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Physiological effects of physical activity on neurocognitive function in people living with HIV: A systematic review of intervention and observational studies

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Abstract

The inadequacy of antiretroviral therapy in the treatment of HIV-associated neurocognitive disorders paves a way for regular physical activity as a lifestyle modification alternative. However, uncertainty exists among scholars regarding the use of physical activity as a means of managing cognitive disorders among HIV-seropositive individuals. The objective of the review was to examine the potential therapeutic value of physical activity intervention in the rehabilitation of people living with HIV (PLWHIV) experiencing cognitive disorders. Undertaken in this study was a systematic literature review by narrative and quantitative synthesis examining studies from 2000 to 2019. Data sources for the review included the following electronic databases: Medline, PubMed, Cochrane Library, CINAHL (The Cumulative Index to Nursing and Allied Health Literature), Academic Search Complete, PsycINFO and relevant reference lists. The eligibility criteria for the selected studies included in the review were interventional and observational studies, which investigated the interaction of physical activity and cognitive function in adult PLWHIV. Fourteen studies met the inclusion criteria. The study outcomes were cognitive function, aerobic fitness and sociodemographic characteristics. Meta-analyses were executed using RevMan 5.3 and MedCalc, with alpha set at 0.05. A total of 2516 PLWHIV with a mean age of 54±8 years and education, 13±2 years participated in the studies reviewed. Men constituted a greater percentage (60%) of the study participants. Physical activity was not superior to control over cognitive function (Z=0.86; p=0.39; Tau^2=61.79 and I^2=94%). However, there was a significant correlation between physical activity and neurocognitive function (r=0.26; $p<0.05$). It was concluded that physical activity was not superior to control over cognitive function in PLWHIV with no reported cognitive deficit.

Keywords: HIV infection, cognition, neurocognitive disorder, physical activity, exercise.

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Introduction

Neurocognitive disorder predominates among people living with HIV (PLWHIV) despite the widespread use of combination antiretroviral therapy (ART) (Animut, Sorrie, Birhanu, & Teshale, 2019). This may be attributed to long-term use of ART and its poor pharmacokinetics in relation to the blood-brain barrier (Kumar et al., 2018; Thakur *et al.*, 2019). Others risk factors included virologic failure, drug resistance, inadequate access to ART, and age 50 years and above (Valcour *et al.*, 2004). Additionally, many resource-constrained countries like Nigeria remain pillars of the treatment regimen. Unfortunately, these drugs, carry substantial neurotoxicity and often results in neurotoxicity and patients remain at risk for severe immunosuppression, central nervous system opportunistic infections and consequent neurological disorders (Thakur *et al.*, 2019). To date, HIV-associated neurocognitive disorders (HAND) are the most prevalent neurological complications among PLWHIV (Kumar *et al.*, 2018). It affects participation in activities of daily living including employment as well as quality of life, thus resulting in dependency and poverty-stricken conditions (South Africa National Research and Development Strategy, 2002). Hence, a clinical redress of HIV-neurological complications is warranted within such settings (Society of Neuroscientists of Africa, 2015).

The ART-linked inadequacies observed in HIV-associated neurological complications may be instrumental in the implementation of lifestyle changes, such as regular physical activity as a complement to traditional therapy. Various pharmacotherapy adjuncts to ART have been explored by PLWHIV experiencing HAND, which include intranasal insulin or cambinol (Figuera-Losada *et al.,* 2016), psychostimulants (Singer & Thames, 2016) and others like minocycline, rivastigimine, memantine and valproic acid (McGuire, Barrett, Vezina, Spitsin, & Douglas, 2014; *Meintjes et al., 2017*) have been tried among PLWHIV experiencing HAND (Bougea, Spantideas, Galanis, Gkekas, & Thomaides, 2019). However, pharmacotherapy treatment remains ineffective thus far for impairment among PLWHIV (Bougea *et al.*, 2019; O'Brien *et al.*, 2014). In addition, behavioural interventions are preferred options when treating HAND especially in the face of complexity of multiple system impairments, including hepatic and renal insufficiency and polypharmacy associated with ART use (Hossain *et al.*, 2017).

Physical activity intervention, a behavioural intervention, has gained much interest as a rehabilitative tool for people living with long-term diseases (Marques, Santos, Martins, Matos, & Valeiro, 2018), and warrants further investigation in the management of PLWHIV experiencing HAND. Despite the demonstrated beneficial effects of physical activity amongst PLWHIV (Jagger & Hand, 2016), the manner in which it improves the quality of life amongst those diagnosed with HAND remains unclear. Several neurological benefits have been associated with physical activity at cellular as well as system and organism levels (Dishman *et al.*, 2006; Ten Brinke *et al.,* 2015). These benefits include the stimulation of synaptic and neuronal plasticity; protection against neuronal damage or neurotoxicity and improved cerebrovascular fitness (Dishman *et al.,* 2016; Ten Brinke *et al.,* 2015; Vecchio *et al.,* 2018). To date, research has hardly investigated the effect of physical activity and HAND. However, a limited number of studies have investigated relationship of physical activity with cognitive function in PLWHIV. The preponderance of observational study designs is the major limitation observed. In addition, findings from these studies (Chow *et al.,* 2019; Mapstone *et al.*, 2013, McDermott *et al.,* 2017; Monroe *et al.,* 2017; Ortega *et al.,* 2015) depict a state of ambivalence, thereby necessitating a systematic synthesis as carried out in this study. A scoping review exists on the subject of the study (Quigley, O'Brien, Parker & MacKay-Lyons, 2018). However, our study is unique as it is probably the first to apply quantitative synthesis in providing evidence regarding the use of physical activity for neurocognitive rehabilitation amongst PLWHIV. Therefore, the objective of this review was to ascertain the potential therapeutic effects of physical activity on cognitive function in PLWHIV.

