Metformin and the risk of dementia based on an analysis of 396,332 participants

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Abstract

Background: AMPK has attracted widespread interest as a potential therapeutic target for age-related diseases, given its key role in controlling energy homeostasis. Metformin (Met) has historically been used to treat Type 2 diabetes and has been shown to counteract age-related diseases. However, studies regarding the relationship between Met and a variety of age-related classifications of cognitive decline have reported mixed findings.

Objective: To assess the potential effect of Met on the onset of dementia and discuss the possible biological mechanisms involved.

Methods: This study was registered in the PROSPERO database (CRD420201251468). PubMed, Embase, and Cochrane Library were searched from inception to 25 May 2021, for population-based cohort studies. Effect estimates with 95% confidence intervals (CIs) were pooled using the random-effects model. Meta-regression and subgroup analyses were performed to explore sources of heterogeneity and the stability of the results.

Results: Fourteen population-based cohort studies (17 individual comparisons) involving 396,332 participants were identified. Meta-analysis showed that Met exposure was significantly associated with reduced risk of all subtypes of dementias [relative risk (RR) = 0.79, 95% CI = 0.68–0.91; p < 0.001]. Conversely, no significant reduction in risk was observed for those who received Met monotherapy at the onset of vascular dementia (VD), Parkinson’s disease (PD), and Alzheimer’s disease (AD). The effect was more prominent in patients who had long-term Met exposure (≥4 years) [RR = 0.38, 95% CI = 0.32–0.46; p < 0.001], while no such significant effect was found with short-term Met exposure (1–2 years) [RR = 1.20, 95% CI = 0.87–1.66; p < 0.001]. Moreover, no association was observed for Met exposure in participants of European descent [RR = 1.01, 95% CI = 0.66–1.54; p = 0.003] compared with those from other countries.

Conclusion: Based on the evidence from population-based cohort studies, our findings suggest that the AMPK activator, Met, is a potential geroprotective agent for dementias, particularly among long-term Met users. Due to the significant heterogeneity among the included studies, we should interpret the results with caution.

Keywords: cohort study, dementia, diabetes mellitus, neurodegenerative disease, metformin

Introduction

AMPK is well known for regulating whole-body energy metabolism. AMPK has sparked widespread interest as a potential therapeutic target for age-related diseases because of its critical role in energy homeostasis control.1 Metformin (Met) is an AMPK activator, and there is growing evidence that suggests it can help prevent age-related diseases. Diabetes and pre-diabetes have been linked to accelerated cognitive decline. Patients with diabetes display an approximately twofold increased risk of dementia.2 Studies also revealed that patients with Type 2 diabetes mellitus (T2DM) have a 2.2-fold increased risk of developing Parkinson’s disease (PD),3 Insulin resistance and consequent glucose metabolism in patients with
diabetes could play critical roles in the progression of Alzheimer’s disease (AD) and dementia. A number of researchers have focused on the effect of diabetes mellitus (DM) on the cognitive decline within the elderly population. Studies have shown that elderly patients with diabetes and impaired fasting glucose have different risk factors for cognitive impairment compared with elderly patients with normal glucose levels. Evidence strongly supports the concept that insulin resistance plays a crucial role in both cognitive decline and dementia, which further suggests that when brain insulin signals are stimulated, the protective effect against cognitive deficits may be activated. The link between diabetes and dementia is probably multifactorial, and the mechanisms may involve chronic low-grade inflammation, oxidative stress, atherosclerosis, amyloid-β deposition, brain insulin resistance with hyperinsulinemia, advanced glycation end products, and dysregulation of lipid metabolism. Furthermore, some evidence suggests that insulin acts on the central nervous system to modulate behavior and systemic metabolism. Insulin sensitivity involving central and peripheral regions may be mediated by dopamine, suggesting a potential association between cognitive health and glucose metabolism.

Met is a widely used, cost-effective, and safe drug for the treatment of T2DM. The mechanism of action of Met is similar to caloric restriction, which depends on the activation of AMPK. Animal studies have shown that both caloric restriction and Met can slow down the aging process. Several in vitro experiments and animal studies have shown that Met affects brain function, including its inhibitory effect on mammalian target of rapamycin (mTOR) via activation of AMPK and suppression of tau hyperphosphorylation and inflammation. Similarly, another study has shown that Met, and its derivatives, can improve the activity of human acetylcholinesterase (AChE) and inhibit beta-amyloid aggregation.

