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Original Article

Opposite causal effects of type 2 diabetes and metformin on Alzheimer's disease

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ABSTRACT

Background: Type 2 diabetes (T2D) is commonly co-morbid with Alzheimer's disease (AD). However, it remains unclear whether T2D itself or the antidiabetic drug metformin contributes to the progression of AD.
Objective: This study aimed to investigate the overall and independent effects of T2D and metformin use on the risk of AD.
Methods: Summary genome-wide association study datasets were utilized for the Mendelian randomization (MR) and multivariable MR (MVMR) analyses, including ones for T2D (N = 455,017), metformin (N = 456,276), and AD (N = 453,733). Additionally, using the proportional imbalance method, we analyzed AD-related adverse drug events in the FDA Adverse Event Reporting System (FAERS) database (covering Q1 2004 to Q2 2024).
Results: Our two-sample MR analysis indicated that T2D is not associated with the risk of AD (OR: 1.03, CI: 0.99–1.08, P = 0.128). However, while not statistically significant, genetic signature for metformin exposure demonstrated a trend toward an increased risk of AD (OR: 1.05, CI: 1.00–1.09, P = 0.053). Interestingly, in MVMR analysis, which evaluates independent effects of T2D and metformin exposure on T2D, we found a robust association of T2D with a decrease in the risk of AD (OR: 0.82, CI: 0.68–0.98, P = 0.031), while the use of metformin was associated with a higher risk of AD (OR: 1.26, CI: 1.06–1.50, P = 9.45E-3). In the FAERS database, a total of 228,283 metformin-related adverse event reports from 67,742 cases were found. For metformin as the target drug and AD as the target adverse event, signal analysis reported 29 cases of AD (ROR: 0.83, 95 % CI: 0.58–1.19, P = 0.3126).
Conclusions: Our study reveals the opposite independent causal effects of T2D and metformin exposure on AD. These findings highlight the importance of assessing AD risk when prescribing metformin to patients with T2D.

1. Introduction

Type 2 diabetes (T2D) is associated with an increased risk of developing Alzheimer's disease (AD). Both hallmarks of T2D, insulin resistance and chronic inflammation, impact brain health negatively. In particular, elevated blood sugar levels and metabolic dysfunction may contribute to the accumulation of amyloid plaques and tau tangles. Additionally, vascular changes, which are characteristic of T2D, may impair cerebral blood flow, further exacerbating cognitive decline and the progression of AD.

In AD, there is an abnormal accumulation of toxic proteins agglomerates, increased inflammation, neuronal loss and heightened glial response, often accompanied by local resistance to insulin [1]. Epidemiological evidence suggests a link between AD and T2D, as these conditions share certain pathological commonalities such as insulin resistance and impaired glucose metabolism [2,3]. Dysfunctional insulin signaling pathways are a critical link between neurodegeneration in AD and cognitive impairment in T2D, suggesting that these conditions may exacerbate each other [4]. This connection underscores the importance of exploring integrated therapeutic approaches that address both insulin

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resistance and neurodegeneration. Medications like semaglutide have shown potential protective effects against AD, highlighting the possibility of repurposing diabetes treatments to mitigate dementia risk [2]. Furthermore, lifestyle interventions such as exercise, which improve insulin sensitivity, may also reduce the risk of AD and related dementia in individuals with prediabetes, emphasizing the need for preventive strategies targeting metabolic health [5]. While metformin has been suggested to lower dementia risk, further research is necessary to confirm its efficacy in this context [6]. Overall, the interplay between T2D and AD suggests that managing diabetes effectively could be a crucial component in reducing the incidence and progression of AD.

