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Epidemiology and patterns of cerebral venous thrombosis in low- and middle-income countries: a systematic review and meta-analysis protocol

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Complete List of Authors:	Danwang, Celestin; Faculty of Medecine and Biomedical Sciences, Surgery and specialities Mazou, Temgoua Ngou ; Faculty of Medecine and Biomedical Sciences, Internal medicine and specialities Tochie, Joel Noutakdie; Universite de Yaounde I Faculte de Medecine et des Sciences Biomedicales, Tankeu, Ronni; FMBS, internal medicinie Bigna, Jean Joel; Centre Pasteur of Cameroon, Department of Epidemiology and Public Health
Keywords:	Thrombosis, Cerebral Veins, low- and middle-income countries

Epidemiology and patterns of cerebral venous thrombosis in low- and middle-income countries: a systematic review and meta-analysis protocol

Celestin Danwang[1]*, Mazou N. Temgoua[2], Joël Noutakdie Tochie[1], Ronni Tankeu[2], Jean Joël Bigna[4, 5]

1. Department of Surgery and Specialties, Faculty of Medicine and Biomedical Sciences, University of Yaoundé I, Yaoundé, Cameroon.

2. Department of Internal Medicine and Specialties, Faculty of Medicine and Biomedical Sciences, University of Yaoundé I, Yaoundé, Cameroon.

3. Department of Epidemiology and Public Health, Centre Pasteur of Cameroon, Yaoundé, Cameroon.

4. School of Public Health, Faculty of Medicine, University of Paris Sud XI, Le Kremlin-Bicêtre, France.

E-mail addresses: CD: danram07@yahoo.fr; MNT: neurotemgoua@yahoo.fr; JNT: joeltochie@gmail.com; RT: Ronnitank@gmail.com; JJB: bignarimjj@yahoo.fr;

*Corresponding author: Dr. Celestin Danwang, MD.
Department of Surgery and Specialties, Faculty of Medicine and Biomedical Sciences, University of Yaoundé I, Yaoundé, Cameroon.
E-mail: danram07@yahoo.fr
Phone number: +237696783172

Abstract

Introduction

Venous thrombosis can affect all veins in the body including cerebral veins, where it causes cerebral venous thrombosis (CVT). CVT is an aetiology of stroke, particularly in children and young adults. Its clinical features vary widely according to the occluded vessel. In low- and middle-income countries (LMICs), data concerning the epidemiology of CVT are scare. This protocol for a systematic review and meta-analysis aims to critically synthesize data concerning prevalence, incidence, risk factors, clinical presentation and mortality rate of CVT in people living in LMICs.

Methods and analysis

MEDLINE, EMBASE, ISI Web of Sciences databases will be searched for relevant abstracts of studies published between the 1st of January 1990 and the 31st of October 2017, without language restriction in LMICs. After screening of abstracts, study selection, data extraction and assessment of risk of bias, we will assess studies individually for heterogeneity. Random-effect meta-analysis will be then used to pool studies judged to be clinically homogenous. Funnel-plots analysis and Egger's test will be used to detect publication bias. Results will be presented by region (Africa, Americas, Eastern Mediterranean, Europe, South East Asia and Western Pacific).

Ethics and dissemination

Since the current study will be based on published data, ethical approval is not required. This review is expected to provide relevant data to help in evaluating the burden of CVT in LMICs. The final report of this study will be published in a peer-reviewed journal.

Protocol and registration:

PROSPERO International Prospective Register of systematic reviews, registration number: CRD42017074266.

Keywords: Thrombosis; Cerebral Veins; low- and middle-income countries.

Strengths and limitations of the study

- A limitation to the current review may be the limited amount of data; mainly cases series done in urban settings which may pose a major restriction to this study, as the result may not reflect the true burden of cerebral venous thrombosis (CVT) in the population of low- and middle-income countries (LMICs).
- This review will be in the best of our knowledge, the first one to summarized available data on the burden of CVT in LMICs.
- We plan to use powerful meta-analysis technique to have accurate estimates.

Introduction

Venous thrombosis can affect all veins in the body including the cerebral venous system leading to cerebral venous thrombosis (CVT)(1). Although rare, CVT is a potential aetiology of stroke, particularly in children and young adults (2, 3). All ages are concerned by this pathology including neonates(2). CVT accounts for 0.5% of all strokes and its annual incidence ranges from three to four cases per million population to up to seven cases per million among the youth worldwide (2, 3), with young adult females being more affected than males. The established risk factors of CVT are ear, nose and facial infections as well as intracranial tumours, pregnancy and the puerperium, systemic diseases, coagulopathies, oral contraceptives, and dehydration(4). The clinical presentation varies widely according to the occluded cerebral vessel **(3).**

The recent advances in neuroimaging techniques with the vulgarization of magnetic resonance imaging (MRI) even in low- and middle-income countries (LMICs) have made the diagnosis of CVT easier, hence, improving on the overall prognosis of CVT(2). The various therapeutic options are heparin, mechanical thrombectomy, intravenous thrombolytic and decompressive hemicraniectomy(2).

Unlike arterial strokes, there is scant consistent or representative data on CVT-related strokes, especially in LMICs(5) **,** where most of the population is made up of young people and is therefore at risk of developing CVT. We propose this protocol for a systematic review and meta-analysis to critically synthesis contemporary data on the prevalence, incidence, mortality rate, and risk factors of CVT in LMICs.

Objective

This systematic review and meta-analysis aims at determining the prevalence, incidence, risk factors and mortality associated with CVT as well as the clinical presentation of this disease in people living in LMICs.

Review questions

Specifically, the proposed systematic review will answer the following questions:

1. What are the prevalence and incidence of CVT in low- and middle-incomes countries?
2. What are the risk factors of CVT in this population?
3. What are the clinical features of CVT in this population?
4. What is the case-fatality rate due to CVT in this population?

