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Characterization and stratification of risk factors of stroke in people living with HIV: A theory-informed systematic review

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Abstract

Background Identification and stratification of risk factors for stroke among individuals living with HIV (PLWH) will facilitate primary prevention and prognostication, as well as strategies aimed at optimizing neurorehabilitation. This review sought to characterize and stratify the risk factors associated with stroke in PLWH.

Methods The review was structured in accordance with the preferred items for reporting systematic reviews and meta-analysis (PRISMA) checklist. The epidemiological triangle, Bradford criteria, and Rothman causality model further informed the review. The review outcomes encompassed cardiovascular factors, HIV-related factors, and personal and extrinsic factors associated with stroke in PLWH. We conducted searches in PubMed, Scopus, Medline, Web of Science, Cumulative Index for Nursing and Allied Health Literature, and African Journal (SABINET). Data screening and extraction were independently performed utilizing predefined eligibility criteria and a data-extraction template. Narrative synthesis and risk stratification were employed to analyze the results.

Results Thirty studies (22 cohorts and eight case–control) with a sample size of 353,995 participants were included in this review. The mean age of the participants was 45.1 ± 10.7 years. The majority of the participants (72.4%) were male. Risk factors for stroke in PLWH include cardiovascular factors (advanced age, tobacco use, hypertension, diabetes, atrial fibrillation, etc.), HIV-related factors (high viral load and low nadir CD4 count), personal factors (advanced age and female sex), and comorbidities (hepatitis C virus infection, chronic kidney disease, coronary artery disease, and liver fibrosis or cirrhosis). Diabetes, atrial fibrillation, smoking habits, hypertension, age, and viral load demonstrated a high likelihood of association with stroke in PLWH and should be prioritized when constructing clinical prediction algorithms for HIV-related stroke.

Conclusions The most important factors were hypertension and chronic kidney disease, followed by smoking, dyslipidemia, diabetes, HCV, HBV, CD4 count, use of ART, TB, and substance use (cocaine). The least important factors were age, sex, ethnicity, obesity, alcohol use, ART duration, and viral load. The predictive significance of these factors is still evolving, given the average moderate certainty of evidence. Predictive and preventative models should target factors with a high causality index and low investigative costs.

Trial registration The review is part of a larger review registered with the PROSPERO (ID: CRD42024524494).

Keywords HIV, Stroke, Risk factors, Prevention, Disease causation, Theory

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Introduction

The development of antiretroviral medication has turned human immunodeficiency virus (HIV) infection from an acutely fatal disease to a chronic disease with a longer life expectancy [1]. As a result, the risk of cardiovascular disease (CVD) has increased among people living with HIV (PLWH) [2]. Every year, approximately 2.6 million years of healthy living are lost due to CVD worldwide [3]. The risk of stroke is especially concerning in an era of effective anti-retroviral therapy (ART) and long-term viral suppression [4, 5]. Currently, around one to four PLWH have a stroke [6]. This is projected to increase when PLWH life expectancy rises due to scientific development [3]. The specific cause of stroke in PLWH is unknown. However, various variables, including HIV-induced chronic inflammation and ART-induced cardiometabolic risk factors such as hyperglycemia and dyslipidemia, have been linked [7, 8]. Other variables, such as myocardial cytotoxicity from HIV infection, immunological responses, increased cardiac steatosis, and diastolic dysfunction, may all contribute to an elevated risk of stroke, independent of atherosclerotic CVD [9–12]. Stroke is a significant burden on the healthcare system, accounting for over $50 billion in annual costs in the United States alone, as well as high rates of hospitalizations, readmissions, and outpatient visits [13]. Early identification and stratification of risk variables could aid in the development of high-risk prevention and intervention strategies for PLWH.

Stroke, like other noncommunicable diseases, is polygenic and complicated, and this impedes risk reduction attempts [14]. Effective and lasting risk reduction programs should include health promotion, lifestyle changes, early detection, and treatment [15]. Several risk factors in the general population, including ischemic heart disease, hypertension, smoking, obesity, and diabetes, have been linked to the incidence and severity of stroke [15, 16]. New risk factors, including common carotid artery intima-media thickness, carotid bulb intima-media thickness, bilirubin, and urbanization, have come to light [17–19]. However, the relative contribution of the risk factors to the development of stroke is still debated in both the general population [20–24] and among PLWH [6]. Their predictive value may vary from location to place and over time [25, 26]. The diversity in the pattern and relative contributions of stroke risk factors in PLWH may pose a challenge to health promotion and risk reduction programs aiming at lowering the overall burden of CVD in PLWH, particularly in low- and middle-income countries [27].

This is especially true, given the rapidly evolving HIV treatment and management strategies. Studies have shown that both HIV and treatment factors contribute to the development of stroke among PLWH. For example, multimorbidity, ART use, lower cluster of differentiation-4 (CD4) T cells count, higher viral load, depression, and substance abuse have been implicated, with conflicts, though, in the development of stroke among PLWH [28]. In recent decades, particularly in low- and middle-income countries (LMICs), HIV is a major contributor to the chronic non-communicable disease, including stroke. As access to ART keeps expanding, it is expected that the population of PLWH with CVD will increase, thus making HIV the most common risk factor for CVD, including stroke [29]. Therefore, it is crucial to identify factors that contribute to the development of HIV-related stroke and stratify them based on a number of factors, including clinical relevance.

Conceptual and Theoretical underpinning

This review utilized a range of concepts and theories to explore and categorize the risk factors for stroke in people living with HIV (PLWH). To examine the connection between potential exposures and stroke in PLWH, we applied four theoretical perspectives: the epidemiological triangle, Bradford Hill's criteria, Rothman's causal pie model, and emerging hypotheses. The use of the four theoretical perspectives draws from the inability of a single theory to justify the scientific basis for the principles employed in this evidence synthesis. Hence, the theories are complementary in providing a scientific basis underscoring the review methods. Each theory was finely presented, with application to the study and weakness succinctly highlighted. The weakness in one theory was complemented by at least one other theory. The principles are as follows:

Principle 1: Broad spectrum sampling of risk factors

The first principle employed in this study was the sampling of all risk factors of HIV-related stroke, irrespective of time, setting, and age. We employed a broad search strategy including six major databases. This was necessary to ensure we did not omit any single putative risk factor or predictor of HIV-related stroke. To do this, we employed the epidemiological triangle [30, 31]. Following the epidemiological triangle, we sampled all variables associated with stroke in PLWH, whether they were HIV-specific (cluster of differentiation-4 (CD4) count, viral load, use of antiretroviral therapy), cardiovascular risk factors (hypertension, diabetes, smoking, dyslipidemia, obesity, coronary artery disease), intrinsic variables (age, sex, education), or extrinsic variables (income, employment status, access to healthcare). Notably, one weakness of the epidemiological triangle is its limitations in explaining causal relationships between exposure and outcome in the context of non-communicable diseases,

where several causative factors (agents) may be implicated in the development thereof.

Principle 2: A non-communicable disease (NCD) is a product of the interaction of several causative/risk factors

While the epidemiological triangle acknowledges that a disease is not only the outcome of the agent but also of the host and environmental factors, it is incapable of explaining the extent to which each factor contributes to the development of an NCD, which is polygenic in nature. It is important to present risk or contributing factors in the order of clinical importance, as this will aid the pursuit of cost-effective public health promotion and preventative strategies. The risk stratification technique employed in the study draws essentially from Bradford Hill's criteria [32–38], Rothman's causal pie [39, 40], and Nweke's hypotheses [41]. Insufficiency of one model was complemented by another model. Based on the Bradford criteria, risk factors may be stratified based on the strength of association. This is a common practice; however, it is widely acknowledged that the sole strength of association as an index of causality is no best practice [41]. The current practice of sole reliance on the strength of association is owing to a lack of conceptual and quantitative models for estimating other components of causality, including temporality, consistency, biological gradients, and specificity. To estimate the causal attribute of a risk factor, beyond the strength of association, we applied relevant emerging hypotheses.

Principle 3: Objective application of Bradford Hill's criteria and Rothman's causal pie in the deduction of causality from exposure-outcome association

Objectively evaluating Hill's criteria and Rothman's perspectives can be complex, especially when assessing consistency and biological gradients. Nweke et al. [41, 42] developed methods to evaluate these criteria based on a few emerging hypotheses. Central to their argument is that the evaluation of risk attribution and modeling for NCDs based solely on statistical significance (magnitude of association) is an inadequate technique. Further, they introduced the cumulative risk index principle and emphasized the importance of specificity in exposure-outcome associations for inclusive and cost-effective modeling of NCDs. In addition to Bradford Hill's criteria and Rothman's causal pie, Nweke and colleagues postulated further theories [42] to aid objective estimation of causal attributes (causality index) from exposure-outcome association, leading to the development of a nuanced causality framework for assessment of causal attributes of risk factors [42].

Application to review methods

No one theory could provide the scientific justification for the techniques employed in this study. Hence, we employed several theoretical reasons, with each complemented by one or two others. From the epidemiological triangle, we understand the importance of considering traditional, intrinsic, and extrinsic stroke risk factors. Hill's criteria indicate that multivariate models are superior to univariate ones in modeling non-communicable diseases and health outcomes. Rothman's causal pie supports the use of multivariate models and allows the prioritization of a sufficient combination of risk factors and cost-effective routes, given that there are various ways in which a given set of risk factors can interact to induce a non-communicable disease. Cohort and prospective experimental designs are essential for meeting the temporality criterion, while case–control studies are preferred for rare diseases. The prevalence of stroke is 1% among PLWH aged ≥ 15 years and 4% among those aged ≥ 50 years [43], and this informed the inclusion of both case–control and cohort studies in the review. Hill's criteria also emphasize the need to look beyond statistical significance in ascertaining the causal attributes of a risk factor. The causality index estimates the relative causal contribution of each risk factor to stroke in PLWH using strength of association, temporality, consistency, biological gradients, and specificity.

Review Methods

Protocol and registration

The review was structured according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist. It is part of a larger review registered with PROSPERO (ID: CRD42024524494). As mentioned earlier, the epidemiological triangle, Bradford Hill criteria, Rothman's causation model, and emerging hypothesis provided the context for the review process and discussion.

PECOT criteria

The population consists of HIV-seropositive individuals, sampled either proactively or retrospectively. The exposures include agent factors (cardiovascular and HIV-related), intrinsic factors (age, sex, and nutrition), and extrinsic factors (education, income, and access to health). The primary outcomes are the variables associated with stroke in PLWH, along with the underlying direction and strength of these associations. Derived outcomes include temporality, consistency, and the causality index. Other outcomes include setting, design, sampling technique, and sample size. The review was conducted from January to June 2024.

Inclusion criteria.

1. Studies involving adult PLWH with or without stroke, irrespective of setting
2. Cohort studies and/or case–control
3. Studies that reported risk factors of stroke in PLWH and their corresponding risk estimates (odds ratio, hazard ratio, or relative risk) or that include enough details to enable the computation of risk estimates.

Exclusion criteria.

1. Cross-sectional studies
2. Studies involving a mixed population of HIV-positive and HIV-negative people and in which it is difficult to distinguish the data of HIV-positive persons from the HIV-negative counterparts
3. Study articles with a high risk of bias
4. Studies describing the frequency of factors associated with stroke in PLWH and which did not include a risk estimate, such as an odds ratio or its equivalent, will be excluded

Outcome and outcome measurement

The primary outcomes included agent factors (duration of HIV, type of ART, duration of ART, CD4 count, viral load), cardiovascular factors (hypertension, diabetes, dyslipidemia, obesity, smoking, and CVD events), intrinsic factors (sex, age, and education), and extrinsic factors (nutrition and income). Studies were included regardless of the outcome measures used to assess these exposures. Stroke was ascertained using standard procedures.

