Title: Baseline 10-year cardiovascular risk scores predict cognitive function in older persons, and particularly women, living with HIV infection

Authors: Felicia C. Chow[1,2], Asya Lyass[3], Taylor F. Mahoney,[4] Joseph M. Massaro[4], Virginia A. Triant[5], Kunling Wu[6], Baiba Berzins[7], Kevin Robertson[8], Ronald J. Ellis[9], Katherine Tassiopoulos[10], Babafemi Taiwo[7], Ralph B. D'Agostino Sr[3] for the ACTG A5322 Study Team

Affiliations: [1]Weill Institute for Neurosciences, [2]Department of Neurology and Division of Infectious Diseases, University of California, San Francisco, USA; [3]Department of Mathematics and Statistics, Boston University, Boston, USA; [4]Department of Biostatistics, School of Public Health, Boston University, Boston, USA; [5]Division of General Internal Medicine and Division of Infectious Diseases, Massachusetts General Hospital, Boston, USA; [6]Center for Biostatistics in AIDS Research, Harvard T.H. Chan School of Public Health, Boston, USA; [7]Division of Infectious Disease, Northwestern University, Chicago, USA; [8]Department of Neurology, University of North Carolina, Chapel Hill, USA; [9]Department of Neurosciences and Psychiatry, University of California, San Diego, USA; [10]Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, USA

Corresponding author: Felicia C. Chow, MD, MAS, University of California, San Francisco at Zuckerberg San Francisco General Hospital, 1001 Potrero Avenue, Building 1, Room 101, San Francisco, CA, 94117. Telephone: 415-206-4449, Email: felicia.chow@ucsf.edu

Summary: Baseline 10-year cardiovascular (CV) risk scores predicted future cognitive function in older persons living with well-controlled HIV. CV risk scores may help to identify individuals, especially women, with HIV who are at risk for worse cognition over time.

Abstract

Background

Cardiovascular disease (CVD) and associated comorbidities increase the risk of cognitive impairment in persons living with HIV (PLWH). Given the potential composite effect of multiple cardiovascular risk factors on cognition, we examined the ability of the Atherosclerotic Cardiovascular Disease (ASCVD) risk score and the Framingham Heart Study Global CVD risk score (FRS) to predict future cognitive function in older PLWH.

Methods

We constructed linear regression models evaluating the association between baseline 10-year CV risk scores and cognitive function (measured by NPZ-4 score) at a Year 4 follow up visit.

Results

Among 988 participants (mean age 52 years, 20% women), mean 10-year ASCVD risk score at entry into the cohort was 6.8% (SD 7.1%) and FRS was 13.1% (SD 10.7%). In models adjusted only for cognitive function at entry, the ASCVD risk score significantly predicted Year 4 NPZ-4 in the entire cohort and after stratification by sex (for every 1% higher ASCVD risk, Year 4 NPZ-4 was lower by 0.84 SD +/- 0.28 overall, p=0.003; lower by 2.17 SD +/- 0.67 in women, p=0.001; lower by 0.78 SD +/- 0.32 in men, p=0.016). A similar relationship was observed between FRS and Year 4 NPZ-4. In multivariable models, higher 10-year ASCVD risk and FRS predicted lower NPZ-4 in women.

Conclusion

Baseline 10-year ASCVD risk and FRS predicted future cognitive function in older PLWH with well-controlled infection. CV risk scores may help to identify individuals, especially women, living with HIV who are at risk for worse cognition over time.

Keywords: HIV infection, cardiovascular risk, risk prediction, cognitive function

Background

Cardiovascular (CV) disease (CVD) and associated risk factors have been consistently linked to cognitive impairment in persons living with HIV (PLWH). A history of CVD, subclinical CVD (e.g., carotid intima media thickness), diabetes mellitus-related variables (e.g., insulin resistance), and abdominal obesity, for example, have all been associated with measures of cognitive function in PLWH[1-7]. While these individual CV risk factors or markers of CVD have been shown to correlate with cognitive impairment in HIV infection, results have varied from study to study, most of which have been cross-sectional, without one risk factor or combination of risk factors emerging as the single most important CV indicator of poor cognitive function.

CV risk prediction scores, which take into account the collective importance of several risk factors, are designed to calculate absolute 10-year risk of CV events. Given the potential composite effect of multiple CV risk factors on cognition, we examined the utility of two commonly used CV risk scores—the Atherosclerotic CV disease (ASCVD) risk score[8] and the Framingham Heart Study Global CVD risk score (FRS)[9]—to predict future cognitive function[10] in a cohort of older PLWH. Based on our recent cross-sectional analyses from this same cohort demonstrating differences between women and men in the cardiometabolic risk factors associated with cognitive impairment[11], we evaluated the ability of the ASCVD risk score and FRS to predict cognitive performance in women and men separately.

