Sleep disturbances and their correlation with cardiovascular risk, obesity, and mood disorders in people with HIV

Maria Mazzitelli[a,*], Mattia Trunfio[b,c,*], Ana Milinkovic[d,e], Eleonora Castelli[a], Lolita Sasset[a], Davide Leoni[a], Margherita Salvucci[e], Riccardo Cazzaro[e], Ilaria Calcinoni[e], Pietro Balducci[e], Gustavo Coelho Quirino Ribeiro[e], Giacomo Filagrana[f], Vincenzo Scaglione[a] and Anna M. Cattelan[a,g,h]

See related paper on page 993

Background: The relationship between sleep disorders (SDs), cardiovascular risk (CVR), and mood disorders (MDs) has been studied in detail in the general population, but far less in people with HIV (PWH).

Methods: Cross-sectional analysis in single centre cohort of PWH. Sleep quality was assessed using by Epworth Sleepiness Scale (ESS), Insomnia Severity Index (ISI), Berlin Questionnaire (BQ), Pittsburgh Sleep Quality Index (PSQI); anxiety and depression were evaluated by the Generalized Anxiety Disorder-7 and Patient Health Questionnaire-9. Demographic, clinical and HIV-related data were collected, and Framingham and Data collection on Adverse effects of anti-HIV Drugs (DAD)-10 scores were computed in modelling associations with each SDs scale.

Results: Data were collected for 721 PWH on stable combination antiretroviral therapy (cART) (median age of 53 years, 71.8% males, 96% with undetectable HIV RNA, 50.3% on cART potentially affecting sleep, and 20.4% on hypno-inducing drugs), 76.9% had SDs 60.3, 31.3, 31.1, and 7.9% at PSQI, BQ, ISI, and ESS, respectively. Anxiety and depression were detected in 28.3 and 16.1% participants, respectively. BQ score was independently associated with high BMI ($P < 0.001$), Framingham risk >10% ($P < 0.001$), and both DAD-10R and -10F score >10% ($P < 0.001$ and $P = 0.031$). PSQI and ISI scores were independently associated with depression and anxiety ($P < 0.001$). No association between SDs and specific antiretroviral regimens, nor HIV-related parameters was detected.

Conclusions: In our cohort of PWH on stable ART, despite the alarmingly higher prevalence, SDs were associated with the same determinants (cardiovascular risk factors and MDs) observed in the general population.

AIDS 2023, **37**:925–934

Keywords: cardiovascular risk, depression, HIV, people with HIV, sleep, sleep disturbances

[a]Department of Molecular Medicine, Infectious and Tropical Diseases Unit, Department of Medical Sciences, Padua University Hospital, Padua, [b]Infectious Diseases Unit, Department of Medical Sciences, University of Turin at Amedeo di Savoia Hospital, Turin, Italy, [c]HIV Neurobehavioral Research Program and Departments of Neurosciences and Psychiatry, School of Medicine, University of California, San Diego, California, USA, [d]Chelsea and Westminster Foundation Trust, [e]Imperial College London, London, UK, [f]Unit of Psychiatry, [g]Student at University of Padua, Padua University Hospital, and [h]University of Padua, Padua, Italy.

Correspondence to Maria Mazzitelli, MD, PhD, Infectious and Tropical Disease Unit, Padua University Hospital, Via Giustiniani, 3, 35128, Padua, Italy.

Tel: +39 0498213765; e-mail: maria.mazzitelli@aopd.veneto.it

[*] M.M. and M.T. contributed equally to this work.

Received: 31 October 2022; revised: 13 January 2023; accepted: 16 January 2023.

DOI:10.1097/QAD.0000000000003493

Introduction

Sleep is crucial to physiological functions [1–3]. Therefore, sleep disturbances (SDs) affect daytime functioning, attention, performance, and overall quality of life, and have consequences on the long-term health (especially metabolic and cardiovascular) [2–4]. Prevalence of SD in the general population ranges from 10 to 30% [5–7], but less than 20% of people who complain about SD are diagnosed properly [8].

Several studies demonstrated that people with HIV (PWH) have a higher prevalence of SD (up to 73%) when compared to the general population [9–11]. Mechanisms of such correlation have been linked with length of HIV disease, persistent inflammatory status, and the overrepresentation of the traditional risk factors for SD, such as alcohol use disorder or intravenous drug use (IVDU) [12–16]. Moreover, some components of antiretroviral therapy and stigma may have an impact both on sleep quality and SD onset [17–19]. There are some antiretroviral drugs, which have been historically recognized as associated with SD, such as efavirenz [20–22], that has been associated with insomnia, vivid dreams, and increased daytime sleepiness [20–23]. Most recently, integrase inhibitors have shown the effect on sleep and central nervous system [24–27]. Dolutegravir was associated with nightmares, anxiety, suicidal thoughts, dizziness, and mood disorders (MD) [24–27]. Neuropsychiatric adverse effects and SD were also reported in PWH on bictegravir-based combination antiretroviral therapy (cART) [24,28].

The two most commonly diagnosed SDs in PWH are insomnia and sleep apnoea [16,29]. More than 50% individuals report symptoms of insomnia, which have a significant impact on quality of life and psychosocial functioning, but also can lead to lower cART adherence [30,31]. Insomnia is closely related to psychiatric disorders such as major depressive disorder, which can reach a prevalence of up to 42% among PWH [31–33]. Furthermore, insomnia can also be a risk factor for increased cardiovascular risk and major incidence of cardiovascular events, because of alterations in immune, inflammatory and coagulation systems [8,34,35].

Daytime sleepiness and fatigue are commonly reported in PWH, for which the main underlying condition remains the depressive disorder [36].

Though breathing-related sleep disturbances (mainly apnoea), have pulmonary and cardiac consequences, the correlated factors in PWH have not been fully elucidated. Several studies have shown that risk factors associated with sleep apnoea in PWH are younger age, opioid dependence, lower body mass index (BMI), lipodystrophy, large neck circumference, and chronic obstructive pulmonary disease [37–40]. These risk factors are not in line with those detected in the general population, which include older age, hypertension, and snoring [41]. By contrast, other studies reported snoring as the main symptom in moderate-severe sleep apnoea in PWH, also showing an association with increased $CD4^+$ T-cell count, and a long history of HIV disease [38,42–44].

Assessment of SD in PWH is complex, required specific tools and skills, and it is not routinely performed in clinical practice, and as a result data on correlation between SD and cardiovascular risk, obesity, and mood disorders (MD) in PWH remain scarce. Therefore, our objective was to describe SD and to assess their possible correlation with cardiovascular risk, obesity, and MD.

Methods

Study design and participants

This prospective cross-sectional study was conducted at Infectious and Tropical Diseases Unit of Padua University Hospital (Italy), in accordance with principles of good clinical practices and Declaration of Helsinki. All participants were requested to sign an informed consent. Study protocol received Ethical approval (21.10.2021, no. 2763). Participation was offered to all PWH ≥18 years of age attending HIV outpatient clinic for their routine visits from 1 November 2021 to 31 March 2022. People with educational and language barriers, physical or sensory impairments were provided with appropriate help to complete the questionnaires (i.e. cultural mediators, and people able to communicate in sign languages). Participants with severe neurological or psychiatric conditions (including PWH with active substance consumption), and inability to complete the questionnaires were excluded.

