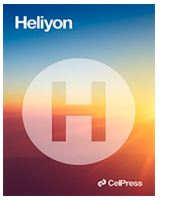
Heliyon 10 (2024) e30909

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Research article

Effects of antidiabetic agents on platelet characteristics with implications in Alzheimer's disease: Mendelian randomization and colocalization study

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A B S T R A C T

Background: Observational studies have found a potential link between the use of thiazolidinediones (TZDs) and a lower risk of Alzheimer's disease (AD) development. Platelets were the great source of amyloid-β (Aβ) and involved in the development of AD. This study aimed to assess the correlation between antidiabetic agents and platelet characteristics, hoping to provide a potential mechanism of TZDs neuroprotection in AD.
Method: Drug-targeted Mendelian randomization (MR) was performed to systematically illustrate the long-term effects of antidiabetic agents on platelet characteristics. Four antidiabetic agent targets were considered. Positive control analysis for type 2 diabetes (T2D) was conducted to validate the selection of instrumental variables (IVs). Colocalization analysis was used to further strengthen the robustness of the results.
Result: Positive control analysis showed an association of four antidiabetic agents with lower risk of T2D, which was consistent with their mechanisms of action and previous evidence from clinical trials. Genetically proxied TZDs were associated with lower platelet count (β[IRNT] = −0.410 [95 % CI -0.533 to −0.288], $P = 5.32E\text{-}11$) and a lower plateletcrit (β[IRNT] = −0.344 [95 % CI -0.481 to −0.206], $P = 1.04E\text{-}6$). Colocalization suggested the posterior probability of hypothesis 4 (PPH4) > 0.8, which further strengthened the MR results.
Conclusion: Genetically proxied TZDs were causally associated with lower platelet characteristics, particularly platelet count and plateletcrit, providing insight into the involvement of platelet-related pathways in the neuroprotection of TZDs against AD. Future studies are warranted to reveal the underlying molecular mechanism of TZDs' neuroprotective effects through platelet pathways.

What is already known on this topic?

- Observational studies have suggested that the use of TZDs is associated with a reduced risk of AD.

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https://doi.org/10.1016/j.heliyon.2024.e30909
Received 26 October 2023; Received in revised form 7 May 2024; Accepted 7 May 2024
Available online 9 May 2024

- There is a linkage network between platelets and brain, and platelets were the source of amyloid precursor protein and Aβ peptide in blood.

What this study adds?

- This is the first MR analysis to comprehensively explore the causal relationship between antidiabetic agents and platelet characteristics.

How this study might affect research, practice or policy?

- This study provided insight that platelet-related pathways might be involved in the neuroprotective effects of TZDs against AD.

1. Introduction

AD is a destructive, progressive neurodegenerative disease, which is characterized by abnormal protein aggregation and neuron loss in the brain, leading to cognitive decline, memory loss, and ultimately death. It is the main cause of dementia and is quickly becoming one of the most lethal and burdensome diseases worldwide [1]. The pathophysiology of AD has also not been fully understood. The combination of numerous pathological processes, including neuro-inflammation, aging, alterations in the vessels, and malfunction of the glymphatic system, might contribute to AD [1]. Based on the similarities between platelets and neuronal biology, it has been hypothesized that platelet-associated biological processes might be a part of the pathophysiological mechanism of AD. Platelets have been identified as the source of amyloid precursor proteins and Aβ peptides in the blood, contributing to the pathophysiology of AD by facilitating the formation of soluble Aβ into Aβ aggregates [2,3]. Increased platelet activation in AD has been reported in several studies [4,5].

However, AD medications are progressing slowly. The U.S. Food and Drug Administration has only approved seven pharmacological therapies for AD treatment, and none of them serve as a cure [6]. In the past 20 years, only two new therapeutic agents have become available for AD treatment until 2020, thereby urging development of the new medications [7]. Due to sharing common characteristics with T2D, such as insulin resistance and impaired glucose control located in the cerebrum, AD was proposed as "type 3 diabetes" [8]. Therefore, antidiabetic agents have been highlighted as repurposing candidates for AD [9,10].

