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Midlife Vascular Risk Burden and Dementia-Free Survival Years

The Atherosclerosis Risk in Communities Neurocognitive Study

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Abstract

Background and Objectives

Midlife vascular risk factors are associated with both dementia and premature death; however, their combined association with dementia-free survival years remains unclear. This patient-centered outcome is critical for shared goal-setting. We estimated dementia-free survival from age 55 to 95 years according to midlife vascular risk burden.

Methods

We conducted a prospective cohort study (Atherosclerosis Risk in Communities study) with participants from 4 US communities. Participants were alive and dementia-free at age 55 years and had visit 2 (1990–1992) measurements of diabetes (self-report, medication use, or HbA1c ≥ 6.5%), hypertension (BP ≥ 140/90 mm Hg or medication use), and current smoking. Vascular risk burden was defined as the count of these risk factors (0–3). Dementia was identified through cognitive assessments, informant interviews, and continuous surveillance through 2022 with expert adjudication. Death without dementia was ascertained from multiple sources, including the National Death Index. Using age as the time scale and accounting for competing mortality, we estimated cumulative incidence, cause-specific hazards, and restricted mean survival time of dementia. Analyses were stratified by sex, race, and apolipoprotein E (*APOE*)-ε4 status.

Results

Among 12,409 participants (mean age 56.2 ± 5.2 years; 56% female), over a median follow-up of 26.3 years (IQR 18.9–30.4), 3,008 developed dementia and 5,238 died dementia-free. Compared with 0 risk factors, 3 risk factors were associated with higher hazards of dementia (hazard ratio [HR] 2.69, 95% CI 1.94–3.73) and death without dementia (HR 5.61, 95% CI 4.67–6.74). Higher vascular burden was associated with fewer dementia-free survival years, declining from 30.1 years (95% CI 29.9–30.4) for 0 risk factors to 17.5 years (95% CI 16.3–18.7) for 3 risk factors. Dementia cumulative incidence rose earlier but was lower by age 95 years in the highest-risk group because competing mortality was substantially greater. Women lived longer dementia-free than men (18.1 vs 16.6 years with 3 risk factors). Black participants had shorter dementia-free survival than White participants (16.0 vs 19.6 years).

Discussion

Maintaining optimal midlife vascular health was associated with up to 12.6 additional dementia-free survival years, reflecting both higher dementia hazard and markedly higher competing mortality. Expressing vascular risk in time-based terms offers a clear, patient-centered framework to motivate prevention strategies that preserve both cardiovascular and cognitive health.

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Glossary

APOE = apolipoprotein E; **ARIC** = Atherosclerosis Risk in Communities; **BMI** = body mass index; **CIF** = cumulative incidence functions; **HR** = hazard ratio; **RMST** = restricted mean survival time.

Introduction

Dementia poses an enormous clinical and public health challenge, with approximately 42% of US middle-aged adults potentially developing dementia during their lifetime.[1] Prevention is critical given the limited availability of effective disease-modifying therapies. Vascular risk factors—including diabetes,[2-4] hypertension,[2,4-6] and smoking[2,7]—are well-established contributors to dementia risk. These factors often emerge in midlife and exert lasting effects on neurodegenerative pathology, underscoring the critical importance of early identification and management.[4,8-10] Although previous research has demonstrated that poorer cardiovascular health at age 50 years increases dementia incidence risk,[11,12] these studies have largely focused on etiologic associations or cumulative risk metrics, which do not directly capture how vascular health shapes the timing and duration of dementia-free survival years.

We recently[13] demonstrated that 22%–44% of dementia cases by age 80 years could be attributed to midlife and late-life vascular risk factors, accounting for their combined contribution.[13] Although population attributable fractions are valuable for public health planning and resource allocation, they do not directly inform how vascular profiles could affect both overall and dementia-free lifespan.

Our study complements this important work by shifting focus from probability-based and attributable risk metrics to a time-based estimand—dementia-free survival years, which quantifies the expected duration of life lived cognitively intact. This outcome integrates 2 clinically relevant processes: incident dementia and death before dementia, therefore reflecting the competing risks that shape real-world aging trajectories. In contrast to previous Atherosclerosis Risk in Communities (ARIC) studies, this framework emphasizes how vascular health influences the balance between longevity and cognitive health over the life course. As a time-based measure, dementia-free survival is intuitive for clinical communication, supports shared decision-making, and provides concrete motivation for long-term implications of vascular risk factor management.

In this study, we aimed to quantify dementia-free survival from age 55 to 95 according to midlife vascular risk burden, overall and across key demographic characteristics and genetic susceptibility. To achieve these aims, we analyzed data in the ARIC study, a community-based study with rigorous ascertainment of dementia, comprehensive measurement of midlife vascular risk factors, and long-term follow-up into late life.

