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Association of Midlife Smoking Status with Change in Processing Speed and Mental Flexibility Among Hiv-Seropositive and Hiv-Seronegative Older Men: The Multicenter Aids Cohort Study

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Abstract

Introduction—Smoking is a potential risk factor for age-related cognitive decline. To date, no study has examined the association between smoking and cognitive decline in men living with human immunodeficiency virus (HIV).

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Objective—To examine whether smoking status and severity in midlife is associated with rate of decline in cognitive processing speed among older HIV-seropositive and HIV-seronegative men who have sex with men.

Methods and Outcome Measures—Data from 591 older HIV-seropositive and HIV-seronegative men who have sex with men from the Multicenter AIDS Cohort Study were examined. All participants had information on smoking history collected before age 50 years and at least 5 years of follow-up after age 50. Smoking history was categorized as never smoker; former smoker; and current smoker and cumulative pack years was calculated. The raw scores of 3 neuropsychological tests (Trail Making A, Trail Making B, and Symbol Digit Modalities tests) were log transformed (Trail Making A and B) and used in linear mixed models to determine associations between smoking history and at least subsequent 5-year decline in cognitive processing speed.

Results—There were no significant differences in the rates of neurological decline among never smokers, former smokers, and current smokers. Findings were similar among HIV-seropositive participants. However, an increase of 5 pack-years was statistically significantly associated with a greater rate of decline in the Trail Making Test B score and Composite Score (β: -0.0250 [95% CI, -0.0095 to -0.0006] and -0.0077 [95% CI, -0.0153 to -0.0002], respectively).

Conclusions—We found no significant association between smoking treated as a categorical variable (never smoked, former smoker, or current smoker) and a small change in every increase of 5 pack-years on measures of psychomotor speed and cognitive flexibility. To optimize healthy aging, interventions for smoking cessation should be tailored to men who have sex with men.

Introduction

Since the introduction of antiretroviral therapy (ART), human immunodeficiency virus (HIV)–positive individuals are living longer than before (Justice, 2009). In 2013, people living with HIV (PLWH) older than the age of 50 years accounted for 26% of the population of PLWH (Centers for Disease Control and Prevention, 2015). In some communities, the proportion of PLWH older than 50 years already exceeds 50% (Canizares et al, 2014). As the epidemic reaches its fourth decade, more information is needed on how the virus, therapy, behaviors associated with PLWH, and natural aging process interact with each other. Human immunodeficiency virus and its treatments affect the aging process or the development of morbidities that are associated with aging (High et al, 2012).

Impairment in cognition related to HIV is known as HIV-associated neurocognitive disorder (HAND). People living with severe HAND are less likely to adhere to medication recommendations, struggle to perform complex daily tasks, and have worse quality of life, difficulty in obtaining employment, and a shorter survival rate (Nabha et al, 2013). As PLWH begin to age, interactive effects of immune function and aging on the central nervous system could precipitate HAND. As many as 40% of HIV-seropositive individuals have HAND (Sacktor et al, 2001; Lindl et al, 2010). Conservative estimates suggest that HAND diagnoses will increase 5- to 10-fold by 2030 (Lindl et al, 2010).

Smoking, a modifiable behavior, is highly prevalent among PLWH (Akhtar-Khaleel et al, 2016). Smoking is a risk factor for many vascular diseases, such as atherosclerosis and

thrombosis, which may increase the risk for cerebrovascular diseases and vascular dementia (Reitz and Mayeux, 2014). Furthermore, recent studies have shown that cognitive changes in older PLWH are likely to include a cerebrovascular pathology (Sacktor et al, 2010; Valcour et al, 2004). Additionally, public health messages have led many to give up smoking, but the extent to which this change influences subsequent cognitive decline remains unclear.

In the general population, many studies have found that smoking increases the risk of cognitive decline (North et al, 2015; Durazzo et al, 2014; Sabia et al, 2012; Sabia et al, 2008; Collins et al, 2009; Knopman et al, 2009; Nooyens et al, 2008; Peters et al, 2008). Yet, the association between smoking and cognitive decline in PLWH remains unclear (Durazzo et al, 2007; Wojna et al, 2007; Bryant et al, 2013), but there are reasons to suspect the impact could be greater. In PLWH, HIV first enters the central nervous system during the acute infection, but the neurons remain uninfected (Valcour et al, 2011). It is theorized that, once in the central nervous system, the virus establishes a reservoir that resists ART and causes extensive inflammation, which then leads to neuronal dysfunction and synaptodendritic injury (Valcour et al, 2011). Therefore it is possible that extensive inflammation could increase the risk for cognitive decline among PLWH and smoking can act on that mechanism. The aim of this present study is to examine the association between midlife smoking status and future rate of cognitive decline in HIV-seropositive and HIV-seronegative men who have sex with men. Additionally, we assess whether a difference in cognitive decline exists by HIV serostatus.

