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PAMJ One Health

Review

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Received: 09 Nov 2023 - **Accepted:** 31 Mar 2024 - **Published:** 02 May 2024

Keywords: Africa, manufactured alcoholic beverage, traditional alcoholic beverage, esophageal cancer

Cite this article: Eugene Jamot Ndebia et al. The link between alcohol consumption pattern and esophageal cancer risk in Africa: protocol for systematic review and meta-analysis. PAMJ - One Health. 2024;14(1). 10.11604/pamj-oh.2024.14.1.42149

Available online at: https://www.one-health.panafrican-med-journal.com/content/article/14/1/full

The link between alcohol consumption pattern and esophageal cancer risk in Africa: protocol for systematic review and meta-analysis

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Abstract

Esophageal cancer presents a pressing public health concern in Africa, particularly in Eastern and Southern regions, where it stands as a leading cause of mortality. Various factors, including alcohol consumption, have been implicated in the high incidence of this disease. However, the absence of a consensus regarding its precise etiology has hindered the implementation of effective preventive measures. As such, this study aims to present a detailed protocol for assessing the strength of the association between alcohol consumption patterns and esophageal cancer risk in the African context. To achieve this, we will meticulously identify relevant observational studies via a predefined search strategy applied to electronic databases like Medline/PubMed, Excerpta Medica Database (Embase), Web of Science, Scopus, Cochrane Library, and African Journals Online. Additionally, a manual search will be conducted. Quality assessment will be performed utilizing established standards tools. Assessment for potential publication bias will involve the use of funnel plots and Egger's statistical test. To estimate summary effects, we will conduct meta-analyses, utilizing random-effects models with the Review Manager software. Heterogeneity among studies will be assessed via the I2 statistical test. Reporting of our findings will be by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Our systematic review, based on existing published data, will provide vital insights to inform policymakers, practitioners, and researchers regarding the role of alcohol consumption in the etiology of esophageal cancer among African populations. The outcome of this research will serve as a roadmap for developing targeted interventions in this population, potentially reducing the burden of this devastating disease. The final systematic review report, in the form of a scientific article, will undergo peer review and be made available to National Health Service clinicians, and healthcare professionals, and presented at scientific conferences.

Introduction

The incidence of esophageal cancer has witnessed a significant upsurge in Africa over recent decades. Particularly in South and East Africa, the disease has reached epidemic proportions, presenting a formidable public health challenge [1,2]. Esophageal cancer is a disease in which malignant (cancer) cells form in the tissues of the esophagus [3]. It is caused by many factors including habits (tobacco use, alcohol consumption, opium consumption, maté drinking, hot drinks, consumption of carbonated soft drinks, eating pickled vegetables), nutritional deficiencies (low intake of fresh fruit and vegetables, vitamin, and mineral deficiencies), medications (non-steroidal anti-inflammatory drugs, medications that relax lower esophageal sphincter, H2 receptor antagonists), infections (Helicobacter pylori, Human papillomavirus), chemical carcinogens (polycyclic aromatic hydrocarbons, nitrosamines, acetaldehyde), physiologic predisposing conditions (gastroesophageal acid reflux, hiatal hernia, achalasia, gastric atrophy, poor oral health), occupational exposure (to silica and asbestos), and low socioeconomic status [4].

The disease manifests through a spectrum of distressing symptoms, including dysphagia, unintentional weight loss, heartburn, esophageal erosion, ulceration, stricture, and even the development of Barrett's esophagus [5]. In severe cases, it can lead to life-threatening complications such as esophageal hemorrhage, perforation, and respiratory damage [6]. It is usually treated with surgery, radiotherapy, chemotherapy, or a combination of these [7]. The global burden of esophageal cancer is pronounced, with roughly 60,400 new cases and 54, 4076 deaths occurring annually, as per the latest GLOBOCAN estimates [8]. Notably, Africa alone accounts for nearly 49% of these worldwide cases [9]. This disease persists as a formidable challenge for health authorities in developing nations, notably in sub-Saharan Africa.

