

Carotid inflammation on FDG-PET is associated with lower cognitive performance in people with treated HIV infection

Meg Wilson^a, Alaa Abdellatif^{b,c,d}, Shady Abohashem^e, Elissa S. Epel^f, Ahmed Tawakol^{e,g}, Priscilla Y. Hsue^h and Felicia C. Chow^{a,i}

Objectives: Carotid atherosclerosis is an established risk factor for cognitive impairment. FDG-PET detects subtle inflammatory changes in the arterial wall that may precede plaque formation and rupture. We investigated whether carotid inflammation is associated with cognitive function and its relative importance as a predictor of concurrent cognitive function compared with other factors.

Design/methods : In this cross-sectional study, we recruited individuals ≥ 40 years with undetectable viral load at moderate-to-high cardiovascular risk. Participants underwent FDG-PET, stress and cognitive assessments. We used pairwise partial correlations to identify significant associations between arterial inflammation and cognition. We applied a machine learning analysis workflow to evaluate the ability of carotid inflammation alone, and in combination with other factors, to predict cognition.

Results: Among 47 people, carotid inflammation was independently correlated with global cognition [$r = -0.405$, 95% confidence interval (CI) -0.618 to -0.100 , $P = 0.007$]. In the machine learning analysis, the probability of carotid inflammation predicting cognitive function within one standard deviation of the true value was 68% (95% CI 52–80). The predictive accuracy improved marginally when individual cardiometabolic factors were added to the model (73%, 95% CI 57–84). When all potential variables were considered, predictive accuracy improved substantially (85%, 95% CI 71–93), with carotid inflammation remaining as the most important cardiometabolic predictor of cognitive function.

Conclusion: Carotid inflammation on FDG-PET outperformed most other factors in predicting concurrent cognitive function and provided unique predictive information beyond traditional cardiometabolic risk factors. Future longitudinal studies should examine whether carotid inflammation predicts incident cognitive impairment, which would support its use as a clinical risk marker in people with HIV.

Copyright © 2026 Wolters Kluwer Health, LLC. All rights reserved.

AIDS 2026, **40**:1624–1633

Keywords: arterial inflammation, atherosclerosis, carotid artery disease, cognitive function, HIV

^aDepartment of Neurology, Weill Institute for Neurosciences, ^bCenter for AIDS Research (CFAR), ^cAIDS Research Institute, ^dData Science CoLab, University of California, San Francisco, San Francisco, ^eCardiovascular Imaging Research Center, Massachusetts General Hospital and Harvard Medical School, Boston, ^fDepartment of Psychiatry and Behavioral Sciences, Weill Institute for Neurosciences, University of California, San Francisco, San Francisco, ^gDepartment of Medicine (Cardiology), Massachusetts General Hospital and Harvard Medical School, Boston, ^hDepartment of Medicine (Cardiology), University of California, Los Angeles, Los Angeles, and ⁱDepartment of Medicine (Infectious Diseases), University of California, San Francisco, San Francisco, USA.

Correspondence to Felicia C. Chow, MD, MAS, University of California, San Francisco, San Francisco, CA, USA.

E-mail: felicia.chow@ucsf.edu

Received: 22 December 2025; revised: 19 April 2026; accepted: 23 April 2026.

DOI:10.1097/QAD.0000000000004573

Introduction

Atherosclerosis is a chronic inflammatory condition of the arteries that causes cardiovascular disease (CVD) events, including stroke. Like individual cardiometabolic comorbidities such as hypertension, carotid atherosclerosis is an established risk factor for cognitive impairment in the general population [1–3]. A similar picture has emerged in people with treated, virally suppressed HIV (people with HIV, PWH) whereby mounting data suggest cardiometabolic and other co-occurring conditions play a more substantial role in the development of cognitive impairment than HIV-specific factors [4,5]. Delineating modifiable risk factors and specific mechanisms underlying cognitive impairment in PWH is a critical first step toward developing more tailored interventions that can slow or prevent cognitive decline in this at-risk population [6].

¹⁸F-Fluorodeoxyglucose-positron emission tomography (FDG-PET) can detect arterial wall inflammation and plaque vulnerability, hallmarks of the presence and severity of atherosclerosis [7,8]. Arterial inflammation, as indicated by increased FDG uptake, is strongly predictive of ischemic stroke and other CVD events, independent of cardiovascular risk prediction scores or a history of cardiometabolic factors [10–12]. Excellent reproducibility and favorable inter- and intraobserver agreement [13] support the use of FDG-PET as a surrogate endpoint to assess therapeutic response in cardiovascular interventional trials [14]. Most studies have employed ultrasound to assess carotid disease, including quantifying carotid intima-media thickness and luminal stenosis [4,15]. However, while ultrasound can characterize the presence of arterial plaque and flow-related changes due to stenosis, it is less sensitive than FDG-PET in identifying subtle inflammatory changes in the arterial wall that may precede plaque formation and rupture [16].

In this cross-sectional study, we investigated whether arterial inflammation is associated with cognitive function in PWH and its relative importance in predicting concurrent cognitive function compared with individual cardiometabolic and other factors. Given the ability of FDG-PET to detect subtle atheroinflammatory changes in the vessel wall, we hypothesized that arterial inflammation would emerge as an important cross-sectional predictor of cognitive function.

Methods

Study design

In this single-center, cross-sectional study, we analyzed data from participants who were recruited between 2018 and 2021 from a parent study evaluating the impact of alirocumab on cardiovascular risk in PWH (NCT03207945). The study was completed in San Francisco, California, USA through

the University of California, San Francisco (UCSF) and Zuckerberg San Francisco General Hospital and Trauma Center and was approved by the UCSF Institutional Review Board. Written informed consent was obtained from all study participants.

Participants

The inclusion criteria for the parent trial included: age ≥ 40 years, on stable antiretroviral (ART) therapy, undetectable plasma viral load, and at moderate to high cardiovascular risk defined as a history of CVD [e.g., prior myocardial infarction (MI) or stroke, coronary heart disease, peripheral arterial disease] or of at least one cardiometabolic comorbidity (e.g., hypertension, hyperlipidemia, diabetes mellitus, cigarette smoking). Participants completed all procedures for this neurologic sub-study prior to randomization in the parent trial and within 3 months of FDG-PET.

