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Research article

Causal association and mediating effect of blood biochemical metabolic traits and brain image-derived endophenotypes on Alzheimer's disease

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ABSTRACT

Background: Recent genetic evidence supports that circulating biochemical and metabolic traits (BMTs) play a causal role in Alzheimer's disease (AD), which might be mediated by changes in brain structure. Here, we leveraged publicly available genome-wide association study data to investigate the intrinsic causal relationship between blood BMTs, brain image-derived phenotypes (IDPs) and AD.

Methods: Utilizing the genetic variants associated with 760 blood BMTs and 172 brain IDPs as the exposure and the latest AD summary statistics as the outcome, we analyzed the causal relationship between blood BMTs and brain IDPs and AD by using a two-sample Mendelian randomization (MR) method. Additionally, we used two-step/mediation MR to study the mediating effect of brain IDPs between blood BMTs and AD.

Results: Twenty-five traits for genetic evidence supporting a causal association with AD were identified, including 12 blood BMTs and 13 brain IDPs. For BMTs, glutamine consistently reduced the risk of AD in 3 datasets. For IDPs, specific alterations of cortical thickness (atrophy in frontal pole and insular lobe, and incrassation in superior parietal lobe) and subcortical volume (atrophy in hippocampus and its subgroups, left accumbens and left choroid plexus, and expansion in cerebral white matter) are vulnerable to AD. In the two-step/mediation MR analysis, superior parietal lobe, right hippocampal fissure and left accumbens were identified to play a potential mediating role among three blood BMTs and AD.

Conclusions: The results obtained in our study suggest that 12 circulating BMTs and 13 brain IDPs play a causal role in AD. Importantly, a subset of BMTs exhibit shared genetic architecture and

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potentially causal relationships with brain structure, which may contribute to the alteration of brain IDPs in AD.

1. Introduction

Alzheimer's disease (AD) is the predominant form of dementia, representing 50–70% [1] of cases, with most patients diagnosed after age 65 [2]. The disease is characterized by β-amyloid plaque deposition, neurofibrillary tangle aggregation, and synaptic loss, leading to pronounced brain atrophy, particularly in the hippocampus and areas linked to memory and cognition [3,4]. In 2018, Alzheimer's Disease International estimated that approximately 50 million people worldwide suffered from dementia, and this number is expected to triple by 2050 [5]. Regrettably, no therapeutics have been found to prevent or reverse the pathology of AD [1]. Therefore, it is critical to explore biomarkers that can help identify high-risk individuals, make early diagnoses, and assess the therapeutic effect, which also benefits understanding the pathogenesis of AD [6].

A consensus of brain structural abnormalities in AD has been recognized, which could be observed even in the prodromal phase. From a neuroimaging perspective, alterations in cortical surface area, cortical thickness and subcortical volume of specific brain regions involved in AD have also been extensively reported [7]. Importantly, the results from observational studies are partially corroborated by genetic evidence supported by Mendelian randomization (MR) analysis [8]. Doubtlessly, these data help dissect the histopathological mechanism of AD. However, performing magnetic resonance imaging (MRI) or positron emission tomography - computed tomography (PET-CT) detection for people who do not complain of cognitive decline signs is unrealistic. Therefore, recognizing high-risk individuals or identifying patients before apparent clinical or imaging abnormalities occur is a challenge. Accumulating evidence indicates that blood [7]biomarkers, such as serum p-tau, Aβ42, Aβ40, and even eurofilament light chain (NfL) and glial fibrillary acidic protein (GFAP), have the potential to help solve this problem [9,10]. However, special methods, such as RT-QuIC, are needed to detect such molecules, and the alternative level is not easily modified using available treatments.

Recently, multiomics has promoted the discovery of biomarkers and explanations of disease pathogenesis; among them, circulating biochemical and metabolic traits (BMTs) are readily available, cost-effective and stable. In AD, recent observational studies found that changes in blood BMTs from patients with different severities indicated disease progression [11]. More importantly, genetic evidence from MR analysis suggests that blood BMTs play a causal role in AD [12]. However, compared with brain structural abnormalities, the reproducibility of the reported results from blood BMTs remains challenging. Interestingly, previous observational studies have found that abnormal blood BMTs were associated with reduced brain structure in cognitive impairment patients [13,14]. Furthermore, a recent study identified genetic overlap and causal relationships between blood BMTs and cortical anatomy [15]. All of these findings

