Worldwide Prevalence of HIV Associated Neurocognitive Disorders (HAND) and its associated factors: A systematic review and meta- analysis

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Abstract

Background: HIV associated neurocognitive disorders are common in people living with HIV/AIDS and affects adherence of patients to prescription, activities of daily living and quality of life of patients. However, there is a lack of summative evidence in the area. The present meta-analysis was therefore employed to address this gap.

Methods: we used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines during our electronic search in Psych-Info, EMBASE, Scopus and PubMed. The retrieved articles were stored with endnote reference manager and data was extracted using Meta-XL version 5.3. The quality of studies were evaluated with modified Newcastle–Ottawa Scale (NOS). A random-effect model and STATA-16 were used to compute the average estimate of HAND. Heterogeneity was weighed with I^2 statistics. A sensitivity analysis and subgroup analysis were employed. The existence /nonexistence of a publication bias were checked with the eye ball test and eggers test of publication bias.

Results: The average prevalence of HAND was 50.41% (95% CI: 45.56, 55.26). The average estimate of HAND in Europe was found to be 50.015% whereas in Africa, Asia and United States of America (USA) it was 49.566%, 52.032 %, 50.407% respectively**.** The prevalence of HAND in studies which used HIV Dementia Scale (IHDS) was 36.883% & 59.956% at a cutoff points of IHDS< 9.5 & IHDS <10 respectively. In addition the estimated average of HAND with the global dementia scale (GDS) was 40.766%. The prevalence of HAND in cross-sectional, cohort and case control studies was 49.52%, 54.087% and 44.45% in that order. Sociodemographic variables such as low level of education and older age, clinical and HIV related variables such as advanced stage of the illness and CD4 count of 500 cells/dl or less and psychological variables such as comorbidity of depression increases the risk of HAND.

Conclusion: The average prevalence of HAND was high (more than half of participants) and factors such as low level of education, older age, advanced stage of the illness and comorbidity of depression increases the risk of HAND. Public health interventions to HIV patients should target these essential problems.

1. Introduction

HIV/AIDS is a global public health issue with more than 34 million individuals living with the virus currently (1). Mental, neurological and substance (MNS) related disorders are very common in individuals living with HIV/AIDS (2). Latest systematic review and Meta-analysis studies by Necho et al 2020 (3) revealed that 35.8% of HIV/AIDS patients had depressive symptoms (3). Another systematic review and meta-analysis studies reported that the prevalence of post-traumatic stress disorder (PTSD), alcohol use disorder (AUD), suicidal ideation in individuals living with HIV/AIDS were 32.67%(4), 22.02% (5) and 21.7%(6) respectively.

Since HIV is a neurotropic virus, it affects the cortical and sub-cortical parts of the brain resulting in cognitive impairment (7). This impact of HIV on cognitive domain of patients is known as HIV-associated neurocognitive disorder (HAND)(8, 9). The level of HAND arrays from asymptomatic impairment to minor neurocognitive disorder and full blown dementia (10-13). HIV-associated neurocognitive disorder affects memory, attention, problem solving ability, language, higher executive functioning and independent activities of daily living (14).

HIV associated neurocognitive disorders are very common in HIV/AIDS patients. A study by Abdulrazaq G. Habib et al 2013(15) reported that the burden of neurocognitive impairment (NCI) among ART attendants was 30.39%. Based on the report of multiple earlier studies the world wide burden of HIV associated neurocognitive disorders(HAND) varies from a minimum of 7.3% to a maximum of 85% (8, 10, 12-14, 16-49). In addition, the frequency of HIV

associated neurocognitive disorder (HAND) in developed and developing countries varies between 19% to 52% (30, 50), and 14% to 64% (12, 13) respectively.

Different studies reported varieties of sociodemographic and clinical factors associated with HIV associated neurocognitive disorders in individuals living with HIV/AIDs. For example studies from, Cameroon, Nigeria, Botswana, Singapore , Malawi and Dessie Ethiopia reported that sociodemographic variables such as older age, female sex, and lower educational level were a risk factors for HIV associated neurocognitive disorder(13, 14, 45, 49, 51, 52). In addition, from Clinical variables CD4 count of < 500 cells/mm3 was related to HIV-associated neurocognitive disorder based on reports of studies from Brazil, Singapore and Northern Nigeria (14, 49, 53). Moreover, advanced stage of AIDS and not being on highly active anti-retroviral treatment (HAART) were associated with HIV-associated neurocognitive disorder in South Africa (50-52). In Uganda behavioral and psychological variables such as depression, Body mass index and alcohol abuse were associated with HIV-associated neurocognitive disorder (10). Moreover, medication non-adherence and opportunistic infections were associated with HIV-associated neurocognitive disorder (45, 54).

Presence of HIV-associated neurocognitive disorder predisposes HIV infected patients substance abuse, poor medication adherence, and unsafe sex so that poor quality of life and lost to follow up from treatment are final outcomes. These conditions speed up the progression of the virus to its advanced stages and development of severe opportunistic infections and death (11, 12).

Despite the fact that high proportion of the world population has been living with HIV/AIDS and high prevalence of mental, neurological and substance use disorders in this population, these problems especially neurocognitive disorder are not investigated well. Despite the presence of some studies in the area, they are of mostly confined to a small population and to a narrow geographical area (8, 10, 12-14, 16-49). Consequently, there arises a need to have aggregate data regarding HIV-associated neurocognitive disorder and its associated factors.

Therefore, this systematic review and meta-analysis study was designed to have summative empirical data on (1): The commonness of HIV-associated neurocognitive disorder on people living with HIV AIDS (2): The associated factors for HIV-associated neurocognitive disorder in people with HIV AIDS and in conclusion to clear a reference point for officials, future scientists and clinicians.

2. Methods

2.1: Search strategy

This systematic review and meta-analysis study was done using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines as a framework (55). We have performed our search strategy for this review in different ways. Initially we did an electronic exploration for eligible articles regarding HIV-associated neurocognitive disorder on people living with HIV AIDS in the databases of Psych-Info, EMBASE, Scopus and PubMed. As a sample of our search strategy with PubMed database, we have used the following key terms: **(Prevalence OR screening OR burden AND "neurocognitive disorder" OR "neurocognitive deficit" OR "neurocognitive impairment" OR "HIV-associated neurocognitive disorder" OR "Intellectual impairment" OR "HAND" AND "PLWHA" OR "HIV/AIDS" OR HIV OR AIDS OR ART AND "associated factor" OR determinant OR "risk factor")**. Moreover, Psych-Info, EMBASE and SCOPUs databases were investigated in line with the searching guidelines of each database. In addition, the reference lists of included studies were searched manually for additional eligible articles. There was no time restriction to the publication year of the articles during the searching process.

