Metformin therapy and cognitive dysfunction in patients with type 2 diabetes
A meta-analysis and systematic review

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Abstract
Background: Type 2 diabetes (T2D) is a risk factor for cognitive dysfunction. The relationship between metformin therapy and cognitive function in patients with T2D is unknown. Therefore, we determined the relationship between metformin therapy and cognitive function in patients with T2D using a meta-analysis.

Methods: We systematically searched the Cochrane library, PubMed, and Embase to identify studies showing correlations, and we calculated hazard ratios (HRs).

Results: We identified 10 studies including 254,679 participants. Metformin significantly reduced the occurrence of cognitive dysfunction in patients with T2D (HR 0.90; 95% CI [0.88, 0.92]). Compared with other hypoglycemic drugs, sulfonylureas also improved cognitive dysfunction (HR 0.92; 95% CI [0.88, 0.95]). Thiazolidinediones gave no statistically significant improvement in cognitive dysfunction (HR 0.97; 95% CI [0.87, 1.07]). The use of insulin aggravated cognitive dysfunction (HR 1.34; 95% CI [1.24, 1.43]). In the subgroup analysis of various regions controlling for age, gender, education, diabetes course, complications, metformin administration and dosage, and follow-up time, metformin significantly improved cognitive dysfunction in patients in the Americas and Europe (HR 0.69; 95% CI [0.63, 0.74], (HR 0.71; 95% CI [0.66, 0.76], respectively), while metformin did not significantly improve cognitive dysfunction in Asian patients (HR 0.99; 95% CI [0.96, 1.01]).

Conclusions: Metformin significantly improved cognitive dysfunction in patients with T2D. Sulfonylureas also improved cognitive dysfunction. Thiazolidinediones had no significant effect on cognitive dysfunction. The use of insulin aggravated cognitive dysfunction. Metformin improved cognitive dysfunction more significantly in patients in the Americas and Europe than in Asia.

Abbreviations: CIs = confidence intervals, HR = hazard ratio, NOS = newcastle–ottawa scale, RR = relative risk, T2D = type 2 diabetes.

Keywords: cognitive dysfunction, meta-analysis, metformin, type 2 diabetes

1. Introduction
Type 2 diabetes (T2D) is a risk factor for cognitive dysfunction, including cognitive decline, mild cognitive impairment, and dementia.\cite{1,2} Cognitive dysfunction is defined as the development of several cognitive deficits that cause severe social and occupational dysfunction, representing significant declines from previous functional levels.\cite{3} Several investigators reported cognitive dysfunction in patients with T2D. A strong relationship between the two conditions has been demonstrated.\cite{4} As many as 60\% of patients with T2D suffer from cognitive dysfunction.\cite{5,6}

In the previous studies, the relationship between metformin and cognitive dysfunction in patients with T2D is controversial. Several studies found that metformin improved cognitive abilities\cite{7,8} and neurons survival rate.\cite{9,12} The mechanism include activating the mTOR pathway and tau hyperphosphorylation, which thereby inhibits hepatic gluconeogenesis, reduces insulin resistance, and increases insulin sensitivity, while inhibiting the inflammatory status.\cite{13} However, other studies have suggested that metformin in patients with T2D may increase the risk of cognitive dysfunction.\cite{14,15} Therefore, we performed a meta-analysis aimed to evaluate the relationship between the use of metformin and cognitive outcomes in patients with T2D.
2. Materials and methods

2.1. Ethical approval

This study was performed based on guidelines governing the creation of meta-analyses of observational and epidemiological studies. No ethics committee approval was required, because only published research data were analyzed.

2.2. Literature retrieval and research selection

Two investigators (Qing-Qing Zhang and Wen-Shan Li) independently searched the Cochrane Library, PubMed, and Embase for all studies that reported associations between metformin and cognitive dysfunction in patients with T2D (up to May 31, 2019). Three groups of keywords contain the Boolean operator “OR,” no language restriction was applied. To ensure a comprehensive search of the literature, we also reviewed the full bibliography of relevant publications, as well as the relevant reviews. When the required data were not clear or missing, we contacted the author.

