

SGLT2 inhibition, circulating biomarkers, and Alzheimer's disease: A Mendelian randomization study

Journal of Alzheimer's Disease
2025, Vol. 103(4) 1126–1134
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DOI: 10.1177/13872877241309674
journals.sagepub.com/home/alz



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Abstract

Background: Sodium-glucose cotransporter 2 (SGLT2) inhibitors is a novel category of medications for diabetes, exhibiting neuroprotective potential. However, evidence regarding whether the use of SGLT2 inhibitors effectively reduces the risk of Alzheimer's disease (AD) remains unclear.

Objective: Our study employed Mendelian randomization (MR) analysis to investigate potential causal relationships between SGLT2 inhibition, metabolites, and AD.

Methods: In our research, we used a two-sample MR method to explore the link between SGLT2 inhibitor use and AD, addressing both its late-onset and early-onset forms. Furthermore, we executed a two-step MR analysis to explore how circulating metabolites, primarily endogenous in nature due to SGLT2 inhibition, mediate the relationship between SGLT2 inhibition and AD. The genetic instruments for SGLT2 inhibition were pinpointed through their association with SLC5A2 gene expression and the decreased glycated hemoglobin (HbA1c) levels.

Results: Genetic analysis indicated that SGLT2 inhibition, which effectively reduces HbA1c by enhancing renal glucose excretion and improving glycemic control, was associated with a lower likelihood of developing AD for every 1 SD decrease in HbA1c (OR = 0.48, [0.36, 0.63], $p < 0.001$). Our MR analysis revealed that SGLT2 inhibition significantly affected 27 of the 123 metabolites examined, adhering to a Bonferroni correction threshold ($p < 4.06 \times 10^{-4}$). Among these 27 significant metabolites, citrate was also associated with AD, showing a significant association (0.81 [0.79, 0.83], $p < 0.001$).

Conclusions: The study provides strong evidence linking SGLT2 inhibition with a lower AD risk, highlighting citrate's potential mediating role for subsequent clinical research.

Keywords

Alzheimer's disease, circulating biomarkers, Mendelian randomization, sodium-glucose cotransporter 2 inhibition

Received: 15 April 2024; accepted: 11 November 2024

Introduction

Sodium-glucose cotransporter 2 (SGLT2) inhibitors, represent a notable advancement in managing type 2 diabetes mellitus (T2DM), functioning by inhibiting SGLT2 in the kidneys, thus reducing glucose reabsorption and boosting urinary glucose excretion.¹ Their utility extends beyond glucose regulation, showing effectiveness in improving cardiovascular and renal outcomes.^{2,3} These drugs have a notable influence on various circulating metabolites, although the precise nature of these interactions remains somewhat elusive, with research yielding mixed results.^{4,5}

Given the broader implications of such systemic effects, researchers have begun exploring the potential of repurposing medications like SGLT2 inhibitors for neurodegenerative diseases, including Alzheimer's disease (AD). AD is a disease

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marked by amyloid- β plaques accumulation and tau protein tangles, resulting in cognitive decline and memory loss.⁶ It manifests in two variations: early-onset AD (EOAD), linked to genetic factors, and late-onset AD (LOAD), which occurs more sporadically in the elderly population. Despite similar pathological markers, they exhibit distinct disease progressions.^{7,8}

Recent research has pointed to a potential connection between T2DM and a heightened risk of AD, possibly mediated by insulin resistance and disrupted glucose metabolic process in the brain.⁹ Given their anti-inflammatory and vasculoprotective qualities, SGLT2 inhibitors might offer a therapeutic avenue in AD management.¹⁰ Establishing a direct causal link, however, remains a challenge, largely due to the complexity of reverse causality.

Mendelian randomization (MR) offers a robust approach to explore potential cause-and-effect links between exposures, like SGLT2 inhibition, and outcomes such as AD. By leveraging genetic variants as instrumental variables (IVs), MR minimizes reverse causation and confounding, simulating the effects of randomized controlled trials.¹¹ This approach is particularly relevant in disentangling the complex interplay between metabolic disorders and neurodegenerative diseases and could be instrumental in identifying more definitive causal links. This is crucial for developing targeted therapeutic strategies for AD.^{12,13}

In our study, employing MR, we first rigorously examine the relationship between SGLT2 inhibition and AD. This initial investigation sets the foundation for a deeper exploration into how circulating metabolites may mediate this relationship. This offers a fresh perspective on the future therapeutic impact of SGLT2 inhibitors on AD, potentially paving the way for novel treatment strategies in this challenging and increasingly prevalent condition.

