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Depression, lifestyle factors and cognitive function in people living with HIV and comparable HIV-negative controls

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Objectives

We investigated whether differences in cognitive performance between people living with HIV (PLWH) and comparable HIV-negative people were mediated or moderated by depressive symptoms and lifestyle factors.

Methods

A cross-sectional study of 637 'older' PLWH aged ≥ 50 years, 340 'younger' PLWH aged < 50 years and 276 demographically matched HIV-negative controls aged ≥ 50 years enrolled in the Pharmacokinetic and Clinical Observations in People over Fifty (POPPY) study was performed. Cognitive function was assessed using a computerized battery (CogState). Scores were standardized into *Z*-scores [mean = 0; standard deviation (SD) = 1] and averaged to obtain a global *Z*-score. Depressive symptoms were evaluated via the Patient Health Questionnaire (PHQ-9). Differences between the three groups and the effects of depression, sociodemographic factors and lifestyle factors on cognitive performance were evaluated using median regression. All analyses accounted for age, gender, ethnicity and level of education.

Results

After adjustment for sociodemographic factors, older and younger PLWH had poorer overall cognitive scores than older HIV-negative controls ($P < 0.001$ and $P = 0.006$, respectively). Moderate or severe depressive symptoms were more prevalent in both older (27%; $P < 0.001$) and younger (21%; $P < 0.001$) PLWH compared with controls (8%). Depressive symptoms ($P < 0.001$) and use of hashish ($P = 0.01$) were associated with lower cognitive function; alcohol consumption ($P = 0.02$) was associated with better cognitive scores. After further adjustment for these factors, the difference between older PLWH and HIV-negative controls was no longer significant ($P = 0.08$), while that between younger PLWH and older HIV-negative controls remained significant ($P = 0.01$).

Conclusions

Poorer cognitive performances in PLWH compared with HIV-negative individuals were, in part, mediated by the greater prevalence of depressive symptoms and recreational drug use reported by PLWH.

Keywords: cognitive disorder, cognitive function, depression, HIV, HIV-associated neurocognitive disorders, people living with HIV

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Introduction

Despite the widespread use of antiretroviral therapy (ART), high rates of cognitive impairment, especially in its milder forms, are reported among people living with HIV (PLWH). While the burden of cognitive impairment varies depending on the population studied, the method used to define cognitive impairment, the uptake of ART in the population and resulting rates of viral suppression, the reported prevalence of cognitive impairment ranges between 17 and 74% [1–3]. We previously reported that middle-aged PLWH showed poorer overall cognitive performance and were more likely to experience cognitive impairment even when compared with appropriately selected HIV-negative controls with similar sociodemographics and lifestyles [4].

The increased burden of cognitive problems in PLWH compared with HIV-negative individuals may be partially explained by social factors, mood disorders and lifestyles, including substance use. Depression, for example, is the most common psychiatric condition among PLWH [5], with a prevalence that can be up to three times higher than that reported in the general population [6,7]. In one meta-analysis based on general population studies, depression was reported to be associated with reduced cognitive functioning in several domains including psychomotor speed, attention, visual learning and memory and verbal fluency [8]. Among PLWH, contrasting results have been reported regarding the association of depressive problems with cognitive function; while a few studies have reported depressive problems to be associated with poorer cognitive performance [9] as well as earlier cognitive decline [10], other studies have not [11,12].

Lifestyle factors such as alcohol and illicit drug use are also more prevalent in PLWH than in the general population [13–15] and can result in brain injury, neurodegeneration and disrupt body processes, especially when used regularly over a long period of time. These negative effects may ultimately lead to cognitive disorders [16]. However, depression and lifestyle factors are rarely considered when comparing the cognitive performance of PLWH to that of HIV-negative individuals. Whether the higher rates of depression and substance use seen in PLWH are responsible, at least in part, for the increased burden of cognitive disorders remains unclear.

The aims of this study were to compare cognitive performances between PLWH and comparable HIV-negative controls and to investigate whether differences between PLWH and HIV-negative controls were either mediated through or moderated by depressive symptoms and lifestyle factors.

Methods

Study design and participants

Cohorts of 'older' PLWH aged ≥ 50 years, 'younger' PLWH aged < 50 years and demographically matched 'older' HIV-negative controls aged ≥ 50 years were prospectively enrolled in the Pharmacokinetic and Clinical Observations in People Over Fifty (POPPY) study between April 2013 and January 2016 as detailed elsewhere [17]. Inclusion criteria for PLWH were documented presence of HIV infection, self-defined white or black African ethnicity, likely route of HIV acquisition via sexual exposure (either by male-to-male exposure if white or by heterosexual exposure if white or black African) and the ability to comprehend the study patient information leaflet. These inclusion criteria ensured that study participants were representative of the vast majority of PLWH in the UK and Ireland [18] as has previously been shown [17]. Older HIV-negative controls were frequency matched to the older HIV-positive group on gender, ethnicity, sexual orientation and location (in or out of London) and were recruited from sexual health clinics affiliated with the HIV clinics, as well as through advertising at community events, in churches and in targeted publications and from community groups. The study was approved by the UK National Research Ethics Service (NRES; Fulham, London; UK number 12/LO/1409). All participants provided written informed consent. Analyses presented here are based on the 637 older PLWH, 340 younger PLWH < 50 years old and 276 older HIV-negative participants who completed the assessment of cognitive function as detailed below.

