INPLASY PROTOCOL

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None declared.

Metformin use is associated with reduced risk of cognitive impairment in adults with diabetes mellitus? a systematic review and meta-analysis

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Review question / Objective: **How metformin impact on cognition in adluts with diabetes? P: diabetes E: metfotmin C: not using metformin or other antidiabetics Outcome: cognition Study: observational studiesControversy exists regarding the influence of metformin, which is related to both increased and decreased the incidence of cognitive impairment. Therefore, this meta-analysis was conducted to determine the relationship between metformin therapy and cognitive function in patients with diabetes.**
Information sources: **Electric databases (PubMed, EMBASE, PsycINFO, Cochrane Library and Web of Science) respectively were manually searched by two investigators from their inception date until March 1, 2022.Data of all eligible studies were extracted by two investigators. If there are any divergences, discussion will be carried out between the same investigators. A senior author will be consulted, if need. In order to acquire missing data of included observational study designs, we will contact the first and/or corresponding authors.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 11 May 2022 and was last updated on 11 May 2022 (registration number INPLASY202250065).

INTRODUCTION

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between metformin therapy and cognitive function in patients with diabetes.

Condition being studied: Diabetes, cognitive performance with oral metformin.

METHODS

Participant or population: Adults with diabetes (as diagnosed by a clinician, or using any recognized diagnostic criteria) will be included.

Intervention: studies in which participants received metformin monotherapy at any dose for any duration were included.

Comparator: any study that included a control group in which participants were not being treated with metformin was eligible for inclusion. This included people not receiving any therapy as well as those receiving other treatments for diabetes.

Study designs to be included: Only published observational study designs (including cohort, case-control or cross-sectional studies) examining cognitive performance compared oral metformin treatment with other antidiabetics were eligible for inclusion. We included detailed meeting summary information. Case reports/series, randomized controlled trial, meta-analyses, and systematic reviews were excluded.

Eligibility criteria: This systematic review was conducted according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines.

Information sources: Electric databases (PubMed, EMBASE, PsycINFO, Cochrane Library and Web of Science) respectively were manually searched by two investigators from their inception date until March 1, 2022.Data of all eligible studies were extracted by two investigators. If there are any divergences, discussion will be carried out between the same investigators. A senior author will be consulted, if need. In order to acquire missing data of included observational study designs, we will contact the first and/or corresponding authors.

Main outcome(s): Change in cognitive scale score from baseline to the last available follow-up, measured using the Mini-Mental State Examination. There was no cognitive impairment in the outcome (measured from randomisation). The correlation between metformin and cognition was determined by scale assessment.The main outcome of this meta-analysis on the relationship between metformin and cognitive dysfunction.

Quality assessment / Risk of bias analysis: Two investigators will independently assess the study quality. The evaluation criteria for an observational study of the Agency for Healthcare Research and Quality (AHRQ) were used to evaluate the cross-sectional study , and the Newcastle–Ottawa Quality Assessment Scale (NOS) was used for the cohort study and case–control study. Publication bias exists when the Begg's funnel plot shows asymmetry or when the P-value of the Egger's test is less than 0·05.

Strategy of data synthesis: Where possible, odds ratios (ORs), Hazard Ratio (HR) were pooled using the inverse variance method with a random effects model from Stata SE 16.0. Maximally adjusted data were included in all analyses. For one study that reported OR and showed that their incidence ratio was constant, OR was substituted for HR which could not otherwise be calculated. Heterogeneity was assessed using the $\chi 2$ and I^2 tests. Analysis of publication bias was planned, Sensitivity analyses have been performed based on control groups utilized, diagnostic criteria and to identify sources of heterogeneity.

Subgroup analysis: Subgroup were conducted to explore sources of heterogeneity. The following categorical variables were analyzed in subgroup analyses: (1) dementia: diabetes with oral MET vs. diabetes without oral MET. (2) Alzheimer's disease: diabetes with oral MET vs. diabetes without oral MET.

Sensitivity analysis: Sensitivity analysis was conducted by moving each study individually. All statistical significance was set at P < 0.05 (two-tailed).

Language: English.

Country(ies) involved: China.

Keywords: Metformin; dementia; Alzheimer's disease; diabetes; cognitive dysfunction.

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