The Effect of Acupuncture for ATP Activity in Brain Diseases: Protocol of a Systematic Review and Meta-Analysis of Animal Experiments

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Protocol

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Abstract

Background: Brain is an energy-consuming organ, which is highly depended on adenosine triphosphate (ATP) supplying energy to maintain the functions of memory, thinking, cognition etc. Some animal experiment findings have indicated that ATP depletion was correlated with multiple brain diseases [brain injury, Parkinson disease (PD), stroke, brain tumor, Alzheimer's disease (AD), vascular dementia (VD), etc.]. Acupuncture has been identified that it has a therapeutic effect for brain diseases. However, the mechanism of acupuncture for brain diseases remains to be determined. Lack of high-quality evidence of underlying mechanism could result in a limitation of acupuncture in clinical practice. Therefore, we aim to conduct a systematic review (SR) and meta-analysis of animal experiments to identify the effect of acupuncture for ATP activity in brain diseases and hope to provide a robust evidence for acupuncture in brain disease.

Methods: Six databases [PubMed, Embase, web of Science, the China National Knowledge Infrastructure (CNKI), the Chinese Science and Technology Periodical Database (VIP) and Wan Fang database] will be systematically searched from the inception dates to July, 2020. Two researchers will independently screen titles and abstracts for eligibility. Eligible articles will be restricted to animal studies correlated with acupuncture treatment for brain diseases. The primary outcomes are ATP activity, ATP content, Na^{+}-k^{+}-ATPase activity, and Ca^{2+} activity. Secondary outcomes are as following: the context of glucose (Glu) and mitochondrial respiratory enzyme activity including complex I, complex II, complex III, complex V and cytochrome c (Cyt c) enzyme activity etc. Data extraction and evaluation of risk of bias will be operated by two researchers independently. The SYstematic Review Centre for Laboratory animal Experimentation (SYRCLE) tool will be utilized to examine the risk of bias. Review Manager 5.3 and Stata.12 software will be used for data synthesis.

Discussion: Numerous animal experiments have been conducted and investigated the underlying mechanism of acupuncture in brain diseases. We will retrieve the current animal experiments associated with the mechanism of acupuncture and perform a SR to provide a robust evidence for acupuncture improving ATP activity in brain diseases.

Systematic review registration: The registration number is CRD 42020184971.

Introduction

Adenosine triphosphate (ATP) is the primary energy currency of all cells [1], governing the energy-producing and energy-demanding process. The mechanism of ATP synthesis is correlated with glucose. Glucose can be catabolized in 3 processes to produce ATP, that is glycolysis, tricarboxylic acid cycle (TCA), and oxidative phosphorylation. In general, oxidative phosphorylation is occurred in mitochondria and completed by the respiratory chain complexes [complex I, complex II, complex III, complex V and cytochrome c (Cyt c) enzyme] [2]. In addition, an electrochemical gradient occurred in the mitochondria

membrane could be generated by the low concentration of Ca 2^{+} in the matrix and be regulated by Na^{+}-k^{+}-ATPase. (Fig. 1).

Figure 1 The mechanism of ATP synthesis. Glucose is main source of energy, which can be catabolized in the 3 processes to produce ATP, that is glycolysis, tricarboxylic acid cycle (TCA), and oxidative phosphorylation. Oxidative phosphorylation was usually completed by the respiratory chain complexes, which contains complex I, complex II, complex III, complex V and cytochrome c (Cyt c).

Brain is a high energy-consuming organ [3]. Some findings indicated that it is highly depended on ATP suppling energy to maintain brain function. In the healthy brain, researchers [4, 5, 6] have found that ATP can control energy transduction, as well as mediate the metabolic reactions, improve the post-translational modifications and regulate the signal transduction. ATP depletion may bring about the shortage of energy for brain working, consequently leading to the occurrence of a series of brain diseases, such as stroke, Alzheimer’s disease (AD), epilepsy and so on. Typically, when the ability of astrocytes to generate ATP is impaired due to dysfunctional mitochondria, it tends to increase the occurrence of AD [7]. In addition, ATP plays a key role in the cascade reaction of ischemia and reperfusion. Once ATP depletion occurs, cell damage in brain can lead to cell death due to necrosis or apoptosis [8, 9]. Guan [10] and Zhen [11] et al. both pointed out that the decrease of ATP and lacking of nutrient and oxygen are the main cause of cell death and tissue infarction after ischemic stroke.

