Association Between Midlife Vascular Risk Factors and Estimated Brain Amyloid Deposition

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➕ **Supplemental content**

IMPORTANCE Midlife vascular risk factors have been associated with late-life dementia. Whether these risk factors directly contribute to brain amyloid deposition is less well understood.

OBJECTIVE To determine if midlife vascular risk factors are associated with late-life brain amyloid deposition, measured using florbetapir positron emission tomography (PET).

DESIGN, SETTING, AND PARTICIPANTS The Atherosclerosis Risk in Communities (ARIC)–PET Amyloid Imaging Study, a prospective cohort study among 346 participants without dementia in 3 US communities (Washington County, Maryland; Forsyth County, North Carolina; and Jackson, Mississippi) who have been evaluated for vascular risk factors and markers since 1987-1989 with florbetapir PET scans in 2011-2013. Positron emission tomography image analysis was completed in 2015.

EXPOSURES Vascular risk factors at ARIC baseline (age 45-64 years; risk factors included body mass index ≥30, current smoking, hypertension, diabetes, and total cholesterol ≥200 mg/dL) were evaluated in multivariable models including age, sex, race, *APOE* genotype, and educational level.

MAIN OUTCOMES AND MEASURES Standardized uptake value ratios (SUVRs) were calculated from PET scans and a mean global cortical SUVR was calculated. Elevated florbetapir (defined as a SUVR >1.2) was the dependent variable.

RESULTS Among 322 participants without dementia and with nonmissing midlife vascular risk factors at baseline (mean age, 52 years; 58% female; 43% black), the SUVR (elevated in 164 [50.9%] participants) was measured more than 20 years later (median follow-up, 23.5 years; interquartile range, 23.0-24.3 years) when participants were between 67 and 88 (mean, 76) years old. Elevated body mass index in midlife was associated with elevated SUVR (odds ratio [OR], 2.06; 95% CI, 1.16-3.65). At baseline, 65 participants had no vascular risk factors, 123 had 1, and 134 had 2 or more; a higher number of midlife risk factors was associated with elevated amyloid SUVR at follow-up (30.8% [n = 20], 50.4% [n = 62], and 61.2% [n = 82], respectively). In adjusted models, compared with 0 midlife vascular risk factors, the OR for elevated SUVR associated with 1 vascular risk factor was 1.88 (95% CI, 0.95-3.72) and for 2 or more vascular risk factors was 2.88 (95% CI, 1.46-5.69). No significant race × risk factor interactions were found. Late-life vascular risk factors were not associated with late-life brain amyloid deposition (for ≥2 late-life vascular risk factors vs 0: OR, 1.66; 95% CI, 0.75-3.69).

CONCLUSIONS AND RELEVANCE An increasing number of midlife vascular risk factors was significantly associated with elevated amyloid SUVR; this association was not significant for late-life risk factors. These findings are consistent with a role of vascular disease in the development of Alzheimer disease.

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ncreasing evidence supports a role of vascular risk factors and markers in the development and etiology of Alzheimer disease (AD). Most major vascular risk factors, including hypertension,[1-4] diabetes,[5] smoking,[3,6] and hypercholesterolemia,[4,7] particularly when measured in midlife, have been associated with risk of dementia generally and AD specifically. Whether these risk factors directly increase the neurodegeneration specifically associated with AD (such as through increasing amyloid deposition) or lead to other cerebral changes that, in conjunction with ongoing neurodegeneration, might worsen cognitive performance is not yet known.

The role of the *APOE* ε4 allele as a genetic risk factor for AD is well established,[8] but its role as a modifier of the relationship between vascular disease and AD is less well understood. *APOE* ε4 carriage in combination with vascular disease may work synergistically to increase risk of AD,[9] with worse cognitive outcomes in persons with both increased genetic and vascular risks. These relationships are further complicated by the direct association between *APOE* and vascular disease: the ε4 allele is proatherogenic,[10] so evaluation of the interactive effects of *APOE* and vascular risk factors on AD neuropathology must also consider the independent contribution of *APOE* to vascular disease.