Methods

Study design

In our study (Figure 1): 1) We first identify genetic variants that act as indicators for the inhibitory effects of SGLT2; 2) We then select 123 metabolites as potential mediators from GWAS summary statistics; 3) Our analysis includes three outcomes: AD, LOAD, and EOAD; 4) We employ a two-step MR approach to determine the causal connections. Initially, we assess the effect of SGLT2 inhibition on the selected outcomes. Subsequently, we assess the influence of SGLT2 inhibition on the metabolites. Finally, we evaluate the significant metabolites for their role in AD.

Our commitment to the Strengthening the Reporting of Observational Studies in Epidemiology using Mendelian Randomization (STROBE-MR) guidelines guarantees the clarity and rigorous documentation of our research's methods and findings.¹⁴

Genetic instruments for SGLT2 inhibition

In our study, we identified genetic variants associated with SGLT2 inhibition through a detailed four-step process. We began by using Genotype-Tissue Expression (GTEx)¹⁵ and eQTLGen Consortium¹⁶ data to identify variants linked to the mRNA levels of the SLC5A2 gene, which encodes SGLT2. We then examined how these variants influenced glycated hemoglobin (HbA1c) levels, as a marker for glucose reduction, selecting variants with significant associations. Only variants with a significant correlation with HbA1c ($p < 1 \times 10^{-4}$) were advanced for further analysis.

The analysis of HbA1c leveraged genome-wide association study (GWAS) data from 344,182 individuals without diabetes of European ancestry, sourced from the UK Biobank (Supplemental Table 1). Our analysis included a colocalization assessment to ensure shared causality between SLC5A2 expression and HbA1c levels.¹⁷ Variants with a high posterior probability (>70%) for shared causality were considered supportive of colocalization. Finally, we grouped these variants based on linkage disequilibrium (LD) ($r^2 < 0.8$ within a 250 kb range), referencing the 1000 Genomes European panel.

Genetically determined metabolites

For metabolites with genetic determinants, we sourced GWAS summary data for 123 circulating metabolites, drawn from an analysis across 14 cohorts.^{18,19} This dataset was initially compiled and analyzed through a comprehensive GWAS to determine the levels of various metabolites in human serum.¹⁸ The original research considered adjustments for the duration of fasting. These metabolites cover a wide array of systemic metabolic processes, categorized into 12 classes, including a range of compounds from fatty acyls to steroids. We accessed data for these biomarkers from the IEU Open-GWAS Project database, under the identifier 'met-c' (Supplemental Table 1), concentrating on genetic variants that achieved genome-wide significance ($p < 5 \times 10^{-8}$) and were not in linkage disequilibrium (LD $r^2 < 0.001$ over a span of 10,000 kb).

Outcomes

For our primary outcome, we employed GWAS summary statistics from a significant 2019 meta-analysis by a major consortium, involving 21,982 cases of AD and 41,944 controls. This meta-analysis, comprising groups like Alzheimer Disease Genetics Consortium (ADGC), the European Alzheimer's Disease Initiative (EADI), the Cohorts for Heart and Aging Research in Genomic Epidemiology Consortium (CHARGE), and the Genetic and Environmental Risk in AD/Defining Genetic, Polygenic, and Environmental Risk for Alzheimer's Disease

Consortium (GERAD/PERADES), identified risk loci and pathways related to key factors in AD.²⁰ Subsequently, different forms of AD, including LOAD and EOAD, were obtained from the tenth round of results (R10) in the FinnGen database.²¹ Specifically, for late-onset AD, the dataset comprised 7308 cases and 183,753 controls, while for early-onset AD, there were 1451 cases matched with an equal number of controls.

Statistical analyses

We conducted a two-sample MR analysis to assess the impacts of SGLT2 inhibition on AD. We applied the Mendelian Randomization Pleiotropy RESidual Sum and Outlier (MR-PRESSO)²² to identify and adjust for potential horizontal pleiotropy and heterogeneity, excluding outlier genetic variants prior to the MR analysis. The primary method we used was the Inverse Variance Weighted (IVW) approach, ideal when all the genetic variants are valid instruments.²³

In the mediation MR analysis, we adopted a sequential approach to analyze how circulating metabolites mediate the connection between SGLT2 inhibition and AD. Initially, we calculated the total effect of genetic variations on all outcomes (β_0), without distinguishing between direct and mediating factor-mediated impacts. Subsequently, we assessed the influence of genetic variations on circulating metabolites (β_1). Finally, we assessed the effect of significant mediating metabolites on AD (β_2). The mediation effect was computed by multiplying β_1 and β_2 .²⁴ The Delta method was used to calculate the 95% confidence intervals for these mediation proportions.²⁵