When considering the interplay between chronic comorbidities, there is often a tendency to accept that there is an underlining 'vicious cycle' of worsening pathophysiological conditions, leading researchers to pursue specific lines of inquiry to validate this assumption. This predisposition also fosters the belief that treatments effective for disease A should likewise benefit its comorbid counterpart, disease B. T2D and AD represent a classic example of age-related comorbidities: numerous observational studies and animal studies suggest that T2D may increase the risk of AD and that T2D treatments could potentially mitigate this risk [7,8]. For example, metformin, a widely used medication for T2D, has shown potential neuroprotective effects that may benefit AD by improving insulin sensitivity, activating chaperone-mediated autophagy, and reducing inflammation in the brain [8,9]. On the other hand, some studies suggest that metformin facilitates the generation of amyloid-β by β- and γ-secretases through autophagy activation [10].

Clinical observational studies are often susceptible to biases related to sample size, participant selection, and reverse causality. Additionally, the animal models used in some studies are far from being accurate reflection of respective human pathophysiology, making it difficult to figure out the relevance of the studied treatments to actual T2D patients. Mendelian Randomization (MR) uses genetic variants to infer causal relationships between risk factors and outcomes, minimizing bias. It has been widely applied to study both somatic [11,12] and mental disorders [13–15]. To circumvent these issues, we employed MR and multivariable MR (MVMR) analyses, which can evaluate both the overall and independent effects of T2D and metformin exposure on T2D. In this study, we utilized the largest genome-wide association study (GWAS) datasets to conduct both MR and MVMR analyses in T2D and AD. Employing the MVMR framework allowed us to investigate the direct effects of T2D and the associated use of metformin on AD while accounting for the confounding influences of each factor. Additionally, we utilized the FDA Adverse Event Reporting System (FAERS) database to analyze real-world adverse drug reactions associated with metformin use. Surprisingly, we found that after accounting for confounding influences, T2D primarily exerts a protective effect on AD, whereas exposure to metformin significantly increases the risk of AD.

2. Methods

2.1. GWAS summary datasets

Publicly available summary results of the GWAS were used for the MR and MVMR analyses in this study. The datasets on T2D (21,969 cases and 433,048 controls) and metformin (11,358 cases and 444,918 controls) from the UK Biobank were obtained YangLab [16]. We obtained an independent AD dataset from the FinnGen project R11, including 16,902 cases and 436,831 controls (N = 453,733) [17]. Information on the included datasets is summarized in **Supplementary Table S1**. All participants in the datasets were of European origin. Ethical approvals were obtained in all original studies.

2.2. MR analysis

The MR analyses were conducted using three models in TwoSampleMR [18]. The inverse-variance weighted (IVW) model was selected as the main method, while the MR-Egger and weighted median (WM) models were used as complementary methods. The intercept from the MR-Egger regression was employed to evaluate the average directional pleiotropy. Heterogeneity was assessed using both I^2 statistics and Cochran's Q test (with $I^2 > 0.25$ and $P < 0.05$ indicating significant heterogeneity) [19]. Single nucleotide polymorphisms (SNPs) with genome-wide significance ($P < 5 \times 10^{-8}$) in the exposure datasets were used to derive independent instrumental variables (IVs) ($r^2 < 0.001$ within a 10 Mb window). To further identify and correct for potential outlier SNPs due to horizontal pleiotropy, the MR-pleiotropy residual sum and outlier (MR-PRESSO) method was applied. SNPs not detected as pleiotropic outliers were included in the final MR analysis.

2.3. MVMR analysis

To assess the direct effects of each exposure on AD, we performed a MVMR analysis using the TwoSampleMR package [18]. Genetic instruments for each exposure were identified and combined, then incorporated into the analysis pipeline.

2.4. Adverse effect analysis of metformin

Adverse event data were sourced from the U.S. FAERS database and analyzed through the online tool "FastSignal" (http://www.faers.tritbio.com/). The drug of interest was METFORMIN, and the preferred item (PT) for the target adverse event was "Alzheimer's disease", respectively. The presence or absence of adverse event signals was assessed by screening for associations. Disproportionality analysis was employed to identify adverse event signals, with the reporting odds ratio (ROR) serving as the statistical measure. An association between the drug and the adverse event was indicated if the lower 95 % CI for the ROR was greater than 1 and the number of cases (N) was at least 3. The dataset spanned from the first quarter of 2004 to the second quarter of 2024, with duplicate reports excluded during data processing.