Methods and analysis

This systematic review and meta-analysis will be reported in conformity with Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines(6). For the present protocol, the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) for Protocol was used for the reporting(7). An additional file shows the PRISMA for protocol checklist **[see Additional File 1]**.

Criteria for considering studies for the review

Inclusion criteria

1. We intend to include cross-sectional studies, case–control, cohort studies, and case-series with at least 30 participants.
2. Published between January 1st, 1990 and October 30th 2017, without any language restriction.
3. Observational studies with sufficient data on: the prevalence and/or incidence of CVT, mortality rate, risk factors or clinical pattern in LMICs.

Exclusion criteria

We will exclude:

1. Commentaries, editorials, letters and reviews.
2. Studies with inaccessible full text either online or from the corresponding author.
3. Studies in which relevant data on CVT are impossible to extract.
4. For duplicates, or studies published in more than one report, the one reporting the largest sample size will be considered.

Search strategy for identifying relevant studies

The search strategy will be as follow:

Bibliographic database searches

1. Excerpta Medica Database (EMBASE), MEDLINE through PubMed, Web of Science (Science Citation Index) databases will be searched for relevant studies concerning CVT in LMICs from January 1st, 1990 to October 31st 2017, with no language restriction. The researched strategy will be designed for MEDLINE and adapted for other databases, using both text words and medical subject heading terms related to CVT **(Table 1)**. In addition, the individual name of all LMICs will also be used as key search terms**.**
2. Secondly, the abstracts of all eligible articles will be reviewed and full-text articles will be accessed through PubMed, EMBASE, Scopus Database, AJOL, Google Scholar, HINARI, or journals' websites. The authors of papers whose full-text cannot be obtained by internet-based sources will be directly contacted to provide them.

Searching for others sources

The references cited by identified studies will also be searched for additional data source.

Selection of studies for inclusion in the review

The titles and abstracts of papers obtained from the search will be independently scrutinized by two reviewers (CD and TNM) using an assessment guide. The full texts of potentially eligible papers will be retrieved by one reviewer (CD). Thereafter, they will independently review the full text of each potentially eligible study, compare their results and resolve any discrepancy by discussion. If agreement is not reached after discussion a third reviewer (JNT) will be consulted for arbitration.

Assessment of methodological quality and reporting of data

An adapted version of the Risk of Bias Tool for Prevalence Studies developed by Hoy *et al.*(8), will be used to evaluate included studies for quality and risk of bias, and will be applied to screened full-text articles by two reviewers.

Data extraction and management

A data extraction form will be used by two independent reviewers (CD and TNM) to collect information on the last name of the first author, year of publication, region (Africa, Americas, Eastern Mediterranean, Europe, South East Asia and Western Pacific), country, study design, study area (rural versus urban), study setting (intensive care unit, surgery unit, post mortem), sample size, mean or median age, age range and male proportion, specific characteristics of the study population (woman on oral contraceptives, patients with HIV**,** pregnant/post-partum women and post-operative patients), prevalence, incident and/or mortality rate of CVT and risk factors or CVT in the study population. For multinational studies, the prevalence, incidence or mortality will be reported for the individual countries.

Data synthesis and analysis

When data collection will be complete, a meta-analysis will be conducted. The study-specific estimates will be pooled by using a random effects meta-analysis model to obtain an overall summary estimate of the prevalence and/or incidence across studies, after stabilizing the variance of individual studies with the use of the Freeman-Tukey double arc-sine transformation(9)**.** Standard errors for the study-specific estimates will be determined from the point estimate and the appropriate denominators**.** Heterogeneity will be assessed using the $\chi 2$ test on Cochrane's Q statistic(10) which is quantified by I^2 values, assuming that I^2 values of 25%, 50% and 75%, respectively, represent low, medium and high heterogeneity(11). We will assess the presence of publication bias using funnel plots and Egger's test(12). Publication bias will be confirmed if *p* value on Egger's test<0.10. Where substantial heterogeneity will be detected, subgroup and meta-regression analyses will be performed to investigate the possible sources of heterogeneity using previously mentioned variables and the study methodological quality. In case of substantial clinical heterogeneity, a narrative summary of findings will be done. The inter-rater agreement for study inclusion will be assessed using Cohen's κ coefficient(13). Data analyses used the *'meta'* package of the statistical software R (version 3.2.2 [2014-08-14], The R Foundation for statistical computing, Vienna, Austria).

Presentation and reporting of results

The study selection process will be summarize by a flow diagram. Quantitative data will be presented in evidence tables of individual studies as well as in summary tables and forest plots where appropriate. The quality scores and risk of bias for each eligible study will be reported accordingly. This may be tabulated and accompanied by narrative summaries.

Conclusion

Thrombosis of the cerebral veins and sinus represent one of the causes of stroke, especially in children and young adults. With the current scarcity of representative epidemiological data on CVT in resource-limited settings, this systematic review will provide this data so as to inform policymakers on the burden of this deadly disease in LMICs.

Ethics and disseminations

The current review will use published studies. Therefore, there is no requirement for ethical approval. The review is expected to provide the current burden of CVT in LMICs, in order to inform health authorities and decision makers to elaborate effective preventive strategies to reduce de burden of CVT in theseresource-challenged settings. The resulting manuscript will be published in a peer-reviewed journal.

Competing interests

None.

Funding

None.

Authors' Contributions:

Had the idea: CD. Designed and conceived the protocol: CD. First draft: CD. Critically revised the methodology and intellectual content: CD, TNM, JNT, RT and JJB. Guarantor of the review: JJB. All authors approved the final version of this manuscript.