Methodology

Eligibility Criteria

Included in this review were studies conducted among PLWHIV. There was no regard for participants' age, HIV stage, duration of infection or treatment status. Instead, we included studies that examined the relationship of physical activity with neurocognitive impairment or functioning. Physical activity constituted the intervention in this study. Studies were selected if a relationship between cognitive deficit/function and physical activity was explored in PLWHIV, irrespective of whether there was manipulation or not. We resorted to this approach because our feasibility study showed paucity of evidence regarding the effects of physical activity on neurocognitive impairment/function among PLWHIV. Trials were included only if they explicitly stated or implied the incorporation of structured physical activity using standard exercise protocols. It was also required that mention be made of the frequency, intensity, type and period (FITT) of exercises.

Studies that met the inclusion criteria were included in this preliminary synthesis, irrespective of whether a control group was employed or not. Primary outcomes of interest were cognitive function and physical activity and constituted the independent variables. Cognitive function refers to multiple mental abilities necessary for survival and maintenance of independence in day-to-day activities (Nouchi & Kawashima, 2014). Physical activity has been defined as any bodily movement resulting from skeletal muscles activation and which require energy expenditure (World Health Organisation [WHO], 2010). Secondary outcomes were sociodemographic characteristics and cardiovascular fitness. An outcome was included as long as an assessment was conducted and reported on independent and dependent variables. However, for the interventional studies, outcome assessment before and on completion of the intervention was required.

Design

A systematic review of interventional and observational studies was undertaken, with the focus on synthesising data to verify the apparent state of clinical equipoise on the use of physical activity to mitigate cognitive disorder among PLWHIV. The review was structured and guided by the PRISMA checklist (Shamseer *et al.*, 2015).

Setting

Studies were all hospital-based and, were included irrespective of the level of healthcare namely primary, secondary and tertiary healthcare. Studies were carried in USA, UK, Germany, Ireland and Australia.

Study characteristics

The review included controlled clinical trials as well as observational studies published in English language between 2000 and 2019, regardless of sample size, race, year of publication and test statistics.

Information sources

Five databases were searched for peer reviewed evidence, namely PubMed, MEDLINE, Academic Search Complete (EBSCO), CINAHL (EBSCO), PsycINFO (EBSCO), and SPORTSDiscus (EBSCO)**.** Searches were performed between 18th and 22nd December, 2019. We contacted one author for the full-text of an article but the attempt was unsuccessful, however, the study was included because sufficient information was provided in the abstract.

Search strategy

Searches involved a careful mix of search terms from medical subject headings (MeSH), and keywords in the title, abstract and/or text of the key articles. Firstly, a PubMed pilot search was conducted to establish the sensitivity of the search strategy. The pilot search included various combinations of MeSH terms, keywords or free text terms. The most sensitive and specific search strategy was chosen, refined and reported in Appendix 1 These terms were then adopted and adapted to the syntax and subject headings of the remaining databases. We conducted a final search using five databases namely PubMed, Academic Search Complete, CINAHL, PsycINFO, and SPORTSDiscus. Also, we undertook further search of the reference lists of the identified clinical trials, systematic reviews and meta-analyses.

Data records and management

Results of the literature search were exported into EndNote 8 where we checked for duplicate copies. Data were saved in the EndNote where the articles were screened for eligibility. Eligibility questions for screening of studies were framed, piloted and refined. Selected articles were exported to the desktop for later use in RevMan 5.3 and MedCalc.

Selection process

Initial screening of title and abstract was simultaneously undertaken by the lead author. The primary reviewer undertook this review as part of his PhD studies at the University of Pretoria, South Africa. Critical cross-checking of results of the initial screening and reading through the full text of the selected studies for further screening using the eligibility criteria were done by the first author under the supervision of his supervisors (second, third and fourth authors). The full texts of eight articles were downloaded and further screened. One study abstract was included with sufficient information to inform the outcome of the review, after an attempt to reach the author for the full text was unsuccessful. All the selection processes were executed by the primary reviewer. We presented details of the selection process including reasons for exclusion using PRISMA diagram (Figure 1).

Data items and collection process

Data extraction was independently done by the first author using the piloted evidence table (Appendix 1). Data were extracted from variables of interest including authors' references, participants' characteristics, inclusion criteria, exclusion criteria, study sample size, components of the intervention setting, duration of intervention, the outcome measurement, methods/techniques, and key findings.