Procedures and data collection

Participants were administered eight different self-assessment questionnaires:

(1) Epworth Sleepiness Scale (ESS). Excessive daily sleepiness was considered as present whenever the total score was >10 [45].
(2) Insomnia Severity Index (ISI) for the presence and severity of insomnia. The score was deemed altered whenever greater than >15 [46].
(3) Pittsburgh Sleep Quality Index (PSQI) evaluating the sleep quality and habits. Poor sleep quality was deemed present when the score was >5 [47–49].
(4) Berlin Questionnaire (BQ) assessing the risk of sleep apnoea. When two or more categories were positive, obstructive sleep apnoea was considered present [50].
(5) Fatigue Severity Scale (FSS) evaluating the presence and severity of fatigue. A score higher than 36 was suggestive of fatigue [51].
(6) Generalized Anxiety Disorder (GAD-7). For anxiety, a cut-off ≥8 is considered positive for anxiety [52].

(7) Patient Health Questionnaire (PHQ-9) for depression. The presence of depression is likely when the total score is >10 [53].
(8) Wellness Thermometer (Wellness) evaluating the current state of people well being. The value ranges from 1 to 10, with a growing degree of well being as the values increase [54].

The presence of MDs (anxiety and depression) was then confirmed by a psychiatric consultation.

Cardiovascular risk (CVR) was assessed by the following validated scores: Framingham score identifies the 10-year [55] and Data collection on Adverse effects of anti-HIV Drugs (DAD)-10 Risk Score validated in PWH [56]. Two different variants of this score were calculated: the DAD full (DAD-F), which includes exposure to different antiretroviral classes, and DAD restricted (DAD-R) does not include ART-related variables [56].

Demographics (sex, ethnicity, age), life-style habits, laboratory, and clinical data (comorbidities, co-medications) were collected from medical health records. The presence of regular physical exercise was defined as per WHO definitions, as well as alcohol use disorder [57,58]. The patient underwent clinical examination, and blood pressure, heart rate, weight, height, and abdominal circumference were recorded. Multimorbidity and polypharmacy were defined as the presence of two or more non-communicable diseases and by the intake of five or more non-antiretroviral medications in the same person, respectively [59,60]. Drugs potentially affecting sleep quality were classified as follows. Among antiretrovirals, we considered dolutegravir, efavirenz and bictegravir, while among non-antiretrovirals we included corticosteroids, analgesic opioids, and medications for opioid use disorders (OD/MOUDs). Hypno-inducing drugs, recreational drugs and other drugs potentially affecting the sleep-wake cycle were separately considered.

Statistical analysis

All data were collected in a pseudo-anonymized electronic spreadsheet. Data were reported as median (interquartile range, IQR) for continuous variables and absolute number (proportion) for categorical variables. Unadjusted odds ratio (OR) and the 95% confidence interval (95% CI) were calculated through logistic regression for the binary outcome normal/altered per each assessed SD scale as effect measure of risk association. For the binary outcome of alteration in the four scales assessing SD, multivariate logistic regression models (standard entry method) were eventually run including age, gender and covariates of significance at univariable analysis (level of significance was set as P-value < 0.05). Due to potential co-linearity between MDs and HIV-related parameters [11,13,21], subgroup analyses were also performed in participants without MDs; to limit multiple testing and collinearity and to consider multidimensionality and potential cross-domain overlap of the four SDs scales we also performed dimension reduction and factor analysis (loading value cut-off of 0.30, and varimax rotation method) to be compared with the results of regression models. Data were analysed through SPSS v27 (IBM Stat. Corp., Armonk, New York, USA).

Results

Study population

During the study period, participation was offered to 734 PWH (five refused to participate, two were not able to fill questionnaires for severe neurological/psychiatric issues, and six did not complete all the questionnaires). Hence, 721 PWH were enrolled and their demographic, clinical and HIV-related characteristics are reported in Table 1, section A. Of note, 518 (71.8%) participants were male, with a median age and duration of HIV infection of 53 (44–59) and 15 years (7–24), respectively. Plasma HIV RNA was undetectable in 96.1% of participants and the median $CD4^+$ T-cell count was 638 (474–811) cells/μl; 261 participants (36.2%) were on dual antiretroviral regimen (dolutegravir plus lamivudine), while the second most prescribed regimen was emtricitabine/tenofovir alafenamide plus rilpivirine (28.3%). Multimorbidity and polypharmacy were detected in 65% and 20.1% of participants, respectively. The most common comorbidities were hypertension (33.1%), dyslipidaemia (29.7%), and obesity (22.3%).

Survey prevalence and type of sleep disorders

Overall, 555 (76.9%) PWH reported SDs: 60.3% had poor sleep quality, 31.3% sleep apnoea, 31.3% insomnia, and 7.9% high daily sleepiness according toPSQI, BQ, ISI, and ESS, respectively. Thirteen participants (1.8%) also complained of other SDs: three cases of parasomnia (somnambulism in one case and *pavor nocturnus* in two cases), seven cases of restless leg syndrome, and three cases of bruxism. Two hundred and one (27.9%), 77 (11.7%), and 10 participants (2.09%) had alterations in two, three and all four analysed SDs scales, respectively. Anxiety and depression were confirmed to be present in 204 (28.3%) and 116 (16.1%) PWH, respectively, while 482 participants (66.8%) had no anxiety nor depression. All sleep metrics and questionnaire alterations are listed in Table 1, section B. Four hundred and forty-three participants (61.4%) were on at least one drug potentially affecting sleep of which 156 were non-antiretroviral drugs: 62 participants were on either zolpidem, benzodiazepines or other products prescribed to facilitate sleep (8.6%), 12 were on chronic corticosteroids (1.7%), 32 were on analgesic opioids (4.4%), and 89 were on drugs potentially altering the sleep–wake cycle (mainly antidepressant and antiepileptic drugs, 12.3%). As for antiretrovirals

Table 1. Demographics, clinical characteristics, sleep metrics and results of screening for sleep disturbances.