Within the spectrum of potential causes of esophageal cancer worldwide, the consumption of alcoholic beverages occupies a prominent and contentious position. The adverse health effects associated with regular alcohol consumption are diverse in Africa, including the heightened risk of esophageal cancer. However, the proliferation of disparate findings within independent studies conducted across Africa, often within the same country, has rendered it difficult to establish a definitive link between patterns of alcoholic beverage consumption and the risk of esophageal cancer. Some studies, exemplified by Segal *et al*. [10], Middleton *et al*. [11], and Musukume *et al*. [12], point to elevated risks among those who consume alcohol, while others, including studies by Leon *et al*. [13] and Deybasso *et al*. [14], suggest lower risks when comparing alcoholics to non-alcoholics individuals. Despite the existence of a few global meta-analyses exploring the association between alcohol consumption and esophageal cancer [15], none have comprehensively examined this relationship within the unique African context.

Moreover, the rich diversity of African cultures has given rise to a multitude of traditional alcoholic beverages, the precise composition of which often remains unknown. This diversity further complicates efforts to discern the link between alcohol consumption patterns and esophageal cancer. Therefore, our study will carry out a thorough qualitative and quantitative analysis of literature relevant to the association between alcohol consumption patterns and esophageal cancer to shed light on the rising incidence of this disease in Africa. This systematic review, seeks to answer a pivotal question: what is the magnitude of the association between alcohol consumption patterns and the risk of esophageal cancer in the African population? This research endeavor aims to provide insights that can guide public health initiatives and interventions tailored to this high-risk population.

Methods

Protocol registration: this protocol was written by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol (PRISMA-P) [16] and MOOSE guidelines for meta-analyses and systematic reviews of observational studies [17]. The review protocol was registered in the Prospective International Register of Systematic Reviews (PROSPERO) as CRD42023463704. This study has followed the PRISMA guidelines.

Eligibility criteria: the following eligibility criteria will be used to identify studies. Inclusion criteria: (1) observational studies (cohort study, case-control study, cross-sectional study) with alcoholic beverage consumption as exposure and esophageal cancer (OC) risk as the main outcome; (2) all studies must contain available data on the relationship between alcohol consumption and esophageal cancer; (3) studies must have been conducted on the African continent (East and Southern African region) and involve adult human participants (age ≥18) (African only); (4) no restrictions on sample size will be considered. Studies will be excluded according to the following criteria: (1) unpublished articles, non-human research, anonymous reports, editorials, letters, commentaries, and reviews will be excluded; (2) studies that do not provide estimates of effect in the form of odds ratios, rate ratios, risk ratios, or relative risks, or that do not allow these values to be calculated, will also be excluded; (3) studies whose data are inaccessible, even after request to their authors, will also be excluded; (4) studies with a low score (0-3 points) will be excluded. Patient, intervention, comparison, outcomes (PICOS) criteria for eligible studies are given in Table 1.

Data sources and search strategy: electronic database searches and manual searches of other resources will be conducted by a professional librarian under the supervision of the authors (GTK and EJN) to identify published studies for

review. Studies published in the Medline/PubMed, Excerpta Medica Database (Embase), Web of Science, Scopus, Cochrane Library, and African Journals Online databases will be searched. These searches will include a mix of free text and index terms to maximize the retrieval of potentially relevant articles (Table 2). Searches will then be adjusted according to the requirements of each specific database (i.e. the use of operators and symbols). The keyword combinations to be used are as follows: “alcohol” OR “alcoholic beverage” OR “alcohol drinking” OR “alcohol consumption” OR “alcohol intake” OR “drink beer” OR “drink wine” OR “drink spirit” OR “local produced alcohol drinking” OR “traditional beer” OR “drink kachasu” OR “drink busaa” OR “drink chang´aa” OR “drink gongo” OR “risk factor” OR “risks factors” AND “esophageal neoplasm” OR “esophagus neoplasm” OR “cancer of esophagus” OR “esophagus cancer” OR “esophageal cancer” OR “esophageal squamous cell carcinoma” OR “esophageal adenocarcinoma” OR “ESCC”. Manual cross-searches will then be carried out in Google Scholar and the list of references of studies meeting the eligibility criteria. No historical time constraint (date of publication), and even less the language of publication, will be considered during the searches, to sufficiently reduce the risk of selection and detection bias [18].

