

Physical Activity and Cognitive Health Among People Living With HIV: An Integrative Review

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Abstract

The purpose of our review was to analyze evidence related to physical activity (PA) and cognitive health in people living with HIV (PLWH), appraise psychometric characteristics of study measures, and calculate effect sizes. A computerized database search of the literature published between 1996 and 2017 was examined for correlational and observational studies that included a sample of PLWH, measured PA, and measured cognitive health. Seven articles met the sampling criteria. Of which, six studies used a cross-sectional design; one used a longitudinal design. All but one found significant positive associations between PA and cognitive health in PLWH. Four studies showed a moderate to high effect for PA on cognitive function (Cohen's *d* values = 0.45–0.58). None reported sample-specific reliability and validity estimates for PA and cognitive health instruments. PA is a modifiable factor that may delay the onset of cognitive impairment and decline among PLWH.

Key words: cognition, exercise, HIV, integrative review, PLWH

wing to advances in the efficacy of combination antiretroviral therapy (cART), HIV infection has transitioned from a fatal illness to a chronic, manageable condition that affects an estimated 1.1 million people in the United States (Centers for Disease Control and Prevention, 2019). Although cART has been effective in decreasing HIV-related mortalities, people living with HIV (PLWH) show a higher prevalence of comorbidities compared with their uninfected counterparts (Maciel, Klück, Durand, & Sprinz, 2018). These comorbidities include cardiovascular disease (Duprez et al., 2012), hypertension (Medina-Torne, Ganesan, Barahona, & Crum-Cianflone, 2012), diabetes (Butt et al., 2009), kidney failure (Winston et al., 2008), and HIV-related cognitive impairment (Watkins & Treisman, 2015).

HIV-related cognitive impairment is of particular concern because it can significantly limit self-care abilities needed to manage HIV infection and its sequelae (Watkins & Treisman, 2015). HIV-related cognitive impairment is associated with chronic systemic inflammation (Saylor & Sacktor, 2016), which has been

found to be reduced with physical activity (PA; Jarvie, Whooley, Regan, Sin, & Cohen, 2014). Regular engagement in PA may have protective effects against the onset and progression of HIV-related cognitive impairment. Thus, incorporating PA into HIV treatment plans could improve cognitive health outcomes for PLWH.

Although research has found an association between PA and cognitive function in PLWH, the psychometric properties of the study instruments and effect size findings have not been widely reported (Quigley, O'Brien, Parker, & MacKay-Lyons, 2018), thus limiting conclusions about the strength and validity of the exposure/ outcome relationship. Therefore, the purpose of our review was to (a) critically analyze evidence related to PA and cognitive health in HIV infection, (b) appraise psychometric characteristics of study measures, and (c) calculate the effect sizes and advance evidence-based practice and research implications.

Background

HIV-related cognitive impairment, also known as HIV-associated neurocognitive disorder (HAND), is caused by HIV dissemination to the brain with subsequent activation of neurotoxic signaling pathways that alter brain function (Ragin et al., 2015). It is estimated to affect approximately 50% of PLWH (Saylor & Sacktor, 2016) and disproportionately affect African American and Latino PLWH (Mindt et al., 2008; Tedaldi, Minniti, & Fischer, 2015). HAND is associated with deficits in memory, attention span, problem-solving, and reasoning skills and slower speed in performing activities of

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*Corresponding author: Barbara Swanson, e-mail: barbara_a_swanson@rush.edu Copyright © 2019 Association of Nurses in AIDS Care http://dx.doi.org/10.1097/JNC.00000000000141 daily living (Vance, Fazeli, & Gakumo, 2013). Although HAND can affect five cognitive domains (memory, executive function, attention, language and communication, and sensory/motor function), only two domains have to be affected to meet diagnostic criteria for HAND (Vance et al., 2013). Risk factors for HAND are multifactorial, including low CD4⁺ T-lymphocyte count and depression (Heaton et al., 2010), diabetes (Sanmarti et al., 2014), lower education level (Winston et al., 2013), higher viral load (Saylor & Sacktor, 2016), and older age (Fazeli et al., 2014).