References

1. Heit JA. Epidemiology of venous thromboembolism. *Nat Rev Cardiol* 2015 ;12:464-74.
2. Bousser MG, Ferro JM. Cerebral venous thrombosis: an update. *Lancet Neurol* 2007 ;6:162-70.
3. Stam J. Thrombosis of the cerebral veins and sinuses. *N Engl J Med* 2005 ;352:1791-8.
4. Saadatnia M, Fatehi F, Basiri K, Mousavi SA, Mehr GK. Cerebral venous sinus thrombosis risk factors. *Int J Stroke* 2009 ;4:111-23.
5. Sidhom Y, Mansour M, Messelmani M, Derbali H, Fekih-Mrissa N, Zaouali J, et al. Cerebral venous thrombosis: clinical features, risk factors, and long-term outcome in a Tunisian cohort. *J Stroke Cerebrovasc Dis* 2014 ;23:1291-5.
6. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 2000 ;283:2008-12.
7. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015 ;4:1.
8. Hoy D, Brooks P, Woolf A, Blyth F, March L, Bain C, et al. Assessing risk of bias in prevalence studies: modification of an existing tool and evidence of interrater agreement. *J Clin Epidemiol* 2012;65:934-9.
9. Miller JJ. The Inverse of the Freeman – Tukey Double Arcsine Transformation. *The American Statistician* 1978 ;32:138.
10. Kulinskaya E, Dollinger MB. An accurate test for homogeneity of odds ratios based on Cochran's Q-statistic. *BMC Med Res Methodol* 2015 ;15:49.
11. Huedo-Medina TB, Sanchez-Meca J, Marin-Martinez F, Botella J. Assessing heterogeneity in meta-analysis: Q statistic or I2 index? *Psychol Methods*. 2006;11:193-206.
12. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997 ;315:629-34.
13. McHugh ML. Interrater reliability: the kappa statistic. *Biochem Med (Zagreb)*;22:276-82.

Table 1: Search strategy for PubMed

Search	Search terms
#1	Cerebral Venous Thrombosis OR Cerebral Vein Thrombosis OR Thrombosis of the cerebral vein and sinus OR Cavernous sinus thrombosis
#2	(((Afghanistan [tiab] OR Albania [tiab] OR Algeria [tiab] OR American Samoa [tiab] OR Angola [tiab] OR Argentina [tiab] OR Armenia [tiab] OR Azerbaijan [tiab] OR Bangladesh [tiab] OR Belarus [tiab] OR Belize [tiab] OR Benin [tiab] OR Bhutan [tiab] OR Bolivia [tiab] OR Bosnia and Herzegovina [tiab] OR Botswana [tiab] OR Brazil [tiab] OR Bulgaria [tiab] OR Burkina Faso [tiab] OR Burundi [tiab] OR Cabo Verde [tiab] OR Cambodia [tiab] OR Cameroon [tiab] OR "Central African Republic" [tiab] OR Chad [tiab] OR China [tiab] OR Colombia [tiab] OR Comoros [tiab] OR Congo, Dem. Rep. [tiab] OR Congo, Rep. [tiab] OR Costa Rica [tiab] OR "Ivory Coast" [tiab] OR "Cote d'Ivoire" [tiab] OR Cuba [tiab] OR Djibouti [tiab] OR Dominica [tiab] OR "Dominican Republic" [tiab] OR Ecuador [tiab] OR "Egypt". [tiab] OR El Salvador [tiab] OR "Equatorial Guinea [tiab]" OR Eritrea [tiab] OR Ethiopia [tiab] OR Fiji [tiab] OR Gabon [tiab] OR Gambia [tiab] OR Georgia [tiab] OR Ghana [tiab] OR Grenada [tiab] OR Guatemala [tiab] OR Guinea [tiab] OR Guinea-Bissau [tiab] OR Guyana [tiab] OR Haiti [tiab] OR Honduras [tiab] OR India [tiab] OR Indonesia [tiab] OR Iran, Islamic Rep. [tiab] OR Iraq [tiab] OR Jamaica [tiab] OR Jordan [tiab] OR Kazakhstan [tiab] OR Kenya [tiab] OR Kiribati [tiab] OR "Korea, Dem. People's Rep." [tiab] OR Kosovo [tiab] OR "Kyrgyz Republic" [tiab] OR Lao PDR [tiab] OR Lebanon [tiab] OR Lesotho [tiab] OR Liberia [tiab]

	OR Libya [tiab] OR Macedonia [tiab] OR Madagascar [tiab] OR Malawi [tiab] OR Malaysia [tiab] OR Maldives [tiab] OR Mali [tiab] OR Marshall Islands [tiab] OR Mauritania [tiab] OR Mauritius [tiab] OR Mexico [tiab] OR Micronesia [tiab] OR Moldova [tiab] OR Mongolia [tiab] OR Montenegro [tiab] OR Morocco [tiab] OR Mozambique [tiab] OR Myanmar [tiab] OR Namibia [tiab] OR Nepal [tiab] OR Nicaragua [tiab] OR Niger [tiab] OR Nigeria [tiab] OR Pakistan [tiab] OR Palau [tiab] OR Panama [tiab] OR Papua New Guinea [tiab] OR Paraguay [tiab] OR Peru [tiab] OR Philippines [tiab] OR Romania [tiab] OR "Russian Federation" [tiab] OR Rwanda [tiab] OR Samoa [tiab] OR "São Tomé and Princip" [tiab] OR Senegal [tiab] OR Serbia [tiab] OR "Sierra Leone" [tiab] OR Solomon Islands [tiab] OR Somalia [tiab] OR "South Africa" [tiab] OR South Sudan [tiab] OR Sri Lanka [tiab] OR St. Lucia [tiab] OR St. Vincent and the Grenadines [tiab] OR Sudan [tiab] OR Suriname [tiab] OR Swaziland [tiab] OR Syrian Arab Republic [tiab] OR Tajikistan [tiab] OR Tanzania [tiab] OR Thailand [tiab] OR Timor-Leste [tiab] OR Togo [tiab] OR Tonga [tiab] OR Tunisia [tiab] OR Turkey [tiab] OR Turkmenistan [tiab] OR Tuvalu [tiab] OR Uganda [tiab] OR Ukraine [tiab] OR Uzbekistan [tiab] OR Vanuatu [tiab] OR Venezuela [tiab] OR Vietnam [tiab] OR West Bank and Gaza [tiab] OR Yemen, Rep. [tiab] OR Zambia [tiab] OR Zimbabwe [tiab] NOT ("guinea pig" OR "guinea pigs" OR "aspergillusniger")))
#3	#1 AND #2
#4	Limits 01/01/1990 to 10/31/2017