Methods

We analyzed data collected from participants in the AIDS Clinical Trials Group (ACTG) Protocol A5322. A5322, also known as the HIV Infection, Aging, and Immune Function

Long-Term Observational Study (HAILO), is an ongoing, prospective, multicenter observational study of older PLWH who initiated antiretroviral therapy (ART) through an ACTG clinical trial and were subsequently followed in the observational ACTG Longitudinal Linked Randomized Trial (ALLRT) Study. In 2013, a subset of ALLRT participants 40 years of age and older (n=1,035) rolled over into HAILO for continued longitudinal follow up of clinical, behavioral, and immunologic parameters. At semi-annual visits, data are collected through medical chart abstraction, questionnaires, anthropometric measurements, neurocognitive evaluation, and laboratory testing. All HAILO participants who underwent neurocognitive evaluation at entry and at Year 4 were included in this analysis.

Study measurements

Neurocognitive performance in HAILO is assessed using the Brief Neurocognitive Screen, which consists of a battery of four neuropsychological tests: Trail Making Tests A and B, the Wechsler Adult Intelligence Scale-Revised Digit Symbol subtest, and the Hopkins Verbal Learning Test-Revised (HVLT-R). The raw score for each test is standardized using demographic-adjusted normative means and combined in a summary z-score, termed the NPZ-4. Participants undergo neurocognitive testing at entry into HAILO and every 48 weeks thereafter. The NPZ-4 in Year 4 of follow up was the primary outcome of interest.

Predictors: Baseline 10-year ASCVD risk score and FRS were the primary predictors. The ASCVD risk score was calculated using these variables collected at entry into HAILO: age, sex, self-reported race/ethnicity, systolic blood pressure, anti-hypertensive medication use, smoking (current versus past/never), diabetes (established diagnosis or hemoglobin A1c greater than or equal to 6.5%), total and high-density lipoprotein

cholesterol. The FRS was calculated using the same variables at entry with the exception of race/ethnicity.

Covariates: In addition to the components of the CV risk prediction scores, we accessed baseline data collected at entry into HAILO for body mass index (BMI), waist circumference, statin use, injection drug use (current versus past/never), anti-depressant medication use, hepatitis C virus (HCV) infection, current and nadir CD4 count, plasma HIV RNA viral load, ART duration, and efavirenz and integrase inhibitor use. The International Physical Activity Questionnaire, which includes questions about vigorous (e.g., heavy lifting, fast bicycling) and moderate (e.g., carrying light loads, bicycling at a regular pace) physical activity in the preceding week, is administered annually in HAILO. We dichotomized the questionnaire results into: 3 or more versus less than 3 days of vigorous or moderate physical activity in the preceding week.

Statistical analysis

Descriptive statistics were generated, presenting means and standard deviations (SD) for the continuous variables and counts for the categorical variables by sex. We then assessed if baseline ASCVD risk score and FRS predicted NPZ-4 at Year 4 in linear regression models. We constructed multivariable models predicting Year 4 NPZ-4 with the ASCVD risk score and FRS adjusting for covariates. Covariates of interest were grouped into demographics (age, sex, race, education), clinical variables (BMI, waist circumference, physical activity, statin use, injection drug use, anti-depressant use, HCV status), and HIV-related factors [CD4 count, nadir CD4 count, HIV RNA dichotomized as detectable ($\geq$400 copies/mL) versus undetectable (<400 copies/mL), years of ART use, integrase inhibitor and efavirenz use]. For each group of variables, we ran simple linear regression models predicting Year 4 NPZ-4 with each covariate. Covariates that were

significant at the level of 0.10 within each group were included in a stepwise linear regression model, with NPZ-4 as the outcome, using entry and stay cut-offs of p=0.10. This approach yielded a set of covariates within each category that was significantly related to NPZ-4 at the level of p=0.10. From here, the overall models were run, using stepwise linear regression to predict Year 4 NPZ-4 with either baseline ASCVD risk score or baseline FRS, adjusting for all selected covariates from each category as described above, using the entry and stay cut-offs of 0.10. Because of the strong association between education and cognitive performance, education was forced into the final models. In addition, to account for the relationship between NPZ-4 performance at entry into HAILO and at Year 4, all models were adjusted for entry NPZ-4. The analyses were then repeated stratified by sex. We also examined the associations between individual components of the risk scores and Year 4 NPZ-4 to evaluate how well they predicted cognitive performance compared with the risk scores.