Methods

Study Population

We used data from the Multicenter AIDS Cohort Study (MACS), an ongoing longitudinal study of the natural and treated history of HIV infection and AIDS among men who have sex with men. As has been described in detail elsewhere (Kaslow et al, 1987; Dudley et al, 1995), the MACS began in 1984, sampled 6973 men, recruited at 4 centers: the Baltimore, Maryland, and Washington, DC, area; Chicago, Illinois; Los Angeles, California; and Pittsburgh, Pennsylvania. The MACS protocols were approved by the institutional review board of each center, and written informed consent was obtained from all participants. Participants return biannually for a detailed interview, physical examination, and blood draw for laboratory testing. In 1986, the MACS began examining participants' longitudinal neuropsychological test performance to assess the effects of HIV on the brain and nervous system (Miller et al, 1990). The full battery is performed every 2 years, while a shorter battery – which includes the Trail Making and Symbol Digit Modalities tests -- is administered every 6 months. Since 2005, 5470 participants have completed at least 1 test battery; 1502 men who did not provide data were on average younger, less educated, more likely to use recreational drugs, and be non-Hispanic white (Becker et al, 2015). We studied only MACS participants who provided data on smoking behavior before age 50 and at least 5 years (10 follow-up visits) after age 50. Time was anchored at age 50; this yielded 591 men and 10 821 observations.

Exposure of Interest: Smoking Behavior

Smoking behavior, prior to age 50, was was collected via self-report. At each visit, participants were classified as never, former, and current smokers. Participants were asked: “Did you ever smoke cigarettes?” “Do you smoke cigarettes now?” Participants who answered “yes” to both questions were categorized as current smokers. Participants were categorized as former smokers if they answered “yes” to the first question and “no” to the second. Participants answering “no” to both questions were categorized as never smokers.

Number of packs smoked was defined using MACS standardized categories: less than half a pack per day; at least half a pack but less than 1 pack per day; at least 1 but less than 2 packs per day; and 2 or more packs per day. Pack-years were based on the number of cigarettes smoked per day; they were calculated by determining the average pack (based on the choices listed here) and multiplying by 0.5. If a participant smoked 1 to 2 packs a day, then his current smoking exposure was calculated as 1.5 × 0.5 years = 0.75 pack-years. The calculation determined pack-days for 1 year for that specific visit. To assess cumulative smoking using pack-years, we added each pack-year observed before age 50.

Outcome of Interest: Cognitive Performance

The outcome of interest, the average rate of change in cognitive performance, was assessed with 3 tests: Trail Making A, Trail Making B, and Symbol Digit Modalities. These tests were chosen because past studies suggested that smoking is associated with poor mental flexibility and inhibitory abilities (Trail Making Test B) and processing speed (Trail Making A and Symbol Digit Modalities tests) and because of the large amount of repeated measures in the data set.

Trail Making Test raw scores (time to completion) were log10-transformed to stabilize the variance and to have a better approximation of a normal distribution. The number of correct responses were recorded for the Symbol Digit Modalities Test. Using the mean and SD of baseline HIV-negative participants at age 50, we calculated z scores to standardize the raw scores to assess change over time. We averaged the z score for all 3 tests to create a Composite Score.

Covariates of Interest

Because all participants were aged 50, the year of birth recorded during the baseline visit was used to assess cohort effects. Education was categorized as high school diploma or less, some college or college degree, and graduate work or more. Race/ethnicity was categorized as non-Hispanic white, non-Hispanic black, or other (includes Hispanic, American Indian or Alaskan Native, Asian or Pacific Islander; and mixed or other).