Data management and selection process: the search results will first be exported to Endnote, where duplicates will be removed, and then transferred to the Rayyan software to better organize the selection and review process [19]. The authors will independently conduct a preliminary review of the studies that have been identified based on titles and abstracts, by the eligibility criteria. Then, a second independent selection will be carried out by examining the full text of the articles retained at the end of the first review and those whose eligibility is not clear will be identified. Finally, a consultation meeting will be organized by the authors to compare the results of the selections, to rule on the studies of doubtful eligibility, and possibly to find a consensus on the discordant studies. If necessary, a neutral evaluator will be consulted. This procedure makes it possible to minimize bias when deciding to include or exclude studies [18]. A PRISMA flow diagram (Figure 1) will be employed to visually elucidate the study selection process.

Data extraction: for each study that meets our eligibility criteria, we will systematically collect a comprehensive set of data to ensure a thorough analysis. The information to be gathered will encompass the study's title, country of origin, first author, publication date, the number of cases and controls, methods employed for participant recruitment, data collection duration, data collection methods, and characteristics of the study population. Specifically, outcomes related to alcohol consumption will be a central focus, including:

Alcohol status: we will categorize participants into three groups based on their alcohol consumption: never-drinkers, current drinkers, and former drinkers.

Type of alcoholic beverages consumed: this will encompass a detailed breakdown of the types of alcoholic beverages consumed, including beer, whisky, wine, and traditional drinks.

Quantity of beverages consumed: we will collect information regarding the quantity of alcoholic beverages consumed per day or week.

Alcohol content: data on the alcohol content of the beverages will be recorded.

Measures of association: this includes the relative risk and its associated 95% confidence interval (CI), or the odds ratio (OR) and its 95% CI. We will compute these measures with the appropriate statistical software for studies that do not provide them directly. To ensure robust analysis, we will classify study participants into two primary groups: those who consume alcoholic beverages and those who do not. Furthermore, studies that present results based on the type of beverage

consumed or the quantity of consumption will be initially grouped to calculate the overall strength of association. Subsequently, sub-groups will be created to analyze these parameters separately. In the cases where studies have been conducted across multiple countries, we will separate the data by country and identify them by appending the author's name with the initials of the respective country. The data extraction process will be carried out independently by the research team, utilizing a structured coding form. This form has been developed, pre-tested on relevant articles, and refined as necessary to ensure its accuracy and comprehensiveness. Subsequently, a collaborative meeting among the research team members will be organized to standardize the coding of variables according to the form. This rigorous approach will promote high levels of coding reliability across all data evaluators, ensuring the quality and consistency of our analysis.

Quality and risk of bias assessment: the assessment of study quality is a critical component of our research methodology. To ensure an objective evaluation, each study will be independently appraised by the authors. We will employ two well-established tools tailored to the study design: the Newcastle-Ottawa Scale (NOS) for case-control and cohort studies [20], and the Agency for Healthcare Research and Quality (ARHQ) tool for cross-sectional studies [21]. Only studies classified as moderate and good quality (studies scoring 4 to 9 points), as determined by these assessment tools, will be included in the subsequent meta-analysis. This stringent criterion ensures that our analysis is based on sound and reliable data. Furthermore, potential risks of publication bias will be systematically examined. To assess the risk of bias in prevalence studies, we will use the tools developed by Hoy *et al*. [22], and for non-randomized studies, the tool by Kim *et al*. [23] will be applied. These tools will help us gauge the risk of bias in the included studies, providing valuable insights into the credibility of the data. To enhance the robustness of our evaluation process, we will test the assessment checklist on relevant articles, refining it as necessary. This iterative process will guarantee consistency and objectivity when reviewers assess the studies. To comprehensively evaluate potential publication bias, we will employ a funnel chart, a widely accepted method in systematic reviews and meta-analyses. This visual tool allows for a more intuitive assessment of bias across the included studies. Following the individual assessments, a debriefing meeting will be convened among the authors to compare results and address any potential disparities or uncertainties. This collaborative approach ensures a unified and rigorous evaluation process, enhancing the reliability and validity of our research findings.