PRISMA-P 2015 Checklist

This checklist has been adapted for use with systematic review protocol submissions to BioMed Central journalsfrom Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews*2015 **4**:1

An Editorial from the Editors-in-Chief of *Systematic Reviews* details why this checklist was adapted -Moher D, Stewart L & Shekelle P: Implementing PRISMA-P: recommendations for prospective authors. *Systematic Reviews*2016**5**:15

Section/topic	#	Checklist item	Information reported		Page number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☒	
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☒	☐	3
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	10
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☐	☒	
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	9
Sponsor	5b	Provide name for the review funder and/or sponsor	☒	☐	9
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☒	☐	9
INTRODUCTION					

2

Section/topic	#	Checklist item	Information reported		Page number(s)
			Yes	No	
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	4-5
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	5_6
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	6-7
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐	11-12
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	7
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	7
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	7
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	5
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	6
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☒	☐	7
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☒	☐	7-8
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of	☒	☐	7-8

Section/topic	#	Checklist item	Information reported		Page number(s)
			Yes	No	
		handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)			
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☒	☐	8
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☒	☐	8
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☒	☐	8
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☒	☐	8

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Global epidemiology and patterns of cerebral venous thrombosis: a systematic review and meta-analysis protocol

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Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Epidemiology, Neurology
Keywords:	Thrombosis, Cerebral Veins, EPIDEMIOLOGY

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Celestin Danwang[1]*, Mazou N. Temgoua[2], Joël Noutakdie Tochie[1], Ronni Tankeu[2], Jean Joel Bigna[4, 5]

1. Department of Surgery and Specialties, Faculty of Medicine and Biomedical Sciences, University of Yaoundé I, Yaoundé, Cameroon.

2. Department of Internal Medicine and Specialties, Faculty of Medicine and Biomedical Sciences, University of Yaoundé I, Yaoundé, Cameroon.

3. Department of Epidemiology and Public Health, Centre Pasteur of Cameroon, Yaoundé, Cameroon.

4. School of Public Health, Faculty of Medicine, University of Paris Sud XI, Le Kremlin-Bicêtre, France.

E-mail addresses: CD: danram07@yahoo.fr; MNT: neurotemgoua@yahoo.fr; JNT: joeltochie@gmail.com; RT: Ronnitank@gmail.com; JJB: bignarimjj@yahoo.fr;

*Corresponding author: Dr. Celestin Danwang, MD.
Department of Surgery and Specialties, Faculty of Medicine and Biomedical Sciences, University of Yaoundé I, Yaoundé, Cameroon.
E-mail: danram07@yahoo.fr
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Abstract

Introduction

Venous thrombosis can affect all veins in the body including cerebral veins, where it causes cerebral venous thrombosis (CVT). CVT is an aetiology of stroke, particularly in children and young adults. Its clinical features vary widely according to the occluded vessel. Data concerning the epidemiology of CVT are scarced. This protocol for a systematic review and meta-analysis aims to critically synthesize data concerning prevalence, incidence, risk factors, clinical presentation, and mortality rate of CVT in the global population.

Methods and analysis

MEDLINE, EMBASE, ISI Web of Sciences databases will be searched for relevant abstracts of studies published between the 1st of January 1990 and the 31st of October 2017, without language restriction. After the screening of abstracts, study selection, data extraction and assessment of risk of bias, we will assess studies individually for heterogeneity. Random-effect meta-analysis will be then used to pool studies judged to be clinically homogenous. Funnel-plots analysis and Egger's test will be used to detect publication bias. Results will be presented by region (Africa, America, Europe, Asia and Oceania).

Ethics and dissemination

Since the current study will be based on published data, ethical approval is not required. This review is expected to provide relevant data to help in evaluating the global burden of CVT. The final report of this study will be published in a peer-reviewed journal.

Protocol and registration:

PROSPERO International Prospective Register of systematic reviews, registration number: CRD42017074266.

Keywords: Epidemiology; Thrombosis; Cerebral Veins.

Strengths and limitations of the study

- A limitation to the current review may be the scant amount of data; mainly cases series done in urban settings which may pose a major restriction to this study, as the result may not reflect the true burden of cerebral venous thrombosis (CVT).
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- We plan to use powerful meta-analysis technique to have accurate estimates.

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The recent advances in neuroimaging techniques with the vulgarization of magnetic resonance imaging (MRI) even in low- and middle-income countries (LMICs) have made the diagnosis of CVT easier, hence, improving on the overall prognosis of CVT(2). The various therapeutic options are anticoagulation therapy (mainly with heparin), mechanical thrombectomy, intravenous thrombolytic and decompressive hemicraniectomy(2).