Procedures

Arterial inflammation on FDG-PET

For the parent trial, FDG-PET of the neck and chest were performed at the UCSF Imaging Center at China Basin on a GE Discovery STE PET/computed tomography (CT) scanner, following a previously described protocol [14]. A low-dose CT scan was performed for attenuation correction before PET acquisition. FDG uptake corrected for background venous activity was assessed in the target vessels of interest (bilateral carotid arteries and ascending aorta) using previously validated methods [9,12]. Briefly, measurements were made in the axial plane, and maximum standardized uptake values (SUVmax) were recorded from predefined sections of the carotid and ascending aorta walls. The target-to-background ratio was defined as the ratio of the mean of the SUVmax measurements along the length of the target vessel to the background venous activity derived from either the internal jugular veins (for correction of carotid values) or the superior vena cava (for correction of aortic values).

Neuropsychological testing

Participants underwent the following neuropsychological test battery: the Hopkins Verbal Learning Test-Revised [17], Wechsler Adult Intelligence Scale-Revised Digit Symbol subtest [18], Grooved Pegboard Test [19], Stroop Color and Word Test [20], Controlled Oral Word Association Test (COWAT-FAS) [21], and Trail Making Test Parts A and B [22]. *z*-scores were derived by comparing raw scores to demographics and education-matched norms. Individual *z*-scores for each test were averaged into a global cognitive score, which was the primary measure of cognitive function. We also evaluated performance on each neuropsychological test using individual *z*-scores.

Psychological stress

The 10-item Perceived Stress Scale [23], which is a self-appraisal of stress in the past month; the Chronic Burden

Scale [24], which assesses chronic stress for a 6-month or longer interval; Adverse Childhood Experiences (ACEs) [25], which evaluates early life stress and trauma; the HIV Stigma Scale [26]; and Post-Traumatic Stress Disorder (PTSD) Civilian-Checklist were administered [27]. The Patient Health Questionnaire-9 was used to measure the presence and severity of depressive symptoms.

Other variables

Demographics, cardiometabolic comorbidities, health-related behaviors, and HIV-specific variables were extracted from data obtained at screening or entry for the parent trial or neurologic sub-study. This included information on prior MI or stroke; history of diabetes, hyperlipidemia, or hypertension; use of statins or antiplatelet medications; self-reported cigarette smoking or use of alcohol, stimulants, marijuana, and/or injection drugs; most recent and nadir CD4 count, year of HIV diagnosis, and current ART regimen.

Statistical analyses

Associations between arterial inflammation and global cognition and individual neuropsychological test z -scores were evaluated using pairwise Spearman partial correlations adjusted for age, race (dummy-coded), and education. For each pair, variables and covariates were rank-transformed, residualized on the full covariate set using ordinary least squares, and the partial correlation was computed as the Pearson correlation between residuals. Two-sided P -values were obtained from Pearson correlation tests on residuals (null: zero partial correlation). Analyses used complete cases per comparison. Although neuropsychological test z -scores were normed for demographics and education, we additionally adjusted for age, race, and education to minimize residual confounding beyond normative standardization and to account for cohort-specific associations of these factors with inflammation and cognition. Ninety-five percent confidence intervals (CIs) were estimated via nonparametric bootstrapping (5000 resamples), repeating the full procedure within each resample; CIs were defined by the 2.5th and 97.5th percentiles. Multiple comparisons were controlled using the Benjamini–Hochberg false discovery rate (FDR) across unique off-diagonal pairs ($q < 0.05$).

Based on the correlation results, we focused on carotid inflammation only. Cross-sectional machine learning models were then used to evaluate prediction of global cognition, using a Random Forest architecture to capture nonlinear relationships. A baseline model included carotid inflammation as the only predictor of global cognition. This was extended by adding candidate cardiometabolic variables (“CVD model”), followed by demographics, health-related behaviors, stress, and HIV-specific variables (“full model”). In a sensitivity analysis, a model that considered all candidate cardiometabolic factors, except for carotid inflammation, was compared with the CVD model to assess the incremental predictive value of carotid

inflammation. Data on statin use, which was missing for one participant, was imputed using the population mean in the training set only. Continuous features (i.e., predictors) were z -standardized within each split using training-set parameters; categorical variables were label-encoded except for race (one-hot encoded).

Feature selection for CVD and full models was performed once on the first train-test split by sequentially adding predictors and only retaining those that improved threefold cross-validated negative root-mean squared error (RMSE). Model training and evaluation were then repeated across eight random (90/10) train-test splits. Within each split, hyperparameters (number of estimator trees, maximum tree depth, minimum samples per split) were optimized via grid search with threefold cross-validation on training data only. The final model was refit on the training set and evaluated on the held-out test set.

Performance was assessed by the probability that predictions fell within one standard deviation (SD) of observed values, along with RMSE and mean absolute error (MAE) scores. Ninety-five percentage CIs for the probability metric were computed using the Wilson score method across pooled test predictions. Alternatively, RMSE and MAE uncertainty was estimated by bootstrapping across splits (10 000 resamples of per-split metrics; percentile CIs). A null model predicting the training-set mean was included for comparison. All evaluation procedures were repeated across eight random splits to improve robustness.

After training and evaluating the CVD and full models, feature importance was estimated using permutation importance on held-out test data, defined as the change in negative RMSE after permuting each predictor. This procedure used 50 permutation repeats per feature within each split and was repeated across eight splits; importance was summarized as mean $\pm$ SD, and within-split rankings were used to assess stability.

Finally, we repeated the same methodology that was applied to global cognition to develop models evaluating the cross-sectional predictive performance of carotid inflammation for the individual neuropsychological tests that were significantly associated with carotid inflammation in the initial pairwise partial correlation analyses.

All analyses were conducted in Python using Pandas (1.5.3), Pingouin (0.5.3), scikit-learn (1.2.2), SciPy (1.10.1), and Matplotlib (3.7.1).