To better understand this issue, we conducted data analysis to comprehensively evaluate the link between Met exposure and the risk of dementias. Moreover, we investigated potential moderators, including study design, geographic regions, age and gender, age at T2DM diagnosis, sample size, length of Met exposure, dementia type, and methodologic quality.

Methods
This systematic review was carried according to a predefined protocol and in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

Search strategy and selection criteria
The cohort studies published in PubMed, Cochrane Library, and Embase were systematically searched from inception to 25 May 2021, by two independent investigators (S.J. and X.Z.) without time restrictions. We employ the following search strategies (including synonyms and near-synonyms words) that were associated with Met and dementias. The detailed search strategy and specific terms (metformin/Met) AND (neurodegenerative diseases OR vascular dementia/VD OR Parkinson Disease/PD OR Alzheimer Disease/AD OR Dementia OR Cognitive disorder/CD) AND (cohort/longitudinal/follow-up/prospective/retrospective studies) were used, which were searched as free text words and as MeSH/Emtree terms. Moreover, we manually scrutinized the reference lists of meta-analyses, reviews, reports, and other possibly relevant articles. When ≥2 articles used the same cohort data, we preferred the most up-to-date one with full-text information available.

Eligibility criteria
Studies were considered appropriate when meeting the following criteria: (1) participants: patients previously exposed to Met, who had no history of dementias; (2) design: prospective or retrospective, population-based cohort studies and simultaneously, the primary outcome of the study was the incidence of various dementias reported in English; and (3) the calculation of association: relative risk (RR), hazard ratio (HR), and odds ratio (OR) or provided data. We excluded hospital-based or community-based...
observational studies and those studies that did not provide adequate data to generate risk ratios for the association between Met exposure and risk of dementia.

**Study selection, data collection, and data extraction**

Two investigators (S.J. and X.Z.) independently extracted data by using standardized, predesigned extraction forms. Discrepancies were discussed between the researchers, and a consensus was reached. The following data were extracted: author, period/year of publication, design, geographic region, country of the population studied, matched for age and gender, patient age at diabetes diagnosis, sample size, length of Met exposure, dementia type, primary outcome reported, and estimates of the association of Met exposure with dementias.

**Quality assessment**

Two authors (S.J. and Y.D.) evaluated the methodological quality separately in accordance with the 9-star Newcastle–Ottawa scale (NOS) tool. These are based on the main terms, which included representativeness and election of the participants, detection of exposure, assessment of denouements, and evaluation of follow-up. Any disagreement was resolved by a joint re-evaluation and consensus was reached. The cumulative NOS score of $\geq 7$ was considered a high-quality study.

**Statistical analysis**

All analyses were conducted using STATA (version 14.0; Stata Corp, College Station, TX). The main outcome was the pooled RR of dementias for Met use compared with the RR in non-Met users. Due to the anticipated heterogeneity of enrolled patients, we also used the Der Simonian and Laird random-effects model to calculate RR along with the 95% CIs. In studies that did not report the RR of dementias, other risk measurements (HR or OR) were used and were considered as approximations of RR to compare the risks between Met exposure and dementias. When the incidence of outcome was relatively low, we proposed RR, HR, and OR to be comparable. In order to explain the confounding variables, adjusted RR was used for analysis. $P$ test was calculated to assess heterogeneity with an $I^2 \geq 50\%$ representing substantial heterogeneity.

We first assessed whether Met use might reduce the risk of dementias. To test the potential sources of heterogeneity, we carried out several stratified analyses based on study design (prospective or retrospective cohort), geographic regions (the USA, Europe, and Asia), sample size ($<10,000$ or $\geq 10,000$), patient age at diabetes diagnosis ($<70$ or $\geq 70$ years), matched for age and sex (yes or no), length of Met exposure ($1–2$, $2–4$, or $\geq 4$ years), dementias type (dementia, PD, AD, VD, or CD), and methodologic quality (low or high). We also carried out meta-regression to examine the causes of inter-subgroup heterogeneity. We test publication bias by observing funnel plot symmetry, combined with Egger’s or Begg’s test. Sensitivity analysis was conducted by the leave-one-out method. Furthermore, the trim-and-fill technique was used to further adjust the risk estimates.