Assessment of cognitive function

Assessment of cognitive function was performed using the CogState battery [19], a computerized battery of neuropsychological tests that has been used in different clinical settings [20–22], including cohorts of PLWH [23,24]. The battery covered six cognitive domains commonly reported to be affected by HIV-associated cognitive impairment, including visual learning, psychomotor function, visual attention, executive function, verbal learning and working memory [25] (see Table S1 for details of individual tests and how they map onto cognitive domains). Raw test scores were log-transformed or arcsine root-transformed as appropriate (and as recommended by the CogState guidelines for analysis; Table S1) and integrity and quality checks were applied to ensure that scores were generated from completed and fully understood tasks for each subject. Individual test scores not meeting integrity and quality checks were

excluded from the analysis. Individual test scores were converted into *Z*-scores (with a mean of 0 and a standard deviation of 1) using the means and standard deviations (SDs) obtained in the whole cohort. A single *Z*-score was calculated for each of the six cognitive domains by averaging individual test *Z*-scores within each domain. A global *Z*-score of overall cognitive function was also obtained by averaging *Z*-scores across the six domains. For all *Z*-scores, a higher value indicates better cognitive function. Analyses accounted for the role of obvious determinants of cognitive performance such as age, gender, ethnicity and level of education as described in the statistical analysis section.

Lifestyle and depressive symptoms

At enrolment, information was collected on demographics, socioeconomic status, anthropometrics and lifestyle factors. In particular, information on past and current alcohol consumption (including age at which participants started and stopped consuming alcohol in those who were abstinent now), smoking habits, use of injected drugs, and current use of any recreational drugs was collected via a structured interview with trained staff. Participants were also asked to specify what recreational drug(s) they had used over the 6-month period preceding the study visit, selecting from a predefined list of drugs. Marijuana and hashish were kept separate; while they originate from the same plant and contain the same active substance, they are derived from different parts of the plant and with different procedures [26]. As, in general, hashish is stronger than marijuana and their use may reflect different lifestyles related to cognitive function, they were analysed separately.

Severity of depressive symptoms was evaluated using the Patient Health Questionnaire-9 (PHQ-9) [27]. Scores range from 0 (no depression) to 27 (severe depression); participants were categorized as having no (≤ 4), mild (5–9), moderate (10–14) and severe (≥ 15) depressive symptoms using standard cut-offs [27] with the two categories 'moderately severe' and 'severe' grouped into a single category (i.e. 'severe') because of the small number of participants falling in each of these two categories.

Statistical analysis

Pairwise group comparisons of sociodemographic characteristics, lifestyle and severity of depressive symptoms were carried out using χ^2 and Wilcoxon rank-sum tests as appropriate. *Z*-scores were reported as median and interquartile range (IQR) and pairwise differences between groups were assessed using the Wilcoxon rank-sum test. Associations with the global *Z*-score of cognitive function were evaluated using multivariable median regression models to minimize the influence of large outliers. In all regression models, the covariates age, gender, ethnicity and level of education were included as adjusting factors to mimic the use of normative scores. Appropriate normative scores were not available for these analyses given the lack of adequate normative CogState data for older individuals and the lack of a control group for the younger PLWH. All regression models included core covariates such as age, gender, ethnicity and level of education. Associations with the global *Z*-score were then initially assessed using a series of models that included these core covariates as well as each factor (i.e. depressive symptoms and sociodemographic and lifestyle factors) one at a time (step 1). Subsequently, all factors demonstrating a significant association (at the 5% significance level) were simultaneously included in a single model, together with the core covariates (step 2). Only those factors that remained significantly associated with the outcome in this model were retained in the next model which also included the core covariates (step 3). Finally, HIV status/group was added to this model to evaluate whether differences between groups appeared to be mediated by these factors (step 4). We also evaluated interactions between HIV status/group and factors in this final model, to test whether the associations between these factors and the global *Z*-score differed across the three study groups (i.e. whether the associations between lifestyle factors and cognitive function were modified by HIV status/group). In order to assess the clinical relevance of differences in overall cognitive scores, we classified as cognitively impaired participants with a global *Z*-score < -0.5, after adjustment for core covariates.

Results

Participant characteristics

Demographic, lifestyle and HIV-related characteristics of the 637 older PLWH, 340 younger PLWH and 276 older HIV-negative participants are summarized in Table 1. Older and younger PLWH had been diagnosed with HIV infection for a median (IQR) of 16.0 (10.1, 22.4) and 9.6 (5.4, 15.2) years, respectively. The median (IQR) CD4 T-cell count was 620 (470, 799) and 654 (490, 833) cells/μL, respectively, and 92.3 and 85.8% had a suppressed viral load (< 50 HIV-1 RNA copies/mL), respectively.