Grading the quality of evidence: we will use the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) system to evaluate the evidence of quality [24]. The quality of evidence will be assessed using five criteria for down-grading confidence in effect estimates (risk of bias, inconsistency, imprecision, indirectness, and publication bias), as well as three criteria for upgrading confidence (large effect, dose-response gradient, and opposing confounding) [25]. The various bodies of evidence will be dealt with according to the scale described by Cuello-Garcia *et al*. [26].

Statistical analysis and data synthesis: the data synthesis and analysis process will be carried out systematically, beginning with a global overview of the studies and subsequently categorizing them to gain deeper insights. Our data presentation will include global summaries, followed by subgroup analyses based on the type of alcoholic drink (beer, whisky, red wine, traditional beer), frequency of consumption (occasional, weekly, daily), quantities of drinks consumed, and alcohol content within the beverages. People whose interval between drinks is ≥ 1 month are occasional drinkers. A weekly drinker is anyone who drinks every weekend, and a daily drinker is anyone who cannot abstain from drinking every

day. In instances where a sufficient number of studies or data are available, we will conduct both meta-analysis and meta-regression analyses for similar covariates found in the identified studies, as advocated by Kufe *et al*. [19]. The characteristics of the included studies will be effectively summarized through the creation of a comprehensive summary table and visual representation in the form of a forest diagram. The statistical analyses will be executed using the Review Manager (RevMan) software for Windows. To gauge the relative heterogeneity among the included studies, we will calculate the I2 statistic, as defined by Higgins *et al*. [27].

An I^2 value of 25% will denote low heterogeneity, while 50% will signify medium heterogeneity, and values ranging from 75% to 100% will denote high heterogeneity. To identify potential outliers and assess their influence on the overall estimates, we will utilize a "one study removed" approach. Outliers will be identified as studies falling outside the 95% confidence interval for the mean effect size. Additionally, subgroup analyses and meta-regressions will be conducted, exploring various categories such as study type, age, alcohol status, type of beverage consumed, frequency of beverage consumption, quantity of beverage consumed (per day and week), and alcohol content. To evaluate publication bias, the funnel plot will be employed, and the strength and stability of associations will be assessed using Egger's regression test [28,29]. Publication bias will be recognized when the p-value is less than 0.10. If publication bias is proven, the Trim-and-Fill method suggested by Duval and Tweedie will be implemented [30]. In the event of low variability between studies, a meta-analysis will be performed to calculate a pooled estimate. Conversely, if the data cannot be pooled due to significant heterogeneity, we will present the results of each study descriptively. The odds ratio will serve as the primary measure to express the relationship between alcohol consumption and esophageal cancer. To test the robustness of the results, we will employ the Taylor and Tweedie [31] adjustment and filling methods. In cases where a meta-analysis is not feasible, a narrative synthesis will be undertaken, adhering to the guidelines outlined by Popay *et al*. [32].

Current status of knowledge

The results of the selection process will be presented in the form of a complete PRISMA flow chart (Figure 1). The creation of a synoptic table will effectively summarise the characteristics of the included studies. The meta-analysis results will be meticulously documented and presented for publication by PRISMA guidelines [33]. This comprehensive approach will ensure the rigor, transparency, and reliability of our research findings. This comprehensive work will systematically synthesize the existing evidence regarding the relationship between alcoholic beverage consumption patterns and the risk of esophageal cancer in Africa. The implications of our findings extend to a broader understanding of how alcoholism contributes to the etiology of esophageal cancer, facilitating the development of robust policies to combat this increasingly prevalent disease in Africa. Importantly, our work aims to dispel the controversies that have emerged from independent studies published in various regions of Africa. This knowledge, once elucidated, has the potential to guide national governments and sub-regional organizations in the formulation of legislation governing the production and distribution of alcoholic beverages. Furthermore, it can provide valuable insights into determining safe and responsible levels of consumption that are the least detrimental to public health. Collectively, these measures hold the promise of reducing the incidence and impact of a disease that often culminates in tragic outcomes.

