



Worldwide Occurrence of HIV-Associated Neurocognitive Disorders and Its Associated Factors: A Systematic Review and Meta-Analysis

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Background: HIV-associated neurocognitive disorders are common in people living with HIV/AIDS and affect the adherence of patients to prescriptions, 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 addressing this gap.

Methods: We did our electronic search in Psych-Info, EMBASE, Scopus, and PubMed. The retrieved articles were stored with the endnote reference manager and data was extracted using Meta-XL version 5.3. The quality of studies was evaluated with the 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 was checked with the 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 the United States of America (USA) it was 49.566, 52.032, and 50.407% respectively. The prevalence of HAND in studies that used the HIV Dementia Scale (IHDS) was 36.883% and 59.956% at cutoff points of IHDS < 9.5 and IHDS < 10 respectively. Besides, 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. Socio-demographic variables; low level of education and older age, clinical and HIV related variables; the 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 prevalence of HIV-associated neurocognitive disorders was about 50.41%. Low level of education and older age, clinical and HIV related variables such as

the advanced stage of the illness and CD4 count of 500 cells/dl or less, and comorbidity of depression were associated with HIV associated neurocognitive disorders. Public health interventions for HIV patients should target these essential problems.

Keywords: meta-analysis, HIV/AIDS, hand, world, wide

INTRODUCTION

HIV/AIDS is a global public health issue with more than 34 million people living with HIV/AIDS (PLHIV) currently (1). Mental, neurological, and substance (MNS) related disorders are very common in People living with HIV/AIDS (2). The latest systematic review and Meta-analysis studies by Necho et al. (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), and 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 subcortical parts of the brain resulting in cognitive impairment (7). This impact of HIV on the cognitive domain of patients is known as HIV-associated neurocognitive disorder (HAND) (8, 9). The level of HAND ranges from asymptomatic impairment to minor neurocognitive disorder and full-blown dementia (10–13). The HIV-associated neurocognitive disorder affects memory, attention, problem-solving ability, language, higher executive function, and independent activities of daily living (14).

HIV-associated neurocognitive disorders are very common in HIV/AIDS patients (15). A study by Habib et al. (16) reported that the burden of neurocognitive impairment (NCI) among patients on Antiretroviral therapy (ART) attendants was 30.39%. Based on the report of multiple earlier studies the worldwide burden of HIV-associated neurocognitive disorders (HAND) varies from a minimum of 7.3% to a maximum of 85% (8, 10, 12–14, 17–50). Besides, the frequency of HIV-associated neurocognitive disorder (HAND) in developed and developing countries varies between 19–52% (31, 51), and 14–64% (12, 13), respectively.

Different studies reported varieties of socio-demographic and clinical factors associated with HIV-associated neurocognitive disorders in people living with HIV/AIDS. For example studies from, Cameroon, Nigeria, Botswana, Singapore, Malawi, and Dessie Ethiopia reported that socio-demographic variables such as older age, female sex, and lower educational level were risk factors for HIV associated neurocognitive disorder (13, 14, 46, 50, 52, 53). Besides, 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, 50, 54). Moreover, advanced stages of AIDS and not being on highly active antiretroviral treatment (HAART) were associated with HIV-associated neurocognitive disorder in South Africa (51–53). 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 (46, 55).

The presence of HIV-associated neurocognitive disorder predisposes people living with HIV/AIDS to substance abuse, poor medication adherence, and unsafe sex so the poor quality of life and loss of follow-up from treatment are outcomes. These conditions speed up the progression of the virus to its advanced stages and the development of severe opportunistic infections and death (11, 12).

Even though a high proportion of the world population has been living with HIV/AIDS and a high prevalence of mental, neurological, and substance use disorders in this population, these problems, especially neurocognitive disorders, are not investigated well. Despite the presence of some studies in the area, they are mostly confined to a small population and a narrow geographical area (8, 10, 12–14, 17–50). Consequently, there arises a need to have aggregate data regarding HIV-associated neurocognitive disorder and its associated factors from the global context.

Therefore, this systematic review and meta-analysis aimed to estimate the prevalence of HIV-associated neurocognitive disorder in people living with HIV AIDS and to analyze the associated factors for HIV-associated neurocognitive disorder in people with HIV AIDS.

METHODS

Search Strategy

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 disorders in people living with HIV AIDS in the databases of Psych-Info, EMBASE, Scopus, and PubMed. As a sample of our search strategy with the PubMed database, we have used the following key terms: **[(neurocognitive disorder or HIV-associated neurocognitive disorder or HAND) and (adults)] and (Human immunodeficiency virus or HIV or acquired immunodeficiency syndrome or AIDS)**. Moreover, Psych-Info, EMBASE, and Scopus databases were investigated in line with the searching guidelines of each database. Besides, the reference lists of included studies were searched manually for additional eligible

Abbreviations: AIDS, Acquired Immune-Deficiency Syndrome; ANI, Asymptomatic neurocognitive impairment; ART, Anti-Retroviral Therapy; 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.

articles. There was no time restriction to the publication year of the articles during the searching process.

Eligibility Criteria

During our study of a systematic review and meta-analysis on HIV-associated neurocognitive disorder in people living with HIV/AIDS, we have set the following inclusion and exclusion criteria based on the: 1) the primary inclusion criteria to analyze where the study should assess prevalence OR associated factors of HIV-associated neurocognitive disorder in people living with HIV/AIDS. 2) The HIV-associated neurocognitive disorder had also to be investigated using the 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 taking psychotropic medication. (3) Studies that are letters to the editor with non-original data content, earlier reviews, case studies, studies involving non-human subjects, and articles published in a language other than the English language were also excluded from the analysis. After all relevant articles were searched in the mentioned databases; 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. Next to that, the above two authors carefully read the full length of articles that passed the initial screening and decided independently articles suitable for inclusion in the final meta-analysis. Any disagreement between them regarding eligibility criteria was resolved by agreement and with a third reviewer (WY).

Data Extraction and Quality Assessment Techniques

The extraction of relevant data from the 40 final included articles was separately done by two authors (MN and YZ) using an identical data extraction form as suggested by PRISMA guidelines (56), using Meta-XL version 5.3 (57) and the result was summarized in a table. Disagreements among these two authors were settled with a discussion. The contents of the data extraction template were author name, year of publication, the country where the study was done, study design, study sample population, an 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 40 included studies (8, 10, 12–14, 17–50) had been evaluated using the modified Newcastle–Ottawa Scale (NOS) (58) as the 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, a

score of 5 to 6 was categorized as having satisfactory quality, and a score less than 5 was taken as unsatisfactory quality.

Data Analysis and Synthesis

The random-effect model was used to compute the average estimate of HIV-associated neurocognitive disorders and their associated factors with 95% CIs (59). The STATA-16 Meta-prop package (60) was employed to find the average estimate of HIV-associated neurocognitive disorders. Heterogeneity among the 40 involved studies (8, 10, 12–14, 17–50) was weighed with Q and I^2 statistics (61). An I^2 numerical value of more than 50% implies a significant degree of heterogeneity among 40 studies (61). As there existed a potential heterogeneity during analysis, we further conducted a sensitivity analysis to identify an influential study outweighing the study found. 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 with the funnel plot test (62) and eggert test of publication bias.