Brain disease is comprised of a spectrum of brain disorders that are developmental (e.g., autism and mental retardation), neuropsychiatric (e.g., depression and addiction), and neurodegenerative (e.g., AD and Parkinson’s disease [PD]) [12]. In terms of disability-adjusted life years, brain disfunction resulting from brain disease accounts for more than 6.3% of the global disease burden [13], the proportion of which is projected to increase by 12% from 2005 to 2030 reported by the World Health Organization (WHO) [14].

Acupuncture, as a classic treatment in traditional Chinese medicine (TCM), has been identified that it is a relatively safe treatment with less side effects [15, 16]. Globally, it is becoming more and more popular as a complementary and alternative treatment for brain diseases. Some findings have showed that it has a definite therapeutic effect for brain diseases, such as stroke [17, 18, 19], AD [20, 21, 22], PD [23, 24, 25], depression [26, 27] etc. For example, Qi Huang et al [28] conducted a meta-analysis and found that acupuncture could improve clinical efficacy rate, Mini-Mental State Examination score, Ability of Daily Living Scale score and Alzheimer's Disease Assessment Scale-Cognition score in AD patients. The results of a meta-analysis [29] showed that acupuncture was an effective treatment for patients with depression. In addition, Yonghui Hong and her colleagues [30] found that acupuncture was beneficial to improve the motor function and the ability of daily living of patients with stroke. However, application of acupuncture in brain diseases is to some extent limited owing to lacking robust evidence of clear underlying mechanisms.

Recently, some animal experiments findings indicated that acupuncture tended to increase the release of ATP. In 2009, Autonomic Neuroscience Centre from Royal Free and University College Medical School [31] proposed that boosting ATP release may be a novel hypothesis for understanding the underlying mechanism of acupuncture. Zhong et. al. [32] reported that an increase of Na^{+}-k^{+}-ATPase activity was found in the acupuncture group of cerebral ischemia and reperfusion injury rats. Suotang Kou [33] et. al. has concluded that acupuncture can upregulate ATP activity by increasing Na^{+}-k^{+}-ATPase activity and Ca^{2+}-ATP activity in AD rats. Dai et al. [34] reported that Adenosine levels in the electroacupuncture group were greater than those of the sham and control groups in middle cerebral artery occlusion (MCAO) rats. These animal experiments indicated that the underlying mechanism of acupuncture shares correlation with ATP release in brain diseases.

Robust evidence from animal experiments may provide a reliable theory for clinical practice [35, 36]. For the potential values, such as promoting the development of basic research and providing a robust evidence to translate the achievement of basic research to clinical application in acupuncture for brain diseases, we attempt to conduct a SR/meta-analysis of relevant animal experiments to clarify the effect of acupuncture improving ATP activity in brain diseases.

Method

Review question

The primary research question for this review is: can we provide a reliable, robust and evidence-based conclusion from animal experiments to identify that acupuncture may increase the ATP activity in brain disease?

The secondary research question is: which factors would influence the results of acupuncture for ATP release?

Protocol registration and reporting

This project has been registered on the International Prospective Register of Systematic Review (PROSPERO) platform, and the registration number is CRD 42020184971. The reporting of this protocol has been in accordance with the reporting guidance provided in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) statement [37]. The details have been shown in additional file 1.

Search strategy

We will systematically retrieve PubMed, Embase, web of Science, the China National Knowledge Infrastructure (CNKI), the Chinese Science and Technology Periodical Database (VIP) and Wan Fang database from the inception dates to July 25, 2020. MeSH terms and free-text terms will be employed during search. Important Search terms will include: brain disease, basal ganglia diseases, hypothalamic

diseases, brain abscess, brain damage, brain neoplasms, acupuncture, needle, manual acupuncture, electroacupuncture, ATP, adenosine triphosphate, energy, mitochondrial respiratory enzyme and so on. The full search strategy was listed in additional file 2. There will be no limitation to language. In addition, we will perform additional search to ensure that more eligible studies can be retrieved, such as citation searches, contacting experts, and manual searches. Literature retrieval will be carried out independently by two researchers (SLH/ZHL).

Inclusion and exclusion criteria

Studies will be included in this analysis if satisfied with the following requirements: (□) study design: controlled studies with a separate control group. (□) animals: animal studies correlated with brain diseases. There is no restricts for animals and model establishment methods. (□) inventions: all timings, frequencies and durations of acupuncture treatment (electroacupuncture or traditional manual acupuncture) will be eligible for inclusion. (□) comparison: model group will be set as comparison. (□) outcomes: the primary outcomes are ATP activity, ATP content, Na^+-k^+-ATPase activity, and Ca^{2+} activity. Secondary outcomes are the context of glucose (Glu) and mitochondrial respiratory enzyme activity including complex I, complex II, complex III, complex V and cytochrome c (Cyt c) enzyme activity etc.