**Results**

**Characteristics of included studies**

The selection process is based on PRISMA and Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines (Figure 1). The 1022 potentially relevant citations were retrieved in the initial search and were reduced to 732 after removing duplicates. Subsequently, we excluded 699 irrelevant studies, and the remaining articles were screened by reading the full text. There were two studies that were published throughout multiple publications, but in the quantitative analysis, we treated them as one cohort. We excluded non-population-based cohorts, reviews, meta-analyses, or other unqualified studies; 14 studies in total involving 10,479,530 participants (8,493,998 metformin exposure versus 1,985,532 controls) satisfied the inclusion criteria and ultimately were entered into the analysis.

The baseline characteristics of the included studies are presented in Tables 1 and 2. Among the studies published between 2011 and 2020, four were performed in the United States, three were from Europe, and seven were from Asia. Most of the studies (8 out of 14) were retrospective cohort studies, and 86% of the included studies (12 out of 14) had a NOS score $\geq 8$. The sample size of the studies included ranged from 365 to 112,845 participants, with a median sample size of 28,309. The median length of Met exposure ranged from 1 to 6 years.
Six studies enrolled patients with Met and non-Met controls matched for age and gender.20,24,25,27,29,31 Most studies identified dementia and NDs through medical records, according to the International Classification of Diseases (9th Revision, Clinical Modification; ICD-9-CM) or ICD-10.

Quality assessment
The quality evaluation is summarized in Table 3. Using the NOS tool for cohort studies, we found that a total of two studies had a moderate risk of bias and each study had two to three possible sources of bias.21,28 Bias was most common when the adequacy of exposure time and treatment compliance was self-reported. In addition, all studies provided detailed information about participant drop-out and therefore were considered to have a low risk of bias in the reporting of results.

Effects of Met use on incidence of dementias
When we meta-analyzed the 14 studies, as shown in Figure 2, the results showed that the pooled
Table 1. Summary findings of the included studies.

| Study                      | Year | Study design     | Location         | Observation period | Population, n (exposure versus control) | Age, years (mean/SD) | Control population                                      | Reported outcomes                                      |
|----------------------------|------|------------------|------------------|--------------------|------------------------------------------|----------------------|----------------------------------------------------------|--------------------------------------------------------|
| Samaras et al. [27]        | 2020 | Prospective cohort study | Australia       | NA                 | 123 [67 versus 56]                       | 78.25 [4.6] versus 80.0 [4.7] | The Sydney Memory and Ageing Study                        | Incident dementia and cognitive decline                |
| Salas et al. [22]          | 2020 | Retrospective cohort study | USA             | 1996–2015          | 112,865 [18,904 versus 93,941]; 14,333 [1793 versus 12,560] | 59.5 [7.8] versus 63.2 [9.1]; 59.9 [7.8] versus 64.3 [9.9] | Veterans Health Affairs (VHA); Kaiser Permanente Washington (KPW) | Risk of incident dementia                              |
| Chin-Hsiao et al. [23]     | 2019 | Retrospective cohort study | China, Taiwan    | 1999–2011          | 31,352 [15,676 versus 15,676]             | 63.5 ± 9.9 versus 63.4 ± 10.4 | Taiwan’s National Health Insurance                        | Risk of dementia                                       |
| Shi et al. [28]            | 2019 | Retrospective longitudinal cohort | USA             | 2004–2010          | 396 [219 versus 177]                      | 63.2 ± 10.9          | Veterans Affairs electronic medical record database      | The risk of neurodegenerative disease (NDI)             |
| Kuan et al. [20]           | 2017 | Prospective cohort study | China, Taiwan    | 2000–2010          | 9302 [4651 versus 4651]                  | 64.7 [9.46] versus 64.7 [10.0] | Taiwan’s National Health Insurance Research Database     | Risk of dementia and PD                                |
| Brakedal et al. [21]       | 2017 | Retrospective cohort study | Norway           | 2005–2014          | 10,274 [94,349 versus 8396]              | 64.3 [11.6] versus 62.6 [10.7] | Norwegian Prescription Database                           | Risk of incident PD                                    |
| Orkaby et al. [22]         | 2017 | Retrospective cohort study | USA              | 2001–2012          | 14,562 [10,437 versus 4125]; 14,078 [6763 versus 7315] | 65≥Age < 75 years; Age ≥75 years | US veterans                                              | Risk of dementia                                       |
| Wang et al. [26]           | 2017 | Retrospective cohort study | USA              | 2004–2012          | 41,204 [8393 versus 32,811]              | 74.6 ± 5.8           | Male veterans in the United States                       | Age-related comorbidity (ARC) diagnoses                |
| Heneka et al. [30]         | 2015 | Prospective cohort study | Germany          | 2004–2010          | 5332 [1478 versus 3854]                 | ≥60, Age 60–69; Age 70–79; Age 80+ | General population                                       | Incidence of dementia                                 |
| Cheng et al. [29]          | 2014 | Prospective cohort study | China, Taiwan    | 2004–2009          | 1829 [1033 versus 796]                  | 73.2 [6.0] versus 74.1 [6.5] | General population                                       | Risk of dementia                                       |
| Ng et al. [25]             | 2014 | Prospective cohort study | Singapore        | 2003–2005          | 365 [204 versus 161]                    | 67.0 [6.55] versus 67.6 [7.14] | Population-based Singapore Longitudinal Aging Study     | Risk of cognitive impairment                           |
| Huang et al. [21]          | 2014 | Retrospective cohort study | China, Taiwan    | 1997–2007          | 30,170 [4978 versus 25,192]             | 58.7 ± 14.0          | Taiwanese population                                      | The risk of AD                                         |
| Wahlqvist et al. [2]       | 2012 | Retrospective cohort study | China, Taiwan    | 1996–2007          | 5313 [1879 versus 3431]                 | 64.8 ± 9.5 versus 65.3 ± 9.44 | General population                                       | Risk of Parkinson’s disease                           |
| Hsu et al. [24]            | 2011 | Prospective cohort study | China, Taiwan    | 2000–2007          | 12,383 [1864 versus 10,519]             | >50                  | Taiwan’s National Health Insurance database              | Incidence of dementia                                  |