Section A

Characteristic	Study population ($n=721$)
Demographics	
Age, years, median (IQR)	53 (44–59)
Male sex, *n* (%)	518 (71.8)
Ethnicity, *n* (%)	
Caucasian	613 (85.0)
Black African	74 (10.3)
Others	34 (4.7)
Education and behaviours	
Education, years, median (IQR)	13 (8–13)
Smoker, *n* (%)	338 (46.9)
Regular physical exercise, *n* (%)	196 (21.2)
Alcohol use disorders, *n* (%)	64 (8.9)
HIV-related parameters	
Acquisition routes, *n* (%)	
MSM	379 (52.6)
Heterosexual	250 (34.7)
IVDU	78 (10.8)
Others	14 (1.9)
Length of HIV infection, years, median (IQR)	15 (7–24)
cART, *n* (%)	
Dual therapy (DTG+3TC)	261 (36.2)
2NRTI-INI	179 (24.8)
2NRTI-nNRTI	204 (28.3)
2NRTI-PI	72 (10.0)
Others	5 (0.7)
Current $CD4^+$ cell count, cells/μl, median (IQR)	638 (474–811)
Nadir $CD4^+$ cell count, cells/μl, median (IQR)	299 (160–459)
Past AIDS episodes, *n* (%)	130 (18.0)
Detectable plasma HIV-RNA (>50 copies/ml), *n*	28 (3.9)
Coinfections*, *n* (%)	
HBsAg	75 (10.4)
HCV Ab (+)	126 (17.5)
Positive HCV-RNA, *n*	34 (4.7)
Comorbidities* and polypharmacy	
Autoimmune disorders, *n* (%)	54 (7.5)
Cancer, *n* (%)	105 (14.6)
Chronic kidney disease, *n* (%)	57 (7.9)
Chronic obstructive pulmonary disease, *n* (%)	44 (6,1)
Diabetes, *n* (%)	68 (9.4)
Dyslipidaemia, *n* (%)	214 (29.7)
Ischemic heart disease, *n* (%)	51 (7.1)
Hypertension, *n* (%)	239 (33.1)
Liver cirrhosis, *n* (%)	24 (3.3)
Neurological diseases, *n* (%)	107 (14,8)
Obesity, *n* (%)	161 (22.3)
Osteoporosis, *n* (%)	139 (19.3)
Multimorbidity (yes), *n* (%)	469 (65.0)
N comorbidities/patient, median (IQR)	2 (1–4)
Polypharmacy (yes), *n* (%)	145 (20.1)
N comedications/patient (excluding antiretrovirals), median (IQR)	2 (1–4)

*Each patient may have more than one

Section B

Item/parameter	Overall population = 721
Sleep disorders*	
Overall, *n* (%)	555 (77)
Altered BQ, *n* (%)	226 (31.3)
Altered ISI, *n* (%)	224 (31.1)
Altered ESS, *n* (%)	57 (7.9)
Altered PSQI, *n* (%)	435 (60.3)
Parasomnia, *n* (%)	3 (0.4)

Table 1 (*continued*)

Section B

Item/parameter	Overall population = 721
Sleep movement disorders, *n* (%)	7 (1.0)
Bruxism, *n* (%)	3 (0.4)
*Each patient may have more than one	
Self-reported insomnia severity	
None, *n* (%)	258 (35.8)
Mild, *n* (%)	225 (31.2)
Moderate, *n* (%)	150 (20.8)
Severe/extremely severe, *n* (%)	88 (12.2)
Self-reported snoring, *n* (%)	349 (48,4)
Sleeping hours per night, hours, median (IQR)	7.0 (6.0–7.5)
Time to fall asleep > 30 min, *n* (%)	218 (30.2)
Early awakening, *n* (%)	348 (42.3)
Issues in sleep maintenance, *n* (%)	391 (54.2)
Issues in falling asleep, *n* (%)	352 (48.9)
Afternoon nap (yes), *n* (%)	506 (70.2)
Drugs affecting sleep, *n* (%)	
Antiretrovirals	364 (50.5%)
Corticosteroids	12 (1.7%)
Medical opioids/derivatives	32 (4.4%)
Hypno-inducing drugs	62 (8.2%)
Drugs with effect on the sleep-wake cycle	89 (12.3%)
FSS, altered, *n* (%)	112 (15.5)
Self-reported wellness (0–10), median (IQR)	7 (6–8)

%, percentage; BIC, bictegravir; BMI, body mass index; BQ, Berlin Questionnaire; CI, 95% confidence interval; COPD, chronic obstructive pulmonary disease; DTG, dolutegravir; EFV, efavirenz; GAD-7, General Anxiety Disorder-7; INI, integrase inhibitors; IQR, interquartile range; IVDU, intra-venous drug use; MSM, men who have sex with men; *n*, number; NNRTI, non-nucleos(t)ide reverse transcriptase inhibitors; OR, odds ratio; PHQ-9, Patient Health Questionnaire-9; PI, protease inhibitors.

potentially affecting sleep, 261 (36.2%), 101 (14%), and two (0.3%) were receiving dolutegravir, bictegravir, and efavirenz, respectively. According to reported CDC estimated time for sleeping for age groups [61], the proportions of subjects who spent sleeping an adequate number of hours was overall decreased (83.4% in the 18–25 year age group, 51.8% in the 26–64 year age group, and only 48.7% in the over 65-year group).

Sleep disorders and associated factors

Univariate and multivariable analyses for the factors that were associated with the likelihood of ranking below normative reference scores at the BQ, ISI, PSQI and ESS are reported in supplementary material (see Tables 1–4, Supplemental Digital Content, http://links.lww.com/QAD/C799). Specifically, for BQ univariate analysis detected associations with several cardiovascular risk factors and all the three CVR scores; considering the collinearity of CVR scores and the variables computed to calculate these scores, multiple multivariable models were run. The first model included univariate relevant covariates without composite CVR scores and observed an independent association between abnormal BQ results and age (2% increase of risk per year more: aOR=1.02, $P=0.041$), altered PHQ-9 (aOR=1.75, $P=0.048$), hypertension (aOR=2.83, $p<0.001$), and BMI (aOR=1.12, $P<0.001$;

Table 1, Supplemental Digital Content, http://links.lww.com/QAD/C799). The further models included one specific composite CVR score each plus univariate-significant variables without those computed to calculate the respective score: the likelihood of ranking below normative threshold at BQ was independently predicted by BMI (adjusted odds ratio [aOR] = 1.25, $P < 0.001$), and either by an intermediate and high Framingham score (aOR = 1.82, $P = 0.024$ and aOR = 2.12, $P = 0.022$), by DAD-R score >10% (aOR = 2.20, $P = 0.020$) and by DAD-F score >10% (aOR = 2.24, $P = 0.024$; Table 1, Supplemental Digital Content, http://links.lww.com/QAD/C799).

ISI, ESS, and PSQI did not observe significant associations with CVR scores and single cardiovascular risk factors, thereby one model per each scale was run. Depression (aOR = 6.69, $P < 0.001$), anxiety (aOR = 2.40, $P < 0.001$) and being on drugs with potential side effects on sleep-wake cycle (aOR = 2.06, $P = 0.015$) were the only factors independently associated with increased likelihood of alterations at ISI (Table 2, Supplemental Digital Content, http://links.lww.com/QAD/C799). Similarly, depression (aOR = 7.61, $P < 0.001$) and anxiety (aOR = 2.22, $P < 0.001$), and other routes of HIV acquisition (different from sexual intercourse and intravenous drug use; aOR = 0.19, $P = 0.030$) were the only factors independently associated with PSQI results (Table 3, Supplemental Digital Content, http://links.lww.com/QAD/C799). Lastly, higher likelihood of altered ESS results independently associated with increasing number of non-antiretroviral drugs (aOR = 1.12, $P = 0.037$) and OD/MOUDs use only (aOR = 2.56, $P = 0.042$; Table 4, Supplemental Digital Content, http://links.lww.com/QAD/C799).