During our sensitivity analysis within the MR investigation of the effect of SGLT2 inhibition on the outcomes, we utilized multiple techniques such as MR-Egger, weighted median, simple mode, and weighted mode methods to ensure the reliability of our results. In our sensitivity analysis, the MR-Egger method played a crucial role in detecting directional pleiotropy by inspecting its intercept.²⁶ A non-zero intercept in MR-Egger would indicate such pleiotropy, potentially affecting the IVW estimates. Meanwhile, the weighted median approach was effective when a majority (at least 50%) of the genetic instruments were valid.²⁷ Moreover, the simple mode and weighted mode approaches proved valuable when the predominant cluster of instruments showed no signs of horizontal pleiotropy.^{28,29}

We performed heterogeneity assessments using the MR Egger and IVW methods to examine the variability among the genetic instruments; a p-value over 0.05 suggested no significant heterogeneity. For horizontal pleiotropy assessment, MR Egger regression was employed, with a p-value greater than 0.05 denoting its absence.

For selecting IVs, we determined each IV's variance explained and calculated the F-statistic using the equation

$F = (n - k - 1 / k) * (R^2 / (1 - R^2))$, where n represents the sample size, k denotes the number of genetic instruments, and R^2 indicates the proportion of variance in the exposure explained by these instruments.³⁰ An instrument was considered strong if its F-statistic exceeded 10. To verify the robustness of our findings, we employed the leave-one-out approach, removing each SNP in turn to detect any substantial impacts on the results.³¹

We used the TwoSampleMR and MRPRESSO packages in the R software (version 4.2.2) to investigate MR analysis, considering a two-sided p-value for statistical significance and applying the Bonferroni correction for multiple comparisons. Nevertheless, for estimating the effects of SGLT2 inhibition on AD, a p-value under 0.05 was regarded as significant.

Standard protocol approvals, registrations, and patient consents

This study is based on GWAS summary statistics from meta-analysis. All individual participants in the constituent cohorts of the meta-analysis had given written informed consent, and the protocols for each cohort received approval from the respective local institutional review board.

Results

Influence of SGLT2 inhibition on AD

In our research, we utilized 10 independent SNPs as genetic markers for SGLT2 inhibition, all demonstrating an F statistic above 10 (Supplemental Table 1). The MR assessments indicated a notable link between SGLT2 inhibition and a decreased incidence of AD (Figure 2). For AD, the odds ratio (OR) for each standard deviation decrease in HbA1c was 0.48 (95% CI: 0.36 to 0.63) (Figure 2). These results were corroborated through sensitivity analyses using MR-PRESSO, which showed no signs of heterogeneity ($Q = 1.312$, $p = 0.998$) or horizontal pleiotropy (Egger intercept = -0.0300 , $p = 0.374$) (Table 1). Consistent outcomes were observed for both LOAD and EOAD. For LOAD, the OR was 0.29 (95% CI: 0.14 to 0.60, $p = 0.001$), and for EOAD, the OR was also 0.29 (95% CI: 0.09 to 0.89, $p = 0.03$) (Table 1). There was no significant heterogeneity for LOAD ($Q = 4.94$, $p = 0.839$) or EOAD ($Q = 3.034$, $p = 0.963$), nor was there evidence of horizontal pleiotropy for LOAD (Egger intercept = -0.016 , $p = 0.719$) or EOAD (Egger intercept = 0.077 , $p = 0.391$). The leave-one-out approach also verified the consistency of these outcomes for AD (Figure 3).

Mediation effect

Mediation MR of analysis of SGLT2 inhibition, metabolite levels, and AD. Our mediation MR assessment scrutinized the

Table 1. Mr analysis of SGLT2 inhibition's impact on Alzheimer's disease (AD) related outcomes.