The current epidemiological data on CVT is derived from primary studies in which all ethnicities are often not represented making it impossible to appraise the global scene (5, 6). Despite this significant gap in knowledge on the subject, no study has so far focused on global epidemiology and the distribution of risk factors for CVT in different populations worldwide(7). Thus, we propose this protocol for a systematic review and meta-analysis to critically synthesis contemporary data on the prevalence, incidence, mortality rate, and risk factors of CVT in the world.

Objective

This systematic review and meta-analysis aims at determining the prevalence, incidence, risk factors and mortality associated with CVT as well as the clinical presentation of this disease on a global basis.

Review questions

Specifically, the proposed systematic review will answer the following questions:

1. What are the global prevalence and incidence of CVT?
2. What are the risk factors of CVT?
3. What are the clinical features (signs and symptoms) of CVT?
4. What is the global case-fatality rate due to CVT?

Methods and analysis

This systematic review and meta-analysis will be reported in conformity with Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines(8). For the present protocol, the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) for Protocol was used for the reporting(9). **Additional file 1** shows the PRISMA checklist used for this study protocol.

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2. All aforementioned studies published between January 1st, 1990 and October 31st, 2017, without any language restriction.

3. Observational studies with sufficient data on the prevalence and/or incidence of CVT, mortality rate, risk factors or clinical pattern.

Exclusion criteria

We will exclude:

1. Commentaries, editorials, letters and reviews.
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1. Excerpta Medica Database (EMBASE), MEDLINE through PubMed, Web of Science (Science Citation Index) databases will be searched for relevant studies concerning CVT from January 1st, 1990 to October 31st, 2017, with no language restriction. The researched strategy will be designed for MEDLINE and adapted for other databases, using both text words and medical subject heading terms related to CVT **(Table 1)**.
2. Secondly, the abstracts of all eligible articles will be reviewed and full-text articles will be accessed through PubMed, EMBASE, Scopus Database, AJOL, Google Scholar, HINARI, or journals' websites. The authors of papers whose full-text will not be obtained by internet-based sources will be directly contacted to provide them.

Searching for others sources

The references cited by identified studies will also be searched for additional data source.

Selection of studies for inclusion in the review

The titles and abstracts of papers obtained from the search will be independently scrutinized by two reviewers (CD and TNM) using an assessment guide. The full texts of potentially eligible papers will be retrieved by one reviewer (CD). Thereafter, they will independently review the full text of each potentially eligible study, compare their results and resolve any discrepancy by discussion. If an agreement is not reached after discussion, a third reviewer (JNT) will be consulted for arbitration.

Assessment of methodological quality and reporting of data

An adapted version of the Risk of Bias Tool for Prevalence Studies developed by Hoy *et al.*(10) **[see Additional File 2]**, will be used to evaluate included studies for the quality and risk of bias and will be applied to screened full-text articles by two reviewers.

Data extraction and management

A data extraction form **[see Additional File 3]** will be used by two independent reviewers (CD and TNM) to collect information on the last name of the first author, year of publication, region (Africa, Americas, Europe, Asia, Oceania), country, study design, study area (rural versus urban), study setting (intensive care unit, surgery unit, post mortem), sample size, mean or median age, age range and male proportion, specific characteristics of the study population (woman on oral contraceptives, patients with HIV**,** pregnant/post-partum women and post-operative patients), clinical feature (signs and symptoms), prevalence, incident and/or mortality rate of CVT and risk factors for CVT in the study population. For multinational studies, the prevalence, incidence or mortality will be reported for the individual countries.

Data synthesis and analysis

When data collection will be complete, a meta-analysis will be conducted. The study-specific estimates will be pooled by using a random-effect meta-analysis model to obtain an overall summary estimate of the prevalence and/or incidence across studies, after stabilizing the variance of individual studies with the use of the Freeman-Tukey double arc-sine transformation(11)**.** Standard errors for the study-specific estimates will be determined from the point estimate and the appropriate denominators**.** Heterogeneity will be assessed using the $\chi 2$ test on Cochrane's Q statistic(12) which is quantified by I^2 values, assuming that I^2 values of 25%, 50%, and 75%, respectively, represent low, medium and high heterogeneity(13). We will assess the presence of publication bias using funnel plots and Egger's test(14). Publication bias will be confirmed if *p*-value on Egger's test<0.10. Where substantial heterogeneity will be detected, subgroup and meta-regression analyses will be performed to investigate the possible sources of heterogeneity using previously mentioned variables and the study methodological quality. In case of substantial clinical heterogeneity, a narrative summary of findings will be done. The inter-rater agreement for study inclusion will be assessed using Cohen's κ coefficient(15). Data analyses will use the *'meta'* package of the statistical software R (version 3.2.2 [2014-08-14], The R Foundation for statistical computing, Vienna, Austria).

Presentation and reporting of results

The study selection process will be summarized in a flow diagram. Quantitative data will be presented in evidence tables of individual studies as well as in summary tables and forest plots where appropriate. The quality scores and risk of bias for each eligible study will be reported accordingly. This may be tabulated and accompanied by narrative summaries.

Conclusion

Thrombosis of the cerebral veins and sinus represent one of the causes of stroke, especially in children and young adults. With the current scarcity of a global representative epidemiological data on CVT, the findings of this systematic review may help inform policymakers on the global burden of this deadly disease.

Ethics and disseminations

The current review will use published studies. Therefore, there is no requirement for ethical approval. The review is expected to provide the current global burden of CVT, in order to inform health authorities and decision makers to elaborate effective preventive strategies to reduce the burden of CVT. The resulting manuscript will be published in a peer-reviewed journal.

Competing interests

None.

Funding

None.

Authors' Contributions:

Had the idea: CD. Designed and conceived the protocol: CD. First draft: CD. Critically revised the methodology and intellectual content: CD, TNM, JNT, RT and JJB. Guarantor of the review: CD and JJB. All authors approved the final version of this manuscript.