Results

Forty-seven ART-treated, virally suppressed PWH (mean age 60 years [SD 8], 98% male sex) were included

in the study. By virtue of the parent study enrolling participants at moderate to high cardiovascular risk, cardiometabolic factors were prevalent. Over half of participants (53%) had hypertension, and 37 (79%) had hyperlipidemia. The median carotid and aorta inflammation, quantified by the target-to-background ratio, were 2.11 [IQR 0.39] and 2.96 [IQR 0.62], respectively. The median global cognitive score was -0.42 [IQR 1.32]. Additional demographic and clinical characteristics are shown in Table 1.

Carotid inflammation was significantly correlated with global cognition ($r = -0.405$, 95% CI -0.618 to -0.100 ; $P = 0.007$), as well as Trail Making Test Part B ($r = -0.408$,

95% CI -0.623 to -0.125 ; $P = 0.007$), Stroop word-reading trial ($r = -0.411$, 95% CI -0.623 to -0.147 ; $P = 0.006$), and Stroop interference trial ($r = -0.346$, 95% CI -0.574 to -0.042 ; $P = 0.025$). In contrast, aorta inflammation was not significantly correlated with global cognition or performance on any individual neuropsychological tests.

In the baseline model, the overall probability of carotid inflammation predicting global cognitive function within one SD of the true value (i.e., predictive performance) was 68% (95% CI 52–80) (Table 2). When individual cardiometabolic factors were added to the model, we observed marginal improvement in the cross-sectional predictive accuracy of the CVD model compared with the baseline model (73%, 95% CI 57–84 versus 68%, 95% CI 52–80) (Table 2). In the CVD model, carotid inflammation remained as one of the top two most important cross-sectional predictors of global cognition, along with cigarette smoking (Fig. 1a).

With the addition of demographics, health-related behaviors, stress measures, and HIV-specific variables to the CVD model, the cross-sectional predictive accuracy of the full model was substantially higher than the baseline model, with an increase in predictive performance from 68% (95% CI 52–80) to 85% (95% CI 71–93) (Table 2). The overall trends in predictive performance among the different models of global cognition were consistent with the RMSE on the test samples (Fig. 2, Supplemental Table, Supplemental Digital Content, <http://links.lww.com/QAD/D928>). In the full model, the most important cross-sectional predictors of global cognition were race and carotid inflammation, followed by the PTSD Checklist and early life stress (Fig. 1b). After carotid inflammation, the next most important cardiometabolic factor in predicting cognitive function was hyperlipidemia, which was the seventh most important variable overall.

In a sensitivity analysis, a cross-sectional predictive model that considered only candidate individual cardiometabolic factors without carotid inflammation performed worse than the CVD model (58%, 95% CI 42–72 versus 73%, 95% CI 57–84). In the model that considered only individual cardiometabolic factors, cigarette smoking ranked as the most important feature, trailed by antiplatelet and statin use, prior MI/stroke, and hyperlipidemia. When carotid inflammation was also considered, it emerged as one of the top two most important cross-sectional predictors of global cognition, alongside cigarette smoking.

The cross-sectional predictive accuracy of the baseline, CVD, and full models for performance on individual neuropsychological tests that were significantly correlated with carotid inflammation in the partial correlation analyses – Trail Making Test Part B, Stroop word-reading and interference trials – are shown in Table 2. The cross-

Table 1. Demographics and clinical variables of participants.

Characteristic, no. (%), unless stated	Participants (n = 47)
Demographics	
Age (years), mean (SD)	60 (8)
Male sex at birth	46 (98)
Education (years), mean (SD)	16 (2)
Race	
White	37 (79)
Black	8 (17)
Other	2 (4)
Cardiometabolic	
History of prior MI or stroke	4 (9)
Hyperlipidemia	37 (79)
Hypertension	25 (53)
Diabetes mellitus	10 (21)
Use of antiplatelet therapy	20 (43)
Use of statin ^a	28 (61)
Health-related behaviors	
Cigarette smoking	
Current	9 (19)
Prior	25 (53)
Never	13 (28)
Marijuana use	
Current	25 (53)
Prior	15 (32)
Never	7 (15)
Cocaine use	
Current	3 (6)
Prior	27 (57)
Never	17 (36)
Methamphetamine use	
Current	1 (2)
Prior	21 (45)
Never	25 (53)
Injection drug use	
Current	0 (0)
Prior	9 (19)
Never	38 (81)
HIV-related variables	
CD4 ⁺ cell count (cells/mm ³), mean (SD)	539 (159)
Global cognitive z-score, median (IQR; min, max)	-0.42 (1.32; -3.42 , 0.97)
Aorta inflammation (TBR), median (IQR; min, max)	2.96 (0.62; 1.63, 4.67)
Carotid inflammation (TBR), median (IQR; min, max)	2.11 (0.39; 1.45, 3.08)

IQR, interquartile range; SD, standard deviation; TBR, target-to-background ratio.

^aOne participant missing data for statin use.

Table 2. Predictive performance^a of models.

Cognitive outcome	Null model ^b [95% CI]	Baseline model ^c [95% CI]	CVD model ^d [95% CI]	Full model ^e [95% CI]
Global cognition	55% (40, 69)	68% (52, 80)	73% (57, 84)	85% (71, 93)
Trail Making Test Part B	63% (47, 76)	60% (45, 74)	70% (55, 82)	90% (77, 96)
Stroop Word-Reading Trial	60% (45, 74)	65% (50, 78)	73% (57, 84)	80% (65, 89)
Stroop Interference Trial	73% (57, 84)	75% (60, 86)	78% (63, 88)	78% (63, 88)

CVD, cardiovascular disease.

^aDefined as the overall probability of being within 1 standard deviation of the true score.

^bComparator (null) model predicting the training set mean (constant) for each train-test split.

^cVariables in the baseline model: carotid inflammation.

^dVariables tested in the CVD model: carotid inflammation + individual cardiometabolic comorbidities (prior MI or stroke; history of diabetes, hyperlipidemia, or hypertension; use of statins and antiplatelet medications; cigarette smoking).

