Causal association evaluation of diabetes with Alzheimer’s disease and genetic analysis of antidiabetic drugs against Alzheimer’s disease

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Abstract
Background: Despite accumulating epidemiological studies support that diabetes increases the risk of Alzheimer’s disease (AD), the causal associations between diabetes and AD remain inconclusive. The present study aimed to explore: i) whether diabetes is causally related to the increased risk of AD; ii) and if so, which diabetes-related physiological parameter is associated with AD; iii) why diabetes drugs can be used as candidates for the treatment of AD. Two-sample Mendelian randomization (2SMR) was employed to perform the analysis.

Results: Firstly, the 2SMR analysis provided a suggestive association between genetically predicted type 1 diabetes (T1D) and a slightly increased AD risk (OR = 1.04, 95% CI = [1.01, 1.06]), and type 2 diabetes (T2D) showed a much stronger association with AD risk (OR = 1.34, 95% CI = [1.05, 1.70]). Secondly, further 2SMR analysis revealed that diabetes-related physiological parameters like fasting blood glucose and total cholesterol levels might have a detrimental role in the development of AD. Thirdly, we obtained 74 antidiabetic drugs and identified SNPs to proxy the targets of antidiabetic drugs. 2SMR analysis indicated the expression of three target genes, ETFDH, GANC, and MGAM, were associated with the increased risk of AD, while CPE could be a protective factor for AD. Besides, further PPI network found that GANC interacted with MGAM, and further interacted with CD33, a strong genetic locus related to AD.

Conclusions: In conclusion, the present study provides evidence of a causal association between diabetes and increased risk of AD, and also useful genetic clues for drug development.

Keywords: Alzheimer’s disease, Diabetes, Causal association, Drug targets, Mendelian randomization
Diabetes Federation, 1 in 11 adults had diabetes (425 million people), and 12% of the global health expenditure was spent on diabetes in 2017 [2].

More recently, increasing attention has been paid to the associations of AD with several chronic disorders, among which diabetes has attracted much interest due to a series of pathogenic associations. For instance, in the past few decades, significant epidemiological evidence indicated that diabetes patients had an increased risk of developing AD by approximately 53% [3–5]. Besides, the mechanisms associated with diabetes, such as dysfunctional IR/PI3K/Akt signaling, increased inflammation, oxidative stress, and others, might accelerate the development of pathological events in AD [6, 7]. Moreover, a growing number of studies also supported the associations between AD and diabetes at the genetic level. A previous study has identified 395 SNPs to be shared the same risk allele for AD and T2D, suggesting common genetic aetiological risk factors between two disorders [8]. Correspondingly, inspired by the close association between two disorders, the studies of examining antidiabetic drugs against AD have increased tremendously. Excitedly, preliminary studies have indicated that many antidiabetic drugs, such as li拉glutide, pioglitazone, lixisenatide, rosiglitazone, insulin, and exendin-4, exhibited therapeutic effects on AD [9–14], suggesting that diabetes and AD may share genetic etiological risk factors, especially provide a potential novel approach for AD drug development.

These studies imply that diabetes is closely associated with the risk of AD, and antidiabetic drugs also attracted much attention in the treatment of AD; however, it is unclear whether diabetes has causal associations with AD, and the impact of antidiabetic drug targets against AD remains to be further estimated. Mendelian randomization uses genetic variants as proxies for modifiable risk factors to test whether the risk factor is causally relevant to an outcome of interest, which could minimize the impact of confounding factors [15]. Thus, the present study performed a two-sample Mendelian randomization (2SMR) analysis to assess: i) whether diabetes is causally related to the increased risk of AD; ii) and if so, which diabetes-related physiological parameters, like blood glucose, insulin, and others, is associated with AD; iii) how diabetes drugs can be used as a candidate for the treatment of AD.

