (0.79-0.99)	0.87 (0.72-1.06)	0.92 (0.80-1.05)
Black	1.36 (1.21-1.54)	NA	NA
Visit 1 age, y[b]			
44-49	1 [Reference]	1 [Reference]	1 [Reference]
Visit 1 smoking[b]			
Current	1.41 (1.23-1.61)	1.07 (0.85-1.35)	1.62 (1.37-1.92)
Former	1.00 (0.89-1.13)	0.77 (0.61-0.98)	1.13 (0.97-1.31)
Never	1 [Reference]	1 [Reference]	1 [Reference]
APOE ε4 genotype[b]			
0 Alleles	1 [Reference]	1 [Reference]	1 [Reference]
≥1 Alleles	1.98 (1.78-2.21)	1.61 (1.34-1.92)	2.23 (1.96-2.54)
Unknown *APOE*	1.18 (0.89-1.56)	1.84 (0.97-3.47)	1.11 (0.81-1.52)
Visit 1 diabetes	1.77 (1.53-2.04)	1.85 (1.50-2.29)	1.69 (1.39-2.07)
Visit 1 hypertension			
Normal	1 [Reference]	1 [Reference]	1 [Reference]
Prehypertension	1.31 (1.14-1.51)	1.17 (0.86-1.59)	1.35 (1.14-1.59)
Hypertension	1.39 (1.22-1.59)	1.36 (1.04-1.77)	1.37 (1.17-1.60)
Visit 1 total cholesterol, mg/dL			
<200	1 [Reference]	1 [Reference]	1 [Reference]
200 to <240	0.87 (0.77-0.98)	0.91 (0.74-1.13)	0.86 (0.74-1.00)
≥240	0.91 (0.80-1.04)	0.78 (0.62-0.98)	0.99 (0.84-1.16)

JOHNS HOPKINS MEDICINE

Table 2. Cox Proportional Hazards Regression Model of Time to Incident Dementia Overall and Stratified by Race

Variable	Hazard Ratio (95% CI)		
	Full Eligible Cohort (n = 15 407)[a]	Black (n = 4004)	White (n = 11 403)
Female	0.89 (0.79-0.99)	0.87 (0.72-1.06)	0.92 (0.80-1.05)
Black	1.36 (1.21-1.54)	NA	NA
Visit 1 age, y[b]			
44-49	1 [Reference]	1 [Reference]	1 [Reference]
50-54	2.04 (1.66-2.49)	2.22 (1.66-2.98)	1.98 (1.49-2.62)
55-59	3.97 (3.28-4.81)	3.53 (2.63-4.73)	4.37 (3.37-5.65)
60-66	8.06 (6.69-9.72)	6.20 (4.64-8.28)	9.54 (7.41-12.27)
Educational attainment			
<High school	1.37 (1.20-1.57)	1.61 (1.28-2.03)	1.29 (1.09-1.53)
High school graduate or GED	1.05 (0.93-1.20)	1.17 (0.90-1.53)	1.02 (0.88-1.18)
>High school	1 [Reference]	1 [Reference]	1 [Reference]
Visit 1 BMI			
Underweight	0.99 (0.53-1.87)	1.15 (0.36-3.66)	0.92 (0.43-1.97)
Normal	1 [Reference]	1 [Reference]	1 [Reference]
Overweight	1.05 (0.92-1.19)	0.95 (0.73-1.22)	1.08 (0.93-1.26)
Visit 1 diabetes	1.77 (1.53-2.04)	1.85 (1.50-2.29)	1.69 (1.39-2.07)
Normal	1 [Reference]	1 [Reference]	1 [Reference]
Prehypertension	1.31 (1.14-1.51)	1.17 (0.86-1.59)	1.35 (1.14-1.59)
Hypertension	1.39 (1.22-1.59)	1.36 (1.04-1.77)	1.37 (1.17-1.60)
Visit 1 total cholesterol, mg/dL			
<200	1 [Reference]	1 [Reference]	1 [Reference]
200 to <240	0.87 (0.77-0.98)	0.91 (0.74-1.13)	0.86 (0.74-1.00)
≥240	0.91 (0.80-1.04)	0.78 (0.62-0.98)	0.99 (0.84-1.16)