The availability of imaging biomarkers for brain amyloid allows the study of individuals before the development of dementia and thereby allows consideration of the relative contributions of vascular disease and amyloid to cognition, as well as the contribution of vascular disease to amyloid deposition. In the current study, vascular risk factors were collected for more than 25 years in participants from the Atherosclerosis Risk in Communities (ARIC) Study, with brain amyloid positron emission tomography (PET) imaging obtained in late life, to evaluate the associations among vascular risk factors, *APOE* genotype, and brain amyloid deposition.

Methods

The ARIC-PET Study is an ancillary to the ongoing ARIC-Neurocognitive Study, which itself is a major ancillary of the ARIC study. The study was approved by each institution's institutional review board. All participants provided written informed consent.

Participant Inclusion
Participants underwent a baseline visit in 1987-1989, when 15 792 individuals were recruited from 4 US communities,[11] with 4 additional in-person visits, most recently in 2011-2013 and with annual/semiannual telephone calls throughout the study duration. Each visit (including baseline) has included in-person assessment of vascular risk factors, with a shorter cognitive evaluation at the second and fourth visits and a more extensive neuropsychological assessment including informant interview at visit 5 (2011-2013).

Nearly 2000 participants without contraindication to magnetic resonance imaging (MRI) were invited for brain MRI based on any of the following[12]: (1) prior research brain MRI as part of the cohort; (2) low cognitive scores or cognitive

Key Points

Question Are midlife vascular risk factors associated with late-life brain amyloid deposition?

Findings In a prospective cohort study of 346 members of the community-based Atherosclerosis Risk in Communities (ARIC)–PET cohort without dementia, having 2 or more midlife vascular risk factors compared with none was significantly associated with elevated amyloid deposition in the brain (61.2% vs 30.8%). There was no significant association for late-life risk factors.

Meaning These findings are consistent with a role of vascular disease in the development of Alzheimer disease.

decline at visit 5; and (3) a random age-stratified sample of cognitively healthy participants. This study recruited from this subset, with the additional exclusion criteria of heavy current alcohol use, renal dysfunction, prolonged (>450 milliseconds) QTc interval, or neuropsychological results consistent with dementia. Methods used to adjudicate mild cognitive impairment and dementia research diagnoses are described elsewhere,[13] but for the purposes of this study, participants were excluded if they had an already adjudicated research diagnosis of dementia, a Clinical Dementia Rating sum-of-boxes score of greater than 3, a Functional Activities Questionnaire score of greater than 5, or a Mini-Mental State Examination score of less than 19 (among black participants) or less than 21 (among white participants).[13]

Brain MRI and PET
Brain MRI scans, obtained as research studies at a 3T MRI facility near each field center, were read centrally at the Mayo Clinic.[12] Positron emission tomographic images were co-registered using magnetization prepared rapid acquisition gradient-echo sequences.

The details of PET image processing and coregistration with MRI, carried out at the Johns Hopkins University reading center, were described previously.[14] A global cortical measure of florbetapir uptake was used as a weighted average (based on region of interest size) of the orbitofrontal, prefrontal, and superior frontal cortices; the lateral temporal, parietal, and occipital lobes; the precuneus, the anterior cingulate, and the posterior cingulate. An automated region for cerebellum gray was used as a reference.[14-17] Standardized uptake value ratios (SUVRs) were dichotomized at the sample median of an SUVR of greater than 1.2,[14] although other cut points (1.11[18] and 1.10[19]) were explored in sensitivity analyses. Positron emission tomographic scans were obtained within 1 year of MRI scans, ideally within 6 months.

Positron emission tomography image analysis took place from 2012-2015, and statistical analysis for the current study was completed in 2016.