Methods

Study Population

The ARIC study, initiated in 1987–1989, is a community-based longitudinal cohort of 15,792 adults aged 45–64 years from 4 US communities: Forsyth County, North Carolina; Jackson, Mississippi; Minneapolis Suburbs, Minnesota; and Washington County, Maryland.[14] All participants provided written informed consent, and the study received approval from the institutional review boards at all participating research sites.

We chose visit 2 (1990–1992, participants age 46–70 years) as the baseline because it was the first visit that included cognitive assessments and measurement of HbA1c, a key exposure in this analysis (n = 13,165). We excluded participants with prevalent dementia (n = 4), individuals who self-reported their race as Asian or American Indian/Alaskan Native/other because of small sample sizes (n = 41), individuals with less than 1 year of follow-up (n = 62), and individuals who died or were lost to follow-up before visit 2 or age 55 (the index age for our primary analyses, n = 59). Participants with missing information on covariates (n = 590; 4.5%) were excluded, consistent with ARIC analytic standards when the proportion of missingness is low. The resulting analytic sample comprised 12,409 participants.

Exposure Assessment

We examined diabetes, hypertension, and smoking status in midlife (visit 2). Diabetes was defined by a self-reported history of a physician's diagnosis, use of diabetes medication, or an HbA1c level ≥6.5%. Hypertension was defined as a systolic blood pressure of 140 mm Hg or higher, a diastolic blood pressure of 90 mm Hg or higher, or the utilization of blood pressure-lowering medications. Smoking status was classified according to self-report as current, former, or never smoker with former and never smokers combined as the reference group. We focused on hypertension, diabetes, and smoking because they were consistently measured in ARIC, are major modifiable risk factors of both dementia and mortality, and demonstrated comparable strengths of association with dementia-free survival (eFigure 1). To evaluate the cumulative impact of vascular risk factors, we categorized participants into 4 groups based on the number of risk factors present (0, 1, 2 or 3).

Ascertainment of Dementia and Mortality

Dementia was defined based on a comprehensive, multisource ascertainment approach to ensure robust classification. Cognitive function was assessed using 3 sources of data: in-person

study visits, telephone-based interviews, and surveillance of medical and death records.[15]

First, during in-person study visits, cognitive testing began with a 3-test neurocognitive battery at visit 2 (1990–1992) and visit 4 (1996–1998), followed by an extensive 10-test neuropsychological battery[16] in subsequent visits from visit 5 (2011–2013) through visit 10 (2022), using standardized and well-validated measures evaluating a range of cognitive domains. From visit 5 onward, dementia evaluations also included informant interviews incorporating the Clinical Dementia Rating scale and the Functional Activities Questionnaire.[17,18] Diagnoses of dementia were initially determined using a computerized algorithm that adhered to the guidelines by the National Institute on Aging and the Alzheimer's Association, as well as the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.[19] These diagnoses were subsequently adjudicated by an expert panel to ensure accuracy.

Second, for participants who were unable to attend study visits, dementia was ascertained through annual phone calls before 2012 or semiannual phone calls started in 2012. These interviews employed with participants and informants using validated instruments including the Telephone Interview for Cognitive Status, the Clinical Dementia Rating scale, the Functional Activities Questionnaire, the Six-Item Screener, and the Ascertain Dementia 8-item screener.[17,18,20-23]

Third, ARIC investigators conducted continuous surveillance using diagnostic codes in hospital records or death certificates for all participants following ARIC standard procedures.[14] When feasible, we confirmed these dementia diagnoses through informant interviews using the Ascertain Dementia 8-item screener.[23]

The date of dementia onset was defined as the earliest diagnosis recorded from any of these sources. For cases identified through informant telephone interviews or hospital or death records, an adjustment of 180 days was applied to account for potential reporting delays.

Mortality was ascertained by contacting participant proxies, obituaries, hospital records, death certificates, or vital statistics from the National Death Index.

Covariates Collection and Processing

Most covariates were assessed at visit 2 (1990–1992), with sociodemographic variables collected at visit 1 (1987–1989). Physical activity was also carried forward from visit 1.

Sex, race, and educational attainment were self-reported at visit 1. Educational attainment was classified as less than high school, high school graduate or equivalent, and some college or higher. ARIC study centers (Forsyth County, Jackson, Minneapolis Suburbs, and Washington County) were included to account for geographic variability. Physical activity levels were evaluated at visit 1 using the Baecke questionnaire[24] with classifications aligning with AHA guidelines into ideal, intermediate, and poor levels of activity.[25]

Weight and height were measured at visit 2, and body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). BMI was then categorized based on clinically meaningful cutoffs into 4 groups: normal weight (<25 kg/m^2); overweight (25 to <30 kg/m^2); obesity (30 to <40 kg/m^2); and extreme obesity (≥40 kg/m^2). Prevalent stroke was initially identified through self-report before visit 1, and subsequently adjudicated by an expert committee before or at visit 2 based on medical records. Apolipoprotein E (*APOE*)-*ε4* allele status (0, 1 or 2 alleles) was determined at visit 2 to account for genetic predispositions, using TaqMan assay (Applied Biosystems, Foster City, CA).

