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Effects of Framingham 10-year cardiovascular risk score and viral load on brain integrity in persons with HIV

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Abstract

Background.—Combination antiretroviral therapy (cART) has allowed for viral load (VL) suppression and increased life expectancy for persons with HIV (PWH). Altered brain integrity, measured by neuropsychological (NP) performance and neuroimaging, is still prevalent among virally suppressed PWH. Age-related conditions such as cardiovascular disease may also affect brain integrity. This study investigated effects of cardiovascular risk, VL, and HIV serostatus on cerebral blood flow (CBF), brain volumetrics, and cognitive function in PWH and persons without HIV (PWoH).

Methods.—Ten-year cardiovascular risk, using the Framingham Heart Study criteria, was calculated in PWH (n=164) on cART with undetectable (≤20 copies/mL; n=134) or detectable (>20 copies/mL; n=30) VL and PWoH (n=66). Effects of cardiovascular risk on brain integrity (CBF, volume, cognition) were compared for PWH (undetectable and detectable VL) and PWoH.

Results.—PWH had smaller brain volumes and worse NP scores than PWoH. PWH with detectable and undetectable VL had similar brain integrity measures. Higher cardiovascular risk was associated with smaller volumes and lower CBF in multiple brain regions for PWH and PWoH. Significant interactions between HIV serostatus and cardiovascular risk on brain volumes were observed in frontal, orbitofrontal, and motor regions. Cardiovascular risk was not associated with cognition for PWH or PWoH.

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Conflicts of Interest

No conflicts of interest were declared.

Conclusions.—Neuroimaging but not cognitive measures were associated with elevated cardiovascular risk. HIV serostatus was associated with diminished brain volumes and worse cognition while CBF remained unchanged, reflecting potential protective effects of cART. Neuroimaging measures of structure (volume) and function (CBF) may identify contributions of comorbidities, but future longitudinal studies are needed.

Keywords

Cardiovascular; viral load; cognition; neuroimaging; cerebral blood flow

Introduction

Approximately thirty-eight million people are infected with HIV worldwide [1]. The introduction of combination antiretroviral therapy (cART) has changed HIV to a more chronic condition. Successful viral load (VL) suppression with cART has led to a longer life expectancy for persons with HIV (PWH) [2]. However, changes in brain integrity as measured by neuropsychological (NP) testing and neuroimaging are still prevalent among PWH who have achieved viral suppression [3,4].

Neuroimaging provides non-invasive measures for evaluating brain structure and function in PWH. Previous studies using structural magnetic resonance imaging (MRI) have shown that volumetric loss occurs in both subcortical and cortical gray matter in PWH [5-7]. Cerebral blood flow (CBF), a measure of brain function that can be quantified with arterial spin labeling (ASL), is also decreased in PWH compared to persons without HIV (PWoH) [8,9]. Observed changes on neuroimaging may persist despite viral suppression [10], with multiple etiologies contributing to these phenotypes, including legacy effects due to neurological damage from initial infection.

Age-related health conditions such as cardiovascular disease (CVD) may affect brain integrity in PWH [11,12]. Cardiovascular conditions such as hypertension, diabetes mellitus, and hypercholesterolemia are modifiable risk factors in PWH [13], and reduction of cardiovascular risk may mitigate the ongoing effects of HIV on brain integrity. Cardiovascular risk can be assessed using the Framingham ten-year risk score [14], which predicts future cognitive function in older virally suppressed PWH [15]. Within PWH, an increase in cardiovascular risk has been associated with worse cognitive performance [16] and decreased CBF [9] but not changes in brain volumetrics [17]. However, many of these studies have focused on single metrics rather than multiple measures of brain integrity including neuroimaging and cognitive impairment. Furthermore, many studies have combined PWH who have detectable and undetectable VL. Because VL is a prognostic risk factor for cognitive impairment in PWH, the presence of detectable viremia should be considered when evaluating the effects of cardiovascular risk on brain integrity measures in PWH.

This study investigates the effects of cardiovascular health, as assessed by Framingham ten-year risk [14], on brain structure and function in PWH and PWoH using neuroimaging and NP testing. We hypothesized that brain integrity would be reduced with higher cardiovascular risk, regardless of HIV status. We also hypothesized that the effects of

cardiovascular risk factors on brain integrity measures would be augmented in PWH who have a detectable VL (>20 copies/mL) compared to undetectable VL (≤20 copies/mL). Finally, we hypothesized that HIV infection would be associated with reduced brain integrity including imaging biomarkers and NP performance.