Outcome	Method	OR (95%CI)	p	Q statistic	p-heterogeneity	Egger intercept	p-intercept
AD	IVW	0.48 (0.36–0.63)	1.59E-07	1.312	0.998		
	MR Egger	4.28 (0.04–439.67)	0.555	0.426	1.000	–0.0300	0.374
	Weighted median	0.55 (0.23–1.34)	0.192				
	Simple mode	0.54 (0.15–1.98)	0.375				
	Weighted mode	0.59 (0.18–1.94)	0.406				
LOAD	IVW	0.29 (0.14–0.60)	0.001	4.940	0.839		
	MR Egger	0.94 (0.00–460.28)	0.984	4.801	0.779	–0.016	0.719
	Weighted median	0.44 (0.12–1.68)	0.232				
	Simple mode	0.62 (0.07–5.93)	0.692				
	Weighted mode	0.59 (0.10–3.51)	0.574				
EOAD	IVW	0.29 (0.09–0.89)	0.030	3.034	0.963		
	MR Egger	0.00 (0.00–223.60)	0.306	2.212	0.974	0.077	0.391
	Weighted median	0.26 (0.02–3.07)	0.284				
	Simple mode	0.30 (0.01–13.19)	0.547				
	Weighted mode	0.25 (0.01–9.95)	0.483				

This table presents odds ratios (OR), 95% confidence intervals (CI), and p-values derived from various MR analysis methods to assess the impact of SGLT2 inhibition on AD. Heterogeneity for the inverse-variance weighted (IVW) methods was assessed using Cochran's Q statistic, while the MR-PRESSO method utilized the global test. Significance was determined at a threshold of $p < 0.05$.

AD: Alzheimer's disease; LOAD: Late-onset Alzheimer's disease; EOAD: Early-onset Alzheimer's disease; IVW: Inverse-variance weighted; p-heterogeneity: p-value for the heterogeneity test; p-intercept: p-value for the MR-Egger regression intercept.

influence of SGLT2 inhibition on metabolite concentrations in the bloodstream and their subsequent effect on AD (Figure 4A). Out of 123 metabolites analyzed, 27 showed significant associations after applying the stringent Bonferroni correction (p value threshold = $4.06 \times 10e^{-4}$ [0.05/123]). These metabolites encompass diverse classes, highlighting the broad metabolic modulation by SGLT2 inhibitors. Notably, several lipid-related metabolites displayed negative associations, marked by beta values less than zero. This was particularly evident in subclasses of VLDL and HDL particles. Certain amino acids, such as Alanine, Isoleucine, and Tyrosine, also showed decreased levels. Conversely, a positive correlation was observed for metabolites like Lactate and amino acids like Glycine, suggesting their upregulation upon SGLT2 inhibition.

Further, we assessed the influence of these 27 metabolites on AD risk (Figure 4B). Notably, Citrate emerged as the sole metabolite with a robust inverse correlation with AD risk (OR = 0.81 [0.79, 0.83], $p < 0.001$), surpassing the Bonferroni-adjusted significance threshold of 0.0019 ([0.05/27]). Citrate accounted for a mediated portion of 20.15%, with the 95% confidence interval spanning 9.84% to 30.72%, in the total effect size noted. This result was further corroborated by MR-PRESSO analysis, which detected no signs of heterogeneity or horizontal pleiotropy. Notably, the presence of 'NA' in rows indicates insufficient SNP data to conduct MR analyses for those specific metabolites. Additionally, Lactate was not further analyzed due to an insufficient number of SNPs, thereby not fulfilling the criteria for the sensitivity assessment. The genetic variants for the 27 metabolites were determined to be robust (All F statistics > 10) (Supplemental Table 3).

Discussion

Key outcomes

Our research explored the links between genetic proxies for SGLT2 inhibition and the risk of AD. Additionally, we examined how circulating metabolites might mediate the relationship between SGLT2 inhibition and AD. These findings suggest that genetic alterations affecting SGLT2 inhibition are correlated with decreased risks AD. Moreover, our findings suggest the potential mediating role of citrate in the effect of SGLT2 inhibition on AD.

The association between SGLT2 inhibition and AD

Given the overlapping pathological elements between T2DM and AD, and the broad expression of SGLTs in brain tissue, there is a compelling argument for exploring the use of SGLT2 inhibitors in AD therapy.³² The putative neuroprotective properties of SGLT2 inhibitors have gathered attention for their potential to lower the likelihood of dementia and bolster cognitive capabilities via mechanisms such as reducing blood pressure, enhancing cardiac health, modulating inflammation, promoting weight reduction, and slowing the progression of atherosclerotic plaques.^{33,34} Preclinical research in animal models demonstrates that SGLT2 inhibitors, specifically empagliflozin, can decrease A β plaque accumulation, limit brain cortex atrophy, lessen neuronal loss, and improve cognitive functions in AD model mice.³⁵ In humans, evidence is emerging, with studies showing that older individuals with T2DM taking SGLT2 inhibitors exhibit a lower dementia risk compared