AD, Alzheimer’s disease; NA, not applicable; PD, Parkinson’s disease; SD, standard deviation.
Table 2. Characteristics of included studies of metformin use in relation to risk of NDs: exposure and outcome assessment, results, and measure of associations.

| Study | Ascertainment of metformin exposure | Ascertainment of outcome | Results | Measure of associations | Type of dementia | Adjusted variables |
|-------|-------------------------------------|--------------------------|---------|------------------------|-----------------|-------------------|
| Samaras et al. | T2DM with Met | Dementia/ICD-10-CM | Incident dementia was significantly higher in DM-MF compared with DM (ratio 2.0, CI 1.7–2.3; p < 0.01) | AD, PD, HD, and dementia, and mild cognitive impairment | AD, vascular dementia | Adjusted for age, sex, Charlson Comorbidity Index |
| Salas et al. | Early diabetic with Met | Dementia/ICD-9-CM | After PS IPTW adjustment, results remained significant in veterans, 75 years of age (HR = 0.89; 95% CI = 0.79–1.00), but not for those <75 years of age (HR = 0.96; 95% CI = 0.87–1.05) | Dementia; AD; vascular dementia | Dementia; AD; vascular dementia | Adjusted for age, sex, education, and so on |
| Shi et al. | DM with Met | ND/ICD-9-CM | Analyses in the matched cohort showed an overall HR > 1.00 | NA | NA | NA |
| Kuan et al. | Early diabetic with Met | Dementia/ICD-9-CM | The relative rate of dementia at 1.5 years was lower in the metformin group compared with the noMF group (HR = 0.7, 95% CI = 0.6–0.8, p < 0.01) | AD, PD, vascular dementia | AD, PD, vascular dementia | Inverse probability of treatment weighting |
| Brakkala et al. | Early diabetic with Met | Dementia/ICD-9-CM | Metformin use showed a significant inverse association with cognitive impairment (OR = 0.49, 95% CI = 0.25–0.95) | Cognitive impairment | Cognitive impairment | Adjusted for age, gender, education, and so on |
| Wang et al. | DM with Met | Dementia/ICD-10 | Metformin reduced likelihoods of CVD (18.8%), cancer (3.9%), dementia (3.8%), depression (5.6%), and FRD (23.8%) | OR | NA | NA |
| Heneka et al. | Early diabetic with Met | Dementia/ICD-10 | Metformin as monotherapy: 0.69 (0.28–1.71) | AD | Adjusted for age, sex, comorbidities |
| Wahlqvist et al. | Early diabetic with Met | Dementia/ICD-9-CM or A-code | Not reported | PD | Adjusted for monthly income; delete those diabetes patients who have used insulin |
| Hsu et al. | Early diabetic with Met | Cognitive dysfunction/MMSE | Not reported | NA | NA | NA |

