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MAJOR ARTICLE

Physical Activity Is Associated With Lower Odds of Cognitive Impairment in Women but Not Men Living With Human Immunodeficiency Virus Infection

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Background. Cardiovascular comorbidities are risk factors for human immunodeficiency virus (HIV)–associated cognitive impairment. Given differences in cardiometabolic risk profiles between women and men with HIV, we investigated whether associations between cardiometabolic risk factors and prevalent cognitive impairment differ by sex.

Methods. Separate logistic regression models were constructed for women and men at entry into a prospective study of older persons with HIV (PWH) to assess the association of cardiometabolic and other risk factors with cognitive impairment.

Results. Of 988 participants, 20% were women. Women had higher total cholesterol (194 vs 186 mg/dL; $P = .027$), hemoglobin A1c (5.9% vs 5.7%; $P = .003$), and body mass index (30.8 vs 27.4 kg/m^2; $P < .001$) compared with men, and were less physically active (43% vs 55%; $P = .005$). In a multivariable model, physical activity was associated with lower odds of cognitive impairment in women (odds ratio, 0.35 [95% confidence interval, .15–.80]; $P = .013$) but not men.

Conclusions. Physical activity may have a greater positive impact on cognitive health in women than in men with HIV. This finding should be confirmed in studies examining the longitudinal association between physical activity and incident cognitive impairment in PWH and the effect of interventions that increase physical activity on cognitive impairment in women with HIV.

Keywords. cardiovascular disease; physical activity; cognitive impairment; sex differences; HIV infection.

Cardiovascular disease and associated comorbidities are established risk factors for dementia [1–3]. Interventions that lower cardiovascular risk may protect against the development of cognitive impairment in the general population [4–6]. For persons with human immunodeficiency virus (HIV) infection (PWH), in whom cognitive impairment remains a major concern, cardiovascular disease and associated risk factors have been linked to HIV-associated neurocognitive disorders [7, 8]. As PWH reach older age, the contribution of cardiovascular comorbidities to cognitive impairment may become increasingly relevant. In a cohort of virologically suppressed men aging with HIV from the AGE$_h$IV Study, prior cardiovascular disease was associated with cognitive impairment [9]. Similarly, in the Central Nervous System HIV Anti-Retroviral Therapy Effects Research (CHARTER) Study, diabetes was associated with cognitive impairment among individuals aged ≥55 years [10]. If cardiometabolic risk factors are associated with cognitive impairment in PWH, these can be targeted for modification to prevent or delay cognitive decline.

In this study, we investigated associations between cardiometabolic risk factors and prevalent cognitive impairment in a large prospective study of older individuals living with HIV infection. Given differences in the cardiometabolic risk profiles of women and men with HIV [11, 12] and the suggestion that cardiovascular risk conferred by HIV may be greater for women [13–15], we evaluated women and men separately to determine if risk factors associated with cognitive impairment in PWH differ by sex.

METHODS

Study Design and Population

We performed a cross-sectional analysis of participants at entry into 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 PWH

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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 rolled over into HAILO (n = 1035) for continued longitudinal follow up of clinical, behavioral, and immunologic parameters. At semiannual visits, data are collected through medical chart abstraction, questionnaires, body measurements, neurocognitive evaluation, laboratory testing, and biologic specimen storage. All HAILO participants who underwent neurocognitive evaluation at entry were included in this study.

Study Measurements

All data included in this analysis were collected between August 2013 and July 2014 at entry into HAILO.

Outcome

Neurocognitive performance in HAILO is assessed using the Brief Neurocognitive Screen (administered in English or Spanish), which consists of a battery of 4 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; total learning over 3 trials subscore). The raw score for each test is standardized using demographics adjusted normative means, which adjust for sex, age, education, and race/ethnicity. The primary outcome was a dichotomous variable for cognitive impairment, defined as either (1) ≥1 standard deviation below the mean on 2 or more tests or (2) ≥2 standard deviations below the mean on 1 or more tests [16].

Predictors and Covariates

To capture cardiometabolic risk, we used a combination of a history of comorbidities, medication use, laboratory data, and measurements from the physical examination at the HAILO entry visit. For example, we considered antihypertensive medication use as a proxy for hypertension, and also included systolic and diastolic blood pressure measurements. We evaluated statin use and total, low-density lipoprotein, and high-density lipoprotein (HDL) cholesterol levels. For diabetes mellitus, we used an established diagnosis or hemoglobin A1c ≥6.5%. To assess renal function, we used the estimated glomerular filtration rate calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula. Data on history of atrial fibrillation, congestive heart failure, prior myocardial infarction, and stroke were also available.

The International Physical Activity Questionnaire, which includes questions about vigorous (eg, heavy lifting, aerobics, fast bicycling) and moderate (eg, carrying light loads, bicycling at a regular pace) physical activity in the preceding week, is administered annually in HAILO. We dichotomized the questionnaire results as ≥3 vs <3 days of vigorous or moderate physical activity in the preceding week. We also included body mass index (BMI) and waist circumference measurements. Smoking and intravenous drug use were categorized as never, current, or prior use.