Assessment of risk of bias

We carried out quality appraisal for the included studies after selection and during data extraction and synthesis. The Mixed Method Appraisal Tool (MMAT) (Hong *et al.*, 2018) was used for quality appraisal and risk of bias assessment. The overall quality for each of the studies was computed and graded as follows: (1–25%)-low quality, where minimal criteria were met; (26–50%)-average; (51–75%)-above average and (76-100)-high quality, where all criteria were met (Pluye *et al.*, 2011). The study was judged unclear where information was inadequate to make informed judgment on risk of bias. The primary reviewer independently made a judgment regarding risk of bias.

Data synthesis and assessment of heterogeneity

Firstly, the question of the effect of physical activity on neurocognitive impairment/function among PLWHIV was answered narratively. In doing so, all the selected studies and effect size parameters were compared summarised, and presented in an evidence table. Secondly, a random-effect model of meta-analysis was fitted to synthesize study effects, which was a useful indicator of whether true ambivalence regarding the superiority of physical activity intervention over control exists. To generate weighted mean difference and correlation coefficient in the meta-analysis, all other effect size, usually odds ratio, was converted to mean difference and correlation coefficients (Borenstein *et al.*, 2009; Bonett *et al.*, 2007). A narrative display of measures of heterogeneity (study characteristics) was sorted by year of publication and presented in an evidence table. This provided information on authors' references, sample size, study design, setting, outcomes and key findings.

Ethical consideration
This review was approved by the Research Ethics Committee of the Faculty of Health Sciences, School of Healthcare Science, University of Pretoria, which complies with the US Federal wide Assurance, and the ICH-GCP guidelines. Ethics reference number: 152/2020).

Data analysis
We undertook a meta-analysis of mean difference as well as meta-correlation using RevMan 5.3, and MedCalc, respectively. To assess heterogeneity in the meta-analysis of difference in mean, we computed summary effect, tau-squared (τ^2) and the ratio of true heterogeneity to total variation in observed effect (I^2). For the meta-correlation, a funnel plot was generated to assess study heterogeneity.

Results

A total of 423 articles were identified and exported to EndNote 12. Of these, 101 duplicate copies were identified and de-duplicated appropriately. We subjected the remaining 322 papers to eligibility screening and 14 of them passed the pre-defined eligibility criteria (Figure 1). Studies included were published between 2002 and 2019 (Appendix 1). The sample size for each study included, varied from 11 (McDermott *et al.,* 2017) to 988 (Chow *et al.,* 2019) (Table 1). The publications comprised six interventional studies (four RCTs – Randomised controlled trials, and two quasi experiments) and eight observational studies. Of the interventional studies, two were conducted in the USA, and one each in the UK, Germany, Ireland and Australia. All the observational studies were carried out in the USA and comprised three cross-sectional studies, one cohort and four case control studies (Appendix 1).

Sociodemographic characteristics of the study participants and Risk of Bias Assessment
A total of 2516 PLWHIV, with a mean age of 53.89±7.7 years and years of education (13.38±2.4) participated in the studies included in this review. Men constituted a greater percentage (60%) of the study participants while 56% were white. The sample size varied considerably between 11-99 (interventional) and 37-988 (non-interventional). Approximately 12% of the participants in this review were involved in the interventional studies, while 88% participated in the

observational studies. Of the six interventional studies included in this review, two were of average and above average quality, while another two were of high quality (Table 1).