Health behaviors were assessed starting at ageg 50 included alcohol consumption and marijuana use (yes/no). Self-reported alcohol use included frequency of drinking and the average number of drinks the participant consumed since his last visit. We categorized participants into 4 groups: (1) having no drinks since the last visit; (2) low to moderate consumption (1-2 drinks per day or 3-4 drinks per day no more than once a month), (3) moderate to heavy consumption (3-4 drinks per day for more than once a month or ≥5 drinks

per day for less than once a month), and heavy (≥5 drinks for at least once a month) (Substance Abuse and Mental Health Services Administration, 2014). High depressive symptoms were defined as a score of 16 or more at any time during the study period on the Center for Epidemiological Studies–Depression Scale (Lewinsohn et al, 1997).

Time-dependent covariates included hypertension, incident self-reported angina, incident self-reported heart attack, and incident self-reported stroke. Among HIV-seropositive participants, CD4+ count, viral load, and highly active ART (HAART) use were also included as time-dependent covariates. Hypertension was measured using blood pressure measurements from each visit (systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg). Self-reported angina, heart attack, and stroke were measured using the questionnaire section for each visit. Participants were asked: “Has a doctor or other medical professional ever told you that you had [comorbidity]?” Human immunodeficiency virus serostatus was assessed using enzyme-linked immunosorbent assay with confirmatory Western blot tests on all MACS participants at each participant's initial visit and at every semiannual visit for those who were initially HIV seronegative. Standardized flow cytometry was used to quantify CD4+ T-lymphocyte subset levels by each MACS site (Giorgi et al, 1990; Schenker et al, 1993).

Statistical Analysis

Linear mixed models were used to estimate the association between smoking status at age 50 and 5-year cognitive decline. We fitted the intercept as a random effect to account for individual differences in baseline cognitive performance. The model included terms for year of birth, number of previous tests, education, and race/ethnicity (model 1) and the interaction of each of the covariates with time. We included the interaction of each covariate with time because we hypothesized that all covariates influence the rate of decline. We expanded the model to include time-dependent variables and their interaction with time: drug use, depressive symptoms, and health measures (model 2). We repeated the analysis using only HIV-seropositive men and also tested for an interaction between each covariate and time. Finally, we repeated the same analysis using cumulative pack-years as the exposure variable.

To account for death and drop-out, we used inverse probability of attrition weighting (Weuve et al, 2012). We weighted study participants by using the inverse of the probability that they would either die or drop out. This was estimated using logistic regression models to compensate for the underrepresentation of persons with characteristics associated with death and drop-out. Once these individual probabilities were calculated, they were applied to our linear mixed model.

Results

Of the 5470 men who completed at least 1 test battery, we included only participants who had at least 10 visits after age 50: 582 men, yielding 10 821 observations. The median number of visits was 17 (interquartile range, 13-22).

Among men in the MACS at age 50, current smokers were more likely to be born between 1960 and 1969, be non-Hispanic black, and have a college degree or less (Table 1). Current

smokers at the age of 50 were also more likely to be depressed compared with never smokers (18.9% and 10.6%, respectively). Overall, there were 23 incident clinical events of diabetes, heart attack, heart failure, stroke, or transient ischemic attack. Although the sample was small, current smokers were more likely to have diabetes compared with never smokers (5.9% and 3.5%, respectively). Current smokers were more likely to be HIV seropositive compared with never smokers (42.4% and 35.1%, respectively). Among HIV-seropositive participants, there were no differences in CD4+ T-cell count and HAART use by smoking status at age 50.

Linear Mixed Models

Smoking Status—Table 2 shows the estimates of cognitive change over 10 visits (approximately 5 years) among HIV-seropositive and HIV-seronegative participants (n=582). There were no statistically significant differences in the rates of decline among never smokers, former smokers, and current smokers. Although not statistically significant, we observed a small increased rate of decline across all tests (Composite Score – Former Smokers: -0.0027 [95% CI, -0.0070 to 0.0014] and Current Smoker: -0.0034 [95% CI, -.0079 to 0.0007]). Former smokers had a higher rate of decline in Trail Making B than current smokers (-0.221 [95% CI, -0.5202 to 0.0570] and -0.0987 [95% CI, -0.521 to 0.0135], respectively). We observed the same trend when the analysis was restricted to HIV-seropositive participants (Table 3).