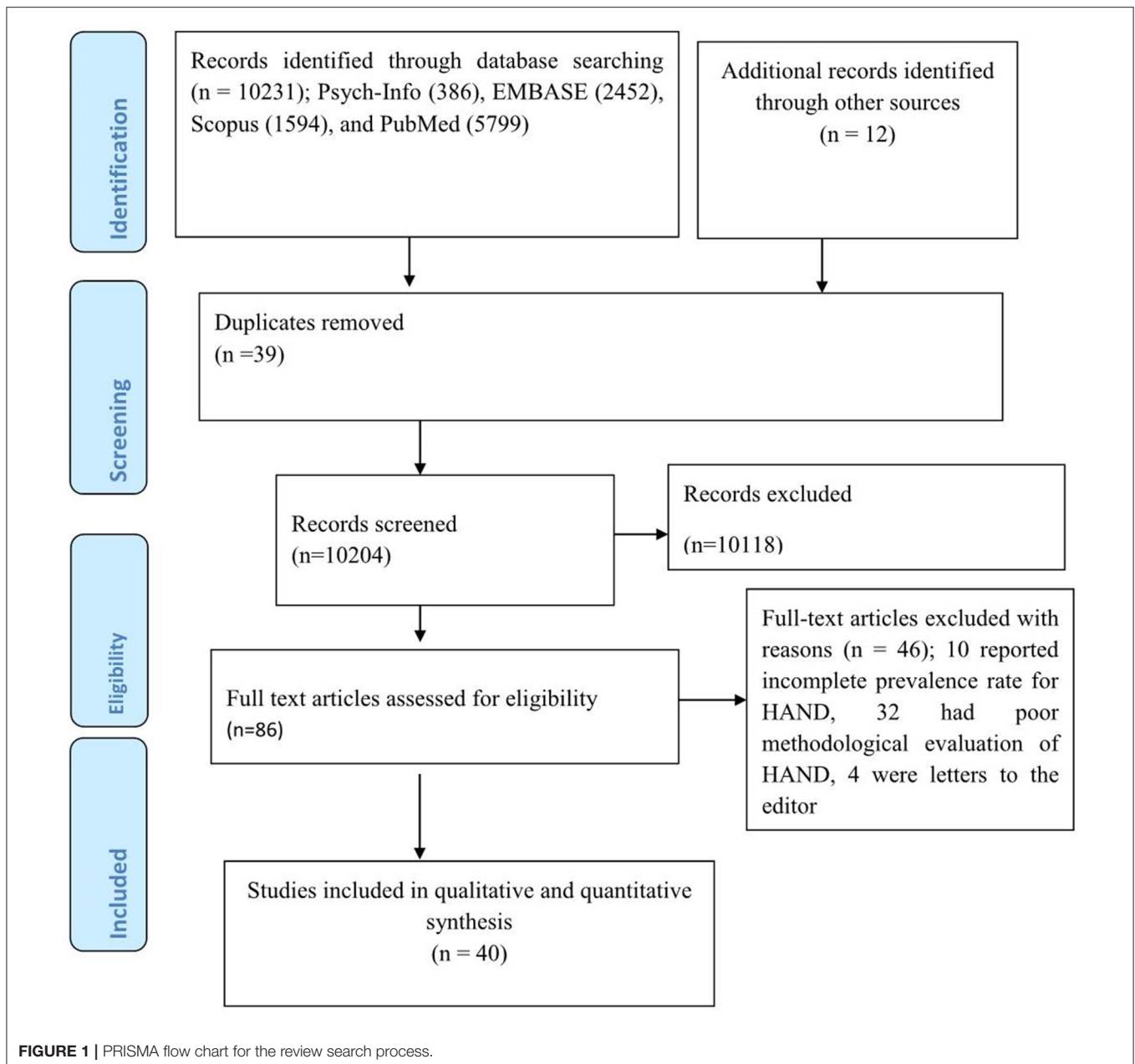
RESULTS

Identification of Studies

Our electronic search gave a total of 10231 articles; Psych-Info (386), EMBASE (2,452), Scopus (1,594), and PubMed (5,799). Additionally, 12 articles were retrieved by looking for a reference list of earlier articles. Thus, a total of 10,243 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 (10,118) were excluded merely by looking at their title or abstract. The remaining 86 articles were completely inspected for suitability for inclusion in the study but only 40 articles were suited for the final meta-analysis as the remaining 46 studies were excluded; 10 reported an incomplete prevalence rate for HAND, 32 had a poor methodological evaluation of HAND, and 4 were letters to the editor (Figure 1).

Characteristics of Included Studies

A total of 40 studies (8, 10, 12–14, 17–50) that surveyed HIV-associated neurocognitive disorders in 14,107 HIV/AIDS patients were integrated into the current systematic review and meta-analysis study. Of the 40 included studies; 11 were from Europe, 21 were from Africa, six were from Asia, and two were from the United States of America (USA). Most of the included studies were cross-sectional in design whereas the remaining 10 and 2 were cohort and case-control, respectively. Regarding tools used for the assessment of HIV-associated neurocognitive disorders, half of the included studies (twenty) used the International HIV Dementia Scale (IHDS). Frascati criteria, global dementia scales (GDS), and Montreal Cognitive Assessment (MoCA) were also used to assess HIV-associated neurocognitive disorders in three, three, and three studies, respectively. The reported prevalence of HIV-associated neurocognitive disorders included in the meta-analysis differs from 7.3% in the United Kingdom (28) to 88% in Kenya (35) (Table 1).



Quality of Included Studies

Among the 40 included studies; the majority (twenty-nine) had scored from 7 to 10 so good quality scores on the scale. Of the remaining 11 studies, seven had a satisfactory quality, and the remaining four studies had unsatisfactory quality (Additional File 1).

The reported prevalence of HIV-associated neurocognitive disorders included in the meta-analysis differs from 7.3% in the United Kingdom (28) to 88% in Kenya (35). The average prevalence of HIV-associated neurocognitive disorders using the random effect model was 50.41% (95% CI: 45.56, 55.26) ($I^2 = 100\%$, $p \leq 0.001$; **Figure 2**).

The Prevalence of HIV-Associated Neurocognitive Disorders Among People Living With HIV/AIDS

Forty studies that evaluated HIV-associated neurocognitive disorders in HIV/AIDS had been included to determine the average prevalence of HIV-associated neurocognitive disorders.

Subgroup Analysis of the Prevalence of HIV Associated Neurocognitive Disorders Among People Living With HIV/AIDS

Since the average estimate of HIV-associated neurocognitive disorders was predisposed to considerable heterogeneity, we employed a subgroup analysis based on the country where

TABLE 1 | Characteristics of studies on HIV associated neurocognitive disorders in HIV/AIDS patients which are incorporated in this meta-analysis.

References	Country	Study design	Sample size	Tools with cut off points	Sampling technique	Response rate	Age of respondents	Prevalence of HAND	Cases with the outcome	CD4 count	Viral load	Study population
Lawler et al. (13)	Botswana	CS	120	IHDS \leq 9.5	Randomly selected	100%	M & F 21-50 years	39.2%	47	20%, CD4 count <200/mm3	80%, <400 copies/ml	HIV positive individuals
Pinheiro et al. (14)	Brazil	CS	434	IHDS \leq 10	NA	90.3%	M & F \geq 18 years	HAND =54.1%	235	14.4%, CD4 count <200/mm3	6.3%, <50 copies/ml	HIV positive individuals
Elham et al. (26)	Iran	CS	93	Frascati neuropsychological criteria	NA	100%	M & F 18-60 years	HAND=50.5%	47	Mean CD4 count is 536.47(254.4)		On ART patients
Haddow et al. (28)	UK	CS	150	ADC	Randomly selected		M & F Median age = 43 years	HAND =7.3%	11	Median, 540 cells/mL		HIV positive people
Kelly et al. (31)	Malawi	CS	106	Frascati criteria	Consecutively	93.8%	M & F >18 years	HAND =70%	74	Median CD4 count 323.5		On ART patients
Yakasai et al. (47)	Nigeria	CS	80	Frascati criteria	NA	100%	\geq 18 years	HAND=40%	32			Both ART& ART naïve patients
Belete et al. (20)	Ethiopia	CS	254	IHDS \leq 9.5	Systematic random sampling technique	92.1%.	M & F 18-64 years	HAND=33.3%	85	10.7%, CD4 count <200/mm3		HIV positive people
Araya et al. (18)	Ethiopia	CS	584	Mini-mental state exam	Systematic random sampling	99.49%	\geq 18 years	HAND=35.6%	208			
Yitbarek et al. (49)	Ethiopia	CS	328	IHDS	Systematic random sampling	97.04%	\geq 18 years	HAND=37.7%	124			
Belete et al. (20)	Ethiopia	CS	423	IHDS	Systematic random sampling	100%	\geq 18 years	HAND=24.8%	105			
Nyamayaro et al. (38)	Zimbabwe	CS	155	GDS \geq 0.5	NA	100%	M & F 18 years or older	HAND=49.7%	77	Median (range) CD4 count 520 (300-699)		On ART patients
Tsegaw et al. (46)	Ethiopia	CS	595	International HIV Dementia Scale (IHDS) \leq 9.5	Systematic random sampling technique	99%	M & F 18 and 65 years	HAND=36.4%	217	60.9%, CD4 count <500/mm3		On ART patients
Focà et al. (27)	Italy	cohort	206	MMSE		100%	>18 years	HAND= 47.1%	97			
Pascal et al. (39)	Central African Republic	CS	244	International HIV Dementia Scale (IHDS) \leq 8.36		100%	M & F >18 Years	HAND= 25%	61	Average CD4 was 175 \pm 126 CD4/mm3		On ART patients
Awori et al. (19)	Kenya	CS	218	MoCA < 26.	Consecutively sampled	98.6%	18 – 65 years	HAND = 69%	150			HIV positive people
Achappa et al. (17)	India	CS	101	IHDS \leq 10	Convenient sampling	100%	M & F 18-60 years	HAND=90.1%	91	Mean CD4, 450.9 \pm 283.49		On ART patients

(Continued)