Subgroup analyses according to mood disorders and type of antiretroviral regimens

After restricting the unadjusted and adjusted ORs calculation for SDs to participants without MDs only ($n = 482$), similar findings were observed for ISI and PSQI questionnaires (data not shown). Similarly, the factors that associated with BQ outcome in the whole study population were confirmed in this subgroup, but for Framingham risk at 10 years (aOR 1.79 [0.94–3.42], $P = 0.078$ and aOR 2.13 [0.97–4.72], $P = 0.061$ for medium and high risk versus low risk, respectively) and DAD-10F that did no more independently associate with BQ outcome (aOR 1.53 [0.80–2.94], $P = 0.198$ and aOR 1.73 [0.79–3.80], $P = 0.175$ for medium and high risk versus low, respectively) (data not shown). No subgroup analysis was performed for participants with altered ESS and no MDs ($n = 35$).

As confirmation of the null association between SDs and antiretroviral classes observed in the previous analyses, we also compared the median scores of SDs scales according to different classification of ART regimens (DTG/EFV-based vs. BIC-based vs. others, as shown in Fig. 1; DTG/EFV-based vs. others; dual regimens vs. protease inhibitors+nucleos(t)ide reverse transcriptase inhibitors (PI-NRTIs) vs. integrase inhibitors+NRTIs (INI-NRTIs) vs. non-nucleos(t)ide reverse transcriptase inhibitor+NRTIs (NNRTI-NRTIs) vs. four or more drugs regimens) in the whole study population as well as in the subgroup of participants without MDs: no difference in SDs score were observed in any comparison (data not shown).

Factor analysis

The four SDs scales presented fair-to-moderate reciprocal correlations, therefore we proceeded with factor analysis that identified two components: factor 1 clustered ISI and PSQI score, whereas factor 2 identified as cluster BQ and ESS scores, as shown in Table 2.

We thereby run univariate linear regression models for the regression coefficients resulting by the identified

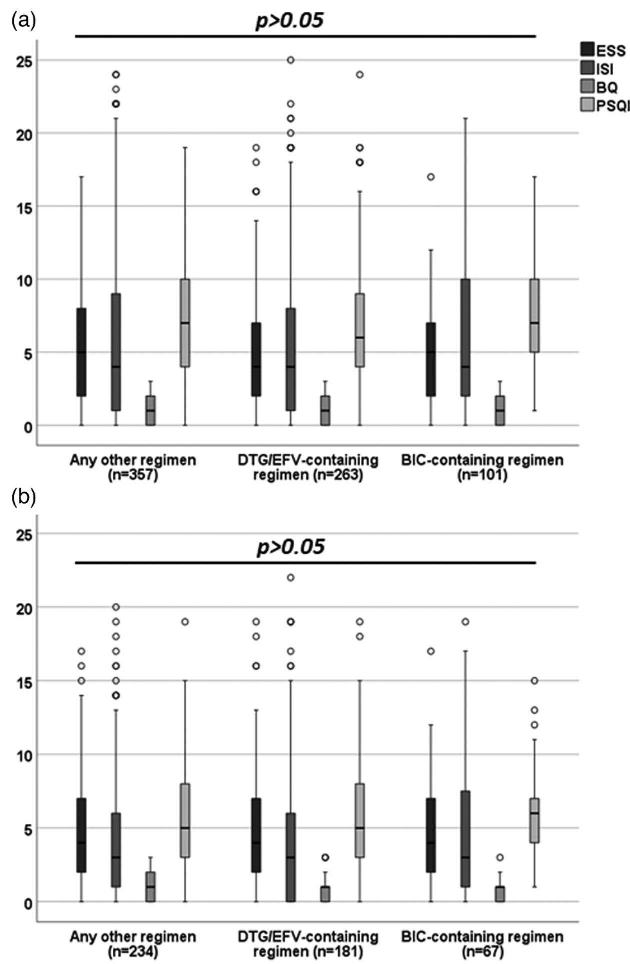

Fig. 1. Comparison of the scores at the four questionnaires assessing sleep disorders between participants on DTG/EFV-based regimens versus BIC-based regimens versus any other antiretroviral regimen, in the whole study population (panel a) and in the subgroup of participants without mood disorders (panel b).

Table 2. Correlations among the scores of PSQI, ISI, BQ and ESS scale and components identified by factor analysis.

	ISI	BQ	PSQI
ESS	ρ 0.111 $P=0.001$	ρ 0.215 $P<0.001$	ρ 0.082 $P=0.014$
ISI	–	ρ 0.120 $P=0.001$	ρ 0.716 $P<0.001$
BQ	–	–	ρ 0.099 $P=0.004$
Factors	Scores of the sleep disorders scales and corresponding loading value[a]		
Factor 1	ISI score 0.92 + PSQI score 0.93		
Factor 2	BQ score 0.77 + ESS score 0.78		

BQ, Berlin Questionnaire; ESS, Epworth Sleepiness Scale; ISI, Insomnia Severity Index.
[a]The loading value represents magnitude of correlation of variables with the factor.

factors, and the results are shown in Table 5, Supplemental Digital Content, http://links.lww.com/QAD/C799. Multivariable linear regression models for factor one and factor two are shown in Table 3. Specifically, after dimension reduction, the variables that were independently associated with increasing (worse) scores at both ISI and PSQI were increasing (worse) score at PHQ-9 (depression, $a\beta$ 0.105, $P<0.001$) and at GAD-7 (anxiety, $a\beta$ 0.031, $P<0.001$) only. Conversely, the variables that were independently associated with increasing (worse) scores at both BQ and ESS were increasing score at PHQ-9 ($a\beta$ 0.026, $P=0.014$), higher BMI values ($a\beta$ 0.046, $P<0.001$) and hypertension ($a\beta$ 0.38, $P<0.001$).

Further models for factor 2 included CVR scores: Framingham score instead of age, dyslipidaemia, hypertension, cardiovascular events and diabetes; DAD-10 R or F instead of age, diabetes, dyslipidaemia, and hypertension. The first model confirmed the independent association of depression, BMI, and of Framingham score [$a\beta$ 0.008 (0.001;0.017), $P=0.048$], the second and the third models observed an independent association of depression and BMI, but not with DAD-10 scores (data not shown).

Discussion

The present study highlighted that sleep disorders are a very common problem in PWH, with an overall prevalence of 77%. Over 60% of participant reported low sleep quality and over 30% of patients suffered from insomnia or obstructive sleep apnoea.

Table 3. Multivariable linear regression models for factor one (ISI and PSQI scores) and factor two (BQ and ESS scores).