Cumulative Smoking—Table 4 shows the estimates of cognitive change over at least 10 visits using cumulative pack-years among HIV-seropositive and HIV-seronegative participants (n=528). An increase of 1 unit of 5 pack-years was statistically significantly associated with an increased rate of decline in Trail Making Test B score and Composite Score (-0.0250 [95% CI, -0.0095 to -0.0006) and -0.0077 [-0.0153 to -0.0002], respectively). We repeated the same analysis among only HIV-seropositive men, and the rates of decline for Trail Making A and B and Symbol Digit Modalities test scores and Composite Score were not statistically significant (Table 5).

Discussion

We found no statistically significant association between smoking status at age 50 (never smoked, former smoker, or current smoker) and changes in cognitive functioning, five years later, on measures of psychomotor speed and cognitive flexibility. However, analysis of a more sensitive outcome variable --the quantitative measure of cumulative pack-years – found that an increase of a unit of 5 pack-years was significantly associated with an increased rate of decline in Trail Making Test B score and in our Composite Score of an average of all 3 tests.

Among the general population, several large studies have found an association of smoking with increased risk for cognitive decline and dementia among older adults (Sabia et al, 2008; Peters et al, 2008; Nooyens et al, 2008; and Peters et al., 2008). Further, research among the general population has shown that former and active smoking is associated with increased risk for Alzheimer disease and that smoking-related cerebral oxidative stress may be a potential mechanism (Durazzo et al, 2014).

To date, few studies have assessed the association of smoking on cognitive performance among PLWH and the results are inconsisten. Durazzo et al (2007) cross-sectionally assessed 44 HIV-seropositive alcohol drinkers and found that smokers performed more poorly than nonsmokers inauditory-verbal learning, auditory-verbal memory, and cognitive efficiency. Yet, Wojna et al (2007), performed a cross-sectional study of 56 PLWH, found no statistically significant associations between cognitive performance and current smoking or smoking history. (Wojna et al, 2007). Bryant et al (2013) found a negative association between PLWH who were current smokers and learning, memory, and global cognitive functioning. More recently, Monnig et al (2016) assessed the association of smoking and alcohol use with cognitive functioning among PLWH. Smoking was associated with lower cognitive scores in verbal learning and processing speed (Monnig et al, 2016); however, the study used a smaller sample size and was cross-sectional. Most of the significant associations with smoking were related to memory, a domain that was not assessed in our study.

Smoking has been associated with deficiencies in executive functions, cognitive flexibility, general intellectual abilities, learning and memory processing speed, and working memory (Durazzo et al, 2010). Among older adults, smoking is associated with abnormal rates of brain volume loss, especially in anterior frontal regions, subcortical nuclei, and commissural white matter. Human immunodeficiency virus staining has shown that the virus is concentrated in the subcortical deep gray matter structures (Gabrieli, 1995; Gray et al, 2001; Woods et al, 2009). Smoking is also moderately or strongly associated with cardiovascular disease, stroke, diabetes, hypertension, and hypercholesterolemia, all of which are potential modifiable risk factors for cognitive decline (Durazzo et al, 2014). As these conditions are also associated with aging among PLWH, we had hypothesized that the association would be present among this subgroup. The incidence of these comorbidities were low among our sample and despite these independent effects of smoking and HIV on brain function, the current study did not find a combined effect.

Among HIV-uninfected individuals', factors such as small vessel disease, hypertension, diabetes, and neural inflammation affect brain structure in cognitively normal individuals (Ho et al, 2010; Ho et al, 2011; Raji et al, 2010; Raji et al, 2010). Altering the otherwise “normal” substrate of brain structure and function reduces brain or cognitive reserve, rendering individuals more vulnerable to any HIV-related neuropathologies (Satz et al, 1993 and Stern et al, 1996). First, measures of lung function, including both FEV and DLCOPP, are significantly associated with brain regional volumes. Second, there is a significant interaction between HIV disease and lung function such that regional volumes in the cerebellum are significantly smaller among HIV-infected men for a given level of diffusion lung capacity. Third, performance on neuropsychological tests is significantly associated with the volume of the region in the caudate nucleus that was associated with FEV.

Limitations

More than half of the participants in the MACS were initially recruited in the mid-1980s, when no treatments were available for HIV. The participants who survived this era in the AIDS epidemic likely differed in systematic ways from those who died. In a recent study by

Becker et al (2015), of 5470 men who had cognitive testing in the MACS, only 32% of participants were still active. Selection bias from mortality or other forms of attrition may have occurred to participants after study enrollment (Weuve et al, 2012). When studying cognitive decline, impaired cognition was strongly associated with morbidity, mortality, and attrition after study enrollment. With a risk factor such as smoking, which is also associated with morbidity and mortality, we were vulnerable to bias due to selective attrition. We used inverse probability of attrition weighting to account for this, but our results remained the same.