References

1. Heit JA. Epidemiology of venous thromboembolism. Nat Rev Cardiol. 2015 Aug;12(8):464-74.
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Table 1: Search strategy for PubMed

Search	Search terms
#1	Cerebral Venous Thrombosis OR Cerebral Vein Thrombosis OR Thrombosis of the cerebral vein and sinus OR Cavernous sinus thrombosis
#2	Limits: 01/01/1990 to 10/31/2017; no language restriction
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PRISMA-P 2015 Checklist

This checklist has been adapted for use with systematic review protocol submissions to BioMed Central journalsfrom Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews*2015 **4**:1

An Editorial from the Editors-in-Chief of *Systematic Reviews* details why this checklist was adapted -Moher D, Stewart L & Shekelle P: Implementing PRISMA-P: recommendations for prospective authors. *Systematic Reviews*20165:15

Section/topic	#	Checklist item	Information reported		Page number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☒	
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☒	☐	3
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	10
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☐	☒	
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	9
Sponsor	5b	Provide name for the review funder and/or sponsor	☒	☐	9
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☒	☐	9
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	4

Section/topic	#	Checklist item	Information reported		Page number(s)
			Yes	No	
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	4-5
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	5_6
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	6-7
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐	11-12
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	7
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	7
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	7
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	5
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	6
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☒	☐	7
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☒	☐	7-8
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☒	☐	7-8

Section/topic	#	Checklist item	Information reported		Page number(s)
			Yes	No	
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☒	☐	8
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☒	☐	8
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☒	☐	8
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☒	☐	8

Additional File 2. Risk of bias assessment tool for prevalence, incidence and aetiologies outcomes

Risk of Bias Item	Answer: Yes (Low Risk) or No (High risk)
External Validity	
1. Was the study target population a close representation of the national population in relation to relevant variables?	
2. Was the sampling frame a true or close representation of the target population?	
3. Was some form of random selection used to select the sample, OR, was a census undertaken?	
4. Was the likelihood of non-participation bias minimal?	
Internal Validity	
5. Were data collected directly from the subjects (as opposed to medical records)?	
6. Were acceptable case definition of condition used?	
7. Was a reliable and accepted diagnosis method utilized?	
8. Was the same mode of data collection used for all subjects?	
9. Was the length of the shortest prevalence period for the parameter of interest appropriate?	
10. Were the numerator(s) and denominator(s) for the calculation of the prevalence appropriate?	
11. Summary item on the overall risk of study bias LOW RISK OF BIAS: 8 or more "yes" answers. Further research is very unlikely to change our confidence in the estimate. MODERATE RISK OF BIAS: 6 to 7 "yes" answers. Further research is likely to have an important impact on our confidence in the estimate and may change the estimate. HIGH RISK OF BIAS: 5 or fewer "yes" answers. Further research is very likely to have an important impact on our confidence in the estimate and is likely to change the estimate.	

Additional File 3: data extraction form

First author name	Year of publication	Region	Country	Design	Random sampling	Setting	Area	Age Range (years)	Mean age	Sample Size	%Male	Prevalence of CVT (%)	Incidence of CVT	Mortality rate (%)	Diagnostic method for CVT	Risk factors for CVT	Signs and symptoms	Disease specific to the study population	Risk of bias in methodology	observation

BMJ Open

Global epidemiology and patterns of cerebral venous thrombosis: a systematic review and meta-analysis protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-019939.R2
Article Type:	Protocol
Date Submitted by the Author:	28-Feb-2018
Complete List of Authors:	Danwang, Celestin; Faculty of Medecine and Biomedical Sciences, Surgery and specialities Mazou, Temgoua Ngou ; Faculty of Medecine and Biomedical Sciences, Internal medicine and specialities Tochie, Joel Noutakdie; Universite de Yaounde I Faculte de Medecine et des Sciences Biomedicales, Tankeu, Ronni; FMBS, internal medicinie Bigna, Jean Joel; Centre Pasteur of Cameroon, Department of Epidemiology and Public Health
Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Epidemiology, Neurology
Keywords:	Thrombosis, Cerebral Veins, EPIDEMIOLOGY

Global epidemiology and patterns of cerebral venous thrombosis: a systematic review and meta-analysis protocol

Celestin Danwang[1]*, Mazou N. Temgoua[2], Joël Noutakdie Tochie[1], Ronni Tankeu[2], Jean Joel Bigna[4, 5]

1. Department of Surgery and Specialties, Faculty of Medicine and Biomedical Sciences, University of Yaoundé I, Yaoundé, Cameroon.

2. Department of Internal Medicine and Specialties, Faculty of Medicine and Biomedical Sciences, University of Yaoundé I, Yaoundé, Cameroon.

3. Department of Epidemiology and Public Health, Centre Pasteur of Cameroon, Yaoundé, Cameroon.

4. School of Public Health, Faculty of Medicine, University of Paris Sud XI, Le Kremlin-Bicêtre, France.

E-mail addresses: CD: danram07@yahoo.fr; MNT: neurotemgoua@yahoo.fr; JNT: joeltochie@gmail.com; RT: Ronnitank@gmail.com; JJB: bignarimjj@yahoo.fr;

*Corresponding author: Dr. Celestin Danwang, MD.
Department of Surgery and Specialties, Faculty of Medicine and Biomedical Sciences, University of Yaoundé I, Yaoundé, Cameroon.
E-mail: danram07@yahoo.fr
Phone number: +237696783172

Abstract

Introduction

Venous thrombosis can affect all veins in the body including cerebral veins, where it causes cerebral venous thrombosis (CVT). CVT is an aetiology of stroke, particularly in children and, young adults. Its clinical features vary widely according to the occluded vessel. Data concerning the epidemiology of CVT is scant. This protocol for a systematic review and meta-analysis aims to critically synthesize data concerning prevalence, incidence, risk factors, anatomical patterns, diagnostic and therapeutic delays, and mortality rate of CVT in the global population.