Vascular Risk Factors and Other Covariates
Vascular risk factors were evaluated at all in-person visits. Analyses in this study focused on risk factor status in midlife (visit 1 at age 45-64 years) as well as concurrent with PET (visit 5 at age 67-88 years). For demographic factors, date of

birth, queried at visit 1, was used to calculate age at each visit, and sex and educational level were self-reported in visit 1. Race was self-selected from several fixed categories (Asian, black, American Indian/Alaskan Indian, or white); race was evaluated given previously reported differences in dementia rates[20] and baseline differences in amyloid SUVR in this study.[14] Blood pressure was measured 2 to 3 times per visit; hypertension was present if the mean of the last 2 measurements was greater than 140 mm Hg (systolic) or greater than 90 mm Hg (diastolic) or if the participant was taking an antihypertensive medication at that visit. Diabetes was defined as a fasting glucose level of at least 126 mg/dL, a nonfasting glucose of at least 200 mg/dL, self-report of physician-diagnosed diabetes, or use of oral diabetes medications or insulin. Estimated 10-year stroke risk, calculated at visits 1 and 5, was based on a previously published algorithm for stroke risk,[21] and smoking history was self-reported as current/former/never. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Fasting lipids were measured at each visit[22]; plasma total cholesterol was measured using enzymatic methods.[23] *APOE* was genotyped previously and defined based on the number of ε4 alleles (0,1, or 2).

To evaluate cumulative burden of vascular risk factors, the number of vascular risk factors present in midlife (visit 1) and in late life (visit 5) was tallied, up to 5 maximum, including current smoking, hypertension, diabetes, obesity (BMI ≥30), and elevated total cholesterol (≥200 mg/dL). Because very few individuals had 3 or 4 risk factors and none who were included in our study had 5 risk factors, the number of midlife risk factors was categorized as 0, 1, or 2 or more.

Statistical Analysis

Stata SE, version 13 for Macintosh (Stata Corp), was used for all analyses. Group comparisons were evaluated visually and with descriptive statistics. Florbetapir uptake was evaluated as a dichotomous (SUVR >1.2) measure in logistic regression models; additional cut points were evaluated in sensitivity analyses. Because of the highly skewed florbetapir SUVR variable, regression analyses did not evaluate continuous florbetapir uptake. Multivariable logistic regression models evaluating the described vascular risk factors in the same model included age, sex, race, educational level, and *APOE* status; model goodness of fit was confirmed with the Hosmer-Lemeshow test (*P* = .27). Models had low residuals and were without evidence of high leverage points. The same analyses were then repeated using a single variable for the number of vascular risk factors (midlife or late life in separate models). Based on a priori hypotheses, models were then stratified by race, sex, and *APOE* status (1 or 2 ε4 alleles vs 0 ε4 alleles), with formal tests for interaction by race, sex, and *APOE* status. *P*<.05 was considered statistically significant; testing was 2-sided.

Sensitivity analyses stratified the sample by cognitive status, with separate analysis of individuals with normal cognition or with mild cognitive impairment, in addition to the evaluation of other florbetapir cut points. In addition, multiple imputation was used as a sensitivity analysis for the 21 indi-

viduals excluded because of missing covariate data. Amyloid deposition in distinct regions of interest was also considered.

Results

Participants were a mean age of 52 years at the time of midlife vascular risk factor assessment and 76 years at the time of PET imaging; median follow-up was 23.5 years (interquartile range, 23.0-24.3 years). Fifty-seven percent of the sample was white and 43% black (**Table 1**). Rates of hypertension and diabetes increased from midlife to late life (Table 1), as did BMI and the stroke risk score, and lipid levels and smoking rates decreased. No participant had 5 vascular risk factors at either visit 1 or 5, and the number of risk factors was greater at visit 5 than at visit 1. At visit 1, 65 participants (20%) had no risk factors, 123 (38%) had 1 risk factor, and 134 (42%) had 2 or more risk factors. Of the 346 participants who underwent florbetapir PET imaging, 24 were excluded, leaving 322 participants for analysis (eFigure and eTable 1 in the Supplement). Defined as positive above the sample median, 164 (50.9%) of the cohort had an elevated amyloid SUVR.