2.2: Eligibility criteria's

During our study of a systematic review ad meta-analysis on HIV-associated neurocognitive disorder in people living with HIV AIDS, we have set the following inclusion and exclusion criteria's based on the **PICO criteria** : (1) the primary inclusion criteria was the design of the study. In this context all observational studies (case control, cross-sectional ad cohort) were eligible for analysis. (2) The next criteria for inclusion to analysis were the study should assessed prevalence OR associated factors of HIV-associated neurocognitive disorder in people living with HIV AIDS. (3) The HIV-associated neurocognitive disorder had also to be investigated using International HIV Dementia Scale (IHDS), Frascati criteria, Mini-mental state exam(MMSE), global dementia scale(GDS), Brief Neurocognitive Screen, Neuropsychological battery, Montreal Cognitive Assessment (MoCA),In-depth neuropsychological assessment, Wechsler Adult Intelligence Scale and ADC.

We excluded studies 1) that assessed neurocognitive disorder in samples other than people living with HIV/AIDS. 2) That assessed neurocognitive disorder in individuals that had a history of depression or other forms of mental illness or those taking a psychotropic medication. 3) Studies which are letters to the editor with non-original data content, earlier reviews, case studies, studies involving non-human subjects, articles published in a language other than English language were also excluded from the analysis. After all relevant articles were searched in the mentioned data bases; they were stored in an endnote reference manager. Two of the authors (MN and YZ) individually screened the titles and abstracts of articles stored in an endnote reference manager using the eligibility criteria's. Next to that, the above two authors carefully read the full length of articles which passed the initial screening and decided independently articles suitable for inclusion in the final meta-analysis. Any disagreement in between them regarding eligibility criteria was resolved by agreement and with a third reviewer (WY).

2.3: Data extraction and quality assessment techniques

Once the articles for inclusion to the final analysis were settled, the previously mentioned two authors (MN and YZ) extracted all the necessary data individualistically using an identical data extraction form. The forty final incorporated studies were extracted using the data extraction template as suggested by PRISMA guidelines (55), using Meta-XL version 5.3 (56) and the result was summarized in a table presentation. The contents of the data extraction template were author name, year of publication, country where the study was done, study design, studied sample population, assessment tool for HIV associated neurocognitive disorders, number of cases with HIV associated neurocognitive disorders, prevalence of HIV associated neurocognitive disorders, sampling technique employed to recruit participants, and response rate of the study.

The quality of forty included studies (8, 10, 12-14, 16-49) had been evaluated using modified Newcastle–Ottawa Scale (NOS) (57) as gold standard. Representativeness of sample and sample size, statistical quality, comparability among participants and ascertainment of cases were the components of this quality assessment scale. Based on this scale studies with a quality score of 7 to 10 were categorized as very good/good, score of 5 to 6 were categorized as having satisfactory quality, and a score less than 5 was take as unsatisfactory quality.

2.4: Data analysis and synthesis

The random-effect model was used to compute the average estimate of HIV associated neurocognitive disorders and its associated factors with 95% CIs (58). The STATA-16 Meta-prop package (59) was employed to find the

average estimate of HIV associated neurocognitive disorders. Heterogeneity among the forty involved studies (8, 10, 12-14, 16-49) was weighed with Q and I^2 statistics (60). An I^2 numerical value of more than 50% imply a significant degree of heterogeneity among forty studies(60). As there existed a potential heterogeneity during analysis, we further conducted a sensitivity analysis to identify an influential study outweighing the study finding. Additionally, we did a subgroup analysis regarding the country of the study, study design and the assessment tools used to screen HIV associated neurocognitive disorders. The presence /absence of a publication bias was done visually with the eye ball test (61) and eggers test of publication bias.

2.5: Review registration

This systematic review ad meta-analysis has been registered in PROSPERO with a registration number of ----------

3. Results

3.1: Identification of studies

Our electronic search in Psych-Info, EMBASE, Scopus and PubMed gave to a total of 10231 articles. Additionally 12 articles were retrieved by looking for reference list of earlier articles. Thus, a total of 10243 articles were retrieved during the overall searching process, of which 39 were removed as they were duplicates. During the initial stage of screening, most of the articles (10118) were excluded merely by looking at their title or abstract. The lasting 86 articles were completely inspected for suitability of inclusion to the study but only 40 articles were suited for final meta-analysis as the 46 studies were excluded with limitations in methodology **(Figure 1)**.

3.2: Characteristics of included studies

A total of forty studies (8, 10, 12-14, 16-49) that surveyed HIV associated neurocognitive disorders in 14107 HIV/AIDS patients were integrated in the current systematic review and meta-analysis study. Of the forty included studies; eleven were from Europe (8, 14, 20, 22, 23, 26, 27, 39, 40, 43), twenty one were from Africa(10, 13, 17, 19, 24, 29, 30, 34, 36-38, 44-49), and six were from Asia(16, 25, 33, 35, 42) (**fazel**) and two from United States of America (USA) (28, 40). Most of the included studies (28)(8, 10, 12-14, 16-19, 22, 24, 25, 27, 29, 30, 33-39, 44-49) were cross-sectional in design whereas the remaining ten and two were cohort(8, 20, 22, 23, 26, 28, 40, 42, 43) and case control(29, 62) respectively. Regarding tools used for the assessment of HIV associated neurocognitive disorders, half of the included studies (twenty) used International HIV Dementia Scale (IHDS)(8, 10, 12-14, 16, 19, 24, 34-36, 38, 42, 43, 45, 47-49, 62) . Frascati criteria, global dementia scale (GDS) and Montreal Cognitive Assessment (MoCA) were also used to assess HIV associated neurocognitive disorders in three(25, 30, 46), three(29, 37) (**Yechoor et al.2016**) and three (18, 22) (**Chan et al.2016**) studies respectively. HIV associated neurocognitive disorders were assessed on a total of 14107 HIV/AIDS patients **(Table 1).**

3.3: Quality of Included Studies

Using the modified version of Newcastle Ottawa quality assessment scale, we assessed the quality of forty studies (8, 10, 12-14, 16-49). This scale divides the quality score of 40 studies in to three; 7 to 10 categorized as very good/good, 5 to 6 categorized as having satisfactory quality and a score less than 5 as unsatisfactory quality.