^eVariables tested in the full model: carotid inflammation + individual cardiometabolic comorbidities (prior MI or stroke; history of diabetes, hyperlipidemia, or hypertension; use of statins and antiplatelet medications; cigarette smoking) + demographics (age, race, education, ethnicity) + stress measures (Perceived Stress Scale, Chronic Burden Scale, Adverse Childhood Experiences, HIV Stigma Scale, Post-Traumatic Stress Disorder Civilian-Checklist, Patient Health Questionnaire-9) + health-related behaviors (alcohol, stimulants, marijuana, injection drugs) + HIV-specific (CD4⁺ cell count, year of HIV diagnosis, current ART regimen).

sectional predictive accuracy of the full model for Trail Making Test Part B, which had the highest performance overall at 90% (95% CI 77–96), was higher than both the baseline model (60%, 95% CI 45–74) and the CVD model (70%, 95% CI 55–82)(Table 2). In the CVD model, cigarette smoking was nearly twice as important in predicting performance on the Trail Making Test Part B as carotid inflammation (Fig. 3a), while in the full model, carotid inflammation was again the most important cardiometabolic factor and the second most important cross-sectional predictor overall after race (Fig. 3b).

In contrast to Trail Making Test Part B, the CVD and full models did not substantially improve cross-sectional predictive performance compared with carotid inflammation alone for the Stroop word-reading and interference trials (Table 2). In the CVD models, carotid inflammation remained the most important cross-sectional predictor of the Stroop interference trial and second most important for the Stroop word-reading trial, after only cigarette smoking (Fig. 3E and C). In the full models, carotid inflammation was again the most important cardiometabolic feature for both Stroop tests

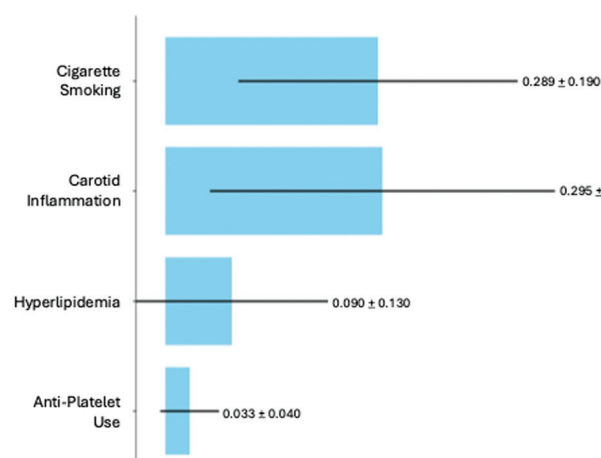
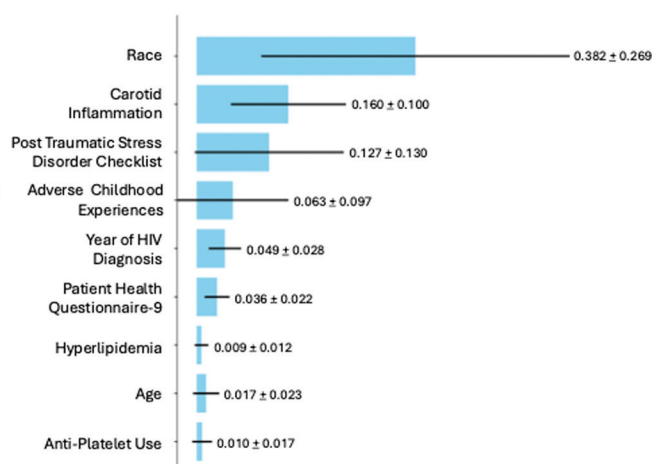
(a) CVD Model**(b) Full Model****Importance Score for Predictors of Global Cognition**

Fig. 1. Relative importance of predictors of global cognition. The relative importance scores of the variables that improved the cross-sectional predictive capability of the CVD model (a) and full model (b) for global cognitive function are shown. The full model was more accurate in predicting global cognition than carotid inflammation alone by almost 17%. In contrast, addition of individual cardiometabolic factors to the baseline model that contained only carotid inflammation to create the CVD model improved the ability to predict global cognition by only 5%. CVD, cardiovascular disease.