Methods

Participants

PWH were recruited from the Washington University School of Medicine (WUSM) Infectious Disease Clinic and Washington University School of Medicine AIDS Clinical Trial Unit. PWoH were recruited from the Research Participant Registry at WUSM as well as leaflets distributed throughout the St. Louis community.

Inclusion criteria were as follows: ability to provide informed written consent, ability to read and write in English, at least 8 years of education, and available clinical data regarding cardiovascular risk factors including: hypertension treatment history, current smoking status, diabetes mellitus history, systolic blood pressure, and total and high-density lipoprotein (HDL) cholesterol or body mass index (BMI) at the time of study. Exclusion criteria included loss of consciousness >30 minutes, seizures, previous strokes, a Beck Depression Inventory (BDI-II) score>29, major psychiatric disorders, and alcohol or substance abuse disorder according to Diagnostic and Statistical Manual of Mental Disorders (DSM) 5.

Clinical Characteristics of Participants

All PWH had a documented history of HIV and were on stable cART for at least 6 months. For all PWH, VL was obtained from either blood samples collected on the date of study participation or from medical evaluations that occurred within one month of assessment. Nadir CD4 and CD8 T-cell counts were obtained from medical records or self-report. Recent CD4 and CD8 T-cell counts were obtained from medical records within three months of assessment when available. Participants were divided into three groups: PWoH, PWH with undetectable VL (≤20 copies/mL), and PWH with detectable VL (>20 copies/mL).

Framingham Heart Study 10-year cardiovascular risk was calculated using sex-specific Cox proportional-hazards regressions, developed by the Framingham Heart Study [14]. Sex-specific risk scores, which represent the risk of developing CVD over the subsequent ten years, were based on the following covariates: age, hypertension treatment history, current smoking status, history of diabetes mellitus, systolic blood pressure, and total and HDL cholesterol. If total and HDL cholesterol values were unavailable, then body mass index (BMI) was substituted in the model [18]. Data were obtained from available medical records within three months of assessment.

MRI Acquisition and Processing

Neuroimaging was performed on a 3T Siemens Tim Trio MR scanner (Siemens AG, Erlangen Germany) with a 12-channel head coil. A high-resolution 3-dimensional magnetization-prepared rapid gradient echo scan (MPRAGE) T_1-weighted scan was acquired (repetition time [TR] = 2400ms, echo time (TE) = 3.16 ms, flip angle = 8°,

inversion time = 1000 ms, voxel size = 1×1×1 mm3 voxels, 256×256×256 acquisition matrix, 162 slices).

FreeSurfer software, version 5.3 (Martinos Center, Boston, USA) [19,20] was used to segment cortical and subcortical volumes. Segmentations were inspected and corrected, if necessary, by a trained research technician. Each regional volume was adjusted for total intracranial volume with linear regression to account for differences in head sizes. Volumes were then normalized for age and sex within each group using linear regression.

Pseudo-continuous ASL (pCASL), a noninvasive technique that uses arterial blood water as a contrast medium, was used to measure CBF (TR = 3500 seconds, TE = 9.0 ms, flip angle = 90°, labeling time = 1.5 seconds, post-labeling delay = 1.2 seconds, 90 degrees flip angle, voxel size = 3.4 x 3.4 x 5.0 voxels, 64 x 64 acquisition matrix, 22 axial slices with a 1-mm gap) [21]. Preprocessing involved registering each volume to a mean volume and calculating framewise displacement. Framewise displacement was computed from movement parameters extracted from the realignment, and pairs with more than 0.5mm displacement between the control and label volumes were censored. pCASL images were registered to each participant's T_1-weighted images, which were linearly then nonlinearly registered to an MNI atlas brain. The affine transform and nonlinear warp were then combined into a single warp to align pCASL images to MNI space [22].

CBF was quantified using a single-compartment model [23]. CBF measurements were corrected for age and sex with a linear regression. Volume and CBF measurements were obtained from nine regions of interest (ROIs) previously shown to be affected by HIV: frontal lobe, orbitofrontal cortex, motor cortex, parietal lobe, temporal lobe, occipital lobe, thalamus, basal ganglia, and the combination of the insula and amygdala [24]. For each region, volume and CBF measures were averaged between hemispheres.

NP Evaluations

Participants completed a NP battery designed to assess cognitive domains frequently affected by HIV [25]. Fifteen NP tests were completed representing five domains: learning, recall, executive function, motor/psychomotor speed, and language. Raw scores were converted into demographically adjusted (age, sex, race, education) z-scores using published normative standards, and averaged into domain specific z-scores [25,26]. Domains were then averaged to create a global z-score. Only participants who completed at least ten of fifteen NP tests were included.

