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### ADMINISTRATIVE INFORMATION

**Support** - No one.

**Review Stage at time of this submission** - Preliminary searches.

**Conflicts of interest** - None declared.

**INPLASY registration number:** INPLASY202440053

**Amendments** - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 12 April 2024 and was last updated on 12 April 2024.

### INTRODUCTION

**Review question / Objective** The research question was structured according to the PECOS search strategy (population/patients, exposure, comparison, results, and study design), where: P (participants): Adult patients. E (exposure): Exposure to periodontitis. C (control): Absence of periodontitis. O (outcome): Risk of ischemic stroke. S (study design): Cohort and case-control studies. QUESTION: Is periodontitis a risk factor for ischemic stroke in adult patients?

**Rationale** Evidence would indicate a possible association between periodontitis and ischemic stroke. Due to individual studies having insufficient power to reach a reliable conclusion, the present systematic review (and a meta-analysis, if feasible) of the observational, cohort, and case-control design studies will be performed. In addition, this

review will incorporate new studies to present an update to previous reviews.

**Condition being studied** Stroke is one of the leading causes of death and disability worldwide, causing significant sequelae and high consumption of health resources. It can be ischemic if the damage is characterized by occlusion of the cerebral blood vessels or hemorrhagic if their rupture causes it. The evidence would indicate a possible association between periodontitis and ischemic stroke, with indirect damage to vascular function and direct damage by infectious agents, such as *Porphyromonas gingivalis*, being among its main mechanisms.

### METHODS

**Search strategy** For articles, electronic searches will be done in PubMed-MEDLINE, Embase,

Scopus, Web of Science, and BVS, using keywords and controlled vocabulary terms (i.e., MeSH, Emtree). Also, hand searches will be conducted of the reference lists of eligible primary studies. The basic search terms will be the following: "periodontitis", "periodontal disease", "ischemic stroke", "ischaemic stroke", "brain ischemia", "thrombotic stroke", "brain thromb\*", "cerebral thromb\*", "intracranial thromb\*" and "cerebral infarction". Those that will be adapted according to the requirements of each database.

**Participant or population** Adult patients.

**Intervention** Exposure to periodontitis.

**Comparator** Absence of periodontitis.

**Study designs to be included** Cohort and case-control studies.

**Eligibility criteria** This review will include cohort and case-control studies published until March 2024, that studied periodontitis as a risk factor for ischemic stroke in adult patients (over 18 years of age) and calculated the relative risk (RR), hazard ratio (HR), and odds ratio (OR). Studies with incomplete data will be excluded. Periodontitis will be defined as clinical attachment loss (CAL) > 3 mm. Diagnosis of ischemic stroke will be based on definitive medical examinations (i.e., ischemic lesion on brain imaging and/or on clinical examination, with neurological deficit).

**Information sources** PubMed-MEDLINE, Embase, Scopus, Web of Science, and BVS, using keywords and controlled vocabulary terms (i.e., MeSH, Emtree). Also, hand searches will be conducted of the reference lists of eligible primary studies. If these data were not found in the article, an email will be sent to the authors.

**Main outcome(s)** Ischemic stroke. All outcome measures that assessed the association between periodontitis and ischemic stroke will be considered. The information required for each study will be collected in preliminary summary tables. If these data were not found in the article, an email will be sent to the authors to request them. Results with sufficient data to calculate an estimate of the effect will be used for meta-analysis.

**Additional outcome(s)** Development time of ischemic stroke.

**Quality assessment / Risk of bias analysis** Newcastle-Ottawa Scale will be used to assess

bias. A third author will resolve any disagreements. All the studies will be included irrespective of their risk of bias rating.

**Confidence in cumulative evidence:** the quality of the evidence will be evaluated using the GRADE guidance. The risk of analytical and publication bias and inconsistency in reporting will be assessed. An overall judgment of "high," "moderate," "low," and "very low" will be provided for the quality of the cumulative evidence for review outcomes.

**Strategy of data synthesis** A narrative synthesis of the key findings from the included studies will be presented according to the review question with summary tables for study characteristics and participant and outcome details. A quantitative synthesis will be performed to demonstrate overall effect estimates and variability if possible. Propositions of individuals meeting each primary endpoint outcome in the independent clinical studies will be included in the meta-analysis to provide summary estimates of proportions.

**Subgroup analysis** According to design: cohort and case-control studies.

**Sensitivity analysis** Sensitivity analyses will be performed if heterogeneity is high, defined by the I<sup>2</sup> test.

**Country(ies) involved** Perú.

**Keywords** "periodontitis"; "periodontal disease"; "ischemic stroke"; "ischaemic stroke"; "brain ischemia"; "cerebral infarction".

**Dissemination plans** This review will be published in a scientific journal.

**Contributions of each author**

Author 1 - Angel Steven Asmat Abanto - Choice of topic. Search for articles. Selection of articles. Writing the draft of the manuscript. Drafting of the final manuscript. Submission to the scientific journal. Correction of comments by reviewers.

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