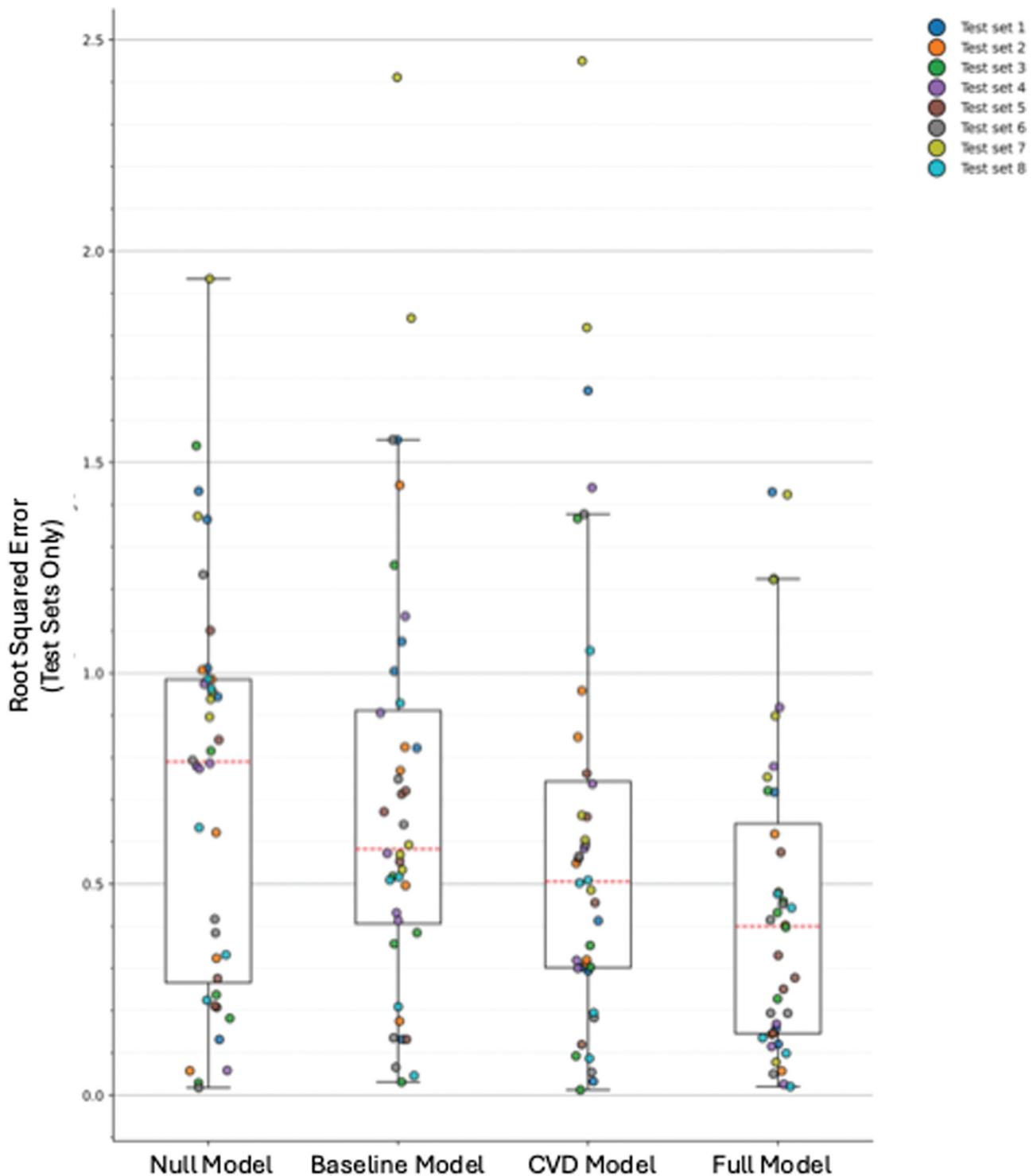
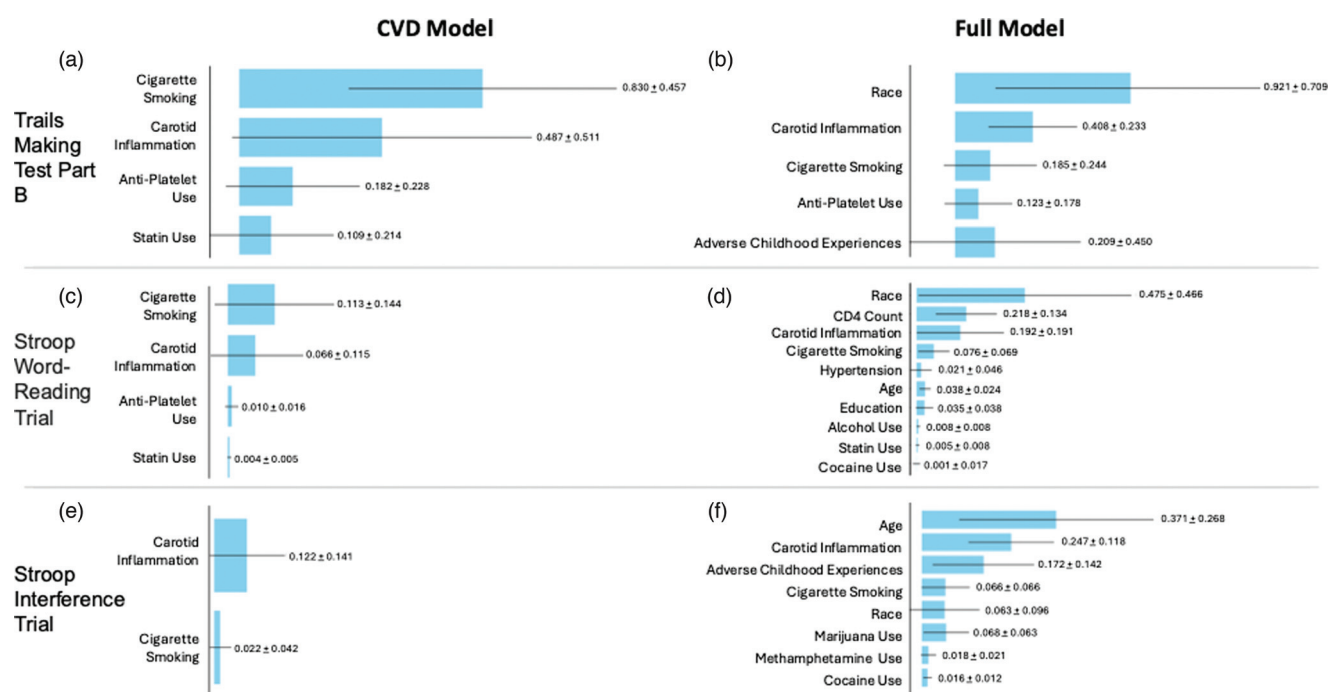


Fig. 2. Root-mean squared error to estimate predictive accuracy of global cognition. Box plots of the root-mean squared errors of the null (comparator), baseline, CVD, and full models on each sample using repeated ($n = 8$) stratified hold-out (10%) evaluation on the test set. CVD, cardiovascular disease.



Importance Score for Predictors of Individual Neuropsychological Tests

Fig. 3. Relative importance of predictors of individual neuropsychological test performance. The relative importance scores of the variables that improved the cross-sectional predictive capability of the CVD model (a) and full model (b) for performance on Trail Making Test Part B are shown. The cross-sectional predictive accuracy of the full model was higher than the baseline model that contained only carotid inflammation and the CVD model by 30% and 20%, respectively. In contrast, the cross-sectional predictive accuracy of the full model was only marginally higher than the baseline model and observed to be the same as the CVD model in predicting performance on the Stroop interference trial. For the Stroop word-reading trial, the full model's predictive performance was higher than the baseline and CVD models by 15% and 7%, respectively. The relative importance scores of the variables that improved the predictive performance of the CVD models and full models for the Stroop word-reading and Stroop interference trials are presented in (c)–(f). CVD, cardiovascular disease.

and consistently ranked in the top three most important cross-sectional predictors overall (Fig. 3D and F).

RMSE and MAE performance metrics were generally consistent with performance trends based on our predefined metric (Supplemental Table, Supplemental Digital Content, <http://links.lww.com/QAD/D928>).