The two older groups of PLWH and HIV-negative controls were comparable in terms of age [median age was 56 (interquartile range (IQR) 53, 62) and 58 (IQR 53, 63) years in older PLWH and HIV-negative participants, respectively;

Table 1 Demographic, lifestyle and HIV-related characteristics of people living with HIV (PLWH) ≥ 50 and < 50 years old, and HIV-negative study participants ≥ 50 years old at enrolment

Variable	PLWH ≥ 50 years (*n* = 637)	PLWH < 50 years (*n* = 340)	P^1	HIV-negative ≥ 50 years (*n* = 276)	P^2	P^3
Gender			0.001		< 0.001	< 0.001
Male	564 (88.5)	275 (80.9)		180 (65.2)		
Female	73 (11.5)	65 (19.1)		96 (34.8)		
Age (years)	56 (53, 62)	43 (37, 47)	< 0.001	58 (53, 63)	0.11	< 0.001
Ethnicity			0.002		0.13	0.001
Black African	77 (12.1)	66 (19.4)		24 (8.7)		
White	560 (87.9)	274 (80.6)		252 (91.3)		
Country of birth			< 0.001		0.41	< 0.001
UK/Ireland	446 (70.0)	173 (50.9)		207 (75.0)		
Rest of Europe	41 (6.4)	54 (15.9)		15 (5.4)		
Africa	111 (17.4)	78 (22.9)		37 (13.4)		
Rest of the world	39 (6.1)	35 (10.3)		17 (6.2)		
Sexual orientation			0.007		< 0.001	< 0.001
MSM/homosexual	509 (79.9)	246 (72.4)		138 (50.0)		
Heterosexual	128 (20.1)	94 (27.6)		138 (50.0)		
Education			0.34		0.05	0.12
No qualifications	63 (9.9)	22 (6.5)		14 (5.1)		
O levels/GCSEs	93 (14.6)	54 (15.9)		37 (13.4)		
A levels	82 (12.9)	52 (15.3)		35 (12.7)		
University	258 (40.5)	142 (41.8)		109 (39.5)		
Other/not known	141 (22.1)	70 (20.6)		81 (29.4)		
Marital status			0.002		< 0.001	< 0.001
Single	301 (47.3)	174 (51.2)		83 (29.6)		
Married/in a relationship	269 (42.2)	154 (45.3)		149 (54.0)		
Divorced	43 (7.1)	7 (2.1)		32 (11.6)		
Widow/widower	22 (3.5)	5 (1.5)		12 (4.4)		
Alcohol consumption			0.35		0.007	0.08
Never consumed	46 (7.2)	29 (8.5)		14 (5.1)		
Previously consumed only	84 (13.2)	35 (10.3)		19 (6.9)		
Currently consuming	507 (79.6)	276 (81.2)		243 (88.0)		
If current/previous consumption						
Years drinking	39 (35, 45)	25 (19, 30)	< 0.001	41 (36, 46)	0.04	< 0.001
Units/week	8 (3, 18)	6 (2, 16)	0.08	10 (3, 20)	0.35	0.02
Smoking status			0.002		0.03	< 0.001
Never smoked	247 (39.0)	145 (42.9)		123 (44.7)		
Ex-smoker	242 (38.2)	93 (27.5)		110 (40.0)		
Current smoker	145 (22.9)	100 (29.6)		42 (15.3)		
If current/ex-smoker						
Years smoked	33 (20, 39)	21 (14, 27)	< 0.001	29 (16, 38)	0.009	< 0.001
Cigarettes per day	11 (5, 20)	10 (5, 15)	0.02	10 (3, 20)	0.32	0.76
Ever injected drugs	59 (9.3)	46 (13.6)	0.04	6 (2.2)	< 0.001	< 0.001
Recreational drugs	164 (25.8)	116 (34.1)	0.006	42 (15.2)	< 0.001	< 0.001
Depressive symptoms			0.36		< 0.001	< 0.001
None	303 (51.8)	172 (54.8)		214 (82.0)		
Mild	126 (21.5)	75 (23.9)		27 (10.3)		
Moderate	84 (14.4)	36 (11.5)		12 (4.6)		
Severe	72 (12.3)	31 (9.9)		8 (3.1)		
Duration of HIV infection (years)	16.0 (10.1, 22.4)	9.6 (5.4, 15.2)	< 0.001	NA	NA	NA
CD4 T-cell count (cells/μL)	620 (470, 799)	654 (490, 833)	0.20	NA	NA	NA
CD4 T-cell %	31 (24, 38)	33 (26, 39)	0.01	NA	NA	NA
Nadir CD4 count (cells/μL)	180 (85, 270)	258 (158, 384)	< 0.001	NA	NA	NA
On ART	631 (99.1)	325 (95.6)	< 0.001	NA	NA	NA
HIV RNA < 50 copies/mL	586 (92.3)	290 (85.8)	0.001	NA	NA	NA

Values are *n* (%) or median (interquartile range). P^1: test comparing PLWH ≥ 50 years and PLWH < 50 years; P^2: test comparing PLWH ≥ 50 years and HIV-negative individuals ≥ 50 years; P^3: test comparing PLWH < 50 years and HIV-negative individuals ≥ 50 years.ART, antiretroviral therapy; GCSE, General Certificate of Secondary Education; MSM, men who have sex with men; NA, not applicable.