TABLE 1 | Continued

References	Country	Study design	Sample size	Tools with cut off points	Sampling technique	Response rate	Age of respondents	Prevalence of HAND	Cases with the outcome	CD4 count	Viral load	Study population
Sunmonu et al. (45)	Nigeria	Prospective	58	WAIS		100%	M & F >16 years	HAND=63.8%	37	None has CD4 count <200/mm3		HIV positive people
Robertson et al. (40)	Europe and Canada	CS	2,884	Brief Neurocognitive Screen		99.3%	M & F ≥18 years	HAND=41.5%	1,197			Both ART& ART naïve patients
Chan et al. (9)	Singapore	CS	132	MoCA		100%	M & F 21 to 80 years	HAND =22.7%	30			
Cysique et al. (24)	China	Cohort	192	Neuropsychological battery		94.6%	Mean (SD)= 40.2 (6.3)	HAND = 27%		Median rangeCD4 count 375 (11–1,173)		HIV positive people
Harezlak et al. (29)	USA	cohort	268	ADC stage ≥ 1		89.6%	Median=47.0 (43.0–57.0)	HAND = 48%	129			On ART patients
Nakasujja et al. (37)	Uganda	CS	156	IHDS	Consecutively recruited	100%	M & F 18–59 years	HAND =64.7%	101			HIV positive people
Robertson et al. (41)	USA	cohort	1,160	Brief Neuro-Cognitive Screen	Randomized Trials	100%	M & F 34–55 years	HAND=65%	754	Median(range) CD4 count 424 (438–408)		On ART patients
Chan et al. (23)	Singapore	Cohort	53	(MoCA)= ≥ 26 MMSE IHDS≤10		100%	Males >21 years	HAND=52.8%	28			HIV positive people
Kabuba et al. (30)	Zambia	C-C	266	GDS ≥ 0.5		100%	M & F 18 to 65 years	HAND=34.6 %	93	Mean CD4 count/SD 480.28 (242.60)	80.6%, undetectable viral load	On ART patients
Yechor et al. (63)	Uganda	CS	181	GDS ≥ 0.5		100%	M & F 18–50 years	HAND =38%	69			On ART patients
Nakku et al. (10)	Uganda	CS	680	International HIV Dementia Scale (IHDS) ≤10		90.9%	M & F ≥18 years	HAND=64.4%.	438		Undetectable VL, 66.6% (n=76)	HIV positive people
Troncoso et al. (8)	Brazil	CS	114	International HIV Dementia Scale (IHDS) ≤10		97.4%	M & F ≥18 years	HAND =53.2%	61	7.9%, CD4 count <200/mm3	1.8%, VL ≥100,000 copies/ml	On ART patients
Fasel et al. (64)	Switzerland	Cohort	30	In-depth neuropsychological assessment		100%	M & F ≥18 years	HAND=83%	25	Median CD4 count, 658 cells/μL (IQR 497–814)		HIV positive people
Oshinaike et al. (65)	Nigeria	CC	208	IHDS≤10 MMSE=26	Consecutively	100%	M & F 18–60 years	HAND=54.3%	113	Mean CD4 count/SD 257.2		On ART patients

(Continued)

TABLE 1 | Continued

References	Country	Study design	Sample size	Tools with cut off points	Sampling technique	Response rate	Age of respondents	Prevalence of HAND	Cases with the outcome	CD4 count	Viral load	Study population
Atashili et al. (12)	Cameroon	CS	400	International HIV Dementia Scale (IHDS) ≤ 10	Consecutively	100%	M & F 18 to 55 years	HAND =85%	340			On ART patients
Bonnet et al. (21)	France	Cohort	400	Neurocognitive tests	Consecutively	100%	M & F ≥ 18 years	HAND =58.5%	234	Median CD4 cell count was 515 cells/ml		On ART patients
Simioni et al. (44)	Belgium	Cohort	200	IHDS ≤ 10			M & F, Median age of 46.	HAND= 84%	168			
Saini et al. (43)	India	cohort	80	IHDS ≤ 10	Randomly selected	100%	21 to 50 years	HAND=32.50%	29			On ART patients
Marin-Webb et al. (33)	Germany	Cohort	480	International HIV Dementia Scale (IHDS) ≤ 10			M & F 19 to 80 years	HAND=43%	207	Median CD4 cell count was 554cells/ml		On ART patients
Yusuf et al. (50)	Nigeria	CS	418	IHDS ≤ 9.5		100%	M & F ≥ 18 years	HAND =21.5%	90			On ART patients
McNamara et al. (34)	Ireland	CS	604	Weschler Adult Intelligence Scale		100%	M & F >18 years	HAND =51.5%	311	Mean/SD CD4 cell count was 538/259.16cells/ml		Both ART& ART naïve patients
Debalkie Animut et al. (25)	Ethiopia	CS	684	International HIV Dementia Scale (IHDS) <9.5	Systematic random sampling method	98%	M & F 18 to 64 years	HAND =67.1%	459	Mean CD4 count was 610 \pm 278 cells/mm3		On ART patients
Muniyandi et al. (36)	India	CS	33	IHDS ≤ 10	Consecutively	100%	M & F 25 to 50 years	HAND =63.6%	21			
Mugendi et al. (35)	Kenya	CS	345	International HIV Dementia Scale (IHDS) ≤ 10 MOCA ≤ 26	Convenient sample	100%	M & F Mean age=42 years (SD \pm 9.5)	HAND =88%	304	Median CD4 count, 446 cells/ mm3 (IQR) 278–596		On ART patients

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.

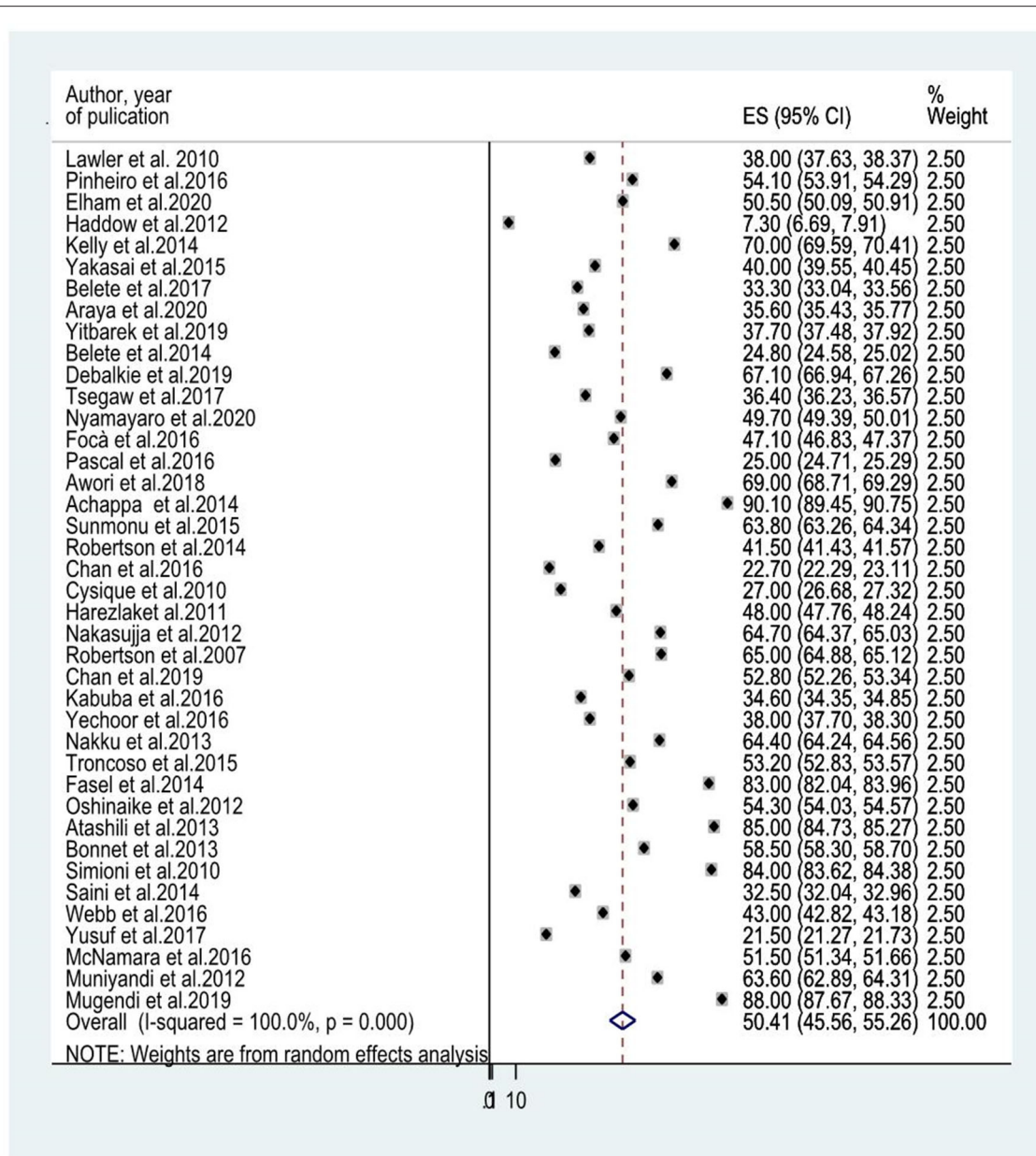


FIGURE 2 | A forest plot for the prevalence of HIV associated neurocognitive disorders.