JOHNS HOPKINS MEDICINE

Table 2. Cox Proportional Hazards Regression Model of Time to Incident Dementia Overall and Stratified by Race

Variable	Hazard Ratio (95% CI)		
	Full Eligible Cohort (n = 15 407)[a]	Black (n = 4004)	White (n = 11 403)
Female	0.89 (0.79-0.99)	0.87 (0.72-1.06)	0.92 (0.80-1.05)
Black	1.36 (1.21-1.54)	NA	NA
Visit 1 age, y[b]			
44-49	1 [Reference]	1 [Reference]	1 [Reference]
50-54	2.04 (1.66-2.49)	2.22 (1.66-2.98)	1.98 (1.49-2.62)
55-59	3.97 (3.28-4.81)	3.53 (2.63-4.73)	4.37 (3.37-5.65)
60-66	8.06 (6.69-9.72)	6.20 (4.64-8.28)	9.54 (7.41-12.27)
Educational attainment			
<High school	1.37 (1.20-1.57)	1.61 (1.28-2.03)	1.29 (1.09-1.53)
High school graduate	1.05 (0.93-1.20)	1.17 (0.90-1.53)	1.02 (0.88-1.18)
Visit 1 hypertension			
Normal	1 [Reference]	1 [Reference]	1 [Reference]
Prehypertension	1.31 (1.14-1.51)	1.17 (0.86-1.59)	1.35 (1.14-1.59)
Hypertension	1.39 (1.22-1.59)	1.36 (1.04-1.77)	1.37 (1.17-1.60)
Visit 1 total cholesterol, mg/dL			
<200	1 [Reference]	1 [Reference]	1 [Reference]
200 to <240	0.87 (0.77-0.98)	0.91 (0.74-1.13)	0.86 (0.74-1.00)
≥240	0.91 (0.80-1.04)	0.78 (0.62-0.98)	0.99 (0.84-1.16)

Table 2. Cox Proportional Hazards Regression Model of Time to Incident Dementia Overall and Stratified by Race

Variable	Hazard Ratio (95% CI)		
	Full Eligible Cohort (n = 15 407)[a]	Black (n = 4004)	White (n = 11 403)
Visit 1 hypertension			
Normal	1 [Reference]	1 [Reference]	1 [Reference]
Prehypertension	1.31 (1.14-1.51)	1.17 (0.86-1.59)	1.35 (1.14-1.59)
Hypertension	1.39 (1.22-1.59)	1.36 (1.04-1.77)	1.37 (1.17-1.60)

JOHNS HOPKINS MEDICINE

Table 2. Cox Proportional Hazards Regression Model of Time to Incident Dementia Overall and Stratified by Race

Variable	Hazard Ratio (95% CI)		
	Full Eligible Cohort (n = 15 407)[a]	Black (n = 4004)	White (n = 11 403)
Female	0.89 (0.79-0.99)	0.87 (0.72-1.06)	0.92 (0.80-1.05)
Black	1.36 (1.21-1.54)	NA	NA
Visit 1 age, y[b]			
44-49	1 [Reference]	1 [Reference]	1 [Reference]
50-54	2.04 (1.66-2.49)	2.22 (1.66-2.98)	1.98 (1.49-2.62)
Visit 1 BMI			
Underweight	0.99 (0.53-1.87)	1.15 (0.36-3.66)	0.92 (0.43-1.97)
Normal	1 [Reference]	1 [Reference]	1 [Reference]
Overweight	1.05 (0.92-1.19)	0.95 (0.73-1.22)	1.08 (0.93-1.26)
Obese	1.14 (0.99-1.31)	0.92 (0.71-1.20)	1.22 (1.03-1.45)
Visit 1 total cholesterol, mg/dL			
<200	1 [Reference]	1 [Reference]	1 [Reference]
200 to <240	0.87 (0.77-0.98)	0.91 (0.74-1.13)	0.86 (0.74-1.00)
≥240	0.91 (0.80-1.04)	0.78 (0.62-0.98)	0.99 (0.84-1.16)