3. Results

3.1. MR analysis

As a first step, we tested the "overall causal effects" of the genetic components predicting T2D and the use of metformin on AD in MR. We found that neither of these genetic components, one for T2D (OR: 1.03, CI: 0.99–1.08, $P = 0.128$) and one for metformin (OR: 1.05, CI: 1.00–1.09, $P = 0.053$) were associated with the risk of AD (Table 1 and Fig. 1).

The MR sensitivity analysis indicated that the causal effect directions were consistent across the various methods used (Table 1). The MR-Egger regression did not suggest directional pleiotropy in the MR analysis (MR-Egger intercept < 0.02). Nevertheless, evidence was found indicating potential heterogeneity in the MR results. Detailed MR results and heterogeneity tests are summarized in **Supplementary Table S2**. The MR-PRESSO analysis did not detect any outlier SNPs and relevant results are summarized in **Supplementary Table S3-S4** and **Supplementary Figure S1**.

3.2. MVMR analysis

To further investigate the direct causal effects of each factor on AD, we used MVMR, which accounts for the combined influence of interconnected factors. As such, each association identified by MVMR was interpreted as a "direct" or "independent" causal effect. The MVMR analysis results are presented in Fig. 2 and **Supplementary Table S3**. We found that T2D may strongly protect against the risk of AD (OR: 0.82, CI: 0.68–0.98, $P = 0.031$), while the genetic signature underlining preference to

Table 1
Causal associations between T2D, metformin, and AD.

Exposure	Outcome	Method	N_IV	P_IV	b (se)	OR [95 %CI]	P
T2D	AD	IVW	71	5.00E-08	0.034 (0.022)	1.03 [0.99–1.08]	0.128
T2D	AD	WM	71	5.00E-08	0.052 (0.030)	1.05 [0.99–1.12]	0.08
T2D	AD	MR-Egger	71	5.00E-08	0.052 (0.052)	1.05 [0.95–1.17]	0.327
Metformin	AD	IVW	44	5.00E-08	0.045 (0.023)	1.05 [1.00–1.09]	0.053
Metformin	AD	WM	44	5.00E-08	0.060 (0.031)	1.06 [1.00–1.13]	0.054
Metformin	AD	MR-Egger	44	5.00E-08	0.111 (0.058)	1.12 [1.00–1.25]	0.06

Note: T2D, type 2 diabetes; AD, type 2 diabetes; IVW, inverse variance weighted; WM, weighted median; N_IV, number of instrumental variables; OR, odds ratio.