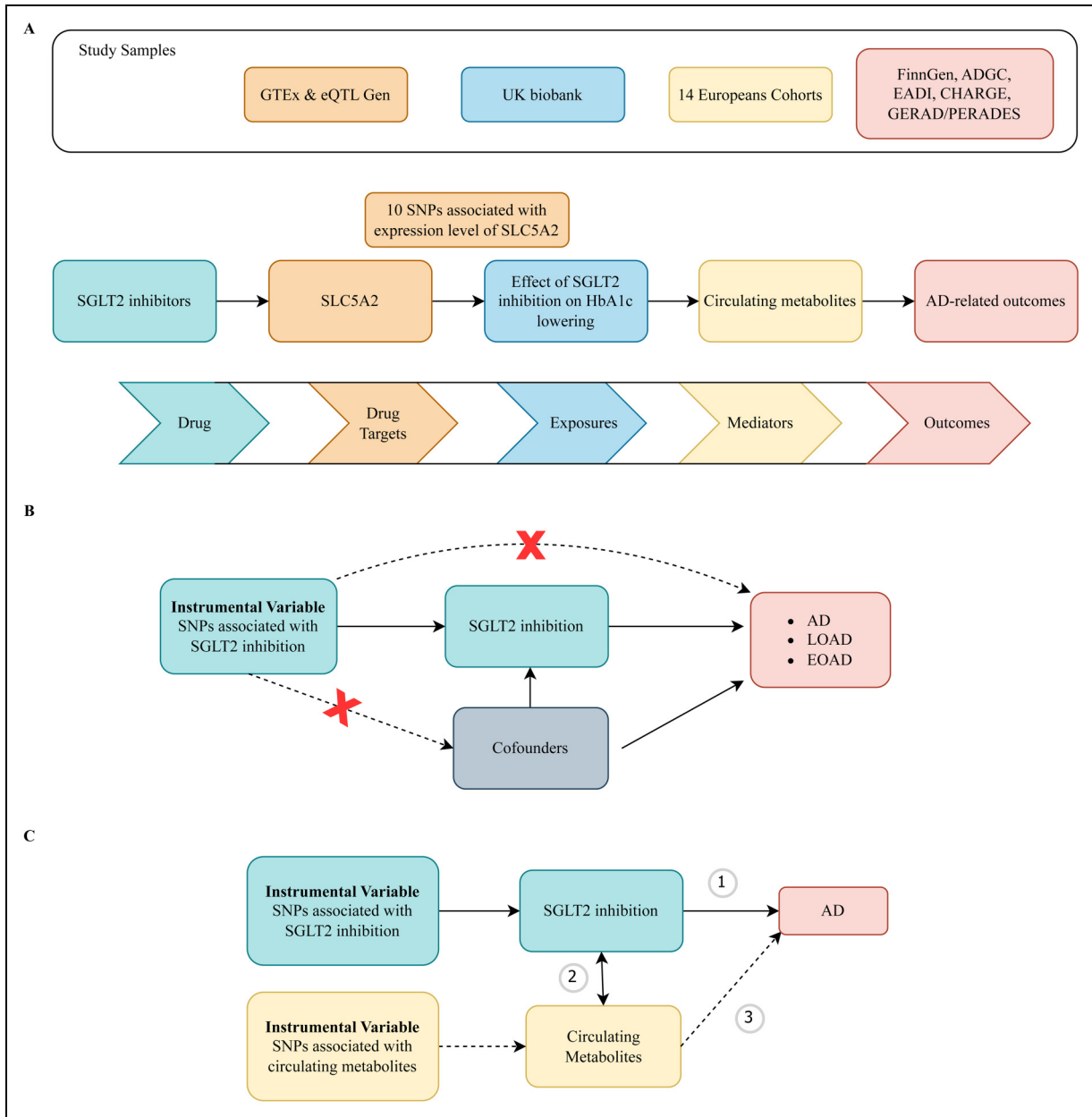


Figure 1. Study Design. (A) Two-sample Mendelian randomization (MR) analyses were conducted to assess the impact of SGLT2 inhibition on AD-related outcomes. Genetic variants representing the effect of SGLT2 inhibition were selected, and AD-related outcomes, including AD, LOAD, and EOAD, were chosen as outcomes. Summary data for exposure and outcomes were obtained from relevant meta-analyses of genome-wide association studies. The primary analysis employed the generalized inverse variance-weighted approach, with several sensitivity analyses performed. (B) To establish a causal relationship, three conditions were required: (1) instrumental variables should not be associated with confounders (dashed line), (2) instrumental variables should be linked to the exposure (solid line), and (3) instrumental variables should not directly affect the outcome (dashed line). (C) The two-step MR method was employed to estimate the mediation effect. SGLT2: Sodium-glucose cotransporter 2; HbA1c: glycated hemoglobin level; AD: Alzheimer's disease; LOAD: late-onset Alzheimer's disease; EOAD: early-onset Alzheimer's disease.