Statistical Analysis

Baseline Characteristics

We summarized baseline characteristics using proportions for categorical variables and means with SD for continuous variables, overall and stratified by the number of vascular risk factors.

Survival Analysis and Follow-Up

We used age as the time scale, with age 55 as the time origin. Participants who were aged 55 or older at visit 2 (1990–1992) entered the study at their baseline age (late entry), whereas those younger than 55 entered the risk set at age 55. To ensure comparability, we included only individuals who were alive and dementia-free at age 55. Follow-up time was measured from study entry until the age at first occurrence of dementia, death, loss to follow-up, or administrative censoring on November 1, 2022. To enhance robustness, we set age 95 as the study exit, given the limited number of participants surviving beyond this age.

Cumulative Incidence Estimation of Dementia and Mortality

To estimate crude dementia cumulative incidence while accounting for competing mortality, we used the nonparametric cumulative incidence functions (CIF).[26,27] Separate CIFs were estimated for dementia and for death without dementia, treating each as a competing event for the other. This approach removes individuals from the risk set at the time of death, appropriately accounting for competing mortality and preventing overestimation of dementia risk. The equation is in eMethods 1. We presented CIF curves for both dementia and dementia-free death to fully characterize the joint distribution of these competing outcomes.

Dementia-Free Survival and Postdementia Survival

We quantified dementia-free survival years using restricted mean survival time (RMST) analysis,[28] defined as the expected number of years lived alive and without dementia (dementia-free survival years) between ages 55–95 years. RMST was estimated as the integral of the probability of

remaining alive and dementia-free over age, where this probability was defined as 1 – dementia CIF – dementia-free death CIF, based on the nonparametric cumulative incidence curves. Thus, dementia-free survival reflects the time spent in the dementia-free state, derived directly from the empirical (crude) competing-risk curves. To examine robustness across different starting ages, we repeated analyses with left truncation at ages 65, 75, 85, and 90 years, allowing individuals to enter the risk set only if they remained alive and dementia-free at the corresponding age.

Postdementia survival years were estimated using Kaplan-Meier estimation, with follow-up time defined from dementia onset until death, loss to follow-up, or censoring at age 95. Because death is the only terminal event after dementia onset, no competing-risk adjustment was required.

We conducted subgroup analyses to examine variations in dementia-free survival and postdementia survival across key demographic subgroups and *APOE-ε4* genotype. 95% confidence intervals were computed using bootstrap methods with bias correction and acceleration (1,000 replications).

Cause-Specific Proportional Hazards Models

To examine the relative hazards, we used cause-specific Cox proportional hazards models for dementia and for dementia-free death, treating one outcome as a censoring event when modeling the other. These models adjusted for sex, education, race, physical activity, BMI, prevalent stroke, and *APOE-ε4* genotype. In addition, we modeled a composite outcome of dementia or dementia-free death to summarize the overall risk of experiencing either event. The proportional hazards assumption was assessed using Schoenfeld residuals.

Sensitivity Analysis

We conducted several sensitivity analyses. First, we estimated CIFs separately for each vascular risk factor to assess their individual impacts. Second, we computed age-specific cumulative incidence estimates across 10-year age intervals by the number of vascular risk factors. Third, we estimated dementia-free survival using model-based cumulative incidence functions derived from cause-specific hazards to assess consistency with the primary nonparametric estimates (equation in eMethods 2). Fourth, we repeated analyses excluding prevalent stroke to assess potential overadjustment. Fifth, we formally tested interactions by sex, race, and *APOE*-ε4 status.

All statistical analyses were performed using Stata/SE 17.0 (StataCorp, College Station, TX). A p value of less than 0.05 was considered statistically significant for all analyses.

Standard Protocol Approvals, Registrations and Patient Consents

The study was approved by each institution's institutional review board. All participants provided written informed consent.

Data Availability

ARIC data are available upon request.

Results

Baseline Characteristics

Among 12,409 participants, we observed 3,008 dementia cases and 5,238 deaths without dementia over a median follow-up of 26.3 years (Q1-Q3, 18.9–30.4 years). Participants with a greater burden of vascular risk factors had higher BMI, lower physical activity, lower educational attainment, and a greater prevalence of stroke (Table 1). They were also more likely to be Black and to carry at least one *APOE-ε4* allele.

Cumulative Incidence Estimates of Dementia and Competing Mortality

The incidence rate of dementia increased from 8.8 per 1,000 person-years for those with no vascular risk factors to 12.5 per 1,000 for those with 3 risk factors. The incidence of dementia-free mortality increased more substantially, from 10.5 per 1,000 person-years for those with no vascular risk factors to 42.3 per 1,000 for those with 3 risk factors (eTable 1). Thus, higher vascular risk burden was associated with increases in both dementia and mortality, with a markedly stronger gradient observed for mortality.