$P = 0.11$], ethnicity ($P = 0.13$) and country of birth ($P = 0.41$). Older PLWH were more likely to be male (88.5 versus 65.2%, respectively; $P < 0.001$), men who have sex with men (MSM) (79.9 versus 50.0%, respectively; $P < 0.001$) and single (47.3 versus 29.6%, respectively; $P < 0.001$) and to have reported recreational drug use in the 6 months preceding study entry (25.8 versus 15.2%, respectively; $P < 0.001$) compared with older HIV-negative controls. In

particular, older PLWH were more likely to have reported use of marijuana (14.3 versus 4.7%, respectively; $P < 0.001$), amphetamine (7.4 versus 4.0%, respectively; $P = 0.05$) and cocaine (6.9 versus 3.3%, respectively; $P = 0.03$), compared with older HIV-negative controls (Table S2). Current smoking was more common in PLWH ($P = 0.03$), while current alcohol consumption was more prevalent in HIV-negative controls than PLWH ($P = 0.007$).

Compared with older PLWH, younger PLWH were less likely to be male (80.9%; $P = 0.001$) and MSM (72.4%; $P = 0.007$) and more likely to be single (51.2%; $P = 0.002$). There were no differences in terms of educational attainment ($P = 0.34$) or alcohol consumption ($P = 0.35$); however, current smoking (22.9% in PLWH ≥ 50 years versus 29.6% in PLWH < 50 years; $P = 0.002$), use of any recreational drug (25.8 versus 34.1%, respectively; $P = 0.006$) and use of most individual drugs (Table S2) were more frequent in younger PLWH compared with older PLWH.

Depressive symptoms

Fifty-two older PLWH, 26 younger PLWH and 15 older HIV-negative participants did not complete the questionnaire on depressive symptoms and were excluded from analyses that incorporated this measure. Of note, a sensitivity analysis showed that those who did not complete the questionnaire on depressive symptoms were similar to those who did with regard to most sociodemographic and lifestyle characteristics. However, black Africans and those with lower educational attainment were less likely to have completed the questionnaire compared with those of white ethnicity (87.4 versus 93.4%, respectively; $P = 0.006$) and those with higher qualifications (88.9 versus 96.2% in those with O levels/GCSEs, 95.3% in those with A levels and 95.9% in those with a university degree; $P = 0.03$), respectively.

The median (IQR) PHQ-9 score was 4 (1, 10), 4 (1, 8) and 1 (0, 3) in older PLWH, younger PLWH and older HIV-negative participants, respectively. Scores were significantly higher in both older and younger PLWH, compared with older HIV-negative controls (both $P < 0.001$) but did not differ significantly between older PLWH and younger PLWH ($P = 0.23$). Similarly, moderate and severe depressive symptoms were more prevalent in the two groups of PLWH compared with the older HIV-negative group (both $P < 0.001$), but there were no differences between older and younger PLWH ($P = 0.36$; Table 1).

Domain and global *Z*-scores

After adjustment for age, gender, ethnicity and level of education, older PLWH had poorer cognitive scores overall ($P < 0.001$) and in the psychomotor ($P = 0.008$), visual attention ($P = 0.01$), executive function ($P = 0.04$) and verbal learning ($P = 0.007$) domains compared with older HIV-negative participants (Fig. 1 and Table S3). After adjustment, younger PLWH had poorer cognitive scores overall ($P = 0.006$) and in the visual attention ($P = 0.006$), verbal learning ($P = 0.05$) and working memory ($P = 0.02$) domains than older HIV-negative controls. While older PLWH had poorer visual learning scores compared with younger PLWH ($P = 0.03$), there were no differences in overall cognitive scores ($P = 0.82$) and scores for other domains.

One hundred and thirteen (17.7%) older PLWH, 54 (15.9%) younger PLWH and 34 (12.3%) older HIV-negative controls were classified as cognitively impaired. While this proportion was greater in older PLWH compared with HIV-negative controls ($P = 0.04$), there were no differences between younger PLWH and older controls ($P = 0.21$) and between older and younger PLWH ($P = 0.46$).

Associations between global cognitive function and lifestyle

We evaluated associations between lifestyle factors and the global *Z*-score in the whole study population. From univariate analyses (model 1), marital status ($P = 0.04$), alcohol consumption ($P = 0.03$), years of alcohol consumption ($P = 0.02$), use of marijuana ($P = 0.03$) and use of hashish ($P = 0.01$) were associated with global cognitive scores, independently of the core covariates (age, gender, ethnicity and level of education; Table 2). Severity of depressive symptoms was significantly associated with global *Z*-scores, with better scores for participants without symptoms ($P < 0.001$) or only reporting mild symptoms ($P = 0.003$) compared with those reporting severe symptoms.

When considered simultaneously (model 2), only depressive symptoms ($P < 0.001$), previous alcohol consumption ($P = 0.04$) and use of hashish ($P = 0.03$) showed associations that were independent of the other factors. In particular, previous and current alcohol consumption were both associated with better global *Z*-scores compared with no consumption ($P = 0.007$ and $P = 0.006$, respectively) with no differences between previous and current consumption ($P = 0.55$), while use of hashish was associated with poorer global cognitive scores ($P = 0.01$). Associations remained similar after excluding the factors that were not significantly associated (model 3), with use of hashish and more severe depressive symptoms being associated with poorer cognitive scores.