to those on other anti-diabetic drugs.³⁶ Additionally, a prospective cohort study suggested that prolonged treatment with SGLT2 inhibitors may lead to cognitive enhancements in overall cognitive assessment scores, as well as in specific areas like language and executive functioning among individuals with T2DM.³⁷

In our study, the findings that SGLT2 inhibition exerts a negative causal effect on both late-onset and early-onset AD. The observed uniform negative causal effect of SGLT2 inhibition on both AD types indicates a possible universal influence of disrupted glucose metabolism in the disease's pathology, regardless of onset age. This aligns with emerging evidence

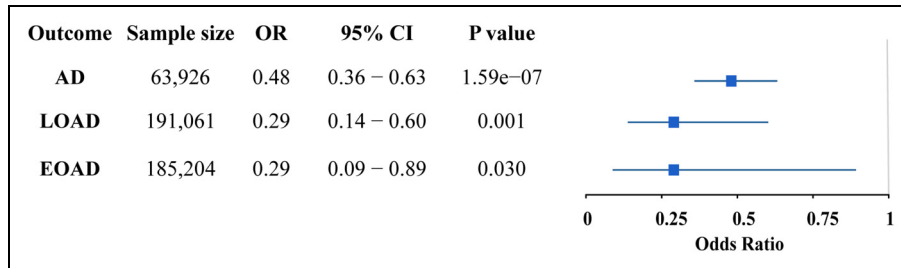


Figure 2. Mr estimates of the association between genetically proxied SGLT2 inhibition and Alzheimer's disease. Estimates represent odds ratios (95% CIs) for Alzheimer's disease per SD increase in genetically predicted SGLT2 inhibition. OR: Odds ratio; AD: Alzheimer's disease; LOAD: Late-onset Alzheimer's disease; EOAD: Early-onset Alzheimer's disease.

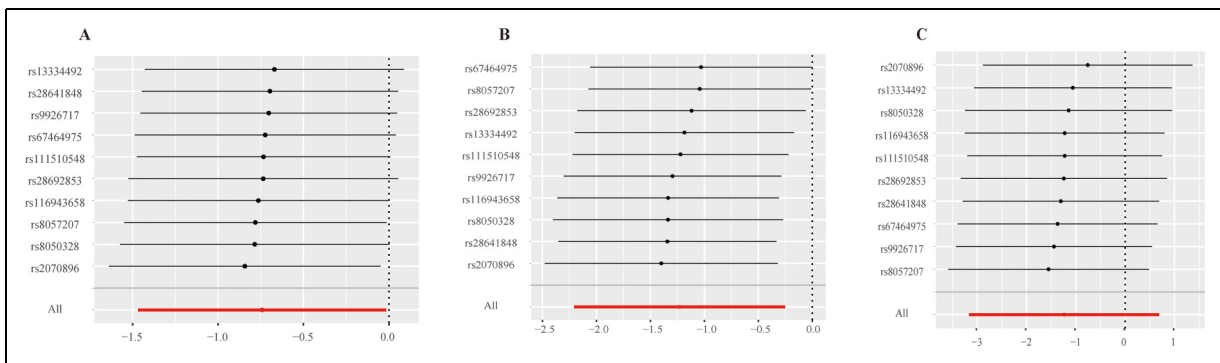


Figure 3. Leave-one-out sensitivity analysis of SGLT2 inhibition on AD, LOAD, EOAD. (A) AD. (B) LOAD. (C) EOAD. The leave-one-out method is used to evaluate the excessive effect of a single SNP on MR analysis if the comprehensive effect of the remaining SNPs is consistent with the main effect after removing one SNP. SNP: single nucleotide polymorphisms; SGLT2: sodium-dependent glucose transporter 2; AD: Alzheimer's disease; LOAD: Late-onset Alzheimer's disease; EOAD: Early-onset Alzheimer's disease.

highlighting glucose metabolism abnormalities in AD brains, even in the absence of diabetes.³⁸ Furthermore, these findings underscore the potential of modulating systemic and cerebral glucose metabolism as a therapeutic strategy for AD, highlighting the need to consider metabolic interventions in future AD research and treatment paradigms.³⁹ Moreover, the consistent effect across AD subtypes emphasizes the importance of acknowledging disease heterogeneity in AD therapeutic exploration. It suggests that interventions targeting metabolic pathways could have broad applicability in AD, offering new avenues for research and therapeutic development.

