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Metformin and dementia risk: "a systematic review with respect to time related biases"

THESIS

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MASTER OF SCIENCE

in Epidemiology

by

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Thesis Committee:
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Professor Maria M Corrada-Bravo

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DEDICATION

To

my parents and husband

for the endless support and love.

To

my friends

for always being there for me

"The secret of getting ahead is getting started."

Mark Twain

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ABSTRACT OF THE THESIS

Metformin and dementia risk: "a systematic review with respect to time related biases"

by

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Dr. Luohua Jiang, Chair

When studying drug effects using observational data, time-related biases such as immortal time bias, time-window bias, and time lag bias may exist and result in spurious associations. Many of the recent studies investigating the effects of metformin on dementia risk were based on large health care administrative databases and might be subject to time-related biases. This systematic review aims to assess if time-related biases exist in previous studies investigating the association between metformin use and dementia risk among diabetes patients. The electronic databases of PubMed, Web of Science, and ProQuest were searched for the terms “Metformin” AND “dementia” OR “Alzheimer’s Disease” OR “cognitive decline” OR “cognitive impairment.” These databases were searched from inception through 03/10/2021. Only English language articles and human subjects research were eligible. In total, twelve retrospective cohort studies, two case-control studies, and two nested case-control studies were identified. Twelve studies reported a reduced risk of dementia associated with metformin use, two articles reported increased risk, and two articles indicated no significant association between metformin use and dementia risk. In these sixteen studies, immortal time bias existed in eleven articles, time

lag bias was found in seven articles, time-window bias was identified in three articles, while only one article was not identified any time-related biases. Most previous studies investigating the association between metformin and dementia risk did not carefully considered time-related biases. Future observational studies may need to take these time-related biases into consideration.

CHAPTER 1

INTRODUCTION

Dementia is a disease that can impair people's ability to think, remember, make decisions, and can interfere with daily activities. The most common type of dementia is Alzheimer's disease (AD). Around 6.2 million U.S. people age 65 and older are living with AD and related dementias in 2021, which involved 4.5 million elders are age 75 or older.[1] The number of people aged 65 years and older with Alzheimer's dementia in the U.S. is predicted to reach approximately 13.8 million by 2060, which almost a 22.6% increase from the year of 2021.[1] 121,499 individuals died from Alzheimer's disease in 2019 based on the data from the Center for Disease Control and Prevention (CDC).[2] 271,872 people died from some forms of dementia, which included 121,499 from Alzheimer's disease in 2017.[3] Therefore, the number of death cases from all causes of dementia is more than twice as high as the number of reported Alzheimer's deaths alone. Between 2000 and 2019, the death rate of Alzheimer's dementia increased from 17.6 to 37.0 per 100,000 people.[2] Alzheimer's disease was listed as the sixth leading cause of death among the US population and the fifth leading cause of death in adults aged 65 and older.[4]

Metformin, a biguanide, has become the preferred first-line medication for the treatment of type 2 diabetes.[5] It can decrease insulin resistance effectively, improve glycemic control, and combine with other antidiabetic medications safely.[6] The primary biological mechanism of metformin to manage diabetes is through activating AMP-activated protein kinase (AMPK), enhancing insulin sensitivity of peripheral tissues, decreasing glucose production by inhibiting hepatic gluconeogenesis, and reducing

intestinal absorption of glucose to improve hyperglycemia.[7] AMPK also regulated tau phosphorylation, β-amyloid (Aβ) production, and autophagy, which are all thought to be involved in the pathogenesis of AD (figure 1.1).[8] Consequently, many investigators hypothesized metformin could reduce the risk of AD and tested this hypothesis using observational data. Campbell et al. (2018) conducted a systematic review and meta-analysis to synthesize the best available evidence on the relationship of metformin-use with dementia risk; they indicated most of the reviewed observational studies supported metformin was associated with a reduced risk of dementia.[9]

In observational studies, time-related biases may exist that lead to spurious associations.[10] For example, immortal time bias, time-window bias, and time lag bias have been described in previous studies that investigated the effects of diabetes therapies on cancer risk.[11] Some studies found metformin significantly reduced cancer risk, but those studies seemed to suffer from certain types of time-related biases.[12-22] In contrast, several studies reported no associations between metformin use and cancer incidence after addressing both immortal time and time-window biases by applying statistical models with time-varying exposure.[23-25]

Immortal time bias is very common in observational studies of drug effects. It was introduced when the immortal time was misclassified as exposure.[26] For instance, when cohort entry or time zero is different from the date of first prescription, then the period between time zero and first prescription date is immortal for the exposed subjects since the subjects are misclassified as being exposed during this time, when in fact are unexposed. Time lag bias was introduced when comparing the effects of medications given at different stages of the disease.[11] For instance, when a first-line therapy is compared with

a second or third-line therapy, time lag bias likely exists because longer duration of diabetes may be associated with a higher incidence of dementia. Suissa et al. (2011) indicated the source of time-window bias for case-control studies resulted from their methods of selecting controls and measuring their exposure. Using a time-independent sampling method to select controls in the case-control study might cause time-window bias because this method could not ensure cases and controls had the same exposure opportunity time.[27]

CHAPTER 2

OBJECTIVES

Many of the recent studies investigating the effect of metformin on dementia risk were based on large health care administrative databases and might be subject to time-related biases.[28-43] Searches of the Cochrane database and PROSPERO did not find any completed or pending reviews on this topic with respect to time-related biases. To better understand the effects of metformin on the risk of dementia, we conducted a systematic review to understand if time-related biases exist in previous observational studies exploring the effects of metformin use on the risk of dementia among patients with diabetes.

CHAPTER 3

METHODS

3.1 Selection criteria

Previous studies were included if they fulfilled the following eligibility criteria: 1) An original article published in English; 2) human subjects with diabetes but without any type of dementia at baseline; 3) participants using metformin at any dose for any duration comparing with participants with no antidiabetic medications or other active antidiabetic agents other than metformin; 4) a major outcome of dementia or any type of dementia, cognitive decline or cognitive impairment; 5) quantitative measures of association between metformin use and the risk of dementia or other relevant outcomes with their 95% confidence intervals (CIs) or P-value being reported; 6) observational studies including cohort studies and case-control studies. Exclusion criteria were: 1) publication that was a review, case report, animal study, or letters; 2) studies that used a cross-sectional study design; 3) studies that did not clearly define exposure groups and comparison groups; 4) studies that did not clearly define major outcomes; 5) exposure or outcome data could not be obtained; 6) duplicated studies. Cross-sectional studies were not eligible in the present review because cross-sectional studies analyze data from a population at a specific point in time, for which time-related biases are not applicable.