**Methods**

Based on existing data sources of the MR-base platform, we selected genetic variants associated with the exposure measure as an instrument to estimate causal effects. Candidate genetic variants of outcome (AD) were obtained from the International Genomics of Alzheimer’s Project (IGAP) [16]. As for exposures, we searched the EBI-GWAS database by the MR-base platform with the following terms: “type 1 diabetes” and “type 2 diabetes”. And 10 T1D-related SNPs were extracted from a European ancestry-specific joint GWA study to estimate the association between T1D and AD [17], while a total of 37 SNPs provided by the summary statistics of 48,286 cases and 250,671 controls were included to test the causal effect of T2D on AD [18]. Further, to investigate how diabetes affects the risk of AD, we also analyzed AD and diabetes-related parameters, including fasting blood glucose, total cholesterol levels, and insulin levels [19–21]. Data extraction and 2SMR analyses were automatically conducted using the software R and TwoSample MR package 0.5.0, and genome-wide significant (p-value < 5 × 10⁻⁸) was chosen for computational analysis [15]. We selected inverse variance weighting (IVW) as the main analytical method, and various 2SMR methods, including weighted median, weighted mode, and MR-Egger, were employed to improve the reliability of the causal inference. P-value < 0.05 was chosen as the discriminant criterion for the statistical significance of the 2SMR study. Besides, to ensure the robustness of results, leave-one-out sensitivity analysis was used to test whether there is an SNP that has an excessive impact on MR estimates. Heterogeneity and pleiotropy tests were implemented based on the code contained in the TwoSample MR package. Cochran’s Q statistics were used to explore the size of heterogeneity, and whether there is pleiotropy was decided by the intercept term of MR-Egger method.

Besides, inspired by the benefits of antidiabetic drugs for AD, we then performed a further 2SMR analysis for the causal associations between antidiabetic drug targets and AD risk to assess the therapeutic effects. Firstly, we searched the DrugBank database (http://www.drugbank.ca/) with the term “diabetes” to retrieve antidiabetic drugs and target genes [22]. Drugs or compounds that have been approved or were being developed for the treatment of diabetes were collected as available antidiabetic drugs. The information was extracted from each drug, including the name of antidiabetic drug, DrugBank ID, target gene, and target type. Secondly, using the TwoSample MR package, we identified target-related SNPs based on the GTEx eQTL catalog [23]. By using SNPs associated with antidiabetic drug target genes and without any linkage disequilibrium, we calculated MR estimates and did not define tissue types. Since the number of SNPs contained in each drug target was relatively small, a more liberal P-value threshold (p-value < 5 × 10⁻⁵) was used to filter available instrumental variables. In addition to the above four methods, we also added another MR method, Wald ratio, which used a single instrumental variable to estimate the causal association.
Furthermore, based on the IGAP database, the threshold of p-value $< 1 \times 10^{-5}$ was used to screen susceptibility-associated SNPs of AD. The identified significant SNPs were mapped into related susceptibility genes according to the location of the SNPs on human chromosomes. We constructed network-based analyses by the Search Tool for the Retrieval of Interacting Genes (STRING) databases to investigate the protein–protein interaction (PPI) information between the identified targets and susceptibility genes [24], and the final network was visualized by Cytoscape software (Version 3.7.1) [25].

Results

Diabetes and AD

The 2SMR analysis provided a suggestive association between genetically predicted T1D and higher risks of AD (IVW, OR = 1.04, 95% CI = [1.01, 1.06], p = 2.90E-03, Table 1, Fig. 1). Cochran’s Q statistics showed little evidence of heterogeneity between T1D and AD, and the MR-Egger intercept suggested that there was no pleiotropy in the SNPs included in this study. The further leave-one-out analysis also found that there were no SNP had an excessive impact on the results (all lines are on the right side of 0). However, compared with other SNPs, the independent SNP rs9272346 exerted a relatively significant effect on the association between T1D and AD risk. According to the NCBI database, rs9272346 was located at HLA-DQA1, and the protein encoded by which plays a central role in the immune system by presenting peptides derived from extracellular proteins.