Covariate	$a\beta$ (95%CI)	P value
Factor 1 (ISI and PSQI scores)		
Age, per year more	0.002 (−0.004; 0.009)	0.440
GAD-7 score, per unit more	0.031 (0.015; 0.047)	***<0.001***
PHQ-9 score, per unit more	0.105 (0.087; 0.122)	***<0.001***
Positive HCV-RNA (ref. none)	0.199 (−0.086; 0.485)	0.171
Smoking (ref. none)	0.095 (−0.028; 0.217)	0.129
Physical activity (ref. none)	−0.118 (−0.253; 0.018)	0.090
Alcohol use disorders (ref. none)	0.086 (−0.131: 0.303)	0.438
COPD (ref. none)	0.069 (−0.204; 0.343)	0.619
Number of comorbidities per patient, per unit more	−0.028 (−0.068; 0.012)	0.167
OUD/MOUDs use (ref. none)	0.070 (−0.245; 0.386)	0.662
Drugs affecting sleep−wake cycle (ref. none)	0.152 (−0.058; 0.361)	0.155
Number of non-antiretroviral drugs, per unit more	0.007 (−0.027; 0.042)	0.670
Factor 2 (BQ and ESS scores)		
Age, per year more	0.000 (−0.008; 0.008)	0.955
GAD-7 score, per unit more	0.008 (−0.011; 0.027)	0.423
PHQ-9 score, per unit more	0.026 (0.005; 0.047)	***0.014***
Length of HIV infection, per year more	0.004 (−0.004; 0.012)	0.308
Dyslipidaemia (ref. none)	0.003 (−0.176; 0.182)	0.974
Alcohol use disorders (ref. none)	0.231 (−0.015; 0.477)	0.065
Cardiovascular events (ref. none)	0.088 (−0.227; 0.402)	0.583
Hypertension (ref. none)	0.385 (0.207; 0.564)	***<0.001***
Cirrhosis (ref. none)	0.325 (−0.078; 0.729)	0.114
Diabetes mellitus (ref. none)	0.060 (−0.198; 0.319)	0.648
BMI, per unit more	0.046 (0.030; 0.061)	***<0.001***
Number of comorbidities per patient, per unit more	−0.006 (−0.061; 0.049)	0.826
Number of non-antiretroviral drugs, per unit more	−0.001 (−0.040; 0.038)	0.963

BMI, body mass index; BQ, Berlin Questionnaire; COPD, chronic obstructive pulmonary disease; ESS, Epworth Sleepiness Scale; GAD-7, General Anxiety Disorder-7; ISI, Insomnia Severity Index; OUD/MOUDs, medications for opioid use disorders; PHQ-9, Patient Health Questionnaire-9.

Results of our study confirmed associations between BQ and elevated cardiovascular risk. Although insomnia and poor sleep quality have not been associated with increased cardiovascular risk in our cohort.

ISI and PSQI results are instead more sleep focused. Indeed, the first one includes both a psychological and a pharmacological component, while the second one seems more psychologically driven. ESS in our population seemed to be more like an iatrogenic problem rather than a manifestation of mood disorders or anything else since our analyses showed a significant correlation with polypharmacy.

Despite an excellent viro-immunological profile and excellent tolerance to antiretrovirals, which were not associated with sleep disturbances, our population reaching the 95–95–95 UNAIDS target still maintain a very high prevalence of sleep disturbances, greater than the general population (as shown by literature), and with a potential significant effect on quality of life. The main drivers of the problem remain mood disorders, and the iatrogenic effects of drugs other than antiretroviral ones (warning on opioids, methadone/buprenorphine and all drugs with psychotropic effects that could identify pop targets to be screened for sleep disorders). Possible underlying mechanisms such as inflammation/chronic immune activation and microbial translocation could play a role, even if our study design is not able to clear this query.

Our data, compared to what has been previously reported in PWH, showed some similarities and discrepancies. They appeared to be fairly in line with the prevalence studies of SD. A meta-analysis from 2015 (including 9246 patients), found an overall prevalence of self-reported poor-quality sleep of 58% [62]. This prevalence appeared to be slightly lower in a French study involving 1354 patients, in which poor sleep quality was reported by 47% of participants [63]. Similarly, an English study [12], conducted on a population of about 250 MSM, found a low quality of sleep in a similar measure to that found in the French study by Allavena *et al.* [63], but lower than that found in our study.

By contrast, in the study conducted by Milinkovic *et al.* [12], the prevalence of insomnia was lower than that detected in our cohort (22% vs. 31.3%) and excessive daytime sleepiness was significantly higher (21% vs. 7.9%). These discrepancies can be attributed in the first instance to a substantial difference in the demographic and clinical characteristics of the two populations. Indeed, PWH recruited by Milinkovic *et al.* [12] were almost all MSM with a high prevalence of chemsex use, a practice which is correlated with excessive daytime sleepiness. In our cohort instead we had 30% of women and use of drugs was reported by 10% participants.

Our analyses showed a correlation between sleep breathing disorders (in particular obstructive apnoea) with age, BMI, hypertension, depression and with higher cardiovascular risk. This is in line with what has been demonstrated in the general population. An Indian study conducted on 182 patients has shown that there is a correlation between BMI, depressive symptoms, and sleep apnoea, especially in women [64]. In our study, we did not detect any correlations between SD and gender, this might be due to the small number of women recruited (about 30%). Sleep disorders and sleep irregularity in timing and duration have been also associated with a high cardiometabolic risk and myocardial infarction [65–68]. Moreover, SD affects the individual capability of performing regular exercise and a healthy diet [69,70]. This may further increase the cardiovascular risk.

Interestingly, in our cohort nearly 50% of people who reported insomnia also reported eating meals or snacks overnight. This may contribute to increase the risk of weight gain and cardiometabolic complications.

An American study found that obstructive sleep apnoea syndrome is due to the concomitance of several factors, such as depression and obesity, rather than the presence of a single alteration [71]. The authors also demonstrate how the presence of daytime sleepiness (detected in our sample in 7.9% of participants) is a predictor of depressive syndrome in patients with obstructive sleep apnoea (OSA), regardless of the apnoea/hypopnea index and peripheral saturation values detected during polysomnography [71]. Furthermore, in the same study, the observation that obesity correlates with depression, also through the interaction of psychobiological mechanisms, and that excessive daytime sleepiness can be both an effect of apnoea, but also a symptom of onset of depression. Regarding the apnoea-hypertension association, a meta-analysis somewhat dated [72], has highlighted how OSA is a secondary cause of hypertension, since the same episodes of apnoea produce, through the stimulation of the system sympathetic, blood pressure peaks during the night. This effect persists in patients even during the day time, when breathing 'normalizes' [73]. These phenomena inevitably lead to progressive increase in cardiovascular risk over time. In the literature, there are not many data that clearly demonstrate these correlations in people with HIV, as the phenomenon is little and only recently being studied. An American study conducted in 2015, showed that although patients with HIV more frequently complain of symptoms associated with apnoea, such as fatigue and chronic fatigue, they are less likely to be diagnosed with OSA [44]. Furthermore, compared to the general population, people with HIV appear to develop OSA earlier, with lower BMI values and less frequent hypertension.

Our data confirmed the correlation of insomnia to ISI and poor sleep quality to PSQI both with the presence of depressive disorder at PHQ9 and with the presence of anxiety disorder at GAD-7, similarly to what has already

been demonstrated by numerous studies in about it and, more recently, by Milinkovic *et al*. [12]. Furthermore, the use of intravenous drugs, compared to other risk factors for acquiring HIV infection, correlates with the presence of these disorders. In the general population, sleep disturbances are frequently reported among recreational drug users and alcohol disorder users in 25–72% of cases [15,75–77]. In this category, the persistence of sleep disturbances after cessation of alcohol and recreational drug use is the main risk factor for relapse, particularly for alcohol and opioids [78,79].