JOHNS HOPKINS MEDICINE

Table 2. Cox Proportional Hazards Regression Model of Time to Incident Dementia Overall and Stratified by Race

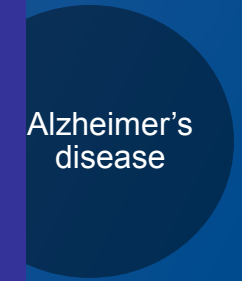
Variable	Hazard Ratio (95% CI) Full Eligible Cohort (n = 15 407)[a]	Black (n = 4004)	White (n = 11 403)
Female	0.89 (0.79-0.99)	0.87 (0.72-1.06)	0.92 (0.80-1.05)
Black	1.36 (1.21-1.54)	NA	NA
Visit 1 age, y[b]			
44-49	1 [Reference]	1 [Reference]	1 [Reference]
50-54	2.04 (1.66-2.49)	2.22 (1.66-2.98)	1.98 (1.49-2.62)
55-59	3.97 (3.28-4.81)	3.53 (2.63-4.73)	4.37 (3.37-5.65)
60-66	8.06 (6.69-9.72)	6.20 (4.64-8.28)	9.54 (7.41-12.27)
Educational attainment			
<High school	1.37 (1.20-1.57)	1.61 (1.28-2.03)	1.29 (1.09-1.53)
High school graduate	1.05 (0.93-1.20)	1.17 (0.90-1.53)	1.02 (0.88-1.18)
APOE ε4 genotype[b]			
0 Alleles	1 [Reference]	1 [Reference]	1 [Reference]
≥1 Alleles	1.98 (1.78-2.21)	1.61 (1.34-1.92)	2.23 (1.96-2.54)
Unknown *APOE*	1.18 (0.89-1.56)	1.84 (0.97-3.47)	1.11 (0.81-1.52)
Visit 1 diabetes	1.77 (1.53-2.04)	1.85 (1.50-2.29)	1.69 (1.39-2.07)
Hypertension	1.39 (1.22-1.59)	1.36 (1.04-1.77)	1.37 (1.17-1.60)
Visit 1 total cholesterol, mg/dL			
<200	1 [Reference]	1 [Reference]	1 [Reference]
200 to <240	0.87 (0.77-0.98)	0.91 (0.74-1.13)	0.86 (0.74-1.00)
≥240	0.91 (0.80-1.04)	0.78 (0.62-0.98)	0.99 (0.84-1.16)

Vasc

- Many
  vascu
  deme
  neuro
- Vascu
  chole
  indivi
- This r
  - V
    c
  - V

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



ementia

changes of Alzheimer's together make it more likely
that a patient will decline clinically to the point to be
labeled with AD

Atherosclerosis Risk in Communities (ARIC)

JOHNS HOPKINS MEDICINE

- 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
Age	45-64	48-67	51-70	54-73			
Cognition		N=14,306		N=11,625		N=6,538	N=4,003
Brain MRI			N=1,929		N=1,134	N=1,974	Ongoing *
Florbetapir PET						N=346	Ongoing *

Cognitive analyses through visit 5 consider:
Change in cognition
Incident MCI, dementia, and progression

*Imaging recruitment during visits 6 *and* 7; planned ~300 (PET) and 1000 (MRI)

The ARIC-PET amyloid imaging study

Brain amyloid differences by age, race, sex, and *APOE*

Neurology® 2016;87:1-8

Rebecca F. Gottesman, MD, PhD
Andrea L.C. Schneider, MD, PhD
Yun Zhou, PhD
Xueqi Chen
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, Jr., PhD