Discussion

In this cohort of virally suppressed PWH, carotid inflammation was the most important cardiometabolic cross-sectional predictor of global cognition. In fact, the addition of individual cardiometabolic risk factors (e.g., hypertension, cigarette smoking) to a model that contained only carotid inflammation did not substantially enhance the ability of the model to predict cognitive function. When evaluated in combination with carotid inflammation and other factors that could plausibly impact cognition, including age, stress, and health-related behaviors, most individual cardiometabolic factors were not important features in the cross-sectional predictive

model. One noteworthy example is cigarette smoking, which was comparable in predictive importance to carotid inflammation in the CVD model but no longer an important predictive feature in the full model. This pattern suggests that the variance captured by cigarette smoking in the CVD model was subsumed by correlated variables in the full model, such as early life stress and depression-related symptoms, which likely encode overlapping behavioral and psychosocial information. When these exposures were included, the independent predictive contribution of cigarette smoking was attenuated. In contrast, carotid inflammation remained an important feature across all models, indicating it contributes unique predictive information not captured by other cardiometabolic or psychosocial variables.

These findings build upon existing evidence that carotid atherosclerosis assessed by ultrasound is associated with cognitive impairment in PWH, independent of individual cardiometabolic factors [4,5,28,29]. Some studies of PWH have demonstrated an association between carotid atherosclerosis, but not individual cardiometabolic factors, and cognitive function [29]. This is in line with the general framework of vascular cognitive impairment as

the culmination of cardiometabolic comorbidities in aggregate, as opposed to a single factor alone [30]. Taken together, our findings suggest that carotid inflammation, which may reflect the collective impact of multiple comorbidities, may outperform individual cardiometabolic factors in risk stratification for cognitive impairment in PWH.

A related concept has been observed regarding the enhanced performance of cardiovascular risk scores over individual cardiometabolic factors in predicting cognitive function in PWH. In the AIDS Clinical Trials Group HIV Infection, Aging, and Immune Function Long-term Observational Study, few individual cardiometabolic factors were significantly associated with cognitive function, whereas both the Atherosclerotic CVD risk score and the Framingham Heart Study Global CVD risk score predicted future cognition in the cohort [31]. When taken into account individually, cardiometabolic factors may not reach the required threshold to impact cognitive function; rather, consideration of the compound effect of comorbid vascular burden across the life course on brain health may be a more informative approach.

Carotid FDG-PET is superior to ultrasound in predicting future CVD and stroke events, in part due to its ability to characterize plaque inflammation and instability, which ultrasound cannot assess [32]. One hypothesis is that the greater sensitivity of FDG-PET to identify early and high-risk atheroinflammatory changes that strongly predict stroke risk may translate into a more accurate risk estimate for cognitive impairment than the presence of atherosclerotic changes on ultrasound. We found that inflammation of the carotid arteries, but not the aorta, predicted poorer cognitive function in cross-sectional assessment. The internal carotid arteries, proximate to the end organ of interest (i.e., the brain), supply the anterior cerebral circulation. This suggests that carotid inflammation may be a specific indicator of cognitive function beyond merely reflecting a higher comorbid vascular burden, which would be expected as much in the aorta as in the carotid arteries.

In addition to global cognition, carotid inflammation was an important cross-sectional predictor of executive function, measured by performance on Trail Making Test Part B (cognitive flexibility, task-shifting) and the Stroop interference trial (response inhibition, management of cognitive interference). Other studies have similarly found that executive function may be particularly sensitive to cardiovascular insult compared with other domains [33,34]. Moreover, patients who suffer from a vascular-predominant dementia often present with subcortical white matter injury and small vessel infarcts affecting the frontal lobes and connectivity with subcortical regions of the brain responsible for mental flexibility, organization, and other core executive functions [35].

Although a discussion of vascular cognitive impairment is relevant when exploring the link between carotid atherosclerosis and cognition, carotid inflammation is, in fact, a marker of large artery disease rather than microvascular ischemia, which is the dominant pathology in vascular dementia [36]. The association between carotid disease and cognitive impairment may be related to shared risk factors between large artery and small vessel disease (e.g., hypertension, cigarette smoking). Other mechanisms, however, are likely at play, including subclinical brain injury from microemboli and chronic cerebral hypoperfusion secondary to carotid atherosclerosis that could result in cognitive impairment even in the absence of clinical strokes [15]. Carotid inflammation may also be a marker of widespread chronic systemic inflammation, including of the brain, that is associated with adverse health outcomes in PWH, including stroke and cognitive impairment.

The identification of a core group of modifiable risk factors for brain health highlights the opportunity to potentially intervene on upstream determinants like carotid inflammation to prevent or delay cognitive impairment in PWH. Arterial inflammation has been shown to be highly responsive to lipid-lowering and anti-inflammatory therapies and to changes in health-related behaviors like exercise [14,37–40]. Precision medicine interventions that target cardiovascular risk and atheroinflammation to preserve and promote cognitive health should be evaluated in PWH and other populations at increased risk for CVD due to chronic inflammation.

Aside from carotid inflammation, psychosocial factors like stress and depressive symptoms were also strongly associated with cognition, similar to results from other studies of PWH [41–43]. Although data on social support, coping, resilience, and other potential moderators of the impact of stress on brain health were unavailable, they represent promising interventional targets that may be among the most actionable strategies for reducing stress-related cognitive dysfunction in PWH. In none of the models developed were HIV-related variables important features in the prediction of cognitive function, with the exception of CD4⁺ cell count, which was the second most important predictor of performance on the Stroop word-reading trial. This echoes comparable findings in the current era of effective ART and well controlled infection that point to co-occurring conditions as playing a more substantive role in the development of cognitive impairment than HIV itself [28].

Our findings should be interpreted in the context of several limitations. First, we did not perform ultrasound or other vessel imaging to assess luminal stenosis or dynamic flow-related changes in response to a vasodilatory stimulus. Data from ultrasound, a more accessible, lower-cost alternative to FDG-PET, would have provided complementary information. Second, the cross-sectional design of the study precludes inferences about the direction of the

observed association between carotid inflammation and cognition, though the plausibility of reverse causation is low. Third, the sample size was small, and observed results may have been subject to sampling variability. Fourth, our study population was a convenience sample recruited from a parent trial of primarily white male participants with higher educational attainment, many of whom are active in the research community and frequently volunteer for studies. This may limit the generalizability of our study results to the broader population of people with treated HIV, including harder to reach HIV populations. A final, major limitation was the absence of data on social and structural determinants of health that disproportionately affect racial and ethnic minority groups and exert powerful independent effects on cognitive function and risk of dementia. Race emerged as the most predictive feature for global cognition in the full model, a finding that should be interpreted not as evidence of biological determinism but as a reflection of the influence of these unmeasured structural exposures for which race serves as an imperfect surrogate. Future studies should incorporate measures of structural racism and social disadvantage to better characterize the drivers of cognitive disparities in PWH.