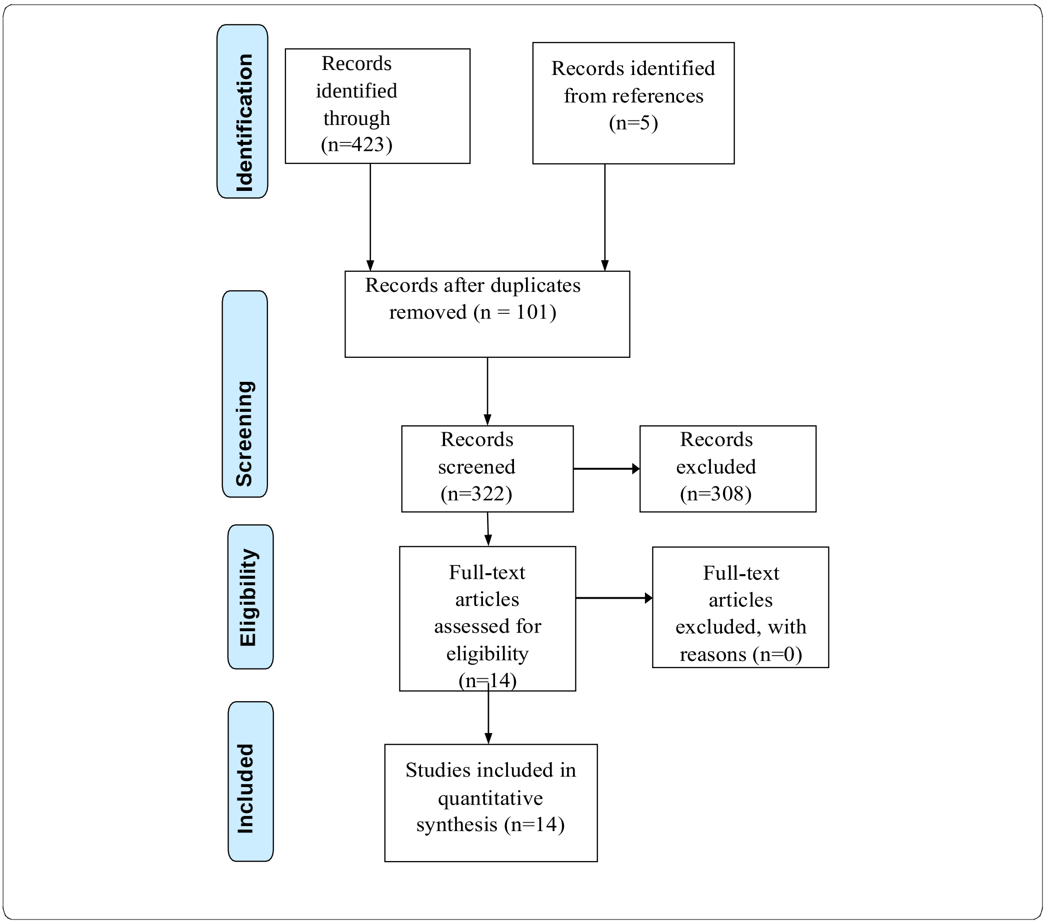


Figure 1: PRISMA flow diagram (Shamseer *et al.*, 2015).

The eight non-interventional studies (Chow *et al.*, 2019; Dufour *et al.*, 2013; Dufour *et al.*, 2018; Fazeli *et al.*, 2014; Fazeli *et al.*, 2015; Mapstone *et al.*, 2013, McDermott *et al.*, 2017; Monroe *et al.*, 2017; Ortega *et al.*, 2015) were of high quality (Table 1).

Cognition function and cardiovascular fitness of control and physical activity groups

Five of the six interventional studies were included in this analysis. Results showed that exercise improved cognitive function in one (Fillipas, Oldmeadow, Bailey, & Cherry, 2006) ($p<0.05$) of the five interventional studies. In three of the four studies in which exercise had no significant effect on cognitive function, cardiovascular fitness did not differ (*p*>0.05) between exercise and control groups (Table 2).

Table 1: Sociodemographic characteristics of the study participants and quality appraisal

Study ID	Sample Size	Age Mean±SD	Sex (% Male)	Education (Years)	Race (% White)	Qlty
Interventional						
McDermatt et al. (2017) (RCT)	11	43.50±7.5	8 (73)	NR	NR	3/5
Baigis et al. (2002) (RCT)	99	37±9.3	79 (80)	NR	32 (32)	4/5
Fillipas et al. (2006) (RCT)	40	43.5±8.85	NR	NR	38 (95)	5/5
Galantino et al. 2005 (RCT)	38	NR	NR	NR	NR	2/5
Brown, Claffey, & Harding (2016)	92	51.5±10	75 (82)	NR	65 (71)	3/5
Schlabe *et al.* (2017)	13	42±5.8	12 (92)	NR	NR	2/5
Non-interventional						
Mapstone *et al.* (2013)	37	58.92±5.6	30 (82)	13.51(3.0)	27 (73)	4/5
Monroe *et al.* (2017)	601	38.10±NR	NR	NR	356 (59)	5/5
Chow *et al.* (2019)	998	51.5±8.0	790 (80)	14(12-16) ⵜ	485 (49)	5/5
Ortega *et al.* (2015)	70	42.3±16.4	65 (16)	13.3(2.7)	52 (74)	4/5
Fazeli *et al.* (2014)	139	48.20±10.0	111 (80)	13.85(2.3)	83 (59.7)	5/5
Fazeli *et al.* (2015)	100	58.20±6.5	88 (88)	14.3(2.6)	82 (82)	5/5
Dufour *et al*. (2013)	335	47.70±10.5	246 (74)	13(3.2)	172 (51)	5/5
Dufour *et al*. (2018)	235	49.30±9.8	172 (73)	13.3 (3.1)	139 (59)	5/5
Total	2516	53.89±7.7	1510 (60)	13.38(2.4)	1397 (56)	

NR= not reported; Qlty=quality; ⵜ=median (interquartile range).

Table 2: Comparison of cognition and cardiovascular fitness between exercise and control groups

	Cognitive function			**Cardiorespiratory fitness**			
	Control	**Exercise**		**Control**	**Exercise**		
Study ID	Mean±SD	Mean± SD	*P*	Mean±SD	Mean±SD	*P*	CRFI
McDermatt *et al.* (2017)	26.3±2.7	27.2±1.7	>0.05	30±NR	30±NR	>0.05	VO2 max
Baigis *et al.* (2012)	48.3±7.8	46.9±7.6	>0.05	30.8±8.5	30.5±6.3	>0.05	VO2 max
Fillipas *et al.* (2006)	13.5±19.5	27.3±22	<0.05*	– 19.6±11.7	0.6±2.9	<0.05*	HR(bpm)
Brown *et al.* (2016)	6.9±3.2	7.2±3.5	>0.05	322.5±NR	408.4±NR	<0.05*	6MWT(meters)
Schlabe *et al.* (2017)	53.0±5.75	56.0±11.3	>0.05	NR	NR	NR	NR

CRFI: cardiorespiratory fitness index; *=significant at α=0.05; NR = Not reported.