We included data on antidepressant use and hepatitis C virus (HCV) infection. HIV-related variables at entry included current and nadir CD4 count, plasma HIV RNA viral load, and ART duration. We divided current ART regimens by class (nucleos[t]ide reverse transcriptase inhibitor; nonnucleoside reverse transcriptase inhibitor [NNRTI]; protease inhibitor; integrase inhibitor) and also evaluated efavirenz given its neuropsychiatric adverse effects.

Statistical Analysis

We compared demographic and clinical characteristics between women and men using Student *t* test, Wilcoxon rank-sum test, or χ^2 test. Logistic regression models were constructed in the overall cohort and separately in women and men to evaluate the association of individual cardiometabolic and other risk factors with prevalent cognitive impairment adjusted for age, race/ethnicity, and education. Because the results of these demographics and education-adjusted analyses differed by sex, we performed multivariable models, again in women and men separately, adjusting for age, race/ethnicity, education, and any cardiometabolic risk factor, HIV-associated variable, and health-related behavior significant in the demographics and education-adjusted models at $P < .10$. We then checked for potential statistical interactions in the overall cohort between sex and factors differentially associated with cognitive impairment between women and men, adjusting for all of the covariates from the multivariable models in women and men combined. All *P* values were 2-sided using $\alpha = .05$ as the significance criteria.

RESULTS

Demographics

Demographic and clinical characteristics are shown in Table 1. Of 988 participants, the mean age was 52 years (standard deviation, 8 years), and 20% (n = 195) were women. The race/ethnicity distribution differed between women and men, with 52% of women being black and 22% white, whereas 56% of men were white and 25% black ($P < .001$). Women also had fewer median years of education than men (12 vs 14 years; $P < .001$).

HIV-Associated Factors

The mean CD4 count for the cohort was 661 cells/μL, with women having a higher CD4 count compared with men (747 vs 639 cells/μL; $P < .001$). The majority of participants (90%) had an undetectable viral load. The median duration of ART use was 7.6 years, with women having been on ART for a shorter duration than men (7.1 vs 7.7 years; $P = .017$). In the entire cohort, 33% of participants were currently on a treatment regimen that included efavirenz compared with 22% on an integrase inhibitor and 41% on a protease inhibitor. Women were more likely to be on an integrase inhibitor and less likely to be on efavirenz compared with men.

Table 1. Demographic and Clinical Characteristics of Human Immunodeficiency Virus Infection, Aging, and Immune Function Long-term Observational Study (HAILO) Participants at Entry

Characteristic	All (N = 988)	Women (n = 195)	Men (n = 793)	*P* Value[a]
Sociodemographics				
Age, y, mean (SD)	52 (8)	51 (8)	52 (8)	.80
Race/ethnicity				<.001
White	485 (49)	42 (22)	443 (56)	
Black	299 (30)	102 (52)	197 (25)	
Hispanic/Latino	204 (21)	51 (26)	153 (19)	
Education, y, median (IQR)	14 (12–16)	12 (11–14)	14 (12–16)	<.001
Education (highest level attained)				<.001
High school education or less	373 (38)	118 (61)	255 (32)	
Some college/university degree	480 (49)	66 (34)	414 (52)	
Some graduate school/graduate degree	135 (14)	11 (6)	124 (16)	
Cardiometabolic and other risk factors				
Antihypertensive use	359 (36)	82 (42)	277 (35)	.064
Statin use	267 (27)	45 (23)	222 (28)	.17
Diabetes mellitus	125 (13)	32 (16)	93 (12)	.078
Atrial fibrillation	2 (0.2)	0 (0)	2 (<1)	.48
Congestive heart failure	5 (0.5)	1 (1)	4 (1)	.99
Prior myocardial infarction	34 (3)	1 (1)	33 (4)	.012
Prior stroke	23 (2)	5 (3)	18 (2)	.81
Total cholesterol, mg/dL, mean (SD)	188 (44)	194 (59)	186 (40)	.027
LDL cholesterol, mg/dL, mean (SD)	109 (39)	111 (56)	108 (33)	.39
HDL cholesterol, mg/dL, mean (SD)	49 (16)	58 (17)	47 (15)	<.001
HbA1c, %, mean (SD)	5.7 (1.0)	5.9 (1.0)	5.7 (1.3)	.003
eGFR, mL/min/1.73^2, mean (SD)	90 (19)	91 (20)	89 (18)	.13
BMI, kg/m^2, mean (SD)	28.1 (5.5)	30.8 (7.5)	27.4 (4.7)	<.001
Waist circumference, cm, mean (SD)	97 (14)	100 (17)	97 (13)	.009
≥3 d of vigorous or moderate physical activity in past week	491 (53)	78 (43)	413 (55)	.005
Smoking				.087
Never	396 (41)	87 (45)	309 (40)	
Current	252 (26)	55 (29)	197 (25)	
Prior	321 (33)	51 (26)	270 (35)	
Intravenous drug use				.11
Never	917 (93)	182 (93)	735 (93)	
Current/prior	71 (7)	13 (7)	58 (7)	
Antidepressant use	212 (21)	45 (23)	167 (21)	.54
HIV-related factors				
CD4 count, cells/μL, mean (SD)	661 (308)	747 (361)	639 (289)	<.001
Nadir CD4 count, cells/μL, mean (SD)	205 (164)	209 (178)	204 (160)	.68
HIV RNA undetectable (<40 copies/mL)	894 (90)	173 (89)	721 (91)	.35
ART duration, y, median (IQR)	7.6 (4.3–11.3)	7.1 (3.9–11.1)	7.7 (4.4–11.3)	.017
Protease inhibitor use	409 (41)	87 (45)	322 (41)	.31
NRTI use	962 (97)	189 (97)	773 (97)	.67
NNRTI use	396 (40)	60 (31)	336 (42)	.003
Efavirenz use	323 (33)	50 (26)	273 (34)	.019
Integrase inhibitor use	219 (22)	54 (28)	165 (21)	.038
HCV coinfection	123 (12)	20 (10)	103 (13)	.30
History of CNS infection and/or malignancy	11 (1)	3 (2)	8 (1)	.53
Neurocognitive performance				
Cognitively impaired	275 (28)	71 (36)	204 (26)	.003