Methods and analysis

MEDLINE, EMBASE, ISI Web of Sciences databases will be searched for relevant abstracts of studies published between the 1st of January 1990 and the 31st of October 2017, without language restriction. After the screening of abstracts, study selection, data extraction and assessment of risk of bias, we will assess studies individually for heterogeneity. Random-effect meta-analysis will then be used to pool studies judged to be clinically homogenous. Funnel-plots analysis and Egger's test will be used to detect publication bias. Results will be presented according to economic level of the various countries (high income versus low- and middle-income countries).

Ethics and dissemination

Since the current study will be based on published data, ethical approval is not required. This review is expected to provide relevant data to help in evaluating the global burden of CVT. The final report of this study will be published in a peer-reviewed journal.

Protocol and registration:

PROSPERO International Prospective Register of systematic reviews, registration number: CRD42017074266.

Keywords: Epidemiology; Thrombosis; Cerebral Veins.

Strengths and limitations of the study

- A limitation to the current review may be the scant amount of data; mainly cases series done in urban settings which may pose a major restriction to this study, as the result may not reflect the true burden of cerebral venous thrombosis (CVT).
- To the best of our knowledge, this is the first review to summarize available data on the global burden of CVT.
- The current review will include studies without language restrictions, and thus, will allow to enroll the maximum of studies published on the topic.

Introduction

Venous thrombosis can affect all veins in the body including the cerebral venous system leading to cerebral venous thrombosis (CVT) (1). Although rare and affecting all age groups, CVT is a potential aetiology of stroke, particularly in children and, young adults (2, 3). CVT accounts for 0.5% of all strokes and, its annual incidence ranges from three to four cases per million among the general population to up to seven cases per million among the youths (2, 3), with young adult females being more affected than males. The established risk factors for CVT are ear, nose and facial infections as well as intracranial tumours, pregnancy and the puerperium, systemic diseases, coagulopathies, oral contraceptives use, and dehydration (4). The clinical presentation varies widely according to the occluded cerebral vessel (3).

The recent advances in neuroimaging techniques with the widespread use of magnetic resonance imaging (MRI) even in low- and middle-income countries (LMICs) have made the diagnosis of CVT easier, hence, improving on the overall prognosis of patients with CVT (2). The various therapeutic options are anticoagulation therapy (mainly with heparin), mechanical thrombectomy, intravenous thrombolytic and decompressive hemicraniectomy (2).

The current epidemiological data on CVT is derived from primary studies in which all ethnicities are often not represented making it impossible to appraise the global scene (5, 6). Despite this gap in knowledge on the subject matter, till date, no study has focused on the global epidemiology and, the risk factors for CVT in all racial backgrounds and all countries of various income levels (7). Accordingly, we propose this protocol for a systematic review and meta-analysis to critically synthesis contemporary evidence on the occurrence of CVT in the world. The overall research goal is to provide useful data for health authorities.

Objective

This systematic review and meta-analysis aims at determining the prevalence, incidence, risk factors, anatomical patterns, diagnostic and therapeutic delays and, mortality rate of CVT on a global basis.

Review questions

Specifically, the proposed systematic review will answer the following questions:

1. What are the global prevalence and, incidence of CVT?
2. What are the risk factors of CVT?
3. What are the neuroimaging features (the various anatomical locations) of CVT?
4. What is the delay between the onset of symptoms, the diagnosis and, initiation of treatment according to the income level (Low- and middle-incomes countries versus high income countries)?
5. What is the global case-fatality rate due to CVT?

Methods and analysis

This systematic review and meta-analysis will be reported in conformity with Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines (8). For the present protocol, the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) for Protocol was used for the reporting (9). **Additional file 1** shows the PRISMA checklist used for this study protocol.

Criteria for considering studies for the review

Inclusion criteria

1. We intend to include cross-sectional studies, case–control, cohort studies, and, case-series with at least 30 participants.

2. All aforementioned studies published between January 1st, 1990 and October 31st, 2017, without any language restriction.

3. Observational studies with sufficient data on the prevalence and/or incidence, risk factors, anatomical patterns, diagnostic and therapeutic delays and mortality rate of CVT.

Exclusion criteria

We will exclude:

1. Commentaries, editorials, letters and, reviews.
2. Studies with inaccessible full text either online or from the corresponding author.
3. Studies in which relevant data on CVT are impossible to extract.
4. For duplicates or studies published in more than one report, the study reporting the largest sample size will be considered.

Search strategy for identifying relevant studies

The search strategy will be as follow:

Bibliographic database searches

1. Excerpta Medica Database (EMBASE), MEDLINE through PubMed, Web of Science (Science Citation Index) databases will be searched for relevant studies concerning CVT from January 1st, 1990 to October 31st, 2017, with no language restriction. The researched strategy will be designed for MEDLINE and, adapted for other databases, using both text words and, medical subject heading terms related to CVT **(Table 1)**.

2. Secondly, the abstracts of all eligible articles will be reviewed and, full-text articles will be accessed through PubMed, EMBASE, Scopus Database, AJOL, Google Scholar, HINARI, or journals' websites. The authors of papers whose full-text will not be obtained by internet-based sources will be directly contacted to provide them.

Searching for others sources

The references cited by identified studies will also be searched for additional data source.

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The titles and, abstracts of papers obtained from the search will be independently scrutinized by two reviewers (CD and, TNM) using an assessment guide. The full texts of potentially eligible papers will be retrieved by one reviewer (CD). Thereafter, they will independently review the full text of each potentially eligible study, compare their results and, resolve any discrepancy by discussion. If an agreement is not reached after discussion, a third reviewer (JNT) will be consulted for arbitration.