In summary, this study offers preliminary evidence that carotid inflammation may provide unique information to predict concurrent cognitive function beyond cardiometabolic and other risk factors. Future studies should evaluate whether carotid inflammation can be used in a clinical setting in conjunction with medical history, laboratory biomarkers, and other data to risk stratify PWH who are vulnerable to developing cognitive impairment. Further, carotid inflammation may be a potential therapeutic target to prevent cognitive decline in PWH.

Acknowledgements

We are grateful to the EPIC study participants and caregivers, without whom the study would not have been possible. We would also like to thank the UCSF-Bay Area Center for AIDS Research and UCSF AIDS Research Institute for data analysis support. This work was supported by NIH grants K23 NS105575 (F.C.C.), R01 NS126086 (F.C.C.), and K24 AI112393 (P.Y.H.). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Author contributions: Study concept and design: E.S.E., P.Y.H., F.C.C.; Acquisition of funding: F.C.C.; Oversight of data acquisition and management: F.C.C., A.T., P.Y.H.; Data acquisition: S.A.; Data analysis: F.C.C., A.A.; Data interpretation: M.W., A.A., S.A., F.C.C.; Drafting of the manuscript: M.W., F.C.C. Review of draft and approval of final manuscript: All authors. All

authors had full access to all the data in the study and accept responsibility to submit for publication.

Funding: This work was supported by NIH grants K23 NS105575 (FCC), R01 NS126086 (FCC), and K24 AI112393 (PYH).

Conflicts of interest

There are no conflicts of interest. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

References

1. Anbar R, Jones S, Chaturvedi N, Sudre C, Richards M, Sultan SR, et al. **Associations of carotid atherosclerosis with cognitive function and brain health: findings from a UK tri-ethnic cohort study (Southall and Brent Revisited).** *Atheroscler Plus* 2024; **55**: 39–46.
2. Reis JP, Launer LJ, Terry JG, Loria CM, Al Hazzouri AZ, Sidney S, et al. **Subclinical atherosclerotic calcification and cognitive functioning in middle-aged adults: the CARDIA Study.** *Atherosclerosis* 2013; **231**:72–77.
3. Ihle-Hansen H, Ihle-Hansen H, Sandset EC, Hagberg G. **Subclinical carotid artery atherosclerosis cognitive function: a mini-review.** *Front Neurol* 2021; **12**:705043.
4. Fabbiani M, Ciccarelli N, Tana M, Farina S, Baldonero E, Di Cristo V, et al. **Cardiovascular risk factors and carotid intima-media thickness are associated with lower cognitive performance in HIV-infected patients.** *HIV Med* 2013; **14**:136–144.
5. Huck DM, Hanna DB, Rubin LH, Maki P, Valcour V, Springer G, et al. *J Acquir Immune Defic Syndr* 2018; **78**:338–347.
6. Zenebe Y, Necho M, Yimam W, Akele B. **Worldwide occurrence of HIV-associated neurocognitive disorders and its associated factors: a systematic review and meta-analysis.** *Front Psychiatry* 2022; **13**:814362.
7. Tawakol A, Migrino RQ, Bashian GG, Bedri S, Vermylen D, Cury RC, et al. **In vivo 18F-fluorodeoxyglucose positron emission tomography imaging provides a noninvasive measure of carotid plaque inflammation in patients.** *J Am Coll Cardiol* 2006; **48**: 1818–1824.
8. McCabe JJ, Evans NR, Gorey S, Bhakta S, Rudd JHF, Kelly PJ. **Imaging carotid plaque inflammation using positron emission tomography: emerging role in clinical stroke care, research applications, and future directions.** *Cells* 2023; **12**:2073.
9. Emami H, Singh P, MacNabb M, Vucic E, Lavender Z, Rudd JHF, et al. *JACC Cardiovasc Imaging* 2015; **8**:121–130.
10. Iwatsuka R, Matsue Y, Yonetsu T, O'uchi T, Matsumura A, Hashimoto Y, et al. **Arterial inflammation measured by 18F-FDG-PET-CT to predict coronary events in older subjects.** *Atherosclerosis* 2018; **268**:49–54.
11. Figueroa AL, Abdelbaky A, Truong QA, Corsini E, MacNabb MH, Lavender ZR, et al. **Measurement of arterial activity on routine FDG PET/CT images improves prediction of risk of future CV events.** *JACC Cardiovasc Imaging* 2013; **6**: 1250–1259.
12. Tawakol A, Ishai A, Takx RA, Figueroa AL, Ali A, Kaiser Y, et al. **Relation between resting amygdalar activity and cardiovascular events: a longitudinal and cohort study.** *Lancet* 2017; **389**: 834–845.
13. Rudd JHF, Myers KS, Bansilal S, Machac J, Rafique A, Farkouh M, et al. **(18)Fluorodeoxyglucose positron emission tomography imaging of atherosclerotic plaque inflammation is highly reproducible: implications for atherosclerosis therapy trials.** *J Am Coll Cardiol* 2007; **50**:892–896.
14. Tawakol A, Fayad ZA, Mogg R, Alon A, Klimas MT, Dansky H, et al. **Intensification of statin therapy results in a rapid reduction in atherosclerotic inflammation: results of a multicenter fluorodeoxyglucose-positron emission tomography/computed tomography feasibility study.** *J Am Coll Cardiol* 2013; **62**:909–917.