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: ART, antiretroviral therapy; BMI, body mass index; CNS, central nervous system; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HCV, hepatitis C virus; HDL, high-density lipoprotein; HIV, human immunodeficiency virus; IQR, interquartile range; LDL, low-density liproprotein; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleos(t)ide reverse transcriptase inhibitor; SD, standard deviation.

[a]Comparing men and women by Student *t* test, Wilcoxon rank-sum test, or χ^2 test.

Cardiometabolic and Other Risk Factors

More than one-third of the cohort was being treated with an antihypertensive medication (36%), and more than one-quarter with a statin (27%). Thirteen percent of the cohort had diabetes mellitus, while a minority had a history of myocardial infarction (3%) or stroke (2%). Twelve percent of the cohort was coinfected with HCV, and 21% were on an antidepressant.

The cardiometabolic risk profile differed between women and men. Women had higher total cholesterol (194 vs 186 mg/dL; $P = .027$) and hemoglobin A1c (5.9% vs 5.7%; $P = .003$) compared with men. Women also had greater BMI and waist circumference. Women tended to be more likely to have diabetes mellitus (16% vs 12%; $P = .078$) or to be on an antihypertensive medication (42% vs 35%; $P = .064$) compared with men, though neither of these differences reached statistical significance. In contrast, a history of myocardial infarction was less common in women (1% vs 4%; $P = .012$), and women had higher HDL cholesterol compared with men (58 vs 47 mg/dL; $P < .001$).

More than 50% of the cohort was a current (26%) or prior (33%) smoker, whereas current and prior injection drug use were uncommon (current 0.1%, prior 7%). More than half of the cohort (53%) reported ≥3 days of either vigorous or moderate physical activity in the preceding week, though women were less likely to be physically active than men (43% vs 55%, $P = .005$).

Cognitive Impairment

At entry, 275 participants (28%) met criteria for cognitive impairment. A greater proportion of women were cognitively impaired compared with men (36% vs 26%; $P = .003$).

Association of Cardiometabolic and Other Risk Factors With Cognitive Impairment

In logistic regression models adjusted for age, race/ethnicity, and education, higher HDL and physical activity were protective against cognitive impairment among women (odds ratio [OR], 0.78 for every 10 mg/dL higher HDL [$P = .028$]; OR, 0.33 for ≥3 days per week of physical activity [$P = .003$]) but not among men (Table 2). In contrast, antidepressant use was associated with higher odds of cognitive impairment in men (OR, 1.73 [95% confidence interval {CI}, 1.17–2.54]; $P = .006$), but not in women (Table 2). Longer duration of ART use, current NNRTI use, and current efavirenz use were associated with lower odds of cognitive impairment in demographic- and education-adjusted models in women, while integrase inhibitor use was associated with higher odds of cognitive impairment. Among men, integrase inhibitor use and HCV infection were risk factors for cognitive impairment after adjustment for demographics and education (Table 2).

In a multivariable model in women adjusted for age, race/ethnicity, education, and covariates associated with cognitive impairment in demographics and education-adjusted models ($P < .10$), ≥3 days of physical activity in the preceding week was protective against cognitive impairment (OR, 0.35 [95% CI, .15–.80]; $P = .013$), whereas older age and Hispanic/Latino ethnicity were risk factors for cognitive impairment. We observed trends toward higher HDL and longer duration of ART decreasing the odds of cognitive impairment, and diabetes mellitus increasing the odds of cognitive impairment in women (Table 3 and Figure 1A).

Among men, the cardiometabolic risk factors associated with cognitive impairment in women (eg, HDL, physical activity, and diabetes mellitus) did not reach the statistical threshold in demographics and education-adjusted models to be included in the multivariable model. Only antidepressant use was identified as a statistically significant risk factor for cognitive impairment in men in a multivariable model (OR, 1.60 [95% CI, 1.08–2.38]; $P = .020$; Table 3 and Figure 1B).