Outcome assessment

Cognitive function was assessed using the gold standard measure of neuropsychological test batteries in all the non-interventional studies, except for Chow *et al.* (2019). In contrast, cognition was assessed using the Montreal cognitive assessment scale and the Medical Outcomes Study (MOS)-HIV-cognitive subscale in the low quality RCT, which are less valid measures. Of the six interventional studies, four studies (Baigis *et al.*, 2002; Fillipas *et al.*, 2006; Galantino *et al.*, 2005; Schlabe *et al.*, 2017) utilised the MOS-HIV-cognitive subscale, which constitutes the measure of cognitive function, while functional assessment of HIV infection (FAHI)-cognitive subscale and Montreal cognitive scale were used in Brown *et al.* (2016) and McDermott *et al.* (2017), respectively. The sub-standard approaches towards assessment of cognitive function in the interventional studies call for caution when interpreting the findings of these studies. Measures of cardiovascular fitness in the interventional studies included $VO2_{max}$ (ml.kg-1.min−1), heart rate (bpm) and a six-minute walk test (m) (Appendix 1 and Table 2).

With regards to physical activity, a staff-administered physical activity questionnaire, which was developed by the HIV Neurobehavioral Research Program (HNRP) was used in three of the fourteen studies (Dufour *et al.,* 2013; Dufour *et al.,* 2018; Fazeli *et al.,* 2014). The international physical activity questionnaire (IPAQ) ranked second, being used in two studies (Fazeli *et al.,* 2015; Monroe *et al.*, 2017). A self-reported physical activity questionnaire, a progressive treadmill test and a seven-day accelerometery test were used in studies undertaken by McDermott *et al.* (2017), Mapstone *et al.* (2013) and Ortega *et al.* (2015), respectively (Appendix 1).

Exercise prescription parameters

The exercise intervention comprised single aerobic exercises (Baigis *et al.,* 2002; McDermott *et al.,* 2017), combined aerobic and resistive exercises (Fillipas *et al.,* 2006; Galantino *et al.,* 2005), marathon sprints (Schlabe *et al.,* 2017), and combined aerobic, neuromotor and resistive exercises (Brown *et al.,* 2016) (Table 3). Significant improvement in aerobic fitness was found in two of the three studies in which exercises were performed at both higher intensity (Brown *et al.,* 2016; Fillipas *et al.,* 2006) and duration.

Effects of physical activity on cognitive function among PLWHIV

A significant difference ($p<0.05$) in cognitive function after exercise was reported in one RCT (Fillipas *et al.,* 2006) of the six interventional studies. Similarly, substantial differences ($p<0.05$) in cardiovascular/physical fitness were reported in only two studies (Brown *et al.*, 2016; Fillipas *et al.*, 2006) (Tables 2 & 3).

Significant lower odds of neurocognitive deficit ($p<0.05$) with participation in physical activity were reported in all the eight observational studies (Appendix 1). However, this preliminary synthesis intentionally explored a radical meta-analysis, which included non-interventional studies that met the eligibility criteria. Two models were fitted, one for mean difference and the other for correlation coefficient. For mean difference, five studies with sufficient information were involved and the results showed no significant difference between control and exercise groups ($Z=0.86$; $p=0.39$) (Figure 2).

Table 3: Exercise prescription parameters of the included studies

Study ID	Freq/wk	Intensity (%)	T/session	D(wk)	TH	Type	dVO2m (*p-value*)
McDermott *et al.* [20]	2	40-75HRR	31-52min	16	16.5-28	Circuit training/ (treadmill, cycle ergometer and cross trainer)	$p>0.05$
Baigis et al. [35]	3	75-85HRM	20min	15	60	Aerobics (Fitness Master ski ski machine)	$p>0.05$
Fillipas *et al.* [36]	2	60-75HRM	60min	15	48	Aerobics (ergometer, treadmill, stepper or cross trainer) & resistance machine (and free weight)	$p<0.05$
Galantino *et al.* [37]	2	<60-70HRR	60min	8	16	Aerobic & resistance (low impact aerobics & impact aerobics & theraband exercise)	$p>0.05$
Schlabe *et al.* [39]	3-4	60-70HRM	60-150min	12	36-48	Marathon sprints	NR
Brown *et al.* [38]	2	70% IRM	60min	10	20	Aerobics (cross-trainer rower, treadmill or static cycling), neuromotor exc e.g. balance, coordination & Resistive (press, pulley-based multigym, dumbbells & bodyweight exercise e.g., sit to stand or heel raises)	$p<0.05$