the study was done, the assessment tool used to screen HIV-associated neurocognitive disorders, and the study design. The average estimate of HIV associated neurocognitive disorders in Europe (8, 14, 21, 23, 24, 27, 28, 40, 41, 44) was found to be 50.015% (95% CI: 43.339, 56.691) whereas in Africa (10, 13, 18, 20, 25, 30, 31, 35, 37–39, 45–50), Asia (17, 26, 34, 36, 43) and the United States of America (USA) (29, 41) the average prevalence of HAND were 49.566% (95% CI: 41.342, 57.791) with ($I^2 = 96.6%$, $p < 0.001$), 52.032 % (95% CI: 34.46, 69.604) with ($I^2 = 98%$, $p < 0.001$) and 50.407% (95%CI: 45.555, 55.258) ($I^2 = 100%$, $P < 0.001$), respectively (**Figure 3** and **Table 2**). The average estimate

of HIV associated neurocognitive disorders in studies which used International HIV Dementia Scale (IHDS) (8, 10, 12–14, 17, 20, 25, 35–37, 39, 43, 44, 46, 48–50, 66) was 36.883% (95%CI: 21.196, 52.571) and 59.956% (95%CI: 49.985, 69.928) at a cutoff points of IHDS < 9.5 and IHDS < 10, respectively (**Figure 4**). The estimated average of HAND in studies used the global dementia scale (GDS) (30, 38) was 40.766% (95%CI: 31.995, 49.537). The estimated average of HAND in cross-sectional (8, 10, 12–14, 17–20, 23, 25, 26, 28, 30, 31, 34–40, 45–50) cohort (8, 21, 23, 24, 27, 29, 41, 43, 44) and case-control (30, 66) studies was 49.52% (95% CI: 43.490, 55.545) ($I^2 = 48.6%$, $P = 1.00$), 54.087% (95%

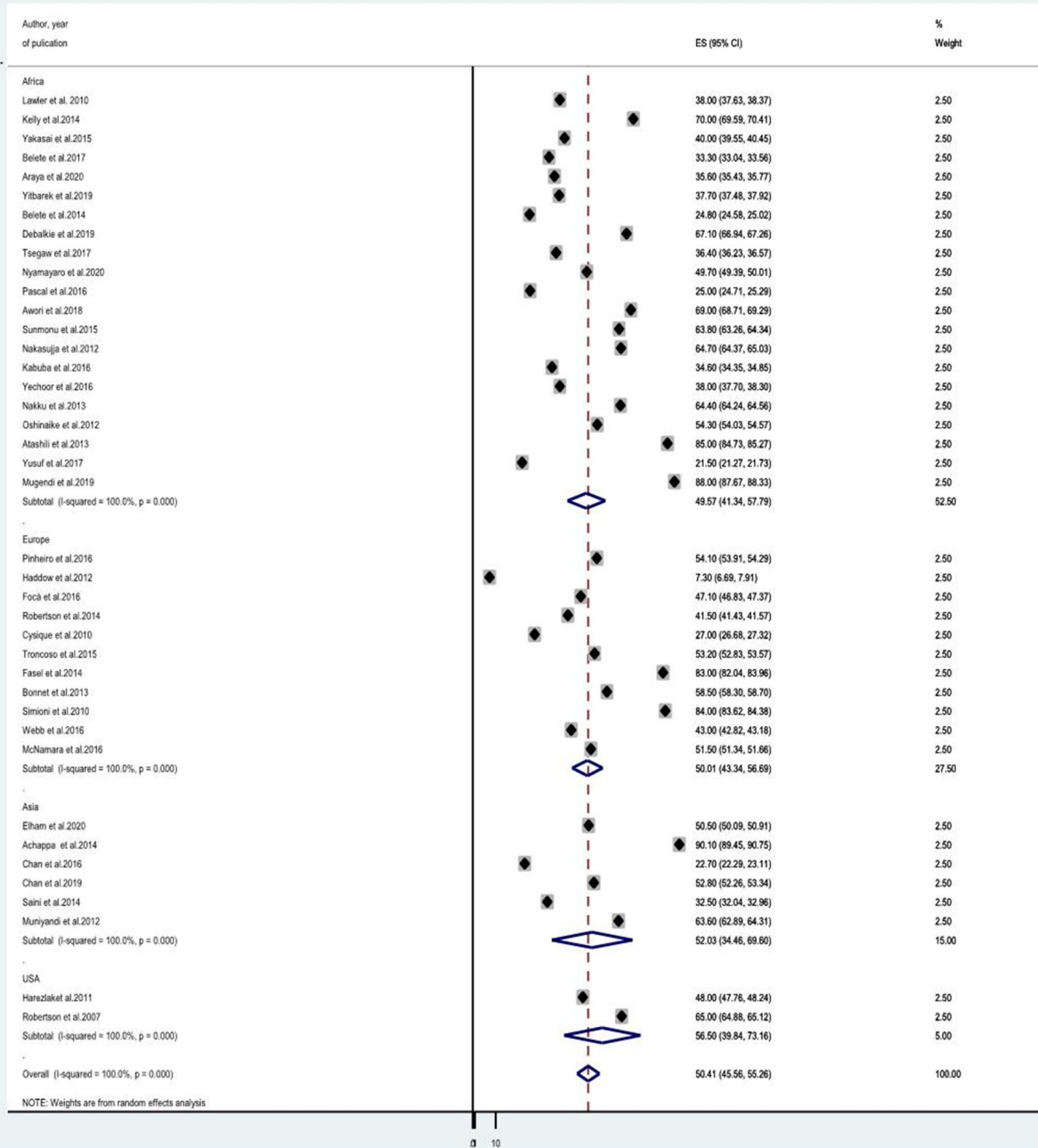


FIGURE 3 | A subgroup analysis for the prevalence of HIV associated neurocognitive disorders based on country of study origin.

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 (Figure 5).

Sensitivity Analysis

In addition to 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 study was omitted from the analysis (Table 2). This implies

TABLE 2 | 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.

S.No	Study omitted	Estimated prevalence of HAND	[95% Conf. Interval]
1	Lawler et al. (13)	48.55587	48.520576,48.591164
2	Pinheiro et al. (14)	48.256584	48.220829, 48.292343
3	Elham et al. (26)	48.443535	48.408272, 48.478798
4	Haddow et al. (28)	48.594143	48.558952,48.629333
5	Kelly et al. (31)	48.303158	48.267899, 48.338417
6	Yakasai et al. (47)	48.511402	48.476162, 48.546646
7	Belete et al. (20)	48.739456	48.703999, 48.77491
8	Araya et al. (18)	49.037079	49.001163, 49.07299
9	Yitbarek et al. (49)	48.732273	48.696697, 48.767849
10	Belete et al. (20)	49.074566	49.038979, 49.110153
11	Debalkie et al. (25)	47.50845	47.472431, 47.544464
12	Tsegaw et al. (26)	49.017803	48.981865, 49.053738
13	Nyamayaro et al. (38)	48.478603	48.407894, 48.443249
14	Focà et al. (27)	48.481682	48.446255, 48.517109
15	Pascal et al. (39)	48.808884	48.773487, 48.844276
16	Awori et al. (19)	48.145374	48.109974, 48.180775
17	Achappa et al. (17)	48.337997	48.302814, 48.37318
18	Sunmonu et al. (45)	48.392574	48.357368, 48.427784
19	Robertson et al. (40)	50.478935	50.439026, 50.518841
20	Chan et al. (23)	48.652199	48.616936, 48.687466
21	Cysique et al. (24)	48.723553	48.688202, 48.7589
22	Harezlak et al. (29)	48.468979	48.43346, 48.504494
23	Nakasujja et al. (37)	48.270924	48.235588, 48.306259
24	Robertson et al. (41)	46.92638	46.889656, 46.963104
25	Chan et al. (9)	48.440395	48.40519, 48.475601
26	Kabuba et al. (30)	48.73357	48.698093, 48.769051
27	Yechor et al. (63)	48.604374	48.568996, 48.639748
28	Nakku et al. (10)	47.618401	47.582355, 47.654449
29	Troncoso et al. (8)	48.415298	48.380005, 48.450592
30	Fasel et al. (64)	48.41259	48.377434, 48.447746
31	Oshinaike et al. (65)	48.360401	48.324974, 48.395828
32	Atashili et al. (12)	47.850132	47.814709, 47.885555
33	Bonnet et al. (21)	48.135502	48.099808, 48.171196
34	Simioni et al. (44)	48.149261	48.113976, 48.184547
35	Saini et al. (43)	48.55426	48.519024, 48.589497
36	Marin-Webb et al. (33)	48.673512	48.637695, 48.709328
37	Yusuf et al. (50)	49.084835	49.049297, 49.120373
38	McNamara et al. (37)	48.30397	48.267956, 48.339989
39	Muniyandi et al. (36)	48.421654	48.386478, 48.456829
40	Mugendi et al. (35)	47.994511	47.959171, 48.02985

HAND, HIV associated neurocognitive disorders.

that there was no single influential study outweighing the average estimate.