Inclusion criteria were as follows:
1. all patients with T2D ≥18 years old, without a history of cognitive dysfunction;
2. Interventions included metformin;
3. the endpoint was cognitive dysfunction;
4. the studies were randomized controlled studies, or observational (prospective or retrospective cohort) studies. We included detailed meeting summary information. For studies using identical populations, the study with the longest follow-up or the largest number of patients was selected;
5. when the studies were conducted by the same author, different subjects were chosen.

The exclusion criteria were as follows:
1. other types of diabetes or patients with T2D and a history of cognitive dysfunction;
2. case-control, cross-sectional studies, case reports, case series, and letters;
3. Hazard ratio (HR) data after metformin use could not be obtained.

2.3. Data extraction and quality assessment

The abstractors independently screened titles and abstracts of the studies and reviewed the full texts of the selected titles and abstracts based on the selection criteria. For each study, the following data were recorded: first author, year of publication, geographical location, study design (observational cohort or randomized controlled study), participants (gender, age, sample size, and history of cognitive impairment), years of follow-up, presence or absence of diabetic complications, and maximum adjusted covariates and hazard risks (HRs) with 95% confidence intervals (CIs). If there was an adjustment of HRs, the most fully adjusted HRs would be extracted. Any disagreements or discrepancies were resolved through consensus. HR was a common indicator in this study, and relative risk (RR) was considered to be equal to HR. All results were expressed as HRs. Often, the original author was contacted to discuss any ambiguity or missing information. Newcastle–Ottawa Scale (NOS) items were employed to evaluate the quality of the article. NOS score ≥6 stars was defined as high quality, and NOS score <6 stars was defined as low quality.

2.4. Statistical analysis

The HR was a common indicator in the studies. Forest plots were drawn to evaluate HRs and the corresponding 95% CIs. HR heterogeneity was evaluated using Cochrane Q statistics (P < .1 was considered statistical heterogeneity), and I^2 statistics (25%, 50%, and 75% were considered to represent low, medium, and high heterogeneity, respectively). To provide a more conservative estimation of the pooled HRs, random rather than fixed effect models were adopted, because the former can explain more about heterogeneity between studies. When heterogeneity was high, subgroup analysis and sensitivity analysis were conducted to explore the sources of heterogeneity. The Beggs test was used to evaluate potential publication bias. P < .05 indicated statistical significance. All statistical analyses were carried out using Stata version 12.0.

3. Results

3.1. Data selection

There were 545 studies identified initially in the Cochrane Library (n = 7), PubMed (n = 26), and Embase (n = 512) (Fig. 1). Twelve articles were retrieved manually, none of which met the inclusion criteria. A total of 510 studies were excluded from 545 studies based on title or abstract, including 17 duplicate studies and eight case reports. Full texts of 35 eligible studies were subsequently reviewed, and 21 lacked the HRs indicators required for this study and were excluded. For the remaining 14 studies, we conducted a more detailed review, including four studies that were excluded for the following reasons:
1. the publication type (one was a systematic review);
2. the study object (one was Alzheimer’s patients);
3. the outcome that was not cognitive dysfunction (one was associated with hypoglycemia causing cognitive dysfunction); and
4. missing data (one was unable to provide raw data).

Finally, ten studies (nine retrospective cohort studies and one prospective cohort study) were included in this meta-analysis, including 254,679 participants.

Table 1 provides detailed characteristics of the study. In the 10 included studies, the effects of various types of hypoglycemic agents on cognitive dysfunction in patients with T2D and the effects of metformin on cognitive dysfunction in patients with T2D in various regions were compared. Table 2 shows that the quality of the included reports was acceptable, as all studies scored no <6 stars on NOS.