Information Sources

We searched eight databases: PubMed, SCOPUS, EMBASE, Academic Search Complete, Cumulative Index for Nursing and Allied Health Literature (CINAHL), Cochrane Library, MEDLINE, and African Journals (SABINET). Databases were searched from inception to January 2024.

Search strategy

The search strategy was developed, evaluated, and refined by the Principal Investigator (MN) and an information expert (SM). Search terms were selected based on the key concepts of the review. Each search utilized a variety of keywords and concepts from the medical subject groups. A pilot search on PubMed was conducted to assess the appropriateness of the search strings (Appendix 1). The search terms were then adjusted to align with the subject headings and syntax of PubMed, MEDLINE, Scopus, Web of Science, Cochrane Library, CINAHL, and African Journals (SABINET). Wildcard searches were performed for keywords in the title, abstract, and MeSH terms sections, and abbreviated terms were used where applicable. To achieve comprehensive results, index terms, keywords, and Boolean operators (AND, OR, NOT) were combined. Due to differences in database structures and indexing, the search approach was tailored for each database.

Data Management

The results retrieved from the literature search were exported to EndNote 20 for duplicate removal and data management. After removing duplicates, the articles were screened based on their titles and abstracts. Included and excluded articles were categorized in EndNote 20, and this information was then used to create the PRISMA flow chart (Figure 1).

Study selection and data extraction

The initial screening of titles and abstracts was conducted independently by the primary reviewer and a trained research assistant using the eligibility criteria. Eligible full texts were then subjected to data extraction by the trained research assistant, following a standardized data extraction template. The data extraction template was adopted from a similar previous study examining the risk factors, risk strata, and predictive models for HIV-related falls and coronary heart disease [41, 42]. The template captured all aspects of the study, including study characteristics (study design, sample size, setting, etc.), risk factors, risk estimate otherwise known as strength of association or effect size, among others. The template stipulated the items of interest, thereby making it easy for the research assistant to locate and document them. The extracted data were verified by MN. The PRISMA diagram was used to illustrate the flow of studies throughout the selection process, including the reasons for exclusion (Figure. 1).

Data items

Primary data items extracted from each included study are as follows.

1. Agent factors: HIV-related (duration of HIV, type of ART, duration of ART, CD4 count, viral load) and cardiovascular (hypertension, diabetes, dyslipidaemia, obesity, smoking, and CVD event)
2. Intrinsic sociodemographic factors (sex, age, and nutrition)
3. Extrinsic sociodemographic factors (education, income, employment, and access to healthcare)
4. Measure of association between exposures and stroke in PLWH

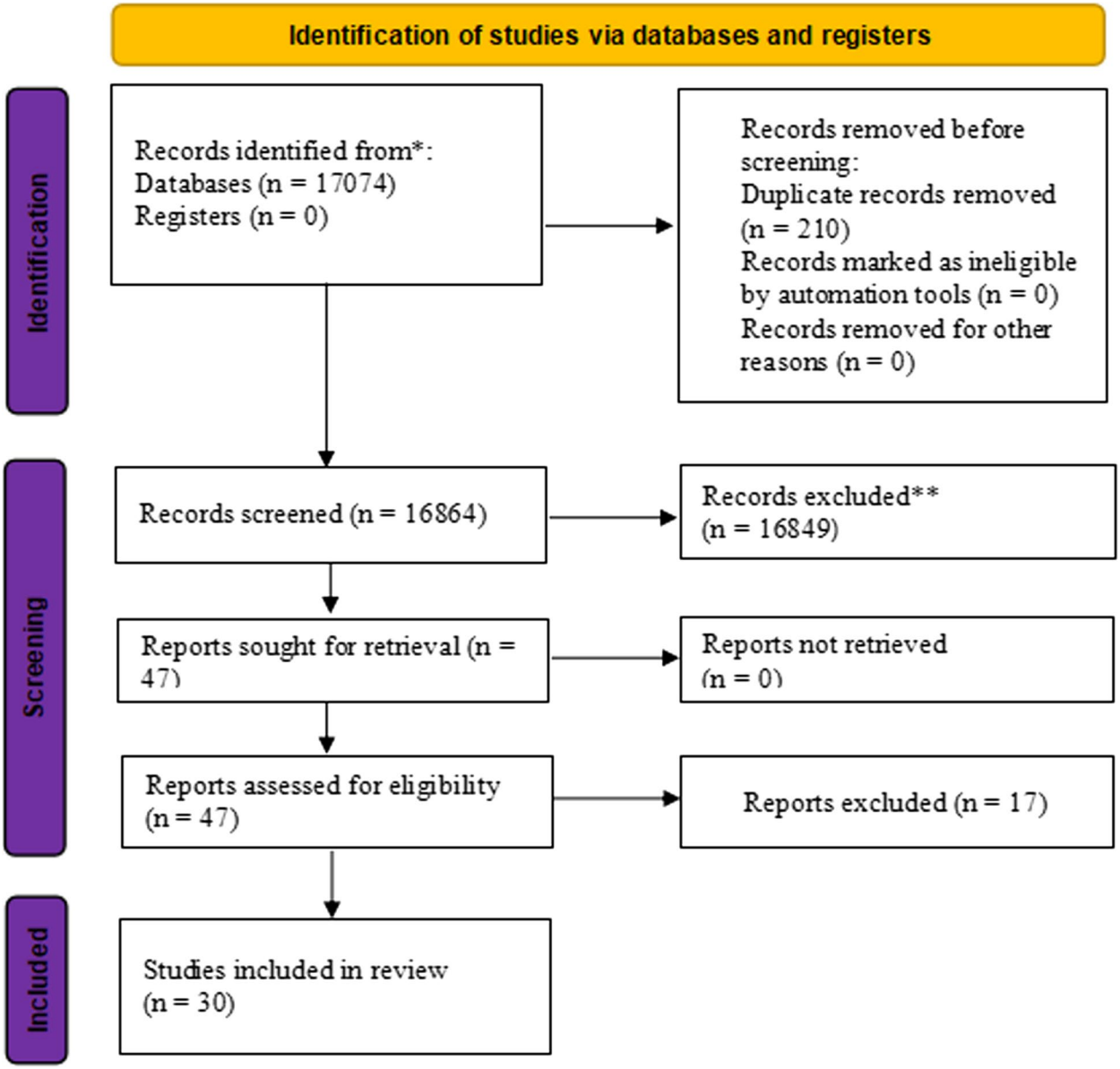

Fig. 1 PRISMA Flow Diagram for the systematic review of the factors associated with stroke in PLWH

Secondary data items included study design, sample size, sampling technique, and setting.

Risk of bias assessment

To evaluate the methodological quality of the included studies, we employed the risk of bias assessment tools for case–control and cohort studies developed by the Joanna Briggs Institute (JBI) [44]. Reviewers MN and Nombeko Mshunqane (NM) conducted the risk of bias assessments. Discrepancies in the risk of bias assessment were resolved through discussions. Final risk of bias ratings were reached by consensus. The use of an iterative process facilitated a systematic and rigorous evaluation of the risk of bias, thereby enhancing the reliability of the study findings.

Confidence in cumulative evidence

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) [45] framework was used to assess the certainty of evidence regarding the predictive potential of stroke risk factors in PLWH:

Risk of bias

Risk of bias was evaluated using the Joanna Briggs Institute tool for case–control and cohort studies [44], categorizing bias as low, moderate, or high. Evidence certainty was downgraded by one, two, or three levels for high, moderate, or significant bias concerns, respectively [46].

Inconsistency

Inconsistency was considered serious if effect estimates varied significantly across studies in magnitude and direction [47, 48], leading to a one-level downgrade in evidence [47].

Indirectness

Indirectness occurs when discrepancies between the population, comparisons, or outcomes of interest and those measured decrease certainty in evidence by one level [49]. In this study, indirectness was severe if patients, intervention, and comparators provided indirect evidence for the clinical question.

Imprecision

Imprecision arises from studies with few patients, events, or significant heterogeneity in patient effects, resulting in broader confidence intervals [50]. The study was imprecise if the confidence interval exceeded a set level or the dataset was incomplete. Precision was assessed using relative risks of 0.75 and 1.25 [50].

Publication bias

Publication bias, which occurs when studies are inadequately reported, can lower the evidence grade by one or two points [51]. It was suspected that fewer than four major databases were searched, or only positive or negative findings were reported [48].

Risk estimate

Odds ratios, risk ratios, or hazard ratios assessed exposure-outcome associations. Evidence quality increased by one notch for a two-fold change in risk and by two notches for a fivefold change [45].

Summary Measures

We described the quantitative characteristics of the review participants using the mean and standard deviation. Sociodemographic and study characteristics were summarized using frequency and percentage.

Data Synthesis and Analysis

We provided a narrative synthesis of each study's findings, comparing their results, design, and sample size. Risk estimates for the factors were reported, and where possible, we calculated the risk estimates using data from tables [34, 41, 52, 53]. Due to variability in the reported effect sizes (odds ratio, hazard ratio, or relative risk), meta-analysis was not feasible. Efforts to standardize all effect sizes were unsuccessful because of inconsistencies, especially with asymmetric confidence intervals. Nonetheless, we assessed the consistency, temporality, and biological gradient of the exposure-outcome association using Bradford Hill's criteria, Rothman's model, and Nweke's hypotheses.

Risk stratification of risk factors using the causality index

We stratified risk factors based on a clinical index known as the causality index (CI) as previously described. The causality index is obtained using Nweke's causality score, which is a five-item scale for assessing the causal attributes of disease predictors. The items include strength of association, temporality, consistency, and irreversibility of the exposure-outcome relationship. Strength of association is deduced using risk estimates such as odds ratio, hazard ratio, or risk ratio, which assess the strength of association. According to Guyatt et al. [45], strengths of association below 2 are valued at 1, a range of 2–4.9 at 2, and estimates of 5 or higher at 3. Temporality is said to be fulfilled in a study that employed a cohort design. Hence, the temporality index is the proportion of cohort studies in the body of evidence that informs a given exposure-outcome association. An excellent temporality index is ≥ 75 (value 3), a range of 0.74–0.5 is fair (value 2), and less than 0.5 is poor (value 1). Consistency is said to be perfect at 1 (value 3), good within 0.8–0.9 (value 2), fair within 0.6–0.7 (value 1), and poor below 0.6 (value 0). Irreversibility is rated 1 (fulfilled) if all significant findings were in the same direction, and 0 (not met) if there was any variation in the direction of effect among significant findings. With a maximum score of 9, scores of 7–10 indicate first-class (most important) risk factors, 5–6 indicate second-class, and 4 or less indicate third-class (least important) factors. Factors lacking two consistent pairs of findings were regarded as "uncertain," meaning there is insufficient data for an interim decision.

Results

Study selection

Following a literature search, we retrieved 17,074 articles, with 210 duplicates. After removing duplicates, 16,864 articles remained for title and abstract screening. During screening, 16,817 articles were found ineligible and excluded, leaving 47 studies for full-text

review. The full texts were screened further, and data were extracted from 30 eligible articles (Figure 1).

Study and demographic characteristics

This review included 30 studies with 353,995 participants. Three studies (1040 participants) were from Africa [54, 19, 55], six (146,593) from Europe [56–61], one (43,564) from Australia [62], fourteen (105,257) from North America [63–76], five (57,468) from Asia [77–81], and one (74) from Russia [82]. The studies comprised 22 cohort and 8 case–control studies. Stroke diagnosis used standard procedures with international classification codes in eleven studies [63–68, 72–75, 77, 78], Trial of Organization in Acute Stroke Treatment (TOAST) categorization in four studies [60, 70, 76, 81], and World health organisation (WHO) Multinational Monitoring of Cardiovascular Diseases (MONICA) criteria in two studies [57, 59]. Eleven studies used other validated algorithms [54, 19, 55–58, 62, 65, 66, 71, 79, 80, 82], while two did not report diagnostic measures [57, 69]. Sample sizes ranged from 73 to 50,310 participants. The mean age was 45.1 ± 10.7 years, with males comprising 72.4% of participants. In North American studies, blacks represented 44.9% and whites 26.3% of participants (Table 1).