Statistical Analyses

Demographic variables including age, sex, education, nadir CD4, recent viral load, BDI-II scores, and Framingham ten-year cardiovascular risk were compared among the three groups (PWoH, PWH with undetectable VL, and PWH with detectable VL) using an ANOVA for continuous variables and chi-square tests for categorical variables.

Linear regression with restricted maximum likelihood estimation was used to evaluate group differences in CBF, volumetrics, and NP among groups. Log transformations of CBF and ROI volumes and square-root transformation of cardiovascular risk were conducted

prior to regression to reduce skew and improve the linearity of model assumptions. Brain integrity measures for each group were evaluated as function of cardiovascular risk to test for additive and interactive effects. BDI-II scores, a significant covariate, were added to each model involving neuroimaging and NP variables. The model was specified as follows: $(ROI\ or\ Domain) \sim \beta_1(CV\ Risk\ *\ Group) + \beta_2(BDI)$, where CV Risk * Group represents an interaction. False discovery rate (FDR) correction was applied to adjust for multiple comparisons for all models. All statistical analyses were performed using R, version 1.2.1335.

Results

Demographics

Demographic and clinical information for the three groups (PWoH, PWH with undetectable VL, and PWH with detectable VL) are summarized in Table 1. The groups did not differ with regards to age, race, or education. However, PWoH had a higher percentage of female participants compared to PWH subgroups ($p<.001$). Since all neuroimaging and NP variables were previously corrected for age and sex, these variables were not included as covariates in subsequent analyses.

BDI-II scores were more likely to be elevated among PWH compared to PWoH ($p=0.02$) and this variable was added as a covariate in linear regression. There were no significant differences in BDI-II between PWH subgroups. PWoH had lower Framingham risk scores compared to PWH ($p=0.02$). Cardiovascular risk did not differ significantly between the two PWH subgroups. PWH subgroups did not differ with regards to nadir CD4 T-cell counts, recent CD4 T-cell counts, or CD4/CD8 ratios ($p=0.220$, $p=0.339$, $p=0.227$ respectively).

Cardiovascular risk was associated with smaller brain volumes and lower CBF

Linear regression of volumes for each ROI showed that a higher cardiovascular risk score was associated with smaller volumes for PWoH and PWH (both undetectable and detectable VL) in all ROIs except the orbitofrontal and occipital regions (see Table 2). Frontal lobe, motor cortex, parietal lobe, and insula/amygdala volumes were reduced with cardiovascular risk ($p<0.05$) with the greatest reductions occurring in the temporal lobe, basal ganglia, and thalamus ($p<0.01$) (Figure 2). Higher cardiovascular risk was also associated with lower CBF, globally ($p<0.05$) and within all ROIs except the motor cortex, occipital lobe, and thalamus. In particular, reductions were greatest in the frontal lobe, orbitofrontal cortex, parietal lobe, temporal lobe, and basal ganglia, and insula/amygdala ($p<0.05$) (Figure 1). Higher cardiovascular risk was not associated with significant differences in global cognition or domain-specific NP function for PWoH, PWH with undetectable VL, or PWH with detectable VL (Figure 3).

HIV serostatus was associated with smaller regional volumes and worse NP

Regional volumes, CBF, and cognition were compared as a function of HIV serostatus. In general, PWH had reduced volumes compared to PWoH, with the greatest reductions seen in cortical (frontal ($p<0.01$), orbitofrontal ($p<0.01$), motor ($p<0.05$) and temporal ($p<0.05$)) and subcortical (thalamus ($p<0.01$) and insula/amygdala ($p<0.05$)) regions (Table 2). In contrast,

no significant differences in CBF were observed between PWH and PWoH. Finally, PWH had reduced global ($p<0.01$) and executive function ($p<0.05$) compared to PWoH. When PWH were subdivided into undetectable and detectable VL, no significant differences were found for brain volumetrics, CBF, or NP.

Cardiovascular risk and HIV serostatus interact to affect volumetrics

Significant positive interactions between HIV status and cardiovascular risk were observed in the frontal lobe ($p<0.01$), orbitofrontal cortex ($p<0.01$), and motor regions ($p<0.01$). No significant interactions were observed between HIV status and cardiovascular risk for either CBF or NP performance.