3.2. Meta-analysis

For 10 articles including 254,679 patients, the forest plot showed that metformin significantly improved cognitive dysfunction in patients with T2D (HR 0.90, 95% CI [0.88, 0.92]) (Fig. 2). I^2 = 95.3%, with high heterogeneity, possibly related to the small sample size. Sensitivity analysis and subgroup analysis were conducted.
3.3. Sensitivity analysis
After excluding each study one by one, the remaining results were combined to measure the extent of changes in the combined results, so as to conduct sensitivity analysis of the research results. Sensitivity analysis results showed that the combined results of metformin on the relationship of cognitive dysfunction in T2D patients were highly stable (Fig. 3). After excluding each study one by one, no significant effect was found on the combined results.

3.4. Subgroup analysis
3.4.1. Metformin and other types of hypoglycemic agents.
Ten articles included 254,679 patients treated with metformin, three articles included 90,898 patients treated with thiazolidinediones, and six articles included 235,505 patients treated with sulfonylureas. Sulfonylureas improved cognitive impairment (HR 0.92; 95% CI [0.88, 0.95]), metformin improved cognitive dysfunction slightly better than sulfonylureas. Thiazolidinediones had no significant effect on cognitive function (HR 0.97; 95% CI [0.87, 1.07]) (Fig. 4).

3.4.2. Metformin and insulin.
In the four articles, including 23,873 patients, the use of insulin aggravated cognitive dysfunction associated with T2D (HR 1.34; 95% CI [1.24, 1.43]). Metformin improved cognitive function (HR 0.72; 95% CI [0.67, 0.76]) (Fig. 5).

3.4.3. Patients taking metformin in different regions.
The 10 articles included 44,237 in the Americas, 200,812 in Asia, and 9630 in Europe. Metformin significantly improved cognitive dysfunction in the patients in the Americas and Europe (HR 0.69; 95% CI [0.63, 0.74]), (HR 0.71; 95% CI [0.66, 0.76]), while metformin did not significantly improve cognitive dysfunction in Asian patients (HR 0.99; 95% CI [0.96, 1.01]) (Fig. 6).

3.5. Publication bias
To check whether there was publication deviation in the included studies, the Begg test funnel graph was applied. In the analysis of the relationship between metformin and cognitive dysfunction in patients with T2D, no significant deviation was observed, and the distribution of funnel plot was approximately symmetrical (Fig. 7).

Figure 1. Flow chart of search result.
Table 1

| Author                     | Year | Geographic area | Study design | Follow-up, y | Patients, n | Female, % | Age, y | Control group | T2D complications | Maximum adjusted covariate |
|----------------------------|------|-----------------|--------------|--------------|-------------|-----------|-------|---------------|---------------------|---------------------------|
| Alexandra M.V. Wennberg    | 2018 | Americas        | Re cohort    | 455 day      | 508         | 40.5%     | 74.6 (70.7, 80.5) | T2D who used Other oral medications OR Insulin only | NO | Age, sex, education, BMI, APOEε4, CCI, number of medications, T2D duration, age of T2D diagnosis, T2D complications, propensity score. |
| Anthony Liccini            | 2016 | Americas        | Re cohort    | 1 y          | 198         | NC        | 64.9 (±8.7)     | T2D who used sulfonylures only OR Insulin only | NO | Age, sex, education, HbA1C levels. |
| Ariela R. Orkaby           | 2017 | Americas        | Re cohort    | 5 y          | 28,640      | NC        | 73.5 (±5.9)     | T2D who used sulfonylures only OR Insulin only | NO | Race, body mass index, renal function, and hemoglobin A1c. |
| Chih-Cheng Hsu             | 2011 | Asia            | Re cohort    | 7 y          | 127,209     | 51.5%     | ≥50       | T2D who used sulfonylures only OR Metformin combination therapy OR Metformin combination therapy OR Metformin combination therapy OR Metformin combination therapy OR Metformin combination therapy | NO | Age group, gender, type of stroke, CCI score. |
| Eileen M. Moore            | 2013 | European        | Re cohort    | 0.5 y        | 1354        | 59.5%     | 73.8 (±8.3)     | T2D but no diabetes drug OR No-diabetes OR No-diabetes OR No-diabetes | NO | Age, sex, reported history of depression, and level of education. |
| Jens Bohlken               | 2018 | European        | Re cohort    | 4 y          | 8276        | 56.2%     | 79.7 (±6.9)     | T2D who used sulfonylures only OR Insulin only OR T2D only OR T2D only | NO | Mean HbA1c value prior to the index date, diabetes duration, co-medications, co-therapies. |
| Rachel Whitmer             | 2013 | Americas        | Re cohort    | 5 y          | 14,891      | NC        | ≥55       | T2D who used insulin only OR T2D only | NO | Age, race, education, diabetes duration. |
| Yi-Chun Kuan               | 2017 | Asia            | Re cohort    | 12 y         | 4651        | 49.7%     | 64.7 (±9.46)    | T2D but no diabetes drug OR No-diabetes | NO | Age, sex, CCI, aDCSI, comorbidity of hypertension, chronic kidney disease, hyperlipidemia, heart failure, arrhythmia, stroke, head injury, and CAD, medication of antidiebetic drug, antihypertensive drug. |
| Chin Cheng                 | 2012 | Asia            | Re cohort    | 5 y          | 67,731      | NC        | ≥55       | T2D who used sulfonylures only OR T2D only OR T2D only OR T2D only | NO | Age, race, education. |
| Naharci, M. I              | 2016 | Asia            | Re cohort    | 2 y          | 1221        | 69.5%     | 75.6 (±6.0)     | T2D but no diabetes drug | NO | Age, sex, BMI, MMSE scores, HbA1C levels. |