Compared with T1D, T2D seemed to show a much stronger association with an increased risk of AD (IVW, OR = 1.34, 95% CI = [1.05, 1.70], p = 0.02, Fig. 2). Cochran’s Q statistics showed little evidence of heterogeneity between T2D and AD. The MR-Egger intercept suggested that there was no pleiotropy in the SNPs included in this study. Moreover, the leave-one-out method did not find that a certain SNP would have an excessive impact on the MR results, which also supported that the MR results were robust.

Diabetes-related parameters and AD

In addition, we also conducted further analysis to investigate the causal association between diabetes-related physiological parameters and the risk of AD. In view of the fact that blood glucose and dyslipidemia are widely recognized as physiological changes in diabetes, we conducted a 2SMR analysis to evaluate their causal association with AD. By performing a 2SMR analysis of the diabetes-related physiological parameters and AD, we found that fasting blood glucose and total cholesterol levels may have a causative role in the development of AD as shown in Fig. 3. Fasting blood glucose was associated with a 57% increase in the risk of AD (IVW, OR = 1.57, 95% CI = [1.14, 2.17], p = 6.33E-03), total cholesterol levels also showed a strong causal association with the risk of AD (IVW, OR = 1.62, 95% CI = [1.21, 2.18], p = 1.23E-03). Besides, as one of the typical characteristics of diabetes, the causal association between insulin level and AD was also included in this study. However, based on the currently available data, the 2SMR analysis results did not support the causal effect of insulin levels on AD risk (data not shown).

Antidiabetic drugs and AD

Based on the DrugBank database, we obtained 74 antidiabetic drugs up to July 2021, covering 96 target and enzyme genes extracted from the involved drugs. The details of these drugs, including drug names, DrugBank ID, target genes, and enzyme genes, are displayed in Table 2.

By using SNPs associated with antidiabetic drug target genes (p-value $< 5 \times 10^{-5}$) as instrumental variables, we conducted a 2SMR analysis for the causal associations between antidiabetic drug targets and AD risk (Table 3). Preliminary results showed that four targets,

| Study | Method                  | Number of SNPs | b   | se  | P-value | OR   | 95% CI | Cochran’s Q statistic (P-value) | MR-egger intercept (P-value) |
|-------|-------------------------|----------------|-----|-----|---------|------|--------|--------------------------------|------------------------------|
| T1D   | Inverse variance weighted | 4              | 0.04 | 0.01 | 2.90E-03 | 1.04 | 1.01–1.06 | 3.66 (0.30)                  |                               |
|       | MR Egger                | 4              | 0.06 | 0.02 | 0.08    | 1.06 | 1.03–1.10 | 0.94 (0.63)                  | -0.02 (0.24)                 |
|       | Weighted median         | 4              | 0.04 | 0.01 | 8.83E-04 | 1.04 | 1.02–1.07 |                             |                               |
|       | Weighted mode           | 4              | 0.04 | 0.01 | 0.04    | 1.04 | 1.02–1.07 |                             |                               |
| T2D   | Inverse variance weighted | 11             | 0.29 | 0.12 | 0.02    | 1.34 | 1.05–1.70 | 9.43 (0.49)                  |                               |
|       | MR Egger                | 11             | 0.70 | 0.40 | 0.11    | 2.01 | 0.93–4.36 | 8.28 (0.51)                  | -0.02 (0.31)                 |
|       | Weighted median         | 11             | 0.18 | 0.17 | 0.28    | 1.20 | 0.86–1.68 |                             |                               |
|       | Weighted mode           | 11             | 0.04 | 0.23 | 0.88    | 1.04 | 0.65–1.64 |                             |                               |
including carboxypeptidase E (CPE), electron transfer flavoprotein-ubiquinone oxidoreductase (ETFDH), neutral alpha-glucosidase C (GANC), and maltase-glucoamylase (MGAM), were identified to be causally associated with AD. Among them, genetically predicted the CPE gene could be a protective factor in AD (IVW, OR = 0.94, 95%CI = [0.89, 1.00], p = 0.05, Fig. 4), while the expressions of ETFDH (IVW, OR = 1.08, 95%CI = [1.01,1.16], p = 0.03, Fig. 5), GANC (IVW, OR = 1.09, 95%CI = [1.02,1.18], p = 0.02, Fig. 6), and MGAM (Wald ratio, OR = 1.04, 95%CI = [1.00,1.09], p = 0.04) were causally associated with the increased risk of AD. Notably, the present study showed high expressions of ETFDH, GANC, and MGAM have causal effects on the increased risk of AD, in other words, inhibiting the expression of three target genes is beneficial to the treatment of AD to a certain extent. Interestingly, based on the pharmacological actions obtained from the DrugBank database, three targets related to antidiabetic drugs, including metformin, miglitol, acarbose, voglibose, were the corresponding inhibitors of the above targets, suggesting that identified targets might provide useful genetic clues to understand the anti-AD effects of selected antidiabetic drugs.