HIV-associated dementia consists of moderate to severe neurocognitive impairment in two or more cognitive domains and typically manifests on neuropsychological testing as difficulty learning new information, decreased information processing, and deficits in attention and concentration (Sanmarti et al., 2014). Although cART has substantially reduced the prevalence of HIVassociated dementia, milder forms of impairment, including mild dysfunction in at least two cognitive domains with and without observable functional impairment, persist (Sanmarti et al., 2014). Despite simpler cART regimens that facilitate adherence, the prevalence of milder forms of HAND has increased, especially among persons older than 50 years (Heaton et al., 2010; Saylor & Sacktor, 2016). This suggests that HAND may partially reflect age-related changes in the brain (Sanmarti et al., 2014).

The pathophysiology of HAND involves the migration of infected macrophages and CD4⁺ T lymphocytes across the blood-brain barrier, which can result in productive infection of brain cells and persistent inflammation that can lead to neuronal dysfunction and death (Williams et al., 2014). The persistence of inflammation is paradoxical in light of the durable viral suppression that can be achieved with cART (Harezlak et al., 2011) and is of major concern because it has been linked to premature senescence, which can manifest as frailty, decreased immune function, and cognitive impairment (Watkins & Treisman, 2015). Potential explanations include suboptimal immune control of chronic viral infections (e.g., cytomegalovirus and Epstein-Barr virus; Hunt, 2012) and HIV-induced disruption of the gastrointestinal mucosa with subsequent bacterial translocation into the systemic circulation (Ancuta et al., 2008).

Given the prevalence of cognitive impairment and persistent inflammation in HIV infection, the identification of modifiable factors to slow cognitive decline and reduce inflammation is an important public health priority. Of particular importance is the body of evidence that supports pleiotropic effects of PA in uninfected persons,

including anti-inflammatory effects (Vella et al., 2017), protection against the development of cognitive impairment in healthy middle-aged and older adults (Pizzie et al., 2014), and slowed progression of cognitive decline in older adults with dementia (Kemoun et al., 2010).

A recent scoping review of cross-sectional studies and randomized clinical trials supported the protective effects of PA on the cognitive health of PLWH (Quigley et al., 2018); however, that review did not report effect sizes, a metric that quantifies differences across studies that use different measures, nor the reliability and validity of the studies' measures. Therefore, the purpose of our review was to critically analyze the evidence related to PA and cognitive health in HIV infection, appraise the psychometric characteristics of the study measures, and calculate the effect sizes.

Methods

An electronic search of the literature was conducted to examine the impact of PA on the cognitive function of PLWH. Using customized keyword strategies (Table 1), the following databases were searched: PubMed, Cumulative Index to Nursing and Allied Health Literature, PsycINFO, and Scopus.

Study Selection

The inclusion criteria for study selection were: (a) sampled PLWH, (b) measured PA, (c) measured cognitive function, (d) peer-reviewed article published between 1996 and 2017, (e) either a nonexperimental descriptive correlational or longitudinal design, and (f) published in English. References of the identified literature were also reviewed for potentially relevant studies. Because our primary purpose was to analyze the exposure—outcome relationship between PA and cognitive function in PLWH, intervention-based studies were excluded. Moreover, including intervention studies would have complicated cross-study comparisons of the calculated effect sizes.

As shown in Figure 1, the search yielded a total of 431 articles. After duplicates were removed using RefWorks software, 319 titles were reviewed for relevance to the inclusion criteria. An additional 236 articles were removed because their titles did not indicate measures of PA and cognitive function. The first two authors independently reviewed the abstracts of the remaining 83 articles and identified 20 that were relevant to the inclusion criteria. Thirteen articles were subsequently excluded because of measurement or design issues, resulting in a final sample of seven articles.