Our study had other limitations as well. First, we examined only MSM and findings may not be generalizable to other subpopulations of HIV-seropositive individuals. Second, we analyzed only cognitive flexibility and speed of information processing. Future studies should examine additional domains that could be affected by smoking, such as learning and memory. Additionally, we had limited data on MSM after age 60 or even 65, where they may be a more rapid decline in cognition.

Conclusions

To our knowledge, this is the first prospective longitudinal study to assess the association between smoking and cognitive decline in MSM living with HIV. Our findings highlight the need for future studies to examine additional risk factors for cognitive impairments related to aging among MSM. Moreover, since smoking is common among persons with HIV we need to continue to innovate interventions -- designed specifically for MSM living with HIV--to reduce smoking and promote health.

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Table 1

Characteristics of a subset of MACS Cohort Study Participants as a Function of Smoking Status at Age 50 Years

Characteristic	No. (%)		
	Never Smoker n=185	Former Smoker n=272	Current Smoker n=125
Birth cohort			
1914-1949	42 (22.7)	27 (9.9)	20 (16.0)
1950-1959	79 (42.7)	116 (42.6)	49 (39.2)
1960-1969	64 (34.6)	129 (47.4)	56 (44.8)
Race/ethnicity			
Non-Hispanic white	161 (87.0)	244 (89.7)	97 (77.6)
Non-Hispanic black	19 (10.2)	18 (6.6)	26 (20.8)
Other/mixed	5 (2.7)	10 (3.7)	2 (1.6)
Site of enrollment			
Baltimore, MD/Washington DC	60 (32.4)	88 (32.4)	30 (24.0)
Chicago, IL	45 (24.3)	51 (18.8)	29 (23.2)
Los Angeles, CA	40 (21.6)	81 (29.8)	29 (19.3)
Pittsburgh, PA	40 (21.6)	52 (19.1)	37 (29.6)
Education			
High school diploma or less	8 (4.3)	18 (6.6)	22 (17.6)
Some college or college degree	71 (38.9)	107 (39.3)	61 (48.8)
Graduate work or more	106 (57.3)	147 (54.0)	42 (33.6)
Unemployed	3 (3.4)	1 (2.0)	1 (2.1)
Depressive symptoms			
CES-D ≥ 16	19 (10.6)	36 (13.5)	23 (18.9)
Cumulative lifetime pack-years	0 (0.0)	19.2 (20.1)	35.5 (22.7)
Marijuana use	31 (20.1)	99 (38.8)	51 (45.5)
Hypertension	37 (44.7)	71 (47.3)	20 (29.4)
Diabetes	3 (3.5)	4 (2.7)	4 (5.9)
Angina	2 (2.7)	6 (4.6)	1 (1.6)
Heart failure	1 (1.4)	1 (0.8)	-
Stroke	1 (1.4)	-	-
HIV seropositive	65 (35.1)	100 (36.8)	53 (42.4)
CD4+ T-cell count (cells/μL)			
>500	62 (74.7)	36 (78.3)	37 (80.4)
>200-500	18 (21.7)	10 (21.7)	8 (17.4)
≤ 200	3 (3.6)	-	1 (2.2)
ART			
No therapy	8 (29.6)	4 (23.5)	6 (37.5)
Monotherapy	5 (18.5)	1 (5.9)	2 (12.5)

Characteristic	No. (%)		
	Never Smoker n=185	Former Smoker n=272	Current Smoker n=125
Combined therapy	6 (22.2)	8 (47.1)	2 (12.5)
Potent therapy	8 (29.6)	4 (23.5)	6 (37.5)

Abbreviations: ART, antiretroviral therapy; CES-D, Center for Epidemiologic Studies– Depression; HIV, human immunodeficiency virus.