Among the forty included studies; the majority (twenty nine) had scored from 7 to 10 so that good quality scores on the scale. Of the remaining eleven studies, seven had a satisfactory quality and remaining four of the studies had unsatisfactory quality.

3.4: The prevalence of HIV associated neurocognitive disorders among HIV/AIDS patients

Forty studies that evaluated HIV associated neurocognitive disorders in HIV/AIDS had been included to determine the average prevalence of HIV associated neurocognitive disorders. The reported prevalence of HIV associated neurocognitive disorders included in the meta-analysis differs from 7.3% in United Kingdom(27) to 88% in Kenya(34). The average prevalence of HIV associated neurocognitive disorders using the random effect model was 50.41% (95% CI: 45.56, 55.26). This average prevalence of HIV associated neurocognitive disorders has been affected by substantial heterogeneity (I^2 =100%, p-value ≤ 0.001) from the difference among forty included studies **(Figure 2).**

3.4: Subgroup analysis of the prevalence of HIV associated neurocognitive disorders among HIV/AIDS patients

Since the average estimate of HIV associated neurocognitive disorders was predisposed to a considerable heterogeneity, we employed a subgroup analysis based on country where the study was done, the assessment tool used to screen HIV associated neurocognitive disorders and study design. The average estimate of HIV associated neurocognitive disorders in Europe (8, 14, 20, 22, 23, 26, 27, 39, 40, 43) was found to be 50.015% (95% CI: 43.339, 56.691) whereas in Africa (10, 13, 17, 19, 24, 29, 30, 34, 36-38, 44-49), Asia (16, 25, 33, 35, 42) (**fazel**) and United States of America (USA) (28, 40) the average prevalence of HAND were 49.566% (95% CI: 41.342, 57.791) with ($I^{2=}$ 96.6%, p-value <0.001), 52.032 % (95% CI: 34.46, 69.604) with (I^2 =98%, p-value<0.001) and 50.407% (95%CI: 45.555, 55.258) (I^2 =100%, P<0.001) respectively **(Table 2).** The average estimate of HIV associated neurocognitive disorders in studies which used International HIV Dementia Scale (IHDS) (8, 10, 12-14, 16, 19, 24, 34-36, 38, 42, 43, 45, 47-49, 62) **(Webb et al.2016)** was 36.883% (95%CI: 21.196, 52.571) & 59.956% (95%CI: 49.985, 69.928) at a cutoff points of IHDS< 9.5 & IHDS<10 respectively. The estimated average of HAND in studies used the global dementia scale (GDS) (29, 37) (**Yechoor et al.2016**) was 40.766% (95%CI: 31.995, 49.537). The estimated average of HAND in cross-sectional (8, 10, 12-14, 16-19, 22, 24, 25, 27, 29, 30, 33-39, 44-49) cohort (8, 20, 22, 23, 26, 28, 40, 42, 43) and case control (29, 62) studies was 49.52% (95% CI: 43.490, 55.545) (I^2= 48.6%, P=1.00) , 54.087% (95% CI: 45.087, 63.087) (I^2= 96%%, P<0.001) and 44.45% (95% CI: 25.144, 63.756) (I^2= 94.8%, P<0.001) respectively(**Table 2)**.

3.5: Sensitivity analysis

In addition to a subgroup analysis, we did a sensitivity analysis to know whether one or more of the individual studies outweighed the overall estimate of HIV associated neurocognitive disorders. The result however reported that the average estimate of HIV associated neurocognitive disorders ranges from 46.92638% (95% CI: 46.889656, 46.963104) to 50.478935% (95% CI: 50.439026, 50.518841) when each studies were omitted from the analysis **(Table 3)**. This implies that there was no single influential study outweighing the average estimate.

3.6: Publication bias

The eggers test of publication bias had been runned and its p-value is not significant; (P-value=0.55) suggesting that there was no publication bias for the prevalence HIV associated neurocognitive disorders. Additionally, a graphical inspection from a funnel plot for a Logit event rate of occurrence of HIV associated neurocognitive disorders in HIV AIDS patients alongside its standard error suggests an accommodating evidence for the nonexistence of a publication bias **(Figure 3).**

3.7: Associated factors of HIV associated neurocognitive disorders among HIV/AIDS patients

Among the forty studies, only fifteen studies described the factors related with HIV associated neurocognitive disorders (8, 10, 12, 14, 17, 19, 20, 24, 25, 33, 34, 45-48). The most frequently reported sociodemographic variable as associated factor of HIV associated neurocognitive disorders were low level of education(12, 14, 17, 20, 29, 45, 46) and older age (8, 14, 19, 45, 48) Among clinical and HIV related variables late clinical stage of the illness (19, 20, 24, 48) and CD4 count of 500 cells/dl or less (8, 17, 45) were the most commonly described factor for HIV associated neurocognitive disorders. In addition, from psychological variables comorbidity of depression increases the risk of HIV associated neurocognitive disorders (14, 20, 34). Moreover, clinical and HIV related variables such as impairment in the activity of daily living(19), duration of HIV infection > 5 years (25), poor medication adherence (45), co-morbid medical illness, highest prior VL >100,000 copies/ml(8), history of neurological disease(20), use of benzodiazepines(33), body mass index< 16 kg/m^2 (24), plasma HIV-1 RNA load between 1.7log10 and 3log10 copies/ml(48), having co-morbid opportunistic infection(19) and psychological variables like negative life events, high stress score index (score>10) (10), generalized anxiety symptoms (20), and substance use (19, 48) were related to HIV associated neurocognitive disorders **(Table 4).**

3.7. 1 Association between old age and HIV associated neurocognitive disorders among HIV/AIDS patients

Older age was reported as the risk factor for HIV associated neurocognitive disorders by five studies (8, 14, 19, 45, 48).

3.7.2 Association between depression and HIV associated neurocognitive disorders among HIV/AIDS patients

As reported with three studies (14, 20, 34) that assessed HIV associated neurocognitive disorders, depression increases the risk of HIV associated neurocognitive disorders.

3.7.3 Association between advanced stages of AIDS and HIV associated neurocognitive disorders among HIV/AIDS patients

Advanced clinical stages of the illness (stage III and stage IV AIDS) (19, 20, 24, 48) were also associated factor for HIV associated neurocognitive disorders.