Publication Bias

Although a graphical inspection from a funnel plot for a Logit event rate of occurrence of HIV-associated neurocognitive disorders in people living with HIV/AIDS alongside its standard error suggests asymmetrical distribution, the quantitative Eggers test of publication bias had been run and its *p*-value was not

significant; ($P = 0.55$). This suggests there was no publication bias for the prevalence HIV associated neurocognitive disorders (Figure 6).

Associated Factors of HIV Associated Neurocognitive Disorders Among People Living With HIV/AIDS

Among the 40 studies, only 15 studies described the factors related to HIV-associated neurocognitive disorders (8, 10, 12, 14, 18, 20, 21, 25, 26, 34, 35, 46–49). The most frequently reported sociodemographic variable as the associated factor of HIV-associated neurocognitive disorders were the low level of education (12, 14, 18, 21, 30, 46, 47) and older age (8, 14, 20, 46, 49). Among clinical and HIV-related variables late clinical stage of the illness (20, 21, 25, 49) and a CD4 count of 500 cells/dl or less (8, 18, 46) were the most commonly described factor for HIV associated neurocognitive disorders. Besides, from psychological variables comorbidity of depression increases the risk of HIV-associated neurocognitive disorders (14, 21, 35). Moreover, clinical and HIV related variables such as impairment in the activity of daily living (20), duration of HIV infection > 5 years (26), poor medication adherence (46), co-morbid medical illness, highest prior VL >100,000 copies/ml (8), history of neurological disease (21), body mass index < 16 kg/m² (25), plasma HIV-1 RNA load between 1.7log₁₀ and 3log₁₀ copies/ml (49), having a co-morbid opportunistic infection (20) and psychological variables like negative life events, high-stress score index (score >10) (10) were related to HIV associated neurocognitive disorders (Table 3).

Association Between Old Age and HIV Associated Neurocognitive Disorders Among People Living With HIV/AIDS

Older age was reported as the risk factor for HIV-associated neurocognitive disorders by five studies (8, 14, 20, 46, 49). The pooled odds ratio for the association between old age and HIV-associated neurocognitive disorder among these five studies was found to be 3.68 (95% CI: 2.95, 4.11) ($I^2 = 98.2\%$, $P = 0.000$; Figure 7).

Association Between Depression and HIV Associated Neurocognitive Disorders Among People Living With HIV/AIDS

As reported in three studies (14, 21, 35) that assessed HIV-associated neurocognitive disorders, depression increases the risk of HIV-associated neurocognitive disorders. The pooled odds ratio for the association between depression and HIV-associated neurocognitive disorder among these three studies was found to be 2.87 (95% CI: 0.87, 4.87) ($I^2 = 99.6\%$, $P = 0.000$).

Association Between Advanced Stages of AIDS and HIV Associated Neurocognitive Disorders Among People Living With HIV/AIDS

Advanced clinical stages of the illness (stage III and stage IV AIDS) (20, 21, 25, 49) were also associated factors for HIV-associated neurocognitive disorders. The pooled

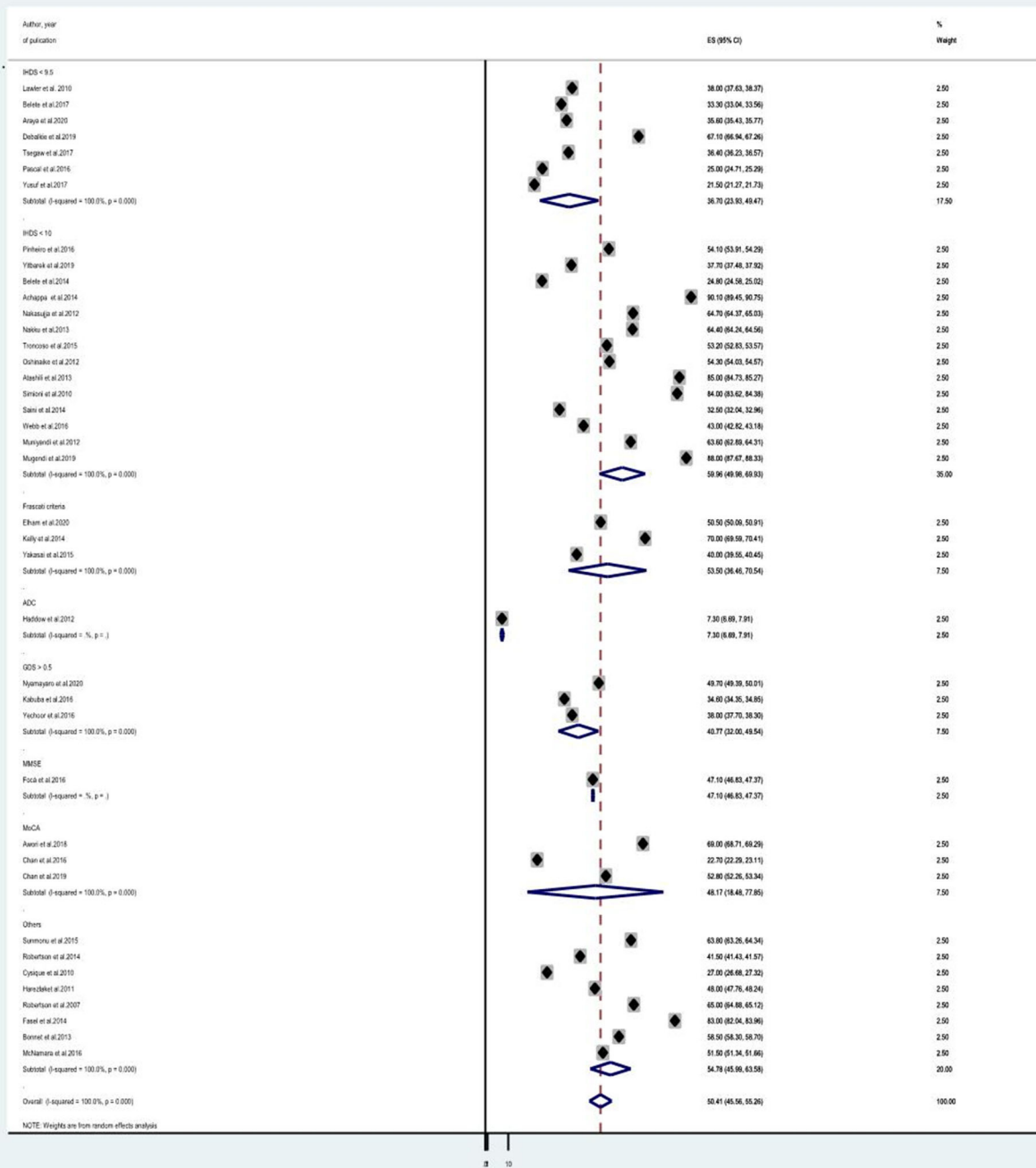


FIGURE 4 | A subgroup analysis for the prevalence of HIV associated neurocognitive disorders based on study tools.

odds ratio for the association between advanced stage of AIDs(stage III& IV) and HIV-associated neurocognitive disorder among the four included studies was found to be 5.68 (95% CI: 3.06, 8.29) ($I^2 = 99.9\%$, $P < 0.001$; **Figure 8**).

