INPLASY PROTOCOL

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

Conflicts of interest:
None declared.

Risk factors associated with amyotrophic lateral sclerosis based on the past decade: a protocol for systematic review and meta-analysis

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Review question / Objective: **To identify and list the risk factors associated with the onset and progression of ALS.**
Condition being studied: **Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder affecting the upper and lower motor neurons in the spinal bulb, cerebral cortex, and spinal cord. The clinical processing symptoms accompany muscle atrophy, fasciculation, and fatigue of limbs, which can lead to general paralysis and death from respiratory failure within 3-5 years after the onset of this disease. Though the pathogenesis of ALS is still unclear, exploring the associations between risk factors and ALS can provide reliable evidence to find the pathogenesis in the future. This meta-analysis aims to synthesize all related risk factors on ALS, comprehensively understand this disease, and provide clues to mechanism research and clinicians.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 28 September 2022 and was last updated on 19 October 2022 (registration number INPLASY202290118).

INTRODUCTION

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onset of this disease. Though the pathogenesis of ALS is still unclear, exploring the associations between risk factors and ALS can provide reliable evidence to find the pathogenesis in the future. This meta-analysis aims to synthesize all related risk factors on ALS, comprehensively understand this disease, and provide clues to mechanism research and clinicians.

METHODS

Search strategy: We will systematically search the following electronic databases: PubMed, EMBASE, Web of Science, Cochrane library, and Scopus. Meanwhile, we will comprehensively search clinical trials, which are ongoing via the WHO International Clinical Trials Registry Platform (WHO ICTRP) and ClinicalTrials.gov. Preprint servers (such as medRxiv and Research Square) will also be searched for unpublished data. We limit the retrieval time to January 2012 to June 2022. The language of included studies is reported English. The keywords contain: 'Amyotrophic Lateral Sclerosis,' 'risk factors,' 'case-control studies,' 'cross-sectional studies,' and 'Cohort Studies.' The search strategy of PubMed is shown in Table 1. The rest of the databases comply in the same way.

Participant or population: Participants were diagnosed with ALS by professional medical institutions.

Intervention: Risk factors for ALS, regardless of risky or protective.

Comparator: Healthy dwellers will be included as the control group for participants not having ALS or neurodegenerative diseases.

Study designs to be included: Observational studies, including case-control, cohort, and cross-sectional studies, will be included to perform the meta-analysis. The characteristics of included studies reported one risk factor least that has a quantitative association with ALS onset or progression.

Eligibility criteria: Observational studies, including case-control, cohort, and cross-sectional studies, will be included to perform the meta-analysis. The characteristics of included studies reported one risk factor least that has a quantitative association with ALS onset or progression. We will search observational studies enrolling participants as follows: 1. Participants were diagnosed with ALS by professional medical institutions. 2. ALS patients will be included in the study regardless of nation, age, gender, or race. Risk factors for ALS, regardless of risky or protective will be regarded as exposures. Healthy dwellers will be included as the control group for participants not having ALS or neurodegenerative diseases.This study aims to identify the risky or protective factors associated with ALS. Hence, the outcome is ALS.

Information sources: We will systematically search the following electronic databases: PubMed, EMBASE, Web of Science, Cochrane library, and Scopus. Meanwhile, we will comprehensively search clinical trials, which are ongoing via the WHO International Clinical Trials Registry Platform (WHO ICTRP) and ClinicalTrials.gov. Preprint servers (such as medRxiv and Research Square) will also be searched for unpublished data. We performed a preliminary search and found a systematic review that reported all-related risk factors associated with ALS, but the last retrieved time was February 16, 2016. The retrieval time will be limited from January 2017 to June 2022. The language of included studies is reported in English. The primary words contain: 'Amyotrophic Lateral Sclerosis,' 'risk factors,' 'case-control studies,' 'cross-sectional studies,' and 'Cohort Studies.' The search strategy of PubMed is shown in Table 1. The rest of the databases comply in the sameway.

Main outcome(s): This study aims to identify the risky or protective factors associated with ALS. Hence, the outcome is ALS.

Quality assessment / Risk of bias analysis: Two independent reviewers will assess the

quality of case-control and cohort studies by the Newcastle-Ottawa scale (NOS). A case-control study in NOS involves three items: Selection, Comparability, and Exposure. In the selection and exposure categories items, only one star maximum can be awarded, and two stars maximum can be given in Comparability. The cohort study in NOS also consists of three items: Selection, Comparability, and Outcome. In the Selection and Outcome categories items, only one star maximum can be awarded, and two stars maximum can be given in Comparability. The quality is high if one study gains more than seven stars in NOS. Agency for Healthcare Research and Quality (AHRQ) will evaluate the quality of cross-sectional studies. Eleven items are listed in AHRQ. Two reviewers mark 'YES,' 'NO,' or 'Unclear' according to the specific description in the studies—one score for 'YES,' no score for 'No' or 'Unclear.' The quality of cross-sectional studies is high if gained more than eight scores. This systematic review will include high-quality studies for more reliable evidence.

Strategy of data synthesis: All risk factors for ALS will be extracted from original studies. If more than three observational studies reported a certain risk factor, we will perform meta-analyses based on this indicator. The primary outcome is the ORs of ALS by possible risk factors in case-control studies and RRs/HRs of ALS risk factors in cohort studies. I2 statistics will assess heterogeneity. I2 > 75% is recognized as significant heterogeneity, 50% < I2 ≤ 75% is recognized as moderate heterogeneity, 25% < I2 ≤50% is recognized as low heterogeneity, I^2 ≤ 25% was recognized homogeneity. We will use the fixed effects model if heterogeneity is low or homogeneous. Otherwise, we choose the random effects model. The statistical analyses mentioned above will be operated by STATA14.0 and Review manager5.3 software.

Subgroup analysis: If data are enough and available, subgroup analyses will be operated by nations and type of studies (case-control studies vs. cohort studies vs. cross-sectional studies)—adequate adjustment for risk factors and whether the study adjusted for confounders.

Sensitivity analysis: Sensitivity analysis will be performed to detect the source of heterogeneity. Every time we remove a potential heterogeneous study, we must explain why. Publication bias is supposed to assess by the Funnel plot (N≥10). Begg's test and Egger's test detected the symmetry of the study. The statistical analyses mentioned above will be operated by STATA14.0 and Review manager5.3 software.

Language restriction: English.

Country(ies) involved: China.

Keywords: amyotrophic lateral sclerosis; risk factors; protocol; systematic review.

Contributions of each author:

Author 1 - Qiaochu Zhu drafted the manuscript.
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