Studies will be excluded if met any of the following criteria: (□) duplicated articles, case reports, review articles or letters; (□) lack of sufficient data or information; (□) comparison of different types of acupuncture; (□) interventions such as ear acupuncture, tongue acupuncture, scalp acupuncture and catgut embedding therapy. Inclusion and exclusion criteria for this study has been shown in Table 1.

Table 1

inclusion and exclusion criteria for the research questions.

Inclusion criteria	Exclusion criteria
Animals: animal studies correlated with brain disease will be included. And there is no restricts for animals and model establishment methods. **Inventions:** all timings, frequencies and durations of acupuncture treatment will be eligible for inclusion. **Comparison:** model group of each study will be utilized as comparison. **Outcomes:** the primary outcomes are ATP activity, ATP content, Na^{+}-k^{-}ATPase activity, and Ca^{2+} activity. Secondary outcomes are the context of glucose (Glu) and mitochondrial respiratory enzyme activity including complex Ⅰ, complex Ⅱ, complex Ⅲ, complex V and cytochrome c (Cyt c) enzyme activity. **Study design:** controlled studies with a separate control group **Language** No limitations	(□) duplicated articles, case reports, review articles or letters; (□) lack of sufficient data or information; (□) Comparison of different type acupuncture.

Data management and data extraction

We will use Endnote X7 (Bod 7072, Thomson Reuters) to perform the data management. After eliminating duplications, two researchers will independently screen titles and abstracts for potentially relevant studies. Full text of these reviews will be downloaded and read for eligible included studies based on inclusion and exclusion criteria. Two researchers will cross-check after completion to avoid mis-entry. Any discrepancies will be discussed by a third reviewer.

Two researchers (YLP/ZYL) will independently complete the data extraction. Discrepancies should be discussed with a third reviewer (LJ). A data extraction form would be developed in advance using excel, covering: (□) General information (title, author, country and language); (□) Study characteristics (disease, species of rats, number of animals, model establishment, (types, timings, frequencies and durations of acupuncture)); (□) Outcomes.

Evaluation of risk of bias

The SYstematic Review Centre for Laboratory animal Experimentation (SYRCLE) is an adapted version of the Cochrane Risk of Bias tool and has been adjusted for aspects of bias that play a specific role in animal intervention studies [38]. We will assess the risk of bias of the included studies with SYRCLE tool by two independently reviewers (ZDL/LYX). This instrument addressed 10 types of bias: sequence generation, baseline characteristics, allocation concealment, random housing, blinding of caregivers and/or investigators, random outcome assessment; blinding of outcome assessor, incomplete outcome data, selective outcome reporting and other sources of bias. Each item will be rated as “yes” (low risk of bias), “no” (high risk of bias) and “unclear” (if insufficient details are obtained). We will cross check to eliminate the mis-entry. Discrepancies will be discussed with a third reviewer (LJ).

Statistical analysis

Descriptive syntheses

Study characteristic and findings of included literatures will be summarized. The results will be presented in a tabular format.

Meta-analyses

We will analyze the extracted data using Review Manager 5.3 and Stata.12 software. Since the major outcomes are continuous variables, the mean and standard deviation will be calculated with 95% confidence interval (CI). Heterogeneity will be tested using the *Q*-test and I^2 test (I^2<25%–low, 25-50%–moderate, and >50%–high degree of heterogeneity). Given heterogeneity is inevitable across studies, random effects meta-analysis will be used to synthesize results. Pooled results will be evaluated and a 2-sided *P* value<0.05 is considered to indicate statistical significance.

Meta-regression and subgroup analysis

Meta-regression and subgroup analysis will be utilized to identify the source of heterogeneity based as follows: the species of animals, the category of brain diseases, the method of model establishment and the timings, frequencies and durations of acupuncture.

sensitivity analysis

We plan to conduct sensitivity analysis to clarify the robustness of conclusion. If a high heterogeneity existed, we will include or exclude the studies where there is some ambiguity as to whether they meet the inclusion criteria.

Publication bias

If there are 10 or more eligible studies included, we will use funnel plot and egger’s test to assess the publication bias.

Reporting

We plan to follow with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (http://www.prisma-statement.org/) to produce a flow chart (Fig.2) and to report our results. Reasons for exclusion will also be listed.

Amendments

If there are any amendments to this protocol, we will reflect in edits to the PROSPERO registration, and present with the findings of the review.