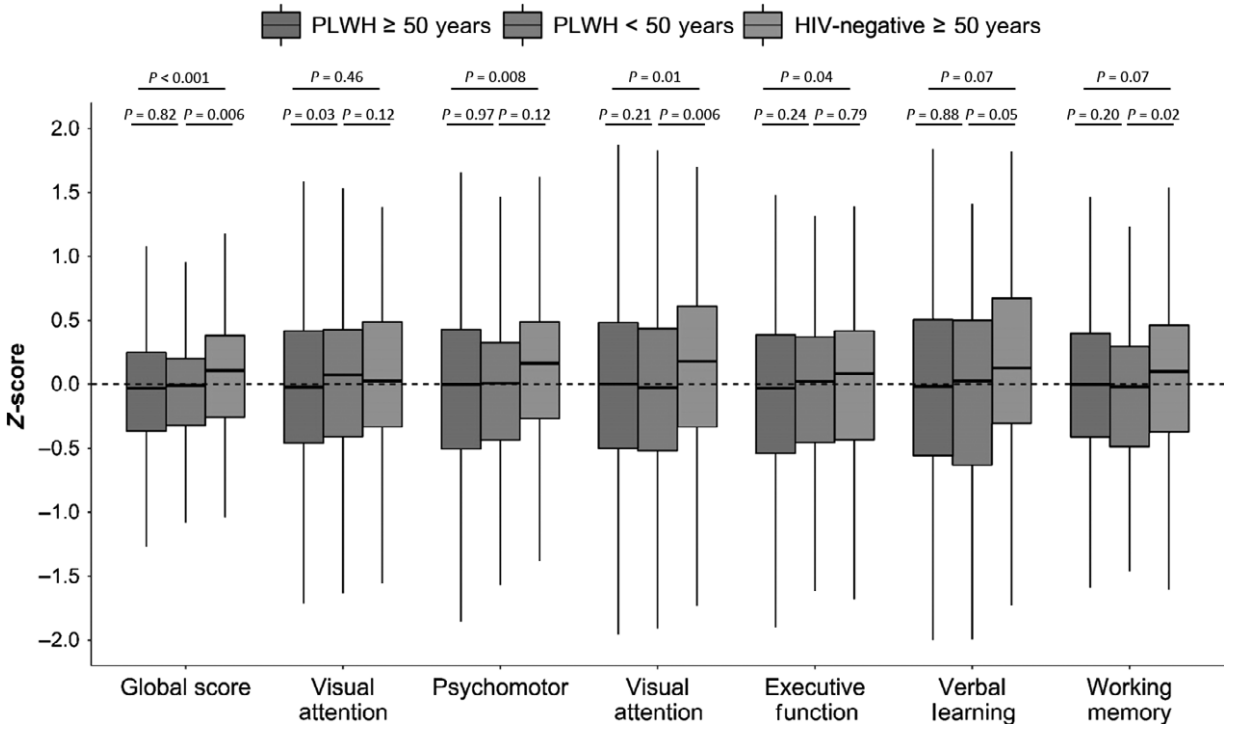

Fig. 1 Domain and global *Z*-scores in people living with HIV (PLWH) ≥ 50 years old, PLWH < 50 years old and HIV-negative participants ≥ 50 years old adjusted for age, gender, ethnicity and level of education.

Mediation/moderation effect of lifestyle and depressive symptoms

In model 4, depressive symptoms, alcohol consumption and use of hashish were still significantly associated with the global *Z*-score independently of each other and of HIV status/group. After the inclusion of these factors, the adjusted difference between the two older groups was attenuated and was no longer significant ($P = 0.08$), while that between younger PLWH and older HIV-negative controls remained similar ($P = 0.01$). Moreover, the adjusted difference (95% confidence interval) between older and younger PLWH remained not significant [0.08 (−0.02, 0.18); $P = 0.11$].

There were no significant interactions between HIV status/group and either alcohol consumption ($P = 0.45$) or use of hashish ($P = 0.19$). The interaction between HIV status and depressive symptoms was, however, significant ($P = 0.03$), suggesting that the association between depressive symptoms and cognitive function is modified by HIV status/group. Figure 2 depicts the estimated differences in the median global *Z*-score associated with depressive symptoms and HIV status/group when compared with the median scores in older HIV-negative individuals with no depressive symptoms. Cognitive scores in those reporting greater depressive symptoms (especially in those with severe depressive symptoms) were poorer in both older and younger PLWH compared with scores observed in older HIV-negative participants. However, this interaction was no longer significant once analyses were restricted to participants without depressive symptoms or with mild or moderate symptoms ($P = 0.16$).

Discussion

These data suggest that poorer cognitive function seen in older PLWH, when compared with similarly aged HIV-negative individuals with similar lifestyles, are, in part, mediated by the greater prevalence of depressive symptoms reported by PLWH. Moreover, differences were also driven by the use of substances such as alcohol and recreational drugs.