Evaluation of Vascular Risk Factors and Late-Life Brain Amyloid

In the overall sample, elevated midlife BMI was the only vascular risk factor with a statistically significant association with elevated late-life brain amyloid (odds ratio [OR], 2.06; 95% CI, 1.16-3.65) (**Table 2**). Risk factor–amyloid relationships did not differ by race, as indicated by non–statistical significance in interaction terms (*P* values between .054 and .93 for each midlife individual risk factor).

Cumulative Number of Vascular Risk Factors

A higher number of vascular risk factors in midlife, but not in late life, was associated with elevated brain amyloid. Thirty-one percent of individuals with 0 vascular risk factors in midlife had elevated amyloid in late life compared with 61% of individuals with at least 2 vascular risk factors in midlife who had elevated amyloid in late life (difference in proportions, 30.4%; 95% CI, 16.4%-44.3%). When evaluated continuously, each additional midlife vascular risk factor was associated with an increased odds of elevated SUVR (OR, 1.41; 95% CI, 1.09-1.83); similar results were seen when numbers of risk factors were categorized, and each category was compared with having 0 risk factors (**Table 3**). Having more risk factors was associated with higher odds of elevated SUVR, with strongest associations in midlife and with decreasing ORs associated with increasing numbers of risk factors as they were considered at older ages (**Figure 1**). Fewer individuals had 0 vascular risk factors in late life, but amyloid levels were elevated in 37% of this group; amyloid positivity was more frequent among people with 2 or more vascular risk factors in late life (compared with no risk factors, difference in proportions, 18.5%; 95% CI, 1.1%-53.1%) (Table 3).

The observed association between number of risk factors and elevated odds of amyloid was found only in white

Table 1. Participant Characteristics Overall and by Race (N = 322)

Characteristics	ARIC Study Visit 1 (1987-1989)			ARIC Study Visit 5 (2011-2013)		
	Overall (N = 322)	Black Participants (n = 139)	White Participants (n = 183)	Overall (N = 322)	Black Participants (n = 139)	White Participants (n = 183)
Age, mean (SD), y	52.2 (5.2)	52.0 (5.1)	52.4 (5.3)	75.8 (5.3)	75.6 (5.2)	76.0 (5.5)
Female, No. (%)	185 (57.5)	85 (61.2)	100 (54.6)	185 (57.5)	85 (61.2)	100 (54.6)
Education level, No. (%)						
College, graduate, or professional school	132 (41.0)	60 (43.2)	72 (39.3)	132 (41.0)	60 (43.2)	72 (39.3)
High school, GED, or vocational school	139 (43.2)	50 (36.0)	89 (48.6)	139 (43.2)	50 (36.0)	89 (48.6)
Less than high school	51 (15.8)	29 (20.9)	22 (12.0)	51 (15.8)	29 (20.9)	22 (12.0)
APOE ε4 genotype, No. (%)						
2/2, 2/3, or 3/3	222 (68.9)	88 (63.3)	134 (73.2)	222 (68.9)	88 (63.3)	134 (73.2)
2/4 or 3/4	92 (28.6)	46 (33.1)	46 (25.1)	92 (28.6)	46 (33.1)	46 (25.1)
4/4	8 (2.5)	5 (3.6)	3 (1.6)	8 (2.5)	5 (3.6)	3 (1.6)
Body mass index, mean (SD)[a]	27.4 (4.4)	28.4 (4.5)	26.7 (4.1)	29.0 (5.3)	29.8 (5.3)	28.4 (5.1)
Body mass index ≥30, No (%)	83 (25.8)	45 (32.4)	38 (20.8)	121 (37.6)	62 (44.6)	59 (32.2)
Current smoking, No. (%)	55 (17.1)	24 (17.3)	31 (16.9)	16 (5.0)	8 (5.8)	8 (4.4)
Hypertension, No. (%)	95 (29.5)	58 (41.7)	37 (20.2)	230 (71.4)	114 (82.0)	116 (63.4)
Diabetes, No. (%)	20 (6.2)	7 (5.0)	13 (7.1)	130 (40.4)	55 (39.6)	75 (41.0)
Total cholesterol, mean (SD), mg/dL	208.3 (39.0)	211.3 (41.9)	206.0 (36.6)	180.8 (39.6)	185.1 (42.2)	177.5 (37.4)
Total cholesterol ≥200 mg/dL, No. (%)	180 (55.9)	79 (56.8)	101 (55.2)	94 (29.2)	47 (33.8)	47 (25.7)
10-y stroke risk score, median (IQR), %[b]	1.0 (0.6-1.7)	1.4 (0.8-2.4)	0.8 (0.5-1.3)	11.9 (5.3-22.6)	14.0 (7.2-27.4)	8.6 (4.0-17.9)
No. of vascular risk factors, No. (%)[c]						
0	65 (20.2)	22 (15.8)	43 (23.5)	35 (10.9)	6 (4.3)	29 (15.9)
1	123 (38.2)	46 (33.1)	77 (42.1)	82 (25.5)	30 (21.6)	52 (28.4)
2	93 (28.9)	46 (33.1)	47 (25.7)	116 (36.0)	57 (41.0)	59 (32.2)
3	40 (12.4)	25 (18.0)	15 (8.2)	79 (24.5)	42 (30.2)	37 (20.2)
4	1 (0.3)	0	1 (0.6)	10 (3.1)	4 (2.9)	6 (3.3)
5	0	0	0	0	0	0
Mild cognitive impairment, No. (%)				87 (27.0)	37 (26.6)	48 (27.3)