Furthermore, a total of 2746 SNPs of AD were discovered from the IGAP database using a genome-wide

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**Fig. 1.** 2SMR analysis of the causal association between T1D and the risk of AD. a Scatter plot. The slope of the line corresponds to a causal estimate using each of the four different methods. b Funnel plot. The vertical line shows a causal estimate using all SNPs combined into a single instrument for each of two different methods. c Forest plot. Each black dot represents the MR estimate of each SNP using the wald ratio, and the horizontal line represents the 95% CI. The red points show a combined causal estimate using all SNPs in a single instrument, including the 2SMR estimates of IVW and MR-Egger. d Leave-one-out sensitivity analysis. Each black dot represents the result of MR-IVW excluding that particular SNP, and the red dot depicts the IVW estimate using all SNPs.
significance threshold \((p < 1 \times 10^{-5})\). By mapping the significant SNPs to genes on the basis of the NCBI database, 152 AD susceptibility genes were identified and included in this study. A PPI network that followed was constructed by identified targets (CPE, ETFDH, GANC, MGAM) and AD susceptibility genes (Fig. 7). It was found that CPE and ETFDH were not interacted with any degree in the network, while GANC was related to MGAM, and further interacted with CD33 (Fig. 8), which was a strong genetic locus associated with AD.

**Discussion**

Through performing a 2SMR analysis of the available data, we found that diabetes had a causal effect on AD risk, which is in line with previous epidemiological studies. There should be multiple mechanisms underlying the association between diabetes and AD. First, insulin signaling dysregulation may be a critical pathological change in AD, and it has been reported that insulin signaling is impaired in postmortem brain tissue from AD patients [26, 27]. The insulin signaling pathway contributes to the control of neuronal excitability and metabolism, and
cerebrovascular changes, such as inflammation and alterations in brain insulin signaling, might play a pivotal role in AD development [28, 29]. Second, as a mechanistic linker between AD and diabetes, inflammation can accelerate the development of diabetes by influencing islet function and peripheral insulin sensitivity. Moreover, as a starting point of AD pathological progression, the normal synaptic function will be disrupted by cerebrovascular and central inflammation, along with the increased accumulation of Aβ [30].

Further 2SMR analysis revealed that some diabetes-related physiological parameters, such as fasting blood glucose and total cholesterol levels, were causally associated with the risk of AD. Previous studies have demonstrated that metabolic dysfunction of diabetes, especially glucose-related dysfunction, may play a causative role in the development of AD. For example, a large-scale genome-wide cross-trait analysis identified 4 loci that were associated with AD and fasting glucose [31]. Also, as the most cholesterol-rich organ, the cholesterol homeostasis in the human brain may be closely related to the occurrence and development of AD [32]. Recent studies have indicated that lipid metabolism-related genes, such as APOC1 and APOE, might be major risk factors for AD due to the involvement in the maintenance of brain lipid homeostasis [33, 34]. Furthermore, our previous study also identified a total of six SNPs shared between T2D and AD and found that lipid metabolism-related pathways were common between the two disorders by functional enrichment analysis [35].