3.2 Search strategy

The electronic databases of PubMed, Web of Science, and ProQuest were searched for the terms “Metformin” AND “dementia” OR “Alzheimer’s Disease” OR “cognitive decline”

OR “cognitive impairment”. No date restrictions were applied; however, only English language articles were eligible. These databases were searched from inception through 03/10/2021. Titles and abstracts screening was followed by potential relevant full-texts reviews compared with inclusion criteria to identify the final eligible studies.

3.3 Data extraction

For each eligible study, the following data were extracted: first author, year of publication, study design, exposure group, comparator, population, statistical methods, primary outcome, and measures of associations with 95% CIs or P-value. If adjusted relative risks were also provided, the most fully adjusted relative risks was extracted.

3.4 Assessment of methodological quality

The methodological quality of case-control and cohort studies was assessed using the Newcastle-Ottawa Scale (NOS).[44] In the NOS, cohort studies were scored across three categories: selection (four questions), comparability (one question), and assessment of outcome (three questions). Case-control studies were scored across selection, comparability, and ascertainment of exposure. All questions had a score of one except for comparability, which separate points were awarded for adjustment of important confounders (maximum of 2 points). NOS scores ≥7 points were considered as high quality, and NOS scores <7 points were deemed as low quality.

3.5 Evaluation of time-related biases

Misclassification of immortal time as exposure is the most common way to induce immortal time bias.[26] Misclassifying immortal time happens when time zero or cohort

entry is not the same as the date of the first prescription. In this case, the subject in the exposure group must be outcome-free until their first prescription is fulfilled. The period between cohort entry and the first prescription may be misclassified as time exposed, but in fact, this individual is not exposed yet during this period. Thus, the period between time zero and the first prescription date is immortal, which results in immortal time bias. The concept of immortal time bias is illustrated in Figure 3.1A, in which the entire follow-up duration, including immortal time, is classified into the exposure group. However, the time between time zero and the first prescription of metformin should be classified as unexposed. Figure 3.1B shows a proper method to classify exposed and unexposed groups. In addition to the different dates of time zero and first prescription, studies using a time-fixed covariates method could also misclassify immortal time during follow-up when patients change their antidiabetic medications. For example, if a patient in the exposure group uses metformin initially but switches to insulin or other antidiabetic medications in the later years of the observation, the time period of other antidiabetic medication intakes rather than metformin should be classified into non-exposure period instead of exposures. Besides, immortal time bias during follow-up periods may happen if the authors use cumulative duration or cumulative prescriptions of metformin as exposures but without applying a time-varying covariates method to estimate the associations between metformin and dementia risk.

Time lag bias is introduced when the studies do not apply new users design or new-onset design, metformin users are compared with users of second- or third-line therapy, diabetes patients without any antidiabetic treatments, or individuals without diabetes. In

case-control studies, time lag bias happens when duration of diabetes is not matched. In these cases, exposure and comparison groups are unlikely to be at the same stage of diabetes (Figure 3.2A). The appropriate comparison should align the stage of diabetes between the comparison groups (figure 3.2B).

Time-window bias will happen if controls are defined as subjects who do not experience the outcome during the observational period, but the observation period was not matched with that of cases. In that case, the exposure may be evaluated during a shorter or longer time interval for cases than for controls, thus, results in time-window bias (Figure 3.3A).[26] Time-window bias can be addressed in case-control studies if cases and controls have the same exposure opportunity time (figure 3.3B).

CHAPTER 4

RESULTS

4.1 Literature search outcomes

We identified 1,482 studies initially in PubMed (NLM), Web of Science, and ProQuest. 720 studies were removed after de-duplicates. 730 studies were excluded after title and abstract screening. The remaining thirty-two studies were eligible for full texts reviews. Finally, sixteen articles were excluded due to absence of the full texts (n = 10), lack of a relevant comparator (n = 2), no relevant outcomes (n=2), or applied cross-sectional study design (n=2). A total of sixteen studies, consisting of twelve cohort studies, two case-control studies, and two nested case-control studies met the inclusion criteria. Figure 4.1 is the inclusion flowchart that was made based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2009 flowchart diagram.[45]

Among these sixteen articles, twelve studies reported a reduced risk of dementia associated with metformin use,[28-39] two articles indicated increased risk,[42-43] and two articles indicated no significant association between metformin use and dementia risk.[40-41] Immortal time bias was the most common time-related bias in these sixteen articles, which existed in eleven articles.[28-36,40,41] Time lag bias was identified in seven articles.[28,29,33,34,38,39,43] Time-window bias was found in three articles.[37,39,43] Only one study was identified as not having any apparent time-related biases.[42] Table 4.1 provides an overview of the sixteen eligible studies.

4.2 Quality of Included Studies

The median NOS quality score for these sixteen observational studies was 7.0. 75% these sixteen studies were considered high quality, 25% of them were low quality. Table 4.2 depicts the methodological quality of all studies.

4.3 Time-related biases analysis

4.3.1 Immortal time bias

Eleven studies were found to have immortal time bias due to misclassification of immortal time.[28-36,40,41] Ten studies did not apply a time-varying covariates method; [28-33,35,36,40,41] six of these ten studies had different dates of time zero and the first prescription.[28,29,30,33,40,41] Five studies used cumulative duration or cumulative prescriptions of metformin as exposures.[28,30,33,34,36]

4.3.1.1 Without applying a time-varying covariates method

In the process of reviewing, ten cohort studies were found to use survival regression models with time-invariant covariates; thereby, immortal time bias may not be addressed.[28-33,35,36,40,41] Three studies by Scherrer et al. (2019), Scherrer et al. (2019), and Orkaby et al. (2017) tried to address immortal time bias and time lag bias.[31,32,35] Orkaby et al. employed a new user design of metformin versus sulfonylurea monotherapy to ensure all cohort members had the same stages of the disease. After the first diabetes medication intake, authors used two years to exclude participants without single antidiabetic drugs or those newly diagnosed with dementia. Participants would be included if they took two prescriptions per year and no other diabetes drug use during these two years. Index date

(time zero) was defined as after the two years, so there was not immortal time issue at the start of follow-up. Besides, participants who switched between metformin and a sulfonylurea during the follow-up period were excluded, but they could take additional diabetes medication during the study of follow-up period.[35] Two of Scherrer and his groups' studies in 2019 also applied the new user design and metformin versus sulfonylurea monotherapy like Orkaby et al.'s study. However, time-dependent covariates methods were not used in these studies. Thus, potential immortal time bias could still be present in these studies.[31,32]