Abbreviations: ARIC, Atherosclerosis Risk in Communities; GED, General Educational Development; IQR, interquartile range.

SI conversion: To convert cholesterol to millimoles per liter, multiply by 0.0259.

[a] Calculated as weight in kilograms divided by height in meters squared.

[b] For the 10-year stroke risk score at visit 1, 305 (n = 134 black participants and n = 171 white participants) had nonmissing data; at visit 5,

304 (n = 131 black participants and n = 173 white participants) had nonmissing data. The 10-year stroke risk score includes race, smoking status, age, prior coronary heart disease, antihypertensive medication use, left ventricular hypertrophy, diabetes status, systolic blood pressure, and sex.[21]

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

participants (eTable 2 in the Supplement), with an increased odds of elevated amyloid per additional vascular risk factor in midlife (OR, 1.66; 95% CI, 1.15-2.39) in white participants compared with a smaller and nonsignificant increase in black participants per additional risk factor (OR, 1.26; 95% CI, 0.85-1.88). However, the statistical test for interaction of race by number of risk factors was not significant (P = .42). Similarly, a significant association was found in men (OR, 6.77; 95% CI, 2.37-19.35) but not in women (OR, 1.71; 95% CI, 0.66-4.45), with imprecise estimates and non–statistically significant tests for interaction (P=.36) (eTable 3 in the Supplement).

Association of APOE With Vascular Risk Factor–Brain Amyloid Associations

No interaction P values for individual vascular risk factors by APOE status reached statistical significance. Odds of el-

evated florbetapir in participants with elevated BMI were statistically similar regardless of APOE status (OR, 2.48 [95% CI, 1.26-4.88] in APOE ε4 carriers and OR, 1.11 [95% CI, 0.85-1.44] in noncarriers; interaction P=.50). All 5 individuals with diabetes in midlife and who had an APOE ε4 allele who were included in the study had elevated SUVR, but continuous fasting glucose in visit 1 among the 299 participants who fasted was not significantly associated with florbetapir uptake in people with an ε4 allele (OR, 1.96; 95% CI, 0.74-5.19) or in those without (OR, 0.89; 95% CI, 0.61-1.32; interaction P=.12).

When continuous SUVR was evaluated visually, increasing numbers of ε4 alleles did appear to be associated with higher florbetapir in the setting of increasing vascular risk (Figure 2).