Surprisingly, we found no significant correlation between sleep disturbances and antiretroviral drug choice, differently to data reported for dolutegravir and efavirenz, nor for specific HIV related factors, except for current $CD4^+$ T-cell count which were found to be a relevant parameter for the quality of sleep. The reasons for this correlation remain to be explored, although it can be hypothesized that a good maintenance of immunological functions contributes to generating a good quality of sleep. In the general population the link between sleep and immunity has been established. In a systematic review, Besedovsky *et al*. [80] summarized the mechanisms by which changes in the immune system alter sleep and vice versa. The stimulation of the immune system by various inflammatory triggers such as insults against the intestinal microbiota, can cause important sleep disturbances. Alterations of the intestinal microbiota are always present in patients with HIV infection and are at the basis of the mechanisms that perpetrate the state of chronic inflammation [81].

There are no correlations with specific factors related to HIV, except for the increased $CD4^+$ T-cell count in the altered quality of sleep. This somewhat unexpected finding is confirmed in a study conducted on 139 South African PWHs, where the same association emerges: it was assumed that this may be related to an underlying immune activation, which affects the quality of sleep [82].

Our study limitations are the lack of follow-up and the lack of supportive evaluations with objective techniques to better define the presence of sleep disorders (e.g., actigraphy and polysomnography).

In conclusion, our study highlighted the high prevalence of SD in PWH, and their close association with psychiatric disorders such as depression and anxiety, as well as an increased cardiovascular risk. In order not to underestimate SD, psychiatric disorders, and other related issues, with the aim of improving the quality of life of PWH, we suggest that the assessment of both sleep and mood disorders in this population should be investigated once a year (for mood disorder, the screening is already suggested by guidelines, but unfortunately poorly applied in clinical practice). Moreover, sleep health and SD assessment should be included as factors significantly contributing to maintain cardiovascular and metabolic health. We believe that, in the light of these results, it would be advisable to consider the possibility of setting up a dedicated service, with a multidimensional medical (including sleep experts) and psychological support [74].

Acknowledgements

We really want to thank all the participants in this study each PWH who kindly accepted to openly shared with us their feelings and experiences.

Funding source: This study did not receive any funding from public or private agencies.

Data sharing: De-identified data are available on reasonable request.

Contributors: M.M. conceived and conceptualized the study. M.T. performed statistical analysis. M.M., E.C., L. S., and D.L. recruited participants. M.S., R.C., I.C., P.B., C.G.Q.R., G.F., and V.S. curated and collected the data. MM and AMC were responsible for the methods and verification of data. AMC supervised the project. M.M., M.T., A.M., and A.M.C. wrote the original draft of the manuscript. All authors reviewed, approved the final version of the manuscript, and by having access to all the data had final responsibility for the decision to submit this paper for publication.

Conflicts of interest

There are no conflicts of interest.

References

1. Zielinski MR, McKenna JT, McCarley RW. **Functions and mechanisms of sleep.** *AIMS Neurosci* 2016; **3**:67–104.
2. Alhola P, Polo-Kantola P. **Sleep deprivation: impact on cognitive performance.** *Neuropsychiatr Dis Treat* 2007; **3**:553–567.
3. Covassin N, Singh P. **Sleep duration and cardiovascular disease risk: epidemiologic and experimental evidence.** *Sleep Med Clin* 2016; **11**:81–89.
4. Smiley A, King D, Bidulescu A. **The association between sleep duration and metabolic syndrome: the NHANES 2013/2014.** *Nutrients* 2019; **11**:2582.
5. Ram S, Seirawan H, Kumar SK, Clark GT. **Prevalence and impact of sleep disorders and sleep habits in the United States.** *Sleep Breath* 2010; **14**:63–70.
6. Ford DE, Kamerow DB. **Epidemiologic study of sleep disturbances and psychiatric disorders. An opportunity for prevention?** *JAMA* 1989; **262**:1479–1484.
7. Quera-Salva MA, Orluc A, Goldenberg F, Guilleminault C. **Insomnia and use of hypnotics: study of a French population.** *Sleep* 1991; **14**:386–391.
8. Ohayon MM. **Prevalence and comorbidity of sleep disorders in general population.** *Rev Prat* 2007; **57**:1521–1528.
9. Gamaldo CE, Gamaldo A, Creighton J, Salas RE, Selnes OA, David PM, *et al*. **Evaluating sleep and cognition in HIV.** *J Acquir Immune Defic Syndr* 2013; **63**:609–616.