Strengths and limitations: this is the first meta-analysis to assess the effect of type of alcoholic beverage, frequency of consumption, and level of alcohol content on the risk of esophageal cancer in Africa. While this systematic review and meta-

analysis hold substantial promise, they are not without limitations. The review is exclusively reliant on data from peer-reviewed publications, inevitably excluding non-peer-reviewed sources. This selectivity, though intended to enhance data quality, exposes the analysis to the risk of "publication bias" [34]. Moreover, the studies to be included may exhibit heterogeneity not only in terms of the populations studied but also in their geographical distribution across the African continent. This heterogeneity may restrict comparability and complicate result interpretation.

Conclusion

As the global incidence of esophageal cancer continues to rise, with a particularly significant impact on Africa, we theorize a compelling association between patterns of alcoholic beverage consumption and susceptibility to esophageal cancer in this region. We aim to deliver precise and data-driven insights into the definitive role of alcoholism in the risk of esophageal cancer. Armed with this knowledge, we can construct effective policies and interventions aimed at curbing the proliferation of this devastating disease in Africa. By emphasizing evidence-based strategies, we strive to make a substantial contribution to the reduction of esophageal cancer's burden in this region.

What is known about this topic

- *Almost 50% of the world's esophageal cancer sufferers live in Africa, and more precisely in the East African corridor stretching from Ethiopia to South Africa; systematic reviews carried out in Europe and America have not shown an association between alcohol and this disease, but in Asia, alcohol consumption is closely linked with the risk of esophageal cancer;*
- *This suggests that the link between alcohol consumption and esophageal cancer risk varies from continent to continent;*
- *However, no meta-analysis of the association between alcoholic beverage consumption and the risk of esophageal cancer in Africa is available; only controversial independent studies on the subject are available.*

What this study adds

- *Ultimately, this work will provide precise information on the role of alcoholic beverage consumption in the etiology of esophageal cancer in Africa;*
- *But also, given that beverage types vary from region to region, the implication of beverage type (traditional, beer, whiskey, etc.), frequency of consumption, and alcohol content of beverages in the etiology of esophageal cancer in Africa.*

Competing interests

The authors declare no competing interests.

Funding

This research is co-funded by the SA Medical Research Council (MRC) Strategic Health Innovation partnerships and the National Research Foundation (NRF) Competitive Support for Unrated Researchers, both awarded by Prof Eugene Jamot Ndebia.

Authors' contributions

Eugene Jamot Ndebia, Gabriel Tchuente Kamsu participated in the design, production, validation, and editing of this work. They also read and approved the final version of the manuscript.

Acknowledgments

We would like to thank Walter Sisulu University for providing free internet and the librarian who helped us develop the search strategies used to search for studies in the databases.

Tables and figures

Table 1: patient, intervention, comparison, outcomes (PICOS) for study eligibility criteria

Table 2: preliminary search strategy in Medline/PubMed database

Figure 1: preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram of studies identified

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Table 1: patient, intervention, comparison, outcomes (PICOS) for study eligibility criteria		
	Inclusion	**Exclusion**
Participants	Esophageal cancer patients; adults only (aged ≥ 18 years); African.	Children and adolescents (aged < 18 years); animals; participants outside of Africa.
Interventions	Alcoholic beverages.	Non-alcoholic beverages.
Comparators	Healthy subjects with no family history of cancer.	Healthy subjects with a family history of cancer.
Outcomes	Alcoholic status (never drinker and current drinker); type of beverage consumed, (manufactured (beer, whisky, red wine) or traditional (busaa; chang'aa, gongo, kachasu; amgba; sha'a; tchapalo; natango; meloucre); frequency of beverage consumption; quantity of beverage consumed (per day and week); alcohol content (percentage of alcohol); drinking duration; age and sexes; study type.	Studies that did not report any of the outcomes.
Study designs	Cohort studies (prospective and retrospective); case-control studies; cross-sectional.	Review papers; comments; conference abstract; unpublish paper
PICOS: population, intervention, control, and outcomes		