A considerable number of studies have shown that multiple categories of antidiabetic medications and natural bioactive compounds have prospective therapeutic effects on AD in pre-clinical experiments, longitudinal observational studies, and clinical trials [11–13]. There are animal testing experiments and systematic reviews suggest that pioglitazone can be corrective and protective, and that its efficacy is enhanced in a time- and dose-dependent manner [14,15]. However, whether platelets play a role in the underlying mechanism and the possible explanations for these discrepancies remain largely unknown.

MR is a statistical tool, which primarily uses genetic variation as an IV to draw causal inferences between exposure and outcome. The genetic variants were randomly assigned at conception and before the occurrence of disease. Therefore, MR is regarded as a natural randomized controlled trial, minimizing the effects of confounding and reverse causality. Further applications in drug targets can also be used in predicting the potential effects of drugs caused by the pharmacological inhibition of drug target genes, reflecting the effects of long-term drug use. Moreover, it is an important analytical tool for exploring the unknown potential effects caused by genetic perturbations of known drug targets. The current study used drug-target MR to investigate the specific effects of genetic variations in antidiabetic drug-target genes on platelet characteristics.

In this study, an MR study was performed to examine the effects of genetic variations in antidiabetic drug targets on platelet characteristics, providing a hypothesis that TZDs exhibit neuroprotective effects on AD through platelet-associated biological processes.

2. Materials and methods

2.1. Approval and data sources

All the data used in this study were publicly available, and all the participants provided written informed consent. Detailed information and references for data sources are provided in Supplementary Table S1.

2.1.1. Hemoglobin A1c GWAS data

IV-exposure correlations were extracted from the HbA1c GWAS analyses of European-origin participants in the UK Biobank (UKB). This prospective cohort included approximately 500,000 individuals aged 40–69 years, who were recruited from 2006 to 2010 [16,17]. Inverse-rank normal transformation (IRNT) was performed for the continuous variables in this dataset. Single nucleotide polymorphism (SNP) summary statistics were rescaled to represent a mmol/mol (0.09 %) unit reduction in HbA1c in order to provide more interpretable effect estimates in MR analyses.

2.1.2. Platelet characteristics GWAS data

IV-outcome correlations were extracted from a GWAS meta-analysis, containing three sub-cohorts, which included 173,480 subjects of European ancestry [18]. In this study, three platelet characteristics, including mean platelet volume, platelet count, and

plateletcrit were considered.

2.2. Study design

The principle of the two-sample MR study depended on three assumptions: 1) relevance assumption: IVs are strongly associated with exposure; 2) independence assumption: IVs are not influenced by confounders; and 3) exclusion-restriction assumption: IVs influence the outcome only through exposure and not via other pathways. Two-sample MR was used to investigate the correlations between genetically proxied therapeutic effects of antidiabetic agents and platelet characteristics. First, from the comprehensive eQTL datasets, independent *cis*-eQTLs were selected as instruments. Second, the MR of genetically proxied antidiabetic agents on the risk of T2D was used to examine the validity of genetic instruments. Finally, the effects of genetically proxied classes of antidiabetic agents on platelet characteristics were assessed using the established genetic instruments. The scope of these analyses was limited to individuals of European ancestry.

2.3. Target genes for the classes of antidiabetic agents

Initially, seven major classes of antidiabetic agents were identified using the DrugBank database (https://go.drugbank.com/), including metformin, dipeptidyl peptidase-4 (DPP-4) inhibitors, sodium/glucose cotransporter 2 (SGLT2) inhibitors, insulin/insulin analogs, glucagon-like peptide-1 (GLP-1) analogs, sulfonylureas, and TZDs [19]. Metformin was not included as a drug target due to its unclear mechanism of action [20,21]. Therefore, six classes of antidiabetic agents were finally selected for further analysis, and their instrumental variables were extracted.

2.4. Selection and validation of instruments

In order to proxy the therapeutic inhibition of six antidiabetic drug target classes as well as balance the efficiency power, reduce variability, and increase precision [22]. The SNPs within 500 kilobases of drug target genes, which were associated with the HbA1c GWAS dataset at a genome-wide significance level ($P < 5 \times 10^{-8}$) were employed as instruments. These SNPs were also subjected to clumping using linkage disequilibrium (LD) with an r^2 threshold <0.2 based on the 1000 Genomes European reference panel [23].