Results

Baseline demographic and clinical characteristics for the 988 participants are shown in Table 1. The mean age in the cohort was 52 years. Twenty percent were women. Approximately half of participants were white (49%), and 30% were black, although the race/ethnicity distribution differed between women and men. The mean CD4 count was 661 cells/mm^3, and the majority of participants (96%) had an undetectable viral load. The mean duration of ART use at entry into HAILO was 8.1 years. Sex differences in baseline characteristics in this cohort have been published previously[11] and are shown in Table 1.

Baseline cardiovascular risk scores

The mean 10-year ASCVD risk in the cohort was 6.8% (SD 7.1%) and mean FRS was 13.1% (SD 10.7%). Both CV risk scores were significantly lower in women than in men (Table 2).

Baseline and Year 4 cognitive performance

The mean NPZ-4 at entry into HAILO was 0.11 (SD 1.00). Women had a lower mean NPZ-4 compared with men (-0.20, SD 0.99, versus 0.18, SD 0.99, $p<0.001$). At Year 4, the mean NPZ-4 score was 0.13 (SD 0.99), with a mean score of -0.15 (SD 0.96) for women and 0.20 (SD 1.01) for men ($p<0.001$).

Baseline 10-year CV risk scores predict Year 4 cognitive performance

Our first objective was to evaluate the association between baseline CV risk and NPZ-4 at Year 4 adjusted only for entry NPZ-4. We found that the 10-year ASCVD risk score significantly predicted NPZ-4 at Year 4. For every 1% higher baseline ASCVD risk, the NPZ-4 at Year 4 was lower by 0.84 SD +/- 0.28 ($p=0.003$). Findings were similar when women and men were evaluated separately, with higher baseline ASCVD risk having a more marked effect on NPZ-4 for women (-2.17 SD +/- 0.67, $p=0.001$) than men (-0.78 SD +/- 0.32, $p=0.016$). A higher baseline FRS was also significantly predictive of worse cognitive performance at Year 4, although the effect was not as pronounced (Table 3).

In bivariate models evaluating the relationships between individual components of the CV risk scores and cognitive performance adjusted only for entry NPZ-4, diabetes mellitus and HDL were the only modifiable CV risk factors significantly associated with Year 4 NPZ-4, while there was a trend toward an association between smoking and Year 4 NPZ-4 (Table 3). Older age and race were also predictive of lower NPZ-4

although, like the modifiable CV risk factors, the observed associations with cognitive performance at Year 4 were considerably smaller for these individual variables than for the CV risk scores (Table 3).

In a multivariable model adjusted for age, sex, race/ethnicity, education, physical activity, HCV infection, and duration of ART use, higher baseline 10-year ASCVD risk was not significantly associated with Year 4 NPZ-4 (-0.29 SD +/- 0.39 per 1% higher risk, p=0.46). In sex-stratified multivariable models (Table 4), higher 10-year ASCVD risk predicted lower NPZ-4 in women (-2.29 SD +/- 0.67, p<0.001) but not in men (-0.002 SD +/- 0.46, p=1.00). A similar pattern, albeit with smaller effect sizes, was observed for the association of baseline FRS with Year 4 NPZ-4; higher FRS was significantly predictive of lower NPZ-4 at Year 4 among women but not in the overall cohort nor in men (Table 4).

In a sensitivity analysis, we removed age and sex from the multivariable models, as both are taken into account when calculating the ASCVD risk score and FRS. After removing age and sex, the size of the effect of both risk scores on Year 4 NPZ-4 was larger and became statistically significant (-0.83 SD +/- 0.29 per 1% higher ASCVD risk, p=0.005; -0.44 SD +/- 0.20 per 1% higher FRS, p=0.026) compared with the models that included age and sex (-0.29 SD +/- 0.39 per 1% higher ASCVD risk, p=0.46; -0.09 SD +/- 0.23 per 1% higher FRS, p=0.70).

Discussion

In this prospective observational cohort, baseline 10-year ASCVD risk and FRS predicted future cognitive function in older PLWH, with higher CV risk having a more marked effect on cognitive function in women than men. These findings suggest that CV

risk scores designed to predict 10-year risk of CV events may also identify individuals, especially women, living with HIV who are at risk for future cognitive impairment.