AD, Alzheimer’s disease; HR, adjusted hazard ratio; CI, confidence interval; CVD, cardiovascular disease; DM, diabetes mellitus; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders (4th ed.); FRD, frailty-related disease; HD, Huntington’s Disease; HR, hazard ratio; ICD, International Classification of Diseases; ICD-10-CM, International Classification of Diseases (10th Revision, Clinical Modification); IPTW, inverse-probability-of-treatment-weighting; MMSE, Mini-Mental State Examination; OR, odds ratio; PS, propensity score; PSW, propensity score weight; RR, relative risk; T2DM, Type 2 diabetes mellitus.
### Table 3. Methodological quality score of the included studies based on the Newcastle–Ottawa scale (NOS) tool.

| Study               | Year | Study design       | Selection                | Comparability          | Exposure/outcome | Total score | Risk of bias |
|---------------------|------|--------------------|--------------------------|------------------------|------------------|-------------|--------------|
| Cheng et al.²⁹       | 2014 | Prospective cohort | *                        | *                      | *                | 8           | Low          |
| Wahlqvist et al.²¹  | 2012 | Retrospective cohort | *                        | *                      | *                | 8           | Low          |
| Hsu et al.²⁴        | 2011 | Prospective cohort | *                        | *                      | *                | 8           | Low          |
| Kuan et al.²⁰       | 2017 | Prospective cohort | *                        | *                      | *                | 9           | Low          |
| Ng et al.²⁵         | 2014 | Prospective cohort | *                        | *                      | *                | 9           | Low          |
| Heneka et al.³⁰     | 2015 | Prospective cohort | *                        | *                      | *                | 9           | Low          |
| Brakedal et al.³¹   | 2017 | Retrospective cohort | *                        | *                      | *                | 7           | High         |
| Orkaby et al.³²     | 2017 | Retrospective cohort | *                        | *                      | *                | 8           | Low          |
| Wang et al.²⁶       | 2017 | Retrospective cohort | *                        | *                      | *                | 6           | High         |
| Huang et al.³³      | 2014 | Retrospective cohort | *                        | *                      | *                | 8           | Low          |
| Chin-Hsiao et al.³⁵ | 2019 | Retrospective cohort | *                        | *                      | *                | 9           | Low          |
| Samaras et al.³⁷    | 2020 | Prospective cohort | *                        | *                      | *                | 8           | Low          |
| Shi et al.³⁸        | 2019 | Retrospective cohort | *                        | *                      | *                | 9           | Low          |
| Salas et al.³²      | 2020 | Retrospective cohort | *                        | *                      | *                | 8           | Low          |

Each asterisk (*) represents one Newcastle–Ottawa Scale score.
RR of dementias reached 0.79 (95% CI = 0.68–0.91) in Met users compared with non-Met controls. Heterogeneity among studies was high ($I^2 = 89.3\%$; $p < 0.001$).