Risk of bias

In more than half (54%) of the studies, the completeness and strategies used to address loss to follow-up were not reported. Nonetheless, all 22 cohort studies possessed a low risk of bias. Similarly, all five case–control studies possessed low risk of bias, although we couldn't ascertain whether the exposure period of interest was long enough to be meaningful due to insufficient information (Appendix 2).

Results of individual studies

For individual studies, we reported the summary of findings in terms of the risk estimate and corresponding confidence interval and/or p-value. To aid interpretation, we reported, along with the summary of findings, the design, setting, and effect size type (Table 2).

Narrative synthesis

Age

Of twelve studies examining age-stroke association in PLWH, six studies [55, 57, 62, 63, 69, 81] showed no significant association, while eight studies [56, 64, 70, 76, 80] reported significant associations. Studies using median age or focusing on individuals aged > 50 years mostly showed statistical significance. Two of four studies using"10-year rise in age"reached statistical significance (Table 2).

Sex

Eleven studies reported the association between sex and stroke in PLWH. Seven of the studies [55–57, 63, 70, 76, 80] reported no statistically significant association, while four of the studies [60, 65, 78, 81] reported statistically significant association. No pattern was observed except that only one African study was involved (Table 2).

Ethnicity/Race

Of the five studies that reported an association between ethnicity/race and stroke in PLWH, only one African case–control study [55] reported a statistically significant association, while four studies [64, 67, 70, 76] reported no such association (Table 2).

Hypertension

Thirteen studies reported an association between hypertension and stroke in PLWH. Eight studies [55–57, 62, 63, 75, 78, 80] showed a statistically significant association, while five [60, 64, 70, 76, 81] showed no significance. The association reached significance in two studies with hemorrhagic stroke cases and in four of five European cohorts and four of five North American studies (Table 2).

Diabetes

Of eleven studies on diabetes and stroke in PLWH, six studies [19, 63, 64, 67, 76, 81] showed no significant association, while four [60, 75, 78, 80] reported significant associations. One study [62] showed both significant and non-significant associations for ischemic and hemorrhagic strokes, respectively. The two studies, including transient ischemic attack (TIA), reached statistical significance (Table 2).

Smoking

Twelve studies reported an association between smoking and stroke in PLWH. Five of the studies [58, 59, 62, 71, 83] reported a statistically significant association, while six studies [56, 65, 66, 69, 80, 82] reported no such association. Regarding the statistical significance of the association between smoking and stroke, no observable pattern was evident except that only one study, with no statistical significance, was conducted in Africa.

Dyslipidemia

Ten studies reported the association between dyslipidemia and stroke in PLWH. Of the ten studies, five studies [62, 64, 70, 78, 80] reported a statistically

Table 1 Study and demographic characteristics

Authors	Definition of stroke	Chronicity	Type of stroke	Age(mean/med + SD/IQR)	Ethnicity (%)	Sex (% female)	Design	Method	Total sample size	Follow-up period	Country
Benjamin et al., 2015 [54]	As per MRI	First-ever stroke	Ischemic & hemorrhagic	Med:58.5 (42–68.5)	Black Africans	51%	Case–control	Prospective	725	NR	Malawi
Chammartin et al., 2022 [56]	In terms of includes cerebral infarction and carotid endarterectomy	First-ever stroke	Ischemic	Med:37 (30–65)	NR	23.4%	Cohort	Prospective	9257	Med: 11.1	Switzerland
Chow et al., 2014 [63]	As per (ICD-9-CM)	First-ever stroke	Ischemic	Mean: 49.15(7.65)	White: 38 Black:49.5	26.5%	Case–control	Prospective	120	NA	USA
Chow et al., 2018(a) [64]	ICD-9-CM code	First-ever stroke	Ischaemic	39.5(12.5)	White: 39 Black: 33	100%	Cohort	Prospective	13,255	Mean: 7	USA
Chow et al., 2018(b) [65]	A focal neurologic deficit lasting > 30 s but rapid revolution of symptoms to maximal deficit in less than 5 min followed by complete resolution, Rapid onset of a focal neurologic deficit persisting for at least 24 h	First-ever stroke	Ischemic & TIA	Med: 37 (30–44)	White: 40 Black: 37	19.8%	Cohort	Prospective	6,933	Med: 3.4	USA
Cole et al., 2004 [66]	Two neurologists reviewed each case to confirm using ICD-9-CM codes; Only patients diagnosed with stroke and met the 1987 CDC AIDS definition		Ischaemic and hemorrhagic	Mean:35.3	Black: 86	72%	Cohort	Retrospective	556	NR	USA
Gutierrez et al., 2019 [67]	ICD-9 defined ischemic events	First ever stroke	Ischaemic	Med: 52 (46–58)	White:10 Black:57	44.3%	Cohort	Retrospective	115	Med: 2 years	USA

Table 1 (continued)

Authors	Definition of stroke	Chronicity	Type of stroke	Age(mean/med + SD/IQR)	Ethnicity (%)	Sex (% female)	Design	Method	Total sample size	Follow-up period	Country
Harding et al., 2021 [68]	ICD-9 code 435 for transient cerebral ischemia or CPT code 93,886 for transcranial dopplers, MRI	First ever stroke	Ischemic and hemorrhagic stroke	Med: 42 (35–49)	White: 42 Black: 43	21%	Cohort	Prospective	15,974	Mean: 4.2 years	USA
Hatleberg et al., 2019 [62]	Presence of focal neurological signs (with/without additional imaging), with duration N24 h and no evidence of any non-vascular cause	First ever stroke	Ischemic	Med: 55 (46–64)	White: 52.5%	18.5%	Multicohort	Prospective	43,564	8.1	Australia
Krsak et al., 2015 [69]	Not reported	First ever stroke	Ischaemic	Mean: 44.3 (7.7)	White: 53% Black: 32%	32%	Cohort	Retrospective	438	6.6 years	USA
Ku et al.2023 [77]	[ICD-9-CM]), ICD-10-CM	acute	Hemorrhagic stroke	All ≥ 18 years	Chinese: 100%	9.04%	Nested case–control	secondary data	31,707	NA	China
Sabin et al., 2013	Not reported	First ever stroke	Ischaemic	Med: 37 (32–44)	White: 53.2 Black: 7	27.0%	cohort	Prospective	31,235	Long follow up	London, Australia, America
Sarfo et al., 2021 [19]	Clinical history and examination with diagnostic investigations	First ever stroke	Ischemic	Mean:50.2 ±9.6	Black Africans	71.6%	Cohort	prospective	255	12 months	Ghana
Tibekina et al., 2019 [82]	Clinical history and examination with diagnostic investigations	First ever stroke	Hemorrhagic and ischemic stroke	Mean:49	Russians	NR	Case–control	Retrospective	73	NA	Russia
Vinikoor et al., 2024 [70]	TOAST categorization	First ever stroke	Ischemic	Med: 48 (42, 55)	Black:58	30%	Cohort	Retrospective	2,515	4.5 years	USA
Yen et al., 2016 [78]	ICD-9-CM codes 430–432, ICD-9-CM codes 433 to 437	First ever stroke	Ischemic and hemorrhagic stroke	Mean:28 (6.38)	Chinese	6.38%	Cohort	Prospective	22,581	4.85 years	China

Table 1 (continued)

Authors	Definition of stroke	Chronicity	Type of stroke	Age(mean/med + SD/IQR)	Ethnicity (%)	Sex (% female)	Design	Method	Total sample size	Follow-up period	Country
Zhang et al., 2022 [79]	Stroke was defined as an acute episode of focal dysfunction of the brain, retina, or spinal cord with typical symptoms or a local infarction or hemorrhage detected on imaging (CT or MRI) associated with symptom	First ever stroke	Ischemic infarction, hemorrhagic stroke, lacunar infarction	Med: 47 (20–83)	Chinese	10.5%	Case–control	Retrospective	2867	NA	China
Adnan et al., 1997	Rapidly developing clinical signs of focal, at times global (as in coma or subarachnoid hemorrhage)	First ever stroke	Ischemic & hemorrhagic	Range: 19–44 years	Black: 85	45.13%	Case–control	Retrospective	226	NA	USA
Allie et al., 2015 [55]	levels of von Willebrand factor and ADAMTS13	First ever stroke	Ischemic	Med: 34.3	Black: 60	57.5%	Case–Control	prospective	60	NA	South Africa
Bizzotte et al., 2003	(ICD-9) or Tenth Revision (ICD-10)	First ever stroke	Ischemic	Range: < 35 yr = 17.6%	White: 62.7 Black: 34.2	22.6%	Cohort	Retrospective	36,766	0.77 years	USA

Table 1 (continued)

Authors	Definition of stroke	Chronicity	Type of stroke	Age(mean/med + SD/IQR)	Ethnicity (%)	Sex (% female)	Design	Method	Total sample size	Follow-up period	Country
Hiransuthikul et al., 2022 [80]	S, defined as an episode of focal neurological dysfunction with brain imaging confirming infarction, or TIA, defined as a focal cerebral ischemic event with symptoms lasting	First ever stroke	Ischemic stroke and TIA	Med: 32.3 (27.3–38)	NR	35.8%	Cohort	Prospective	202	1996- 2020	Thailand
Lee et al., 2012 [81]	CT scan, MRI, TOAST criteria	First ever stroke	Ischemic	Mean: 50.5	NR	19.9%	Cohort	Retrospective	111	2 years	Thailand
Marconi et al., 2018	International Classification of Diseases, Ninth Revision (ICD-9) codes	First ever stroke	Ischemic	Mean: 48.4 (9.4)	Black: 48	97.1%	Cohort	Prospective	2 112	5.7 years	USA
Monforte et al., 2013 [61]	Criteria applied in the WHO MONICA study	First ever stroke	Ischemic	People aged 40–49: 42%	Black:7.2	26.5%	Cohort	Prospective	49 734	About 3 years	DAD study + Europe, Australia & USA
Rasmussen et al., 2011 [58]	Time to first ever CVE defined as the first date an individual was registered	First ever stroke	Ischemic & hemorrhagic	Med: 36.3 years	White: 86.8%	29.05%	Cohort	Prospective	50,310	Median: 7.6 years	Denmark
Sabin et al., 2013	Criteria applied in the WHO MONICA Study	First ever stroke	Hemorrhagic	Mean: 43.3	White: 53.6 Black/non-white: 13.8	25.9%	Cohort	Prospective	6 017	Long follow up	UK
Silva-Pinto et al., 2017 [60]	According to the Trial of Org 10,172 in Acute Stroke Treatment (TOAST)	First ever stroke	Ischemic	Mean: 51.3 year	NR	17.6%	Case–control	Retrospective	40	NA	Portugal
Chow et al., 2013 [63]	As per ICD-9-CM	First ever stroke	Ischemic	Mean: 41.6 (11.4) years	White: 51.3 Black:8.1	61%	Cohort	Retrospective	4308	Long follow up	USA

Table 1 (continued)

Authors	Definition of stroke	Chronicity	Type of stroke	Age(mean/med + SD/IQR)	Ethnicity (%)	Sex (% female)	Design	Method	Total sample size	Follow-up period	Country
Bedimo et al., 2011 [75]	ICD-9	First ever stroke	Stroke & TIA	Median: 46	NR	98%	Cohort	Retrospective	19,424	3.93 years	USA
Vinikoor et al., 2013 [76]	TOAST criteria	First ever stroke	All	39 (21–45) years	White: 32 black: 58	30%	Cohort	Retrospective	2,515	4.5 years (IQR: 2.0, 7.8	USA