Meta-Regression

Firstly, we performed a univariate regression analysis to select the independent variables to incorporate in the final meta-regression model. Then, all variables with $P < 0.8$ were included in the final regression analysis as recommended by Ferrari

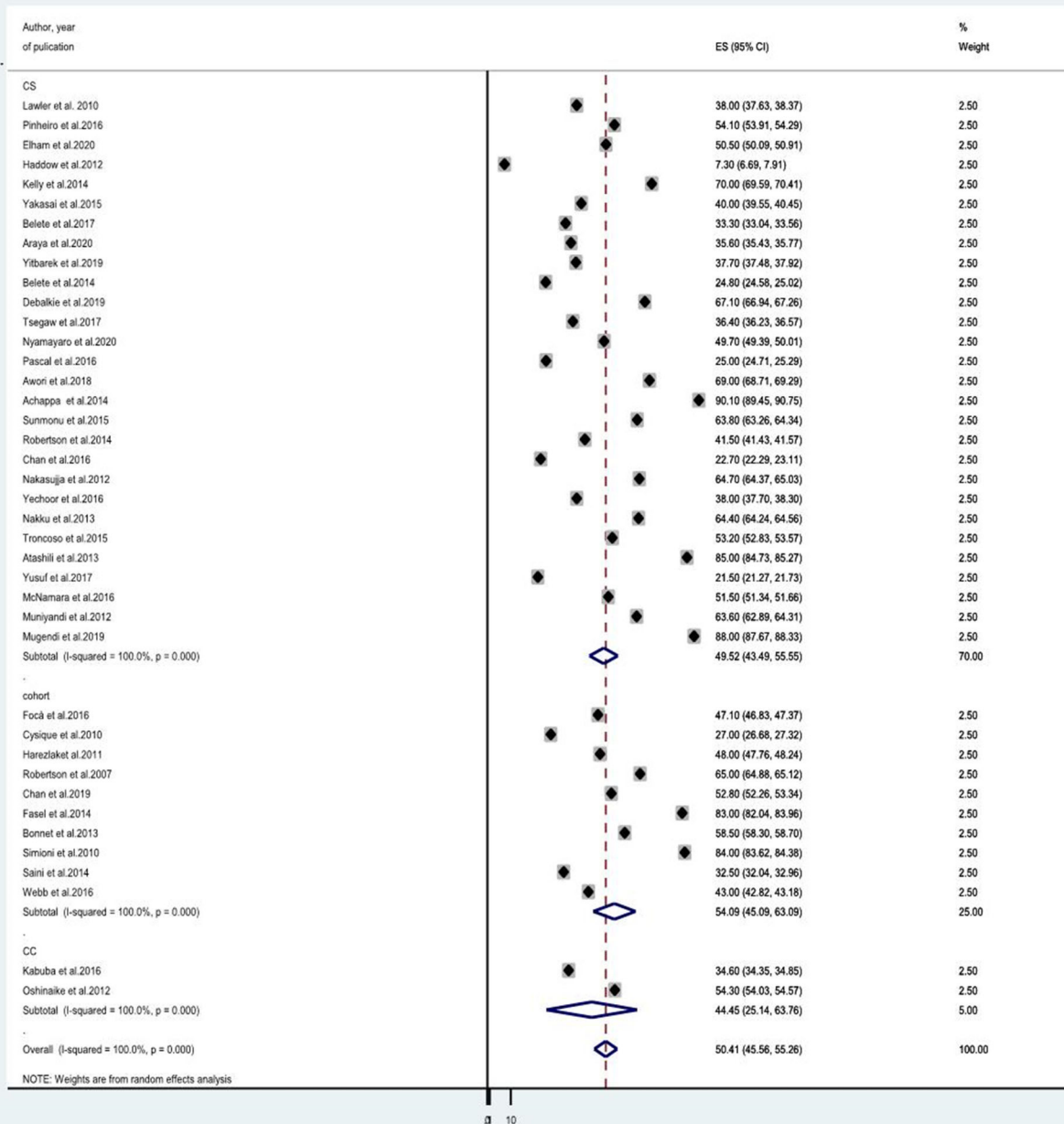
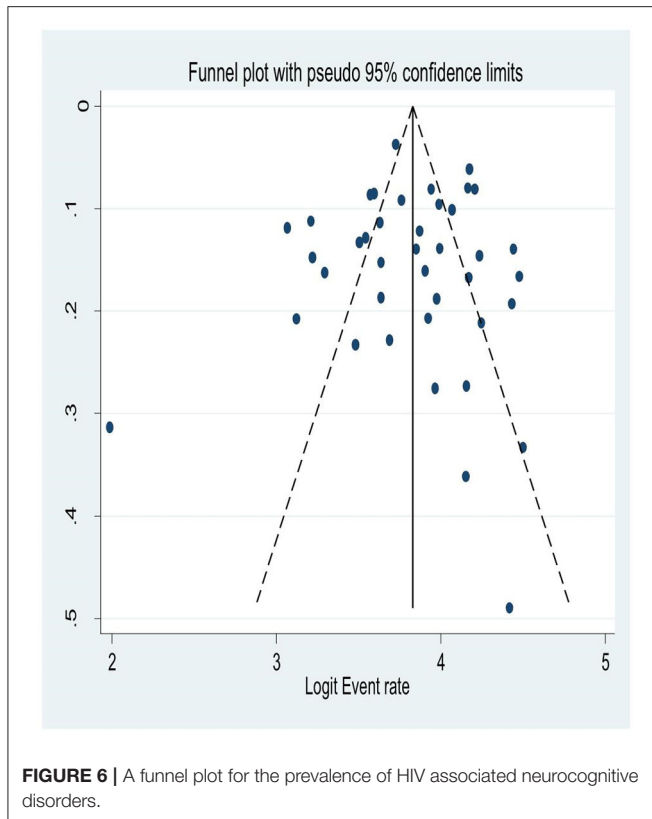


FIGURE 5 | A subgroup analysis for the prevalence of HIV associated neurocognitive disorders based on country of study tools.

et al. 2013 (67). The impacts of the country of origin of the study (Europe, Asia, and Africa), Assessment Tool (IHDS < 9.5, IHDS < 10, Frascati criteria, ADC, MMSE, GDS > 0.5, MoCA, and Other Tools), and study design (case-control, cohort and cross-sectional) were quantified in the meta-regression model. The analysis was conducted for the overall effect on the burden of HIV-associated neurocognitive disorders in HIV/AIDS

patients. The overall proportion of variance explained by these covariates in the final model was 11% ($R^2 = 11\%$; $P = 0.302$). All the three covariates such as country of origin of the study, Assessment Tool, and study design were not statistically significant determinants for the observed variation in the association between HIV-associated neurocognitive disorders and HIV/AIDS.



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 an important suggestion to varied stakeholders. Overall, 40 studies (8, 10, 12–14, 17–50) that measured the prevalence of HIV associated neurocognitive disorders in 14,107 participants from over 28 different countries and 15 studies that described the factors related HIV associated neurocognitive disorders (8, 10, 12, 14, 18, 20, 21, 25, 26, 34, 35, 46–49) were included.

The result of the present study advocated that more than half of people living with HIV/AIDS were affected with HIV-associated neurocognitive disorders. This suggests that HIV-associated neurocognitive disorders are an important public health problem in people living with HIV/AIDS. The result of HIV-associated neurocognitive disorders is consistent with the prevalence of neurocognitive disorders in patients with chronic kidney disease and diabetes; 48% In the UK (68). However, it was higher than the magnitude of neurocognitive disorders in the general urban population in India (1.5%) (69), and the prevalence of dementia in an urban Turkish population (20%) (70). It was also higher than the prevalence of dementia in Norwegian elders of age 75 and above where dementia was prevalent in 16.3% of the population (71). Besides, the present finding was higher than the prevalence rate of dementia among japans community aged 65 or older; 6.7% (72). The added presence of opportunistic

central nervous disease (73–75) in HIV-positive people could be attributing factor to this.

Among studies included in the current review and meta-analysis, the epidemiologic data regarding the prevalence of HIV associated neurocognitive disorders showed a substantial variation across the measurement instrument for HIV associated neurocognitive disorders, and the nature of the study design; however comparable HAND results were found across European, Africa, Asian, US countries. Of the 40 included studies, 20—the majority—were from Africa (10, 13, 18, 20, 25, 30, 31, 35, 37–39, 45–50).

The current study result 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% (16). The difference in the study population and significant variance in the number of included studies might cause the variation. Moreover, the risk factors for HIV-associated neurocognitive disorders might be different in Sub-Saharan Africa and the world in general, which may cause the difference in HIV-associated neurocognitive disorders. On the other hand, the current study was higher than the result of the prevalence of Frascati-Criteria-Based HIV-Associated Neurocognitive Disorder; 43.9% (76). The possible reason for this could be due to the difference in sensitivity and specificity between Frascati-Criteria and other tools to screen HIV-Associated Neurocognitive Disorder.

In a subgroup analysis by type of measurement instrument used for HAND, we found that the prevalence was higher as measured with IHDS < 10 (8, 10, 12–14, 17, 20, 25, 35–37, 39, 43, 44, 46, 48–50, 66) (59.956%) than the result measured with Frascati criteria (53.5%), ADC (27.65%), MMSE (41.349%), and GDS (40.766%) with all these differences at statistically significant level ($P < 0.001$). The possible differences in the estimated magnitude of HIV associated neurocognitive disorders among measurement instruments will be attributed to the difference in the ability of measurement tools to identify truly those HIV patients who have HIV associated neurocognitive disorders (sensitivity) and to exclude HIV patients who do not have HIV associated neurocognitive disorders (specificity) (33, 77–82). In addition, the lack of country-specific NP norms for the assessment of HAND would have contributed to this variation.