Stratified analyses by APOE status showed no significant interaction between APOE and number of risk factors. There was no statistical difference in the odds of elevated amyloid

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

Risk Factors	Midlife (Study Visit 1, 1987-1989)			Late Life (Study Visit 5, 2011-2013)		
	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)

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

SI conversion: To convert cholesterol to millimoles per liter, multiply by 0.0259.

[a] Models are adjusted for age (at visit 5, 2011-2013), sex, race, education level, *APOE* ε4 genotype, body mass index, current smoking, hypertension, diabetes, and total cholesterol at the same visit.

[b] Calculated as weight in kilograms divided by height in meters squared.

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.

in association with a larger number of midlife risk factors among ε4 carriers (OR, 2.46; 95% CI, 1.37-4.42) vs noncarriers (OR, 1.19; 95% CI, 0.87-1.61), with similar results when number of risk factors was treated categorically (Table 3). Increasing numbers of risk factors in late life were not associated with increased amyloid regardless of *APOE* status.

Sensitivity Analysis

When analyses were repeated comparing individuals by cognitive status, estimates for individual risk factors were not statistically significant and were imprecise (eTable 4 in the Supplement). Associations between number of vascular risk factors and amyloid positivity remained statistically significant only in the 87 individuals with mild cognitive impairment (eTable 5 in the Supplement).

Results were similar with SUVR cut points of 1.11 and 1.10 (eTable 6 in the Supplement). Analysis of separate regions of interest yielded similar results as the primary analysis.

Imputing missing covariate data (for the total N = 343) resulted in very similar results for the risk factor analysis (for 1 midlife vascular risk factor, OR, 1.81 [95% CI, 0.92-3.56], and for 2 midlife vascular risk factors, OR, 2.71 [95% CI, 1.39-5.39], compared with 0 midlife risk factors). Results were similar for evaluation of late-life vascular risk factor status when imputed data were included.

Discussion

In this study of brain florbetapir uptake in individuals without dementia from 3 US communities, a cumulative number of midlife vascular risk factors was associated with elevated brain amyloid. Relationships between vascular risk factors and brain amyloid did not differ by race, despite previous findings in this study that amyloid distribution differs by race.[14] Furthermore, these results were not supportive of a

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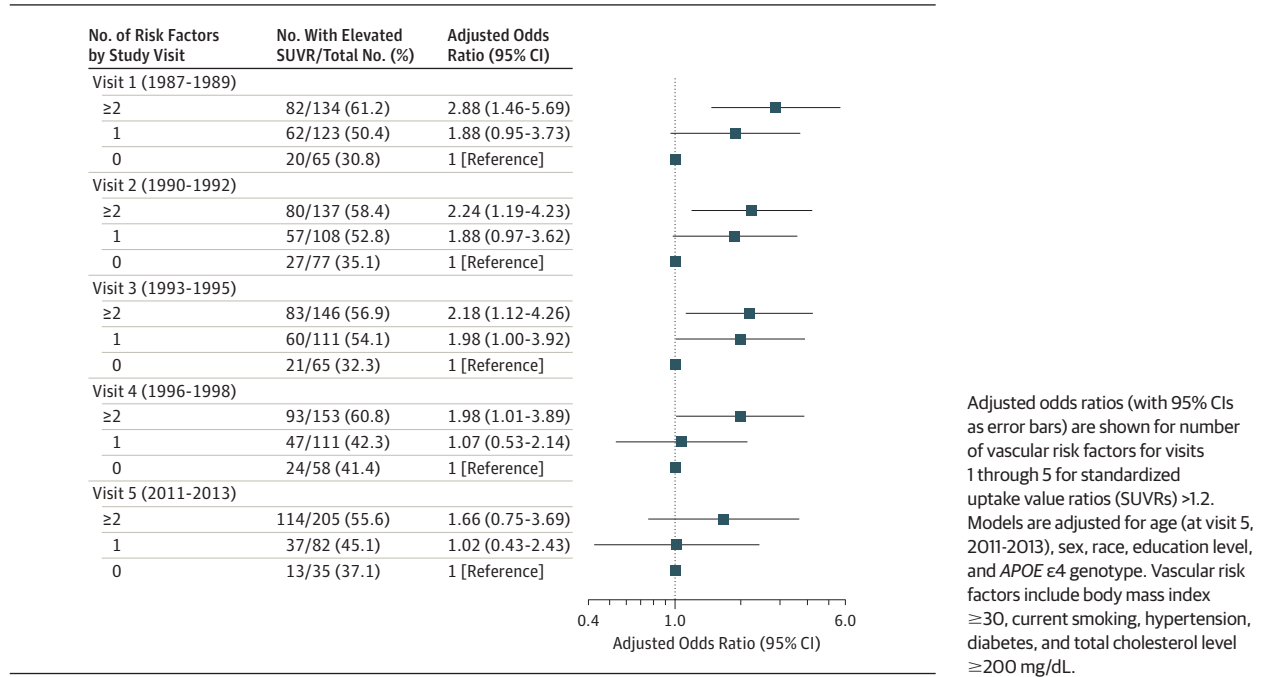