The relationship between SGLT2 inhibition and metabolite levels

Previous research has provided mixed views on the impact of SGLT2 inhibitors on blood metabolites.^{40,41} We observed alterations span a range of metabolic classes, reflecting the diverse biological roles of SGLT2 inhibitors. The negative beta values for VLDL and HDL subclasses, along with specific amino acids, suggest a lipid-lowering effect, consistent with findings from previous studies on the lipid-modifying effects of SGLT2 inhibitors.³ These changes in lipid profiles

could potentially confer cardiovascular benefits, as reduced levels of certain VLDL and HDL particles have been associated with decreased atherosclerotic risk.⁴²

The reduction in amino acids such as Alanine, Isoleucine, and Tyrosine upon SGLT2 inhibition could be indicative of altered protein metabolism or energy utilization.⁴³ These changes might relate to improved insulin sensitivity and glucose utilization, as amino acid metabolism has been linked to insulin resistance and T2DM pathogenesis.⁴⁴ The decreased citrate levels observed may suggest a potential shift in mitochondrial energy metabolism, which could influence ATP production that is crucial for neuronal function. The elevation of glycine levels, observed as a positive beta value, may reflect changes in gluconeogenesis and nitrogen balance, which can be affected by SGLT2 inhibition due to its effects on renal glucose production and amino acid absorption.⁴⁵

The mediation role of blood metabolites in the link between SGLT2 inhibition and AD

The influence of circulating metabolites as mediators presents a complex network of interactions that could modulate

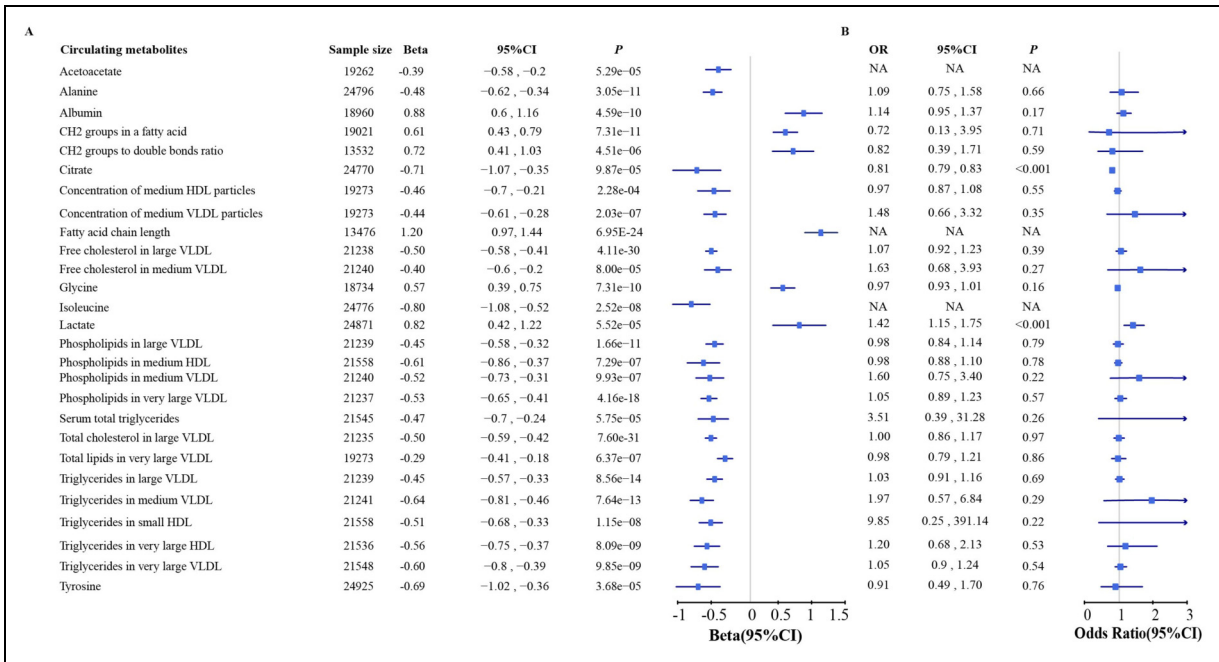


Figure 4. The forest plot of showing the effects of SGLT2 inhibition on circulating metabolites and the effects of metabolites on Alzheimer's disease. (A) The effects of SGLT2 inhibition on 27 out of 123 metabolites, which showed significant association with SGLT2 inhibition (Bonferroni-corrected P value threshold = 4.06×10^{-4} [0.05/123]). (B) The effects of these 27 metabolites on Alzheimer's disease (Bonferroni corrected p value threshold = 0.0019 [0.05/27]). CI: confidence interval; OR: odds ratio.