For the validation of instrumental variables, positive control analysis was performed by examining the correlations between genetically proxied drug target perturbations and T2D. The strength of genetic predictors for each tested exposure was estimated using the F-statistics to quantify the statistical efficacy of genetic instruments. F statistics were calculated as the formula: $F = r^2 \times (N-2)/(1-r^2)$, where r^2 is the variance explained, N is the sample size. For the selected SNPs, the value of F-statistics greater than 10 indicated less likelihood of weak instrument bias, affecting the results [23,24]. Subsequently, the exposure and outcome SNPs were standardized to ensure that the effect estimates were based on the same effect allele in both datasets. The ambiguous and palindromic SNPs were excluded during the harmonization process. In total, four classes of antidiabetic drug target gene instruments were retained.

2.5. Statistical analysis

2.5.1. MR

The inverse variance weighted (IVW) MR method exhibits robust causal detection ability and has been widely used in the MR analysis of multiple genetic instruments. Therefore, IVW was used as the primary MR analysis model in this study. First, we performed positive control to test the validity of genetic instruments, which passed LD, on four classes of antidiabetic agents using genetically proxied antidiabetic agents as exposures and T2D as an outcome. After harmonizing the data, the IVW method was performed to estimate the effects of the genetically proxied antidiabetic agents on T2D. Valid genetic instruments were defined as positive controls for which the IVW method showed results with a *P*-value <0.05. Second, after validating the genetic instruments, the IVW method was used as the main method to investigate the correlations between genetically proxied antidiabetic agents and platelet characteristics. Moreover, Cochran's Q test was performed to test heterogeneity within IVs, and genetic pleiotropy was also diagnosed in this study [25].All the reported causal effect estimates were corresponding to a per unit decrease in IRNT HbA1c level caused by antidiabetic agents. Bonferroni correction was used to adjust the thresholds in multiple testing. The inhibition of antidiabetic drug targets was considered to have a significant causal effect on characteristics when Bonferroni correction exceeded the threshold ($P < 0.05/12 = 4.17E\text{-}3$).

2.5.2. Sensitivity analyses

In order to strengthen the causal estimates and reduce the loss of potential causal signals among characteristics, several sensitivity analyses, including weighted median, weighted mode, simple mode, cML-MA, MR-MRPRESSO, and leave-one-out analysis, were performed to evaluate the causal findings generated by the IVW method described above. When the estimated effects in the same direction were detected in all the models and showed nominal associations ($P < 0.05$) in at least three models, including the IVW model, the result was defined as a statistically significant causal result.

2.5.3. Bayesian colocalization

Bayesian colocalization is an important complementary analysis for a *cis*-MR study when the *cis*-MR and obtained positive results are from a single genetic region [26].

Therefore, for the statistically significant MR results, Bayesian colocalization was performed to further strengthen the evidence of causality by calculating the posterior probability of sharing the same causal signal shared by the drug and characteristics using the R packages "coloc" [27] and "locuscomparer" [28].

Bayesian colocalization approach assumes that 1) there is a maximum of one causal genetic instrument for either trait, 2) the causal probability of a genetic instrument is independent of the causal probability of other genetic instruments in the analysis, and 3) every causal genetic variant (genotyped or imputed) is included in the colocalization analysis.

Based on these assumptions, there are five hypotheses for each performed analysis, which are as follows. Hypothesis 0 (H0): there is no causal genetic instrument present for either trait; H1: there is one causal genetic instrument present for trait 1; H2: there is one causal genetic instrument present for trait 2; H3: both characteristics have a causal variant in the region, but these are distinct; and H4: there is one shared causal genetic instrument present for both characteristics [27].

Colocalization analysis was performed by generating a ±300 kb window in each respective drug target. Furthermore, gene-target pairs were not run if they had less than 25 variants available in the region [29], and only those with minor allele frequency (MAF) of >0.01 were included [22]. A PPH4 of at least 80 % suggested highly likely to colocalize [30]. Default parameters were used for analysis.

2.5.4. Software and R packages

All the statistical analyses were performed using R software (version 4.2.2), TwoSampleMR (version 0.5.6), coloc (version 5.2.2), locuscomparer (version 1.0.0), MR-PRESSO (version 1.0) and MungeSumstats (version 1.6.0).