When compared with HIV-negative individuals with similar lifestyle and sexual risk-taking behaviours, and when accounting for sociodemographic factors only, PLWH exhibit overall poorer cognitive functioning in several domains such as visual attention, working memory and verbal learning. Similar results have been previously reported [4,28] and seem to indicate HIV infection as the

Table 2 Estimated regression coefficients (with 95% confidence intervals) obtained from multivariable median regression models to investigate associations between the global *Z*-score of cognitive function and sociodemographics, lifestyle factors, depressive symptoms and HIV status/group

	Step 1		Step 2		Step 3		Step 4	
	Difference (95% CI) in the median *Z*-score	*P*	Difference (95% CI) in the median *Z*-score	*P*	Difference (95% CI) in the median *Z*-score	*P*	Difference (95% CI) in the median *Z*-score	*P*
HIV status/group (ref. HIV-negative individuals ≥ 50 years)								
PLWH ≥ 50 years	−0.14 (−0.22, −0.06)	< 0.001					−0.08 (−0.16, 0.01)	0.08
PLWH < 50 years	−0.17 (−0.28, −0.05)	0.006					−0.15 (−0.27, 0.03)	0.01
Sexuality (ref. MSM)								
Heterosexual	−0.01 (−0.12, 0.11)	0.94						
Marital status (ref. married/in a relationship)								
Single	−0.09 (−0.16, −0.02)	0.009	−0.05 (−0.11, 0.02)	0.15				
Divorced	−0.07 (−0.20, 0.07)	0.31	0.002 (−0.13, 0.13)	0.98				
Widow/widower	−0.17 (−0.36, 0.03)	0.09	−0.09 (−0.28, 0.95)	0.33				
BMI (per 5 kg/m^2 increase)	−0.03 (−0.07, 0.01)	0.12						
Depressive symptoms (ref. none)								
Mild	−0.08 (−0.17, −0.001)	0.05	−0.09 (−0.17, −0.01)	0.03	−0.09 (−0.17, −0.01)	0.02	−0.09 (−0.17, −0.01)	0.03
Moderate	−0.17 (−0.28, −0.07)	0.001	−0.20 (−0.30, −0.10)	< 0.001	−0.17 (−0.27, −0.07)	0.001	−0.19 (−0.29, −0.09)	< 0.001
Severe	−0.28 (−0.39, −0.17)	< 0.001	−0.31 (−0.42, −0.20)	< 0.001	−0.28 (−0.39, −0.17)	< 0.001	−0.26 (−0.37, −0.15)	< 0.001
Alcohol consumption (ref. never consumed)								
Previously consumed only	0.18 (0.03, 0.33)	0.02	0.20 (0.01, 0.39)	0.04	0.20 (0.05, 0.358)	0.01	0.25 (0.10, 0.40)	0.001
Currently consuming	0.17 (0.05, 0.30)	0.008	0.12 (−0.09, 0.33)	0.26	0.17 (0.04, 0.30)	0.01	0.18 (0.05, 0.30)	0.006
Years of drinking (per 5 years)	0.05 (0.01, 0.04)	0.02	0.003 (−0.002, 0.008)	0.26				
Smoking status (ref. current smoker)								
Ex-smoker	0.04 (−0.04, 0.13)	0.31						
Never smoked	0.02 (−0.07, 0.10)	0.67						
Years of smoking (per 5 years)	0.01 (−0.01, 0.02)	0.50						
Ever injected drugs (yes versus no)	−0.04 (−0.15, 0.07)	0.46						
Recreational drugs in past 6 months (yes versus no)	−0.04 (−0.11, 0.03)	0.29						
Marijuana (yes versus No)	−0.13 (−0.22, −0.05)	0.005	0.04 (−0.06, 0.14)	0.43				
Amphetamine (yes versus no)	−0.03 (−0.14, 0.08)	0.58						
Cocaine (yes versus no)	−0.08 (−0.19, 0.04)	0.21						
GBL/GHB (yes versus no)	−0.02 (−0.16, 0.12)	0.79						
Hashish (yes versus no)	−0.25 (−0.44, −0.05)	0.01	−0.21 (−0.43, −0.002)	0.05	−0.27 (−0.47, −0.06)	0.01	−0.29 (−0.49, −0.09)	0.005
Inhalants (yes versus no)	0.08 (−0.07, 0.22)	0.29						
Ketamine (yes versus no)	0.01 (−0.10, 0.11)	0.93						
LSD (yes versus no)	−0.14 (−0.45, 0.18)	0.39						
MDMA (yes versus no)	−0.05 (−0.19, 0.09)	0.46						
Crystal meth (yes versus no)	−0.03 (−0.15, 0.08)	0.58						

Table 2 (*Continued*)

	Step 1		Step 2		Step 3		Step 4	
	Difference (95% CI) in the median *Z*-score	*P*	Difference (95% CI) in the median *Z*-score	*P*	Difference (95% CI) in the median *Z*-score	*P*	Difference (95% CI) in the median *Z*-score	*P*
Mephedrone (yes versus no)	−0.05 (−0.45, 0.36)	0.83						

Step 1: core covariates (age, gender, ethnicity and education) + one factor at a time; step 2: core covariates + significant factors in the models in step 1 ($P < 0.05$) excluding HIV status/group; step 3: core covariates + significant factors in the model in step 2 ($P < 0.05$); step 4: core covariates + significant factors in the model in step 3 ($P < 0.05$) + HIV status/group.BMI, body mass index; CI, confidence interval; MSM, men who have sex with men; PLWH, people living with HIV; GBL, gamma butyrolactone; GHB, gamma hydroxybutyrate; LSD, Lysergic acid diethylamide; MDMA, 3,4-methylenedioxy-methamphetamine.