4. Discussion

To our knowledge, this is the first systematic review and meta-analysis that assessed the global burden of HIV associated neurocognitive disorders in HIV/AIDS patients. So, the data synthesized will be important suggestion to varied stakeholders. Overall, forty studies (8, 10, 12-14, 16-49) that measured the prevalence of HIV associated neurocognitive disorders in 14107 participants and fifteen studies that described the factors related with HIV associated neurocognitive disorders (8, 10, 12, 14, 17, 19, 20, 24, 25, 33, 34, 45-48) were included.

The average worldwide prevalence of HIV associated neurocognitive disorders in this study was 50.41% (95% CI: 45.56, 55.26). This was higher than the result of a meta-analysis that assessed 16 studies in sub-Sahara Africa where the prevalence of HAND was 30.39% **(Neurocognitive impairment in HIV-1-infected adults in Sub-Saharan Africa: a systematic review and meta-analysis).**

This review and meta-analysis has its own strengths and limitations. Its strength begins with the use of a prespecified search strategy that minimizes reviewer's bias. The second strength was that the data extraction and quality assessment of the study was done by independent reviewers that also further minimize reviewer's bias. The implementation of subgroup analysis and sensitivity analysis to detect the source of heterogeneity was strength. On the contrary, the limitations of the present study rise from the existence of heterogeneity that might affect the conclusion of the study findings. Another limitation is that inclusion of few numbers of studies in the subgroup analysis might minimize validity of estimate.

Conclusion And Recommendation

This systematic review and meta-analysis study reported a high prevalence of HIV associated neurocognitive disorders (more than half of the participants), Sociodemographic variables such as low level of education and older age, clinical and HIV related variables such as advanced stage of the illness and CD4 count of 500 cells/dl or less and psychological variables such as comorbidity of depression increases the risk of HAND. Therefore, to increase independent functioning and improve the quality of life of individuals living with HIV/AIDS, much attention has to be given to lessen these neurocognitive disorders and adjust the allied factors essentially through routine screening and timely intervention of HAND. Moreover, policies and procedures that integrate routine screening and timely intervention of HAND to the routine anti-retroviral therapy should be designed and implemented. Further experimental and follow up studies with greater samples population in the area should be done.

Abbreviations

AIDS: Acquired Immune-Deficiency Syndrome, ANI: Asymptomatic neurocognitive impairment, CC: case control, CD: Cognitive decline, CS: cross-sectional, F: female, GDS: global dementia scale, HAD: HIV associated dementia, HAND: HIV associated neurocognitive disorders, IHDS: International HIV Dementia Scale, II: Intellectual impairment, M: male, MMSE: Mini-mental state exam, MND: Mild neurocognitive disorders, MoCA: Montreal Cognitive Assessment, NA: Not available, NCI: Neurocognitive impairment, SNI: Symptomatic neurocognitive impairment, UK: United kingdom, USA: united states of America.

Declarations

Data availability

All relevant data regarding this research work is included in the manuscript.

Ethical approval

N/A

Conflict of interest

No potential conflict of interest for this study.

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Authors contribution

YZ imagined the idea for the study. YZ & MN established the search approach, extract the relevant data, accomplished the analysis, and inscribed the manuscript. MN, YZ, BA & WY did the quality assessment studies. All authors confirmed the last draft of the manuscript.

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Tables

Table 1:

ear on	Country	Study design	Sample size	Tools with cut off points	Sampling Technique	Response Rate	Age of respondents	Prevalence of outcome	Cases with the outcome
t	Botswana	CS	120	IHDS ≤ 9.5	Randomly selected	100%	M & F 21-50 years		47
et	Brazil	CS	434	IHDS ≤ 10	NA	90.3%	M & F ≥ 18 years	HAND =54.1%	235
	Iran	CS	93	Frascati neuropsychological criteria	NA	100%	M & F 18–60 years	HAND=50.5%	47
et	UK	CS	150	ADC	Randomly selected		M & F Median age = 43 years	HAND =7.3%	11
	Malawi	CS	106	Frascati criteria	Consecutively	93.8%	M & F >18 years	HAND =70%	74
et	Nigeria	CS	80	Frascati criteria	NA	100%	≥18 years	HAND=40%	32
t	Ethiopia	CS	254	International HIV Dementia Scale (IHDS) ≤ 9.5	Systematic random sampling technique	92.1%.	M & F 18-64 years	HAND=33.3%	85
	Ethiopia	CS	584	Mini-mental state exam	Systematic random sampling	99.49%	≥ 18 years	HAND=35.6%	208
et	Ethiopia	CS	328	International HIV Dementia Scale (IHDS)	Systematic random sampling	97.04%	≥ 18 years	HAND=37.7%	124
	Ethiopia	CS	423	International HIV Dementia Scale (IHDS)	Systematic random sampling	100%	≥ 18 years	HAND=24.8%	105
ıro 0	Zimbabwe	CSC	155	GDS ≥ 0.5		100%	M & F 18 years or older	HAND=49.7%	77
et	Ethiopia	CS	595	International HIV Dementia Scale (IHDS) ≤ 9.5	Systematic random sampling technique	99%	M & F 18 and 65 years	HAND=36.4%	217
	Italy	cohort	206	MMSE		100%	>18 years	HAND= 47.1%	97
	Central African Republic	CS	244	International HIV Dementia Scale (IHDS) ≤ 8.36		100%	M & F >18 Years	HAND= 25%	61
	Kenya	CS	218	MoCA < 26.	Consecutively sampled	98.6%	18 – 65 years	HAND = 69%	150
et	India	CS	101	International HIV Dementia Scale (IHDS) ≤ 10	Convenient sampling	100%	M & F 18-60 years	HAND=90.1%	91
ı et	Nigeria	Prospective	58	WAIS		100%	M & F >16 years	HAND=63.8%	37
n et	Europe and Canada	CS	2884	Brief Neurocognitive Screen		99.3%	M & F ≥18 years	HAND=41.5%	1197
	Singapore	CS	132	MoCA		100%	M & F 21 to 80 years	HAND =22.7%	30