Sex–Physical Activity Interaction in a Multivariable Model in the Combined Cohort

Based on the results of the models in women and men, we checked for potential statistical interactions between sex and diabetes mellitus, HDL cholesterol, BMI, physical activity, antidepressant use, and HCV infection. A statistically significant interaction was only present between sex and physical activity ($P = .049$) in a multivariable model in the entire cohort adjusted for age, race/ethnicity, education, and the combined covariates from the multivariable models in women and men (Table 4). In this model, similar to in the separate models, we found that having ≥3 days of physical activity in the preceding week was protective against cognitive impairment only among women and not men. In the combined cohort, HDL cholesterol was the only cardiometabolic risk factor significantly associated with cognitive impairment, with 12% lower odds of cognitive impairment for every 10 mg/dL higher HDL (95% CI, .79–.99; $P = .036$). When HDL was dichotomized using 55 mg/dL as a cutoff, having an HDL >55 mg/dL was associated with a 40% lower adjusted odds for cognitive impairment (OR, 0.59 [95% CI, .40–.88]; $P = .009$).

DISCUSSION

In this cohort of older PWH, cardiometabolic and other risk factors associated with cognitive impairment differed between women and men. Physical activity was protective against cognitive impairment among women, whereas a similar effect was not seen in men. Although higher HDL cholesterol was associated with a lower risk of cognitive impairment in the combined cohort, in separate models in women and men, the protective effect of HDL was only present among women and was not statistically significant.

Recognized risk markers for cognitive impairment in the general population overlap with those for cardiovascular disease and stroke [1–3, 17]. Studies that have examined the association between cardiometabolic risk and cognitive health disaggregated

Table 2. Demographics and Education-Adjusted Association of Demographics[a], Cardiometabolic, and Other Risk Factors[b] With Cognitive Impairment

	All (N = 988)		Women (n = 195)		Men (n = 793)	
Risk Factor	Odds Ratio (95% CI)	*P* Value	Odds Ratio (95% CI)	*P* Value	Odds Ratio (95% CI)	*P* Value
Sociodemographics						
Age (per 10 y)	1.17 (.97–1.41)	.10	1.43 (.93–2.19)	.11	1.13 (.91–1.40)	.27
Female sex	1.53 (1.06–2.20)	.023	…	…	…	…
Race/ethnicity						
White	…	…	…	…	…	…
Black	0.74 (.51–1.07)	.11	1.60 (.67–3.84)	.29	0.63 (.40–.97)	.037
Hispanic/Latino	2.13 (1.46–3.10)	<.001	4.69 (1.75–12.53)	.002	1.97 (1.30–2.99)	.001
Education (highest level attained)						
High school education or less	…	…	…	…	…	…
Some college/university degree	0.60 (.43–.83)	.002	0.59 (.29–1.20)	.15	0.62 (.42–.90)	.013
Some graduate school/graduate degree	0.73 (.45–1.17)	.19	0.10 (.01–.88)	.038	0.85 (.51–1.41)	.53
Cardiometabolic and other risk factors						
Antihypertensive use	0.86 (.63–1.18)	.35	0.64 (.33–1.24)	.18	0.94 (.65–1.35)	.73
Statin use	0.82 (.59–1.15)	.26	1.28 (.58–2.78)	.54	0.73 (.50–1.08)	.12
Diabetes mellitus	1.25 (.82–1.91)	.30	2.09 (.90–4.86)	.088	1.10 (.66–1.82)	.73
Atrial fibrillation	1.97 (.11–35.20)	.65	…	…	2.17 (.12–39.62)	.60
Congestive heart failure	1.51 (.24–9.70)	.66	…	…	0.80 (.08–8.46)	.86
Prior myocardial infarction	0.90 (.39–2.08)	.80	…	…	0.84 (.35–2.02)	.69
Prior stroke	1.32 (.53–3.30)	.55	1.36 (.19–9.94)	.76	1.30 (.44–3.78)	.64
Total cholesterol (per 10 mg/dL)	0.99 (.96–1.03)	.68	1.02 (.96–1.08)	.55	0.98 (.94–1.02)	.33
LDL cholesterol (per 10 mg/dL)	1.01 (.97–1.05)	.55	1.05 (.96–1.14)	.28	0.99 (.94–1.04)	.76
HDL cholesterol (per 10 mg/dL)	0.89 (.81–.99)	.033	0.78 (.62–.97)	.028	0.95 (.84–1.07)	.38
eGFR (per 1 mL/min/1.73^2)	1.00 (.99–1.01)	.67	0.99 (.97–1.01)	.21	1.00 (.99–1.01)	.76
BMI (per 1 kg/m^2)	0.98 (.95–1.00)	.097	0.96 (.92–1.01)	.093	0.99 (.95–1.02)	.42
Waist circumference (per 10 cm)	0.97 (.87–1.08)	.56	0.96 (.78–1.18)	.69	0.96 (.83–1.10)	.52
≥3 d of vigorous or moderate physical activity in past week	0.71 (.53–.97)	.031	0.33 (.16–.68)	.003	0.88 (.62–1.25)	.48
Smoking status						
Never smoker	…	…	…	…	…	…
Current smoker	1.34 (.93–1.93)	.12	1.01 (.47–2.19)	.97	1.49 (.97–2.27)	.066
Prior smoker	1.01 (.71–1.43)	.96	0.57 (.25–1.31)	.18	1.20 (.81–1.77)	.36
Intravenous drug use						
Never	…	…	…	…	…	…
Current/prior	1.11 (.85–1.45)	.45	0.42 (.11–1.67)	.22	1.51 (.84–2.69)	.17
Antidepressant use	1.53 (1.08–2.15)	.016	0.92 (.42–2.00)	.83	1.73 (1.17–2.54)	.006
HIV-related factors						
CD4 count (per 50 cells/μL)	1.00 (.98–1.02)	1.00	0.98 (.94–1.03)	.44	1.01 (.98–1.04)	.59
Nadir CD4 count (per 50 cells/μL)	1.04 (1.00–1.09)	.066	0.98 (.89–1.07)	.65	1.06 (1.01–1.12)	.022
HIV RNA undetectable (<40 copies/mL)	0.89 (.55–1.45)	.64	1.87 (.65–5.42)	.25	0.72 (.42–1.25)	.24
ART duration (per y)	0.94 (.91–.98)	.004	0.88 (.80–.96)	.005	0.96 (.92–1.01)	.088
Protease inhibitor use	0.93 (.69–1.25)	.63	1.27 (.66–2.43)	.48	0.83 (.59–1.16)	.28
NRTI use	1.96 (.66–5.85)	.23	1.93 (.20–18.17)	.57	1.79 (.51–6.27)	.37
NNRTI use	0.65 (.48–.88)	.005	0.43 (.20–.94)	.033	0.72 (.52–1.01)	.058
Efavirenz use	0.68 (.49–.93)	.017	0.39 (.17–.91)	.030	0.78 (.55–1.10)	.16
Integrase inhibitor use	1.84 (1.31–2.57)	<.001	2.52 (1.24–5.13)	.011	1.66 (1.13–2.45)	.011
HCV coinfection	1.48 (.98–2.25)	.065	0.65 (.23–1.86)	.42	1.73 (1.10–2.73)	.018
History of CNS infection and/or malignancy	2.38 (.67–8.45)	.18	1.69 (.14–20.46)	.68	2.48 (.57–10.76)	.22