aDCSI = adapted diabetes complications severity index, BMI = body mass index, CAD = coronary artery disease, CCI = Charlson comorbidity index, HbA1c = hemoglobin A1c, MMSE = mini-mental state examination, T2D = type 2 diabetes.

Table 2

| Study (First author, Year) | Selection | Outcome |
|----------------------------|------------|---------|
|                            | Exposed cohort | Nonexposed cohort | Ascertainment of exposure | Outcome of interest | Comparability | Assessment of outcome | Length of followup | Adequacy of follow-up | Total |
| Alexandra M.V. Wennberg, 2018 | * | * | * | * | * | * | * | * | 7 |
| Anthony Liccini, 2016      | * | * | * | * | * | * | * | * | 8 |
| Ariela R. Orkaby, 2017     | * | * | * | * | * | * | * | * | 8 |
| Chih-Cheng Hsu, 2011       | * | * | * | * | * | * | * | * | 7 |
| Eileen M. Moore, 2013      | * | * | * | * | * | * | * | * | 9 |
| Jens Bohlken, 2018         | * | * | * | * | * | * | * | * | 9 |
| Rachel Whitmer, 2013       | * | * | * | * | * | * | * | * | 9 |
| Yi-Chun Kuan, 2017         | * | * | * | * | * | * | * | * | 9 |
| Chin Cheng, 2012           | * | * | * | * | * | * | * | * | 9 |
| Naharci, M. I, 2016        | * | * | * | * | * | * | * | * | 7 |

* Represent stars used in the Newcastle Ottawa Scale.
** Represents more control groups in the article, and the information provided in the article is more comprehensive.
Figure 2. Effects of metformin on cognitive dysfunction in patients with type 2 diabetes.

Figure 3. Sensitivity analysis of the effects of metformin on cognitive dysfunction in patients with type 2 diabetes.
4. Discussion

Type 2 diabetes is associated with cognitive dysfunction and the development of mild cognitive impairment. The mechanisms of this effect include inflammation, oxidative stress, vascular reaction (affecting the circulation of blood to the brain), increased cerebral β-amyloid peptide, cerebral insulin resistance, hyperinsulinemia, and the formation of advanced glycosylation end products. Scholars believe that several of these factors combine to cause cognitive dysfunction. Nevertheless, whether metformin reduces the incidence of cognitive dysfunction in patients with T2D remains controversial.

