

# INPLASY PROTOCOL

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None declared.

## Environmental toxic metal contaminants and risk of stroke: a systematic review and meta-analysis

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**Review question / Objective:** P: human; I: heavy metal; C: stroke patients vs normal; O: stroke. We included studies that fulfilled the following eligibility criteria: human data, original study, cross-sectional, case-control, or cohort design, reported 5 heavy metal exposures with stroke.

**Condition being studied:** Environmental toxic metal contaminants and risk of stroke.

**Quality assessment /Risk of bias analysis:** Two independent reviewers (B.Q.J. and G.Y.) used the Newcastle-Ottawa scale for case-control and cohort studies to assess quality. The Newcastle-Ottawa Scale uses a series of questions to assess the quality of a study, with a score more than 7 were indicated to be of high quality (maximum score of 9). The Quality Assessment Tool for Cross-Sectional Studies used to assess the quality of Cross-sectional studies in three domains (poor, fair, and good).

**INPLASY registration number:** This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 01 August 2021 and was last updated on 01 August 2021 (registration number INPLASY202180002).

### INTRODUCTION

**Review question / Objective:** P: human; I: heavy metal; C: stroke patients vs normal; O: stroke. We included studies that fulfilled the following eligibility criteria: human data, original study, cross-sectional, case-control, or cohort design, reported 5 heavy metal exposures with stroke.

**Condition being studied:** Environmental toxic metal contaminants and risk of stroke.

### METHODS

**Search strategy:** We referenced the same searching strategy previously developed for mercury exposure and risk of

cardiovascular disease systematic review. We completed an extensive literature search through major database (PubMed, Embase, Cochrane) to find all published epidemiological studies evaluating the association between 5 heavy metal exposure and risk of stroke, and by the end of June 6, 2021. Free text and Medical Subject Headings (MeSH) terms “Arsenic” OR “Mercury” OR “Copper” OR “Cadmium” OR “Lead” AND “Stroke” AND “human”, as well as terms of other stroke, were used.

**Participant or population:** Human.

**Intervention:** Heavy metal exposure.

**Comparator:** Determination of heavy metals in cyclic products.

**Study designs to be included:** Original study, cross-sectional, case-control, or cohort design, reported 5 heavy metal exposures with stroke.

**Eligibility criteria:** We included studies that fulfilled the following eligibility criteria: human data, original study, cross-sectional, case-control, or cohort design, reported 5 heavy metal exposures with stroke.

**Information sources:** Search through major database (PubMed, Embase, Cochrane).

**Main outcome(s):** Stroke.

**Data management:** Noteexpress.

**Quality assessment / Risk of bias analysis:** Two independent reviewers (B.Q.J. and G.Y.) used the Newcastle-Ottawa scale for case-control and cohort studies to assess quality. The Newcastle-Ottawa Scale uses a series of questions to assess the quality of a study, with a score more than 7 were indicated to be of high quality (maximum score of 9). The Quality Assessment Tool for Cross-Sectional Studies used to assess the quality of Cross-sectional studies in three domains (poor, fair, and good).

**Strategy of data synthesis:** For studies that reported stroke, we obtained odds ratios (ORs), hazard ratios (HRs), relative risks

(RRs), and mean of the published data. For the purpose of analysis, ORs or HRs were transformed RRs, relative risk of the comparison of the top versus bottom of the distribution were extracted from each study. For summary purposes, we used an inverse-variance weighted random-effects model to calculate summary relative risks comparing the highest and lowest categories of metal exposure from individual studies. We quantified heterogeneity of findings across individual studies with standard  $\chi^2$  tests and the I<sup>2</sup> statistic. We combine the results of the products of the circulatory system.

**Subgroup analysis:** We used generalised least-squares trend estimation (GLST) analysis to perform dose-response meta-analyses. For studies that reported stroke or ischemic stroke or hemorrhagic stroke results for at least three quantitative exposure categories, dose-response meta-analysis was performed. For stroke, we first plotted the RRs by exposure category from each study. When the article did not provide a median or mean exposure level per category, we assigned the midpoint between the upper and lower limits of each category as the exposure level. If no lower or upper bound was reported for the lowest and highest categories, respectively, we assumed that the boundary had the same range as the nearest category. To control for bias estimates, the article was asked to include each study in the baseline reference dose (first row of each study). Besides linear regression, potential nonlinear dose-response relationships were investigated by simulating toxic metal levels in restricted cubic splines. In order to calculate P value for nonlinearity by testing the null hypothesis, a series of transfections was performed. Due to the absence of some data, it is difficult to draw an accurate dosing response analysis diagram. Robust-error meta-regression (REMR) method was used to draw a rough diagram, and copper data were used to test the results, and the results were consistent. We use Stata version 16 (Stata Corp, College Station, TX) to perform all analyses.

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**Sensitivity analysis:** Little variation in pollutant risk estimates can be explained by any recorded study level characteristics. Among individuals with different exposure types (blood vs urine), there were no significant differences in relative risk of stroke disease, adjusted for possible confounders considered in the included studies, geographic location, baseline health status, or study size. Risk estimates were comparable between studies where there was no evidence of significant heterogeneity between urinary metal levels and blood levels.

**Language:** English.

**Country(ies) involved:** China.

**Keywords:** toxic metal, stroke, meta-analysis.

**Contributions of each author:**

**Author 1 - Bao Qiangji -** Study concept and design, acquisition of data, analysis and interpretation, critical revision of the manuscript for important intellectual content.

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