Discussion

With an aging population, the number of patients for brain diseases tends to be growing which may lead to an urgent of effective, promotional and complementary treatment. Under this situation, acupuncture has become more and more popular and has been identified as a potential effect for brain disease. However, the application of acupuncture is certain limited due to lacking evidence of underlying mechanism. Fortunately, since an influential commentary firstly set out the scientific rational of animal studies in Lancet in 2002[39], a global awareness of merits of SRs of animal studies has been increased rapidly.

Therefore, the purpose of this study is to clarify the hypothesized theory in animal experiments that acupuncture may increase ATP activity to relieve symptoms of brain diseases. We will make a comprehensive search to ensure the results more convincing. In addition, we will publish the results of this SR and meta-analysis in a peer-reviewed journal. By means of conducting this study, we aim to provide a robust evidence of molecular mechanism for acupuncture and hope to promote the application of acupuncture in brain disease.

Strengths And Limitations

Firstly, this study has been registered on PROSPERO platform to keep process transparent and reduce the post hoc decision bias in methodology. Secondly, we will report this study in accordance with the PRISMA statement to ensure that our reporting is well compliance and readers can gain more information from our article. Thirdly, as far as we know, this study is the first SR and meta-analysis of animal experiments to summarize the effect of acupuncture for ATP in brain diseases.

Different types of brain diseases, methods of model establishment, and parameters of acupuncture may lead to certain heterogeneity. A subgroup analysis and meta-regression will be performed to solve this problem and identify the source of heterogeneity.

Abbreviations

ATP: adenosine triphosphate; SR: systematic review; PD: Parkinson disease; AD: Alzheimer’s disease; VD: vascular dementia; CNKI: the China National Knowledge Infrastructure (CNKI), VIP: the Chinese Science

and Technology Periodical Database; Glu: glucose; Cty c: cytochrome; SYRCLE: The SYstematic Review Centre for Laboratory animal Experimentation; WHO: the World Health Organization (WHO); TCM: traditional Chinese medicine (TCM); MCAO: middle cerebral artery occlusion (MCAO); PRISMA-P: the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols; PRISMA: the Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PROSPERO: the International Prospective Register of Systematic Review.

Declarations

Author's contribution

This manuscript was drafted by YLP, XXL and JYJ. ZYL, SLH, and ZHL was contributed to the design and the development of search strategy, ZDL and LYX to the development of methodology. LJ, GL and JRJ revised this review. All authors have read and approved the final manuscript.

Consent for publication

Not applicable.

Availability of data and materials

All data are fully available without restriction.

Competing interests

The authors declare that we have no competing interests.

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Figures

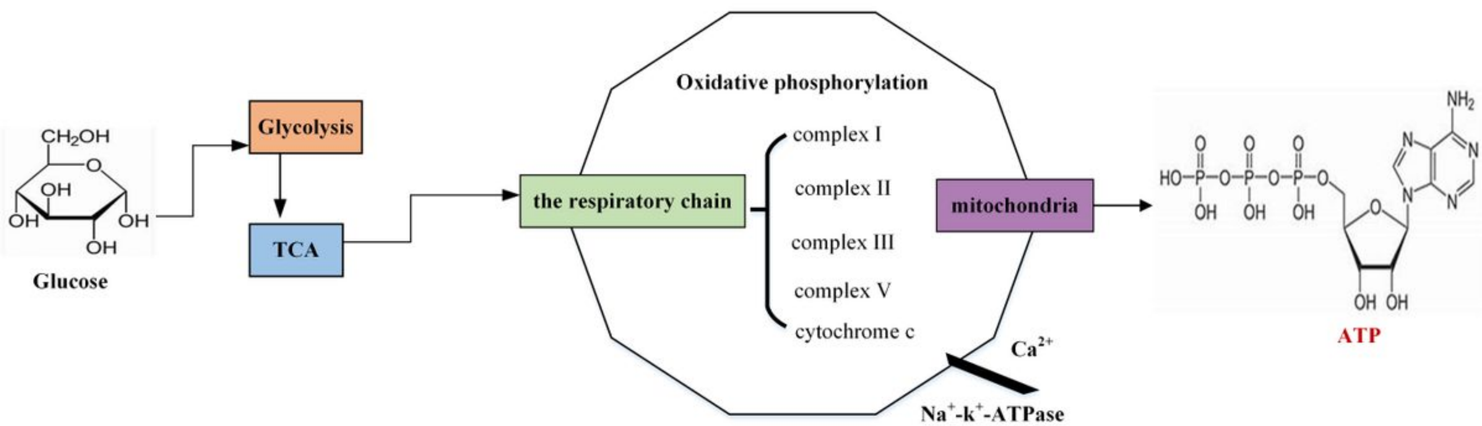

Figure 1

The mechanism of ATP synthesis. Glucose is main source of energy, which can be catabolized in the 3 processes to produce ATP, that is glycolysis, tricarboxylic acid cycle (TCA), and oxidative phosphorylation. Oxidative phosphorylation was usually completed by the respiratory chain complexes, which contains complex I, complex II, complex III, complex V and cytochrome c (Cyt c).