Individuals with a greater number of midlife vascular risk factors experienced higher dementia cumulative incidence at younger ages. However, their lifetime cumulative incidence of dementia was lower, despite higher incidence rates compared with those with fewer or no vascular risk factors. This was consistent with substantially higher competing mortality (Figure 1; eTable 2). By age 75, the cumulative incidence estimates of dementia were 10% (95% CI 6%–15%) and 3% (95% CI 2%–3%) for participants with 3 vs zero vascular risk factors. However, by age 85, cumulative incidence estimates for dementia converged to approximately 18%–20% across all vascular risk factor groups. By age 95, participants with no vascular risk factors had the highest cumulative incidence of dementia of 42% (95% CI 40%–44%), whereas those with 3 vascular risk factors had only 23% (95% CI 17%–30%), reflecting higher competing mortality in this group.

In contrast, cumulative dementia-free mortality showed a consistent gradient based on vascular risk factors, with consistently higher mortality for those individuals with more risk factors. By age 75, 53% (95% CI 46%–60%) of individuals with 3 risk factors had dementia-free mortality, compared with 10% (95% CI 9%–10%) for those with no risk factors. By age 95, 74% (95% CI 67%–80%) of individuals with 3 risk factors had dementia-free mortality, compared with 44% (95% CI 42%–47%) for those with none.

Table 1 Baseline Characteristics Overall and by Number of Midlife Vascular Risk Factors (N = 12,409)

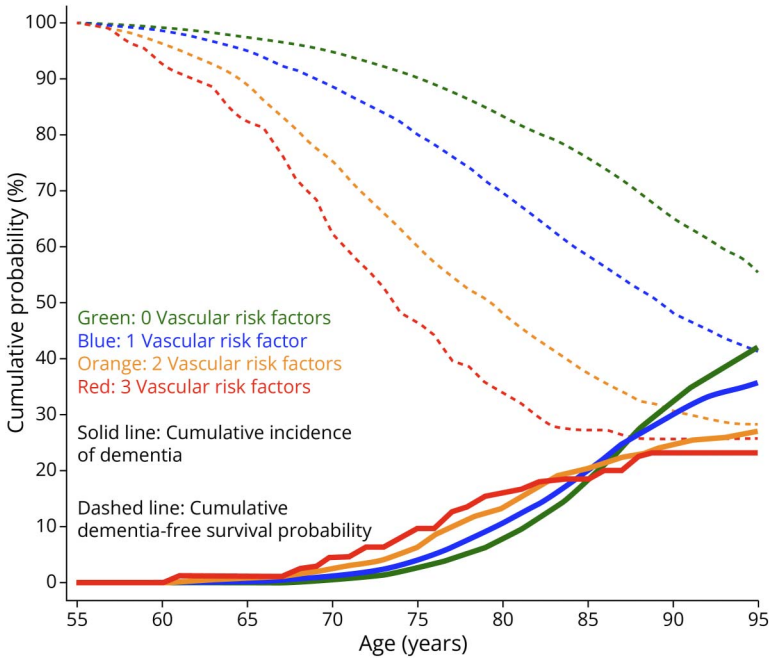
	Overall (N = 12,409)	0 Risk factors (N = 5,271)	1 Risk factor (N = 5,154)	2 Risk factors (N = 1,808)	3 Risk factors (N = 176)
Vascular risk factors, No. (%)					
Diabetes	1,535 (12.4)	0 (0)	409 (7.9)	950 (52.5)	176 (100)
Hypertension	4,959 (40.0)	0 (0)	3,116 (60.5)	1,667 (92.2)	176 (100)
Smoking	2,804 (22.6)	0 (0)	1,629 (31.7)	999 (55.4)	176 (100)
Age, mean (SD), y	56.2 (5.2)	55.6 (5.1)	56.5 (5.2)	57.2 (5.1)	57.3 (5.0)
Women, No. (%)	6,955 (56.0)	2,996 (56.8)	2,857 (55.4)	1,003 (55.5)	99 (56.2)
Race, No. (%)					
White	9,279 (74.8)	4,442 (84.3)	3,764 (73.0)	1,003 (55.5)	70 (39.8)
Black	3,130 (25.2)	829 (15.7)	1,390 (27.0)	805 (44.5)	106 (60.2)
Education, No. (%)					
Less than high school	2,586 (20.8)	707 (13.4)	1,154 (22.4)	644 (35.6)	81 (46.0)
High school graduate or equivalent	5,210 (42.0)	2,215 (42.0)	2,268 (44.0)	672 (37.2)	55 (31.2)
At least some college	4,613 (37.2)	2,349 (44.6)	1,732 (33.6)	492 (27.2)	40 (22.7)
ARIC field center, No. (%)					
Minneapolis suburbs	3,312 (26.7)	1,674 (31.8)	1,342 (26)	279 (15.4)	17 (9.7)
Jackson	2,755 (22.2)	746 (14.2)	1,225 (23.8)	696 (38.5)	88 (50)
Forsyth County	3,130 (25.2)	1,441 (27.3)	1,240 (24.1)	412 (22.8)	37 (21)
Washington County	3,212 (25.9)	1,410 (26.8)	1,347 (26.1)	421 (23.3)	34 (19.3)
Physical activity, No. (%)					
Poor	4,657 (37.5)	1,612 (30.6)	2,055 (39.9)	893 (49.4)	97 (55.1)
Intermediate	2,967 (23.9)	1,330 (25.2)	1,210 (23.5)	389 (21.5)	38 (21.6)
Ideal	4,785 (38.6)	2,329 (44.2)	1,889 (36.7)	526 (29.1)	41 (23.3)
Body mass index, No. (%)					
Normal or underweight, <25 kg/m^2	3,815 (30.7)	1,939 (36.8)	1,465 (28.4)	380 (21)	31 (17.6)
Overweight, 25 to <30 kg/m^2	4,942 (39.8)	2,203 (41.8)	2,052 (39.8)	628 (34.7)	59 (33.5)
Obesity, 30 to <40 kg/m^2	3,248 (26.2)	1,055 (20)	1,439 (27.9)	682 (37.7)	72 (40.9)
Extreme obesity, ≥ 40 kg/m^2	404 (3.3)	74 (1.4)	198 (3.8)	118 (6.5)	14 (8)
Prevalent stroke, No. (%)	209 (1.7)	28 (0.5)	90 (1.7)	75 (4.1)	16 (9.1)
***APOE*-ε*4* alleles, No. (%)**					
0	8,576 (69.1)	3,683 (69.9)	3,557 (69)	1,211 (67)	125 (71)
1	3,502 (28.2)	1,449 (27.5)	1,461 (28.3)	546 (30.2)	46 (26.1)
2	331 (2.7)	139 (2.6)	136 (2.6)	51 (2.8)	5 (2.8)