Abbreviations: ART, antiretroviral therapy; BMI, body mass index; CI, confidence interval; CNS, central nervous system; eGFR, estimated glomerular filtration rate; HCV, hepatitis C virus; HDL, high-density lipoprotein; HIV, human immunodeficiency virus; LDL, low-density liproprotein; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleos(t)ide reverse transcriptase inhibitor.

[a]The estimated odds ratios for the sociodemographic variables are derived from a multivariable model that included only age, sex, race/ethnicity, and education.

[b]The estimated odds ratios for cardiometabolic and other risk factors are derived from multivariable models of each individual risk factor adjusted for age, sex, race/ethnicity, and education. For example, the estimated odds ratio of cognitive impairment for antihypertensive use is derived from a model with antihypertensive use as the predictor and cognitive impairment as the outcome, adjusted for age, sex, race/ethnicity, and education.

Table 3. Multivariable Models[a] of the Association of Demographics, Cardiometabolic, and Other Risk Factors With Cognitive Impairment in Women and Men

	Women (n = 195)		Men (n = 793)	
Characteristic	Odds Ratio (95% CI)	*P* Value	Odds Ratio (95% CI)	*P* Value
Sociodemographics				
Age (per 10 years)[b]	1.90 (1.10–3.28)	.022	1.21 (.97–1.51)	.099
Race/ethnicity[d]				
White	…	…	…	…
Black	1.48 (.52–4.20)	.46	0.64 (.41–1.02)	.059
Hispanic/Latino	6.35 (1.87–21.59)	.003	2.35 (1.51–3.67)	<.001
Education (highest level attained)[c]				
High school education or less	…	…	…	…
Some college/university degree	1.27 (.52–3.06)	.60	0.62 (.42–.91)	.015
Some graduate school/graduate degree	0.24 (.03–2.20)	.21	0.95 (.55–1.63)	.85
Cardiometabolic and other risk factors				
Diabetes mellitus	2.77 (.97–7.90)	.057		
HDL cholesterol (per 10 mg/dL)	0.79 (.61–1.03)	.086		
BMI (per 1 kg/m^2)	0.95 (.89–1.00)	.065		
≥3 d of vigorous or moderate physical activity in past week[b]	0.35 (.15–.80)	.013		
Smoking status				
Never smoker	…	…	…	…
Current smoker	…	…	1.37 (.89–2.12)	.15
Prior smoker	…	…	1.16 (.78–1.72)	.47
Antidepressant use[c]	…	…	1.60 (1.08–2.38)	.020
HIV-related factors				
ART duration (per year)	0.90 (.80–1.02)	.093	0.99 (.94–1.05)	.84
NNRTI use	0.89 (.30–2.59)	.83	0.87 (.57–1.32)	.51
Integrase inhibitor use	1.82 (.75–4.41)	.19	1.43 (.93–2.20)	.11
Nadir CD4 count (per 50 cells/μL)	…	…	1.05 (.99–1.11)	.081
HCV coinfection	…	…	1.50 (.94–2.39)	.092

Abbreviations: ART, antiretroviral therapy; BMI, body mass index; CI, confidence interval; HCV, hepatitis C virus; HDL, high-density lipoprotein; HIV, human immunodeficiency virus; NNRTI, nonnucleoside reverse transcriptase inhibitor.