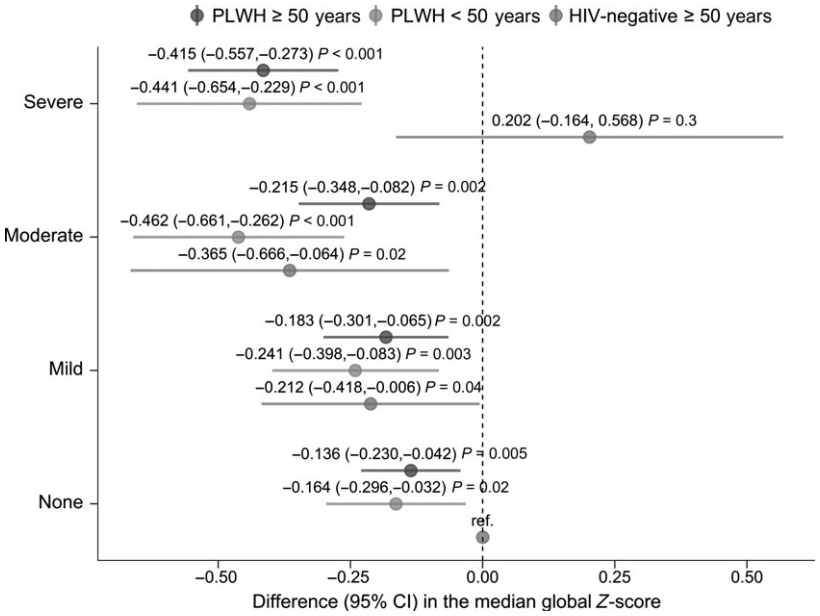

Fig. 2 Difference (95% confidence interval) in the median global *Z*-score by severity of depressive symptoms and group. The median (interquartile range) global *Z*-score for HIV-negative controls ≥ 50 years old with no depressive symptoms was 0.20 (−0.15, 0.46).

main culprit. However, consistent with previous studies, we also found that PLWH reported a greater burden of depressive symptoms [6] which are also associated with reduced overall cognitive scores [9,29]. Adding to these studies, which focused on cohorts of PLWH with lower proportions of ART use and viral suppression, and lower CD4 T-cell counts than would be typical in the current era in resource-rich countries, our findings confirm such an association in ART-treated PLWH with stable viral suppression. More importantly, the difference in overall cognitive scores between HIV-negative individuals and similarly aged PLWH was attenuated when these depressive symptoms were taken into account. This finding suggests that depression may act as confounding factor of the association between HIV infection and cognitive function and, therefore, previous reports of PLWH with poorer cognitive functioning than HIV-negative controls, not accounting for depression, may have overestimated the independent effect of HIV. Of note, however, the attenuation of differences in overall cognitive scores between younger PLWH and older HIV-negative controls, consequent to accounting for depressive symptoms, was less evident, possibly because of lower rates of moderate/severe depressive symptoms seen in younger PLWH compared with those seen in older PLWH.

Differences in cognitive scores between PLWH and older HIV-negative controls appeared at least marginally statistically significant; however, the size of the association with HIV infection itself (effect sizes of −0.14 and −0.17 for older and younger PLWH, respectively) appeared to be moderate, broadly equating to the association seen between mild/moderate depression and the global *Z*-score

(effect sizes of −0.08 and −0.17, respectively). While this is likely to be attributable to the beneficial effects of ART on suppression of HIV replication, the differences in overall scores and in rates of cognitive impairment reported here are smaller than those reported in other studies [30,31]. This may reflect the more appropriate selection of an HIV-negative control group with similar lifestyles to the PLWH. Of note, our findings are consistent with those from the comorbidity in relation to HIV/AIDS study [32,33] in which baseline differences between PLWH and comparable controls did not increase with longer follow-up.

The link between HIV infection and depression is likely to be bi-directional and multifactorial, involving both biological and psychosocial/social factors [7]. Among others, the impact of being diagnosed with HIV infection, associated stigma, social isolation and discrimination may all lead to depressive disorders among PLWH. In turn, depression may cause poor concentration and lack of interest in and apathy towards cognitive testing and therefore confound the association between HIV infection and cognitive function. However, emerging evidence suggests that HIV replication in the central nervous system (CNS) may cause depression through alterations of brain structure [34,35], somatostatin dysregulation [36] and increased concentrations of inflammatory cytokines [37]. As depression is also associated with chronic, low-grade inflammation and cell-mediated immune activation [38,39], cognitive problems and depression may represent a unique manifestation of the same underlying pathological process as a result of the direct and indirect effects of HIV replication in the CNS. More research is justified to investigate the consequences of CNS HIV replication and blood–brain barrier dysfunction for mood disorders and cognitive function.