**Subgroup analysis and meta-regression**

Subgroup analysis was conducted to determine whether the baseline age of the study population affected the incidence of dementias (Table 4). A significant reduction in the incidence of dementias was observed in patients $<70$ years (0.77; 95% CI = 0.62–0.96). Conversely, there was no significant difference for those $\geq 70$ years (0.94; 95% CI = 0.86–1.02), particularly for those $>75$ years (0.96; 95% CI = 0.91–1.02). For specific types of dementia, we noted that the Met was closely related to a lower risk of subsequent dementia than non-Met use (RR = 0.81, 95% CI = 0.70–0.93), while there was no significant difference in PD (RR = 0.70, 95% CI = 0.32–1.52), AD (RR = 0.94, 95% CI = 0.70–1.26), CD (RR = 0.67, 95% CI = 0.36–1.24), and VD (RR = 1.22, 95% CI = 0.79–1.88) (Supplementary Figure S1). Meanwhile, we also explored the effect of glycemic statuses on the incidence of dementia after Met treatment. In the studies collected for analysis, 25% included patients with hyperglycemia, while the remaining studies included patients with T2DM. These results indicated that Met treatment did not reduce the incidence of dementia in patients with early onset of diabetes (0.75; 95% CI = 0.55–1.03), while it significantly lessened the incidence of dementia in patients with late-onset diabetes (0.79; 95% CI = 0.66–0.94). We further investigated whether the length of exposure post-Met treatment impacts the incidence of dementia. We found that the risk of dementia was significantly decreased with the increased length of Met exposure $\geq 2$ to 4 years (0.68; 95% CI = 0.59–0.79), especially in long-term Met exposure ($\geq 4$ years) (RR = 0.38, 95% CI = 0.32–0.46; $p < 0.001$). However, short-term Met exposure (1–2 years) had no significant effect (RR = 1.20,
| Variables                        | RR  | 95% CI   | I², % | No. of studies | p for Interaction |
|---------------------------------|-----|----------|-------|----------------|------------------|
| Overall                         | 0.79| 0.68–0.91| 89.3  | 14             | NA               |
| Study design                    |     |          |       |                | 0.009            |
| Prospective cohort              | 0.88| 0.64–1.20| 86.9  | 6              |                  |
| Retrospective cohort            | 0.73| 0.60–0.87| 90.5  | 8              |                  |
| Geographic regions              |     |          |       |                |                  |
| USA                             | 0.72| 0.58–0.89| 90.4  | 4              | 0.003            |
| Europe                          | 1.01| 0.66–1.54| 82.2  | 3              |                  |
| Asia                            | 0.74| 0.51–1.08| 90.8  | 7              |                  |
| Population sample size          |     |          |       |                | 0.472            |
| <10,000                         | 0.59| 0.40–0.89| 93.3  | 7              |                  |
| ≥10,000                         | 0.88| 0.77–1.01| 82.4  | 7              |                  |
| Age, years                      |     |          |       |                | 0.382            |
| <70                             | 0.77| 0.62–0.96| 92.3  | 9              |                  |
| ≥70                             | 0.94| 0.86–1.02| 48.9  | 6              |                  |
| >75                             | 0.96| 0.91–1.02| 0     | 3              |                  |
| Type of NDs                     |     |          |       |                | 0.424            |
| Dementia                        | 0.81| 0.70–0.93| 90.2  | 10             |                  |
| PD                              | 0.70| 0.32–1.52| 95.8  | 4              |                  |
| AD                              | 0.94| 0.70–1.26| 65.5  | 4              |                  |
| VD                              | 1.22| 0.79–1.88| 74.1  | 2              |                  |
| Cognitive disorder              | 0.67| 0.36–1.24| 12.7  | 2              |                  |
| Glycemic status                 |     |          |       |                |                  |
| Early diabetic with met         | 0.75| 0.55–1.03| 83.4  | 4              | 0.244            |
| T2D with Met                    | 0.79| 0.66–0.94| 91.2  | 10             |                  |
| Length of Met exposure (years)  |     |          |       |                | <0.001           |
| 1–2                             | 1.20| 0.87–1.66| 78.3  | 3              |                  |
| 2–4                             | 0.68| 0.59–0.79| 0     | 3              |                  |
| ≥4                              | 0.38| 0.32–0.46| 0     | 2              |                  |
| Matched for age and sex         |     |          |       |                | 0.021            |
| Yes                             | 0.76| 0.47–1.25| 86.2  | 6              |                  |
| No                              | 0.77| 0.66–0.89| 90.8  | 8              |                  |
| Methodologic quality            |     |          |       |                | 0.218            |
| Moderate (6–7)                  | 0.91| 0.39–2.14| 91.9  | 2              |                  |
| High (≥8)                       | 0.77| 0.66–0.89| 89.7  | 12             |                  |