3. Results

3.1. Positive control analyses

The characteristics of genetic instruments used to proxy antidiabetic drug targets are provided in Supplementary Table S2. The F-statistics results of genetic instruments for all four drug targets were between 30.47 and 165.64, suggesting that causal inferences were less likely to be affected by weak instrumental variables [31]. As shown in Fig. 1, the effects of all four antidiabetic agents showed a causal effect on decreased risk of T2D, which were selected for the subsequent analyses.

3.2. MR analysis of antidiabetic drug on platelet characteristics

At the Bonferroni-corrected threshold, the results of the IVW method combined with sensitivity analysis methods showed that genetically proxied TZDs were correlated with lower platelet count (β[IRNT] = −0.410 [95 % CI -0.533 to −0.288], $P = 5.32E-11$) and lower Plateletcrit (β[IRNT] = −0.344 [95 % CI -0.481 to −0.206], $P = 1.04E-6$). Furthermore, genetically proxied sodium/glucose cotransporter 2 inhibitors were correlated with higher Plateletcrit (β[IRNT] = 0.304 [95 % CI 0.144 to 0.464], $P = 2.00E-4$), lower mean platelet volume (β[IRNT] = −0.252 [95 % CI -0.383 to −0.120], $P = 1.73E-4$) and higher platelet count (β[IRNT] = 0.374 [95 % CI 0.227 to 0.522], $P = 6.89E-7$).

There were no correlations of sulfonylureas and glucagon-like peptide-1 analogs with any of the three types of platelet characteristics. Moreover, leave-one-out analysis provided consistent evidence of a correlation between genetically proxied drug targets and platelet characteristics, suggesting that the overall estimate was not driven by a single influential variant. The details of the results are presented in Fig. 2 and Supplementary Tables S3–S5.

3.3. Colocalization analysis for the significant result

The colocalization analysis mainly focused on the effects of TZDs and sodium/glucose cotransporter 2 inhibitors on platelet characteristics due to the limitation of available variants in the region and statistically significant causal results in previous analyses. In the presence of significant MR results, only between TZDs and platelet characteristics in sharing a causal variant passed colocalization (PPH4 > 0.80), thereby providing strong evidence for the colocalization of the two characteristics. The detailed results of colocalization are provided in Figs. 3–4 and Supplementary Table S6.

4. Discussion

Studies have indicated that platelets play a critical role in the occurrence and development of AD [32,33]. A platelet-brain linkage

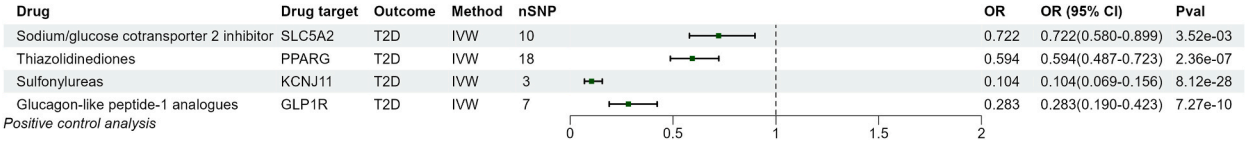

Fig. 1. The effect estimates of four antidiabetic agents on T2D were assessed by the IVW method in positive control analysis. IVW: inverse variance weighted, nSNP: number of single nucleotide polymorphism, OR: odds ratio, CI: confidence interval.

Drug	Drug target	Outcome	Method	nSNP	β	β (95% CI)	Pval
Sodium/glucose cotransporter 2 inhibitor	SLC5A2	Plateletcrit	IVW	7	0.304	0.304(0.144,0.464)	2.00e-04
		Platelet count	IVW	7	0.374	0.374(0.227,0.522)	6.89e-07
		Mean platelet volume	IVW	8	-0.252	-0.252(-0.383,-0.120)	1.73e-04
Thiazolidinediones	PPARG	Plateletcrit	IVW	10	-0.344	-0.344(-0.481,-0.206)	1.04e-06
		Platelet count	IVW	15	-0.410	-0.410(-0.533,-0.288)	5.32e-11
		Mean platelet volume	IVW	15	0.138	0.138(0.035,0.240)	8.41e-03
Sulfonylureas	KCNJ11	Plateletcrit	IVW	3	0.044	0.044(-0.160,0.248)	6.73e-01
		Platelet count	IVW	3	0.063	0.063(-0.141,0.266)	5.46e-01
		Mean platelet volume	IVW	3	-0.051	-0.051(-0.350,0.249)	7.40e-01
Glucagon-like peptide-1 analogues	GLP1R	Plateletcrit	IVW	4	0.233	0.233(0.000,0.465)	4.96e-02
		Platelet count	IVW	7	0.097	0.097(-0.179,0.372)	4.91e-01
		Mean platelet volume	IVW	7	-0.060	-0.060(-0.237,0.117)	5.06e-01