et	China	Cohort	192	Neuropsychological battery		94.6%	Mean (SD)= 40.2 (6.3)	HAND = 27%	
et	USA	cohort	268	ADC stage ≥ 1		89.6%	Median=47.0 (43.0–57.0)	HAND = 48%	129
a et	Uganda	CS	156	IHDS	Consecutively recruited	100%	M & F 18–59 years	HAND =64.7%	101
n et	USA	cohort	1160	Brief Neuro-Cognitive Screen	Randomized Trials	100%	M & F 34-55 years	HAND=65%	754
	Singapore	Cohort	53	Montreal Cognitive Assessment (MoCA)= ≥ 26 MMSE IHDS≤10		100%	Males >21 years	HAND=52.8%	28
t	Zambia	C-C	266	GDS ≥ 0.5		100%	M & F 18 to 65 years	HAND=34.6 %	93
et	Uganda	CS	181	GDS≥ 0.5		100%	M & F 18–50 years	HAND =38%	69
	Uganda	CS	680	International HIV Dementia Scale (IHDS)≤10		90.9%	M & F ≥18 years	HAND=64.4%.	438
et	Brazil	CS	114	International HIV Dementia Scale (IHDS)≤10		97.4%	M & F ≥18 years	HAND =53.2%	61
	Switzerland	Cohort	30	In-depth neuropsychological assessment		100%	M & F ≥18 years	HAND=83%	25
e et	Nigeria	CC	208	IHDS≤10 MMSE=26	Consecutively	100%	M & F 18-60 years	HAND=54.3%	113
et	Cameroon	CS	400	International HIV Dementia Scale (IHDS)≤10	Consecutively	100%	M & F 18 to 55 years	HAND =85%	340
t	France	Cohort	400	Neurocognitive tests	Consecutively	100%	M & F ≥18 years	HAND =58.5%	234
et	Belgium	Cohort	200	International HIV Dementia Scale (IHDS)≤10			M & F Median age of 46 (range 30.3–69.6) years.	HAND= 84%	168
	India	cohort	80	International HIV Dementia Scale (IHDS)≤10	Randomly selected	100%	21 to 50 years	HAND=32.50%	29
	Germany	Cohort	480	International HIV Dementia Scale (IHDS)≤10			M & F 19 to 80 years	HAND=43%	207
	Nigeria	CS	418	International HIV Dementia Scale (IHDS) ≤ 9.5		100%	M & F ≥18 years	HAND =21.5%	90
ra et	Ireland	CS	604	Weschler Adult Intelligence Scale		100%	M & F >18 years	HAND =51.5%	311
t	Ethiopia	CS	684	International HIV	Systematic	98%	M & F	HAND =67.1%	459

				Dementia Scale (IHDS) <9.5	random sampling method		18 to 64 years		
ıdi et	India	CS	33	International HIV Dementia Scale (IHDS)≤10	Consecutively	100%	M & F 25 to 50 years	HAND =63.6%	21
et	Kenya	CS	345	International HIV Dementia Scale (IHDS) ≤10 MOCA≤26	Convenient sample	100%	M & F Mean age=42 years (SD ± 9.5)	HAND =88%	304

Keys: ANI: Asymptomatic neurocognitive impairment, CC: case control, CD: Cognitive decline, CS: cross-sectional, F: female, GDS: global dementia scale, HAD: HIV associated dementia, HAND: HIV associated neurocognitive disorders, IHDS: International HIV Dementia Scale, II: Intellectual impairment, M: male, MMSE: Mini-mental state exam, MND: Mild neurocognitive disorders, MoCA: Montreal Cognitive Assessment, NA: Not available, NCI: Neurocognitive impairment, SNI: Symptomatic neurocognitive impairment, UK: United kingdom, USA: united states of America.

Table 2: A subgroup analysis of the prevalence of HIV associated neurocognitive disorders in HIV/AIDS patients based on random effect analysis

Subgroup		Number of studies	Estimates		Heterogeneity	
			Prevalence	95% CI	I^2	P-value
Country	Africa	21	49.566	41.342, 57.791	96.6%	P<0.001
	Europe	11	50.015	43.339, 56.691	46.6%	P=1.00
	Asia	6	52.032	34.46, 69.604	98%	P<0.001
	USA	2	50.407	45.555, 55.258	100%	P<0.001
Assessment tools used	IHDS< 9.5	6	36.883	21.196, 52.571	99.4%	P<0.001
	IHDS< 10	14	59.956	49.985, 69.928	56.6%	P<0.05
	Frascati criteria	3	53.5	36.457, 70.543	90.6%	P<0.001
	ADC	2	27.65	-12.234, 67.536	99%	P<0.001
	MMSE	2	41.349	30.080, 52.619	100%	P<0.001
	GDS	3	40.766	31.995, 49.537	99.8%	P<0.001
	MoCA	3	48.17	18.482, 77.852	0%	P=1.00
	Others	7	55.75	45.851, 65.653	68%	P<0.05
Study design	Cross-sectional	28	49.52	43.490, 55.545	48.6%	P=1.00
	Cohort	10	54.087	45.087, 63.087	96%	P<0.001
	Case control	2	44.45	25.144, 63.756	94.8%	P<0.001

Keys: IHDS: International HIV Dementia Scale, MMSE: Mini-mental state exam, MoCA: Montreal Cognitive Assessment, USA: united states of America.

Table 3: a sensitivity analysis of the prevalence of HIV associated neurocognitive disorders in HIV/AIDS patients when each indicated studies are omitted at a time with its 95% confidence interval.

No	Study omitted	Estimated prevalence of HAND	[95% Conf. Interval]
1	Lawler et al. 2010	48.55587	48.520576,48.591164
2	Pinheiro et al.2016	48.256584	48.220829, 48.292343
3	Elham et al.2020	48.443535	48.408272, 48.478798
4	Haddow et al.2012	48.594143	48.558952,48.629333
5	Kelly et al.2014	48.303158	48.267899, 48.338417
6	Yakasai et al.2015	48.511402	48.476162, 48.546646
7	Belete et al.2017	48.739456	48.703999, 48.77491
8	Araya et al.2020	49.037079	49.001163, 49.07299
9	Yitbarek et al.2019	48.732273	48.696697, 48.767849
10	Belete et al.2014	49.074566	49.038979, 49.110153
11	Debalkie et al.2019	47.50845	47.472431, 47.544464
12	Tsegaw et al.2017	49.017803	48.981865, 49.053738
13	Nyamayaro et al.2020	48.478603	48.407894, 48.443249
14	Focà et al.2016	48.481682	48.446255, 48.517109
15	Pascal et al.2016	48.808884	48.773487, 48.844276
16	Awori et al.2018	48.145374	48.109974, 48.180775
17	Achappa et al.2014	48.337997	48.302814, 48.37318
18	Sunmonu et al.2015	48.392574	48.357368, 48.427784
19	Robertson et al.2014	50.478935	50.439026, 50.518841
20	Chan et al.2016	48.652199	48.616936, 48.687466
21	Cysique et al.2010	48.723553	48.688202, 48.7589
22	Harezlaket al.2011	48.468979	48.43346, 48.504494
23	Nakasujja et al.2012	48.270924	48.235588, 48.306259
24	Robertson et al.2007	46.92638	46.889656, 46.963104
25	Chan et al.2019	48.440395	48.40519, 48.475601
26	Kabuba et al.2016	48.73357	48.698093, 48.769051
27	Yechoor et al.2016	48.604374	48.568996, 48.639748
28	Nakku et al.2013	47.618401	47.582355, 47.654449
29	Troncoso et al.2015	48.415298	48.380005, 48.450592
30	Fasel et al.2014	48.41259	48.377434, 48.447746
31	Oshinaike et al.2012	48.360401	48.324974, 48.395828
32	Atashili et al.2013	47.850132	47.814709, 47.885555
33	Bonnet et al.2013	48.135502	48.099808, 48.171196
34	Simioni et al.2010	48.149261	48.113976, 48.184547
35	Saini et al.2014	48.55426	48.519024, 48.589497
36	Webb et al.2016	48.673512	48.637695, 48.709328
37	Yusuf et al.2017	49.084835	49.049297, 49.120373
38	McNamara et al.2016	48.30397	48.267956, 48.339989
39	Muniyandi et al.2012	48.421654	48.386478, 48.456829
40	Mugendi et al.2019	47.994511	47.959171, 48.02985