Table 2 Narrative synthesis of the factors associated with stroke in PLWH

Study	Type of stroke	Reference	Categories	Effect size	Lower limit	Upper limit	Setting	Design	Risk estimate	Mode of analysis
Age										
Chammartin et al. 2022 [56]	Ischemic	< 50 years	Age (50–65)	4.27	2.49	7.34	Europe	Cohort	HR	Multivariate
√	√	√	Age (≥ 65)	13.05	6.93	24.6	Europe	Cohort	HR	Multivariate
Chow et al. 2014 [63]	Ischemic	NA	Per 10 years	1.52	0.88	2.62	North America	Case–control	OR	Univariate
Chow et al., 2018(a) [64]	Ischemic	NA	Per 10 years	1.55	1.26	1.90	North America	Cohort	HR	Univariate
Hatleberg et al.2019 [62]	Ischemic	NR	Median age	1.19	1.12	1.25	Australia, Europe & USA	Cohort	HR	Univariate
√	√	√	Median age	1.28	1.17	1.39	Australia, Europe & USA	Cohort	HR	Univariate
Krsak et al.2015 [69]	Ischemic	NR	Median age	1.04	1.01	1.07	North America	Cohort	HR	Univariate
Sarfo et al.2021 [19]	Ischaemic	NA	Each 10-year rise	1.53	0.64	3.64	Africa	Cohort	HR	Univariate
Vinikoor et al. 2024 [70]	Ischemic	< 50 years	> 50 years	1.78	1.25	2.55	North America	Cohort	RR	Multivariate
Allie et al. 2015 [55]	Ischemic	NR	NR	1.44	0.54	3.83	Africa	Case–control	OR	Univariate
Hiransuthikul et al.,2022 [80]	TIA	NR	Age at initiation of ART	114.4759	46.3483	282.7445	Asia	Cohort	OR	Univariate
Lee et al. 2012 [81]	Ischemic & Hemorrhagic	NR	Mean age	1.0144	0.4958	2.0752	Asia	Cohort	OR	Univariate
Sabin et al. 2013	Ischemic Stroke & Hemorrhagic	NA	Per 5 years older	1.41	1.35	1.49	Europe	Cohort	RR	Univariate
Vinikoor et al., 2013 [76]	Ischemic, Hemorrhagic and TIA	NA	Per 10-year increase	1.78	1.25	2.55	North America	Cohort	RR	Univariate
Sex										
Chammartin et al. 2022 [56]	Ischemic	Male	Female	0.81	0.47	1.41	Europe	Cohort	HR	Multivariate
Chow et al. 2014 [63]	Ischemic	Male	Female	1.52	0.88	2.62	North America	Case–control	OR	Univariate
Chow et al. 2018b [65]	Ischemic	Male	Female	2.07	1.17	3.63	North America	Cohort	HR	Univariate
Hatleberg et al.2019 [62]	Ischaemic	Female	Male	0.60	0.35	0.91	North America	Cohort	HR	Univariate
	hemorrhagic	Female	Male	1.62	1.14	2.31	North America		HR	Univariate
Vinikoor et al. 2024 [70]	Ischemic	Male	Female	1.69	0.82	3.48	North America	Cohort	RR	Multivariate
Yen et al. 2016 [78]	Ischemic & hemorrhagic	Male	Female	1.63	1.15	2.32	Asia	Cohort	HR	Univariate
Allie et al. 2015 [55]	Ischemic	Male	Female	1.23	0.41	3.65	Africa	Case–control	OR	Univariate
Hiransuthikul et al.,2022 [80]	TIA	Female	Male	2.419	0.6879	8.5059	Asia	Cohort	HR	Univariate
Lee et al. 2012 [81]	Ischemic & hemorrhagic	Male	Female	0.4	0.1	0.9	Asia	Cohort	OR	Univariate

Table 2 (continued)

Study	Type of stroke	Reference	Categories	Effect size	Lower limit	Upper limit	Setting	Design	Risk estimate	Mode of analysis
Sabin et al. 2013	Ischemic & hemorrhagic	Female	Male	1.19	0.88	1.62	Europe	Cohort	RR	Univariate
Vinikoor et al., 2013 [76]	Ischemic & hemorrhagic and TIA	Male	Female	1.69	0.82	3.48	North America	Cohort	RR	Univariate
Ethnicity/race										
Chow et al., 2018(a) [64]	Ischemic	Others	White	1.11	0.58	2.14	North America	Cohort	HR	Univariate
Gutierrez et al. 2019 [67]	Ischemic	Others	Non-Hispanic black	1.76	0.40	7.82	North America	Cohort	HR	Multivariate
Vinikoor et al. 2024 [70]	Ischemic	White	Black	0.89	0.46	1.74	North America	Cohort	RR	Multivariate
Allie et al. 2015 [55]	Ischemic	White	Black African	0.045	0.0023	0.89	Africa	Case–control	OR	Univariate
Vinikoor et al., 2013 [76]	Ischemic, hemorrhagic and TIA	White	Black race	0.89	0.46	1.74	North America	Cohort	RR	Univariate
Traditional risk factors Hypertension										
Chammartin et al. 2022 [56]	Ischemic	No	Yes	2.3	1.32	3.12	Europe	Cohort	HR	Multivariate
Chow et al. 2014 [63]	Ischemic	No	Yes	3.0	1.35	6.68	North America	Case–control	OR	Univariate
Chow et al., 2018(a) [64]	Ischemic	No	Yes	1.76	0.92	3.39	North America	Cohort	HR	Univariate
Hatleberg et al.2019 [62]	Ischemic	No	Yes	2.24	1.77	1.39	Australia, Europe & USA	Cohort	HR	Univariate
√	Hemorrhagic	No	Yes	3.55	2.29	5.50	Australia, Europe & USA	Cohort	HR	Univariate
Sarfo et al. 2021 [19]	Ischaemic	No	Yes	7.70	1.29	46.08	Africa	Cohort	HR	Univariate
Vinikoor et al. 2024 [70]	Ischemic	No	Yes	1.96	0.99	3.99	North America	Cohort	RR	Multivariate
Yen et al. 2016 [78]	Ischemic & hemorrhagic	No	Yes	6.99	4.64	10.53	Asia	Cohort	HR	Univariate
Hiransuthikul et al., 2022 [80]	TIA	No	Yes	12.3846	3.9729	38.6066	Asia	Cohort	OR	Univariate
Lee et al. 2012 [81]	Ischemic & hemorrhagic	No	Yes	1.331	0.4693	3.7751	Asia	Cohort	OR	Univariate
Sabin et al. 2013	Ischemic & hemorrhagic	No	Yes	2.14	1.66	2.75	Europe	Cohort	RR	Univariate
Silva-Pinto et al. 2017 [60]	Ischemic	No	Yes	2.9167	0.6483	13.1214	Europe	Case–control	OR	Univariate
Bedimo et al. 2011 [75]	Stroke & TIA	No	Yes	2.2571	1.9668	2.5901	North America	Cohort	OR	Univariate
Vinikoor et al., 2013 [76]	Ischemic, hemorrhagic & TTIA	No	Yes	1.96	0.99	3.99	North America	Cohort	RR	Univariate

Table 2 (continued)

Study	Type of stroke	Reference	Categories	Effect size	Lower limit	Upper limit	Setting	Design	Risk estimate	Mode of analysis
Diabetes										
Chow et al. 2014 [63]	Ischemic	No	Yes	1.60	0.52	9.04	North America	Case–control	OR	Univariate
Chow et al., 2018(a) [64]	Ischemic	No	Yes	1.11	0.54	2.30	North America	Cohort	HR	Univariate
Gutierrez et al. 2019 [67]	Ischemic	No	Yes	1.62	0.99	2.63	North America	Cohort	HR	Multivariate
Hatleberg et al. 2019 [62]	Ischemic	No	Yes	1.65	1.20	2.27	Australia, Europe & USA	Cohort	HR	Univariate
√	Hemorrhagic	No	Yes	1.94	0.57	2.43	Australia, Europe & USA	Cohort	HR	Univariate
Sarfo et al.2021 [19]	Ischaemic	No	Yes	0.00	0.00	4.39	Africa	Cohort	HR	Univariate
Yen et al. 2016 [78]	Ischemic & hemorrhagic	No	Yes	4.44	2.48	7.95	Asia	Cohort	HR	Univariate
Hiransuthikul et al.,2022 [80]	TIA	No	Yes	7.6607	2.8199	20.8116	Asia	Cohort	OR	Univariate
Lee et al. 2012 [81]	Ischemic & hemorrhagic	No	Yes	1.331	0.4693	3.7751	Asia	Cohort	OR	Univariate
Silva-Pinto et al. 2017 [60]	Ischemic	No	Yes	11.7333	1.3264	183.9829	Europe	Case–control	OR	Univariate
Bedimo et al. 2011 [75]	Stroke & TIA	No	Yes	1.8333	1.5435	2.1776	North America	Cohort	OR	Univariate
Vinikoor et al., 2013 [76]	Ischemic & hemorrhagic	No	Yes	0.95	0.42	2.18	North America	Cohort	RR	Univariate
Smoking										
Chammartin et al. 2022 [56]	Ischemic	No smoking	Yes smoking	2.46	1.57	3.86	Europe	Cohort	HR	Multivariate
Chow et al. 2014 [63]	Ischemic	No	Yes	0.46	0.18	1.21	North America	Case–control	OR	Univariate
Chow et al. 2018a [64]	Ischemic	No	Yes	1.32	0.68	2.58	North America	Cohort	HR	Univariate
Gutierrez et al. 2019 [67]	Ischemic	No	Yes	2.51	0.47	13.55	North America	Cohort	OR	Multivariate
Hatleberg et al. 2019 [62]	Ischemic	No	Yes	1.90	1.41	2.56	Australia, Europe & USA	Cohort	HR	Univariate
√	Hemorrhagic	No	Yes	1.08	0.68	1.71	Australia, Europe & USA	Cohort	HR	Univariate
Krsak et al. 2015 [69]	Ischemic	No	Yes	1.84	1.13	3.00	North America	Cohort	HR	Univariate
Sarfo et al. 2021 [19]	Ischaemic	No	Yes	0.81	0.40	1.65	Africa	Cohort	HR	Univariate
Hiransuthikul et al., 2022 [80]	TIA	No	Yes	2.1153	0.7904	5.6612	Asia	Cohort	OR	Univariate
Lee et al. 2012 [81]	Ischemic & hemorrhagic	No	Yes:	6.9	2.3	21.2	Asia	Cohort	OR	Multivariate
Sabin et al. 2013	Ischemic Stroke & Hemorrhagic	No	Yes	1.52	1.12	2.06	Europe	Cohort	RR	Univariate
Silva-Pinto et al. 2017 [60]	Ischemic	No	Yes	5.3125	1.4981	18.8395		Case–control		

Table 2 (continued)