[a]The multivariable models for women and men were each adjusted only for the variables shown in each column.

[b]Significantly associated with cognitive impairment in women only.

[c]Significantly associated with cognitive impairment in men only.

[d]Significantly associated with cognitive impairment in women and men.

by sex have found that an unfavorable cardiometabolic risk profile may have a greater negative impact on cognitive function in women than in men [18–20]. Among 985 community-dwelling elders from the Rancho Bernardo Study, women with a Framingham cardiac risk score >7% had a higher rate of cognitive decline compared with women with lower risk, whereas cardiac risk was not predictive of the rate of cognitive decline among men [20]. A similar finding was observed in >1000 participants from the Sacramento Area Latino Study on Aging, in which a higher cardiovascular risk score was associated with greater decline in verbal learning in women but not in men [19].

Our results suggest that physical activity may be one specific cardiometabolic risk factor that is more beneficial for cognitive health in women than men with HIV. Physical activity has been linked in midlife and late life to preserved cognitive function and protection against the development of dementia in the general population [21, 22], and to better cognitive performance and larger putaminal volumes in small cross-sectional studies in PWH [23, 24]. A cross-sectional study of 318 community-dwelling adults in Malaysia, 59% of whom were women, found that self-reported lack of exercise was associated with higher odds of cognitive impairment among women but not men [25]. In 2 prospective, population-based studies of approximately 5000 participants each, low baseline physical activity was predictive of subsequent worse neurocognitive performance [26] and incident dementia [27] in women but not in men. In one of these studies from the Canadian Study of Health and Aging, a dose-response relationship was reported with the highest level of physical activity predicting a 50%–60% odds reduction of incident mild cognitive impairment or dementia compared with no physical activity, again only among women [27]. To our knowledge, an observed beneficial effect of physical activity in women but not men has not been reported previously in PWH.

Results from clinical trials of structured exercise programs and physical activity interventions to improve cognitive function have generally been equivocal. However, several