Abbreviations: *APOE* = apolipoprotein E; ARIC = Atherosclerosis Risk in Communities; CI = confidence interval.

Dementia-Free Survival and Postdementia Survival

Higher vascular burden was associated with fewer dementia-free survival years (Table 2). From age 55, individuals with no vascular risk factors experienced an average of 30.1 (95% CI 29.9–30.4) years dementia-free, while those with one, 2, and 3 vascular risk factors had dementia-free survival of 26.3 (95% CI 26.1–26.6), 21.0 (95% CI 20.5–21.4), and 17.5 (95% CI 16.3–18.7) years, respectively.

Figure 1 Cumulative Incidence of Dementia and Dementia-Free Survival Probability From Age 55 to 95, by Number of Midlife Vascular Risk Factors



Cumulative incidence curves for dementia (solid lines) and dementia-free survival probability (dashed line, 1 – cumulative incidence of dementia-free death) from age 55 to 95, by number of midlife vascular risk factors. Green indicates 0 vascular risk factors (N = 5,271); blue, 1 vascular risk factor (N = 5,154); orange, 2 vascular risk factors (N = 1,808); and red, 3 vascular risk factors (N = 176).

Among individuals with 3 risk factors, dementia risk increased with older index age—rising from 23% at age 55 to 37% at age 75 (eTable 3). By age 85, only 7% (13/176) of individuals with 3 risk factors remained dementia-free, compared with 35% (1,839/5,271) of those with no risk factors. Among those who developed dementia, the average postdementia survival ranged from 3.0 to 4.1 years across number of risk factors (Figure 2). As a result, individuals with higher vascular burden spent a greater proportion of their remaining life with dementia.

Dementia-free survival varied by sex, race, and *APOE-ε4* genotype, although the inverse association with vascular risk burden was consistent across all subgroups (Table 2). Women had longer dementia-free survival than men across all risk levels. Black participants had shorter dementia-free survival than White participants, with disparities widening at higher levels of vascular burden. APOE-ε4 carriers experienced shorter dementia-free survival compared with noncarriers. Formal interaction tests (eTable 4) suggested potential effect modification for dementia by sex (p = 0.020) and for death without dementia by race (p = 0.014).

In sensitivity analysis using model-based cumulative incidence functions derived from cause-specific Cox models, the estimates of dementia-free survival years and postdementia survival years (eTable 5) were consistent with the primary nonparametric estimates.

Relative Risk of Dementia and Mortality

Compared with individuals with no vascular risk factors, those with 3 vascular risk factors had a 2.69-fold (95% CI 1.94–3.73) increased hazard of developing dementia and a 5.61-fold (95% CI 4.67–6.74) increased hazard of mortality without dementia (Table 3). The composite outcome of dementia or dementia-free mortality showed a stepwise increase across risk factors, with HRs ranging from 1.56 (95% CI 1.48–1.64) for one risk factor to 4.38 (95% CI 3.73–5.13) for 3 risk factors.