Study	Type of stroke	Reference	Categories	Effect size	Lower limit	Upper limit	Setting	Design	Risk estimate	Mode of analysis
Vinikoor et al., 2013 [76]	Ischemic, hemorrhagic and TIA	No	Yes	0.81	0.40	1.65	North America	Cohort	RR	Univariate
Dyslipidemia										
Chow et al. 2014 [63]	Ischemic	No	Yes	3.67	1.49	9.04	North America	Case–control	OR	Univariate
Gutierrez et al. 2019 [67]	Ischemic	No	Yes	5.01	0.99	25.25	North America	Cohort	HR	Multivariate
Hatleberg et al. 2019 [62]	Ischemic	No	Yes	1.48	1.16	1.83	Australia, Europe & USA	Cohort	HR	Univariate
√	Hemorrhagic	No	Yes	4.80	2.47	9.36	Australia, Europe & USA	Cohort	HR	Univariate
Sarfo et al.2021 [19]	Ischaemic	No	Yes	1.85	0.17	20.43	Africa	Cohort	HR	Univariate
Vinikoor et al. 2024 [70]	Ischemic	No	Yes	3.02	1.48	6.17	North America	Cohort	RR	Multivariate
Yen et al. 2016 [78]	Ischemic & hemorrhagic	No	Yes	4.79	2.26	10.16	Asia	Cohort	HR	Univariate
Hiransuthikul et al., 2022 [80]	TIA	No	Yes	2.9834	1.0323	8.6223	Asia	Cohort	OR	Univariate
Lee et al. 2012 [81]	Ischemic & hemorrhagic	No	Yes	0.5396	0.2152	1.3531	Asia	Cohort	OR	Univariate
Silva-Pinto et al. 2017 [60]	Ischemic	No	Yes	2.0222	0.6244	6.5489	Europe	Case–control	OR	Univariate
Bedimo et al. 2011 [75]	Ischemic & hemorrhagic	No	Yes	1.00	0.8563	1.1679	North America	Cohort	OR	Univariate
Obesity										
Hatleberg et al. 2019 [62]	Ischemic	18–26	< 18	1.41	0.85	2.34	Australia, Europe & USA	Cohort	HR	Univariate
√	√	18–26	26–29	0.79	0.58	1.06	Australia, Europe & USA	Cohort	HR	Univariate
√	√	18–26	≥ 30	1.09	0.71	1.66	Australia, Europe & USA	Cohort	HR	Univariate
Hiransuthikul et al., 2022	TIA	NR	Mean BMI	3.16	1.29	7.72	Asia	Cohort	OR	Univariate
Sabin et al. 2013	Ischemic Stroke & Hemorrhagic	Normal weight	Underweight	2.06	1.32	3.24	Europe	Cohort	RR	Univariate
√	√	√	Overweight	0.77	0.55	1.08	Europe	Cohort	RR	Univariate
√	√	√	Obesity	1.02	0.64	1.62	Europe	Cohort	RR	Univariate
Alcohol Use										
Chow et al. 2014 [63]	Ischemic	No	Yes	2.83	1.12	7.19	North America	Case–control	OR	Univariate
Hiransuthikul et al.,2022 [80]	TIA	No	Yes	0.2528	0.0719	0.8888	Asia	Cohort	OR	Univariate

Table 2 (continued)

Study	Type of stroke	Reference	Categories	Effect size	Lower limit	Upper limit	Setting	Design	Risk estimate	Mode of analysis
HCV										
Hatleberg et al. 2019 [62]	Ischemic	No	Yes	1.22	0.9	1.65	Australia, Europe & USA	Cohort	HR	Univariate
√	Hemorrhagic	No	Yes	1.32	0.72	2.40	Australia, Europe & USA	Cohort	HR	Univariate
Sarfo et al. 2021 [19]	Ischaemic	No	Yes	1.81	0.85	3.84	Africa	Cohort	HR	Univariate
Hiransuthikul et al., 2022 [80]	TIA	No	Yes	1.3001	0.2934	5.7621	Asia	Cohort	OR	Univariate
Bedimo et al. 2011 [75]	Both	No	Yes	1.252	1.0862	1.4431	North America	Cohort	OR	Univariate
CKD										
Chow et al., 2018(a) [64]	Ischemic	No	Yes	2.32	1.09	4.92	North America	Cohort	HR	Univariate
Gutierrez et al. 2019 [67]	Ischemic	No	Yes	4.25	0.7	25.73	North America	Cohort	HR	Multivariate
Hatleberg et al. 2019	Ischemic	No	Yes	1.04	0.67	1.60	Australia, Europe & USA	Cohort	HR	Univariate
√	hemorrhagic	No	Yes	4.80	2.47	9.36	Australia, Europe & USA	Cohort	HR	Univariate
Yen et al. 2016 [78]	Ischemic & hemorrhagic	No	Yes	3.27	1.05	10.22	Asia	Cohort	HR	Univariate
Hiransuthikul et al., 2022 [80]	TIA	No	Yes	8.8039	3.2694	23.7077	Asia	Cohort	OR	Univariate
Bedimo et al. 2011	Both	No	Yes	2.3445	1.9298	2.8484	North America	Cohort	OR	Univariate
CAD										
Chow et al. 2014 [63]	Ischemic	No	Yes	15.0	1.98	113.56	North America	Case–control	OR	Univariate
Chow et al., 2018(a) [64]	Ischemic	No	Yes	2.93	1.52	5.65	North America	Cohort	HR	Univariate
Sarfo et al. 2021 [19]	Ischaemic	No	Yes	0.81	0.40	1.65	Africa	Cohort	HR	Univariate
Vinikoor et al. 2024 [70]	Ischemic	No	Yes	2.51	0.62	10.17	North America	Cohort	RR	Multivariate
Yen et al. 2016	Ischemic & hemorrhagic	No	Yes	2.89	1.07	7.76	Asia	Cohort	HR	Univariate
Vinikoor et al., 2013 [76[	Ischemic, hemorrhagic and TIA	No	Yes	2.51	0.62	10.17	North America	Cohort	RR	Univariate
Atrial Fibrillation										
Chow et al. 2014 [63]	Ischemic	No	Yes	4.0	0.45	35.79	North America	Case–control	OR	Univariate
Chow et al., 2018(a) [64]	Ischemic	No	Yes	3.82	1.35	10.80	North America	Cohort	HR	Univariate
Lee et al. 2012 [81]	Ischemic & hemorrhagic	No	Yes	10.484	0.4902	2.3498	Asia	Cohort	OR	Univariate

Table 2 (continued)

Study	Type of stroke	Reference	Categories	Effect size	Lower limit	Upper limit	Setting	Design	Risk estimate	Mode of analysis
HBV										
Hatleberg et al. 2019 [62]	Ischemic	No	Yes	1.22	0.9	1.65	Australia, Europe & USA	Cohort	HR	Univariate
	Hemorrhagic	No	Yes	1.19	1.12	1.25	Australia, Europe & USA	Cohort	HR	Univariate
Krsak et al. 2015 [69]	Ischemic	No	Yes	0.47	0.25	0.86	North America	Cohort	HR	Univariate
Hiransuthikul et al., 2022 [80]	TIA	No	Yes	0.3694	0.049	2.7854	Asia	Cohort	OR	Univariate
HIV-related factors ART duration (month/years)										
Benjamin et al., 2016 [54]	Ischemic & Hemorrhagic	Untreated	< 6 months	4.63	1.34	11.90	Africa	Case–control	OR	Univariate
√	√	√	≥ 6 month & undetected VL	0.67	0.28	1.60	Africa	Case–control	OR	Univariate
√	√	√	≥ 6 month & detected VL	0.17	0.02	1.55	Africa	Case–control	OR	Univariate
Chow et al. 2018a [64]	Ischemic	NR	Longer duration	0.83	0.74	0.94	North America	Cohort	HR	Univariate
Hiransuthikul et al., 2022 [80]	TIA	NA	Median years of ART use	2.0104	0.8234	4.9081	Asia	Cohort	HR	Univariate
√	√	√	Duration of PI use	2.03	0.83	4.92	Asia	Cohort	HR	Univariate
√	√	√	Duration of ABC	1.00	0.4098	0.4919	Asia	Cohort	HR	Univariate
√	√	√	Duration of NNTRI	0.4492	0.184	1.0969	Asia	Cohort	HR	Univariate
Silva-Pinto et al. 2017 [60]	Ischemic	Lower Median ART duration	Higher Median duration in month	0.1089	0.0348	0.3413	Europe	Case–control	OR	Univariate
CD4 count (cells/mm^3)										
Benjamin et al., 2016 [54]	Ischemic & Hemorrhagic	> 500cells/mm3	350-500cells/mm3	3.69	0.97	14.0	Africa	Case–control	OR	Univariate
√	√	√	200–350 cells/mm3	7.95	2.14	29.5	Africa	Case–control	OR	Univariate
√	√	√	< 200 cells/mm3	11.47	3.27	40.3	Africa	Case–control	OR	Univariate
Chow et al. 2018a [64]	Ischemic	NA	per 50 cells/mm3	0.83	0.74	0.94	North America	Cohort	HR	Univariate

Table 2 (continued)

Study	Type of stroke	Reference	Categories	Effect size	Lower limit	Upper limit	Setting	Design	Risk estimate	Mode of analysis
√	√	√	Nadir CD4 per 50 cells/mm3	1.01	0.94	1.09	North America	Cohort	HR	Univariate
Gutierrez et al. 2019 [67]	Ischemic	< 200 cells/mm3	Per 50 cells/mm3	1.08	0.97	1.21	North America	Cohort	OR	Multivariate
√	√	√	Nadir CD4 < 200 cells/mm3	10.44	1.64	66.26	North America		OR	Multivariate
Krsak et al. 2015 [69]	Ischemic	NA	Per 50 cells/mm3	0.88	0.82	0.95	North America	Cohort	HR	Univariate
Vinikoor et al. 2024 [70]	Ischaemic	< 200 cells/mm^3	> 200 cells/mm3	2.83	1.27	6.33	North America	Cohort	HR	Multivariate
Lee et al. 2012 [81]	Ischemic & Hemorrhagic	200 cells/mm3	< 200 cells/mm3	0.6201	0.2723	1.4124	Asia	Cohort	OR	Univariate
Rasmussen et al. 2011 [58]	Ischemic & Hemorrhagic	> 200 cells/mm3 and Non-ART	≤ 200 cells/mm3	2.28	1.09	4.76	Europe	Cohort	HR	Multivariate
Sabin et al. 2013	Ischemic Stroke & Hemorrhagic	NA	Per doubling of CD4 cell count	0.81	0.74	0.89	Europe	Cohort	RR	Univariate
Silva-Pinto et al. 2017 [60]	Ischemic	> 200 cells/mm3	< 200 cells/mm3	9.7209	1.0751	87.89	Europe	Case–control	OR	Univariate
Vinikoor et al., 2013 [76]	Ischemic Stroke, Hemorrhagic & TIA	< 200 cells/mm3	< 200 cells/mm3	2.83	1.27	6.33	North America	Cohort	RR	Univariate
Viral load										
Chow et al. 2014 [63]	Ischemic	√	Per log copies/ml	1.24	1.00	1.54	North America	Case–control	OR	Univariate
√	√	√	Virally suppressed 6 months before index date	0.23	0.09	0.60	North America	Case–control	OR	Univariate
Chow et al. 2018a [64]	Ischemic	NA	per 1 log copy/mL	1.13	0.85	1.51	North America	Cohort	HR	Univariate
Harding et al. 2021 [68]	Overall (both)	NA	75 th vs 25 th percentile	1.4	1.1	1.8	North America	Cohort	HR	Multivariate
√	Ischemic	NA	75 th vs 25 th percentile	1.3	0.96	1.7	North America	Cohort	HR	Multivariate

Table 2 (continued)