Our results suggest that current or previous alcohol consumption and recreational use of hashish (but not marijuana) may be important determinants of overall cognitive function, independent of depressive symptoms, and can attenuate differences in cognitive scores between PLWH and HIV-negative individuals. We report better cognitive scores among past or current drinkers compared with nondrinkers in a cohort with overall moderate consumption [the median (IQR) self-reported alcohol consumption was 8 (2, 18) units per week, below the 14 units per week recommended by UK guidelines [40]]. In the general population, most studies have also shown that moderate drinkers tend to perform better on cognitive tests than nondrinkers [41,42], while a few studies have not [43]. An association between moderate alcohol intake and better cognitive function may reflect good physical and mental health and/or social position [44], as well as a decreased risk of cardiovascular disease [45], which has been shown to share common risk factors with cognitive problems even in PLWH [46]. However, current nondrinking status may reflect previous hazardous over-consumption which may be associated with brain injury (i.e. reverse causation).

Long-term use of recreational drugs such as hashish has been linked with poorer cognitive performances in other settings [47], including cohorts of PLWH [1,48]. Interestingly, marijuana use was not related to overall cognitive function after accounting for depressive symptoms, alcohol consumption and use of hashish. As marijuana and hashish contain the same active substance, this is likely to reflect differences in frequency, quantity and age of onset of use and other unmeasured lifestyle factors (e.g. use of other drugs or sexual risk-taking behaviours) between people reporting use of only one of the drugs and those reporting use of both drugs (19 of the 30 participants reporting use of hashish also reported use of marijuana). Moreover, the self-reported nature of information regarding substance use may have introduced a bias as a consequence of the subjective interpretation of the different types of recreational drugs listed in the structured questionnaire. PLWH were more likely to report recreational use of hashish in the 6 months preceding the study visit, compared with older HIV-negative individuals (2.0, 4.1 and 1.1% in older PLWH, younger PLWH and older HIV-negative individuals, respectively). When we accounted for both the use of hashish and alcohol consumption, as well as depressive symptoms, the initial differences in cognitive scores between older PLWH and similarly aged HIV-negative individuals were largely attenuated. This suggests that, together with depression, these important confounding factors should be considered when assessing the cognitive performances of PLWH, especially when the comparison is made with individuals from the general population, where consumption of recreational drugs is less prevalent. Moreover, these findings further highlight the importance of early clinical management of depression and of interventions targeting modifiable risk factors as well as their potential beneficial effects in the short term on cognitive performances among PLWH.

Interestingly, use of other substances, including cocaine, amphetamine and crystal meth, did not seem to be associated with overall cognition. While this may reflect a lack of statistical power (numbers of participants reporting each individual drug may not be sufficient to detect significant associations), detailed information on quantity and frequency of use would be required to shed further light on whether recreational drug use is also associated with cognitive function, independently of other lifestyle factors and depressive symptoms.

While raw cognitive scores were overall poorer in older PLWH compared with younger PLWH (data not shown),

there were no substantial differences after accounting for age and sociodemographic factors, nor after further adjustment for depressive symptoms, alcohol consumption and recreational drug use. Therefore, the difference initially seen between older and younger PLWH can be mainly attributed to the effects of age and other factors potentially associated with age (e.g. level of education). Inclusion of a group of younger HIV-negative individuals would be ideal to investigate whether the effects of age are stronger in PLWH than those expected in HIV-negative individuals.

Our study has limitations. The cross-sectional nature of our analysis does not allow the assessment of causal relationships and the direction of the associations, which is likely to be bi-directional between cognitive performances and depression, alcohol consumption and recreational drug use. Although great effort was made to include a comparable HIV-negative control group, differences in some demographic and lifestyle factors were present. Also, the lack of a younger (i.e. < 50 years old) HIV-negative control group may have resulted in an underestimation of cognitive function of younger PLWH. These issues were addressed by adjusting all statistical analyses for age and other demographic factors; however, it is not possible to rule out the possibility that unmeasured confounders may have affected our results. Another limitation results from the self-reported nature of information provided by study participants, which includes depressive symptoms, smoking, alcohol consumption and recreational drug use. These data were self-reported for practical reasons, but clearly such data may be subject to exaggerations of symptoms or social desirability bias.

In conclusion, our results suggest that comparisons of cognitive performances between PLWH and HIV-negative controls should take into account depressive symptoms and lifestyle factors. Both depression and cognitive problems remain prevalent in PLWH, even among those receiving effective ART, with significant implications for quality of life. It is therefore important to further elucidate the pathogenesis of HIV in the brain and the effect of the interaction between HIV infection and mood disorders on the development of cognitive dysfunction in PLWH.

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Appendix 1

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Description of the cognitive tests administered
Table S2. Prevalence of each recreational drug used in the 6 months preceding the study visit in PLWH ≥ 50 and < 50 years old, and HIV-negative participants ≥ 50 years old
Table S3. Differences in the median *Z*-score for each domain between PLWH ≥ 50 and < 50 years old compared with HIV-negative controls ≥ 50 years old