Of the modifiable components of the ASCVD risk score and FRS, only diabetes mellitus and HDL were significantly associated with lower Year 4 cognitive function, with a trend toward an association for current smoking. Furthermore, the size of the association between the CV risk scores and cognitive function at Year 4 was greater than between any individual risk factor and cognitive function. These results support the hypothesis that the cumulative effect of multiple CV risk factors on cognition may be greater than the effect of any one risk factor alone and that, when taken into account individually, risk factors may not reach the required threshold to impact cognitive function.

Our findings are in line with studies from the general population that have demonstrated that the presence of a combination of CV risk factors increases the risk of dementia. In a study of nearly 9,000 participants from Kaiser Permanente Northern California, midlife smoking, hypertension, high cholesterol and diabetes were associated with an increased risk of dementia in late life. When evaluated in combination, the presence of all four of these factors—which closely mirror the variables included in the ASCVD risk score and FRS—nearly doubled the associated risk of dementia[12]. In a population-based Finnish study, midlife systolic blood pressure and cholesterol, and in particular the two risk factors in combination, were associated with increased risk of Alzheimer's disease in late life[13]. These studies in the general population have focused on mid-life CV risk and dementia typically diagnosed 10 to 30 years later. In our study of PLWH, CV risk scores predicted future cognitive impairment at just 4 years. HIV infection may accentuate the effect of CV risk on the development of cognitive impairment, similar to its effect on CV

disease in which observed CV risk in PLWH exceeds predicted risk[14], leading to earlier or more severe cognitive dysfunction for a given level of CV risk.

In models investigating the association between baseline 10-year CV risk and Year 4 cognitive function, which were intended to simulate a real-world setting in which providers calculate CV risk scores for patients without adjusting for other variables, higher ASCVD risk and FRS were significantly associated with worse cognition at Year 4 in the overall cohort and in women and men evaluated separately. The negative effect of higher ASCVD risk and FRS on cognitive function, however, was greater for women than for men. One potential explanation for this differential effect is that, because baseline CV risk is lower for women, a 1% increase in CV risk represents a greater relative increase for women compared with men, and thus has a greater impact on cognitive function in women[15].

In multivariable models, the association between higher ASCVD risk and FRS and worse cognitive function at Year 4 was present only for women. We previously performed a cross-sectional analysis in this same cohort, which identified sex differences in the association between CV risk factors and baseline cognitive function[11]. In this prior analysis, no CV risk factor was significantly associated with cognition among men, whereas for women, a significant association was present between cognitive impairment and less physical activity, and a trend toward an association between cognitive impairment and lower HDL and diabetes mellitus. A greater negative impact of CV risk on cognition in women compared with men has also been observed in the general population. In a study of 985 community-dwelling elders, women with a FRS greater than 7% had a higher rate of cognitive decline compared with women with lower risk, whereas CV risk was not associated with the rate of cognitive decline in men[16]. Similarly, in the

Sacramento Area Latino Study on Aging, a higher FRS was associated with greater decline in verbal learning in women but not men[10]. The mechanisms underlying the observed sex differences in the relationship between CV risk and cognitive function is unknown. The contribution of CV risk to cognitive health may be overshadowed in men by other critical factors that play an important role in cognition, such as comorbid depression, although why this would differ between women and men is unclear. In our prior cross-sectional analysis, use of an anti-depressant medication was a risk factor for cognitive impairment; in sex-stratified analyses, however, anti-depressant use was associated with cognitive impairment in men but not in women.

Biological differences in vascular physiology by sex may also affect the association between CV and cognitive health. In several large population-based cohort studies, cerebral small vessel disease (e.g., white matter hyperintensities), which is linked to cognitive impairment in the general population and PLWH[17-19], was more prevalent, severe, and/or progressive in women compared with men, even after accounting for age[20-24]. If women have a greater predisposition to develop cerebral small vessel disease, which may be due to smaller arterial size and more frequent vascular remodeling in women[25], then the presence of multiple CV risk factors may be more likely to result in microvascular brain injury and negatively impact cognitive function in women than in men.

This study was not specifically designed to compare the predictive value of the ASCVD risk score versus the FRS for cognitive function. Overall, the ASCVD risk score better predicted cognitive function at Year 4 compared with the FRS, both in terms of the size of the associations with NPZ-4 and the significance level. The greater predictive value of the ASCVD risk score compared with the FRS may reflect the fact that the ASCVD risk

equations were derived from more diverse cohorts and factor in race. Just as the prevalence and control of CV risk factors differ by race, as do the associations of these factors with CVD[26], similar racial differences have been observed in the association between CV risk and cognitive impairment in the general population[27,28] and may also exist in PLWH.