AD, Alzheimer’s disease; CD, cognitive disorder; CI, confidence interval; Met, metformin; NA, not applicable; ND, neurodegenerative disease; PD, Parkinson’s disease; RR, relative risk; T2D, type 2 diabetes; VD, vascular dementia.
95% CI = 0.87–1.66; \( p < 0.001 \)). Despite the fact that subgroup analysis was performed previously, significant heterogeneity remained between some studies. Therefore, a univariate meta-regression analysis was conducted, which indicated that the heterogeneity could be due to various factors, including study design, geographic regions, matched for age and gender, patient age at T2DM diagnosis, sample size, length of Met exposure, and dementia type (all \( p < 0.05 \)). However, the remaining heterogeneity may result from other potential baseline changes between individuals enrolled in each study.

**Sensitivity analyses and publication bias**

Sensitivity analyses were performed by using the leave-one-out method to examine the stability of the results. We found that no individual study significantly changed the pooled RRs (lowest RR = 0.19, 95% CI = 0.12–0.31; highest RR = 1.66, 95% CI = 1.35–2.04). Sensitivity analyses were carried out by summarizing and estimating studies that include only the use of time-to-event risk assessment and HRs. HRs of 10 studies were pooled, yielding a summary estimate of 0.80 (95% CI = 0.67–0.95; \( p = 0.002 \)), which was similar to the prior result. The findings of the contour enhancement funnel chart indicate no potential evidence of publication bias. The Begg’s test for small-study effects was non-significant (\( p = 0.091 \)), and the Egger test was also non-significant (\( p = 0.078 \)). Furthermore, the trim-and-fill method adjusted for publication bias showed no potential for missing studies (Supplementary Figure S2).

**Discussion**

**Principal findings**

According to the present comprehensive meta-analysis with 396,332 participants, we demonstrated Met plays a beneficial role in reducing the risk of dementia. After adjusting for potential publication bias, the results remained consistent. Moreover, our results indicate that Met treatment reduces the future development of dementia for patients with T2DM, whose age at diagnosis is <70 years, and with Met exposure \( \geq 2 \) years. With a population sample size of <10,000, this finding is stable only in the United States.

**Comparisons with previous studies**

Our results are consistent with one systematic review with meta-analyses,\(^39\) which validated our findings of a decreased dementia risk in patients with Met exposure. However, the review article summarized a range of evidence, including one case as control, two RCTs, four cross-sectional, and seven cohorts. Some studies found that the use of Met had a negative or neutral effect on patients with diabetes. The meta-analysis conducted by Ye et al.\(^{40}\) failed to demonstrate a protective effect (RR = 0.79, 95% CI = 0.82–1.01), in which only six observational studies assessed the effect of Met on dementia. The latest meta-analysis performed by Ping et al.\(^{41}\) concluded that Met had no beneficial effect on dementias (OR = 1.04, 95% CI = 0.92–1.17). Furthermore, it may increase the risk of PD development (OR = 1.66, 95% CI = 1.14–2.42). After that, several observational studies with large sample sizes were reported.\(^{27,28,32}\) Among them, Samaras et al.\(^{27}\) and Shi et al.\(^{28}\) demonstrated the protective effect of Met on incidental dementia. The above studies made it possible to include much more comparisons for the evaluation of the relationship between Met and risk of dementias in the present meta-analysis. Furthermore, the previously published meta-analyses came mostly from non-population-based cohorts or small sample RCT studies with a high risk of bias. This study is the first involving representative populations with all dementia types to meta-analyze the relationship between Met use and subsequent dementia risk from high-quality population-based cohort studies rather than previously separated or narrative ones.

The previous meta-analysis found that Met had no beneficial effect on PD and might increase the risk of PD development, which may be related to the previous error combination and the latest research results. As for the two cohort studies included, the results should be interpreted cautiously. Wahlqvist et al.\(^{3}\) was included and concluded that patients with T2DM who used sulfonylureas alone but not on oral anti-hyperglycemic agents had an increased risk of PD (HR = 1.57, 95% CI, 1.15–2.13). However, Met alone did not increase the risk (HR = 0.95, 95% CI, 0.53–1.71). Another study by Shi et al.\(^{28}\) reported that the significantly reduced risk of PD was only associated with more than 4 years of Met treatment as compared with the non-Met
exposure group (aHR=0.04, 95% CI=0–0.37), and there was no association with ≥2–4 years of Met exposure (aHR=0.59, 95% CI=0.29–1.17).