Table 2

Multivariate Association of Smoking History (at Age 50) and Cognitive Change Over 5 Years Among All Participants (N=582)

	β (95% CI)			
	Trail Making Test A[1]	**Trail Making Test B[1]**	**Symbol Digit Modalities**	**Composite Score**
Birth cohort				
1914-1949	-0.0051 (-0.0100 to -0.0003)	-0.8285 (-1.1381 to -0.5188)	-0.0185 (-0.0234 to -0.0136)	-0.1044 (-0.1410 to -0.0312)
1950-1959	-0.0046 (-0.0087 to -0.0004)	-0.3285 (-0.5941 to -0.0629)	-0.0077 (-0.012 to -0.0035)	-0.1134 (-0.2027 to -0.0242)
1960-1969	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Race/ethnicity				
Non-Hispanic white	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Non-Hispanic black	-0.0110 (-0.0236 to 0.0020)	-0.3303 (-1.1514 to 0.4908)	-0.0241 (-0.0371 to -0.0110)	-0.1199 (-0.3958 to 0.1561)
Other/mixed	-0.0160 (-0.0220 to -0.0100)	0.3188 (-0.0763 to 0.7138)	-0.0040 (-0.0103 to 0.0022)	0.0949 (-0.0383 to 0.2281)
Education				
High school diploma or less	-0.0020 (-0.0085 to 0.0050)	-0.4907 (-0.9242 to -0.0572)	-0.0061 (-0.0129 to 0.0007)	-0.1595 (-0.0812 to 0.1086)
Some college or college degree	-0.0003 (-0.0044 to 0.0043)	0.0645 (-0.2851 to 0.3453)	-0.0043 (-0.0089 to 0.0002)	0.0137 (-0.1043 to 0.0607)
Graduate work or more	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Smoking status				
Never smoker	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Former smoker	-0.0027 (-0.0070 to 0.0014)	-0.221 (-0.5202 to 0.0570)	-0.0041 (-0.0089 to 0.0005)	-0.0027 (-0.0070 to 0.0014)
Current smoker	-0.0034 (-0.0079 to 0.0007)	-0.0987 (-0.521 to 0.0135)	-0.0009 (-00048 to 0.0030)	-0.0034 (-0.0079 to 0.0007)

Abbreviation: HIV, human immunodeficiency virus.

[1] Tests were log transformed so results must be interpreted as 10^Est

Table 3

Association of Smoking History (at Age 50) and Cognitive Change Over 5 Years Among HIV-Positive Participants (n=220)

	β (95% CI)			
	Trail Making Test A[1]	**Trail Making Test B[1]**	**Symbol Digit Modalities**	**Composite Score**
Birth cohort				
1914-1949	0.0167 (0.0076 to 0.0258)	0.5237 (-0.0290 to 1.0763)	-0.0104 (-0.0191 to -0.0016)	0.1304 (-0.0586 to 0.3194)
1950-1959	0.0052 (-0.0012 to 0.0116)	0.0720 (-0.3384 to 0.4823)	-0.0044 (-0.0110 to 0.0021)	0.0243 (-0.1135 to 0.1622)
1960-1969	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Race/ethnicity				
Non-Hispanic white	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Non-Hispanic black	-0.0085 (-0.0287 to 0.0117)	0.7714 (-0.5208 to 2.0637)	-0.0359 (-0.0565 to -0.0153)	0.2343 (-0.1977 to 0.6663)
Other/mixed	-0.0176 (-0.0256 to -0.0095)	0.2793 (-0.2366 to 0.7951)	-0.0110 (-0.0192 to -0.0027)	0.0750 (-0.0980 to 0.2581)
Education				
High school diploma or less	-0.0026 (-0.0125 to 0.0073)	-0.1508 (-0.2641 to 0.9575)	-0.0127 (-0.0226 to -0.0027)	-0.0529 (-0.2663 to 0.1606)
Some college or college degree	0.0140 (0.0063 to 0.0217)	0.4655 (-0.1613 to 0.6534)	-0.0050 (-0.0129 to 0.0029)	0.0776 (-0.0599 to 0.2151)
Graduate work or more	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Smoking status				
Never smoker	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Former smoker	0.1862 (-0.0824 to 0.3287)	-0.5458 (-0.8806, 0.0471)	-0.1275 (-0.2485, 0.0074)	-0.1526 (-0.2936 to 0.0117)
Current smoker	-0.0077 (-0.3173, 0.1178)	-0.1186 (-0.5864, 0.3491)	-0.1476 (-0.3449, 0.0078)	-0.0216 (-0.1559 to 0.1126)

Abbreviation: HIV, human immunodeficiency virus.