The ability of the ASCVD risk score and FRS to predict CV risk in HIV populations has been examined[14,29] but not, to our knowledge, to predict risk of cognitive impairment. In the general population, the FRS has been associated with cognitive dysfunction and decline in several large prospective cohorts[15,16]. Similarly, a higher Framingham Stroke Risk Profile, a validated stroke risk function which factors in history of CVD, atrial fibrillation, and left ventricular hypertrophy in addition to variables included in the FRS, has been associated with impaired cognition[30-32]. Cerebrovascular disease may be a critical link between HIV, CV risk, and cognitive impairment, with both clinical and subclinical cerebrovascular disease identified as risk factors for poor cognitive health and dementia[33-35].

As PLWH reach older age, the contribution of comorbid vascular disease to cognitive impairment will become increasingly relevant. Most prior studies examining CV risk and cognition in PLWH have been cross-sectional, and those that have evaluated longitudinal relationships have not considered the composite effect of multiple CV risk factors on cognition[36,37]. The availability of yearly neuropsychological testing in HAILO allowed us to investigate the relationship between CV risk scores and future cognitive function. Because a relatively small proportion of participants had a year over year downward trajectory in cognitive function, we were not able to reliably test the association between baseline CV risk and cognitive decline, which is a limitation of the

study. However, the ASCVD risk score and FRS were predictive of cognitive function at Year 4 after adjusting for baseline cognitive performance, suggesting that CV risk may provide information about change in cognition over time. Another limitation of the study is that the majority of HAILO participants has maintained virologic suppression long-term and volunteered in research studies for years and therefore may not represent the general population of PLWH in the US.

In summary, baseline 10-year ASCVD risk and FRS predicted future cognitive function in this cohort of older PLWH with well-controlled infection, with higher CV risk having a more marked negative effect on cognitive function in women than men. These CV risk scores may help to identify individuals, particularly women, living with HIV who are at risk for worse cognition over time. Our findings raise key questions regarding the mechanisms underpinning the observed associations between CV risk and cognition, including whether a critical window exists during which lowering CV risk may preserve cognitive health and prevent cognitive decline in PLWH.

Acknowledgements: The authors are grateful to the ACTG clinical research sites and the study participants who made this work possible.

Disclaimer: The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Funding: This work was supported by the National Institute of Neurological Disorders and Stroke [K23 NS105575 to F.C.C.]; the National Institute of General Medical Sciences Interdisciplinary Training Grant for Biostatisticians [T32 GM74905 to T.F.M.]; the National Institute of Allergy and Infectious Diseases [UM1 AI068634, UM1 AI068636, UM1 AI106701]; and the National Heart, Lung, and Blood Institute [R01 HL132786 to R.B.D. and V.A.T.] of the National Institutes of Health.

Potential conflicts: K.R. reports consulting fees from Viiv, outside the submitted work. All other report no other relevant conflicts of interest.

References

1. Wright EJ, Grund B, Robertson K, et al. Cardiovascular risk factors associated with lower baseline cognitive performance in HIV-positive persons. Neurology **2010**; 75:864–873.

2. Becker JT, Kingsley L, Mullen J, et al. Vascular risk factors, HIV serostatus, and cognitive dysfunction in gay and bisexual men. Neurology **2009**; 73:1292–1299.

3. Valcour VG, Sacktor NC, Paul RH, et al. Insulin resistance is associated with cognition among HIV-1-infected patients: the Hawaii Aging With HIV cohort. J Acquir Immune Defic Syndr **2006**; 43:405–410.

4. Sattler FR, He J, Letendre S, et al. Abdominal obesity contributes to neurocognitive impairment in HIV-infected patients with increased inflammation and immune activation. J Acquir Immune Defic Syndr **2015**; 68:281–288.

5. Schouten J, Su T, Wit FW, et al. Determinants of reduced cognitive performance in HIV-1-infected middle-aged men on combination antiretroviral therapy. AIDS **2016**; 30:1027–1038.

6. Valcour V, Rubin LH, Tien P, et al. Human immunodeficiency virus (HIV) modulates the associations between insulin resistance and cognition in the current combination antiretroviral therapy (cART) era: a study of the Women's Interagency HIV Study (WIHS). J Neurovirol **2015**; 21:415–421.