Antidiabetic agents on platelet characteristics

Fig. 2. The effect estimates of four antidiabetic agents on platelet characteristics were assessed by the IVW method. IVW: inverse variance weighted, nSNP: number of single nucleotide polymorphism, β: beta coefficient, CI: confidence interval.

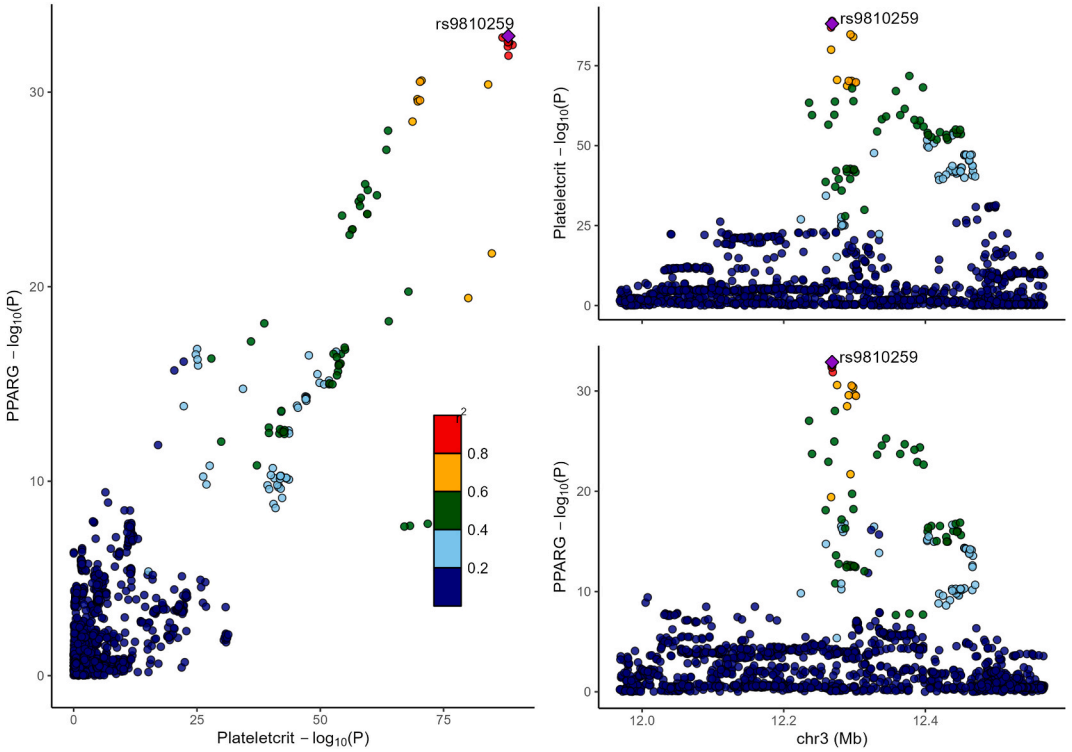

Fig. 3. Colocalization analysis of genetically proxied TZDs and platecrit. PPARG: Peroxisome Proliferator Activated Receptor Gamma as a target of thiazolidinediones; Points were color-coded according to the LD (r2) of each variant relative to the variant with the highest posterior probability of colocalization within the gene region. In the left panel, - log10 *P* values for associations with platecrit are on the *x*-axes, and - log10 *P* values for associations with the PPARG on the *y*-axes. In the right panels, genomic positions are on the *x*-axes, and the *y*-axes show - log10 *P* values for platecrit on the upper panel and - log10 *P* values with the PPARG on the lower panel for the corresponding region. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

network has recently been established [34]. However, the underlying molecular mechanisms have not yet been fully elucidated. The current study found evidence that genetically proxied TZDs target perturbation was causally associated with lower platelet characteristics, particularly the platelet count and plateletcrit. This might aid in demonstrating the underlying mechanism by which TZDs exert neuroprotective effects against AD via platelet-related pathways. Furthermore, this also implied that TZDs could serve as promising novel medications for AD.