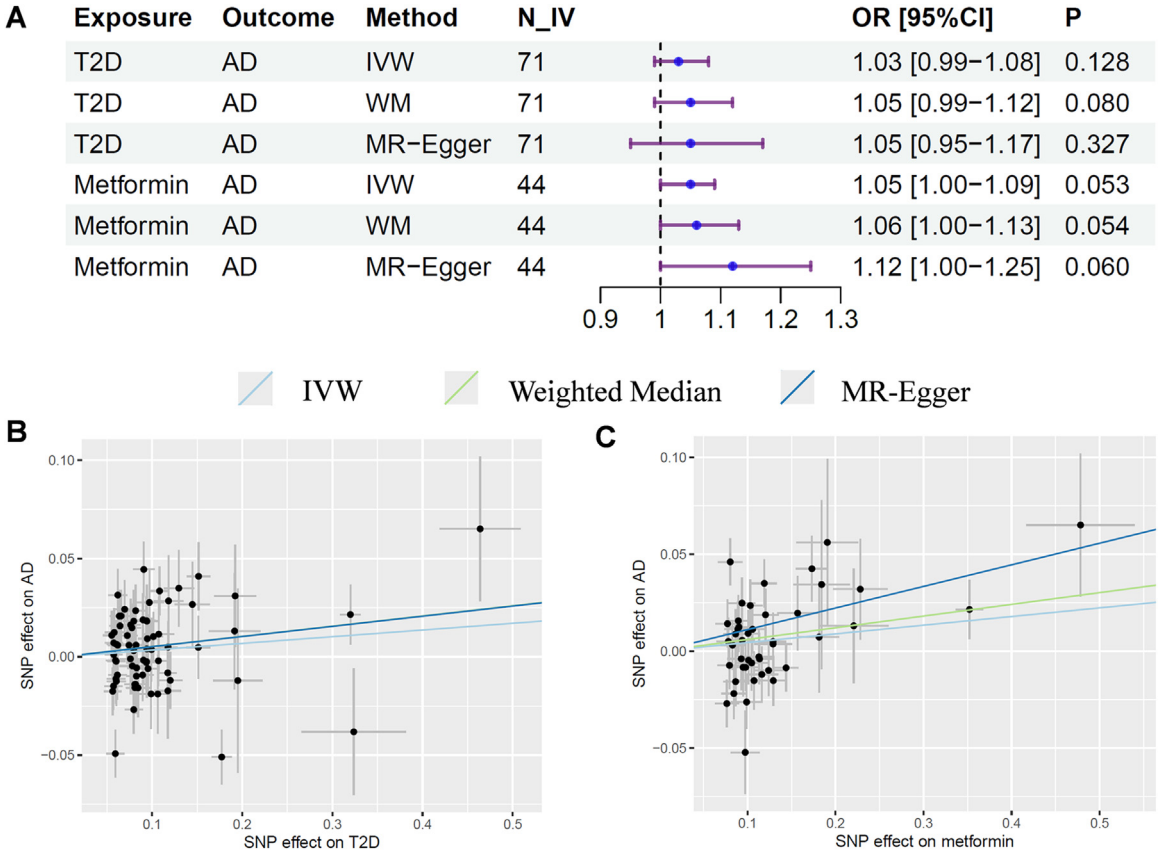

Fig. 1. Causal associations between T2D, metformin, and AD.
A. The forest plot shows causal associations between T2D, metformin, and AD revealed by various MR methods. **B-C.** The trait on the x-axis denotes exposure of T2D (**B**) or metformin (**C**), the trait on the y-axis denotes outcome, and each cross point represents an instrumental variant. The lines denote the effect sizes (b) of an exposure on an outcome. IVW: inverse variance weighted; WM: weighted median.

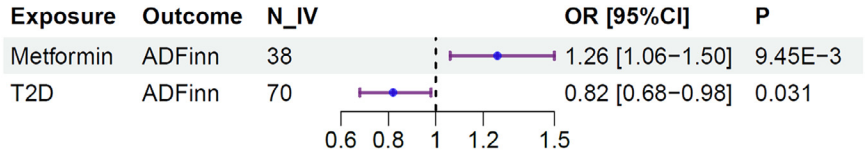

Fig. 2. Multivariable MR analysis between T2D, metformin, and AD.
Legend: Multivariable MR analysis of the association between metformin use and T2D with the risk of AD. The odds ratios indicate that metformin is associated with an increased risk of AD, whereas T2D is associated with a decreased risk of AD.

use metformin as T2D medication was associated with a higher risk of AD (OR: 1.26, CI: 1.06–1.50, P = 9.45E-3).

3.3. Mining of adverse event signals

We used the FAERS database to extract and analyze adverse event signals. When the target drug was metformin and the target adverse event was AD, the adverse reaction signal analysis reported 29 cases of AD (ROR: 0.83, 95 % CI: 0.58–1.19, P = 0.3126) among 228,254 adverse events associated with metformin (**Supplementary Table S4**).

4. Discussion

This study investigates the independent causal effects of T2D and metformin on AD using advanced genetic analysis methods. The hypothesis posits that T2D may increase AD risk due to metabolic dysfunctions, while metformin could have neuroprotective effects. However, MR analysis showed no significant association between genetic signature underlining preference to use metformin as T2D medication or T2D itself on the risk of AD. Further MVMR analysis revealed that the genetic signature contributing to the risk of T2D might actually protect against AD,

while that for the metformin use was linked to a higher AD risk. These findings challenge existing assumptions and could influence clinical decisions regarding T2D management and metformin use in the context of AD risk.