4.3.1.2 Date of time zero and the first prescription was different

Six cohort studies were found to use a time-fixed covariates method and have different dates of time zero and first prescription.[28,29,30,33,40,41] Hsu et al.'s (2011) study examined the effects of metformin and sulfonylureas on the development of dementia. Data were extracted from the longitudinal Health Insurance Database 2000 (LHID2000), which was randomly sampled from the year 2000 registry for beneficiaries of the National Health Insurance of Taiwan Research Database (NHIRD). Exposure was defined as metformin-only users. A Cox proportional hazards model was used to estimate the hazard ratios (HRs), which suggesting a protective effect of metformin on dementia risk (HR=0.76 95% CI 0.58–0.98). Immortal time bias was introduced in this study from its definition of exposure and related analysis. The authors defined the index date (time zero) as the date of diagnosis of diabetes or the date of the first prescription, whichever came first. If they treated the date of diagnosis of diabetes as time zero, then the period between time zero and the first prescription was immortal. In another word, this immortal person-time should be

classified as non-metformin exposure until the start of metformin.[28] The study by Huang et al. (2014), which used the National Health Insurance program in Taiwan to explore the possible effects of hypoglycemic agents on the risk of AD in patients with diabetes. After a maximum of 11 years of follow-up, the investigators stated there was no significant association between metformin use and dementia risk among patients with newly diagnosed DM ($HR_{metformin\ monotherapy}$ =0.69 95% CI 0.28–1.71, $HR_{metformin\ combination\ therapy}$ = 0.57 95% CI 0.26–1.26). This study might have immortal time bias because authors did not define the time zero in exposure and non-exposure groups.[40] A previous study by Cheng et al. (2014) aimed to investigate the relationship between antidiabetic treatments and dementia risk among patients with T2DM. The results from the study indicated no significant association between metformin and dementia risk compared to sulfonylureas were found (aHR=0.82 95% CI 0.52-1.28). The authors defined time zero as of January 2004. Nevertheless, the participants were assigned to the metformin exposure or comparison group based on their information of antidiabetic medications after time-zero. In this case, the period between time zero and the first prescription date was immortal.[41] The study by Samaras et al. (2020) suggested metformin use was associated with an 81% reduction in dementia risk (HR=0.19 95% CI 0.04-0.85), which was considered to have immortal time bias because this study did not define time zero for both metformin and non-metformin groups.[29] The studies by Shi et al. (2019) and Kim et al.(2020), which supported metformin therapy was associated with a lower risk of dementia, both defined time zero as the date of diabetes onset, which could lead to immortal time bias since the time between time zero and the first prescription was immortal.[30,33]

4.3.1.3 Using cumulative duration or prescriptions

Five cohort studies used cumulative duration or prescriptions of metformin as exposures.[28,30,33,34,36] Hsu et al (2011) applied used defined daily dose (DDD)/month (cumulative DDD of metformin from the first prescription to the diagnosis of dementia, the censored date, or the end of 2007, divided by the total follow-up months) to evaluate the effect of metformin on dementia risk.[28] Shi and his colleagues categorized the metformin exposure into five levels from time zero to the date of first clinical outcome happened, death, or the end of data availability. These five levels included never had metformin treatment, metformin treatment ≤1 year, 1 to 2 years, 2 to 4 years, and >4 years.[30] The study by Kim et al. divided metformin exposure into low, mid, and high.[33] Ng et al. (2014) compared non-metformin users and metformin use ≤6 years or >6 years to investigate the effect of metformin on cognitive impairment risk among patients with diabetes.[34] And Tseng's study used tertiles of cumulative duration of metformin therapy (<27.0, 27.0-48.1, >58.1 months) to define exposures.[36] Immortal time bias might happen in these five studies since the investigators collected the cumulative duration or prescriptions of metformin without using time-varying methods. Therefore, during follow-up periods, non-exposures might be misclassified as exposures or vice versa, then resulted in immortal time bias.

4.3.2 Time lag bias

Seven reviewed studies were found to have time lag bias.[28,29,33,34,38,39,43] Four cohort studies did not use a new user design or recruit new onset of diabetes patients.[28,29,33,34] Three case-control studies did not match duration of diabetes in cases and controls.[38,39,43]

4.3.2.1 Without applying a new user design or new-onset design

In the study by Samaras et al. (2020), the primary control group was participants with diabetes without receiving metformin. The investigators did not clarify if or which other oral medications they were using or did not use any antidiabetic medication in the control group. Thereby, it is not clear whether the metformin and non-metformin groups were at the same stage of disease. If metformin was compared with a second- or third-line therapy or non-antidiabetic agent, time lag bias was likely to exist because longer duration of diabetes might be associated with a higher risk of dementia.[29] In a study by Hsu et al., one of the control groups was diabetes patients without any antidiabetic medications; thus, it was unknown if participants in the treatment and control group were at the same stages of diabetes. Comparing the effects of medications given at different stages of the disease could lead to time lag bias.[28] In the study by Kim et al. in 2020, the authors did not indicate if metformin users or non-metformin users had additional antidiabetic treatments. Therefore, the duration of diabetes in the exposure and control groups was unknown, and metformin might be compared with second- or third-line diabetes treatments, which could lead to time lag bias.[33] Ng et al.'s only mentioned the control group was non-metformin users, but the information of other antidiabetic medications used was not provided. Beyond that, some metformin users had a history of using other antidiabetic agents. Therefore, it was unknown if participants in the exposure and comparison group were at the same stages of diabetes, which might lead to time lag bias.[3]

4.3.2.2 Duration of diabetes was not matched

A nested case-control study by Wium-Andersen et al. was found metformin use was associated with lower odds of dementia after multiple adjustments (aOR=0.94 95% CI

0.89–0.99), which suffered from time lag bias. In this study, although all participants were patients with type 2 diabetes, many patients used more than one type of antidiabetic medication. It indicated the participants were most likely at different stages of diabetes, thus, resulted in time lag bias.[38] Another two case-control studies applied PS to create matched controls to cases, but the duration of diabetes was not matched. Therefore, it was possible that cases had more severe diabetes patients than controls, which biased the effects of metformin on dementia risk.[39,43]