[1]Tests were log transformed so results must be interpreted as 10^Est

Table 4

Association of Cumulative Pack-Years (at Age 50) and Cognitive Change Over 5 Years Among All Participants (N=582)

	β (95% CI)			
	Trail Making Test A[1]	**Trail Making Test B[1]**	**Symbol Digit Modalities**	**Composite Score**
Birth cohort				
1914-1949	-0.0046 (-0.0094 to 0.0002)	-0.8151 (-1.1223 to -0.5079) **	-0.0179 (-0.0228 to -0.0130)	-0.3008 (-0.4049 to -0.1967) **
1950-1959	-0.0039 (-0.0080 to 0.0003)	-0.3062 (-0.5729 to -0.0394) *	-0.0075 (-0.0117 to -0.0033)	-0.1062 (-0.1959 to-0.0166) *
1960-1969	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Race/ethnicity				
Non-Hispanic white	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Non-Hispanic black	-0.0110 (-0.0240 to 0.0020)	-0.3859 (-1.2231 to 0.4514)	-0.0257 (-0.0390 to -0.0125) *	-0.1387 (-0.4200 to 0.1427)
Other/mixed	-0.0154 (-0.0216 to -0.0092)	0.3400 (-0.0578 to 0.7379)	-0.0043 (-0.0106 to 0.0020)	0.1009 (-0.0333 to 0.2350)
Education				
High school diploma or less	-0.0018 (-0.0084 to 0.0049)	0.0862 (-0.1953 to 0.3677)	-0.0087 (-0.028 to, 0.0106)	0.0211 (-0.0740 to 0.1162)
Some college or college degree	0.0007 (-0.0037 to 0.0050)	-0.0028 (-0.2474 to 0.2418)	-0.0022 (-0.0061 to 0.0018)	-0.0098 (-0.0928 to 0.0732)
Graduate work or more	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Cumulative pack-years (per 5 pack-years)	-0.0006 (-0.0010 to -0.0003) *	-0.0250 (-0.0495 to -0.0006) *	-0.0003 (-0.0006 to 0.0001)	-0.0077 (-0.0153 to -0.0002) *

* $P<.05$

** $P<.0001$

Abbreviation: HIV, human immunodeficiency virus.

[1] Tests were log transformed so results must be interpreted as 10^Est

Table 5

Association of Cumulative Pack-Years (at Age 50) and Cognitive Change Over 5 Years Among HIV-Positive Participants (n=220)

	β (95% CI)			
	Trail Making Test A[1]	Trail Making Test B[1]	Symbol Digit Modalities	Composite Score
Birth cohort				
1914-1949	0.0160 (0.0073 to 0.0246)	0.5237 (-0.0290 to 1.0763)	-0.0104 (-0.0191 to -0.0016)	0.1304 (-0.0586 to 0.3194)
1950-1959	0.0047 (-0.0016 to 0.0111)	0.0720 (-0.3384 to 0.4823)	-0.0044 (-0.0110 to 0.0021)	0.0243 (-0.1135 to 0.1622)
1690-1969	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Race/ethnicity				
Non-Hispanic white	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Non-Hispanic black	-0.0107 (-0.0306 to 0.0093)	0.7714 (-0.5208 to 2.0637)	-0.0359 (-0.0565 to -0.0153)	0.2343 (-0.1977 to 0.6663)
Other/mixed	-0.0173 (-0.0253 to -0.0092)	0.2793 (-0.2366 to 0.7951)	-0.0110 (-0.0192 to -0.0027)	0.0750 (-0.0980 to 0.2581)
Education				
High school diploma or less	-0.0027 (-0.0125 to 0.0071)	-0.1508 (-0.2641 to 0.9575)	-0.0127 (-0.0226 to -0.0027)	-0.0529 (-0.2663 to 0.1606)
Some college or college degree	0.0071 (0.0009 to 0.0133)	0.4655 (-0.1613 to 0.6534)	-0.0050 (-0.0129 to 0.0029)	0.0776 (-0.0599 to 0.2151)
Graduate work or more	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Cumulative pack-years (per 5 pack-years)	-0.0003 (-0.0313 to 0.0091)	-0.0008 (-0.4984 to 0.2967)	-0.0002 (-0.0049 to 0.0078)	-0.0004 (-0.1559 to 0.1126)

*P<.05

**P<.0001

Abbreviation: HIV, human immunodeficiency virus.

[1]Tests were log transformed so results must be interpreted as 10^Est