Key: HAND: HIV associated neurocognitive disorders

Table 4: Characteristics of associated factors for HIV associated neurocognitive disorders in HIV/AIDS patients by their Odds ratio, Confidence interval, association strength, author and year of publication.

Associated factors	Odds ratio(AOR)	95% CI	Strength of association	Author, year of publication
Age of 50 years and older	4.85	2.34, 10.03	Strong and positive	Pinheiro et al.2016
Less than eight years of education	6.72	3.98, 11.32	Strong and positive	Pinheiro et al.2016
Non-white skin color	1.71	1.04, 2.83	Moderate and positive	Pinheiro et al.2016
Depression	1.96	1.12, 3.42	Moderate and positive	Pinheiro et al.2016
Duration of HIV infection > 5 years	3.1	1.70, 7.40	Strong and positive	Elham et al,2020
Low level of education	1.2	1.04, 1.44	Weak and positive	Ahmad M. Yakasai et al,2015
Late clinical stage of the illness	4.2	1.19,14.44	Strong and positive	Tilahun B et al, 2017
Impairment in the activity of daily living	7.19	1.73, 21.83	Strong and positive	Tilahun B et al, 2017
CD4 count of 500 cells/dl or less	2.368	1.524, 3.680	Moderate and positive	Tsegaw et al, 2017
No formal education	4.287	2.619, 7.016	Strong and positive	Tsegaw et al, 2017
Poor medication adherence	1.487	1.010, 2.180	Weak and positive	Tsegaw et al, 2017
Older age	3.309	1.259, 8.701	Strong and positive	Tsegaw et al, 2017
6 to 10 Negative life events	2.14	1.45, 3.15	Moderate and positive	Nakku et al. 2013
11 ad more Negative life events	2.35	1.33,4.13	Moderate and positive	Nakku et al. 2013
Medium Stress Score index (score 1–10)	2.55	1.73, 3.77	Moderate and positive	Nakku et al. 2013
High Stress Score index (score >10)	3.29	1.99, 5.45	Strong and positive	Nakku et al. 2013
Female gender	2.66	1.22, 5.82	Moderate and positive	Troncoso & Conterno 2015
Older age	2.87	1.24, 6.64	Moderate and positive	Troncoso & Conterno 2015

Table: Characteristics of associated factors for HIV associated neurocognitive disorders in HIV/AIDS patients by their Odds ratio, Confidence interval, association strength, author and year of publication (**continued**).

Associated factors	Odds ratio(AOR)	95% CI	Strength of association	Author, year of publication
Co-morbid medical illness	2.56	1.17, 5.55	Moderate and positive	Troncoso & Conterno 2015
CD4 count <200 cell/mm3	2.71	1.25, 5.86	Moderate and positive	Troncoso & Conterno 2015
Highest prior VL >100,000 copies/ml	2.62	1.12, 6.16	Moderate and positive	Troncoso & Conterno 2015
Low level of education	8.33	3.85, 16.67	Strong and positive	Atashili et al. 2013
Having HIV symptoms	12.16	3.08, 48.05	Strong and positive	Atashili et al. 2013
Advanced AIDS stage	4.87	1.59, 14.90	Strong and positive	Bonnet et al.2013
Techniqual school level of education	2.16	1.31,3.55	Moderate and positive	Bonnet et al.2013
Lower than diploma level of education	3.39	1.48, 7.80	Strong and positive	Bonnet et al.2013
Generalized anxiety symptoms	2.99	1.67, 5.14	Strong and positive	Bonnet et al.2013
Depression symptoms	2.11	1.23, 3.63	Moderate and positive	Bonnet et al.2013
History of neurological disease	2.05	1.18, 3.58	Moderate and positive	Bonnet et al.2013
African country of birth	11.075	4.94, 24.84	Strong and positive	McNamara et al 2016
Use of benzodiazepines	6.746	2.37, 19.18	Strong and positive	McNamara et al 2016
Unemployed	2.16	1.2, 3.84	Moderate and positive	McNamara et al 2016
Body mass index< 16 kg/m^2	4.39	1.60, 12.02	Strong and positive	Debalkie Animut M et al.2019
Unemployed status of occupation	3.18	1.752, 5.777	Strong and positive	Debalkie Animut M et al.2019
Advanced stage of AIDS	3.56	1.406–9.006	Strong and positive	Debalkie Animut M et al.2019

Table: Characteristics of associated factors for HIV associated neurocognitive disorders in HIV/AIDS patients by their Odds ratio, Confidence interval, association strength, author and year of publication (**continued**).