Table 2: preliminary search strategy in Medline/PubMed database	
Search number	**Search detail**
#1	"alcohol"[Mesh] OR "alcoholic beverage"[tiab] OR "alcohol drinking"[tiab] OR "alcohol consumption"[tiab] OR "alcohol Intake"[tiab] OR "drink beer"[tiab] OR "drink wine"[tiab] OR "drink spirit"[tiab] OR "local produced alcohol drinking"[tiab] OR "traditional beer"[tiab] OR "drink kachasu"[tiab] OR "drink busaa"[tiab] OR "drink chang□aa"[tiab] OR "drink gongo"[tiab] OR "risk factor"[tiab] OR "risks factors"[tiab]
#2	"esophageal cancer"[MeSH] OR "esophageal carcinoma"[tiab] OR "oesophageal cancer"[tiab] OR "esophageal tumor"[tiab] OR "oesophageal tumor"[tiab] OR "esophagus cancer"[tiab] OR "oesophagus cancer"[tiab] OR "esophageal squamous-cell carcinoma"[tiab] OR "esophageal adenocarcinoma"[tiab] OR "ESCC"[tiab] OR "esophageal neoplasms"[MeSH]
#3	"Africa" [MeSH] OR "East Africa"[tiab] OR "West Africa"[tiab] OR "Southern Africa"[tiab] OR "North Africa"[tiab] OR "Algeria"[tiab] OR "Angola"[tiab] OR "Benin"[tiab] OR "Botswana"[tiab] OR "Burkina Faso"[tiab] OR "Burundi"[tiab] OR "Cameroon"[tiab] OR "Cabo Verde"[tiab] OR "Cape Verde"[tiab] OR "Central African Republic"[tiab] OR "Chad"[tiab] OR "Comoros"[tiab] OR "Congo"[tiab] OR "Cote d`Ivoire"[tiab] OR "Djibouti"[tiab] OR "Egypt"[tiab] OR "Democratic Republic of Congo"[tiab] OR "Equatorial Guinea"[tiab] OR "Eritrea"[tiab] OR "Eswatini"[tiab] OR "Swaziland"[tiab] OR "Ethiopia"[tiab] OR "Gabon"[tiab] OR "Gambia"[tiab] OR "Ghana"[tiab] OR "Guinea"[tiab] OR "Guinea Bissau"[tiab] OR "Kenya"[tiab] OR "Lesotho"[tiab] OR "Liberia"[tiab] OR "Libya"[tiab] OR "Madagascar"[tiab] OR "Malawi"[tiab] OR "Mali"[tiab] OR "Mauritania"[tiab] OR "Mauritius"[tiab] OR "Morocco"[tiab] OR "Mozambique"[tiab] OR "Namibia"[tiab] OR "Niger"[tiab] OR "Nigeria"[tiab] OR "Rwanda"[tiab] OR "Sao Tome and Principe"[tiab] OR "Senegal"[tiab] OR "Seychelle"[tiab] OR "Sierra Leone"[tiab] OR "Somali"[tiab] OR "South African"[tiab] OR "South Africa"[tiab] OR "South African"[tiab] OR "Sudan"[tiab] OR "North Sudan"[tiab] OR "South Sudan"[tiab] OR "Tanzania"[tiab] OR "Togo"[tiab] OR "Tunisia"[tiab] OR "Uganda"[tiab] OR "Zambia"[tiab] OR "Zimbabwe"[tiab]
#4	#1 AND #2
#5	#1 AND #2 AND #3