No. of Risk Factors by Study Visit	No. With Elevated SUVR/Total No. (%)	Adjusted Odds Ratio (95% CI)
Visit 1 (1987-1989)		
≥2	82/134 (61.2)	2.88 (1.46-5.69)
1	62/123 (50.4)	1.88 (0.95-3.73)
0	20/65 (30.8)	1 [Reference]
Visit 2 (1990-1992)		
≥2	80/137 (58.4)	2.24 (1.19-4.23)
1	57/108 (52.8)	1.88 (0.97-3.62)
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.

Figure 2. Locally Weighted Scatterplot Smoothing Curves Demonstrating Associations Between Midlife Vascular Risk Factors and Global Cortex Florbetapir SUVRs >1.2 by *APOE* Status
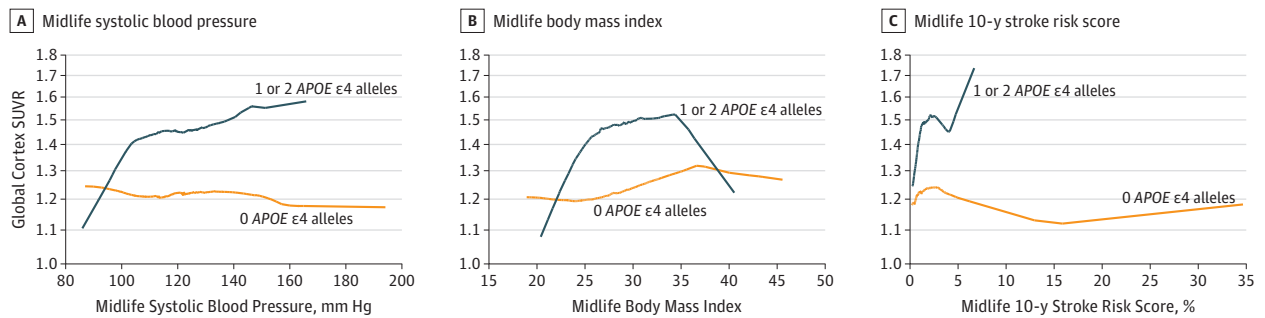
Curves show smoothed associations between vascular risk factors in midlife (visit 1, 1987-1989) and continuous global cortex florbetapir standardized uptake value ratios (SUVRs) by *APOE* status

(0 *APOE* ε4 alleles [n = 222] vs 1 or 2 *APOE* ε4 alleles [n = 100]). Body mass index was calculated as weight in kilograms divided by height in meters squared.

significant difference in association among people who were or were not carriers of an *APOE* ε4 allele. These data support the concept that midlife, but not late-life, exposure to these vascular risk factors is important for amyloid deposition.