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A data extraction form **[see Additional File 3]** will be used by two independent reviewers (CD and, TNM) to collect information on the last name of the first author, year of publication, region (Africa, Americas, Europe, Asia, Oceania), country economic level (high income versus low- and middle-income countries), country, study design, study area (rural versus

urban), study setting (intensive care unit, surgery unit, post mortem), sample size, mean or median age, age range and, male proportion, specific characteristics of the study population (woman on oral contraceptives, patients with HIV**,** pregnant/post-partum women and, post-operative patients), prevalence rate, incidence rate, anatomical patterns (occluded cerebral vessel on neuroimaging studies), diagnostic and therapeutic delays (days or weeks), and/or mortality rate of CVT and, risk factors for CVT in the study population. For multinational studies, the prevalence, incidence or mortality will be reported for the individual countries.

Data synthesis and analysis

When data collection will be complete, a meta-analysis will be conducted. The study-specific estimates will be pooled by using a random-effect meta-analysis model to obtain an overall summary estimate of the prevalence and/or incidence across studies, after stabilizing the variance of individual studies with the use of the Freeman-Tukey double arc-sine transformation (11)**.** Standard errors for the study-specific estimates will be determined from the point estimate and, the appropriate denominators**.** Heterogeneity will be assessed using the $\chi 2$ test on Cochrane's Q statistic (12) which is quantified by I^2 values, assuming that I^2 values of 25%, 50%, and 75%, respectively, represent low, medium and, high heterogeneity (13). We will assess the presence of publication bias using funnel plots and, Egger's test(14). Publication bias will be confirmed if *p*-value on Egger's test<0.10. Where substantial heterogeneity will be detected, subgroup and, meta-regression analyses will be performed to investigate the possible sources of heterogeneity using previously mentioned variables and, the study methodological quality. In case of substantial clinical heterogeneity, a narrative summary of findings will be done. The inter-rater agreement for study inclusion will be assessed using Cohen's κ coefficient (15). Data analyses will use the *'meta'* package of the statistical software R (version 3.2.2 [2014-08-14], The R Foundation for statistical computing, Vienna, Austria).

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Patient and Public Involvement

In this study, data will not be collected directly from patients, but in published studies available in main databases.

Conclusion

Thrombosis of the cerebral veins and, sinus represent one of the causes of stroke, especially in children and, young adults. With the current scarcity of a global representative epidemiological data on CVT, the findings of this systematic review may help inform policymakers on the global burden of this deadly disease.

Ethics and disseminations

The current review will use published studies. Therefore, there is no requirement for ethical approval. The review is expected to provide the current global burden of CVT, in order to inform health authorities and, decision makers to elaborate effective preventive strategies to reduce the burden of CVT. The resulting manuscript will be published in a peer-reviewed journal.

Competing interests

None.

Funding

None.

Authors' Contributions:

Had the idea: CD, TNM and JNT. Designed and conceived the protocol: CD, JNT and JJB. First draft: CD. Critically revised the methodology and intellectual content: CD, TNM, JNT, RT and JJB. Guarantor of the review: CD and JJB. All authors approved the final version of this manuscript.

References

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15. McHugh ML. Interrater reliability: the kappa statistic. Biochem Med (Zagreb). 2012;22(3):276-82.

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Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☒	
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☒	☐	3
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	10
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☐	☒	
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	9
Sponsor	5b	Provide name for the review funder and/or sponsor	☒	☐	9
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☒	☐	9
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	4

Section/topic	#	Checklist item	Information reported		Page number(s)
			Yes	No	
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	4-5
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	5_6
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	6-7
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐	11-12
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	7
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	7
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	7
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	5
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	6
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☒	☐	7
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☒	☐	7-8
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☒	☐	7-8

Section/topic	#	Checklist item	Information reported		Page number(s)
			Yes	No	
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☒	☐	8
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☒	☐	8
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☒	☐	8
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☒	☐	8

Additional File 2. Risk of bias assessment tool for prevalence, incidence and aetiologies outcomes

Risk of Bias Item	Answer: Yes (Low Risk) or No (High risk)
External Validity	
1. Was the study target population a close representation of the national population in relation to relevant variables?	
2. Was the sampling frame a true or close representation of the target population?	
3. Was some form of random selection used to select the sample, OR, was a census undertaken?	
4. Was the likelihood of non-participation bias minimal?	
Internal Validity	
5. Were data collected directly from the subjects (as opposed to medical records)?	
6. Were acceptable case definition of condition used?	
7. Was a reliable and accepted diagnosis method utilized?	
8. Was the same mode of data collection used for all subjects?	
9. Was the length of the shortest prevalence period for the parameter of interest appropriate?	
10. Were the numerator(s) and denominator(s) for the calculation of the prevalence appropriate?	
11. Summary item on the overall risk of study bias LOW RISK OF BIAS: 8 or more "yes" answers. Further research is very unlikely to change our confidence in the estimate. MODERATE RISK OF BIAS: 6 to 7 "yes" answers. Further research is likely to have an important impact on our confidence in the estimate and may change the estimate. HIGH RISK OF BIAS: 5 or fewer "yes" answers. Further research is very likely to have an important impact on our confidence in the estimate and is likely to change the estimate.	

Additional File 3: data extraction form

First author name	Year of publication	Region	Country	Design	Random sampling	Setting	Area	Age Range (years)	Mean age	Sample Size	%Male	Prevalence of CVT (%)	Incidence of CVT	Mortality rate (%)	Diagnostic method for CVT	Risk factors for CVT	Signs and symptoms	Disease specific to the study population	Risk of bias in methodology	observation