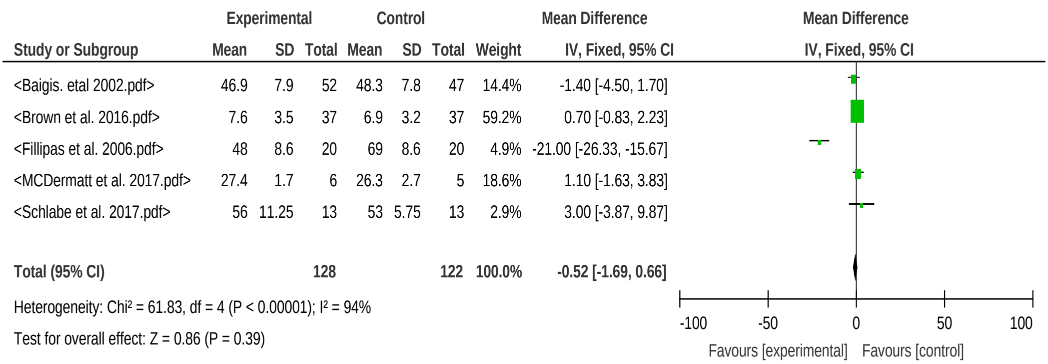
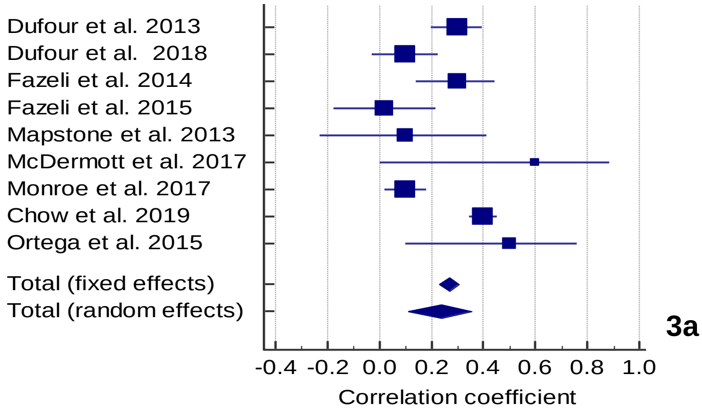
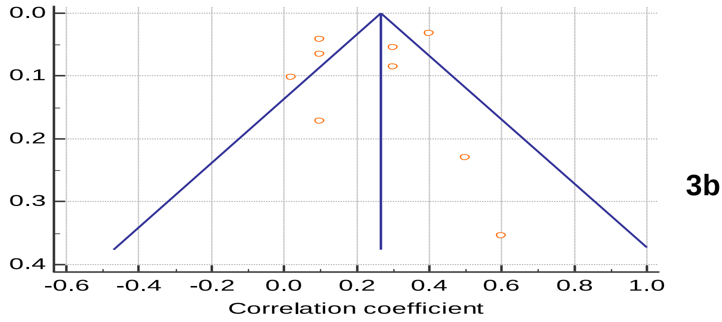


Figure 2: Meta-analysis of mean difference reflecting the effect of exercise on cognition function.

The meta-analysis of correlation coefficients for nine observational studies revealed a significant but weak correlation between physical activity and cognitive function in PLWHIV (r=0.26, $p<0.05$). However, our funnel plot is suggestive of publication bias across the studies (Figures 3a & b).





Figures 3a & b: Forest and Funnel plots displaying summary effects and publication bias across studies included in meta-analysis.

Discussion

This preliminary synthesis suggests that engagement in physical activity reduces the odds of decline in neurocognition in PLWHIV as demonstrated by eight of the studies reviewed, whereas no significant improvement in cognition with exercise was demonstrated by five of the six interventional studies. Evidence from the non-experimental studies is limited as cause-effect relationship cannot be drawn from them. However, the outcomes of all the interventional studies were weakened by the use of inadequate neuropsychological screening measures and poor sample size. Sample size is the single most important factor in the estimation of study effect (Pluye *et al.*, 2011). The fact that physical activity is associated with better neurocognitive function or less cognitive decline suggests that physical activity possesses neuroprotective effects (Ortega *et al.*, 2015).

In some of the studies analysed, aerobic exercise was unable to produce significant improvement in cognitive function amongst PLWHIV (Baigis *et al.*, 2002; Brown *et al.*, 2016; Fillipas *et al.*, 2006; Galantino *et al.*, 2005; McDermott *et al.*, 2017; Schlabe *et al.*, 2017). This lack of improvement may be attributed to the type of aerobic exercise programme implemented and its inability to produce significant change in the participants' aerobic fitness. This data is consistent with those reported by Mapstone *et al.* (2013), which demonstrated a cognitive decline with poor aerobic fitness levels. It is therefore possible that the type as well as the lower intensity of aerobic exercise used in most (three of five) of the interventional studies are unable to demonstrate improvement in cognitive function. This suggests that cognitive function may improve with improved aerobic fitness (Fillipas *et al.,* 2006). The finding that aerobic fitness was not significant following a total of 60 hours of aerobic exercise performed three times per week for 15 weeks (Baigis *et al.,* 2002) was surprising. However, it may be an indication of the failure of the study to exclude participants with high pre-intervention physical activity levels. The fact that most of the participants in the interventional studies were men (82%) may have constituted a bias in the study as men reportedly possessed moderate to high levels of physical activity compared with their female counterparts (Hands, Parker, Larkin, Cantell, & Rose, 2016). A previous study has shown that individuals with high pre-intervention physical activity levels are less likely to benefit from physical activity intervention (Payne, 2018). Furthermore, the exercise prescription parameters utilised in the interventional studies may have played an essential role in the outcome of the study.

