Metformin and dementia risk: A systematic review with respect to time-related biases

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Abstract

Background: Numerous observational studies have found metformin use to be associated with a reduced risk of dementia among individuals with diabetes, while others have found an increased risk. However, time-related biases may exist in observational studies and result in spurious associations. Unaddressed time-related biases can contribute to the inconsistent results of previous studies exploring metformin and dementia. Immortal time bias often produces effect estimates that biased toward an apparent “protective” effect of the medication, whereas time-lag and time-window biases can lead to either a “detrimental” or “protective” effect. The purpose of this study is to conduct a systematic review examining time-related biases in the literature on metformin and dementia.

Method: The electronic databases of PubMed, Web of Science, and ProQuest were searched for the terms “Metformin” AND (“dementia” OR “Alzheimer’s Disease (AD)” OR “cognitive impairment”). No date restrictions were applied; however, only English language articles and human research were eligible. PROSPERO accepted the registration of this systematic review on 04/08/2021 (ID#: CRD42021240034). Data were extracted between 04/09/2021 and 09/24/2021. The Good Research for Comparative Effectiveness (GRACE) was used to evaluate the methodological quality of reviewed studies.

Result: Seventeen studies were identified: thirteen cohort studies, two case-control studies, and two nested case-control studies. Eleven (64.7%) of the identified studies reported a reduced risk of dementia associated with metformin use; two articles (11.8%) suggested metformin increased dementia risk, while four articles (23.5%) concluded no significant association between metformin use and dementia risk. Of the seventeen reviewed studies, immortal time bias was not addressed in eleven studies (64.7%). Time-lag bias was not addressed in ten articles (58.8%), and four articles did not address time-window bias (23.5%) (Table 1). Two studies addressed most time-related biases effectively and received relatively high GRACE scores (9 and 12, respectively).
respectively). Both of them found no significant associations between metformin use and dementia.

**Conclusion:** None of these reviewed studies addressed all time-related biases specifically, illustrating time-related biases are still common in the observational studies investigating the impacts of anti-diabetic medications on dementia risk. The studies addressed most biases concluded no associations between metformin use and dementia.

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**Table 1: Time-related biases and methodological quality assessments of included studies**

| Time-related biases | Frequency | Percentage |
|---------------------|-----------|------------|
| 1: Immortal time bias not addressed | 11 | 64.7% |
| a) Studies supported metformin reduced the risk of dementia | 8 | 72.7% |
| b) Studies supported no associations between metformin and dementia | 3 | 27.3% |
| 2: Time-lag bias not addressed | 10 | 58.8% |
| a) Studies supported metformin reduced the risk of dementia | 5 | 50.0% |
| b) Studies supported metformin increased the risk of dementia | 3 | 30.0% |
| c) Studies supported no associations between metformin and dementia | 2 | 20.0% |
| 3: Time-window bias not addressed | 4 | 23.5% |
| a) Studies supported metformin reduced the risk of dementia | 3 | 75.0% |
| b) Studies supported no associations between metformin and dementia | 1 | 25.0% |
| **Total GRACE scores** | **Mean ± SD** | **Range** |
| Possible range: (0-17) | 7.35 ± 1.66 | (5, 12) |