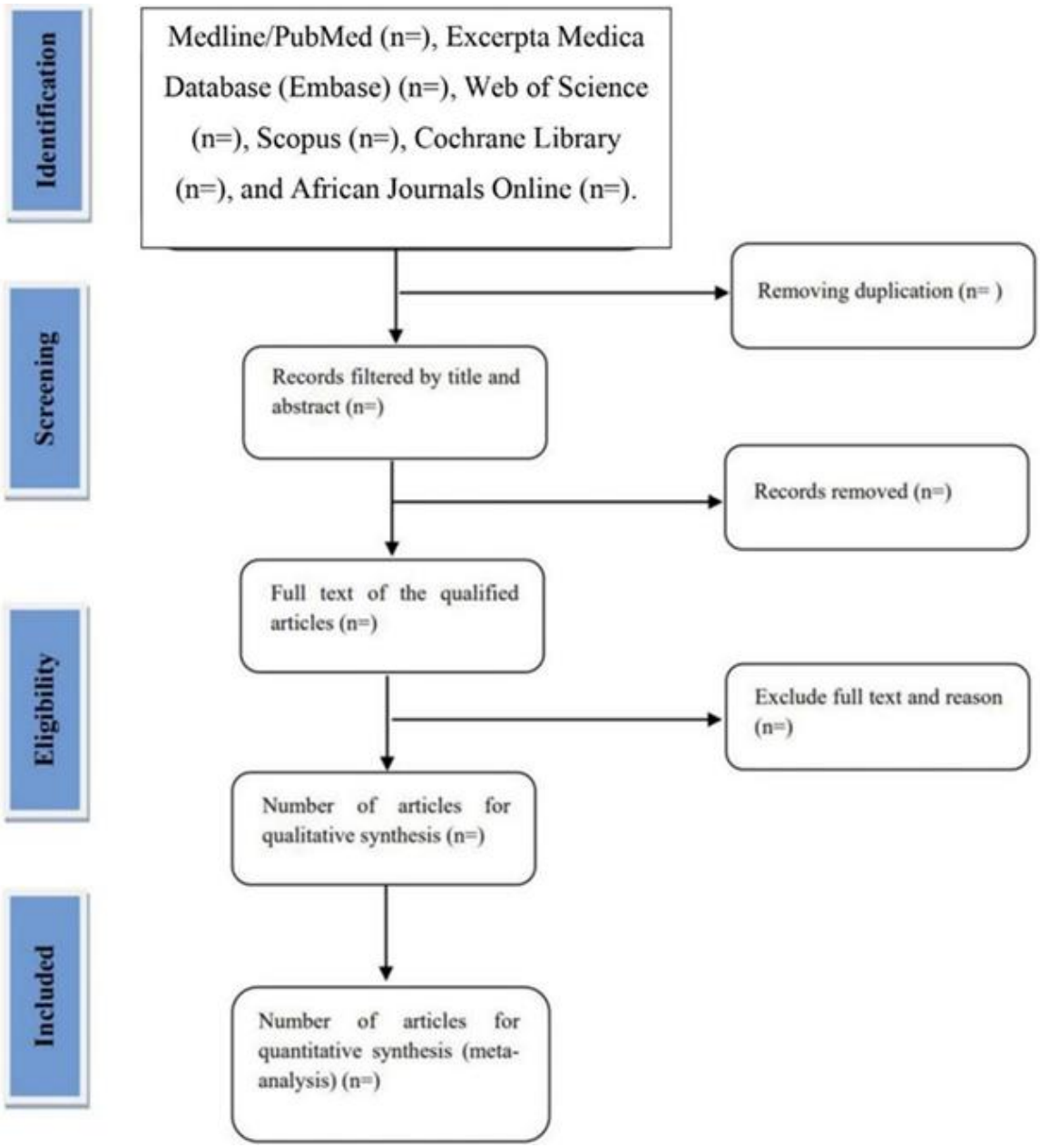

Figure 1: preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram of studies identified