Table 1. Keyword Search Query Table					
Keywords	Database	Number of Articles			
("physical activity" [Title/Abstract] OR "physical activities" [Title/Abstract] OR exercis* [Title/Abstract] OR ((("Exercise" [Mesh]) OR "Exercise Therapy" [Mesh])) OR "Motor Activity" [Mesh:noexp]) AND (cognit* [Title/Abstract] OR (("Cognitive Aging" [Mesh]) OR ("Cognition Disorders" [Mesh] OR "Cognition" [Mesh])) OR ("Memory Disorders" [Mesh] OR "Executive Function" [Mesh] OR "AIDS Dementia Complex" [Mesh]))) AND (HIV [Title/Abstract] OR "human immunodeficiency virus" [Title/Abstract] OR AIDS [Title/Abstract] OR "acquired immunodeficiency syndrome" [Title/Abstract] OR "HIV Long-Term Survivors" [Mesh] OR "HIV" [Mesh] OR "HIV Infections" [Mesh])	PubMed	173			
((hiv OR aids OR "human immunodeficiency virus" OR "acquired immunodeficiency syndrome") AND ("physical activity" OR exercise OR "physical activities" OR exercising OR exercises) AND (cognition OR cognitive))	Scopus	220			
(HIV or "human immunodeficiency virus") AND (DE "Cognition" OR DE "Cognitive Impairment") OR (DE "Cognitive Ability" OR DE "Brain Training" OR DE "Mathematical Ability" OR DE "Reading Ability" OR DE "Spatial Ability" OR DE "Verbal Ability") AND ("physical activity" OR "exercise")	PsycINFO	21			
((MH "Physical Activity") OR (MH "Exercise+") OR (MH "Aerobic Exercises+") AND (MH "Cognition+") OR (MH "Cognition Disorders+") AND ((MH "HIV-Infected Patients+") OR "HIV" OR (MH "Human Immunodeficiency Virus+"))	CINAHL	17			

Data Extraction and Synthesis

Study variables were extracted using the Joanna Briggs Systematic Review template (Godfrey & Harrison, 2010) and included: (a) author(s), publication year, and country of origin, (b) study design, (c) sampling criteria, (d) number of participants, (e) participant demographics, (f) PA measures, (g) cognitive function measures, (h) reliability and validity of instruments, (i) results, and (j) conclusions (Tables 2 and 3).

The effect size was extracted from each study or calculated based on the available values in each article (Table 4). For those studies that did not provide the effect size, the Cohen's *d* statistic was calculated using an effect size calculator developed in Microsoft Excel (DeCoster & Iselin, 2005).

Results

Study Designs and Samples

Tables 2 and 3 summarize data from the seven studies. All the studies were conducted in the United States. Six studies used a cross-sectional design, whereas one used a longitudinal design. Study participants ranged from 20 to 79 years of age. Six of the studies had a sample size equal to or greater than 100 (Dufour et al., 2013, 2018; Fazeli et al., 2014, 2015; Honn, Para, Whitacre, & Bornstein, 1999; Monroe et al., 2017). Two of the studies sampled only men living with HIV (Honn et al., 1999; Monroe et al., 2017), and six of the study samples

comprised predominately White participants (Dufour et al., 2013, 2018; Fazeli et al., 2014, 2015; Honn et al., 1999; Monroe et al., 2017). Only one study's sample comprised predominately African Americans (Ortega et al., 2015). All studies included PLWH, and two studies sampled uninfected persons for comparative purposes (Dufour et al., 2018; Monroe et al., 2017). Only one study exclusively sampled older PLWH, and this sample comprised predominately White men between the ages of 50 and 79 years (Fazeli et al., 2015).

Physical Activity Measures

Five studies used an investigator-developed self-report questionnaire to measure the number of minutes participants reported engaging in PA over a specified time period (Dufour et al., 2013, 2018; Fazeli et al., 2014; Honn et al., 1999; Ortega et al., 2015). Two studies used the International Physical Activity Questionnaire to measure participant PA (Fazeli et al., 2015; Monroe et al., 2017). Six studies categorized the PA responses into ordinal categories that classified participants as either reporting or not reporting participation in PA. In six studies, the time frame for measuring PA ranged from 72 hr to 1 year; one study did not specify a time range.

Cognitive Function Measures

All studies used a battery of neuropsychological tests to measure cognitive function. Four of the studies matched

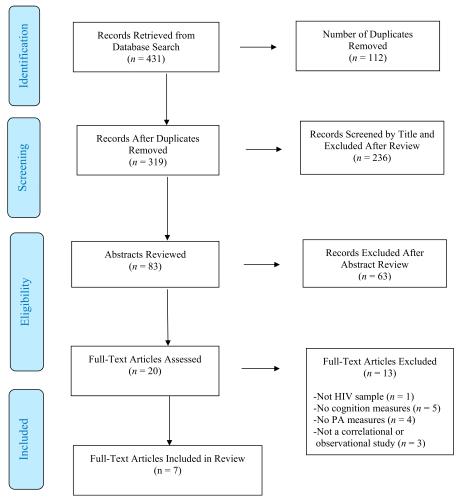


Figure 1. PRISMA flow diagram (Moher, Liberati, Tetzlaff, & Altman, 2009). Note. PA = physical activity. This figure is available in color online (www.janacnet.org).