Discussion

The effects of cardiovascular risk, VL, and HIV serostatus on brain integrity were evaluated in PWH and PWoH. We observed a significant effect of cardiovascular risk on structural and functional neuroimaging measures. Higher cardiovascular risk was associated with decreased regional brain volume and lower CBF in PWH and PWoH. In contrast, no effect of cardiovascular risk was observed on cognition. HIV+ serostatus was associated with smaller regional brain volumes and impaired NP performance, but not alterations in CBF. No significant differences in brain structure, function, or cognition were observed for PWH who had undetectable compared to detectable VL. Finally, an interaction between cardiovascular risk and serostatus was seen for specific cortical volumetric measures.

These results complement previous studies associating Framingham scores with changes in neuroimaging in PWH [27,28]. For example, one study linked higher Framingham risk scores with smaller brain volumes in PWoH across the age spectrum [27]. Likewise, a study of thirty-eight male PWH and thirty-seven PWoH showed that elevated Framingham risk scores were associated with larger volume of white matter hyperintensities, a biomarker of cerebral small vessel disease [28]. Conversely, one study observed that CVD variables were not associated with gray matter or white matter brain volumes [17]. These apparent inconsistencies may reflect the focus of previous investigations on individual CVD variables rather than a comprehensive cardiovascular risk as measured by Framingham scores, or differences in the populations included in studies of CVD risk and neuroimaging. For example, Becker et al., (2012) exclusively examined male participants, with a majority identifying as Caucasian. Conversely, the present study included primarily African American participants, as well as a mix of male and female participants.

The lack of an inverse relationship between cardiovascular risk and cognition is consistent with previous studies that have shown that effects of cardiovascular risk on brain structure and function may precede cognitive decline. In particular, cardiovascular risk scores were predictive of subsequent declines in working memory, episodic memory, and stimulus perception [29]. These results may describe a paradigm in which cardiovascular risk is predictive of future NP outcomes, but descriptive of brain structure and function. However, longitudinal studies are needed to further test this hypothesis in PWH.

HIV serostatus was associated with diminished regional brain volumes and reduced NP performance. These results complement previous studies of reduced NP function [4] and reduced cortical and subcortical volumes in PWH [6,30]. Examination of subcortical topography in PWH has identified accentuation of age-related volume loss in frontal, orbitofrontal and temporal regions, as well as the pallidum, putamen, and hippocampus [6,31]. Likewise, a study of subcortical three-dimensional morphometry found significant effects of HIV on the shapes of the pallidum, hippocampus, caudate, and nucleus accumbens [32], while a study of voxel-based morphometry found significant HIV-related loss in the posterior and inferior temporal lobes and parietal lobes [17].

Our findings suggest that HIV infection poses a potential risk to brain volume loss and corresponding cognitive functions, even in PWH on stable cART. Importantly, some effects of HIV on brain structure and cognition may occur soon after seroconversion. Volume reductions might represent a legacy effect of irreversible neurodegeneration induced by initial viral proliferation and inflammation. It is therefore not surprising that such losses persist later in life, even after viral suppression is attained. Consistent with this idea, CD4 nadirs have been found to correlate with current NP function, raising the possibility that structural damage depends at least partly on early disease course [33].

We found no significant CBF differences between PWH and PWoH controls. Previous literature has varied with regards to the effects of HIV on CBF. Some studies have observed CBF reductions in PWH compared to PWoH [9], while others identified no differences [34] or even higher CBF in PWH [35]. The absence of reduced CBF in this study may be due to a large proportion of PWH who had undetectable VL, as VL has been previously shown to inversely correlate with CBF [36]. Alternatively, CBF reduction in PWH may be age-dependent, as a recent study observed that CBF was markedly reduced in older PWH with detectable VL, but not in younger PWH, suggesting an accelerated aging process [37].

In contrast with volumetrics and NP, CBF may represent current brain function, as hemodynamics are more responsive than volumetrics to biological effects varying over shorter timescales (such as VL). We did not observe CBF differences between PWH and PWoH, possibly indicating that suppression of VL is sufficient to restore baseline CBF and reverse the acute perfusion reductions associated with detectable VL, especially in older PWH [37]. CBF also did not differ between PWH with detectable and undetectable VL, which may be due to the abundance of younger and middle-aged participants in the detectable VL group.

No significant differences in brain integrity (volumetrics, CBF, or NP) were seen between PWH with detectable and undetectable VL. Previous literature suggests that undetectable VL may mitigate the effects of reduced brain integrity in PWH [10] while detectable VL is associated with reduced CBF [36,37]. For the current study PWH who were categorized as having detectable VL had a relatively low VL, with 70% reporting values between 20-200 copies/mL, well below “viral failure,” defined as >1000 copies/mL by the World Health Organization [38]. Additionally, the detectable VL group was smaller than either the group of PWH who had undetectable VL or PWoH. A larger sample of PWH with VL> 200 copies/ mL may be required to have sufficient power to compare between HIV subgroups.