Discussion

In this long-term prospective cohort study, better midlife vascular health was associated with longer dementia-free survival in a dose-response pattern. Individuals with no midlife vascular risk factors lived an average of 13 more dementia-free survival years compared with those with 3 risk factors. This association was consistent across demographic and *APOE-ε4* subgroups. Individuals with higher vascular risk burden were more likely to develop dementia or die at earlier ages, leading to shorter overall survival and fewer dementia-free survival years. These findings indicate that total cardiovascular burden, rather than isolated risk factors, is a key determinant of dementia-free survival.

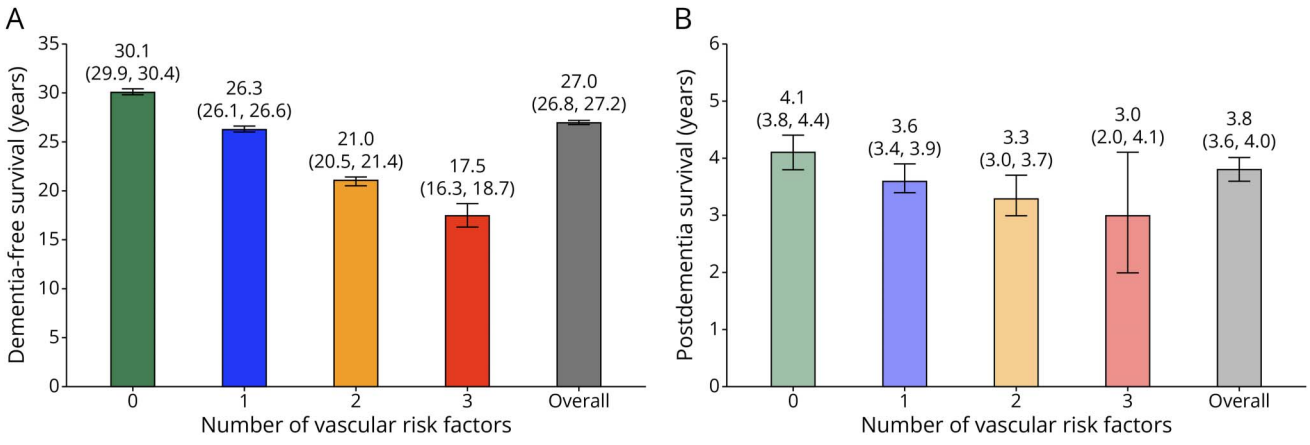
Our findings extend previous research linking midlife vascular health to cognitive aging. Previous studies have shown increased dementia risk with individual midlife vascular risk factors (e.g., hypertension, diabetes, and smoking).[29,30] However, few have examined the combined vascular risk profile to estimate absolute risk across the life course. Previous studies have linked poorer cardiovascular health in midlife to dementia incidence.[11,12] With a few exceptions, previous studies

Table 2 Dementia-Free Survival and Cumulative Incidence of Dementia by Age 95 Years, by Number of Midlife Vascular Risk Factors and Stratified by Sex, Race, and *APOE-ε4* Status

	Overall (N = 12,409)	0 Risk factors (N = 5,271)	1 Risk factor (N = 5,154)	2 Risk factors (N = 1,808)	3 Risk factors (N = 176)
Men					
Dementia-free survival, y (95% CI)	25.6 (25.4–25.9)	28.9 (28.5–29.3)	24.8 (24.4–25.2)	19.8 (19.2–20.4)	16.6 (14.9–18.3)
Cumulative incidence of dementia, % (95% CI)	32.8 (31.0–34.7)	40.6 (36.7–44.6)	30.3 (28.0–32.7)	20.5 (17.4–23.8)	28.6 (18.8–39.1)
Women					
Dementia-free survival, y (95% CI)	28.1 (27.8–28.3)	31.1 (30.8–31.4)	27.6 (27.2–27.9)	21.9 (21.3–22.4)	18.1 (16.5–19.8)
Cumulative incidence of dementia, % (95% CI)	40.3 (38.6–42.1)	43.9 (40.9–47.0)	40.1 (37.6–42.7)	31.8 (28.4–35.2)	18.9 (11.6–27.5)
White					
Dementia-free survival, y (95% CI)	27.8 (27.6–28.0)	30.5 (30.2–30.7)	26.7 (26.4–27.0)	21.2 (20.7–21.7)	19.6 (17.8–21.5)
Cumulative incidence of dementia, % (95% CI)	36.2 (34.7–37.7)	41.2 (38.6–43.7)	34.3 (32.3–36.3)	22.3 (19.5–25.1)	25.9 (16.1–36.9)
Black					
Dementia-free survival, y (95% CI)	24.6 (24.2–24.9)	28.3 (27.6–29.0)	25.4 (24.9–25.9)	20.6 (20.0–21.3)	16.0 (14.5–17.6)
Cumulative incidence of dementia, % (95% CI)	39.3 (36.8–41.9)	47.8 (42.0–53.3)	39.3 (36.0–42.7)	32.1 (28.4–36.0)	21.4 (14.1–29.8)
***APOE-ε4* non-carrier (0 alleles)**					
Dementia-free survival, y (95% CI)	27.6 (27.4–27.8)	30.8 (30.5–31.1)	26.9 (26.6–27.3)	21.2 (20.7–21.7)	17.5 (16.1–18.9)
Cumulative incidence of dementia, % (95% CI)	34.0 (32.4–35.5)	38.1 (35.2–41.0)	33.5 (31.3–35.7)	24.3 (20.9–27.8)	19.5 (12.8–27.3)
***APOE-ε4* carrier (1 or 2 alleles)**					
Dementia-free survival, y (95% CI)	25.6 (25.3–25.9)	28.6 (28.2–29.0)	24.9 (24.5–25.4)	20.5 (19.8–21.2)	17.4 (15.0–19.8)
Cumulative incidence of dementia, % (95% CI)	43.6 (41.5–45.7)	51.2 (47.2–54.9)	41.0 (38.0–43.9)	33.3 (29.2–37.3)	32.4 (20.0–45.4)