We did also conduct a subgroup analysis with the type of study design. The highest estimated prevalence of HAND (54.087%) was found in cohort studies (8, 21, 23, 24, 27, 29, 41, 43, 44), followed by cross-sectional studies (49.52%) (8, 10, 12–14, 17–20, 23, 25, 26, 28, 30, 31, 34–40, 45–50). The lowest estimated prevalence of HAND (44.45%) was found among case-control studies (30, 66). As noted above, the number of case-control and cohort studies is fewer in number (2 and 10 studies, respectively) compared to the number of cross-sectional studies which is 28. So the smaller number of studies included in cohort and case-control studies might be overestimated and underestimate the prevalence of HAND, respectively.

Even though we conducted a subgroup analysis with a country of origin of the study (categorized as Africa, Europe, Asia, and the USA) as a moderator variable, we found a more or less consistent average estimate of HAND; Europe (50.015%), Africa (49.566%), Asia (52.032%), and United States of America (USA)

TABLE 3 | 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	References
Age of 50 years and older	4.85	2.34, 10.03	Strong and positive	Pinheiro et al. (14)
Less than eight years of education	6.72	3.98, 11.32	Strong and positive	Pinheiro et al. (14)
Non-white skin color	1.71	1.04, 2.83	Moderate and positive	Pinheiro et al. (14)
Depression	1.96	1.12, 3.42	Moderate and positive	Pinheiro et al. (14)
Duration of HIV infection > 5 years	3.1	1.70, 7.40	Strong and positive	Elham et al. (26)
Low level of education	1.2	1.04, 1.44	Weak and positive	Yakasai et al. (47)
Late clinical stage of the illness	4.2	1.19, 14.44	Strong and positive	Belete et al. (20)
Impairment in the activity of daily living	7.19	1.73, 21.83	Strong and positive	Belete et al. (20)
CD4 count of 500 cells/dl or less	2.368	1.524, 3.680	Moderate and positive	Tsegaw et al. (46)
No formal education	4.287	2.619, 7.016	Strong and positive	Tsegaw et al. (46)
Poor medication adherence	1.487	1.010, 2.180	Weak and positive	Tsegaw et al. (46)
Older age	3.309	1.259, 8.701	Strong and positive	Tsegaw et al. (46)
6 to 10 Negative life events	2.14	1.45, 3.15	Moderate and positive	Nakku et al. (10)
11 and more Negative life events	2.35	1.33, 4.13	Moderate and positive	Nakku et al. (10)
Medium Stress Score index (score 1–10)	2.55	1.73, 3.77	Moderate and positive	Nakku et al. (10)
High Stress Score index (score > 10)	3.29	1.99, 5.45	Strong and positive	Nakku et al. (10)
Female gender	2.66	1.22, 5.82	Moderate and positive	Troncoso and Conterno (8)
Older age	2.87	1.24, 6.64	Moderate and positive	Troncoso and Conterno (8)
Co-morbid medical illness	2.56	1.17, 5.55	Moderate and positive	Troncoso and Conterno (8)
CD4 count <200 cell/mm ³	2.71	1.25, 5.86	Moderate and positive	Troncoso and Conterno (8)
Highest prior VL > 100,000 copies/ml	2.62	1.12, 6.16	Moderate and positive	Troncoso and Conterno (8)
Low level of education	8.33	3.85, 16.67	Strong and positive	Atashili et al. (12)
Having HIV symptoms	12.16	3.08, 48.05	Strong and positive	Atashili et al. (12)
Advanced AIDS stage	4.87	1.59, 14.90	Strong and positive	Bonnet et al. (21)
Technical school level of education	2.16	1.31, 3.55	Moderate and positive	Bonnet et al. (21)
Lower than diploma level of education	3.39	1.48, 7.80	Strong and positive	Bonnet et al. (21)
Generalized anxiety symptoms	2.99	1.67, 5.14	Strong and positive	Bonnet et al. (21)
Depression symptoms	2.11	1.23, 3.63	Moderate and positive	Bonnet et al. (21)
History of neurological disease	2.05	1.18, 3.58	Moderate and positive	Bonnet et al. (21)
African country of birth	11.075	4.94, 24.84	Strong and positive	McNamara et al. (34)
Use of benzodiazepines	6.746	2.37, 19.18	Strong and positive	McNamara et al. (34)
Unemployed	2.16	1.2, 3.84	Moderate and positive	McNamara et al. (34)
Body mass index < 16 kg/m ²	4.39	1.60, 12.02	Strong and positive	Debalkie Animut et al. (25)
Unemployed status of occupation	3.18	1.752, 5.777	Strong and positive	Debalkie Animut et al. (25)
Advanced stage of AIDS	3.56	1.406–9.006	Strong and positive	Debalkie Animut et al. (25)
Depression	7.47	1.69, 43.53	Strong and positive	Mugendi et al. (35)
Female gender	2.17	1.02, 4.71	Moderate and positive	Mugendi et al. (35)
Older age	3.1	1.3, 7.4	Strong and positive	Yideg Yitbarek et al. (48)
Plasma HIV-1 RNA load between 1.7log ₁₀ and 3log ₁₀ copies/ml	2.2	1.1, 4.3	Moderate and positive	Yideg Yitbarek et al. (48)
Plasma HIV-1 RNA load ≥ 3log ₁₀ copies/ml	7.5	2.6, 21.5	Strong and positive	Yideg Yitbarek et al. (48)
Khat chewing	4.4	2.3, 8.3	Strong and positive	Yideg Yitbarek et al. (48)
Advanced stage of AIDS	5.6	1.7, 19.2	Strong and positive	Yideg Yitbarek et al. (48)
Having no education	3.11	1.37, 7.04	Strong and positive	Mossie et al. (55)
Older age	4.25	1.05, 17.18	Strong and positive	Mossie et al. (55)
Having co morbid opportunistic infection	7.48	4.1, 13.64	Strong and positive	Mossie et al. (55)
Substance use	4.64	2.3, 9.36	Strong and positive	Mossie et al. (55)
Having no education	5.16	2.20, 12.07	Strong and positive	Araya et al. (18)
Primary education	3.29	1.46, 7.29	Strong and positive	Araya et al. (18)
Having a CD4 count (cells/μl) ≤ 500	1.61	1.11, 2.39	Moderate and positive	Araya et al. (18)
Lifetime use of tobacco	2.4	1.44, 4.01	Moderate and positive	Araya et al. (18)

AIDS, Acquired Immune deficiency Syndrome.

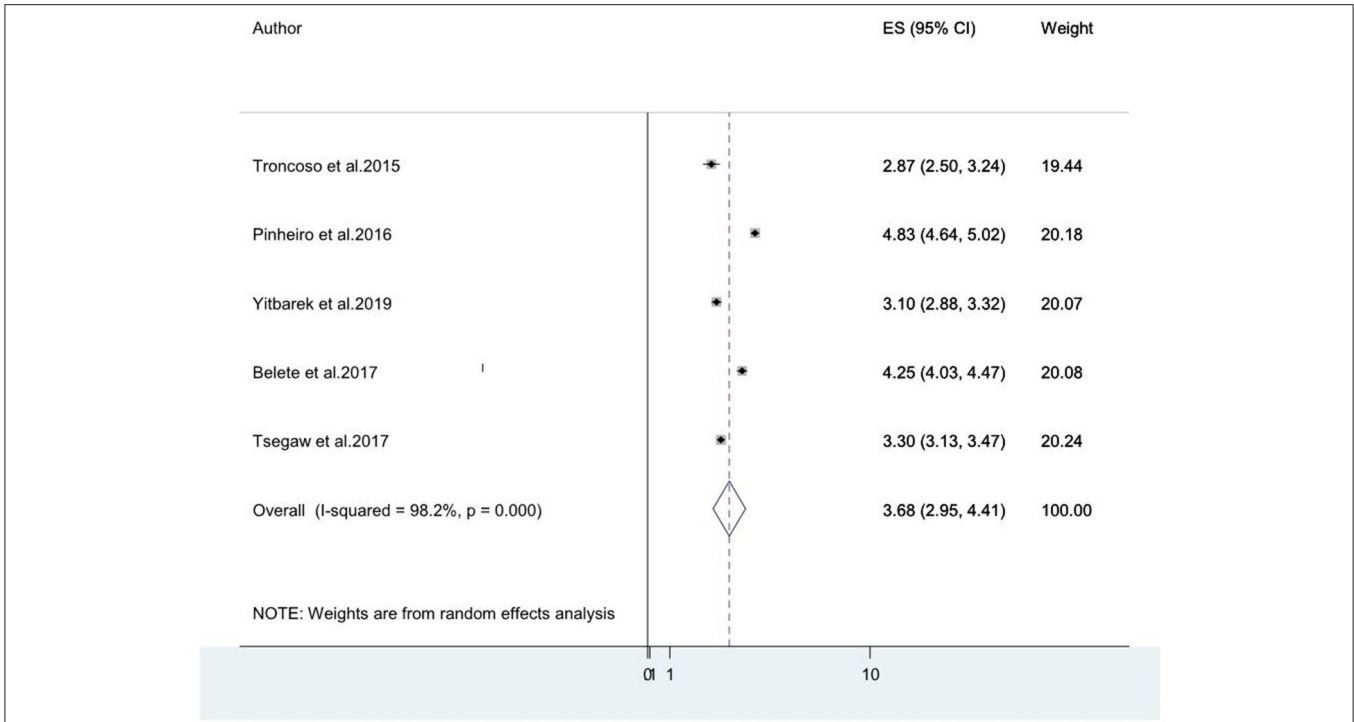


FIGURE 7 | A forest plot for the pooled odds ratio of associated between old age and HIV-associated neurocognitive disorder.