Since T2D is an independent risk factor for AD, diabetic patients have nearly double the risk of developing dementia [35]. One of the hypotheses about this phenomenon is that T2D and AD share some pathogenic mechanisms, such as insulin resistance and microvascular dysfunction. Therefore, investigations are needed to explore the potential of antidiabetic drugs for the patients, who are at risk of or enduring AD. Exploring novel potential applications of TZDs might lead to a comprehensive expansion and present new opportunities for this longstanding class of antidiabetic agents.

TZDs, a classic class of antidiabetic medication, function by increasing the transactivation activity of Peroxisome Proliferators

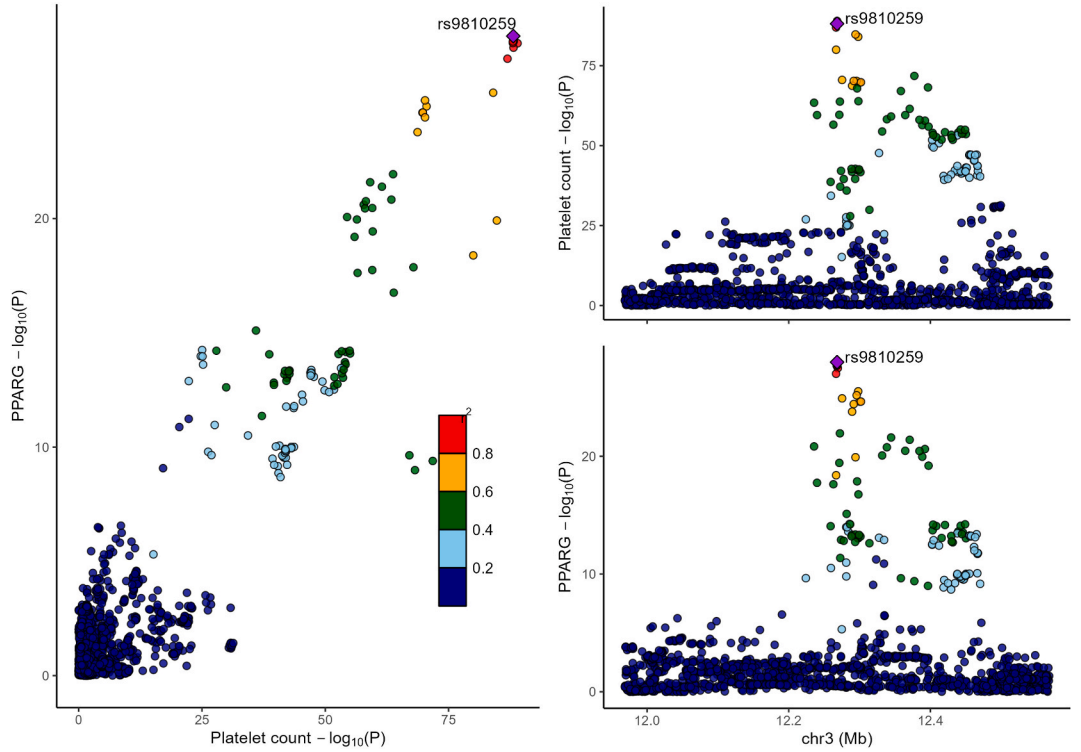

Fig. 4. Colocalization analysis of genetically proxied TZDs and platelet count. PPARG: Peroxisome Proliferator Activated Receptor Gamma as a target of thiazolidinediones; Points were color-coded according to the LD (r2) of each variant relative to the variant with the highest posterior probability of colocalization within the gene region. In the left panel, - log10 *P* values for associations with platelet count are on the *x*-axes, and - log10 *P* values for associations with the PPARG on the *y*-axes. In the right panels, genomic positions are on the *x*-axes, and the *y*-axes show - log10 *P* values for platelet count on the upper panel and - log10 *P* values with the PPARG on the lower panel for the corresponding region. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Activated Receptors (PPARs). During the past decade, an increasing number of large-scale observational studies have suggested that TZDs exerted neuroprotective effects against AD, thereby showing promising application prospects in AD [36,37]. In a longitudinal review of 91,218 T2D patients without prior dementia, the use of pioglitazone was correlated with a lower risk of dementia (adjusted hazard ratio [aHR] = 0.84), particularly among those having a history of ischemic stroke or cardiovascular disease before the onset of T2D (aHR = 0.46) [38]. Consistently, the current study also found a dose-response relationship. Similarly, a prospective cohort of 145, 928 individuals aged ≥60 years demonstrated that the long-term use of pioglitazone was significantly associated with a decreased risk of dementia [39]. Compared to non-diabetic individuals, those who used pioglitazone for more than 8 quarters had a 47 % lower dementia risk (RR = 0.531, $P = 0.029$), while those who used pioglitazone for less than 8 quarters had a comparable risk to the nondiabetic population (RR = 1.161, $P = 0.317$). Furthermore, in a prospective observational study of 559,106 patients with T2D, TZD monotherapy was associated with a 22 % reduced risk of all-cause dementia onset (HR = 0.78, 95 % CI 0.75 to 0.81) and an 11 % reduced risk of AD (HR = 0.89, 95 % CI 0.79 to 0.99) after at least one year of treatment [40]. In a real-world study, TZD users were also found to have a significantly lower risk of developing various types of dementia compared to non-TZD users who received dual oral therapy [41]. At the same time, it is worth noting that a relatively small proportion of clinical and laboratory evidence on the efficacy of TZDs in treating AD currently shows mixed or neutral effects, suggesting that caution is needed when extrapolating our findings [42–44].