Study	Type of stroke	Reference	Categories	Effect size	Lower limit	Upper limit	Setting	Design	Risk estimate	Mode of analysis
√	Hemorrhagic	NA	75 th vs 25 th percentile	3.1	1.6	5.9	North America	Cohort	HR	Multivariate
Hatleberg et al. 2019 [62]	Ischemic	> 500 copies/mL	> 500 copies/mL	1.36	0.96	1.94	Australia, Europe & USA	Cohort	HR	Univariate
√	Hemorrhagic	< 500 copies/mL	> 500 copies/mL	1.03	0.58	1.82	Australia, Europe & USA	Cohort	HR	Univariate
Hiransuthikul et al., 2022 [80]	TIA	> 50 copies/mL	< 50 copies/mL	0.6923	0.16	3.07	Asia	Cohort	HR	Univariate
Silva-Pinto et al. 2017 [60]	Ischemic	NA	Median viral	1.00	0.35	2.853	Europe	Case–control	OR	Univariate
Vinikoor et al., 2013 [70]	Ischemic, hemorrhagic & TIA	< 400 copies	> 400 copies	3.97	1.90	8.31	North America	Cohort	RR	Univariate
ART use										
Vinikoor et al. 2024 [76]	Ischemic	No	Yes	4.16	0.80	21.65	North America	Cohort	RR	Multivariate
Yen et al. 2016 [78]	Ischemic & hemorrhagic	No	Yes	0.44	0.34	0.58	Asia	Cohort	HR	Univariate
Lee et al. 2012 [81]	Ischemic & hemorrhagic	No	Yes	0.3	0.1	0.6	Asia	Cohort	OR	Multivariate
Vinikoor et al., 2013 [70]	Ischemic, hemorrhagic & TIA	No	Yes	4.16	0.80	21.65	North America	Cohort	RR	Univariate
ART Type										
Sarfo et al. 2021 [19]	Ischemic	Others	Protease inhibitors	6.96	0.63	76.76	Africa	Cohort	HR	Univariate
Bizzotte et al. 2003	Ischemic	Others	Protease inhibitor	1.23	0.73	1.93	North America	Cohort	HR	Univariate
√	√	Others	Nonnucleoside reverse transcriptase inhibitors	1.09	0.56	2.09	North America	Cohort	HR	Univariate
√	√	Others	Nucleoside analogues plus protease inhibitor	1.08	0.69	1.67	North America	Cohort	HR	Univariate

Table 2 (continued)

Study	Type of stroke	Reference	Categories	Effect size	Lower limit	Upper limit	Setting	Design	Risk estimate	Mode of analysis
√	√	Others	Nucleoside analogues plus non-nucleoside reverse transcriptase inhibitor	0.95	0.47	1.93	North America	Cohort	HR	Univariate
√	√	Others	Nucleoside reverse transcriptase inhibitor	0.88	0.63	1.22	North America	Cohort	HR	Univariate
Hiransuthikul et al.,2022 [80]	TIA	Others	PI	5.9548	1.6894	20.9887	Asia	Cohort	HR	Univariate
√	√	√	NNRTI	2.2421	0.2972	16.9168	Asia	Cohort	HR	Univariate
√	√	√	ABC	3.0337	0.969	9.4955	Asia	Cohort	HR	Univariate
√	√	√	NRTI	0.0924	0.0044	1.9629	Asia	Cohort	HR	Univariate
√	√	√	NNRTI	1.3696	0.5424	3.4586	Asia	Cohort	HR	Univariate
√	√	√	PI	1.079	0.4448	2.6171	Asia	Cohort	HR	Univariate
Cocaine										
Chow et al. 2014 [63]	Ischemic	No	Yes	1.56	0.67	3.59	North America	Case–control	OR	Univariate
Silva-Pinto et al. 2017 [60]	Ischemic	No	Yes	10.8462	0.5494	214.1338	Europe	Case–control	OR	Univariate
TB										
Yen et al. 2016 [78]	Ischemic	No	Yes	1,53	1,27	3,77	Asia	Cohort	HR	Univariate
Lee et al. 2012 [81]	Ischemic	No	Yes	11,9	1,2	117,2	Asia	Cohort	OR	Univariate
Heroine										
Chow et al. 2014 [63]	Ischemic	No	Yes	0.67	0.19	2.36	North America	Case–control	OR	Univariate
Silva-Pinto et al. 2017 [60]	Ischemic	No	Yes	17.4571	0.9208	330.9635	Europe	Case–control	OR	Univariate

significant association, while five studies [56, 60, 67, 75, 81] reported no such association. No observable pattern was evident except that only one study, with no statistical significance, was conducted in Africa (Table 2).

Obesity

Three studies reported an association between obesity and stroke in PLWH, out of which 1 cohort [62] reported no significant association, while two cohorts [57, 80] reported both statistically significant and non-significant associations for TIA, ischemic, and hemorrhagic stroke outcomes. All the contributing studies were conducted outside Africa (Table 2).

Hepatitis C virus infection (HCV), chronic kidney disease (CKD), and coronary artery disease (CAD)

Of four cohort studies that reported an association between HCV and stroke [19, 62, 75, 80], one [75] reported a significant association between HCV and stroke among PLWH. Four of the six studies reporting the association between CKD and stroke in PLWH reached statistical significance. four cohorts [64, 75, 78, 80]. Six studies reported the association between CAD and stroke in PLWH, with three studies [63, 64, 78] showing a significant association (Table 2).

Atrial fibrillation and hepatitis B virus infection (HBV)

Three studies reported on the association between atrial fibrillation and stroke in PLWH, of which one cohort [63] reported a statistically significant association, while two studies [63, 81] reported no such association. One [69] of the three cohorts that reported an association between HBV and stroke in PLWH reached statistical significance. We did not observe any pattern regarding the association between atrial fibrillation and stroke in PLWH (Table 2).

HIV-related factors (ART duration, CD4 count, Viral load, ART use, and ART type)

Of four studies reporting the association between ART duration and stroke in PLWH, two studies [60, 64] showed statistical significance. Nine [54, 57, 58, 60, 64, 67, 69, 70, 76] of the ten studies that examined the association between CD4 count and stroke in PLWH reached statistical significance. Two [63, 76] of seven studies examining the association between viral load and stroke in PLWH reached significance. Of four cohorts reporting the association between ART use and stroke in PLWH, two studies [78, 81] showed statistical significance. Two [19, 72] of three cohorts exploring the association between ART type and stroke in PLWH showed no significance. Most (83%) studies examining the association between CD4 count $\geq$cells/mm^3 and stroke reached statistical significance irrespective of study setting (Table 2).

Use of alcohol, cocaine, tuberculosis (TB), and heroine

Two studies [63, 80] showed a statistically significant association between alcohol use and stroke in PLWH in the opposite direction. While the North American [63] study showed alcohol may contribute to the genesis of stroke among PLWH, the Asian study [80] showed alcohol may be protective of stroke in PWLH. The two Asian studies which reported the association between TB and stroke reached statistical significance (Table 2).

Stratification (using the causality index) and certainty of evidence

Grading (certainty of evidence) confirms, rejects, or remains neutral about evidence for a finding but doesn't rank risk factors by importance in an epidemiological study. The causality index [42] addresses this. The studies show multiple factors significantly linked to stroke in people with HIV, with varying causality levels (Table 3). The most important factors were hypertension and chronic kidney disease. Second-class factors were smoking, dyslipidemia, diabetes, HCV, HBV, CD4 count, ART use, TB, and substance use (cocaine). Least important were age, sex, ethnicity, obesity, alcohol use, ART duration, and viral load. Certainty of evidence ranged from high —age, hypertension, CKD, and CD4 count, to moderate —sex, ethnicity/race, smoking, obesity, CAD, ART duration, viral load, and ART use, to low —diabetes, dyslipidemia, alcohol use, HCV, atrial fibrillation, HBV, and ART type (Table 4).

Discussion

Smoking

The finding that smoking constitutes a risk for stroke in PLWH aligns with studies that model CVD in PLWH, where smoking consistently emerges as a significant risk factor [83, 84]. Studies have highlighted a strong correlation between smoking and stroke, with passive smoking linked to carotid atherosclerosis [85]. Smoking raises levels of homocysteine, fibrinogen, and oxidized low-density lipoprotein cholesterol [86], explaining its role in stroke risk. The mechanisms through which tobacco smoke exposure elevates stroke and heart disease risk include carboxyhemoglobinemia, enhanced platelet aggregation, increased fibrinogen levels, reduced HDL-cholesterol, and toxic effects from substances like 1,3-butadiene, which accelerates atherosclerosis [87]. A meta-analysis by Pan et al. [85] found no link between former smokers and stroke incidence, highlighting the benefits of quitting. In this review, evidence of smoking's predictive potential for stroke in PLWH was moderate, suggesting further

Table 3 Causality indices for the exposure–outcome associations

Domains Factors	Strengths of associations	Temporality	Consistency	Irreversibility of associations	Causality index
Age	1.01–114.47	Excellent	Poor	Desirable	4/9
Sex	0.4–2.42	Excellent	Poor	Undesirable	3/9
Ethnicity	0.045–1.76	Excellent	Poor	Undesirable	3/9
Hypertension	1.33–12.38	Excellent	Fair	Desirable	7/9
Diabetes	0–11.73	Excellent	Poor	Desirable	5/9
Smoking	2.24–6.9	Excellent	poor	Desirable	6/9
Dyslipidemia	0.54–5.01	Excellent	Fair	Desirable	6/9
Obesity	0.77–3.16	Excellent	Poor	Undesirable	4/9
Alcohol	0.25–2.83	Fair	Poor	Uncertain	3/9
HCV	1.25–1.81	Excellent	Poor	Desirable	5/9
CKD	1.04–8.80	Excellent	Fair	Desirable	7/9
CAD	0.81–15.0	Excellent	Poor	Desirable	6/9
Atrial fibrillation	4.0–10.48	Fair	Poor	Uncertain	4/9
HBV	0.37–1.22	Excellent	Poor	Desirable	5/9
ART duration (month/year)	0.11–2.03	Fair	Poor	Undesirable	3/9
CD4 count	0.62–10.44	Excellent	Poor	Desirable	5/9
Viral load	0.23–3.97	Fair	Poor	Desirable	4/9
Use of ART	0.3–4.16	Excellent	Poor	Desirable	5/9
Type of ART (PI vs others)	0.092–6.96	Excellent	NA	Undesirable	4/9
TB	1.53–11.9	Poor	Excellent	Desirable	6/9
Cocaine	1.56–10.84	Excellent)	Poor	Desirable	6/9
Heroine	0.67–17.46	Poor	Poor	Desirable	4/9

Total cores of 7–10 indicate first-class (most important) risk factors, 5–6 indicate second-class, and 4 or less indicate third-class (least important) factors

research might alter the direction of the evidence. While smoking will likely remain a stroke risk factor among PLWH, its risk weight may change with further research. Nonetheless, its low-cost assessment makes it valuable in modeling CVD in PWLW and the general population.

CAD

Multiple studies have highlighted the connection between CAD and stroke in people living with HIV (PLWH) [88, 89]. Olesen et al. [90] demonstrated an elevated stroke risk in individuals with CAD. CAD is primarily caused by atherosclerosis, where plaques of lipids, cholesterol, calcium, and other substances accumulate in arterial walls, narrowing vessels and impeding blood flow [91]. Atherosclerosis can lead to plaque rupture, exposing prothrombotic substances to the bloodstream, activating platelets and the coagulation cascade, causing thrombus formation. This obstructs blood flow to brain tissue, leading to ischemia and infarction [91, 92]. Systemic inflammatory responses can destabilize atherosclerotic plaques and promote endothelial dysfunction, increasing stroke risk [93]. The link between CAD and stroke is backed by moderate-certainty evidence. Despite its predictive potential, its clinical nature disfavours it when selecting items in model construction. In public health, predictive analytics primarily serves to forecast disease risk at the subclinical stage, making it imprudent to include a clinical disease entity in predicting an independent primary disease.