7. McCutchan JA, Marquie-Beck JA, Fitzsimons CA, et al. Role of obesity, metabolic variables, and diabetes in HIV-associated neurocognitive disorder. Neurology **2012**; 78:485–492.

8. Goff DC, Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation **2014;** 129:S49–73.

9. D'Agostino RB, Vasan RS, Pencina MJ, et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation **2008**; 117:743–753.

10. Zeki Al Hazzouri A, Haan MN, Neuhaus JM, et al. Cardiovascular risk score, cognitive decline, and dementia in older Mexican Americans: the role of sex and education. Journal of the American Heart Association **2013**; 2:e004978–e004978.

11. Chow FC, Makanjuola A, Wu K, et al. Physical Activity Is Associated With Lower Odds of Cognitive Impairment in Women but Not Men Living With Human Immunodeficiency Virus Infection. J Infect Dis **2018**; 42:2672–11.

12. Whitmer RA, Sidney S, Selby J, Johnston SC, Yaffe K. Midlife cardiovascular risk factors and risk of dementia in late life. Neurology **2005**; 64:277–281.

13. Kivipelto M, Helkala EL, Laakso MP, et al. Midlife vascular risk factors and Alzheimer's disease in later life: longitudinal, population based study. BMJ **2001**; 322:1447–1451.

14. Triant VA, Perez J, Regan S, et al. Cardiovascular Risk Prediction Functions Underestimate Risk in HIV Infection. Circulation **2018**; 137:2203–2214.

15. Kaffashian S, Dugravot A, Nabi H, et al. Predictive utility of the Framingham general cardiovascular disease risk profile for cognitive function: evidence from the Whitehall II study. Eur Heart J **2011**; 32:2326–2332.

16. Laughlin GA, McEvoy LK, Mühlen von D, et al. Sex Differences in the Association of Framingham Cardiac Risk Score With Cognitive Decline in Community-Dwelling Elders Without Clinical Heart Disease. Psychosom Med **2011**; 73:683–689.

17. Debette S, Beiser A, DeCarli C, et al. Association of MRI Markers of Vascular Brain Injury With Incident Stroke, Mild Cognitive Impairment, Dementia, and Mortality: The Framingham Offspring Study. Stroke **2010**; 41:600–606.

18. Kuller LH, Lopez OL, Newman A, et al. Risk Factors for Dementia in the Cardiovascular Health Cognition Study. Neuroepidemiology **2003**; 22:13–22.

19. Watson C, Busovaca E, Foley JM, et al. White matter hyperintensities correlate to cognition and fiber tract integrity in older adults with HIV. J Neurovirol **2017**; 23:422–429.

20. Sachdev PS, Parslow R, Wen W, Anstey KJ, Easteal S. Sex differences in the causes and consequences of white matter hyperintensities. Neurobiol Aging **2009**; 30:946–956.

21. Bryan RN, Wells SW, Miller TJ, et al. Infarctlike lesions in the brain: prevalence and anatomic characteristics at MR imaging of the elderly--data from the Cardiovascular Health Study. Radiology **1997**; 202:47–54.

22. van Dijk EJ, Prins ND, Vrooman HA, Hofman A, Koudstaal PJ, Breteler MMB. Progression of Cerebral Small Vessel Disease in Relation to Risk Factors and Cognitive Consequences. Stroke **2008**; 39:2712–2719.

23. Longstreth WT, Jr., Manolio TA, Arnold A, et al. Clinical correlates of white matter findings on cranial magnetic resonance imaging of 3301 elderly people. The Cardiovascular Health Study. Stroke **1996**;27:1274–1282.

24. Vermeer SE, Koudstaal PJ, Oudkerk M, Hofman A, Breteler MM. Prevalence and risk factors of silent brain infarcts in the population-based Rotterdam Scan Study. Stroke **2002**; 33:21–25.

25. Shaw LJ, Bugiardini R, Merz CNB. Women and Ischemic Heart Disease. J Am Coll Cardiol **2009**; 54:1561–1575.

26. Gutierrez J, Williams OA. A decade of racial and ethnic stroke disparities in the

United States. Neurology **2014**; 82:1080–1082.

27. Chen C, Zissimopoulos JM. Racial and ethnic differences in trends in dementia prevalence and risk factors in the United States. Alzheimer's & Dementia: Translational Research & Clinical Interventions **2018**; 4:510–520.