Previous studies have demonstrated inconsistent results evaluating associations between vascular risk factors and brain amyloid. In multiple studies, diabetes has not been associated with elevated amyloid measured by Pittsburgh compound B (PiB) PET,[24,25] whereas others have reported elevated amyloid in association with elevated vascular risk (elevated Framingham coronary risk score was associated with elevated PiB independent of any *APOE* effect[26]). Animal data support a direct effect of vascular disease, especially hypertension, on the deposition of brain amyloid.[27,28]

The concept that vascular risk factors contribute to brain amyloid particularly—or even only—in the setting of an additional risk factor, namely *APOE* status, has been supported by previous studies. In this study, there was no statistical evidence for a difference by *APOE* status, but the study may have been underpowered to detect this interaction. In 118 cognitively healthy adults, hypertension and *APOE* interacted in the prediction of risk of florbetapir amyloid uptake,[29] and in an autopsy study, diabetes was associated with AD neuropathology only among *APOE* ε4 carriers.[30] Further evaluation of these relative pathologies on cognitive performance is needed because it is likely that vascular risk factors, *APOE*, AD neurodegeneration, and amyloid deposition all play a role, some of which may affect each other, in cognition. The Framingham

stroke risk score has been most strongly associated with cognition in individuals without increased AD neuropathology on autopsy,[31] and in the Alzheimer Disease Neuroimaging Initiative, amyloid and vascular pathology acted additively and not synergistically, and independently of one another, in increasing association with cognitive decline.[32]

This study focused on vascular risk factors, rather than clinical or subclinical vascular disease itself. Subclinical vascular disease might mediate the association of cumulative vascular risk factors with amyloid deposition. Although some authors have failed to find an association between radiographic vascular disease on MRI and PiB,[33] arteriolar disease on autopsy has been associated with worsening AD neuropathology, independent of infarctions,[34] suggesting that there may be aspects of brain vascular disease that, if adequately measured, might be important in increasing risk of amyloid deposition. An alternative hypothesis, supported by the findings of this study, is that vascular disease, particularly at the arteriolar level, might reduce vascular clearance of amyloid.[35,36]

Limitations

This study has several limitations. The lack of an association with individual vascular risk factors may not reflect a true null relationship but instead may reflect inadequate sample size; the same may be true for the lack of an association in black participants (inadequate power to detect these associations or to detect interactions by race) or in noncarriers of an *APOE* ε4 allele. This relatively modest sample size makes it difficult to make conclusions about any true interaction by *APOE* status. By excluding individuals with dementia, it is likely that ARIC participants seen in 1987-1989 with the highest amounts of both vascular disease and amyloid deposition were excluded from these analyses because they developed dementia or died prior to ARIC-PET. Thus, in participants reaching late life with relatively healthy cognition, it might be expected that the opposite relationship would have been observed, namely that ARIC survivors with multiple midlife risk factors would have had less brain amyloid. These *APOE* findings would argue against this concern about selection bias, however, because individuals with all 3 risk factors for dementia (ε4 carriage, vascular risk, and elevated amyloid deposition) survived to participate in this study. Furthermore, analysis by cognitive status demonstrated that higher vascular risk in midlife was associated with elevated amyloid among individuals with mild cognitive impairment at the time of amyloid imaging.

Relatively few people with very high vascular risk in midlife survived to the PET visit or met entry criteria for the study, supporting the likelihood that the true strength of association of vascular risk with amyloid risk may have been underestimated as a result of this survival bias. Furthermore, although representative of the community, this study has a higher prevalence of diabetes in late life than has otherwise been described,[37] with very high rates of hypertension; the frequency of these risk factors might dilute their association in late life. In addition, the chronological distinction between midlife and late life is not sharp, so some participants at visits 2 and 3, when an association (although decreased) between number of risk factors and amyloid positivity was still noted, were in their 60s. In addition, prevalence of amyloid positivity is reported to be less than 20% in persons with healthy cognition in the age range of our cohort,[38] but without PET at the midlife visit, it is not certain that none of our participants were amyloid positive at the time of their first visit.

Conclusions

An increasing number of midlife vascular risk factors was significantly associated with elevated amyloid SUVR; this association was not significant for late-life risk factors. These findings are consistent with a role of vascular disease in the development of AD.

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