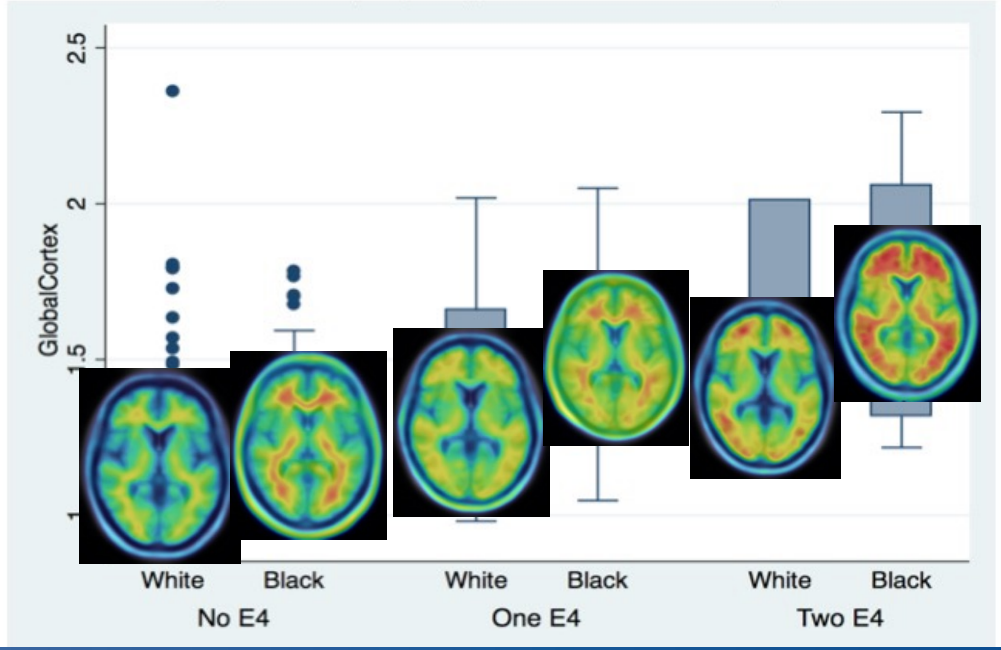
Table 2 Adjusted odds ratios (ORs) (95% confidence intervals [CIs]) for global cortex SUVR >1.2 (median) (n = 329)

	Model 1, OR (95% CI)	Model 2, OR (95% CI)	Model 3, OR (95% CI)
Age (per 10 y)	1.97 (1.26-3.08)	1.91 (1.22-2.99)	1.63 (1.01-2.65)
Female vs male	1.70 (1.05-2.75)	1.72 (1.06-2.79)	1.53 (0.78-2.98)
Black race vs white race	2.29 (1.42-3.70)	2.18 (1.34-3.56)	2.08 (1.23-3.51)
Education level			
College, graduate, or professional school	1 (reference)	1 (reference)	1 (reference)
High school, GED, or vocational school	0.88 (0.52-1.48)	0.87 (0.52-1.46)	0.88 (0.52-1.49)
< High school	1.04 (0.52-2.07)	0.99 (0.49-1.98)	0.88 (0.43-1.80)
APOE ε4 genotype (per 1 additional ε4 allele)	2.62 (1.61-4.24)	2.70 (1.66-4.41)	2.65 (1.61-4.39)

Abbreviations: GED = general educational development; SUVR = standardized uptake value ratio.
Model 1: Adjusted for age, sex, race, education, and *APOE* ε4 genotype. Model 2: Model 1 + hypertension and diabetes. Model 3: Model 2 + mild cognitive impairment status, white matter hyperintensity volume, and total intracranial volume.