In the past decades, theoretical and experimental investigations of novel drugs for AD have attracted much attention. It is noteworthy that drug repositioning based on the approved drugs may represent an important source for AD drug discovery, a case of this is antidiabetic drug repositioning. By the 2SMR analysis, four targets, including CPE, ETFDH, GANC, and MGAM, were identified to be causally associated with AD in this paper. In particular, in combination with the present 2SMR results and pharmacological actions obtained from the DrugBank database, ETFDH-, GANC-, and MGAM-related antidiabetic drugs, including metformin, miglitol, acarbose, voglibose, were precisely the corresponding inhibitors of the above targets, indicating potential therapeutic effects on AD. Notably, among those, miglitol, acarbose, and voglibose are currently used in the management of glycemic control by inhibiting α-glucosidase, which is an important biological target/enzyme that can catalyze the degradation of dietary polysaccharides into monosaccharides. The preliminary data in this paper proposed that the targets of α-glucosidase inhibitors, for example, GANC and MGAM, were causally associated with the increased risk of AD, suggesting the therapeutic implications of α-glucosidase on AD. However, at present, the antidiabetic drugs for the treatment of AD mainly focus on GLP-1R agonists (liraglutide, exenatide), thiazolidinediones (pioglitazone, rosiglitazone), DPP-4 inhibitors (sitagliptin, vildagliptin), and so on, while there are limited studies of α-glucosidase inhibitors in the treatment of AD, and these findings remain to be further estimated.
| Name          | Drugbank ID | Target genes | Target type |
|--------------|-------------|--------------|-------------|
| Ebselen      | DB12610     | EPHX2        | Target      |
| INCB13739    | DB05064     | HSD11B1      | Target      |
| PSN357       | DB05044     | PYGL         | Target      |
| Bisegliptin  | DB06127     | DPP4         | Target      |
| NOX-700      | DB05464     | NFKB2        | Target      |
| CLX-0921     | DB05854     | PPARG        | Target      |
| Reglitazar   | DB04971     | PPARA        | Target      |
| ISIS 113715  | DB05506     | PTPN1        | Target      |
| AT1391       | DB05120     | INSR         | Target      |
| NN344        | DB05115     | INSR         | Target      |
| ApD668       | DB05166     | GPR119       | Target      |
| Dutogliptin  | DB11723     | DPP4         | Target      |
| MB-07803     | DB05053     | FBP1         | Target      |
| PSN9301      | DB05001     | DPP4         | Target      |
| Gliquidone   | DB01251     | ABCB8        | Target      |
|              |             | KCNJ8        | Target      |
|              |             | CYP2C9       | Enzyme      |
| Albiglutide  | DB09043     | GLP1R        | Target      |
| Pramlintide  | DB01278     | CALCRL       | Target      |
|              |             | RAMP1        | Target      |
|              |             | RAMP2        | Target      |
|              |             | RAMP3        | Target      |
| Voglibose    | DB04878     | MGAM         | Target      |
| Dapagliflozin| DB06292     | SLC5A2       | Target      |
|              |             | CYP1A1       | Enzyme      |
|              |             | CYP1A2       | Enzyme      |
|              |             | CYP2A6       | Enzyme      |
|              |             | CYP2C9       | Enzyme      |
|              |             | CYP2D6       | Enzyme      |
|              |             | CYP3A4       | Enzyme      |
|              |             | UGT1A9       | Enzyme      |
| Miglitol     | DB00491     | MGAM         | Target      |
|              |             | GAA          | Target      |
|              |             | GANAB        | Target      |
|              |             | GANC         | Target      |
|              |             | AMY2A        | Enzyme      |
| Vildagliptin | DB04876     | DPP4         | Target      |
| Dulaglutide  | DB09045     | GLP1R        | Target      |
| Phenformin   | DB00914     | PRKAA1       | Target      |
|              |             | KCNJ8        | Target      |
|              |             | CYP2D6       | Enzyme      |
| AMG-131      | DB05490     | PPARG        | Target      |
| Acarbose     | DB00284     | MGAM         | Target      |
|              |             | GAA          | Target      |
| Name                  | Drugbank ID | Target genes | Target type |
|-----------------------|-------------|--------------|-------------|
| Sitagliptin           | DB01261     | SI           | Target      |
|                       |             | AMY2A        | Target      |
|                       |             | DPP4         | Target      |
| Acetohexamide         | DB00414     | CYP3A4       | Enzyme      |
|                       |             | CYP2C8       | Enzyme      |
|                       |             | KCNJ1        | Target      |
|                       |             | CBR1         | Enzyme      |
|                       |             | CYP2C9       | Enzyme      |
| Canagliflozin         | DB08907     | SLC5A2       | Target      |
|                       |             | UGT1A9       | Enzyme      |
|                       |             | UGT2B4       | Enzyme      |
|                       |             | CYP3A4       | Enzyme      |
| Pioglitazone          | DB01132     | PPARG        | Target      |
|                       |             | MAOB         | Target      |
|                       |             | CYP2C8       | Enzyme      |
|                       |             | CYP3A4       | Enzyme      |
|                       |             | CYP1A1       | Enzyme      |
| Glisoxepide           | DB01289     | KCNJ8        | Target      |
|                       |             | CYP2C9       | Enzyme      |
| Glipizide             | DB01067     | ABCC8        | Target      |
|                       |             | PPARG        | Target      |
|                       |             | CYP2C9       | Enzyme      |
|                       |             | UGT1A1       | Enzyme      |
| Insulin Glargine      | DB00047     | INSR         | Target      |
|                       |             | IGF1R        | Target      |
|                       |             | CYP1A2       | Enzyme      |
| Insulin Degludec      | DB09564     | INSR         | Target      |
|                       |             | IGF1R        | Target      |
|                       |             | CYP1A2       | Enzyme      |
| Chlorpropamide        | DB00672     | ABCC8        | Target      |
|                       |             | CYP2C9       | Enzyme      |
|                       |             | CYP2C19      | Enzyme      |
|                       |             | PTGS1        | Enzyme      |
| Linagliptin           | DB08882     | DPP4         | Target      |
|                       |             | CYP3A4       | Enzyme      |
| Repaglinide           | DB00912     | ABCC8        | Target      |
|                       |             | PPARG        | Target      |
|                       |             | CYP2C8       | Enzyme      |
|                       |             | CYP3A4       | Enzyme      |
| Insulin Pork          | DB00071     | INSR         | Target      |
|                       |             | IGF1R        | Target      |
|                       |             | IDE          | Enzyme      |
|                       |             | CYP1A2       | Enzyme      |
| Nataglinide           | DB00731     | ABCC8        | Target      |
|                       |             | PPARG        | Target      |
|                       |             | CYP2C9       | Enzyme      |
|                       |             | CYP3A4       | Enzyme      |
|                       |             | CYP3A5       | Enzyme      |
|                       |             | CYP3A7       | Enzyme      |
### Table 2 (continued)