A significant interaction between HIV status and cardiovascular risk was seen for select brain regional volumes (frontal, orbitofrontal and motor cortex). Previous studies have observed reductions in orbitofrontal and motor volumetrics in PWH compared to PWoH [39]. This may indicate that PWH have greater susceptibility to cerebrovascular effects on specific brain structures compared to PWoH. This is possibly due to the additional morbidity associated with chronic inflammation, or the direct effects of viral proliferation [40,41]. It also remains unclear whether this interaction is due to current HIV pathology, or legacy effects of residual damage from initial stages of infection.

The current study has several limitations. First, while the groups were statistically similar in age and HIV clinical variables, sex differences were observed among the groups, but were accounted for when data were normalized prior to analysis. Second, not all cardiovascular measures were uniformly available. For example, HDL and total cholesterol were not obtained in all participants, requiring a mixed model of BMI and cholesterol to be substituted instead. However, equations that use either of these variables are highly correlated (r=.95, p<.001) in both our sample and in a sample of PWH in Africa [18], and the difference in Framingham equations is unlikely to significantly impact results. Third, Framingham risk scores, rather than Data Collection on Adverse Effects of Anti-HIV Drugs (DAD) scores, a similar measure of cardiovascular risk that accounts for cART exposure in PWH, were used for examination. This was due to the unavailability of several variables required for DAD scores such as duration of exposure to protease inhibitors and nucleoside reverse-transcriptase inhibitors. Additionally, Framingham risk scores may be less reliable for individuals over the age of 65, an age range that describes 10% of our current sample. However, there was no significant difference in the proportion of individuals over age 65 between the three groups. Furthermore, we were unable to fully consider other factors that may affect cognition and brain integrity, including other cardiovascular factors such as coronary heart disease, arrhythmias, C-reactive protein and hemoglobin A1c levels, and exercise or activity levels. Finally, this analysis was cross-sectional and not longitudinal. Therefore, it is unknown whether some individuals in the detectable VL group experienced a “viral blip” rather than sustained elevations of VL. Future studies should consider longitudinal data in order to ensure sustained detectable VL. Additionally, larger group sizes would be beneficial in order to more fully understand these relationships.

Age-related comorbidities such as higher cardiovascular risk remain an ongoing challenge for PWH. The findings presented here suggest that age-related modifiable risk factors such as cardiovascular health affect brain structure and function in both PWH and PWoH; therefore, reduction of cardiovascular risk may mitigate the neurological effects of aging with HIV. Longitudinal analyses with larger detectable VL groups are needed to investigate the long-term effects of cardiovascular risk reduction on brain integrity and cognitive preservation or decline.

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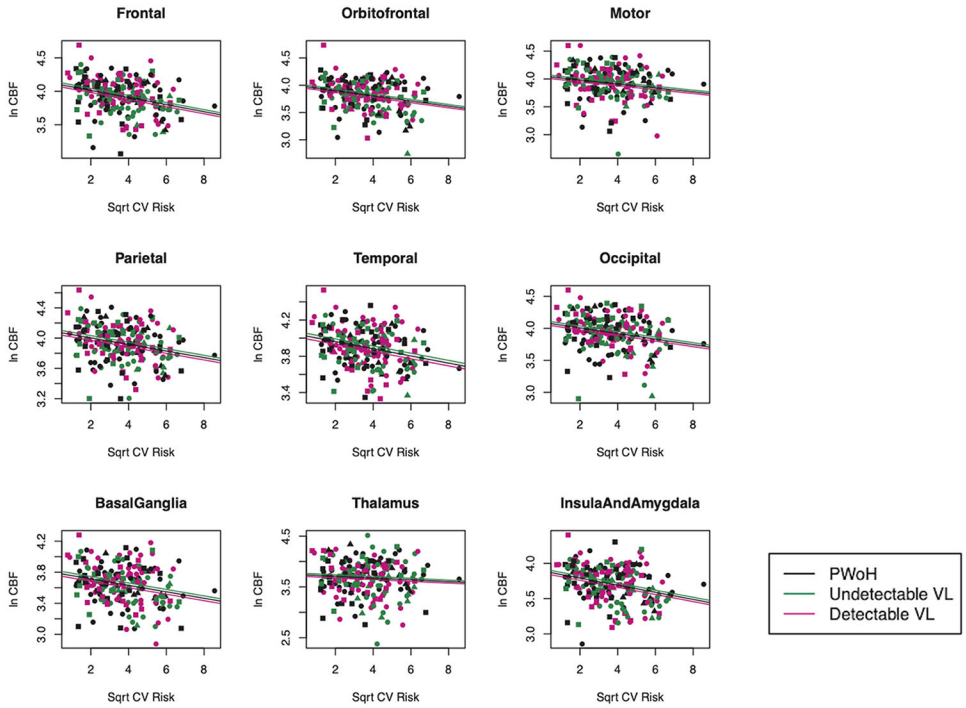