10. Gamaldo CE, Spira AP, Hock RS, Salas RE, McArthur JC, David PM, *et al*. **Sleep, function and HIV: a multimethod assessment.** *AIDS Behav* 2013; **17**:2808–2815.
11. Chaponda M, Aldhouse N, Kroes M, Wild L, Robinson C, Smith A. **Systematic review of the prevalence of psychiatric illness and sleep disturbance as co-morbidities of HIV infection in the UK.** *Int J STD AIDS* 2018; **29**:704–713.
12. Milinkovic A, Singh S, Simmons B, Pozniak A, Boffito M, Nwokolo N. **Multimodality assessment of sleep outcomes in people living with HIV performed using validated sleep questionnaires.** *Int J STD AIDS* 2020; **31**:996–1003.
13. Patterson F, Connick E, Brewer B, Grandner MA. **HIV status and sleep disturbance in college students and relationship with smoking.** *Sleep Health* 2019; **5**:395–400.
14. Duko B, Ayalew M, Ayano G. **The prevalence of alcohol use disorders among people living with HIV/AIDS: a systematic review and meta-analysis.** *Subst Abuse Treat Prev Policy* 2019; **14**:52.
15. Stein MD, Friedmann PD. **Disturbed sleep and its relationship to alcohol use.** *Subst Abus* 2005; **26**:1–13.
16. Gutierrez J, Tedaldi EM, Armon C, Patel V, Hart R, Buchacz K. **Sleep disturbances in HIV-infected patients associated with depression and high risk of obstructive sleep apnea.** *SAGE Open Med* 2019; **7**:2050312119842268.
17. Fekete EM, Williams SL, Skinta MD. **Internalised HIV-stigma, loneliness, depressive symptoms and sleep quality in people living with HIV.** *Psychol Health* 2018; **33**:398–415.
18. Bedaso A, Abraham Y, Temesgen A, Mekonnen N. **Quality of sleep and associated factors among people living with HIV/AIDS attending ART clinic at Hawassa University comprehensive specialized Hospital, Hawassa, SNNPR, Ethiopia.** *PLoS One* 2020; **15**:e0233849.
19. Chambers LA, Rueda S, Baker DN, Wilson MG, Deutsch R, Raeifar E, *et al*. **Stigma, HIV and health: a qualitative synthesis.** *BMC Public Health* 2015; **15**:848.
20. Zareifopoulos N, Lagadinou M, Karela A, Pouliasi F, Economou I, Tsigkou A, *et al*. **Efavirenz as a psychotropic drug.** *Eur Rev Med Pharmacol Sci* 2020; **24**:10729–10735.
21. Shikuma CM, Kohorn L, Paul R, Chow DC, Kallianpur KJ, Walker M, *et al*. **Sleep and neuropsychological performance in HIV+ subjects on efavirenz-based therapy and response to switch in therapy.** *HIV Clin Trials* 2018; **19**:139–147.
22. Gallego L, Barreiro P, del Rio R, Gonzalez de Requena D, Rodriguez-Albarino A, Gonzalez-Lahoz J, *et al*. **Analyzing sleep abnormalities in HIV-infected patients treated with Efavirenz.** *Clin Infect Dis* 2004; **38**:430–432.
23. Abers MS, Shandera WX, Kass JS. **Neurological and psychiatric adverse effects of antiretroviral drugs.** *CNS Drugs* 2014; **28**:131–145.
24. Hoffmann C, Llibre JM. **Neuropsychiatric adverse events with dolutegravir and other integrase strand transfer inhibitors.** *AIDS Rev* 2019; **21**:4–10.
25. Capetti AF, Di Giambenedetto S, Latini A, Sterrantino G, De Benedetto I, Cossu MV, *et al*. **Morning dosing for dolutegravir-related insomnia and sleep disorders.** *HIV Med* 2018; **19**:e62–e63.
26. Elliot ER, Wang X, Singh S, Simmons B, Vera JH, Miller RF, *et al*. **Increased dolutegravir peak concentrations in people living with human immunodeficiency virus aged 60 and over, and analysis of sleep quality and cognition.** *Clin Infect Dis* 2019; **68**:87–95.
27. Fettiplace A, Stainsby C, Winston A, Givens N, Puccini S, Vannappagari V, *et al*. **Psychiatric symptoms in patients receiving dolutegravir.** *J Acquir Immune Defic Syndr* 2017; **74**:423–431.
28. Molina JM, Ward D, Brar I, Mills A, Stellbrink HJ, Lopez-Cortes L, *et al*. **Switching to fixed-dose bictegravir, emtricitabine, and tenofovir alafenamide from dolutegravir plus abacavir and lamivudine in virologically suppressed adults with HIV-1: 48 week results of a randomised, double-blind, multicentre, active-controlled, phase 3, noninferiority trial.** *Lancet HIV* 2018; **5**:e357–e365.
29. Taibi DM. **Sleep disturbances in persons living with HIV.** *J Assoc Nurses AIDS Care* 2013; **24 (1 Suppl)**:S72–85.
30. Omonuwa TS, Goforth HW, Preud'homme X, Krystal AD. **The pharmacologic management of insomnia in patients with HIV.** *J Clin Sleep Med* 2009; **5**:251–262.
31. Rogers BG, Bainter SA, Smith-Alvarez R, Wohlgemuth WK, Antoni MH, Rodriguez AE, *et al*. **Insomnia, health, and health-related quality of life in an urban clinic sample of people living with HIV/AIDS.** *Behav Sleep Med* 2021; **19**:516–532.
32. Hemar V, Hessamfar M, Neau D, Vareil MO, Rouanes N, Lazaro E, *et al*. **A comprehensive analysis of excess depressive disorder in women and men living with HIV in France compared to the general population.** *Sci Rep* 2022; **12**:6364.
33. Ickovics JR, Hamburger ME, Vlahov D, Schoenbaum EE, Schuman P, Boland RJ, *et al*. **Mortality, CD4 cell count decline, and depressive symptoms among HIV-seropositive women: longitudinal analysis from the HIV Epidemiology Research Study.** *JAMA* 2001; **285**:1466–1474.
34. Wong C, Gange SJ, Moore RD, Justice AC, Buchacz K, Abraham AG, *et al*. **Multimorbidity among persons living with human immunodeficiency virus in the United States.** *Clin Infect Dis* 2018; **66**:1230–1238.
35. Polanka BM, Kundu S, So-Armah KA, Freiberg MS, Gupta SK, Zapolski TCB, *et al*. **Insomnia symptoms and biomarkers of monocyte activation, systemic inflammation, and coagulation in HIV: Veterans Aging Cohort Study.** *PLoS One* 2021; **16**: e0246073.
36. Wibbeler T, Reichelt D, Husstedt IW, Evers S. **Sleepiness and sleep quality in patients with HIV infection.** *J Psychosom Res* 2012; **72**:439–442.
37. Chen YC, Lin CY, Li CY, Zhang Y, Ko WC, Ko NY. **Obstructive sleep apnea among HIV-infected men in the highly active antiretroviral therapy era: a nation-wide longitudinal cohort study in Taiwan, 2000-2011.** *Sleep Med* 2020; **65**:89–95.
38. Asgari S, Najafi A, Sadeghniiat K, Gholamypour Z, Akbarpour S. **The association between body mass index and risk of obstructive sleep apnea among patients with HIV.** *J Res Med Sci* 2021; **26**:123.
39. Alikhani M, Ebrahimi A, Farnia V, Khazaie H, Radmehr F, Mohamadi E, *et al*. **Effects of treatment of sleep disorders on sleep, psychological and cognitive functioning and biomarkers in individuals with HIV/AIDS and under methadone maintenance therapy.** *J Psychiatr Res* 2020; **130**:260–272.
40. Schulz R, Lohmeyer J, Seeger W. **Obstructive sleep apnea due to HIV-associated lipodystrophy.** *Clin Infect Dis* 2003; **37**:1398–1399.
41. Chen YC, Chen CC, Strollo PJJr, Li CY, Ko WC, Lin CY, *et al*. **Differences in sleep disorders between hiv-infected persons and matched controls with sleep problems: a matched-cohort study based on laboratory and survey data.** *J Clin Med* 2021; **10**:5206.
42. Patil SP, Brown TT, Jacobson LP, Margolick JB, Laffan A, Johnson-Hill L, *et al*. **Sleep disordered breathing, fatigue, and sleepiness in HIV-infected and -uninfected men.** *PLoS One* 2014; **9**:e99258.
43. Njoh AAMEN, Mbi VO, Mengnjo MK, Nfor LN, Ngarka L, Chokote SE, *et al*. **Likelihood of obstructive sleep apnea in people living with HIV in Cameroon – preliminary findings.** *Sleep Sci Pract* 2017; **1**:2925.
44. Goswami U, Baker JV, Wang Q, Khalil W, Kunisaki KM. **Sleep apnea symptoms as a predictor of fatigue in an urban HIV clinic.** *AIDS Patient Care STDS* 2015; **29**:591–596.
45. Johns MW. **A new method for measuring daytime sleepiness: the Epworth sleepiness scale.** *Sleep* 1991; **14**:540–545.
46. Bastien CH, Vallieres A, Morin CM. **Validation of the Insomnia Severity Index as an outcome measure for insomnia research.** *Sleep Med* 2001; **2**:297–307.
47. Buysse DJ, Reynolds CF 3rd, Monk TH, Berman SR, Kupfer DJ. **The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research.** *Psychiatry Res* 1989; **28**:193–213.
48. Backhaus J, Junghanns K, Broocks A, Riemann D, Hohagen F. **Test-retest reliability and validity of the Pittsburgh Sleep Quality Index in primary insomnia.** *J Psychosom Res* 2002; **53**:737–740.
49. Curcio G, Tempesta D, Scarlata S, Marzano C, Moroni F, Rossini PM, *et al*. **Validity of the Italian version of the Pittsburgh Sleep Quality Index (PSQI).** *Neurol Sci* 2013; **34**:511–519.
50. Netzer NC, Stoohs RA, Netzer CM, Clark K, Strohl KP. **Using the Berlin Questionnaire to identify patients at risk for the sleep apnea syndrome.** *Ann Intern Med* 1999; **131**:485–491.
51. Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. **The fatigue severity scale. Application to patients with multiple sclerosis**