| Name              | Drugbank ID | Target genes | Target type |
|-------------------|-------------|--------------|-------------|
| PTGS1             | UGT1A9      | CYP2D6       | Enzyme      |
| UGT1A9            | CYP2D6      |              | Enzyme      |
| CYP2D6            | UGT1A9      | CYP2D6       | Enzyme      |
| *Insulin Aspart*  | **DB01306** | **INSR**     | Target      |
| IGF1R             | CYP1A2      |              | Target      |
| CYP1A2            | IGF1R       |              | Target      |
| Saxagliptin       | **DB06335** | **DPP4**     | Target      |
| CYP3A4            | CYP3A5      |              | Target      |
| CYP3A5            | INSR        |              | Target      |
| Insulin Glulisine | **DB01309** | **INSR**     | Target      |
| IGF1R             | CYP1A2      |              | Target      |
| Tolbutamide       | **DB01124** | **ABCC8**    | Target      |
| KCNJ1             | CYP2C9      |              | Target      |
| CYP2C8            | CYP2C9      |              | Target      |
| CYP2C19           | CYP2C18     |              | Target      |
| Rosiglitazone     | **DB00412** | **PPARG**    | Target      |
| ACSL4             | PPARA       |              | Target      |
| PPARA             | PPARD       |              | Target      |
| RXRA              | RXRB        |              | Target      |
| RXRG              | RXRG        |              | Target      |
| CYP2C8            | CYP2C9      |              | Enzyme      |
| CYP2C9            | PTGS1       |              | Enzyme      |
| PPARA             | CYP1A2      |              | Enzyme      |
| RXRA              | CYP3A4      |              | Enzyme      |
| RXRB              | CYP2B6      |              | Enzyme      |
| Mitiglinide       | **DB01252** | **ABCC8**    | Target      |
| PPARG             | UGT1A3      |              | Target      |
| PPARA             | UGT2B7      |              | Target      |
| Insulin Human     | **DB00030** | **INSR**     | Target      |
| IGF1R             | CPE         |              | Target      |
| CPE               | NOV         |              | Target      |
| CPE               | LRP2        |              | Target      |
| NOV               | LRP2        |              | Target      |
| LRP2              | IGFBP7      |              | Target      |
| IGFBP7            | IDE         |              | Target      |
| IDE               | PCSK2       |              | Target      |
| PCSK2             | PCSK1       |              | Target      |
| Name                  | Drugbank ID | Target genes     | Target type |
|-----------------------|-------------|------------------|-------------|
| Insulin Lispro        | DB00046     | CYP1A2, INSR, IGF1R, CYP1A2, IDE | Enzyme, Target |
| Lixisenatide          | DB09265     | GLP1R            | Target      |
| Metformin             | DB00331     | PRKAB1, ETFDH, GPD1 | Target, Target |
| Lobeglitazone         | DB09198     | PPARG, CYP1A2, CYP2C9, CYP2C19, CYP3A4 | Enzyme, Target |
| Managlinat dialanetil | DB05518     | FBP1             | Target      |
| Levoketoconazole      | DB05667     | CYP11B1, CYP51A1, CYP3A4, CYP3A5, CYP51A1, CYP17A1, CYP21A2, CYP11B1 | Target, Enzyme |
| Tesaglitazar          | DB06536     | PPARA, PPARG     | Target, Target |
| Ertiprotafib          | DB06521     | PTPN1, IKKB, PPARA, PPARG | Target, Target |
| Glycodiazine          | DB01382     | KCNJ1, ABCC8     | Target, Target |
| Muraglitazar          | DB06510     | PPARA, PPARG, CYP1A2 | Target, Enzyme |
| Troglitazone          | DB00197     | PPARG, ACSL4, SERPINE1, SLC29A1, ESRG, ESRA, PPARD, PPARA, GSTP1, CYP3A4, CYP2C19, UGT1A1 | Target, Enzyme |