Fig 1. Cardiovascular (CV) risk was associated with lower cerebral blood flow (CBF).
Higher CV risk was associated with lower CBF in persons without HIV (PWoH) (black), persons with HIV (PWH) with an undetectable viral load (VL) (green), and PWH with a detectable VL (purple), within all ROIs except the motor cortex, occipital lobe, and thalamus. Reductions were greatest in the frontal lobe, orbitofrontal cortex, parietal lobe, temporal lobe, and basal ganglia, and insula/amygdala ($p<0.05$).

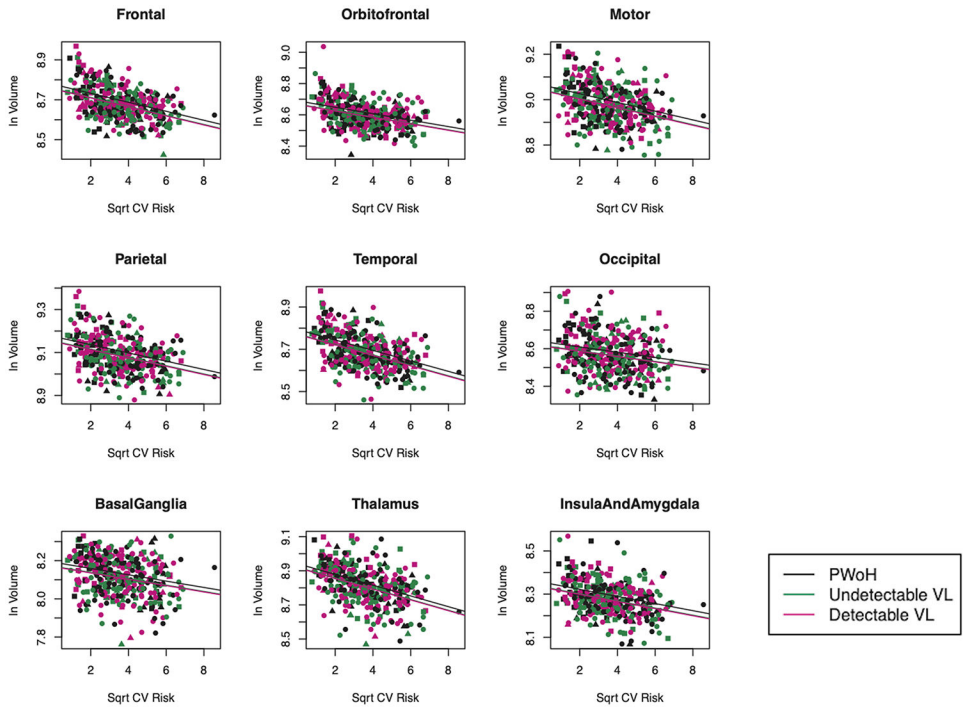

Fig 2. CV risk was associated with smaller brain volumes.

A higher CV risk score was associated with smaller volumes for PWoH (black), PWH with an undetectable VL (green), and PWH with a detectable VL (purple), in all ROIs except the orbitofrontal and occipital regions. Frontal lobe, motor cortex, parietal lobe, and insula/amygdala volumes were reduced with CV risk ($p<0.05$) with the greatest reductions in the temporal lobe, basal ganglia, and thalamus ($p<0.01$).