the risk of AD following SGLT2 inhibition. Previous research has demonstrated both protective and detrimental effects of various metabolites on AD risk, indicating a multifaceted relationship between metabolism and neurodegeneration.^{46,47} Our findings suggest that SGLT2 inhibitors might play a complex role in AD risk modulation. Overall, the inhibition may directly reduce AD risk by influencing glucose metabolism and insulin sensitivity, both of which are associated with the development of AD.⁹ However, this protective effect appears to be moderated by interactions with metabolic products such as citrate. Specifically, while increased citrate levels are generally associated with a decreased risk of AD,⁴⁷ SGLT2 inhibition unfortunately leads to a reduction in citrate levels, thereby potentially mitigating its beneficial effects on AD risk. Therefore, future pharmaceutical developments could consider combining SGLT2 inhibitors with treatments aimed at elevating citrate levels to enhance protective effects against AD. Additionally, although lactate was not analyzed further in our results due to insufficient SNPs, it is important to recognize lactate as a critical bioenergetic fuel for microglia and as a modulator of their proinflammatory activation.⁴⁸ Further research into lactate's role in AD is warranted to fully understand its therapeutic potential. Longitudinal studies and randomized controlled trials could elucidate whether the modulation of these metabolites by SGLT2 inhibitors has long-term benefits or drawbacks for cognitive health. Moreover, investigating how SGLT2 inhibition

affects metabolite concentrations and AD biomarkers could shed light on the viability of SGLT2 inhibitors as treatments for AD.

Limitation

Our research utilizes a strong two-sample MR method to explore the link between SGLT2 inhibition and AD in the general population. This methodology, along with an extensive examination of 123 circulating metabolites and various genetic instruments, enhances the reliability of our insights into the impacts of SGLT2 inhibition and the mediating function of these metabolites. However, several limitations are noteworthy.

First, the genetic information, predominantly sourced from European-descended individuals, might restrict the generalizability of our results to various ethnic groups. Then, while the study identifies associations, it does not fully explain the complex interactions between circulating metabolites and their effect on AD. Also, a potential overlap in the Finnish subpopulations used for circulating metabolites and outcomes might introduce a degree of sample overlap bias, potentially skewing the causality analysis. Additionally, our study considers a limited selection of metabolites, which does not encompass all metabolic pathways relevant to our hypothesis, a limitation primarily due to the lack of comprehensive GWAS data for all metabolites. Finally, current study does not explore how genetic

variability and environmental factors may jointly influence AD risk in the context of SGLT2 inhibition. Future analyses should incorporate more robust methods and sensitivity tests to better verify causal relationship. These aspects underscore the necessity for more nuanced research to comprehensively understand the intricate link between SGLT2 inhibition, circulating metabolites, and AD risk.


Conclusions

This research supported a relationship between genetic indicators of SGLT2 inhibition and AD, highlighting citrate's mediating role in this connection. The findings furnish genetic proof of how SGLT2 inhibition may decrease the risk of AD, offering valuable information for subsequent mechanistic and clinical research.

Acknowledgments

We would like to thank all the individuals who contributed to the GWASs that formed the basis of this research, as well as to the researchers who have facilitated access to this data through public repositories.

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Statements and declarations

Author contributions

Hao Yang (Conceptualization; Data curation; Methodology; Writing – original draft; Writing – review & editing); Yuye Ning (Writing – original draft; Writing – review & editing); Meilin Chen (Writing – original draft; Writing – review & editing); Jianping Jia (Writing – review & editing).

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was supported by the Key Project of the National Natural Science Foundation of China (U20A20354); Beijing Brain Initiative from Beijing Municipal Science & Technology Commission (Z201100005520016, Z201100005520017); STI2030-Major Projects (No.2021ZD0201802); the National Key Scientific Instrument and Equipment Development Project (31627803); the Key Project of the National Natural Science Foundation of China (81530036).

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Data availability

The data utilized in this research are confined to the GWAS summary statistics mentioned previously, accessible from the authors of the cited studies or from publicly available sources as specified.

Supplemental material

Supplemental material for this article is available online.

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