4.3.3 Time-window bias

Two case-control studies and one nested case-control study were found to suffer from time-window bias because cases and controls did not have the same opportunity to exposure to metformin.[37,39,43] Sluggett and his group aimed to explore whether metformin modified the relationship between diabetes and the incidence of AD. Cases were participants who registered in the national Medication Use and Alzheimer's disease (MEDALZ) study and had been diagnosed with diabetes at least 3 years before AD diagnosis. Their results indicated that metformin use≥10 years was associated with a reduced the risk of dementia (aOR=0.85 95% CI 0.76–0.95). At the date of AD diagnosis (index date), the authors selected controls through matching to cases on age, sex, and diabetes duration. Duration of diabetes was matched through five categories: use only during lag period; >0 to <1 year; 1 to <5 years; 5 to <10 years; ≥10 years. However, cases and controls were not matched on the duration of follow-up, which lead to time-window bias. For example, although cases and controls both had ≥10 years of diabetes duration, controls might have a longer follow-up period than cases if without matching on follow-up

periods. In this case, controls would have greater opportunities to receive metformin prescriptions than cases. Therefore, it was unreliable to report long-term metformin use was associated with a reduced dementia risk.[37] Similarly, in the study by Imfeld et al. (2012), cases were matched years of history in the database to cases, which indicated cases and controls might have same follow-up periods. However, duration of diabetes was not matched, thus, time-window bias still might happen because exposure time window for metformin in cases and controls might be different. This study found long-term users of 60 or more metformin prescriptions were at greater risk of developing AD. So, cases might have greater metformin exposure opportunities than controls, which resulted in time-window bias.[43] Time-window bias was also likely to exist in another case-control study by Bohlken and his group because cases were not matched on duration of diabetes and follow-up periods to cases in this study.[39]

4.3.4 Without any time-related biases

Only one cohort study was identified as not having any apparent time-related biases.[42] Kuan et al. (2017) applied a PS to match metformin and non-metformin cohorts on several critical potential confounders, such as age, sex, anti-DM medications other than metformin, and follow-up time, to evaluate the effect of metformin on the risk of dementia. The results from a sensitivity analysis using a time-dependent Cox regression model suggested that metformin exposure was significantly associated with an increased risk of dementia (aHR=1.66 95%CI 1.35, 2.04). In this study, the index date (time zero) in the metformin cohort and non-metformin group was the same, which the 90th days of medication use; thus, there was no immortal time between time zero and the first

prescription. Although the study used the average dose of metformin therapy as exposures, the time-varying covariate method was applied; thereby, misclassification of immortal time during follow-up periods was unlikely to happen. New diagnoses of T2DM patients between January 1, 2000, and December 31, 2010, were included, which could help address time lag bias. Overall, although some details of their study design and statistical analysis were not very clear, the authors tried to consider and address time-related biases in the study carefully.

4.4 Summary

In summary, most reviewed studies investigating the effect of metformin on dementia risk afflicted with some time-related biases, while only one study was found having no time-related biases. Among all reviewed articles with time-related biases, the study by Wium-Andersen et al. has effectively addressed most time-related biases. Immortal time bias was avoided by applying risk-set sampling and time-varying metformin exposure in their study. Moreover, the investigators selected controls through matching to cases on follow-up time, and all the patients had T2DM. Therefore, matching the duration of follow-up ensures the same exposure opportunity for cases and matched controls. Thus, time-window bias is unlikely to happen either.[38] Although time lag bias might exist in this study due to the unmatched duration of diabetes in cases and controls, it might not be a significant bias that could severely bias their results.

CHAPTER 5

DISCUSSIONS

To our knowledge, this is the first study to conduct a systematic review to identify if time-related biases exist in previous observational studies investigating the associations between metformin and dementia risk among patients with diabetes. As a result of our comprehensive systematic review, we found that after adjusting for potential confounding variables, 75% of reviewed studies indicated metformin decreased the risk of dementia; 12.5% of reviewed studies supported metformin increased dementia risk; and 12.5% of studies found no associations between metformin and dementia risk. Eleven out of sixteen reviewed studies were found to have immortal time bias, seven studies suffered from time lag bias, three studies afflicted with time-window bias, and one study was identified as not having any apparent time-related biases. A previous systematic review found that metformin had a protective effect against dementia among individuals who were taking it for diabetes management.[9] However, taking the potential time-related biases into consideration, we found the results from existing observational studies are inconclusive regarding the effects of metformin use for dementia risk.

Although no previous studies have investigated time-related biases existed in previous observational studies exploring the effects of metformin on dementia risk, these biases have been described in some other fields such as antidiabetic medications and cancer.[11,46] A large number of observational studies reported significant reductions in the risk of different types of cancer associated with metformin use. However, many of these studies were found to suffer from time-related biases, such as immortal time bias, time lag

bias, and time-window bias.[12-22] Four previous studies suggested metformin associated with improved survival of cancer patients with diabetes, but they also seem to suffer from some time-related biases.[47-50] Three studies applied statistical models with time-dependent covariates and new user design to address immortal time bias and time-window bias and found no associations between metformin use and cancer incidence.[23-25]

Eighteen clinical trial studies have been completed to investigate the effects of metformin to treat cancer. Among these completed clinical trials, four studies neither had results posted nor published; five studies had results posted but not published. In the nine completed and published clinical trials, five studies supported beneficial effects of metformin for patients with cancer; for example, metformin was associated with improved overall survival of patients with cancer.[51-55] However, four of these five studies were single-arm studies that recruited 41, 39, 90, and 15 participants, respectively.[51-53,55] Although another study used parallel assignment and recruited 102 participants, it was non-randomized.[54] Therefore, there is not enough evidence to conclude that metformin is beneficial for patients with cancer based on the results from these single-arm or non-randomized clinical trials with small sample sizes. Four studies indicated metformin showed no significant effect on overall survival in patients with cancer. All these four clinical trials were randomized, parallel arms, and double/quadruple masked.[56-59] The largest randomized controlled trial (RCT) of these is the ongoing MA.32 conducted by the National Cancer Institute of Canada Clinical Trials Group. MA.32 is a multicenter phase III RCT that recruited 3,600 women with early-stage breast cancer; it primarily aims to compare metformin versus placebo on invasive, disease-free survival among women with early breast cancer. The estimated completion date of this trial is February 28, 2022.

Up to now, only two clinical trials examining the effects of metformin on dementia or cognitive impairment were completed and published their results. One was a double-blind placebo-controlled randomized pilot study, which obtained the preliminary evidence of the effects of 12 months metformin intakes on AD among 90 participants with amnestic mild cognitive impairment (AMCI) at risk. The primary outcomes were total recall in the Selective Reminding Test (SRT) and Alzheimer's Disease Assessment Scale cognitive subscale (ADAS-Cog). After adjusting for baseline difference in the ADAS-Cog, the metformin group showed only significantly greater improvement in total recall in the SRT compared to the placebo group (9.7 ± 8.5 vs. 5.3 ± 8.5; $p = 0.02$).[60] Another clinical trial was also a pilot study, which used a randomized, double-blinded, placebo-controlled, 16 weeks crossover design to investigate the effects of metformin on AD biomarkers. The results of this study are not published, as the results were inconclusive due to 16 weeks crossover design and the tiny sample size, which only recruited 20 participants. Thus, up to now, the completed clinical trials do not provide strong evidence to support a protective effect of metformin on dementia risk.