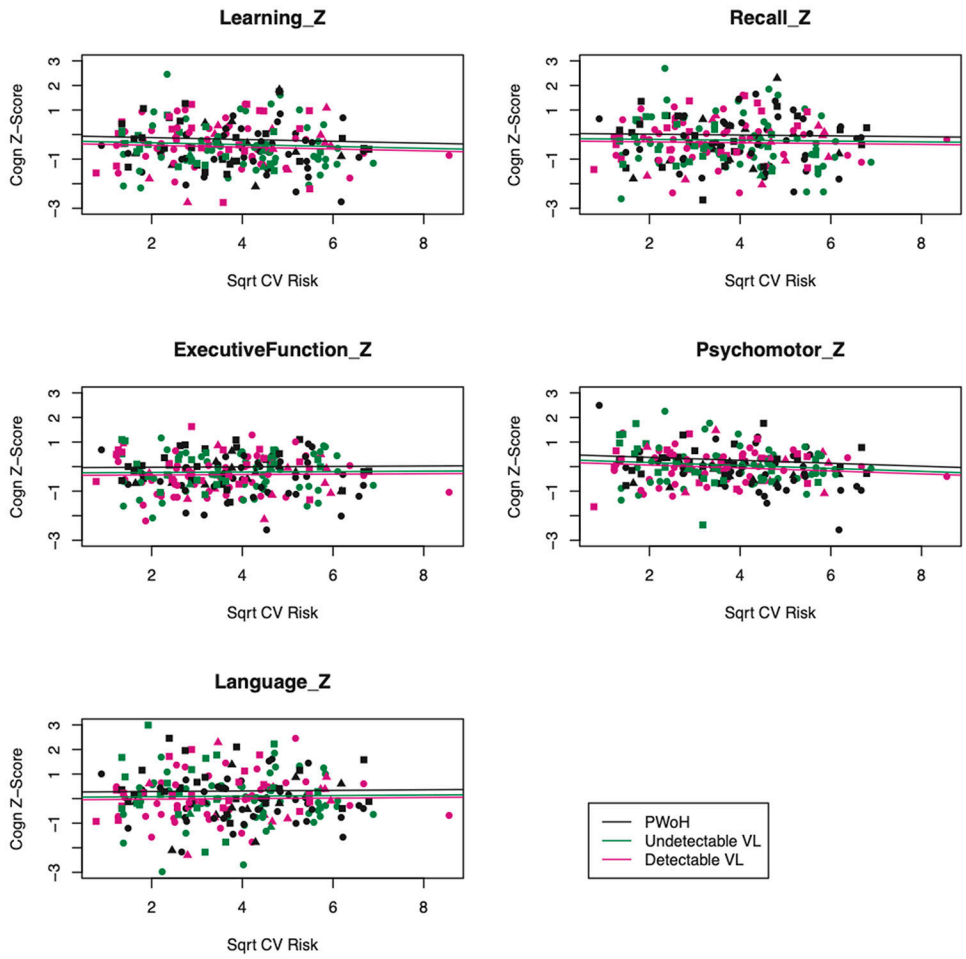

Fig 3. CV risk was not associated with impaired cognitive function.

Group differences in neuropsychological performance z-scores between PWoH (black), PWH with an undetectable VL (green), and PWH with a detectable VL (purple), plotted as a function of CV risk for each of the cognitive domains. Higher CV risk was not associated with significant differences in domain-specific neuropsychological performance function for any group.

Table 1.

Demographic and clinical characteristics

	PWoH (n=66)	PWH with Undetectable VL (n=134)	PWH with Detectable VL (n=30)	P-value
Age (years old); mean (SD)	51.3 (14.2)	53.5 (9.7)	55.1 (8.6)	0.239
Sex (% Female)	48	22	20	<.001*
Race (% AA)	56	62	70	0.199
Education (years); mean (SD)	13.7 (2.4)	13.4 (2.8)	13.1 (2.5)	0.311
Framingham 10 Year Cardiovascular Risk; mean (SD)	12.6 (10.8)	16.9 (12.1)	18.7 (10.3)	0.018*
Systolic Blood Pressure; mean (SD)	120.5 (15.9)	123.3 (13.1)	123.8 (15.2)	0.12
Total Cholesterol; mean (SD)	-	183.63 (30.91)	193.29 (43.62)	0.344
HDL Cholesterol; mean (SD)	-	54.53 (21.86)	53.60 (18.25)	0.881
BMI; mean (SD)	26.95 (5.40)	27.32 (5.93)	27.09 (5.27)	0.912
Diabetes Mellitus (% Yes)	6.1	13.1	16.7	0.239
Hypertension History (% Yes)	21.2	51.4	50.0	<0.001
Current Smoker (% Yes)	30.3	46.7	62.5	0.013
BDI-II; mean (SD)	5.6 (7.2)	9.1 (7.7)	9.1 (6.15)	0.016*
Duration of HIV infection (months); (IQR)	-	204 (122, 297)	178 (112, 248)	0.230
Recent Log Plasma Viral Load (IQR)	-	1.30 (1.3, 1.3)	1.9 (1.6, 2.8)	<.001*
Nadir CD4 T-cell count; IQR	-	23, 286	33.3, 192.2	0.220
Recent CD4 T-cell count; IQR	-	424, 688	299.8, 686.3	0.339
CD4/CD8 Ratio; IQR	-	0.439, 0.941	0.298, 0.583	0.227

VL= viral load; AA=African American, BDI= Beck Depression Index, PWH=persons with HIV, PWoH=persons without HIV, BMI= body mass index, HDL= high density lipoprotein, IQR= interquartile ratio.