Abbreviations: *APOE* = apolipoprotein E; CI = confidence interval.

Figure 2 Dementia-Free Survival Years (A) and Postdementia Survival Years (B) by Number of Midlife Vascular Risk Factors



(A) Dementia-free survival years from age 55 to 95, by the number of midlife vascular risk factors (baseline N = 12,409). Green indicates 0 vascular risk factors (N = 5,271); blue, 1 vascular risk factor (N = 5,154); orange, 2 vascular risk factors (N = 1,808); red, 3 vascular risk factors (N = 176); gray, overall (N = 12,409). (B) Postdementia survival years, defined as the years from dementia development to age 95, by the number of vascular risk factors (baseline N = 3,008). Green indicates 0 vascular risk factors (N = 1,254); blue, 1 vascular risk factor (N = 1,306); orange, 2 vascular risk factors (N = 410); red, 3 vascular risk factors (N = 38); gray, overall (N = 3,008). Error bars reflect 95% confidence intervals. Survival years were estimated using the restricted mean survival time method.

Table 3 Adjusted Cause-specific Hazard Ratios for Dementia, Dementia-Free Mortality, and the Composite Outcome

	Dementia, adjusted HR (95% CI)	Dementia-free mortality, adjusted HR (95% CI)	Composite outcome[a], adjusted HR (95% CI)
Vascular risk factors[b]			
0	1 [Reference]	1 [Reference]	1 [Reference]
1	1.21 (1.12–1.31)	1.84 (1.73–1.97)	1.56 (1.48–1.64)
2	1.67 (1.49–1.88)	3.64 (3.36–3.95)	2.78 (2.61–2.97)
3	2.69 (1.94–3.73)	5.61 (4.67–6.74)	4.38 (3.73–5.13)
Sex			
Men	1 [Reference]	1 [Reference]	1 [Reference]
Women	0.92 (0.85–0.99)	0.59 (0.56–0.63)	0.69 (0.66–0.73)
Race			
White	1 [Reference]	1 [Reference]	1 [Reference]
Black	1.23 (1.12–1.34)	0.99 (0.92–1.06)	1.07 (1.01–1.12)
Education			
Less than high school	1 [Reference]	1 [Reference]	1 [Reference]
High school graduate or equivalent	0.75 (0.69–0.83)	0.87 (0.81–0.93)	0.82 (0.78–0.87)
At least some college	0.69 (0.63–0.77)	0.74 (0.69–0.80)	0.72 (0.68–0.77)
Physical activity			
Poor	1 [Reference]	1 [Reference]	1 [Reference]
Intermediate	0.86 (0.78–0.95)	0.90 (0.84–0.97)	0.89 (0.84–0.94)
Ideal	0.85 (0.78–0.92)	0.91 (0.86–0.98)	0.89 (0.84–0.93)
Body mass index			
Normal or underweight <25 kg/m^2	1 [Reference]	1 [Reference]	1 [Reference]
Overweight 25 to <30 kg/m^2	1.04 (0.95–1.14)	0.92 (0.86–0.98)	0.96 (0.91–1.02)
Obesity 30 to <40 kg/m^2	1.17 (1.06–1.29)	1.05 (0.98–1.13)	1.10 (1.03–1.16)
Extreme obesity ≥ 40 kg/m^2	1.30 (1.05–1.61)	1.39 (1.20–1.61)	1.36 (1.21–1.54)
Prevalent stroke			
No	1 [Reference]	1 [Reference]	1 [Reference]
Yes	1.52 (1.16–2.00)	1.58 (1.33–1.88)	1.57 (1.36–1.82)
***APOE*-ε4 Alleles**			
0	1 [Reference]	1 [Reference]	1 [Reference]
1	1.67 (1.55–1.80)	1.07 (1.01–1.14)	1.26 (1.21–1.33)
2	3.31 (2.80–3.91)	1.07 (0.89–1.29)	1.75 (1.55–1.98)

Abbreviations: *APOE* = apolipoprotein E; CI = confidence interval; HR = hazard ratio.
[a] Composite outcome includes dementia or dementia-free mortality.
[b] Vascular risk factors include diabetes, hypertension, and smoking.

estimating dementia-free or postdementia survival have not examined how these outcomes vary according to combined vascular risk profiles in midlife. Consistent with these studies, our findings further highlight how the accumulation of vascular risk factors affects dementia-free survival. This shift from dementia incidence to dementia-free survival offers a clearer perspective for understanding the impact of vascular health on cognitive aging trajectories.