28. Luchsinger JA, Tang MX, Stern Y, Shea S, Mayeux R. Diabetes mellitus and risk of Alzheimer's disease and dementia with stroke in a multiethnic cohort. Am J Epidemiol **2001**; 154:635–641.

29. Krikke M, Hoogeveen RC, Hoepelman A, Visseren F, Arends JE. Cardiovascular risk prediction in HIV-infected patients: comparing the Framingham, atherosclerotic cardiovascular disease risk score (ASCVD), Systematic Coronary Risk Evaluation for the Netherlands (SCORE-NL) and Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) risk prediction models. HIV Med **2016**; 17:289–297.

30. Elias MF, Sullivan LM, D'Agostino RB, et al. Framingham stroke risk profile and lowered cognitive performance. Stroke **2004**; 35:404–409.

31. Llewellyn DJ, Lang IA, Xie J, Huppert FA, Melzer D, Langa KM. Framingham Stroke Risk Profile and poor cognitive function: a population-based study. BMC Neurol **2008**; 8:1215–1218.

32. Unverzagt FW, McClure LA, Wadley VG, et al. Vascular risk factors and cognitive impairment in a stroke-free cohort. Neurology **2011**; 77:1729–1736.

33. Vermeer SE, Prins ND, Heijer den T, Hofman A, Koudstaal PJ, Breteler MMB. Silent brain infarcts and the risk of dementia and cognitive decline. N Engl J Med **2003**; 348:1215–1222.

34. Seshadri S, Wolf PA, Beiser A, et al. Stroke risk profile, brain volume, and cognitive function: the Framingham Offspring Study. Neurology **2004**; 63:1591–1599.

35. Prins ND, van Dijk EJ, Heijer den T, et al. Cerebral small-vessel disease and decline in information processing speed, executive function and memory. Brain **2005**; 128:2034–2041.

36. Yuen T, Brouillette M-J, Fellows LK, et al. Personalized Risk Index for Neurocognitive Decline Among People With Well-Controlled HIV Infection. J Acquir Immune Defic Syndr **2017**; 76:48–54.

37. Rubin LH, Gustafson D, Hawkins KL, et al. Midlife adiposity predicts cognitive decline in the prospective Multicenter AIDS Cohort Study. Neurology **2019**; 93:e261–e271.

Table 1: Baseline demographic and clinical characteristics of HAILO participants

No. (%) unless otherwise indicated	All (n=988)	Women (n=195)	Men (n=793)
Sociodemographics			
Age (years), mean (SD)	52 (8)	51 (8)	52 (8)
Race/ethnicity			
White	485 (49)	42 (22)	443 (56)
Black	299 (30)	102 (52)	197 (25)
Hispanic/Latino	204 (21)	51 (26)	153 (19)
Years of education, mean (SD)	14 (4)	12 (4)	14 (3)
Cardiometabolic and other risk factors			
Anti-hypertensive medication use	359 (36)	82 (42)	277 (35)
Statin use	267 (27)	45 (23)	222 (28)
Diabetes mellitus	125 (13)	32 (16)	93 (12)
Total cholesterol (mg/dl), mean (SD)	188 (44)	194 (59)	186 (40)
LDL cholesterol (mg/dl), mean (SD)	109 (39)	111 (56)	108 (33)
HDL cholesterol (mg/dl), mean (SD)	49 (16)	58 (17)	47 (15)
Body mass index (kg/m^2), mean (SD	28.1 (5.5)	30.8 (7.5)	27.4 (4.7)
Waist circumference (cm), mean (SD)	97 (14)	100 (17)	97 (13)
$\geq$3 days of vigorous or moderate physical activity in past week	491 (53)	78 (43)	413 (55)
Smoking			
Never	396 (41)	87 (45)	309 (40)
Current	252 (26)	55 (29)	197 (25)
Prior	321 (33)	51 (26)	270 (35)

Intravenous drug use			
Never	917 (93)	182 (93)	735 (93)
Current/Prior	71 (7)	13 (7)	58 (7)
Anti-depressant medication use	212 (21)	45 (23)	167 (21)
HIV-related factors			
CD4 count (cells/mm^3), mean (SD)	661 (308)	747 (361)	639 (289)
Nadir CD4 count (cells/mm^3), mean (SD)	205 (164)	209 (178)	204 (160)
HIV RNA undetectable (<400 copies/ml)	944 (96)	181 (93)	763 (96)
ART duration (years), mean (SD)	8.1 (3.9)	7.6 (3.9)	8.3 (3.9)
Current efavirenz use	323 (33)	50 (26)	273 (34)
Current integrase inhibitor use	219 (22)	54 (28)	165 (21)
Hepatitis C co-infection	123 (12)	20 (10)	103 (13)