cognitive domains with specific neuropsychological tests (Dufour et al., 2013, 2018; Fazeli et al., 2014; Ortega et al., 2015), whereas three studies only reported the specific neuropsychological test (Fazeli et al., 2015; Honn et al., 1999; Monroe et al., 2017). The neuropsychological tests used in all the studies measured cognitive functions commonly affected by HIV, such as verbal fluency, working memory, speed of information processing, verbal and visual learning, delayed recall, executive function, and motor function. Verbal fluency was measured in six of the seven studies (Dufour et al., 2013, 2018; Fazeli et al., 2014, 2015; Honn et al., 1999; Ortega et al., 2015).

Association of Cognitive Function and Physical Activity

A majority (6/7) of the studies found a significant association between PA and cognitive function in PLWH (Dufour et al., 2013, 2018; Fazeli et al., 2014, 2015; Monroe et al., 2017; Ortega et al., 2015). Only one study reported no association between self-reported PA and

cognitive function (Honn et al., 1999). One study found that high-level PA participation was associated with slower cognitive decline (Monroe et al., 2017), whereas another found that engaging in multiple positive lifestyle factors contributed to improved overall cognitive performance (Fazeli et al., 2014). Only one study correlated PA with brain imaging and found that those participants who were categorized as "physically active" had larger putamen volumes compared with participants who were categorized as "sedentary" (Ortega et al., 2015).

Effect Size and Reliability/Validity of Measures

Of the seven studies, four showed a moderate to high effect for PA on cognitive function as demonstrated by a Cohen's d value of 0.45–0.58 (Dufour et al., 2013; Fazeli et al., 2014, 2015; Ortega et al., 2015). The average Cohen's d value across studies was \sim 0.51 (SD = 0.79; Table 4). None of the articles reported reliability and validity data for the PA and cognitive function measures for their samples (Table 3).

Table 2. Articles Reviewed						
				Sample Demographic Characteristics		
Author (Year), Location	Design	Sample	Number of Participants	Male/ Female	Age Range or Mean	Ethnicity
1. Dufour et al. (2018), San Diego, CA	Longitudinal	Community-dwelling adults recruited from various cohort studies by the HIV Neurobehavioral Research Program	235 adult PLWH; 56 adults without HIV	M (71%)/ F (29%)	PLWH—49.2 years (mean); uninfected—51.6 years (mean)	W (63%), AA (18%), and O (19%)
2. Dufour et al., (2013), San Diego, CA	Cross- sectional	Community-dwelling adults recruited from various cohort studies by the HIV Neurobehavioral Research Program	335 adult PLWH	M (74.3%)/F (25.7%)	20-79 years; 47.7 years (mean)	W (51.3%), AA (17%), and H (26%)
3. Fazeli et al., (2015), San Diego, CA	Cross- sectional	Community-dwelling older adult PLWH from Successful Aging Seniors with HIV study at the University of California	100 older adult PLWH	M (88%)/ F (12%)	50-79 years; 58.2 years (mean)	W (82%) and other races not reported
4. Fazeli et al., (2014), San Diego, CA	Cross- sectional	Community-dwelling adult PLWH from the HIV Neurobehavioral Research Center	139 adult PLWH	M (79.9%)/F (20.1%)	20-74 years; 48.7 years (mean)	W (59.7%) and other races not reported
5. Honn et al., (1999), Columbus, OH	Cross- sectional	Asymptomatic gay and bisexual men living with HIV from AIDS clinical trials and HIV-related support groups	139 gay and bisexual men living with HIV	M only	33 years (mean)	W (91%) and O (9%)
6. Monroe et al., (2017), Seattle, WA	Cross- sectional	Men enrolled in the Multicenter AIDS Cohort Study living with and without HIV	601 men living with and without HIV	M only	Mean age across activity groups varied from 36.5 to 41.2 years	W (61%), AA (24%), and O (15%)
7. Ortega et al., (2015), St. Louis, MO	Cross- sectional	Adult PLWH from an infectious disease clinic	70 adult PLWH	M (36%)/ F (64%)	41.6 (mean)	W (26%) and AA (74%)

Note. AA = African American; CA = California; F = female; H = Hispanic; M = male; MO = Missouri; O = other; OH = Ohio; PLWH = person(s) living with HIV; W = White; WA = Washington.