A great number of studies suggest that TZDs might reduce the risk of dementia, highlighting their potential as a therapeutic strategy for dementia protection. However, the molecular mechanisms underlying the neuroprotective effects of TZDs against dementia have not been fully elaborated. The neuroprotective effects of TZDs can be explained in numerous ways. In addition to PPARγ/PGC1α signaling pathway, which directly plays a critical role in mitochondrial biogenesis in neurodegenerative disorder, TZDs might alleviate insulin resistance, decrease Aβ synthesis and neuroinflammation, balance neuronal energy through mitochondria, and enhance glucose metabolism during AD development [45–47] [45–47] [45–47]. However, the platelet pathway seems to have been neglected so far.

In light of the biochemical resemblance between platelet and neuron biology, platelets might serve as an ideal peripheral source for investigating the pathophysiological mechanisms of AD [48,49]. An integral analysis of platelet omics and brain omics data explored their correlation with AD-related pathology and cognitive impairment [34]. A total of 239 differentially expressed proteins were identified, which were present in both the brain and platelets, of which 70.3 % showed accordant changes. Geno ontology pathway

analysis revealed the enrichment of these proteins in multiple dysregulated pathways, including platelet activation and degranulation. Subsequently, the First linkage network between the brain and platelets in AD was established, highlighting the systemic synergetic role of platelet activation in AD.

In this regard, mitochondrial dysfunction has been demonstrated conducive to platelet-mediated Aβ aggregation in vitro [2]. Moreover, the alterations in the platelet amyloid precursor protein (APP) metabolic pathway in AD patients have been investigated and how Aβ elevated platelet activation, and activated platelets serve as a bridge between risk factors and AD have been further illustrated [4]. They proposed that the elevated levels of platelet APP might contribute to the production of Aβ, thereby promoting platelet activation and triggering Aβ fibrillation simultaneously in AD. In addition, peripheral platelet modifications, including cytoskeletal malformations, abnormal cytoplasmic calcium fluxes, and upgraded oxidative stress levels, are also associated with AD pathology [50]. Collectively, these studies highlight the importance of platelets in understanding the underlying mechanisms of AD. They provide valuable insights into potential therapeutic targets and emphasize the systemic role of platelet activation in AD pathology.

In conclusion, this study provided evidence that genetically proxied T2D target perturbation might be causally associated with lower platelet characteristics, particularly the platelet count and plateletcrit, suggesting that platelet pathway may be one of the reasons why TZDs show strong neuroprotective effects against AD. Further studies are required to uncover the role of platelets in TZDs' protective effects against AD at a molecular mechanism level.