For interpretability, we used a simple unweighted count of 3 major vascular risk factors rather than a comprehensive cardiometabolic profile. This may not fully reflect clinical risk assessment but allows transparent translation of vascular burden into time-based outcomes. The findings highlight the importance of preventing the development of vascular risk factors by midlife to support longer, dementia-free lives. Current clinical guidelines already emphasize comprehensive cardiovascular risk assessment.[31,32] Our results support this approach by demonstrating that more adverse midlife vascular risk profile is associated with fewer dementia-free survival years. Beyond reducing risk alone, promoting longer life without dementia may be a meaningful target for both clinical care and public health planning. This dual emphasis on longevity and preservation of cognitive health is especially relevant in the context of global population aging.

Dementia-free survival differed by race, with Black participants experiencing fewer dementia-free survival years compared with White participants. Although the association between vascular risk burden and dementia-free survival was consistent across groups, Black participants had a higher burden of vascular risk factors, which likely contributes to these disparities. As a result, cardiovascular prevention strategies may offer the largest benefit in populations where the vascular burden is highest. Addressing both clinical prevention and social determinants of health will be essential for reducing disparities in dementia.

As more individuals reach older ages, the number living with dementia will continue to grow, even as vascular health improves. Our findings support midlife vascular prevention as a complementary strategy to emerging pharmacologic therapies, which remain limited to early-stage disease.[33-36] Delaying dementia onset through midlife risk factor management may reduce population burden and help extend the effectiveness window for late-life interventions.

Several biologic pathways likely underlie our observed associations between vascular health and dementia-free survival, including chronic cerebrovascular injury, neuroinflammation triggered by vascular damages through hypertension and diabetes,[37-42] and cumulative oxidative stress resulting from smoking.[43,44] Together, these factors likely accelerate atherosclerosis, increase stroke risk, and may facilitate Alzheimer disease pathology through promoting amyloid plaques and tau tangles.

Strengths of our study include the large, diverse cohort with decades of follow-up and comprehensive assessment on vascular risk factors, allowing robust and longitudinal analysis. The ARIC study's rigorous dementia ascertainment and adjudication protocols ensured accurate case identification across the entire cohort. The use of competing risk models allowed for accurate estimation of lifetime dementia risk and dementia-free survival.

Several limitations should be noted. First, our analysis relied on a single midlife assessment of vascular risk factors and therefore does not capture changes over time. However, it avoids potential reverse causation, where early cognitive decline may influence the treatment of vascular conditions and bias associations toward the null. As vascular risk factors tend to worsen over time, this approach may underestimate the cumulative impact of sustained or increasing exposure. Second, dementia ascertainment may have differed between participants who attended recent visits and those who did not. In-person neurocognitive testing provides more comprehensive assessment, potentially leading to differential accuracy in dementia diagnosis. Third, covariates were assessed at visit 1 or 2, while age 55 was used as the time origin. Although this introduces slight misalignment, the use of left truncation at the age of covariate measurement helps minimize potential bias. Last, we could not account for potential interactions among risk factors or fully eliminate the possibility of residual confounding, as with all observational studies.

In summary, individuals with zero midlife vascular risk factors experienced approximately 13 additional dementia-free survival years compared with those with 3 vascular risk factors. Although optimal vascular health extends dementia-free survival, it also increases lifetime dementia risk because of longer survival. These findings highlight the need for early vascular prevention to maintain brain health and extend dementia-free survival, alongside planning for increased dementia care in aging populations.

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Author Contributions

J. Hu: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data. J. Coresh: major role in the acquisition of data; study concept or design. J.R. Smith: drafting/revision of the manuscript for content, including medical writing for content. A.R. Sharrett: drafting/revision of the manuscript for content, including medical writing for content. R.F. Gottesman: drafting/revision of the manuscript for content, including medical writing for content. P.L. Lutsey: drafting/revision of the manuscript for content, including medical writing for content. T.H. Mosley: drafting/revision of the manuscript for content, including medical writing for content. E. Selvin: drafting/revision of the manuscript for content, including medical writing for content; study concept or design. M. Fang: drafting/revision of the manuscript for content, including medical writing for content; study concept or design. J. Weiss: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data.

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Disclosure

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