Potential mechanisms

Our meta-analysis suggests that Met treatment can decrease the risk of developing dementia, which raises a question worth addressing: How does the cheap drug Met prevent dementia? There are several underlying factors that clarify the potential associations between Met use and the subsequent decreased dementia risk. First, Met can penetrate the blood–brain barrier and thus act centrally to exert its neuroprotective function; its concentration in cerebrospinal fluid is nearly 1/10 of that in plasma.42 Second, Met is an extensively used pharmacological agent that improves whole-body insulin sensitivity. Here, insulin resistance affects Adenosine triphosphate (ATP) production and Reactive oxygen species (ROS) release in neurons and astrocytes and in mixed glial cell cultures. Many studies have shown that High-Fat Diet (HFD)-induced insulin resistance leads to significant impairment of mitochondrial function in the brain, which can be mitigated by exercise and Met, both of which improve insulin sensitivity in the brain.43 Third, AMPK, insulin, and glucose transporters serve as mediators of the Met effect in AD. Met enhances neuronal bioenergetics by activating AMPK and autophagy, promotes nerve repair, and reduces toxic protein aggregation in nervous system diseases.44 Met protects against Aβ-induced mitochondrial dysfunction by activating the AMPK pathway in human neural stem cells. It may also act directly on insulin signaling in the brain, which makes Met treatment even more important because it can improve changes in glucose metabolism and reduces advanced glycation end products,9 which promote tissue degeneration and the microvascular complications of hyperglycemia in neural, renal, and vascular tissues. Preclinical and clinical studies have shown that Met has neuroprotective effects on brain structure and function. (3) In insulin signaling, insulin plays an important part in the brain. It serves as a hormonal signal to control ingestion of food, body weight, and metabolic homeostasis.50 Met prevented neuronal insulin resistance, which has shown AD characteristics in cellular models.51 Met decreases blood glucose levels by suppressing gluconeogenesis in the liver via AMPK.52 Met is reported to down-regulate the expression of insulin and insulin-like growth factors (IGF-1) receptors and reduces phosphorylation of insulin receptors, including insulin receptor substrate 1 (IRS-1).53,54 (4) Inflammation, particularly neuroinflammation, is thought to be a primary driving force in the progression of dementias and Met suppresses nuclear factor kappa B (NF-κB) signaling and pro-inflammatory cytokines in various cell types,55 suggesting that Met could protect against neuroinflammation. In clinics, several mechanisms often exist at the same time.

Whether Met reduces the incidence of dementia in diabetic patients may be related to the duration
of Met exposure. In the only RCT that evaluated cognitive responses after Met exposure in diabetic patients, the short 36-week duration of treatment could possibly account for an apparent lack of protective effect. It is thus possible that a protective effect of Met on cognitive function might be more evident after long-term use (≥6 years), as suggested by the data (0.27; 95% CI = 0.12–0.60) in the study. Similar findings were found in two other studies. These studies indicate that Met therapy may be most effective if started early but still beneficial if started after a cognitive decline (Table 4). It is most likely that Met’s main effect is decreasing damage over time rather than directly acting on the brain as a nootropic. This could be confirmed in future studies by comparing the cognitive function of elder people taking Met with that of short-term abstainers.

Future directions
Ultimately, notwithstanding its limitations, the current study includes all dementia types and both prospective and retrospective population-based studies, which provides a large enough sample size for a meaningful and robust statistical analysis. A future clinical investigation should focus on establishing risk assessment and individualized treatment strategies for diabetes-related dementia based on both molecular and macroscopic characteristics.

Conclusion
This systematic review and meta-analysis showed that long-term use of Met in T2DM might result in a decreased risk of dementia. This association remains stratified by most baseline variables and is biologically plausible. However, we should interpret the results cautiously until high-level evidence from prospective cohort studies proves this relationship.

Declarations
Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

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Shiliang Ji: Data curation; Formal analysis; Methodology; Writing – review & editing.
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Conflict of interest statement
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Availability of data and materials
All data relevant to the study can be found in the article or supplementary material.

Supplemental material
Supplemental material for this article is available online.

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