In the studies in which aerobic exercise constituted an intervention, the mean duration (31 minutes) was barely sufficient to induce aerobic fitness (McDermott *et al.,* 2017). In contrast, a more vigorous and long-term structured physical activity (six months combined aerobic and resistance exercises with each session lasting one hour twice a week) yielded a positive change in cognition amongst PLWHIV (Fillipas *et al.,* 2006). Therefore, it could be inferred that the low intensity of the aerobic exercise performed by the participants in most of the studies was partly responsible for the lack of improvement in cognition function reported. For example, the intensity and duration of the aerobic exercise training reported by McDermott and co-workers were quite low when compared to those utilised in other studies (Ten-Brinke *et al.,* 2015; Suzuki *et al.,* 2013). Both Ten-Brinke's and Suzuki's groups highlighted that aerobic exercise significantly improved aerobic fitness in HIV-negative individuals. Likewise, Chin's group demonstrated significant changes in aerobic capacity when exercise intensity was high (Chin, Keyser, Dsurney, & Chan, 2015). These investigators documented maximum heart rate under intensive use of aerobic exercise, and this suggests that the improved cognitive performance in individuals with traumatic brain was linked to exercise intensity. This finding is further strengthened by our meta-correlation analysis in which positive association was found between physical activity and cognitive function.

The meta-analysis of mean difference yielded a non-significant summary effect size. From an interventional perspective, this suggests that physical activity interventions are not superior to control or placebo in rehabilitation of cognitive disorders in PLWHIV. However, in a systematic review of the effect of a rehabilitation intervention, cognitive exercise revealed a significant positive change in cognitive performance in PLWHIV with cognitive deficit (Vance *et al.,* 2019). Hence, the non-significant finding in our study could be due to the fact that the participants in our study were individuals with normal cognitive function. Nonetheless, our data demonstrated a state of clinical equipoise regarding the use of physical activity interventions for HAND. Moreover, it supports the call for the development of rehabilitation interventions for people living with HAND through randomized clinical trial inquiry (Chetty, Maddocks, Cobbing, & Hanass-Hancock, 2018; O'Brien *et al.,* 2014). Based on the similar weight to the effect size of most studies in this synthesis, it also favours more investigation via RCTs, with the objective of testing the true superiority of physical activity interventions over control/placebo in rehabilitation of PLWHIV experiencing HAND.

Overall, in merging evidence from the meta-analyses amidst the state of clinical equipoise, it is reasonable to hypothesize that exercise, a structured physical activity will have significant positive effect on HAND, provided that the exercise is intense enough to induce aerobic fitness. Interestingly, none of the studies was conducted in Africa, which raises a serious concern because the continent contains over 60% of middle-aged adults living with HIV (UNAIDS, 2014), despite containing less than 20% of the world's population. The outcome of this review also confirms the view that rehabilitative measures for people living with HAND are lacking despite the increased prevalence of HAND-related functional impairment and/or disability. Therefore, there is a need for more randomised control trials to ascertain the effectiveness of exercise as a rehabilitative measure against HAND. In conclusion, physical activity is not superior to non-treatment control/placebo over cognitive function in PLWHIV with normal cognition, especially when aerobic capacity is not improved. There is a need for more properly structured RCTs investigating the effects of specific physical activity intervention on HAND.

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Appendix 1: Evidence pooled table displaying effect of physical activity on cognitive function among PLWHIV

Author (s)	Title	Country, Design & Sample size	Intervention/Exposure	Outcome & outcome measure(s)	Summary of findings
Baigis *et al.*, 2002	Effectiveness of a home-based exercise intervention for HIV-infected adults: a RCT	-USA -RCT -99	Aerobic exercise	Medical Outcomes Study (MOS)-HIV-cognitive subscale	Results showed no change in post-treatment cognitive measure (p=0.86)
Fillipas *et al.*, 2006	A six-month, supervised, aerobic and resistance exercise program improves self-efficacy in people with human immunodeficiency virus: a randomised controlled trial	-Australia -RCT -40	Aerobic and resistance exercise	MOS-HIV-cognitive subscale	Results showed that intervention group recorded improvement in cognitive subscale (p=0.04
Galantino *et al.*, 2005	The effect of group aerobic exercise and T'ai chi on functional outcomes and quality of life for persons living with acquired immunodeficiency syndrome	USA RCT 38	Tai Chi vs strength and endurance exercise	MOS-HIV-cognitive subscale	No significant group differences (p=0.46)
Brown *et al.*, 2016	Evaluation of a physiotherapy-led group rehabilitation intervention for adults living with HIV: referrals, adherence and outcomes	United Kingdom; Interventional Cohort 92	Aerobic, Neuromotor and resistance exercise	FAHI-cognitive subscale	No change in cognitive subscale scores (p=0.635)
Schlabe *et al.*, 2017	Moderate endurance training (marathon-training) - effects on immunologic and metabolic	Germany; Setting was not reported Pre-post single Cohort design 21	Progressive aerobic training	MOS-HIV-cognitive subscale	No change in post-treatment cognitive performance index (p>0.05)