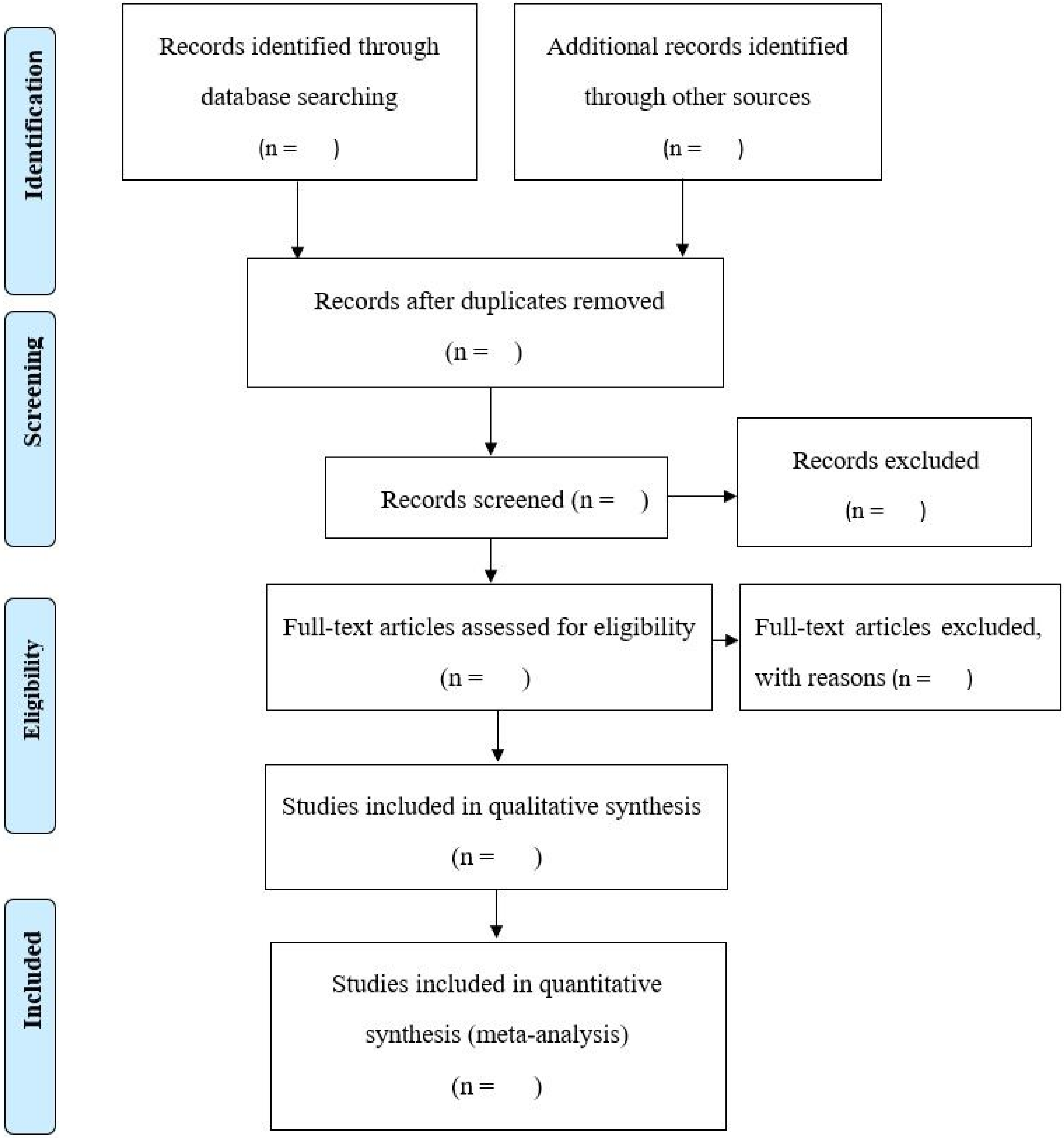

Figure 2

Flow diagram of the study selection process.

Supplementary Files

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