CHAPTER 6

CONCLUSIONS

In conclusion, most of the reviewed observational studies exploring the associations between metformin and dementia risk supporting a reduced risk of dementia associated with metformin use among patients with diabetes. A couple of studies found metformin was associated with increased risk or no associations between metformin and risk of dementia. Therefore, previous observational studies are inconsistent regarding the association between metformin use and dementia risk. However, all reviewed studies except one were afflicted with some types of time-related biases, illustrating that time-related biases are common in the observational studies investigating the impacts of oral anti-diabetic medications on dementia risk. They may be alleviated by using appropriate study designs and analysis methods. Future observational studies should use more rigorous study designs and statistical analyses to avoid or reduce time-related biases.

Figure 1.1: biological mechanism of metformin

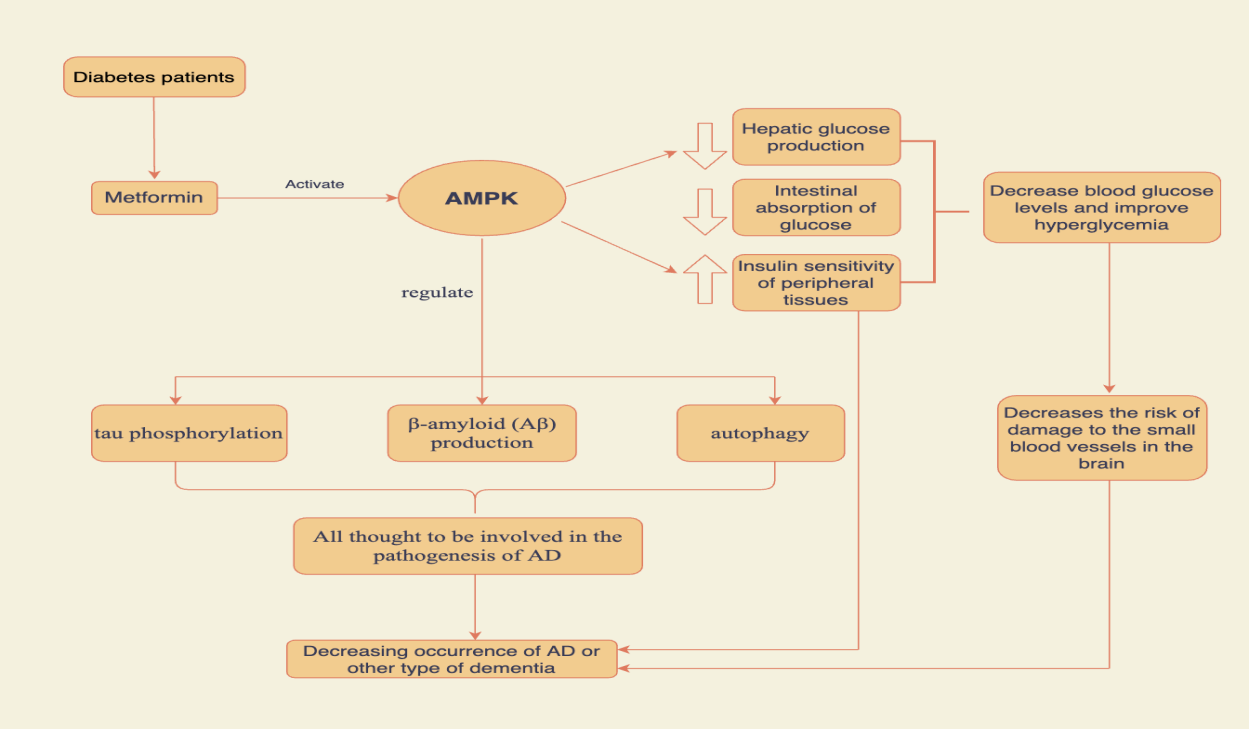

Figure 3.1A: Immortal time bias

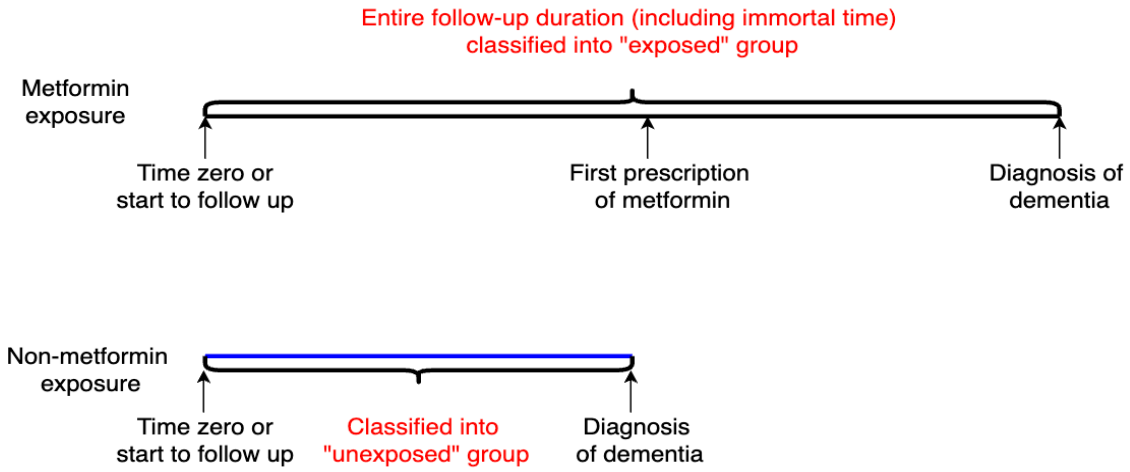

Figure 3.1B: A proper method to deal with immortal time bias

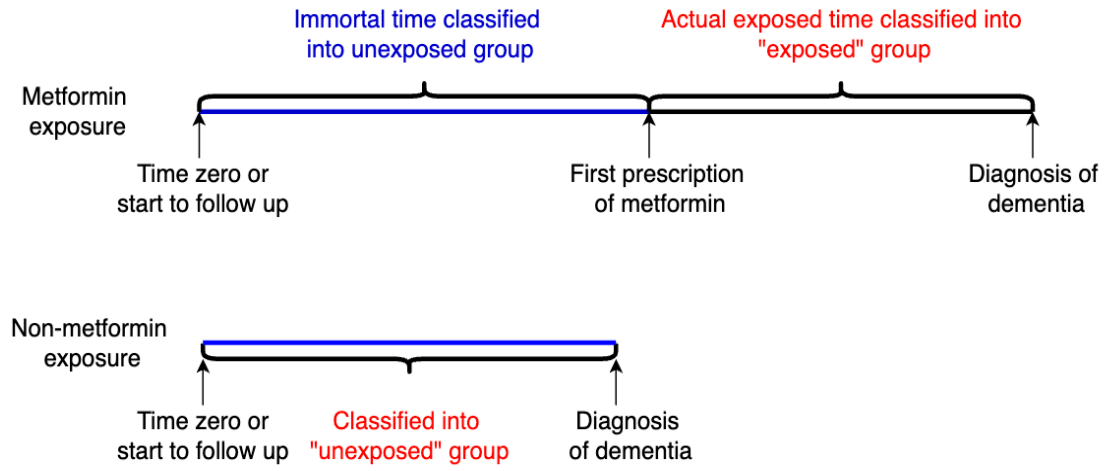

Figure 3.2A: Time lag bias

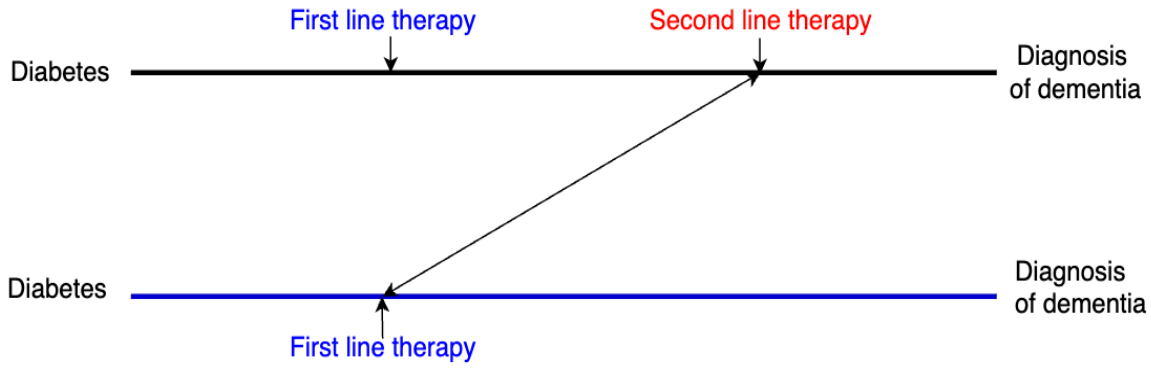

Figure 3.2B: Appropriate comparison to fix time lag bias

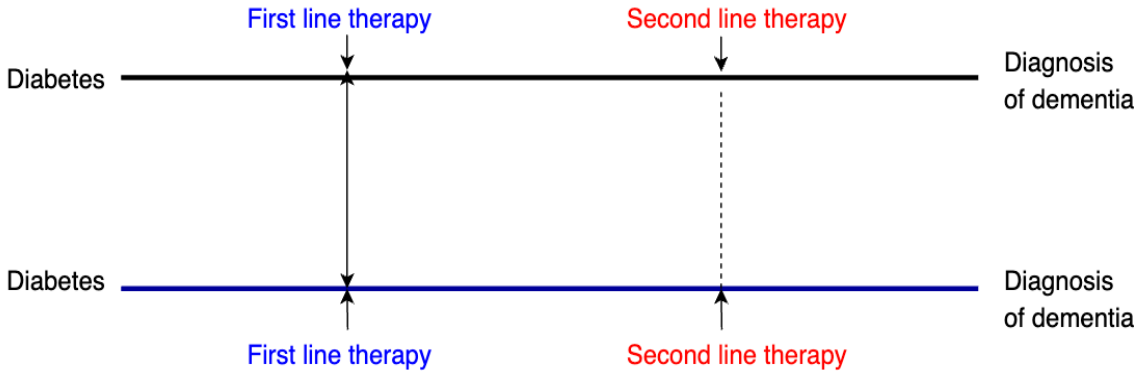

Figure 3.3A: Time-window bias

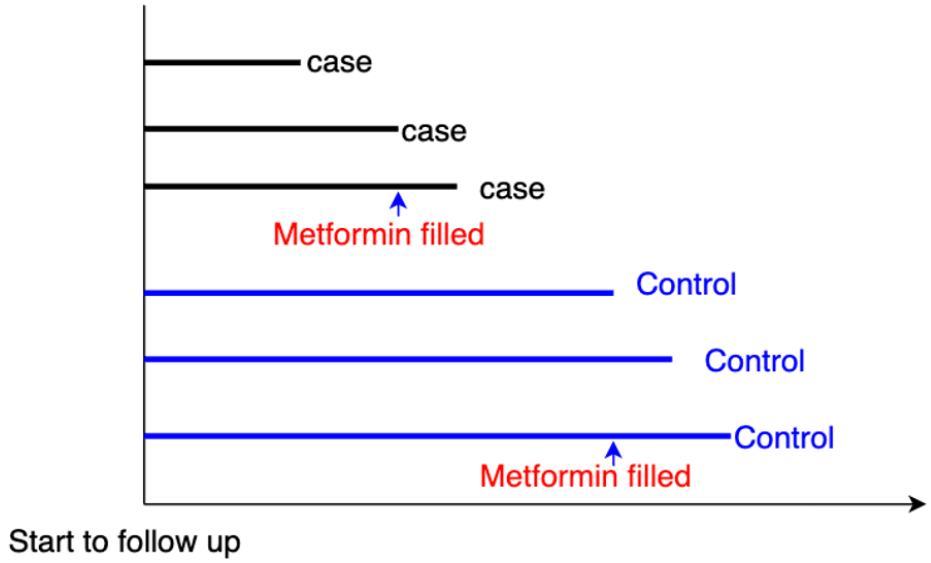