Abbreviations: SD, standard deviation

Table 2: Baseline 10-year cardiovascular risk at entry into HAILO

	All (n=988)	Women (n=195)	Men (n=793)	P value[a]
Atherosclerotic Cardiovascular Disease (ASCVD) risk score, mean (SD)	6.8% (7.1%)	4.1% (5.9%)	7.5% (7.3%)	<0.001
Framingham Heart Study Global Cardiovascular Disease risk score (FRS), mean (SD)	13.1% (10.7%)	8.1% (8.6%)	14.3% (10.8%)	<0.001

[a]Comparisons by sex were made using two-sample t-test

Table 3: Association between baseline 10-year cardiovascular risk scores and cognitive function at Year 4 adjusted for baseline NPZ-4 score

	All (n=988)		Women (n=195)		Men (n=793)	
Cardiovascular risk scores						
	Effect on NPZ-4[a] (SE)	P value	Effect on NPZ-4[a] (SE)	P value	Effect on NPZ-4[a] (SE)	P value
Atherosclerotic Cardiovascular Disease (ASCVD) risk score (per 1% higher risk)*	-0.84 (0.28)	0.003	-2.17 (0.67)	0.001	-0.78 (0.32)	0.016
Framingham Heart Study Global Cardiovascular Disease risk score (FRS) (per 1% higher risk)	-0.44 (0.19)	0.020	-1.25 (0.48)	0.011	-0.44 (0.22)	0.044
Individual components of cardiovascular risk scores						
	Effect on NPZ-4[a] (SE)	P value	Effect on NPZ-4[a] (SE)	P value	Effect on NPZ-4[a] (SE)	P value
Age (per 10 years)	-0.01 (0.003)	<0.001	-0.10 (0.005)	0.16	-0.01 (0.003)	0.001
Female sex	-0.05 (0.05)	0.34	---	---	---	---
Race/ethnicity						
Black (vs. all others)	0.08 (0.04)	0.054	0.16 (0.07)	0.031	0.08 (0.05)	0.14
White (vs. all others)	0.03 (0.04)	0.46	0.06 (0.09)	0.50	0.01 (0.05)	0.76
Systolic blood pressure	-0.0001	0.97	-0.003	0.15	0.001	0.59

(per 1 mmHg increase)	(0.001)		(0.002)		(0.002)	
On anti-hypertensive medication	-0.04 (0.04)	0.38	0.03 (0.07)	0.72	-0.05 (0.05)	0.27
Total cholesterol (per 10 mg/dL increase)	-0.0005 (0.0004)	0.30	-0.0004 (0.001)	0.49	-0.0004 (0.001)	0.44
HDL cholesterol (per 10 mg/dL increase)	-0.003 (0.001)	0.010	-0.002 (0.002)	0.25	-0.003 (0.002)	0.027
Diabetes mellitus	-0.17 (0.06)	0.004	-0.19 (0.10)	0.057	-0.16 (0.07)	0.022
Current smoker	-0.09 (0.04)	0.052	-0.04 (0.08)	0.57	-0.10 (0.05)	0.069

[a]Beta coefficients represent effect of 1% higher CV risk on Year 4 NPZ-4 score

Abbreviations: SE, standard error

Table 4: Adjusted association between baseline 10-year cardiovascular risk scores and cognitive function at Year 4

	All[1] (N=988)		Women[2] (n=195)		Men[3] (n=793)	
	Effect on NPZ-4 (SE)	P value	Effect on NPZ-4 (SE)	P value	Effect on NPZ-4 (SE)	P value
Atherosclerotic Cardiovascular Disease (ASCVD) risk score (per 1% higher risk)	-0.29 (0.39)	0.46	-2.29 (0.67)	<0.001	-0.002 (0.46)	1.00
Framingham Heart Study Global Cardiovascular Disease risk score (FRS) (per 1% higher risk)	-0.09 (0.23)	0.70	-1.45 (0.49)	0.003	0.02 (0.27)	0.93

[1]Adjusted for age, sex, race/ethnicity, education, physical activity, hepatitis C infection, duration of antiretroviral therapy use, baseline NPZ-4

[2]Adjusted for race/ethnicity, education, physical activity, baseline NPZ-4

[3]Adjusted for age, race/ethnicity, education, anti-depressant medication use, baseline NPZ-4

Abbreviations: SE, standard error