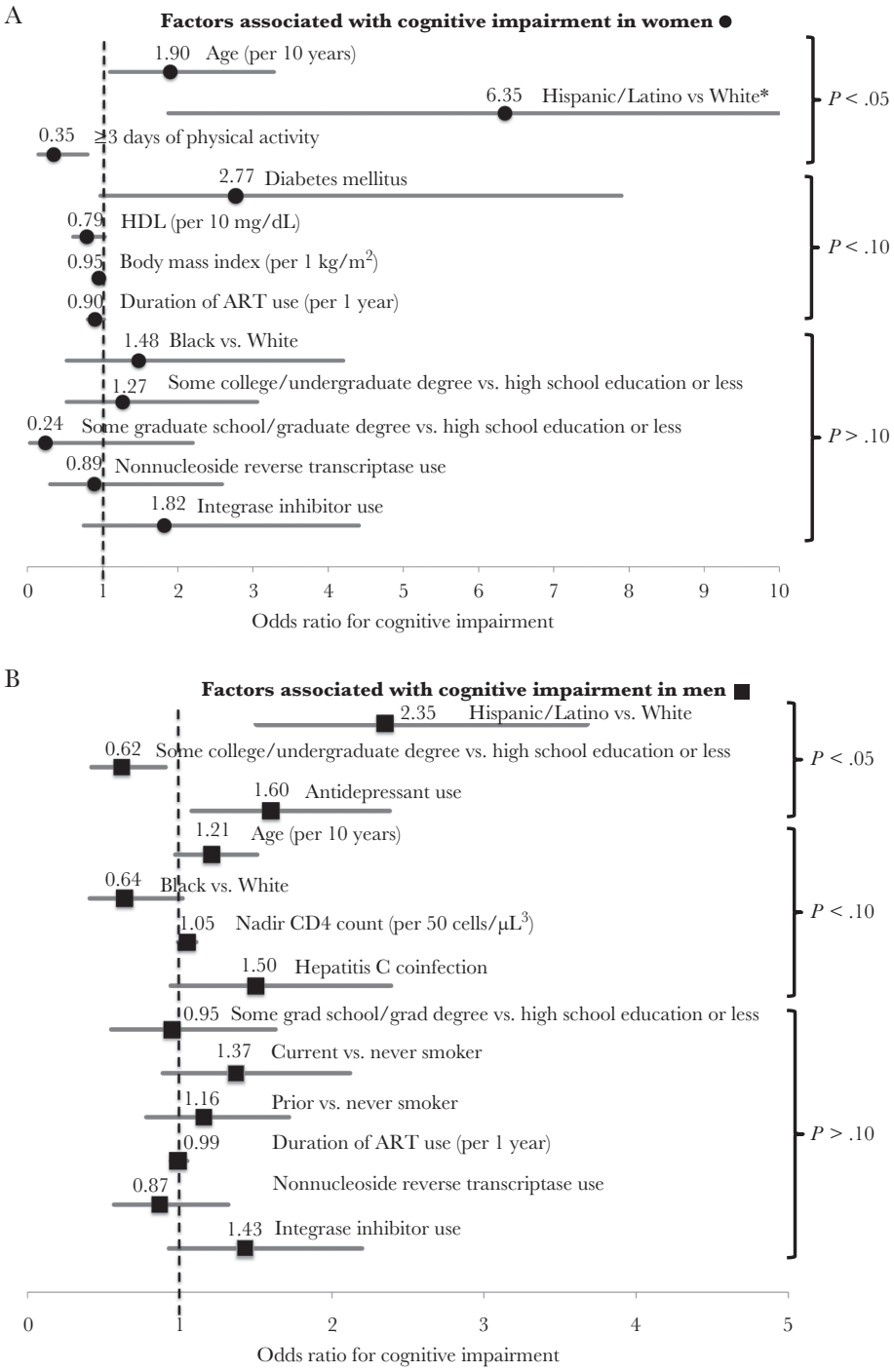

Figure 1. Factors associated with cognitive impairment in women (*A*) and men (*B*) living with human immunodeficiency virus from the AIDS Clinical Trials Group A5322 (HAILO) study. In separate multivariable models for women and men, factors associated with cognitive impairment differed by sex. Among women, greater physical activity was associated with lower odds of cognitive impairment, whereas older age and Hispanic/Latino ethnicity were risk factors for cognitive impairment. For men, no cardiometabolic risk factors were significantly associated with cognitive impairment, whereas antidepressant use and Hispanic/Latino ethnicity were associated with higher odds of cognitive impairment. Separate multivariable logistic regression models were performed for women and men. Each model was adjusted for the variables shown in the figure. *Confidence intervals (1.87–21.59) for Hispanic/Latino ethnicity in Figure 1A not shown to scale. Abbreviations: ART, antiretroviral therapy; HDL, high-density lipoprotein cholesterol.

interventional studies with data disaggregated by sex have demonstrated that exercise may benefit cognitive health more in women than men. In a meta-analysis of 18 trials, aerobic fitness training had greater benefit on cognition in studies with >50% women [28]. In one randomized trial of a high-intensity aerobic exercise program vs stretching, women in the exercise

Table 4. Multivariable Model[a] of the Association of Demographic, Cardiometabolic, and Other Risk Factors With Cognitive Impairment With a Sex-by-Physical Activity Interaction[b]

	All (N = 988)	
Characteristic	Odds Ratio (95% CI)	*P* Value
Sociodemographic characteristics		
Age (per 10 years)	1.30 (1.05–1.61)	.018
Female sex (among non–physically active)	2.16 (1.23–3.79)	.007
Race/ethnicity		
White	…	…
Black	0.75 (.49–1.14)	.18
Hispanic/Latino	2.83 (1.82–4.40)	<.001
Education (highest level attained)		
High school education or less	…	…
Some college/university degree	0.72 (.50–1.04)	.079
Some graduate school/graduate degree	1.07 (.63–1.82)	.81
Cardiometabolic and other risk factors		
Diabetes mellitus	1.31 (.81–2.12)	.27
HDL cholesterol (per 10 mg/dL)	0.88 (.79–.99)	.036
BMI (per 1 kg/m^2)	0.97 (.94–1.00)	.097
≥3 d of vigorous or moderate physical activity in past week among men	0.94 (.48–1.87)	.87
≥3 d of vigorous or moderate physical activity in past week among women	0.41 (.19–.86)	.018
Smoking status		
Never smoker	…	…
Current smoker	1.31 (.87–1.97)	.19
Prior smoker	1.05 (.72–1.55)	.79
Antidepressant use	1.48 (1.02–2.17)	.041
HIV-related factors		
Nadir CD4 count (per 50 cells/μL)	1.03 (.98–1.08)	.23
ART duration (per year)	0.96 (.91–1.01)	.11
NNRTI use	0.90 (.60–1.36)	.62
Integrase inhibitor use	1.46 (.98–2.16)	.062
HCV coinfection	1.30 (.83–2.06)	.20

Abbreviations: ART, antiretroviral therapy; BMI, body mass index; CI, confidence interval; HCV, hepatitis C virus; HDL, high-density lipoprotein; HIV, human immunodeficiency virus; NNRTI, nonnucleoside reverse transcriptase inhibitor.

[a]Multivariable model adjusted for all of the variables shown in the table.

[b]*P* value for sex-by-physical activity interaction = .049.

group demonstrated improved performance on several tests of executive function, whereas men improved on only a single test [29]. In another trial of structured aerobic training vs healthy eating education, regular exercise improved executive function in women but not men, both immediately after the intervention and at 6 months [30].

The mechanisms underlying a potential association between physical activity and cognitive health are not fully understood. Physical activity may simply serve as a proxy of overall good physical and/or mental health and may not directly result in improved or preserved cognitive function. On the other hand, physical activity and exercise have been shown in human and animal models to increase cerebral blood perfusion and hippocampal volumes, and improve functional connectivity between the hippocampus and related medial temporal lobe circuitry [31]. Physical activity boosts brain plasticity and helps to maintain dopamine function through upregulation of growth factors such as brain-derived neurotrophic factor, which is involved in cellular signaling in learning and memory pathways [32], and through suppression of microglial activity [33, 34]. Sex differences in these exercise-induced alterations in the brain could theoretically account for the greater benefit of physical activity for women. Estradiol, for example, regulates dopamine transmission in regions of the brain that control executive function [35, 36] and may modulate brain-derived neurotrophic factor transcription through activation of a promoter region on the brain-derived neurotrophic factor gene [37]. In the aforementioned trial of aerobic training vs healthy eating classes, women in the exercise group who had better executive function had a significant increase in serum brain-derived neurotrophic factor, whereas a similar rise was not seen in men [30]. Taken together, these data highlight biologically plausible mechanisms that may underlie the differential benefit of physical activity on cognition in women compared with men.