Figure 3.3B: A proper method to address time-window bias

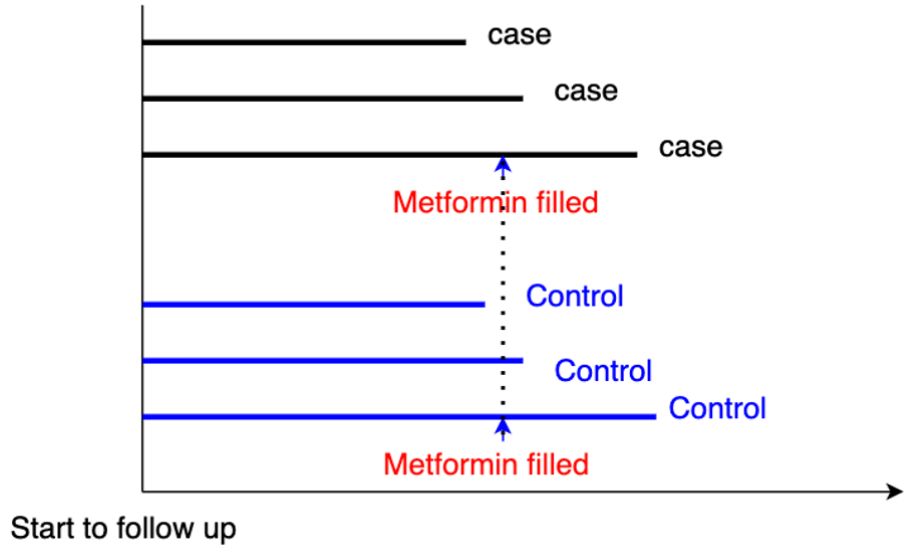

Figure 4.1: Flow diagram summarizing study identification and selection

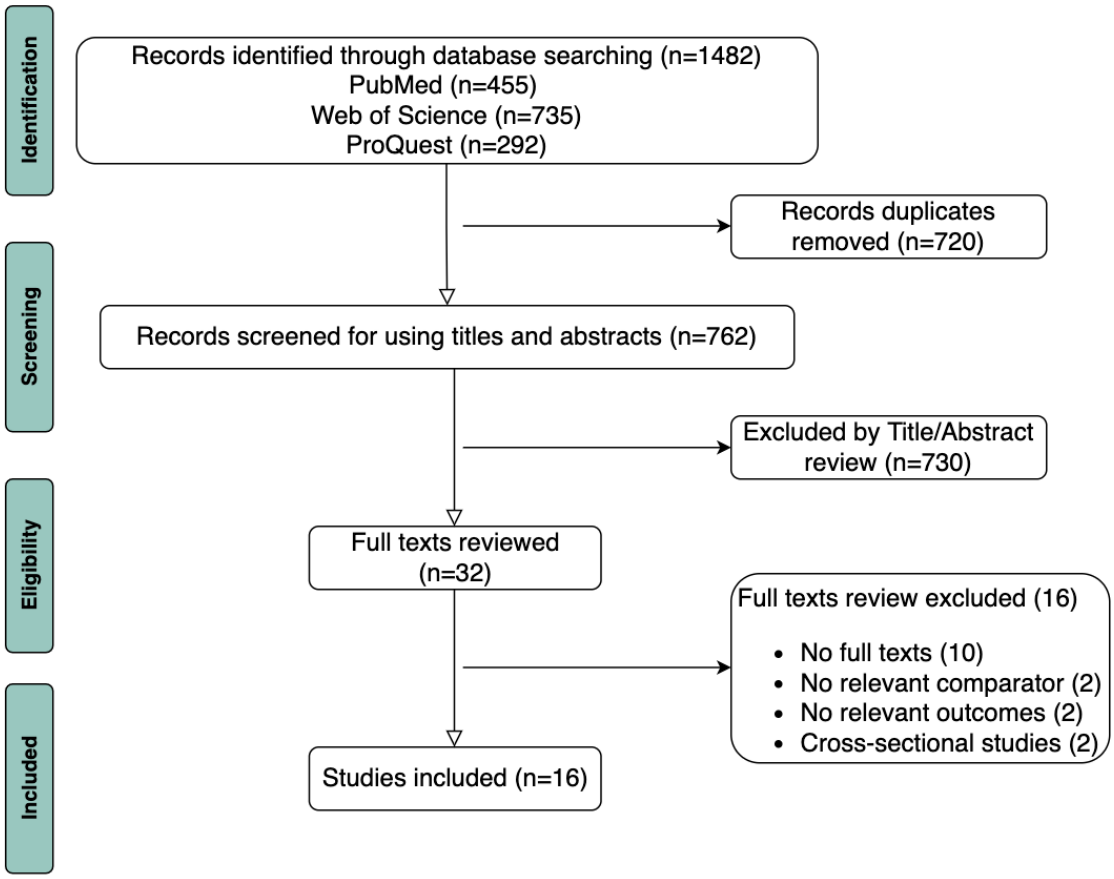

Table 4.1: time-related biases in observational studies investigated the effects of metformin on the risk of dementia

First author (Year) [reference]	Exposure (Sample size)	Comparator (Sample size)	Population (All dementia free at baselines)	Statistical methods	Outcomes	Estimated association (95% CI)	Immortal time bias	Time lag bias	Time-window bias
Cohort studies									
Hsu (2011)[28]	T2DM patients with metformin monotherapy (1864)	Non-medication patients with T2DM (10519). Cohort without T2DM (101816)	Taiwanese, aged ≥50ys	Cox regression model	dementia	0.76 (0.58–0.98) [a]	Yes	Yes	
Samaras (2020)[29]	Participants with diabetes with metformin (combined or monotherapy) (67)	Metformin non-users (non-medication users or antidiabetic medications other than metformin) (56).	Australia, Sydney. Community-dwelling participants aged 70-90ys with DM.	Linear mixed model and cox regression survival analysis	Cognitive decline; Cognitive Performance; dementia	Dementia: 0.19 (0.04–0.85) [a]	Yes	Yes	
Shi (2019)[30]	Insulin and metformin users (3053)	Insulin users but without metformin (2993)	US Veterans with T2DM, aged ≥50ys, insulin users.	Cox regression model	ND, including AD, PD, dementia and mild cognitive impairment.	2-4ys: Dementia: 0.55 (0.38-0.79) [a] >4ys: Dementia: 0.22 (0.13-0.37) [a]	Yes		