Discussion

The purpose of our review was to investigate current scientific evidence regarding the relationship between PA and cognitive health among PLWH by identifying, synthesizing, and critically analyzing existing descriptive studies. We are aware of one other review that focused on examining the relationship between exercise and cognition in PLWH (Quigley et al., 2018), but that was a scoping review that included randomized controlled trials and did not consider effect sizes or the psychometric properties of the study measures. We found seven studies that described the relationship

between PA and cognitive function in PLWH. In six of the seven studies, PA was found to have a positive association with cognitive function, with significant associations found for executive and motor function, working memory, and speed of information processing.

Only one study had a sample comprising greater than 50% non-Whites (Ortega et al., 2015), thus limiting the generalizability of our findings to minority populations. This limitation was significant given the disproportionate number of minorities living with HIV and known barriers, such as crime and higher prevalence of chronic health conditions, that limit participation in PA compared with Whites (Mendoza-Vasconez et al., 2016).

Table 3. Measur	Table 3. Measures				
Author (Year), Location	PA Measures	Cognitive Function Measures	Reliability/Validity	Conclusion	
1. Dufour et al. (2018), San Diego, CA	Investigator- developed questionnaire measured total time spent participating in PA in the past 72 hr. Coded as an ordinal categorical measure—3 levels: no PA, inconsistent PA, and consistent PA	Verbal fluency	PA: not reported Cognitive function: not reported, but the reliability/validity of these measures has been reported in the literature.	Consistent PA was a protective factor for cognitive function in both PLWH and uninfected participants	
2. Dufour et al. (2013), San Diego, CA	Investigator- developed questionnaire measured total time spent participating in PA in the past 72 hr. Coded as an ordinal categorical measure—2 levels: exercise and no exercise	Executive function • Wisconsin Card Sorting Test • Category Test • Trail Making Test Part B • Stroop Color and Word Test Motor Function • Grooved Pegboard Test Learning and recall • Hopkins Verbal Learning Test–Revised • Brief Visuospatial Memory Test Speed of information processing • WAIS-R/III Digit Symbol • WAIS-III Symbol Search • Trail Making Test Part A • Stroop Color And Word Test Verbal fluency • Letter, noun, and verb fluency Working memory • Paced Auditory Serial Addition Test • WMS-III Spatial Span Working memory • Paced Auditory Serial Addition Test • WMS-III Spatial Span	PA: not reported Cognitive function: not reported, but the reliability/validity of these measures has been reported in the literature.	There was a positive association between PA and cognitive function in PLWH	

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Table 3. (continued)				
Author (Year), Location	PA Measures	Cognitive Function Measures	Reliability/Validity	Conclusion
6. Monroe et al. (2017), Baltimore, MD	IPAQ-Short Form • Self-reported PA in the past 7 days • Coded as an ordinal categorical measure—3 levels: low PA, moderate PA, and high PA	Symbol Digit Modalities Test Trail Making Tests A and B	PA/cognitive function: not reported, but the reliability/validity of these measures has been reported in the literature	Higher PA participation was associated with slower decline in cognitive function in adult PLWH
7. Ortega et al. (2015), St. Louis, MO	Self-reported PA over the past year. Coded as an ordinal categorical measure—2 levels: sedentary and physically active	Executive function Trail Making Tests A and B Letter fluency Hopkins Verbal Learning Test-Revised Verb fluency Motor function Trail Making Tests A and B Digit-Symbol Modalities Test Grooved pegboard nondominant	PA/cognitive function: not reported, but the reliability/validity of these measures has been reported in the literature	Physically active PLWH had higher executive function and motor function and larger putamen volumes, when compared with sedentary PLWH

Note. CA = California; IPAQ = International Physical Activity Questionnaire; MD = Maryland; MO = Missouri; OH = Ohio; PA = physical activity; PLWH = person(s) living with HIV; WAIS-R = Wechsler Adult Intelligence Scale—Revised; WAIS-III = Wechsler Adult Intelligence Scale, Third Edition; WMS-III = Wechsler Memory Scale, Third Edition.

Four of the seven studies found a moderate or large effect size for PA on cognitive function. Although this finding was consistent with the large body of literature that supports the protective effect of PA on cognitive function in uninfected adults (Reiner, Niermann, Jekauc, & Woll, 2013), the absence of data to support the psychometric rigor of the PA and cognitive function measures is a concern. Many of the studies' neuropsychological performance measures have been validated in healthy populations, but there are limited data to support the psychometric rigor in PLWH.