Viral load

The risk of stroke among PLWH with higher viral load varied, with statistically insignificant and significant findings. No prior review had examined the impact of viral load on stroke risk among PLWH. While viral load's role in CVD is well-studied, non-suppressed HIV viral load from poor care retention links to higher CVD risk in PLWH. However, viral load has limited predictive value, shown by its exclusion from major CVD predictive models in PLWH, such as D: A: D 2010; HIV-MI-1, HIV MI-2 [94]. Our findings indicate that viral load is crucial for predicting stroke in PLWH. This is biologically plausible, as HIV directly impacts vascular biology through endothelial dysfunction via HIV-induced apoptosis [95], monocyte activation and cytokine secretion, and HIV proteins like tat and gp12 [96]. Randomized trials show that early ART initiation and sustained viral suppression reduce CVD risk [97]. The viral load-stroke association is

Table 4 Certainty of Evidence

Domains Factors	Limitation	Indirectness	Imprecision	Inconsistency	Publication bias	Certainty of evidence
Age	Not serious	Not serious	Not serious	Not serious	Not suspected	⊕⊕⊕⊕
Sex	Not serious	Not serious	Not serious	Serious	Not suspected	⊕⊕⊕◯
Ethnicity/race	Not serious	Not serious	Not serious	Serious	Not suspected	⊕⊕⊕◯
Hypertension	Not serious	Not serious	Not serious	Not serious	Not suspected	⊕⊕⊕⊕
Diabetes	Not serious	Not serious	Serious	Serious	Not suspected	⊕⊕◯◯
Smoking	Not serious	Not serious	Not serious	Serious	Not suspected	⊕⊕⊕◯
Dyslipidemia	Not serious	Not serious	Serious	Serious	Not suspected	⊕⊕◯◯
Obesity	Not serious	Not serious	Not serious	Serious	Not suspected	⊕⊕⊕◯
Alcohol use	Not serious	Not serious	Serious	Not serious	Suspected	⊕⊕◯◯
HCV	Not serious	Not serious	Serious	Serious	Not suspected	⊕⊕◯◯
CKD	Not serious	Not serious	Not serious	Not serious	Not suspected	⊕⊕⊕⊕
CAD	Not serious	Not serious	Not serious	Serious	Not suspected	⊕⊕⊕◯
Atrial fibrillation	Not serious	Not serious	Serious	Serious	Not suspected	⊕⊕◯◯
HBV	Not serious	Not serious	Serious	Serious	Not suspected	⊕⊕◯◯
ART duration	Not serious	Not serious	Not serious	Serious	Not suspected	⊕⊕⊕◯
CD4 count	Not serious	Not serious	Not serious	Not serious	Not suspected	⊕⊕⊕⊕
Viral load	Not serious	Not serious	Not serious	Serious	Not suspected	⊕⊕⊕◯
ART use	Not serious	Not serious	Not serious	Serious	Not suspected	⊕⊕⊕◯
ART type	Not serious	Not serious	Serious	Serious	Not suspected	⊕⊕◯◯
Cocaine	Not serious	Not serious	Serious	Serious	Suspected	⊕◯◯◯
TB	Not serious	Not serious	Serious	Serious	Suspected	⊕◯◯◯
Heroine	Not serious	Not serious	Serious	Serious	Suspected	⊕◯◯◯

supported by moderate-certainty evidence, suggesting a slight likelihood that further research might alter these findings. Its predictive utility may depend on how much the testing cost is impacted by the withdrawal of President's Emergency Plan for AIDS Relief (PEPFAR) funding to LMICs.

Diabetes

Stroke risk increased by 0–11.73 times in PLWH with diabetes compared to those without diabetes, supporting diabetes as a traditional CVD risk factor in PLWH [98, 99]. PLWH with diabetes have higher cardiovascular risk and are more prone to cerebrovascular complications or chronic kidney disease compared to non-diabetic counterparts [100]. Long-term antiretroviral therapy (ART) exposure can alter metabolic processes, favoring insulin resistance and type 2 diabetes mellitus among PLWH [101]. Lower nadir CD4 and longer time to ART initiation contribute to metabolic alteration among PLWH [102]. Diabetes leads to stroke through mechanisms including vascular endothelial dysfunction, arterial stiffness, systemic inflammation, and thickening of the capillary basal membrane [103]. Type 2 diabetes, with prolonged hyperglycemia and insulin resistance, contributes to advanced glycation end products, reactive oxygen species overproduction, and protein kinase C activation, leading to chronic vascular inflammation and atherosclerotic CVD [104]. While the evidence linking diabetes to stroke is low, suggesting further research could alter findings, diabetes will likely remain a stroke risk factor in PLWH, and its causality index may strengthen with additional research.

HCV and HBV

The presence of HCV increased stroke risk by 0.37–1.22 folds in PLWH. This finding aligns with previous theories that CVD in this population has a polygenic etiology, with risk factors including smoking and chronic coinfections like HCV and HBV [105]. Studies have documented elevated CVD risk in PLWH with HCV [106, 107]. While the direct link between chronic HCV infection and cardiovascular risk remains to be definitively established, research suggests higher cardiovascular risk is an extrahepatic manifestation of HCV infection [108].

The elevated cardiovascular risk in HCV infection has a multifactorial pathogenesis. Chronic HCV infection causes immune activation and inflammation, shown by higher levels of proinflammatory cytokines like interleukin 6, tumor necrosis factor-α, C-reactive protein, and fibrinogen, associated with atherosclerotic CVD [109]. HCV-infected patients have a higher risk of type 2 diabetes [107, 110], which is linked to accelerated atherogenesis and increased cardio-cerebrovascular risk [108]. However, the certainty of evidence for the association between HCV and stroke in PLWH is low, suggesting further research could significantly alter current evidence.

The presence of HBV increased stroke risk by 0.37–1.22 times in PLWH. Studies support that a higher prevalence of chronic coinfections like HBV can contribute to increased CVD risk in PLWH [105, 111]. The mechanisms linking HBV to stroke are not fully understood but may involve liver dysfunction, creating an anticoagulant state predisposing to bleeding [112]. However, some studies challenge this association [113, 114], indicating lower stroke risk in HBV-infected patients compared to uninfected controls. HBV infection can cause liver fibrosis and cirrhosis, which are inversely associated with atherosclerosis risk due to impaired coagulation and lower levels of atherogenic factors like triglycerides and cholesterol [113, 115, 116]. Patients with HBV may have increased levels of cytokines, like hepatocyte growth factor, that could protect vascular endothelium and contribute to anti-atherosclerotic effects [113, 117, 118]. This inconsistency in findings could be due to differences in study designs and populations. The certainty of evidence supporting the HBV-stroke link in PLWH is low, indicating further research could significantly change current understanding.

Age and Hypertension

Age and hypertension are established risk factors for CVD in PLWH and are commonly included in predictive models [94]. Our findings showed that advanced age increases stroke risk in PLWH by 1.01 to 114.48 times. This aligns with research by Ly et al. [119], which found that stroke risk rises with age. Yousufuddin et al. [120] identified aging as the primary non-modifiable risk factor for stroke, with risk doubling every 10 years after age 55. While stroke mortality rates in the general population should remain stable over the next decade, they will likely increase among those aged 65 and older [121]. The link between age and CVDs exists because aging often brings comorbidities that elevate CVD risk [122, 123].

Hypertension increased stroke risk by 1.33–12.38 times in PLWH, confirming its role as a stroke risk factor, as shown in previous research [124]. The Global Burden of Disease Study by the WHO identified hypertension as the most critical global risk factor for morbidity and mortality since 2003 [125]. There is a well-documented relationship between hypertension prevalence and fatal stroke [125]. Prolonged hypertension can lead to left ventricular hypertrophy, causing heart failure (both systolic and diastolic) [126]. Eccentric hypertrophy increases myocardial oxygen demand, potentially resulting in angina or ischemic symptoms [126]. Muscle hypertrophy can disrupt conduction pathways, increasing the risk of atrial fibrillation, which can lead to ischemic stroke [126]. The evidence confirms that age and hypertension are significant risk factors for stroke in PLWH, with high-certainty evidence suggesting further research is unlikely to change these findings. Regarding hypertension and ART interaction, cumulative exposure to most ART drugs is not associated with increased hypertension risk [127]. Increased risk of hypertension is mainly linked to traditional CVD risk factors [127].

CD4 Count

The finding that lower CD4 count increases stroke risk in PLWH by 0.62–11.47 times compared to those with higher CD4 counts aligns with research by Crane et al. [128], which found higher stroke risk among PLWH with CD4 counts of 200–500 cells/mm^3 compared to those above 500 cells/mm^3. These results suggest that delaying antiretroviral therapy (ART) initiation until later disease stages may lead to negative cardiovascular outcomes [129], as earlier ART initiation improves CD4 + T-cell recovery [130]. This aligns with our findings that early ART initiation reduces stroke risk in PLWH. A recent cohort study in sub-Saharan Africa by Kroeze and colleagues reported that after 6 years of ART, many patients showed suboptimal CD4 + T-cell recovery, with over a quarter not reaching 350 cells/mm^3 and more than half failing to exceed 500 cells/mm^3 [131]. This was linked to sex, age, lower pre-ART CD4 count, and BMI. CD8 + T-cell activation despite ART treatment may be driven by persistent anti-HIV response and stimulation from poorly controlled co-pathogens like cytomegalovirus [132, 133]. The link between low CD4 + T-cell counts and CVD may relate to chronic inflammation [134] or direct viral effects [128]. Inflammatory markers have been associated with subclinical atherosclerosis, mortality, and CVD in HIV-infected individuals [128]. CD4 count remains an important predictor of CVD in PLWH. Our findings are supported by high-certainty evidence, suggesting further research is unlikely to alter these conclusions.

Dyslipidemia

Our findings reported an increase in risk of stroke in PLWH by 0.54–5.01 folds in those with dyslipidemia.

Moawad and colleagues reported similar findings in a recent review, highlighting dyslipidemia as a risk factor for stroke in PLWH [29]. Several studies also reported that dyslipidemia increases the risk of cardiovascular diseases in PLWH [135]. Dyslipidemia, characterized by elevated low-density lipoprotein cholesterol (LDL-C) and triglycerides, increases stroke risk primarily through atherosclerosis, endothelial dysfunction, and systemic inflammation [136]. LDL-C promotes plaque formation, and its rupture can cause thrombus formation, leading to ischemic stroke [137]. Additionally, triglycerides contribute to endothelial dysfunction, exacerbating vascular resistance and ischemic events [138]. The studies reviewed presented conflicting perspectives on the importance of dyslipidemia as a stroke risk factor in PLWH. However, the level of evidence supporting our findings of dyslipidemia as a risk factor for stroke is low, suggesting that further research could alter our findings.

Obesity

The risk of stroke among people living with HIV (PLWH) who were obese increased 0.77–3.16 times compared to those without obesity. In this study, obesity was determined using body mass index (BMI), with underweight classified as BMI <18, normal as $\geq 18 \leq 26$, overweight as $>26 \geq 30$, and obese as ≥ 30. A Brazilian study showed obesity as the main nutritional issue among PLWH, linked to increased CVD-related mortality and morbidity [128]. Similarly, Gelpi et al. identified obesity as a CVD risk factor [139]. Studies have shown that obesity raises CVD risk [140], with some linking obesity and CVD to chronic low-grade inflammation [141] and insulin resistance [142]. Obesity is characterized by excess adipose tissue, which releases bioactive substances affecting body weight regulation, promoting insulin resistance—a key factor in type 2 diabetes—and causing changes in lipid levels, blood pressure, clotting, fibrinolysis, and inflammation. These changes contribute to endothelial dysfunction and atherosclerosis [143]. Due to established biological connections between obesity and CVD, future research may provide new insights about obesity's role in stroke risk in PLWH.

Use of alcohol

From our findings, the risk of stroke in PLWH increased by 0.25–2.83 folds among those who consumed alcohol compared with those who did not. This finding aligns with previous systematic reviews [144], which reported increased stroke risk in PLWH who consume alcohol. Chichetto [145] defined alcohol consumption levels as: moderate drinking (up to 1 drink daily for women, 2 for men [146]), heavy drinking (exceeding 7 drinks weekly for women, 14 for men [146, 147], and hazardous drinking (14^{+} drinks weekly for women, 21 + for men), posing greater health risks [148]. The CDC [146] defines binge drinking as 4+ drinks for women and 5+ for men in 2 h. Freiberg and colleagues found that hazardous drinking, alcohol abuse, and dependence were linked to higher CVD prevalence compared to infrequent or moderate drinking among veterans [147, 149]. Alcohol may exacerbate CVD through HIV-related factors [145]. HIV infection triggers systemic inflammation and immune activation, which elevate CVD risk [145]. Although ART reduces inflammation by suppressing HIV RNA viral load, alcohol consumption reduces ART adherence, leading to increased viral load and decreased CD4 + T-cell count, raising CVD risk [145]. Recognizing alcohol's impact is crucial for managing CVD in PLWH and makes it valuable for predictive models. The low certainty of evidence linking alcohol use and stroke in PLWH suggests further research will likely alter current evidence.