Scherrer (2019)[31]	New users of metformin monotherapy (55,859)	New users of sulfonylurea monotherapy (17,902)	African American and whites with T2DM and aged ≥50ys.	Cox regression model	dementia	Whites: 0.98 (0.92-1.05) [a] African American: 0.77 (0.64-0.94) [a]	Yes		
Scherrer (2019)[32]	New users of metformin monotherapy (64518)	New users of sulfonylurea monotherapy (21535)	Veterans' Health Affairs (VHA) patients and Kaiser Permanente Washington (KPW) patients with T2DM, aged ≥ 50ys.	Cox regression model	dementia	VHA 0.93 (0.87–0.99) [a] KPW 0.89 (0.74–1.07) [a]	Yes		
Kim (2020)[33]	Metformin use (combined or monotherapy) ≥90 days Low users (1211) Mid users (1210) High users (1211)	Metformin use (combined or monotherapy) <90 days (4436)	Korean National health insurance holders with DM, aged 40-79ys.	Cox regression model	dementia	0.97 (0.73–1.28) [a] 0.77 (0.58–1.01) [a] 0.48 (0.35–0.67) [a] 0.80 (0.65–0.98) [a] 0.61 (0.50–0.76) [a] 0.46 (0.36–0.58) [a]	Yes	Yes	
Ng (2014)[34]	Metformin use (combined or monotherapy) ≤6ys before baseline (114) or metformin use >6ys before baseline (90)	Metformin non-user (non-medication or antidiabetic medication other than metformin in the year before baseline (161)	Singapore, patients with DM, aged ≥55ys with severe mental or physical disabilities	Generalized estimating equation modeling	Cognitive impairment	>6ys: 0.27 (0.12–0.60) [b] ≤6ys: 0.75 (0.35–1.59) [b]	Yes	Yes	