T2D has been linked to various diseases [20]. Epidemiological and observational studies have repeatedly suggested T2D as a comorbidity and risk factor for AD [21,22]. On the other hand, MR studies have provided a more complex view [23,24]. While validating some findings, such as the link between dyslipidemia and increased risk of AD, these studies indicated that T2D may not influence AD risk in direct and causal way [25]. If T2D was a direct risk factor for AD, then amyloid plaques and neurofibrillary tangles would likely be present in most T2D patients. However, this hypothesis is not supported by neuropathological evidence [26]. On the other hand, recent biochemically supported autopsy studies showed that AD brains are characterized by a certain reduction of glucose-derived metabolite levels [27], and that individuals genetically predisposed to AD exhibit inherent defects of glucose metabolism. In T2D, elevated blood glucose may compensate for these deficits. These intriguing questions certainly warrant further mechanistic exploration.

Some MR research has suggested a potential link between T2D and neurological diseases [28,29], through mechanisms involving gut microbiota and blood metabolites [29]. Conversely, other studies have found no significant relationship between the two conditions. These results are consistent with previous causal inference studies based on large sample GWAS data [25]. Our MR analysis adds to this ongoing discussion by showing no significant association between the genetic component of T2D and AD (OR: 1.03, CI: 0.99–1.08, $P = 0.128$). However, the MVMR analysis, which is capable of evaluating independent effects of T2D and metformin exposure on T2D, presents a different perspective. In this study, MVMR analysis indicated a protective effect of T2D against AD (OR: 0.82, CI: 0.68–0.98, $P = 0.031$). This discrepancy suggests that previous conflicting findings might be due to differences in how direct and independent causal effects were assessed. Moreover, the MVMR analysis has identified other factors, such as rheumatoid arthritis, as significant risk factors for late-onset AD, adding to the complexity of understanding T2D's role in AD risk [30]. These findings highlight that while T2D may influence certain pathways related to AD, its overall impact can vary depending on the presence of other interacting factors. The contrasting results underscore the necessity of further research to explore the underlying mechanisms and to reconcile these conflicting findings, focusing particularly on direct and independent causal pathways.

Traditionally, T2D is viewed as a risk factor for AD, with dysregulated insulin signaling playing a critical role. Impaired insulin and insulin-like growth factor signaling contribute to neurodegeneration, cognitive deficits, and neuroinflammation, which are hallmark features of AD [31,32]. Chronic low-grade inflammation and oxidative stress, common in T2D, exacerbate insulin resistance and promote amyloid-beta accumulation and neuroinflammation, further linking T2D to the progression of AD [33,34]. Additionally, protein aggregation, particularly of islet amyloid polypeptide in T2D, parallels the amyloid-beta and tau protein aggregation seen in AD [35,36]. Mitochondrial dysfunction, marked by oxidative stress and impaired adenosine triphosphate (ATP) production, is another shared feature affecting tissue regeneration and cognitive function in both conditions [37,38]. Recent MVMR analyses have introduced a nuanced perspective, suggesting a potential protective effect of T2D against AD, possibly due to complex metabolic interactions and compensatory mechanisms. The interplay between hyperglycemia, oxidative stress, and inflammation might create a unique environment that impacts neuronal health differently in individuals with T2D. Furthermore, medications like semaglutide and metformin, used to manage T2D, have shown potential in reducing AD risk by improving insulin sensitivity and reducing oxidative stress [2,4]. Understanding these intricate mechanisms could unveil novel therapeutic targets, offering new avenues for the prevention and treatment of AD in patients with T2D. Further research is needed to unravel these complex interactions and identify specific pathways that could mitigate AD risk in individuals with T2D.