The reviewed studies had limitations. All the studies used self-report measures of PA, which have been shown to be characterized by measurement errors related to bias and low levels of reliability and validity (Senso, Anderson, Crain, Sherwood, & Martinson, 2014). In addition, the time frame for PA measurements ranged from 72 hr to 1 year, limiting conclusions about the long-term effects of PA in this population. Many of the studies used investigatordeveloped questionnaires with unreported psychometric properties, thus limiting interpretation of the findings and translation to clinical practice. The reviewed studies did not measure potential confounding variables, such as dietary intake, which would allow for more precise estimates of the unique variance in cognitive function that is accounted for by PA.

Implications for Nursing Practice and Research

Our findings suggest beneficial effects of PA on the cognitive function of PLWH. Accordingly, we recommend that clinicians incorporate PA assessment into patient intakes. Kaiser Permanente has developed a two-item "exercise vital sign" (EVS) questionnaire that is part of the electronic medical record (Stoutenberg, Shaya, Feldman, & Carroll, 2017). The EVS is converted into minutes of PA/ week, thus making it possible for clinicians to assess patient adherence to national PA recommendations (U.S. Department of Health and Human Services, 2018). Written PA prescriptions can be given to patients who do not meet the recommended activity level (Thornton et al., 2016).

Although the extant literature suggests a protective effect of PA on the cognitive function of PLWH, additional descriptive research is needed to inform the development and testing of data-driven interventions to improve cognitive outcomes. These descriptive studies should include minority populations and have adequate statistical power to explicate potential racial differences in the relationship between PA and cognitive function (Barnes et al., 2011). In addition, researchers should use objective measures of PA to reduce bias, incorporate reliability and validity estimates to assess psychometric rigor of cognitive tests in PLWH, and measure potential covariates, such as dietary intake.

Ctuali	Study	Comple Cine (n)	Effect Size	Cohen's d	lutovovototiou
1. Dufour et al. (2018)	Design Longitudinal	Sample Size (n) 291 adults living with and without HIV	Yes	Inconsistent PA had an effect size of 0.5 Consistent PA had an effect size of 2.5	Interpretation Consistent PA was a protective factor against cognitive impairment in PLWH.
2. Dufour et al. (2013)	Cross- sectional	335 adult PLWH	No	Exercise group had a moderate effect size of 0.45	Exercise was a protective factor against cognitive impairment in PLWH.
3. Fazeli et al. (2015)	Cross- sectional	100 older adult PLWH	Yes	PA has a moderate effect size of 0.55	Moderate PA was a protective factor against cognitive impairment in olde adult PLWH.
4. Fazeli et al. (2014)	Cross- sectional	139 adult PLWH	Yes	PA had a moderate to high effect size of 0.58	PA was a protective factor, along with other lifestyle factors, against cognitive impairment in adult PLWH.
5. Honn et al. (1999)	Cross- sectional	139 gay and bisexual men living with HIV	No	PA had a small effect size of 0.07	PA was not associated with improved cognitive functioning in male adult PLWH.
6. Monroe et al. (2017)	Cross- sectional	601 men living with and without HIV	No	PA had a small effect size of 0.05	PA was not associated with improved cognitive functioning in adult PLWH.
7. Ortega et al. (2015)	Cross- sectional	70 adult PLWH	No	PA had a moderate to high effect size of 0.54	PA was associated with higher cognitive function in adult PLWH.

Conclusion

Gains in life expectancy for PLWH have been accompanied by concerns about the effects of HIV-related cognitive decline on self-care activities and quality of life. Although our review suggests that PA is associated with

higher cognitive performance in PLWH, additional studies that use objective measures of PA are needed to confirm and extend these findings. Clinicians are advised to incorporate patient PA levels into the vital sign assessment and to include written PA prescriptions as part of the treatment plan.

Key Considerations

- PLWH are at increased risk of experiencing cognitive impairment that can negatively affect quality of life and self-care.
- O PA has been associated with improved levels of cognitive function in PLWH.
- O Minorities have been underrepresented in studies of PA and the cognitive function of PLWH.
- O PA should be considered a vital sign and measured at each intake visit.

Disclosures

The authors report no real or perceived vested interests related to this article that could be construed as a conflict of interest.

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