15. Baradaran H, Sarraimi AH, Gupta A. **Asymptomatic carotid disease and cognitive impairment: what is the evidence?** *Front Neurol* 2021; **12**:741500.
16. Graebe M, Pedersen SF, Højgaard L, Kjaer A, Sillesen H. **18FDG PET and ultrasound echolucency in carotid artery plaques.** *JACC Cardiovasc Imaging* 2010; **3**:289–295.
17. Benedict RHB, Schretlen D, Groninger L, Brandt J. **Hopkins Verbal Learning Test - Revised: normative data and analysis of inter-form and test-retest reliability.** *Clin Neuropsychol* 1998; **12**:43–55.
18. Wechsler D. **Wechsler Adult Intelligence Scale-Revised.** 1981; Psychological Corporation,
19. Kløve H. **Clinical neuropsychology.** *Med Clin North Am* 1963; **47**:1647–1658.
20. Stroop JR. **Studies of interference in serial verbal reactions.** *J Exp Psychol* 1935; **18**:643–662.
21. Benton AL. **Differential behavioral effects in frontal lobe disease.** *Neuropsychologia* 1968; **6**:53–60.
22. Reitan RM. **Validity of the trail making test as an indicator of organic brain damage.** *Percept Mot Skills* 1958; **8**:271–276.
23. Cohen S. **Perceived stress in a probability sample of the United States.** *The social psychology of health* 1988; Sage Publications, Inc., Thousand Oaks, CA, USA: 31–67.
24. Bromberger JT, Matthews KA. **A longitudinal study of the effects of pessimism, trait anxiety, and life stress on depressive symptoms in middle-aged women.** *Psychol Aging* 1996; **11**:207–213.
25. Felitti VJ, Anda RF, Nordenberg D, Williamson DF, Spitz AM, Edwards V, *et al.* **Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. The Adverse Childhood Experiences (ACE) Study.** *Am J Prev Med* 1998; **14**:245–258.
26. Berger BE, Ferrans CE, Lashley FR. **Measuring stigma in people with HIV: psychometric assessment of the HIV stigma scale.** *Res Nurs Health* 2001; **24**:518–529.
27. Conybeare D, Behar E, Solomon A, Newman MG, Borkovec TD. **The PTSD Checklist-Civilian Version: reliability, validity, and factor structure in a nonclinical sample.** *J Clin Psychol* 2012; **68**:699–713.
28. Becker JT, Kingsley L, Mullen J, Cohen B, Martin E, Miller EN, *et al.* **Vascular risk factors, HIV serostatus, and cognitive dysfunction in gay and bisexual men.** *Neurology* 2009; **73**:1292–1299.
29. Crystal HA, Weedon J, Holman S, Manly J, Valcour V, Cohen M, *et al.* **Associations of cardiovascular variables and HAART with cognition in middle-aged HIV-infected and uninfected women.** *J Neurovirol* 2011; **17**:469–476.
30. Badji A, Youwakim J, Cooper A, Westman E, Marseglia A. **Vascular cognitive impairment – past, present, and future challenges.** *Ageing Res Rev* 2023; **90**:102042.
31. Chow FC, Lyass A, Mahoney TF, Massaro JM, Triant VA, Wu K, *et al.* **Baseline 10-year cardiovascular risk scores predict cognitive function in older persons, and particularly women, living with human immunodeficiency virus infection.** *Clin Infect Dis* 2020; **71**:3079–3085.
32. Moon SH, Cho YS, Noh TS, Choi JY, Kim B-T, Lee K-H. **Carotid FDG uptake improves prediction of future cardiovascular events in asymptomatic individuals.** *JACC Cardiovasc Imaging* 2015; **8**:949–956.
33. Yaffe K, Bahorik AL, Hoang TD, Forrester S, Jacobs DR, Lewis CE, *et al.* **Cardiovascular risk factors and accelerated cognitive decline in midlife: the CARDIA Study.** *Neurology* 2020; **95**:e839–e846.
34. Rostamian S, van Buchem MA, Westendorp RGJ, Jukema JW, Mooijaart SP, Sabayan B, *et al.* **Executive function, but not memory, associates with incident coronary heart disease and stroke.** *Neurology* 2015; **85**:783–789.
35. Chang Wong E, Chang Chui H. **Vascular cognitive impairment dementia.** *Contin Minneap Minn* 2022; **28**:750–780.
36. Hainsworth AH, Markus HS, Schneider JA. **Cerebral small vessel disease hypertension and vascular contributions to cognitive impairment and dementia.** *Hypertension* 2024; **81**:75–86.
37. Astley C, Clemente G, Terreri MT, Carneiro CG, Lima MS, Buchpiguel CA, *et al.* **Home-based exercise training in childhood-onset Takayasu arteritis: a multicenter, randomized, controlled trial.** *Front Immunol* 2021; **12**:705250.
38. Hsue PY, Danny L, Ma Y, Ishai A, Manion M, Nahrendorf M, *et al.* **IL-1 β inhibition reduces atherosclerotic inflammation in HIV infection.** *J Am Coll Cardiol* 2018; **72**:2809–2811.
39. Solomon DH, Giles JT, Liao KP, Ridker PM, Rist PM, Glynn RJ, *et al.* **Reducing cardiovascular risk with immunomodulators: a randomised active comparator trial among patients with rheumatoid arthritis.** *Ann Rheum Dis* 2023; **82**:324–330.
40. Srinivasa S, Abohashem S, Walpert AR, Dunderdale CN, Iyengar S, Shen G, *et al.* **Mineralocorticoid receptor antagonism by eplerenone and arterial inflammation in HIV: the MIRABELLA HIV Study.** *JAMA Cardiol* 2024; **9**:189–194.
41. Valdez AN, Rubin LH, Neigh GN. **Untangling the Gordian knot of HIV, stress, and cognitive impairment.** *Neurobiol Stress* 2016; **4**:44–54.
42. Rubin LH, Cook JA, Weber KM, Cohen MH, Martin E, Valcour V, *et al.* **The association of perceived stress and verbal memory is greater in HIV-infected versus HIV-uninfected women.** *J Neurovirol* 2015; **21**:422–432.
43. Watson CW-M, Sundermann EE, Hussain MA, Umlauf A, Thames AD, Moore RC, *et al.* **Effects of trauma, economic hardship, and stress on neurocognition and everyday function in HIV.** *Health Psychol* 2019; **38**:33–42.