Table 2.

Regression coefficients and confidence intervals

		HIV Status (ref=HIV-), coefficient (CI)	Viral Load (ref=Undetectable) coefficient (CI)	Cardiovascular Risk (%) coefficient (CI)
CBF	Global	−0.035 (−0.208, 0.138)	0.179 (−0.120, 0.478)	−0.036 ** (−0.061, −0.011)
	ROI			
	Frontal	−0.010 (−0.206, 0.185)	0.247 (−0.092, 0.585)	−0.041 ** (−0.069, −0.013)
	Orbitofrontal	−0.067 (−0.275, 0.141)	0.319 (−0.042, 0.680)	−0.036 (−0.066, −0.006)
	Motor	−0.084 (−0.143, 0.312)	0.176 (−0.218, 0.571)	−0.022 (−0.055, 0.010)
	Parietal	−0.024 (−0.214, 0.167)	0.216 (−0.114, 0.547)	−0.036 ** (−0.063, −0.009)
	Temporal	0.064 (−0.230, 0.101)	0.105 (−0.181, 0.392)	−0.036 ** (−0.060, −0.012)
	Occipital	−0.096 (−0.299, 0.108)	0.364 (−0.012, 0.717)	−0.037 (−0.066, −0.007
	Basal Ganglia	−0.079 (−0.271, 0.113)	0.014 (−0.318, 0.347)	−0.042 ** (−0.070, −0.015)
	Thalamus	−0.044 (−0.337, 0.248)	0.235 (−0.272, 0.741)	−0.008 (−0.050, 0.034)
	Insula and Amygdala	−0.026 (−0.218, 0.166)	0.080 (−0.252, 0.413)	−0.046 ** (−0.073, −0.018)
Volume	**ROI**			
	Frontal	0.097 *** (0.042, 0.152)	0.045 (−0.035, 0.125)	−0.012 ** (−0.022, −0.003)
	Orbitofrontal	0.102 *** (0.044, 0.160)	0.060 (−0.024, 0.145)	−0.008 (−0.017, −0.001)
	Motor	0.083 ** (0.021, 0.145)	0.005 (−0.085, 0.095)	−0.011 ** (−0.020, −0.001)
	Parietal	0.059 (0.002, 0.116)	0.035 (−0.047, 0.117)	−0.012 ** (−0.021, −0.003)
	Temporal	0.065 ** (0.009, 0.121)	0.022 (−0.060, 0.103)	−0.021 *** (−0.029, −0.012)
	Occipital	0.077 (0.002, 0.152)	0.065 (−0.044, 0.173)	−0.008 (−0.020, 0.003)
	Basal Ganglia	0.055 (−0.020, 0.129)	−0.066 (−0.174, 0.042)	−0.018 *** (−0.030, −0.007)
	Thalamus	0.092 *** (0.016, 0.167)	0.033 (−0.077, 0.143)	−0.024 *** (−0.036, −0.012)
	Insula and Amygdala	0.063 ** (0.005, 0.121)	0.015 (−0.070, 0.099)	−0.010 ** (−0.019, −0.001)
Cognition	Global z-score	0.317, (−0.155, 0.789)	−0.389 (−1.286, 0.508)	−0.007 (−0.082, 0.068)
	Domain			
	Learning	−0.007 (−0.768, 0.116755	−1.684 (−3.130, −0.238)	−0.0001 (−0.121, 0.121)
	Recall	−0.418 (−1.184, 0.348)	−1.095 (−2.550, 0.360)	−0.063 (−0.184, 0.059)
	Executive Function	0.911 ** (0.333, 1.490)	0.314 (−0.785, 1.413)	0.078 (−0.014, 0.170)
	Psychomotor	0.131 (−0.435, 0.697)	−0.185 (−1.261, 0.890)	−0.078 (−0.168, 0.011)
	Language	0.430 (−0.371, 1.230)	−1.031 (−2.551, 0.490)	0.065 (−0.062, 0.192)

** p<0.05

*** p<0.01.