Table 2 (continued)
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| Name           | Drugbank ID | Target genes                  | Target type |
|----------------|-------------|-------------------------------|-------------|
|                |             | CYP2C8                         | Enzyme      |
|                |             | CYP19A1                        | Enzyme      |
|                |             | CYP1A1                         | Enzyme      |
|                |             | CYP2B6                         | Enzyme      |
|                |             | CYP2C9                         | Enzyme      |
|                |             | CYP3A5                         | Enzyme      |
|                |             | CYP3A7                         | Enzyme      |
|                |             | UGT1A3                         | Enzyme      |
|                |             | UGT1A4                         | Enzyme      |
|                |             | UGT1A6                         | Enzyme      |
|                |             | UGT1A7                         | Enzyme      |
|                |             | UGT1A8                         | Enzyme      |
|                |             | UGT1A9                         | Enzyme      |
|                |             | UGT1A10                        | Enzyme      |
|                |             | UGT2B7                         | Enzyme      |
|                |             | UGT2B15                        | Enzyme      |
| Ertugliflozin  | DB11827     | SLC5A2                        | Target      |
|                |             | UGT1A9                         | Enzyme      |
|                |             | UGT2B7                         | Enzyme      |
|                |             | UGT1A1                         | Enzyme      |
|                |             | UGT1A4                         | Enzyme      |
| Exenatide      | DB01276     | GLP1R                         | Target      |
|                |             | DPP4                           | Enzyme      |
| Naveglitazar   | DB12662     | PPARG                          | Target      |
| Alogliptin     | DB06203     | DPP4                           | Target      |
|                |             | CYP3A4                         | Enzyme      |
|                |             | CYP2D6                         | Enzyme      |
| Liraglutide    | DB06655     | GLP1R                          | Target      |
|                |             | DPP4                           | Enzyme      |
|                |             | MME                            | Enzyme      |
| Semaglutide    | DB13928     | GLP1R                          | Target      |
|                |             | DPP4                           | Enzyme      |
|                |             | MME                            | Enzyme      |
|                |             | LPL                            | Enzyme      |
|                |             | AMY1A                          | Enzyme      |
| Glimepiride    | DB00222     | KCNJ11                         | Target      |
|                |             | KCNJ1                          | Target      |
|                |             | ABCC8                          | Target      |
|                |             | CYP2C9                         | Enzyme      |
| Sarpogrelate   | DB12163     | HTR2C                          | Target      |
|                |             | HTR2A                          | Target      |
| Glyburide      | DB01016     | ABCC9                          | Target      |
|                |             | ABCB11                         | Target      |
|                |             | ABCA1                          | Target      |
|                |             | CFTR                           | Target      |
|                |             | CPT1A                          | Target      |
|                |             | TRPM4                          | Target      |
|                |             | CYP2C9                         | Enzyme      |
|                |             | CYP2C19                        | Enzyme      |
Several limitations of the present analysis need to be noted. In the 2SMR analysis, we avoided the influence of different ethnicities to the greatest extent by screening for European ancestry in the involved studies. However, there are also a few studies that have mixed populations with a small proportion outside Europe. At the same time, the limitation of European ancestry also indicates that our findings may not be applicable to other ethnicities. In addition, the small number of variants for each exposure is the limitation of these analyses. These factors may interfere with the stability of the conclusion.