Previous research has highlighted the potential benefits of metformin in reducing the risk of AD, suggesting neuroprotective properties and metabolic effects that may support cognitive function. Some studies have also pointed to metformin's protective effects against various conditions, including certain tumors and osteoarthritis [39–41], while noting increased risks for parkinsonism and erectile dysfunction [42,43]. Our results from the MVMR analysis indicate a higher risk of AD associated with metformin use (OR: 1.26, CI: 1.06–1.50, $P = 9.45E\text{-}3$), while the MR analysis showed no significant association (OR: 1.05, CI: 1.00–1.09, $P = 0.053$). One important reason may be that patients with T2D typically have elevated blood glucose levels and an increased energy supply to the central nervous system. To some extent, this slightly higher glucose supply may have a protective effect on brain health. As a first-line treatment for T2D, metformin effectively controls blood glucose levels but also reduces this compensatory glucose supply to the central nervous system. This could explain the differing impacts of T2D and metformin use on AD risk. It also helps clarify why no significant effect of metformin on AD was observed in the FAERS database: the opposing effects of T2D itself and metformin on AD may offset each other, or may be intertwined in real-world observations. Using MVMR technology, we gain insight into the complex and paradoxical interaction between T2D and metformin in relation to AD risk. This discrepancy underscores the complexity of metformin's effects on AD risk, raising concerns about the drug's safety profile concerning neurodegenerative diseases.

In animal studies, metformin has been implicated in potentially increasing the risk of AD [44,45], while findings from observational studies in humans remain inconsistent. Reported results of clinical trials on metformin in individuals without T2D are plagued by small sample sizes and short study durations, with some suggesting that metformin may have a protective effect against AD. The FAERS database records adverse events for various medical drugs and is widely utilized for monitoring drug safety and making regulatory decisions. After examining FAERS records for metformin as the target drug and AD as the target adverse event, a total of 29 CE cases were found (ROR: 0.83, 95 % CI: 0.58–1.19, $P = 0.3126$). Lack of significance of this finding may be attributed to several factors. In particular, FAERS typically reports short-term, easily observable adverse events, rather vaguely defined onsets of chronic conditions, let alone the conditions already known for their association with aging. Consequently, the impact of drugs on AD in the FAERS database may be underreported. It should be also taken into consideration that the 2024 revision of the ATN diagnostic framework for AD emphasizes objective, biologically defined markers [46], while recognizing that cognitively normal individuals with early-stage AD should be considered as a part of the AD continuum. Historically, entering the case into the FAERS database has not required any biomarkers to support diagnoses of AD or cognitive impairments, which may further underestimate the effect of metformin on AD. The need for further high-quality clinical research aimed at improving our understanding of the relationship between metformin and AD is obvious.

The association between metformin and AD is complex and involves several mechanisms that warrant further investigation. While metformin is primarily known for its glucose-lowering effects in diabetes, its use has shown both potential benefits and risks concerning AD, highlighting a need for a deeper understanding of its pharmacological pathways and patient-specific factors. Metformin has anti-inflammatory properties, which could theoretically benefit AD patients by reducing neuroinflammation, a key factor in AD progression [47]. Additionally, it enhances insulin signaling, crucial since impaired insulin signaling is linked to AD pathology through increased amyloid-beta and tau phosphorylation [31]. However, despite these potential benefits, MVMR analysis has observed an increased risk of AD with metformin use, suggesting adverse effects or interactions that may counteract its expected neuroprotective benefits. One possible mechanism involves metformin's influence on insulin signaling pathways, crucial for neuronal health. The drug's impact

on gut microbiota and systemic inflammation may also play a role in modulating neurodegenerative processes. Furthermore, metformin's effects on amyloid-beta metabolism are mixed, with some studies indicating negative impacts on amyloid-beta levels and cognitive function in AD models [10,48]. This suggests that metformin's influence might vary based on patient-specific factors or disease stages. Additionally, its role in autophagy, crucial for clearing toxic protein aggregates, may not always be positive [10].