Associated factors	Odds ratio(AOR)	95% CI	Strength of association	Author, year of publication
Depression	7.47	1.69, 43.53	Strong and positive	A. G. Mugendi et al.2019
Female gender	2.17	1.02, 4.71	Moderate and positive	A. G. Mugendi et al.2019
Older age	3.1	1.3, 7.4	Strong and positive	Yitbarek et al.2019
Plasma HIV-1 RNA load between 1.7log10 and 3log10 copies/ml	2.2	1.1, 4.3	Moderate and positive	Yitbarek et al.2019
Plasma HIV-1 RNA load ≥ 3log10 copies/ml	7.5	2.6, 21.5	Strong and positive	Yitbarek et al.2019
Khat chewing	4.4	2.3, 8.3	Strong and positive	Yitbarek et al.2019
Advanced stage of AIDS	5.6	1.7, 19.2	Strong and positive	Yitbarek et al.2019
Having no education	3.11	1.37, 7.04	Strong and positive	T B Mossie et al 2014
Older age	4.25	1.05, 17.18	Strong and positive	T B Mossie et al 2014
Having co morbid opportunistic infection	7.48	4.1, 13.64	Strong and positive	T B Mossie et al 2014
Substance use	4.64	2.3, 9.36	Strong and positive	T B Mossie et al 2014
Having no education	5.16	2.20, 12.07	Strong and positive	Araya et al.2020
Primary education	3.29	1.46, 7.29	Strong and positive	Araya et al.2020
Having a CD4 count (cells/µl) ≤ 500	1.61	1.11, 2.39	Moderate and positive	Araya et al.2020
Lifetime use of tobacco	2.4	1.44, 4.01	Moderate and positive	Araya et al.2020