	parameters in HIV-infected patients: the 42 KM cologne project.				
McDermott *et al*,. 2017	The effects of a 16-week aerobic exercise programme on cognitive function in people living with HIV	Ireland RCT 11	Structure physical activity-aerobic exercise	Montreal cognitive Assessment & seven day Accelerometery	Exercise training did not induce any significant improvements in cognitive function or aerobic fitness (p>0.05).
Dufour *et al*,. 2013	Physical exercise is associated with less neurocognitive impairment among HIV-infected adults	USA Case control 335	Unstructured physical activity	Neurocognitive battery test & staff-administered physical activity questionnaire	The present findings suggest that HIV-infected adults who exercised were approximately half as likely to show NCI as compared to those who had no exercise (*p*<0.05; OR=2.19; CI=1.03–4.68)
Dufour *et al*., 2018	A longitudinal analysis of the impact of physical activity on neurocognitive functioning among HIV-infected adults	USA Prospective cohort 235	Unstructured physical activity	Neurocognitive battery test & staff-administered physical activity questionnaire	Results show that the consistent PA group began with, and maintained, significantly better neurocognitive function compared to the those with either inconsistent PA or nil PA (OR=1.28; SE = 0.33; p=0.001)
Fazeli *et al*. 2014	Active lifestyle is associated	USA Cross-	Unstructured physical activity	Neurocognitive battery test &	Results revealed that

	with better neurocognitive functioning in adults living with HIV infection	sectional Survey 139		staff-administered physical activity questionnaire	increased active lifestyle was associated with better global neurocognitive performance as well as a lower prevalence of HAND (OR= 0.59; CI= 0.36–0.93; p=0.02).
Fazeli *et al.*, 2015	Physical activity is associated with better neurocognitive and every-day functioning among older adults with HIV disease	USA Cross-sectional survey 100	Unstructured physical activity	Neurocognitive battery tests & international physical activity questionnaire (IPAQ)	Individuals with higher levels of moderate PA recorded lower odds of having cognitive impairment (OR=0.94; p = 0.01), even when covariates were modelled. The association between moderate PA
Mapstone *et al.*, 2013	Poor aerobic fitness may contribute to cognitive decline in HIV-infected older adults	USA Case control 37	Unstructured physical activity	Neuropsychological battery & aerobic fitness-(VO2max)-progressive treadmill test	Participants with higher VO2 peak were less likely to have more severe forms of HAND, i.e., MNC (OR=0.65; p=0.01) and HAND (OR=0.64; p=0.0006)
Monroe *et al.*, 2017	The association between physical activity and cognition in men with and without HIV infection	USA Case control 601	Unstructured physical activity	Neuropsychological battery tests & IPAQ	High PA was associated with lower odds of impairment of learning, memory,

					and motor function odds ratio (OR) ranging from 0.52 to 0.57; p < 0.05 for all.
Chow *et al.*, 2019	Physical activity is associated with lower odds of cognitive impairment in women but not men living with HIV infection	USA Cross-sectional 988	Unstructured physical activity	Measures not reported	In a multivariable model, physical activity was associated with lower odds of cognitive impairment in women (odds ratio, 0.35; CI=0.15-0.80; p =.013) but not men
Ortega *et al.*, 2015	Physical activity affects brain integrity in HIV + individuals	USA Cross-sectional survey 70	Unstructured physical activity	Brief neuropsychological battery. A self-reported exercise questionnaire	Physically active HIV + individuals performed better on executive (p = .040, unadjusted; p = .043, adjusted) but not motor function (p = .17)

SOP=speed of processing, OR=odd ratio.

Appendix 2: Search strategies

Results of pilot search in PubMed

Search terms	Date of search	Databases	No of articles retrieved
HIV-associated neurocognitive disorder [All Fields] AND (Rehabilitation or Physical activity) [All Fields]	18/12/2019	PubMed	75

Results of search in Cochrane Library

Search terms	Date of search	Databases	No of articles retrieved
HIV-associated neurocognitive disorder [All Fields] AND (Rehabilitation or Physical activity) [All Fields]	19/12/2019	Cochrane Library	11

Results of search in CINAHL

Search terms	Date of search	Databases	No of articles retrieved
HIV-associated neurocognitive disorder [All Texts] AND (rehabilitation or physical activity or intervention or trial) [All Texts]	20/12/2019	CINAHL	28

Results of search in Academic Search Complete

Search terms	Date of search	Databases	No of articles retrieved
HIV-associated neurocognitive disorder [All Texts] AND (rehabilitation or physical activity or intervention or trial) [Subject Terms]	20/12/2019	Academic Search Complete	37

Results of search in PsycINFO

Search terms	Date of search	Databases	No of articles retrieved
HIV-associated neurocognitive disorder [All Texts] AND (rehabilitation or physical activity or intervention or trial) [All Texts]	20/12/2019	PsycINFO	88

Results of search in MEDLINE

Search terms	Date of search	Databases	No of articles retrieved
HIV-associated neurocognitive disorder [All Texts] AND (rehabilitation or physical activity or intervention or trial) [All Texts]	22/12/2019	MEDLINE	179