The strong link between diabetes and obesity underscores the need to consider potential role of excessive adiposity on AD. In clinical and animal studies, both obesity and T2D are associated with cognitive decline. Most prominent pathophysiological driver of T2D is so-called vascular dementia, which is due to endothelial cell dysfunction and capillary damage. Despite the shift toward biologically defined diagnostic frameworks being integrated into AD research, many diabetes-related dementia studies rely on dementia definitions rather than that based on pathological evidence, which makes the impacts of obesity and T2D on the risk of AD inseparable.

Notably, one recent study suggested that non-abdominal fat may offer protection against neurodegenerative diseases like Parkinson's disease (PD), with shared genetic variations between BMI and PD uncovered. PD and AD share similar sensory impairments and brain function abnormalities, and even exhibit co-pathological markers at the pathological level [46,49–52]. While no significant associations between BMI and AD were reported, some other research indicates that obesity increases the expression of AD-related genes. Therefore, while it is possible that obesity or body fat indicators protect against AD, their effects on brain tissue remain to be further explored. It would be important to dissect whether blood sugar-related or obesity-linked cognitive decline corresponds to hallmark AD pathology, such as amyloid deposition and neurofibrillary tangles. By leveraging genetic tools for causal inference, our study attempted to addresses this genetic-level association gaps, though full elucidation of the relationship between glucose metabolism and AD will be the task for the future.

In the clinical setting, long-term metformin treatment in patients with T2D has produced conflicting evidence, with some studies suggesting it may increase the risk of AD while others propose it could slow its progression [53]. Leveraging the largest GWAS data to date, our findings reassess the independent causal effects of T2D and metformin use on AD. We demonstrate that T2D itself does not elevate the risk of AD; instead, the observed association between T2D and AD progression is likely mediated by the extensive use of metformin among these patients. The complexity of these interactions underscores the importance of personalized medicine in AD treatment, where patient-specific factors such as genetic predispositions, existing metabolic conditions, and concurrent medications are considered. Further research is needed to clarify these mechanisms and determine how metformin can be optimally used in the context of AD, balancing its potential benefits against any adverse effects.

4.1. Strengths and limitations

The study employs MR and MVMR analyses to explore the causal relationships between T2D, metformin use, and AD. This approach allows for the assessment of direct and independent causal effects, accounting for potential confounding factors. The use of MVMR is particularly advantageous as it can disentangle the complex interactions between T2D and metformin, providing a more nuanced understanding of their independent impacts on AD risk. A limitation of the study is the potential heterogeneity observed in the MR analyses, which may affect the reliability of the causal inferences. Additionally, while the MR-Egger regression suggests no directional pleiotropy, the presence of heterogeneity indicates that other unaccounted factors might influence the results. The study's findings, particularly the protective effect of T2D and the increased risk associated with metformin, require further validation in diverse populations to ensure generalizability and to rule out population-specific biases.

5. Conclusion

Our study reveals that genetic signature underlining preference to use metformin as T2D medication is an independent risk factor for AD, while T2D may protect against AD. In AD patients with T2D, it is necessary to take into consideration the potential detrimental effects of metformin.

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Consent statement

The consent was not applicable.

Ethical approval

All the summary-level GWAS data used in the analyses are publicly available, and therefore ethical approval was not required for this study. Ethical approval was obtained in all original studies.

Data sharing statement

All GWAS summary statistics analyzed in this study are publicly available for download by qualified researchers.

Code availability

Code and scripts available from the corresponding author on request.

Declaration of interests

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Dongming, Liu reports financial support was provided by The China Postdoctoral Science Foundation AND the Jiangsu Funding Program for Excellent Postdoctoral Talent. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Dongming Liu: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Funding acquisition. **Hongbao Cao:** Writing – review & editing, Writing – original draft, Validation. **Ancha Baranova:** Writing – review & editing, Writing – original draft. **Chenxin Xu:** Writing – review & editing. **Fuquan Zhang:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Methodology, Formal analysis, Data curation, Conceptualization.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tjpad.2025.100129.

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