**Conclusions**

The present 2SMR analysis based on extensive data uncovered causal associations between diabetes and AD. It is interesting to note that T2D seemed to show a more significant association with AD risk than T1D. Further analysis identified several diabetes-related physiological properties.
Fig. 4. 2SMR estimates of the causality between CPE target and AD. a Scatter plot. The slope of the line corresponds to a causal estimate using each of the four different methods. b Funnel plot. The vertical line shows a causal estimate using all SNPs combined into a single instrument for each of two different methods. c Forest plot. Each black dot represents the MR estimate of each SNP using the wald ratio, and the horizontal line represents the 95% CI. The red points show a combined causal estimate using all SNPs in a single instrument, including the 2SMR estimates of IVW and MR-Egger. d Leave-one-out sensitivity analysis. Each black dot represents the result of MR-IVW excluding that particular SNP, and the red dot depicts the IVW estimate using all SNPs.
parameters that may have a causative role in the development of AD. Besides, four targets from antidiabetic drugs were identified to be causally associated with AD, indicating potential therapeutic effects on AD and might provide implications for drug development. In summary, our study indicates that diabetes and antidiabetic drugs were causally relevant to AD and certainly warrants more well-designed studies clinical verifications in the future. At the same time, these findings also inspire us that preventing or delaying the risk factors of AD, such as diabetes, are likely to be more achievable goals in the foreseeable future.
Abbreviations
AD: Alzheimer’s disease; T1D: Type 1 diabetes; T2D: Type 2 diabetes; 2SMR: Two-sample Mendelian randomization; IGAP: International genomics of Alzheimer’s project; SNPs: Single nucleotide polymorphisms.

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Authors' contributions
LS and HFJ conceived and designed the study; LM and ZW collected data; LM and ZW performed calculations; LM, ZW, HFJ and LS analyzed the data; LM, LS and HFJ wrote and revised the paper. All authors read and approved the final manuscript.

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Availability of data and materials
The data is available from the corresponding author upon request.

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Not applicable.

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Competing interests
The authors declare that they have no competing interests.

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