CKD

Our findings showed a 1.04 to 8.80-fold increase in stroke risk among PLWH with CKD compared to those without it. Previous studies, such as Alonso et al. [150], identified CKD as a stroke risk factor in PLWH. Di et al. [151] reported a heightened risk of CVD in individuals with CKD. Cardiovascular event rates are higher in patients with early-stage CKD (stages 1–3) compared to the general population, while those with advanced CKD (stages 4–5) have an even greater risk [152]. The link between CKD and CVD is driven by traditional cardiovascular risk factors (including advanced age, hypertension, diabetes, dyslipidemia) and CKD-specific factors (including anemia, volume overload, mineral metabolism issues, proteinuria, malnutrition, oxidative stress, inflammation), particularly in early CKD stages [153, 154]. CKD can trigger the release of hormones, enzymes, and cytokines that cause vascular changes [152]. Early screening and treatment are recommended to prevent CKD from progressing into CVD [152].

Atrial Fibrillation

Our findings indicate that individuals with atrial fibrillation (AF) among PLWH have a 3.82 to 10.48 times higher stroke risk compared to those without AF. These results align with Odutayo et al. [155], who showed in a systematic review that AF increases stroke risk in PLWH. Prior studies have also identified AF as a stroke risk factor in this population [101, 150]. AF is associated with increased blood clot formation due to disturbances in

hemostatic processes [156, 157]. This elevated stroke risk primarily results from clot formation in the heart's left atrium. The irregular atrial beating allows blood to pool in the left atrial appendage, promoting clots [156]. If a clot dislodges, it can travel through the bloodstream and block brain arteries, causing an ischemic stroke [156]. Impaired atrial contraction disrupts blood flow, further increasing the risk of clot formation [157]. Global AF prevalence was estimated at 20 million in 2020 [158], and this number is expected to rise, particularly in older populations. Given this, AF remains a significant predictor of CVD in PLWH. However, evidence linking AF to stroke risk in PLWH remains limited, and further research may alter existing conclusions.

ART use and ART duration

Our findings suggest that stroke risk in PLWH using ART was reduced by 0.30 to 4.16 times compared to those not on ART. Similarly, longer ART use was associated with a 0.11 to 4.63 times lower stroke risk in PLWH. However, Benjamin and Khoo [159] contradict this, reporting that ART might increase stroke risk in PLWH. Some earlier studies included ART use as a traditional stroke risk factor in this population [160]. These conflicting results may stem from factors like adherence, specific ART drugs, stage of treatment, timing of initiation, and duration. Early ART initiation has been shown to lower overall stroke risk [161], though risk is highest during the first six months due to immunosuppression [52]. Continuous ART leads to increased CD4 cell count, which helps reduce stroke risk. While our study found no adverse effects of ART, previous research has linked it to side effects that may increase stroke risk [160, 162]. Although ART suppresses viral replication and reduces inflammation, certain ART drugs have been associated with metabolic complications like diabetes [163], hypercholesterolemia, elevated LDL-c, and hypertension, which increase cardiovascular disease risk [124], especially with prolonged use.

Our findings demonstrated reduced stroke risk with prolonged ART use among people living with HIV (PLWH), aligning with Abdallah et al. [159] who reported extended ART duration. However, some studies showed increased CVD risk with longer ART duration [124, 162–165], possibly due to metabolic complications like hypertension and diabetes [162]. Kamtchum-Tatuene et al. [165] categorized ART duration as no ART, recent ART (< 6 months), and long-term ART (≥ 6 months). The higher stroke risk was common before ART initiation and during the first 6 months, due to immunosuppression. With prolonged treatment, CD4 cell count increased, lowering stroke risk [165]. In this review, no metabolic complications related to ART contributed to increased stroke risk.

ART type

Our study identified ART type as a stroke risk factor in PLWH, with an increased stroke risk ranging from 0.09 to 6.96-fold. Ismael et al. [101] similarly recognized ART type as a stroke risk factor in PLWH, although our study reported mixed results regarding this association. Previous studies have shown that certain ART drug classes can increase stroke risk by causing endothelial toxicity and vascular dysfunction in individuals with HIV [101, 166]. Prolonged use of protease inhibitors (PIs), such as darunavir, has been linked to stroke risk [167], while atazanavir has been associated with vascular remodeling [168]. Additionally, the nucleoside reverse transcriptase inhibitor (NRTI) abacavir has been reported to raise the incidence of cardiovascular events and stroke [169]. Although ART has effectively reduced HIV virulence and extended life expectancy in HIV-positive individuals, long-term use poses endothelial and metabolic challenges that may elevate stroke risk [101]. The certainty of evidence linking ART type with stroke risk in PLWH is moderate, suggesting that further research could slightly alter the current understanding.

Cocaine and Heroine

Our findings show stroke risk in PLWH increased 1.56 to 10.85 times among cocaine users and 0.67 to 17.46 times among heroin users. Both substances fall under substance use. In a study by Feinstein et al. [170], substance use was identified as a traditional risk factor for stroke in PLWH. Similarly, studies [171, 172] have reported higher prevalence and increased CVD risk among substance users. The exact mechanisms by which substances affect cardiovascular health remain unclear [172]. Cocaine and heroin function as stimulants, reducing catecholamine reuptake, leading to sympathetic overdrive, increased myocardial oxygen demand, vasospasm, and abnormal platelet aggregation. This causes acute arterial hypertension, thrombosis, and accelerated atherosclerosis [172, 173]. The simultaneous abuse of cocaine and heroin raises their blood levels, prolonging cardiovascular risks [173]. While our findings showed no significant link between cocaine and heroin use and stroke risk in PLWH, their mechanisms suggest they remain potential risk factors. The certainty of evidence for this connection remains low, indicating further research could substantially change current understandings.

TB

PLWH co-infected with TB showed a 1.56 to 10.85-fold increase in stroke risk compared to those without TB.

Our results align with earlier studies [174, 175], which reported elevated stroke risk in PLWH with TB, identifying TB as a risk factor for stroke [176]. TB is the ninth leading cause of death globally [177, 178], and has been associated with chronic inflammation and immune activation, contributing to atherosclerosis and CVD through inflammation, triggering host immune responses similar to those in atherogenesis [179]. Mechanisms linking TB to CVD include direct effects on the myocardium and coronary arteries (TB arteritis), increased pro-inflammatory cytokines, and autoimmunity involving antibodies against mycobacterial heat shock protein (HSP65) [177]. Through these pathways, TB survivors have a higher incidence of stroke and cardiovascular diseases [180]. HIV weakens the immune system by targeting white blood cells, making individuals more susceptible to TB, thus increasing stroke risk [181]. While TB is recognized as a stroke risk factor in PLWH, current evidence has low certainty, suggesting further research could alter these findings.

Sex and ethnicity

Sex and ethnicity are known risk factors for CVD in PLWH and are included in predictive models [96]. Our study found that stroke risk in PLWH increased 0.40 to 2.42 times in women and 0.05 to 1.76 times in Black individuals. Consistent with our findings, Kovacs et al. [182] identified sex as a stroke risk factor in PLWH, with women showing higher risk compared to men. Studies have demonstrated that biological sex affects stroke care, including risk factors, incidence, and outcomes [183]. In a study on sex differences in stroke risks, Hanna et al. [184] reported that women's longer life expectancy contributes to higher lifetime stroke incidence. Additionally, sex-specific stroke risk factors include pregnancy, hormonal treatments [184], menopause, contraceptive use, parity, and breastfeeding [185], which increase stroke risk. Moreover, women, as they age, have higher rates of diabetes, hypertension, and atrial fibrillation than men [186].

Alonso et al. [150] recognized race as a stroke risk factor in PLWH. Consistent with our findings, Chow et al. [186] reported higher stroke risk in Black individuals compared to other racial groups. This disparity stems from higher prevalence and poorer management of traditional vascular risk factors among Blacks [64, 187]. Additionally, Blacks have worse cerebrovascular endothelial function compared to other racial groups, even when accounting for traditional vascular risk factors [64]. This contributes to higher stroke prevalence in Black PLWH. The certainty of evidence linking sex and race/ethnicity with stroke risk in PLWH is moderate, indicating further research could refine our understanding.

Limitations

This review faced two major constraints: a limited number of studies that met the inclusion criteria and the absence of a quantitative analysis. Both factors could have enhanced the precision of the findings. Nevertheless, steps were taken to ensure that the narrative synthesis provided the closest possible approximation to a meta-analysis.

Conclusions

For PLWH, several potential risk factors for stroke have been identified. These include advancing age, tobacco use, high blood pressure, diabetes, atrial fibrillation, tuberculosis, viral load, HCV, CKD, CAD, and liver fibrosis or cirrhosis. Of these, the most important factors were hypertension and chronic kidney disease, followed by smoking, dyslipidemia, diabetes, HCV, HBV, CD4 count, use of ART, TB, and substance use (cocaine). The least important factors were age, sex, ethnicity, obesity, alcohol use, ART duration, and viral load. However, it's important to note that the predictive significance of these factors is still evolving, given the average moderate certainty of evidence.

Implications for clinical practice, policy, and research

The outcome of this study provides a list of the predictors of HIV-related stroke in a clinically relevant order, thus providing clinicians and public health professionals with a tool to tackle the rise in incidence of stroke among PLWH. In the face of limited funding for HIV care, it is important to prioritize the most clinically relevant and critical risk factors. Our study supports the call [188] for regular cardiovascular assessment among PLWH. Hence, there is any for a policy to promote such practice in both developed and developing nations. Population-wide strategies targeting critical risk factors are essential. The critical risk factors are those whose summative risk attribution equals the critical threshold, usually, at least a score of 7 out of the 9 maximum causality index score. The mitigation of such risk factors will result in a marked reduction in the population burden of a given NCD. Neurorehabilitation among PLWH should include assessment and redress of these factors using a preventative and/or curative approach. To tame the rising burden of stroke and similar CVD among PLWH, public health interventions must be such that prioritize critical risk factors. Their composition may differ from setting to setting; hence, a pre-intervention assessment to determine the component of the critical risk factors (macro-assessment) in each setting/culture should be best practice. Importantly, health promotion and preventative interventions should adopt

biobehavioral strategies that address both sociocultural and biological determinants of the critical risk factors for stroke and other cardiovascular diseases. The assessment of the bio-behavioural promoters of the critical risk factors (micro assessment) should be conducted prior to instituting public health interventions for a CVD, including stroke. Hence, further research is required to determine biobehavioral correlates of the key global risk factors of stroke, such as hypertension, chronic kidney disease, smoking, dyslipidemia, diabetes, and HCV, among others. There is a need for a prospective cohort study to validate the principles employed in this study.

Abbreviations

OR	Odds ratio
CI	Confidence intervals
Rw	Risk weights
Ri	Risk responsiveness
PLWH	People living with HIV
HIV	Human immunodeficiency virus
CMID	Clinical minimum important difference
CVD	Cardiovascular disease
CAD	Coronary artery disease
CKD	Chronic kidney disease
HCV	Hepatitis C
HBV	Hepatitis B
CI	Causality index
ART	Antiretroviral disease

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

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Authors' contributions
Martins Nweke (MN) and Nombeko Mshunqane (NM) conceived and designed the study. MN and a trained research assistant conducted the search and data screening. Data were extracted by a trained research assistant and verified by MN. MN carried out data curation and analysis. MN and NM contributed to the drafting of the review manuscript. Both authors approved the final manuscript for submission to the journal.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
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Competing interests
The authors declare no competing interests.

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