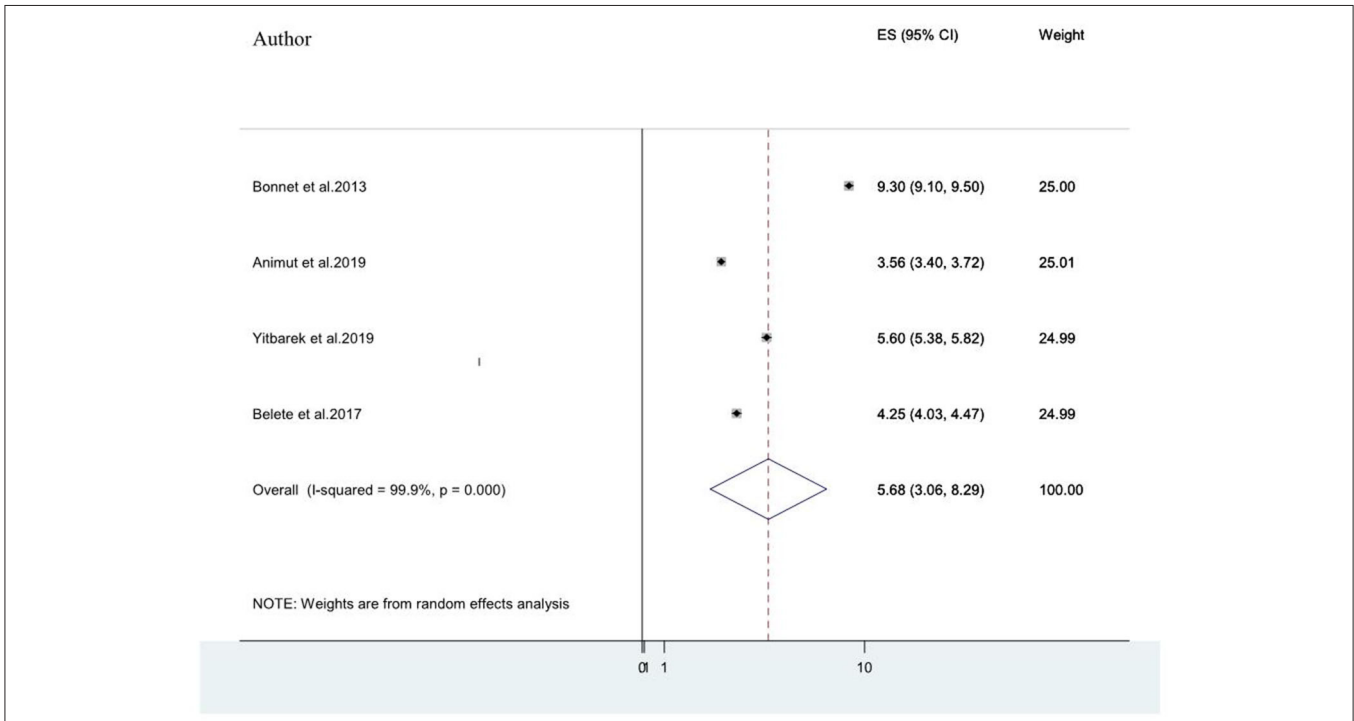


FIGURE 8 | A forest plot for the pooled odds ratio of associated between advanced stage of AIDS and HIV-associated neurocognitive disorder.

(50.407%) with the difference of prevalence estimate of HAND being insignificant.

Concerning the associated factors for HIV-associated neurocognitive disorders, our systematic review suggested that older age was among the commonly reported risk factor for HIV-associated neurocognitive disorders (8, 14, 20, 46, 49). Older age group people were 3.68 times more likely to develop HIV-associated neurocognitive disorder than younger age people. This is supported by multiple earlier studies (83). The accumulation of excessive amyloid deposits and various chronic diseases in old age could account for this (84).

Besides, depression also increases the risk of HIV-associated neurocognitive disorders as reported in three studies (14, 21, 35). The HIV-associated neurocognitive disorder was 2.87 times higher among individuals having comorbidity of depression than those not having comorbidity of depression. Multiple supportive findings for this association are reported (85–87). Pseudo-dementia associated with depression could mimic neurocognitive disorders and amplify the prevalence of neurocognitive disorders.

Moreover, advanced clinical stages of the illness (stage III and stage IV AIDS) (20, 21, 25, 49) were also associated factors for HIV-associated neurocognitive disorders. Advanced clinical stages of the illness increase the risk of HIV-associated neurocognitive disorder by 5.68.

Difference Between Studies Incorporated in the Current Review and the Meta-Analysis Study

This meta-analysis study on HIV-associated neurocognitive disorders was subjected to a high degree of heterogeneity from the variation between 40 of the studies integrated with the final analysis. Therefore, the need for a subgroup and sensitivity analysis was mandatory. The country of origin of the study (Africa, Europe, Asia, and the USA), design of the study, and measurement tool were the parameters for subgroup analysis. However, no major difference in the pooled prevalence of HIV-associated neurocognitive disorders was observed between high-income/(Europe, Asia, and the USA) and low-to-middle income/African countries. These should be a focus of future researchers. Results of the subgroup however revealed the design of the study and measurement tool used to screen HIV-associated neurocognitive disorders were contributors to the high heterogeneity between the 40 studies integrated with the analysis. Furthermore, we did a sensitivity analysis to search for additional sources for the high degree of heterogeneity by exploring a particular study outweighing the overall estimate. However, the result showed that none of the 40 studies had outweighed the average estimated prevalence of HIV-associated neurocognitive disorders in HIV patients.

STRENGTH AND LIMITATIONS OF THE STUDY

This systematic review and meta-analysis on HIV-associated neurocognitive disorders have several strengths. The primary

strength of the study was the large number of studies included in the review, representing the worldwide spread of HAND in people with HIV. The application of subgroup analysis and sensitivity analysis to identify the source of heterogeneity was another quality of the present study. The study also used a well-designed and pre-determined search approach to lessen the reviewer's bias. The third for this study was the extraction of relevant data and assessment of the quality of 40 studies by self-determining assessors which decrease the reviewer's bias. Quality analysis of all the included studies also increases the study validity. On the other hand, the study has many limitations. First, the definition of HIV-associated neurocognitive disorder could be more explicit. In addition, the reasons for exclusions of 46 identified full texts are not explicitly mentioned in the PRISMA flowchart. The presence of a high degree of heterogeneity that influences the inference of the study outcomes was also another limitation. Moreover, biases and lack of methodological rigor could affect the validity of this finding.

CONCLUSION AND RECOMMENDATION

This systematic review and meta-analysis aimed to estimate the prevalence of HIV-associated neurocognitive disorder in people living with HIV AIDS and to analyze the associated factors for HIV-associated neurocognitive disorder in people with HIV AIDS. The prevalence of HIV-associated neurocognitive disorders was about 50.41%. Low level of education and older age, clinical and HIV related variables such as the advanced stage of the illness and CD4 count of 500 cells/dl or less and psychological variables such as comorbidity of depression were associated with HIV associated neurocognitive disorders. Therefore, to increase independent functioning and improve the quality of life of people with HIV/AIDS, much attention has to be given to lessening these neurocognitive disorders and adjusting 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 into the routine anti-retroviral therapy should be designed and implemented. Further experimental and follow-up studies with a greater sample population should be done.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

YZ conceived the idea for the study. YZ and MN established the search approach, extracted the relevant data, accomplished the analysis, and wrote the manuscript. MN, YZ, BA, and WY did the quality assessment studies. All authors confirmed the final draft of the manuscript.

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