The effect of HDL on cognitive impairment also differed by sex, with a trend toward a protective effect of higher HDL against cognitive impairment among women but not men. However, testing the interaction term between sex and HDL did not provide statistical evidence for differences in the association of HDL with cognitive impairment in women vs men. In a combined multivariable analysis of the entire cohort, we found that higher HDL was associated with lower odds of cognitive impairment, which parallels results from studies in the general population [38, 39]. Contrary to our results, however, time-varying higher HDL attenuated the rate of cognitive decline in men living with HIV from the Multicenter AIDS Cohort Study [40].

Several theories have been put forward regarding the link between higher HDL and better cognition. Low HDL cholesterol may be a marker for cerebrovascular disease and atherosclerosis, which are risk factors for dementia. Lower HDL, for example, is associated with ischemic stroke and cerebral small vessel disease [41–43], which in turn are associated with higher risk of Alzheimer disease. (We did not find a significant association between stroke and cognitive impairment in this cohort, although few participants had a history of stroke.) Alternatively, HDL levels may impact dementia risk via nonvascular pathways given HDL's pivotal role in preventing amyloid-β deposition in the brain [44] and its anti-inflammatory and antioxidant properties [45, 46]. HDL could be an intermediary on the proposed causal pathway between physical activity and cognitive health, as exercise has been shown to raise HDL. To explore whether HDL was mediating the association between physical activity and cognitive impairment, we removed HDL from the multivariable model in the entire cohort and in women. When the models were not adjusted for HDL, the estimate of the effect of physical activity on the risk of cognitive impairment in women was essentially unchanged, suggesting that the beneficial effects of higher HDL and greater physical activity on cognitive impairment may be independent of one another. The associations between physical activity, HDL, and cognitive function should be examined longitudinally using formal mediation analysis methods.

Hispanic/Latino ethnicity compared with white race/ethnicity was consistently and strongly associated with a higher risk of cognitive impairment, both among women and men separately and in the combined cohort. Our findings are in agreement with an earlier study of 126 PWH in New York City, in which Latinos performed worse on neurocognitive testing compared to non-Hispanic whites, but only among individuals ≥50 years of age [47]. Unmeasured confounders, including socioeconomic and sociocultural factors (eg, household income, nativity) and comorbid health disparities, could explain the disproportionately high risk of cognitive impairment observed among Latinos. In addition, although we used normative means developed in a monolingual Spanish-speaking population to standardize neuropsychological testing performed in Spanish (eg, HVLT-R), the norms used for testing performed in English may not fit Hispanic/Latino populations as well as non-Hispanic whites or blacks.

Antidepressant use was associated with higher risk of cognitive impairment among men and in the combined cohort. We viewed antidepressant use as a proxy for depression, which could explain the association with cognitive impairment; a specific measure of depression is not currently collected in HAILO, precluding further investigation into this observation. Use of an integrase inhibitor was also associated with a trend toward an elevated risk of cognitive impairment. Neuropsychiatric adverse effects have been reported with integrase inhibitor use [48], most commonly with dolutegravir [49]. The majority of integrase inhibitor users at entry were on raltegravir (65%), with only 7% on dolutegravir. Channeling bias could partially account for worse cognitive performance among integrase inhibitor users; individuals with cognitive impairment on efavirenz may be more likely to switch to an integrase inhibitor, leading to the appearance of an association between integrase inhibitor use and worse cognition. We did not find that individuals on integrase inhibitors had been on a significantly greater number of prior ART regimens compared with those not on an integrase inhibitor, which could be a risk factor for cognitive impairment.

The findings from our study should be interpreted in the context of its limitations. As a cross-sectional study, observed relationships between cardiometabolic risk factors and cognitive impairment cannot address causality. As with any observational study, unmeasured confounders could have biased estimated associations. For example, individuals who are more physically active may be less likely to be depressed. Although we controlled for antidepressant use in the multivariable model of the combined cohort, unmeasured depression could have confounded the observed relationship between physical activity and cognitive impairment. Finally, women comprised only 20% of the nearly 1000 HAILO participants included in these analyses, which may have limited our ability to identify factors associated with cognitive impairment in this key risk group.

CONCLUSIONS

Among older PWH with well-controlled infection, women and men may have unique risk factors for cognitive impairment, with some cardiometabolic factors such as physical activity having a greater impact on cognitive health in women than in men. Although women living with HIV may benefit to a greater extent from physical activity than men, fewer women were taking advantage of this protective lifestyle factor. Critical next steps will be to examine the longitudinal association of physical activity and other cardiometabolic factors on incident cognitive impairment in PWH and to test the effect of interventions that increase physical activity on cognitive impairment in women with HIV.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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

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