Orkaby (2017)[35]	New users of metformin monotherapy (17200)	New users of Sulfonylureas monotherapy (11440)	US veterans aged ≥65ys with T2DM.	Cox regression model	Dementia	<75ys 0.89 (0.79–0.99) [a] ≥75ys 0.96 (0.87–1.05) [a]	Yes		
Tseng (2017)[36]	Metformin ever users (combined therapy) (15,676)	Metformin never users (antidiabetic medication other than metformin) (15,676)	Taiwan's population who aged between 25ys to 75ys. New-onset diabetes patients during 1999 and 2005.	Cox regression model	Dementia	<26.6 months: 1.279 (1.100-1.488) [a] 26.6-57.8 months: 0.70 (0.60-0.83) [a] >57.8 months: 0.39 (0.32-0.47) [a]	Yes		
Huang (2014)[40]	Metformin use (4978)	Diabetes other therapy	Taiwanese population, newly diagnosed diabetes between January 1997 and December 2007.	Cox regression model	AD	Metformin monotherapy: 0.69 (0.28–1.71) [a] Metformin combination therapy: 0.57 (0.26–1.26) [a]	Yes		
Cheng (2014)[41]	Metformin only users (1033)	Sulfonylurea only users (796) or thiazolidinediones only users (28)	Taiwanese population, birth-year period before 1940 (≥65ys) and new-onset diabetes between January 2004 to June 2009.	Cox regression model	Dementia	0.82 (0.52-1.28) [a]	Yes		
Kuan (2017)[42]	Metformin use (alone or combined) (4651)	Metformin non-users, but with other anti-diabetic medications (4651)	Taiwanese population, aged >50ys. New diagnosis of T2DM between January 1, 2000, and December 31, 2010.	Cox regression model	Dementia, PD	Dementia: 1.66 (1.35–2.04) [a] PD: 2.27 (1.68, 3.07) [a]			
Case-control studies or nested case-control studies									
Sluggett (2020)[37]	Metformin users >3 years before AD or individuals who were only exposed to metformin during the 3-year lag period	Metformin non-users (non-medications or antidiabetic medications other than metformin)	Finland. All community-dwelling people with DM in Finland.	Conditional logistic regression models	AD	Metformin ever use: 0.99 (0.94–1.05) [b] Metformin use>10 years: 0.85 (0.76–0.95) [b] DDD > 1825 and metformin intake >1.0 DDD/day: 0.89 (0.82-0.96) [b]			Yes
Wium-Andersen (2019)[38]	Metformin ever users: 0-0.5 daily defined doses (DDD), 0.5-0.75 DDD, 0.75-1 DDD, >1 DDD.	Metformin never users (non-medication or antidiabetic medication other than metformin)	Denmark. Patients in Denmark registered with T2DM in the National Diabetes Register (NDR)	Conditional logistic regression models	Dementia	0.94 (0.89–0.99) [b]		Yes	

Bohlken (2018)[39]	Metformin monotherapy, or metformin as dual therapy with sulfonylureas	Sulfonylurea monotherapy	Germany. Cohort aged ≥60ys with T2DM	Multivariate regression models	Dementia	Metformin monotherapy: 0.71 (0.66–0.76) [b] Metformin+ sulfonylureas (dual therapy): 0.90 (0.89–0.92) [b]		Yes	Yes
Imfeld (2012)[43]	Metformin use: 1-9, 10-29, 30-59, ≥60 prescriptions or Metformin monotherapy: 1-9, 10-29, ≥30 prescriptions	Metformin non-users	UK. Cohort aged ≥65ys with DM	Conditional logistic regression	AD	metformin≥60: 1.71 (1.12–2.60) [b] 30–59: 0.99 (0.68–1.44) [b] 10–29: 1.47 (1.03–2.09) [b] 1–9: 1.08 (0.75–1.56) [b]		Yes	Yes

[a]*Hazard ratio;* [b]*Odds ratio*

All HRs or ORs were obtained after adjustment of potential confounders or inverse probability of treatment weighting for propensity score.

Table 4.2: Quality of included studies Assessing the risk of dementia with metformin use

Studies	Study quality[a]								
Cohort studies	Selection				Comparability	Outcome/exposure			Total scores
	Exposed	Non-exposure	Ascertainment of exposure	Outcome		Assessment of outcome	Length of follow-up	Adequacy of follow-up	
Hsu (2011)[28]	*	*	*	*	*	*	*		7
Samaras (2020)[29]	*	*	*	*	*	*	*		7
Shi (2019)[30]	*	*	*	*	*	*	*		7
Scherrer (2019)[31]	*	*	*	*	*	*			6
Scherrer (2019)[32]	*	*	*	*	*	*			6
Kim (2020)[33]	*	*	*	*	*	*	*		7
Ng (2014)[34]	*	*	*	*	*	*	*		6
Orkaby (2017)[35]	*	*	*	*	*	*	*		7
Tseng (2017)[36]	*	*	*	*	*	*	*		7
Huang (2014)[40]	*		*	*	*	*	*	*	7
Cheng (2014)[41]	*	*	*	*	**	*	*		7
Kuan (2017)[42]	*	*	*	*	*	*	*		6
Case-control studies	Selection				Comparability	Outcome/exposure			Total scores
	Case definition adequate	Representativeness of the case	Selection of controls	Definition of controls		Ascertainment of exposure	Same methods of ascertainment for cases and controls	Non-Response rate	
Sluggett (2020)[37]	*	*	*	*	*	*	*		7
Wium-Andersen (2019)[38]	*	*	*	*	*	*	*		7
Bohlken (2018)[39]	*	*	*	*	*	*		*	7
Imfeld (2012)[43]	*	*	*	*	*	*	*		7

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