and systemic lupus erythematosus. *Arch Neurol* 1989; **46**:1121–1123.
52. Spitzer RL, Kroenke K, Williams JB, Lowe B. **A brief measure for assessing generalized anxiety disorder: the GAD-7.** *Arch Intern Med* 2006; **166**:1092–1097.
53. Kroenke K, Spitzer RL, Williams JB. **The PHQ-9: validity of a brief depression severity measure.** *J Gen Intern Med* 2001; **16**:606–613.
54. Croston M, Petrak J, Ustianowski A. **Use of the wellness thermometer to improve consultations for patients with human immunodeficiency virus.** *Nurs Stand* 2017; **31**:46–53.
55. D'Agostino RBSr, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, *et al*. **General cardiovascular risk profile for use in primary care: the Framingham Heart Study.** *Circulation* 2008; **117**:743–753.
56. Friis-Moller N, Ryom L, Smith C, Weber R, Reiss P, Dabis F, *et al*. **An updated prediction model of the global risk of cardiovascular disease in HIV-positive persons: the Data-collection on Adverse Effects of Anti-HIV Drugs (D:A:D) study.** *Eur J Prev Cardiol* 2016; **23**:214–223.
57. WHO guidelines on physical activity and sedentary behaviour. 2020. Geneva: World Health Organization. Available at: https://www.who.int/publications/i/item/9789240015128 [Accessed 31 October 2022].
58. World Health Organization. Health topics /alcohol. Available at: https://www.who.int/health-topics/alcohol [Accessed 31 October 2022].
59. Beezer J, Al Hatrushi M, Husband A, Kurdi A, Forsyth P. **Polypharmacy definition and prevalence in heart failure: a systematic review.** *Heart Fail Rev* 2022; **27**:465–492.
60. Johnston MC, Crilly M, Black C, Prescott GJ, Mercer SW. **Defining and measuring multimorbidity: a systematic review of systematic reviews.** *Eur J Public Health* 2019; **29**:182–189.
61. Centers for Disease Control and Prevention. How much sleep do i need? Available at: https://www.cdc.gov/sleep/about_sleep/how_much_sleep.html. [Accessed 31 October 2022].
62. Wu J, Wu H, Lu C, Guo L, Li P. **Self-reported sleep disturbances in HIV-infected people: a meta-analysis of prevalence and moderators.** *Sleep Med* 2015; **16**:901–907.
63. Allavena C, Guimard T, Billaud E, de la Tullaye S, Reliquet V, Pineau S, *et al*. **Prevalence and risk factors of sleep disturbances in a large HIV-infected adult population.** *J Int AIDS Soc* 2014; **17 (Suppl 3)**:19576.
64. Shoib S, Malik JA, Masoodi S. **Depression as a manifestation of obstructive sleep apnea.** *J Neurosci Rural Pract* 2017; **8**:346–351.
65. St-Onge MP, Grandner MA, Brown D, Conroy MB, Jean-Louis G, Coons M, *et al*. **Sleep duration and quality: impact on lifestyle behaviors and cardiometabolic health: a scientific statement from the American Heart Association.** *Circulation* 2016; **134**:e367–e386.
66. Huang T, Mariani S, Redline S. **Sleep irregularity and risk of cardiovascular events: the multi-ethnic study of atherosclerosis.** *J Am Coll Cardiol* 2020; **75**:991–999.
67. Wallace ML, Buysse DJ, Redline S, Stone KL, Ensrud K, Leng Y, *et al*. **Multidimensional sleep and mortality in older adults: a machine-learning comparison with other risk factors.** *J Gerontol A Biol Sci Med Sci* 2019; **74**:1903–1909.
68. Huang T, Redline S. **Cross-sectional and prospective associations of actigraphy-assessed sleep regularity with metabolic abnormalities: the multi-ethnic study of atherosclerosis.** *Diabetes Care* 2019; **42**:1422–1429.
69. Frank S, Gonzalez K, Lee-Ang L, Young MC, Tamez M, Mattei J. **Diet and sleep physiology: public health and clinical implications.** *Front Neurol* 2017; **8**:393.
70. Kline CE. **The bidirectional relationship between exercise and sleep: Implications for exercise adherence and sleep improvement.** *Am J Lifestyle Med* 2014; **8**:375–379.
71. LaGrotte C, Fernandez-Mendoza J, Calhoun SL, Liao D, Bixler EO, Vgontzas AN. **The relative association of obstructive sleep apnea, obesity and excessive daytime sleepiness with incident depression: a longitudinal, population-based study.** *Int J Obes (Lond)* 2016; **40**:1397–1404.
72. Dopp JM, Reichmuth KJ, Morgan BJ. **Obstructive sleep apnea and hypertension: mechanisms, evaluation, and management.** *Curr Hypertens Rep* 2007; **9**:529–534.
73. Narkiewicz K, van de Borne PJ, Cooley RL, Dyken ME, Somers VK. **Sympathetic activity in obese subjects with and without obstructive sleep apnea.** *Circulation* 1998; **98**:772–776.
74. Brower KJ, Perron BE. **Sleep disturbance as a universal risk factor for relapse in addictions to psychoactive substances.** *Med Hypotheses* 2010; **74**:928–933.
75. Brower KJ. **Insomnia alcoholism and relapse.** *Sleep Med Rev* 2003; **7**:523–539.
76. Colrain IM, Turlington S, Baker FC. **Impact of alcoholism on sleep architecture and EEG power spectra in men and women.** *Sleep* 2009; **32**:1341–1352.
77. Currie SR, Clark S, Rimac S, Malhotra S. **Comprehensive assessment of insomnia in recovering alcoholics using daily sleep diaries and ambulatory monitoring.** *Alcohol Clin Exp Res* 2003; **27**:1262–1269.
78. Hornyak M, Haas P, Veit J, Gann H, Riemann D. **Magnesium treatment of primary alcohol-dependent patients during subacute withdrawal: an open pilot study with polysomnography.** *Alcohol Clin Exp Res* 2004; **28**:1702–1709.
79. Babson KA, Boden MT, Harris AH, Stickle TR, Bonn-Miller MO. **Poor sleep quality as a risk factor for lapse following a cannabis quit attempt.** *J Subst Abuse Treat* 2013; **44**:438–443.
80. Besedovsky L, Lange T, Haack M. **The sleep-immune crosstalk in health and disease.** *Physiol Rev* 2019; **99**:1325–1380.
81. Lozupone CA, Li M, Campbell TB, Flores SC, Linderman D, Gebert MJ, *et al*. **Alterations in the gut microbiota associated with HIV-1 infection.** *Cell Host Microbe* 2013; **14**:329–339.
82. Redman KN, Karstaedt AS, Scheuermaier K. **Increased CD4 counts, pain and depression are correlates of lower sleep quality in treated HIV positive patients with low baseline CD4 counts.** *Brain Behav Immun* 2018; **69**:548–555.