Key; AIDS: Acquired Immune deficiency Syndrome

Figures

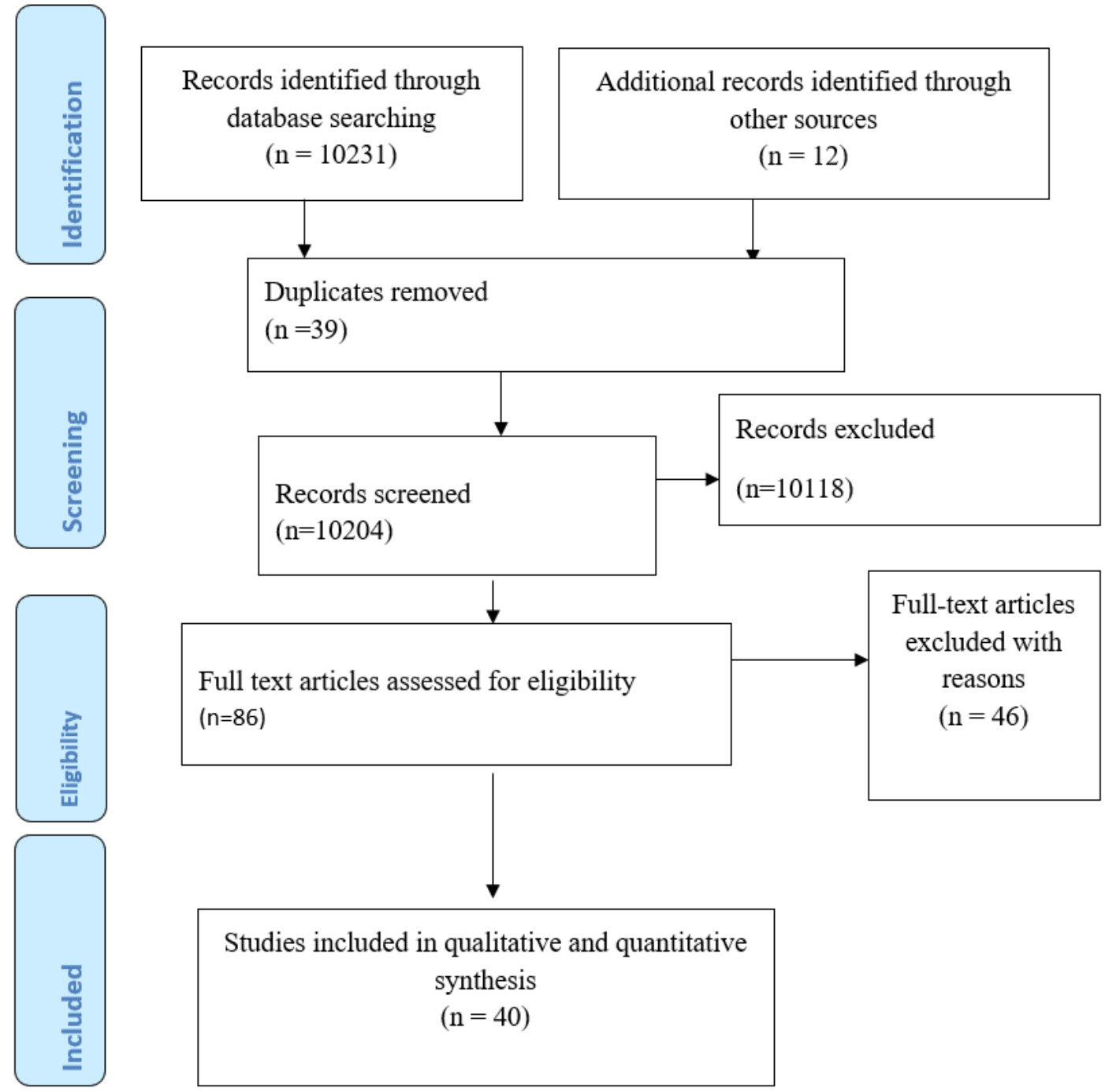

Figure 1

PRISMA flow chart for the review search process

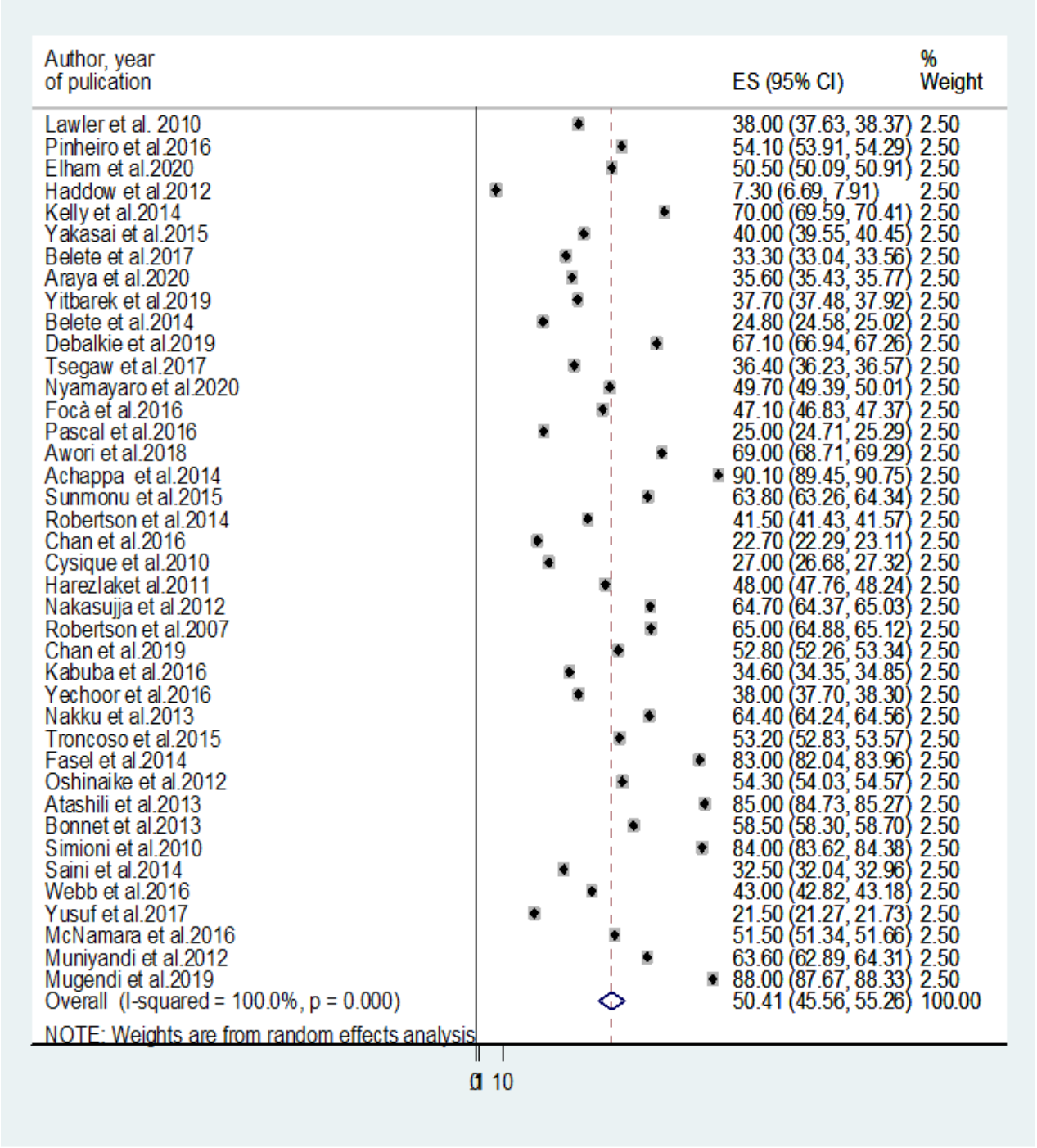

Figure 2

A forest plot for the prevalence of HIV associated neurocognitive disorders

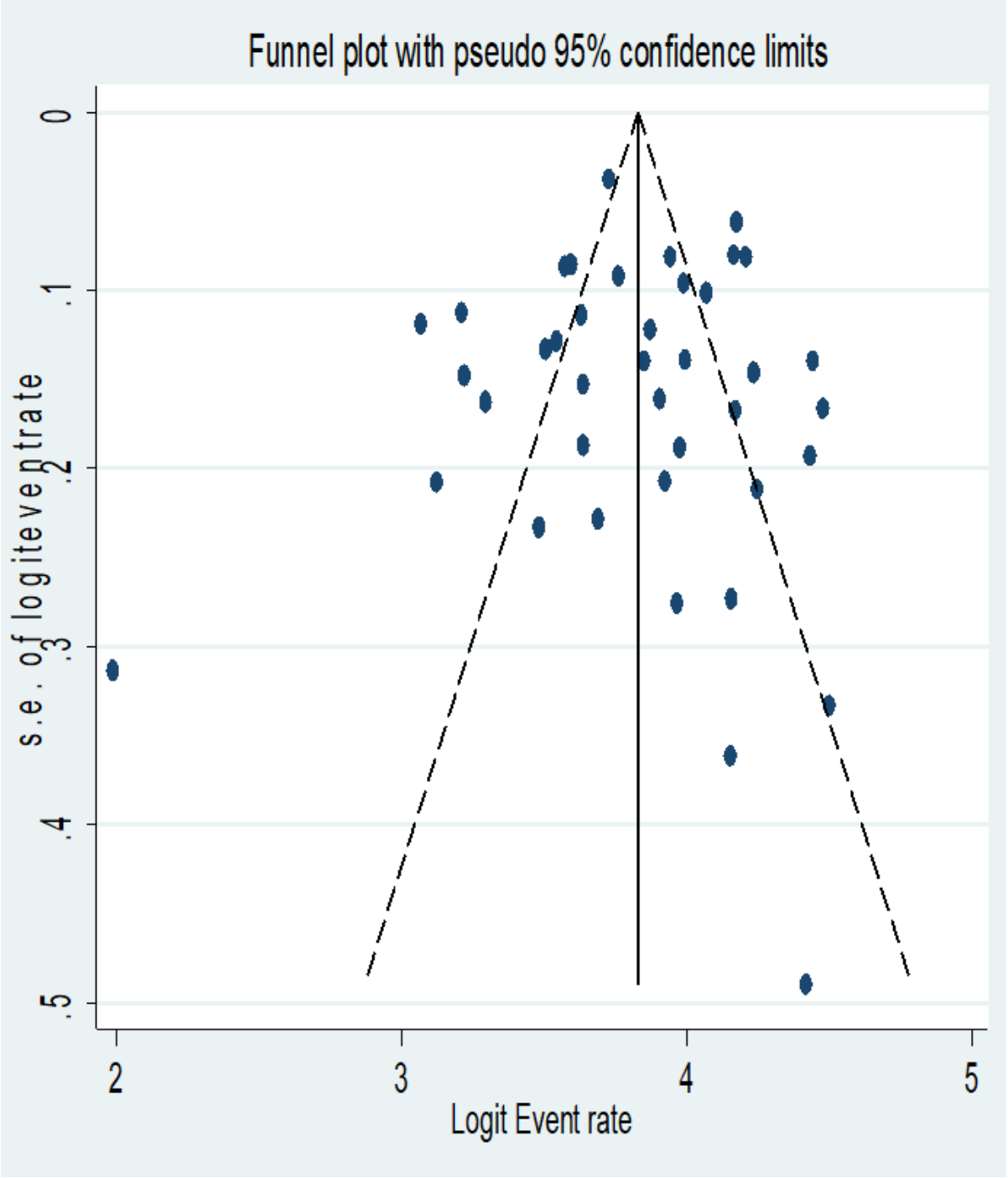

Figure 3

a funnel plot for the prevalence of HIV associated neurocognitive disorders