In our meta-analysis, we found that metformin reduced cognitive dysfunction in patients with T2D. Previous studies have also indicated that metformin may decrease the risk of developing cognitive dysfunction. Similarly, a separate study in an Australian population showed that metformin alone predicted a reduction in the risk for cognitive dysfunction incidence in T2D. There are several possible mechanisms explaining this effect. Studies have shown that metformin reduces insulin levels, improves inflammation and reduces thrombosis, reducing the risk of metabolic syndrome. It also improves insulin sensitivity, which has a potential protective effect on cognitive dysfunction. The most obvious mechanism by which metformin affects the development of cognitive dysfunction in patients with T2D is by preventing hyperinsulinemia that may lead to the formation of amyloid plaques in the brain and the onset of cognitive dysfunction.

Among the various hypoglycemic agents, this meta-analysis suggested that, compared with metformin, sulfonylureas improved cognitive impairment; however, metformin improved cognitive dysfunction slightly better than sulfonylureas. Orkaby et al reported that metformin had more neuroprotective effects than sulfonylureas, consistent with the results of the present study. One study reported that thiazolidinediones may improve cognitive performance. Nevertheless, its potential
cardiovascular adverse effects increase the risk of vascular cognitive dysfunction and Alzheimer’s disease. We found that thiazolidinedione hypoglycemic agents had no significantly greater effect than metformin in terms of improving cognitive function,[39,40] possibly because their adverse cardiovascular effects outweighed the potential benefits. This meta-analysis suggested that the use of insulin increased the risk of cognitive dysfunction in patients with T2D. Bohlken’s case–control study also showed that the use of insulin was a risk factor for exacerbation of cognitive dysfunction.[25]

Controlling for age, gender, education, diabetes course, complications, metformin administration and dosage, and follow-up time, metformin significantly improved cognitive dysfunction in patients in the Americas and Europe, while there was no significant effect in Asians. We speculate that this discrepancy may be attributable to varying lifestyles, eating habits, economic differences and education levels. There are no studies on the effect of metformin on cognitive dysfunction in patients with T2D in different regions.

We conclude that metformin therapy improves cognitive dysfunction in patients with T2D. It has potential to prevent cognitive dysfunction.

The following points support the stability of our conclusions. First, we conducted a comprehensive search of literature outside language constraints, requesting additional data from authors in cases of ambiguity. Second, data extraction was done by two independent investigators, and disputes were resolved via consensus. Third, we performed sensitivity analyses to assess the stability of the results. Fourth, to the best of our knowledge, this was the first study to analyze the relationship between metformin and cognitive impairment in patients with T2D in a large population. Fifth, this study included comparisons of metformin and insulin, as well as the comparison of metformin among people in various geographical regions, increasing the robustness of the conclusion. Sixth, to make the results more stable, the random model was adopted. Finally, objective criteria were used to evaluate the quality of the study. Our study scores were at least 6 (high quality).

5. Limitations
There are several potential limitations in our study. First, in patients with T2D, the relationship between metformin and cognitive function prognosis can change with age and duration of diabetes mellitus. Although the HRs collected were the result of multivariate adjustment, some confounding factors could not be excluded. Second, there was significant heterogeneity in the study, possibly due to differences in study design, sample

Figure 5. Comparison of the effects of metformin group and insulin group on cognitive dysfunction.
Figure 6. Comparison of the effects of patients taking metformin in different regions on cognitive dysfunction.

Figure 7. Funnel graph of the effects of metformin on cognitive dysfunction in patients with type 2 diabetes.
More randomized controlled trials are essential to validate and patients in the Americas and Europe than in patients in Asia. Metformin improved cognitive dysfunction more significantly. The use of insulin aggravates cognitive dysfunction. 6. Conclusions Metformin significantly reduces the incidence of cognitive dysfunction in patients with T2D. Sulfonylureas also improve cognitive dysfunction, but thiazolidinediones had no significant effect. The use of insulin aggravates cognitive dysfunction. Metformin improved cognitive dysfunction more significantly in patients in the Americas and Europe than in patients in Asia. More randomized controlled trials are essential to validate and support this conclusion.

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