ARIC-PET recruited 346 *nondemented* ARIC participants from 3 ARIC sites, with florbetapir PET (2011-2014), and a second florbetapir PET underway (2017-present)

Figure. Boxplots of florbetapir SUVR for a composite global cortex measurement* by race and ApoE genotype; number of ε4 alleles is presented.



JAMA | Original Investigation

Association Between Midlife Vascular Risk Factors and Estimated Brain Amyloid Deposition

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

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

JOHNS HOPKINS MEDICINE

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)

Risk Factors[a]	Overall (n = 322)		0 *APOE* ε4 Alleles (n = 220)		1 or 2 *APOE* ε4 Alleles (n = 100)	
	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.

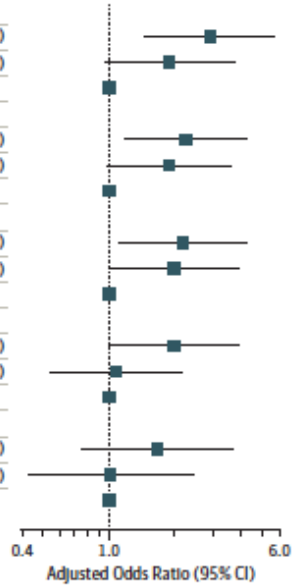
[b] Models are adjusted for age (at visit 5, 2011-2013), sex, race, education level, and *APOE* ε4 genotype.

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

JOHNS HOPKINS MEDICINE

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]



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.

Intracranial plaque is more strongly associated with amyloid in APOE e4 carriers (unpublished)

P-values shown are for interaction between vessel features and APOE e4 status

How do midlife vascular risk and amyloid contribute to cognition?

JOHNS HOPKINS MEDICINE

- Cognitive follow-up after ARIC PET continued through specific study follow-up *and* ARIC-NCS ongoing visits and dementia surveillance
- Relative contributions of vascular risk (mid- and late-life) and amyloid burden to cognition and ~5-year progression were considered

Cognitive level is worse in amyloid-positive participants (unpublished)

JOHNS HOPKINS MEDICINE

Midlife vascular risk factors

Model including all covariates above together, + educational level

Late-life vascular risk factors

Model including all covariates above together, + educational level

Risk of Dementia with level of Amyloid SUVR

JOHNS HOPKINS MEDICINE

ARIC-PET: Burden of risk factors and amyloid on cognition; Results shown adjusted for amyloid (unpublished)

JOHNS HOPKINS MEDICINE

*of these 5: hypertension, hyperlipidemia, diabetes, obesity, and smoking

Conclusions

- Midlife vascular risk factors are strongly related to late-life cognitive outcomes and dementia
- Vascular risk factor status in midlife is associated with later-life amyloid deposition
- Hypertension in *midlife (*but not late-life) is still associated with cognition, even after adjusting for amyloid
- Amyloid remains robustly associated with cognition and its progression, independent of vascular risk
- There may be effect modification in individuals with elevated genetic risk *and* vascular disease or risk factors, with greatest risk of dementia and amyloid in individuals with both

Acknowledgements:

Johns Hopkins:

- Josef Coresh
- A.Richey Sharrett
- Andrea Schneider
- Andreea Rawlings
- Keenan Walker
- Aozhou Wu
- Dean Wong
- Arman Rahmim
- Yun Zhou
- Noble George
- Marilyn Albert

Mayo Clinic:

- David Knopman
- Cliff Jack

George Washington University:

- Melinda Power

Wake Forest University:

- Lynne Wagenknecht
- Akiva Mintz
- Timothy Hughes

University of North Carolina, Chapel Hill:

- Sonia Davis
- Lisa Wruck
- David Couper

University of Mississippi Medical Center

- Thomas Mosley
- Edward Green

Hagerstown Imaging

- Naresh Gupta

Emory University

- Alvaro Alonso

ARIC participants and staff

Acknowledgements

JOHNS HOPKINS MEDICINE

ARIC

Funding Sources:

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