4.1. Strengths and limitations

First, this study systematically investigated the long-term effects of multiple antidiabetic drugs on platelet characteristics to report the prevention of platelet or thrombotic events in diabetic patients, thereby overcoming the limitations of observational studies, such as reverse causality and potential confounders. Second, variants in drug target genes, having F-statistics >10 and associated with HbA1c were used as a proxy for antidiabetic agents in Europeans, minimizing confounding bias. In addition, T2D positive control analyses and a range of MR methods with different assumptions were used to ensure the validity of the genetic variants and improve the robustness of the results. Besides, the colocalization analysis further reinforced the positive results derived from MR.

Despite the novelty of the study, certain limitations must be recognized. First, this study only considered the effects of a single antidiabetic drug on platelet characteristics, whereas TZDs are often used in combination with other agents. Therefore, there are limitations in interpreting the effects of a single antidiabetic drug in the presence of drug interactions [51,52]. However, only publicly available aggregated data were used in this study. Therefore, further breakthroughs regarding these issues in the future should focus on the effects of common antidiabetic agents, which use individual-level data [53]. Second, MR has a natural advantage over traditional observational studies in providing a higher level of causal evidence under the population. However, when further focusing on the individual level, more studies are still needed to predict medication risk, prevention, and prognostic monitoring at the individual level, because it is subjected to the patient's medication use, such as the duration of continuous medication, co-administration, individual differences in medication metabolism, and medication dosage. Third, while performing MR, the optimal dataset obtained by retrieving all publicly available GWAS data on platelet characteristics still has a slight overlap of about 21.8 % in the UKB cohort, which might bias the estimates but infinitesimally [54]. On the other hand, a recent simulation study confirmed that most two-sample estimation methods remain valid in overlapping samples of large cohorts, even in the presence of substantial correlations due to confounding factors, as is the case with the methodology used in this study [55]. Furthermore, the F-statistic in this study was also strong enough to overcome the bias in MR estimates caused by weak instrumental variables when the samples overlapped. Finally, these analyses were based on European samples, so generalization to people of non-European ancestry needs to be validated in the future.

Ethics approval and consent to participate

Participants in this article were drawn from several previous studies. As described in the Methods, informed consent was obtained from all participants in all the corresponding original studies, and there was no personal dimension involved. Hence, ethical approval was not applicable.

Consent for publication

Not applicable.

Data availability statement

Publicly available datasets are analyzed in this study. The summary statistics for T2D can be downloaded from the DIAGRAM database (https://diagram-consortium.org/index.html). Summary human HbA1c dataset is publicly available in Pan-UKB team (https://pan.ukbb.broadinstitute.org). Summary platelet characteristics datasets can be obtained from the NHGRI-EBI GWAS Catalog (https://www.ebi.ac.uk/gwas/)(GWAS ID: GCST004603, GCST004607 and GCST004599). Summary *cis*-eQTLs dataset is publicly available from eQTLGen consortium (https://www.eqtlgen.org/*cis*-eqtls.html).

Funding

The work was conducted with support from the National Natural Science Foundation of China (No. 82274016), Basic and Applied Basic Research Foundation of Guangdong Province (No. 2021A1515220031), Science and Technology Program of Guangzhou (No. 202002030415), Hospital project of Guangdong Provincial People's Hospital (No. 2023–08).

CRediT authorship contribution statement

Zhipeng Xie: Writing – review & editing, Writing – original draft, Visualization, Software, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Yijie Liu:** Writing – original draft, Visualization, Validation, Supervision, Data curation, Conceptualization. **Min Huang:** Writing – original draft, Visualization, Project administration, Data curation, Conceptualization. **Shilong Zhong:** Writing – review & editing, Writing – original draft, Visualization, Validation, Project administration, Funding acquisition, Conceptualization. **Weihua Lai:** Writing – review & editing, Writing – original draft, Validation, Supervision, Project administration, Funding acquisition, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

11. Acknowledgements

The authors would like to thank all the reviewers who participated in the review and MJEditor (www.mjeditor.com) for its linguistic assistance during the preparation of this manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e30909.

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