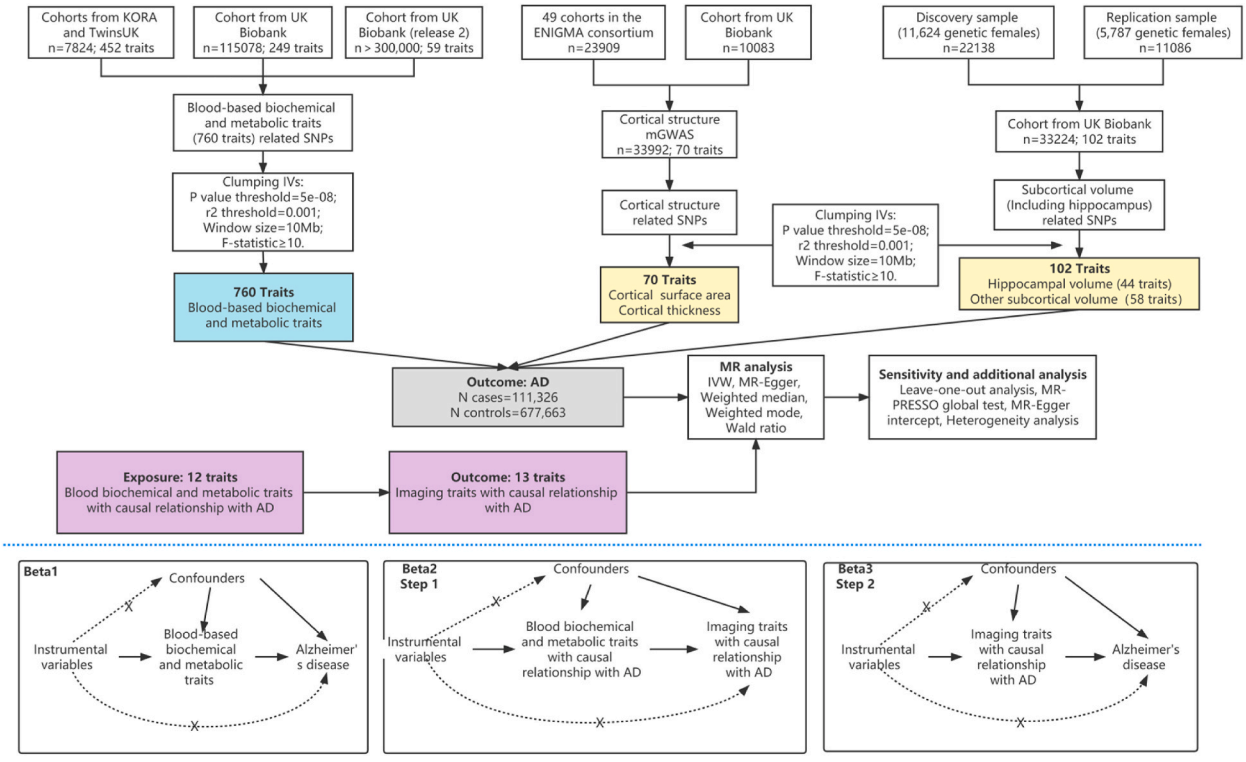

Fig. 1. Study design flowchart of the Mendelian randomization study.

support the theory that alternating circulating molecules could interfere with patterns of neuronal differentiation and migration important for cortical development, while dysregulation in the adult brain may disrupt neuronal cytoarchitecture and integrity [15].

Both observational studies and MR-based genetic evidence have indicated that AD is associated with changes in brain structure and blood BMTs. However, the causal link between altered blood BMTs and brain structural changes in AD remains largely unexplored. Unraveling this connection would be beneficial for elucidating the pathogenesis from molecular changes to brain structure alterations leading to AD. In this study, we aimed to investigate the causal relationship between specific brain image-derived phenotypes (IDPs) and BMTs in relation to AD. We also intended to explore potential mediators that may play a role in the relationship between blood BMTs and AD.

2. Materials and methods

The conceptual diagram of the current MR study is shown in Fig. 1. Initially, we identified blood BMTs and brain IDPs with a causal relationship to AD through two-sample MR analysis, while sensitivity and additional analyses verified the robustness of the results. Subsequently, a two-step/mediation MR analysis was conducted to explore the mediating effects of candidate brain IDPs between blood BMTs and AD. The systematic framework and prevalent statistical methods for MR research are described in Appendix 1 of Supplementary Material B. The datasets used in this study were summary data, and all informed consent and ethical approval were obtained in the original studies.

2.1. Brain imaging-derived phenotypic data

The UK Biobank (UKB) spans six brain magnetic resonance imaging (MRI) modalities, allowing the study of many different aspects of brain structure, function and connectivity [16]. Here, we used the summary statistics of 58 subcortical volume traits and 44 hippocampal volume traits from genome-wide association analysis studies (GWAS) of brain imaging phenotypes in the UK Biobank recruiting discovery (N = 22,138) and replication (N = 11,086) cohorts (Supp A Table S2) [16].

GWAS summary statistics for cortical surface area (SA) and thickness (TH) as measured via MRI were obtained from the Enhancing NeuroImaging Genetics through Meta-Analysis (ENIGMA) consortium study, which were based on 33,992 participants of European ancestry, including 23,909 participating in the ENIGMA Consortium and 10,083 from the UKB [17,18]. We analyzed 70 traits, including the global measures of total SA and mean cortical TH, as well as regional measures for 34 bilateral distinct cortical areas as defined by the Desikan-Killiany atlas (Supp A Table S2).

2.2. Blood-based metabolism and biochemical trait data

We obtained summary statistics for a series of blood-based biochemical traits uniformly produced from a large cohort of >300,000 individuals in the UK biobank (available from http://www.nealelab.is/uk biobank; round 2). In this study, we analyzed 59 biochemical traits, including blood cell count, enzymes, lipids and other biomarkers (Supp A Table S1). In addition, 701 BMTs from two large-scale GWAS summary datasets encompassing a combined total of 122,902 European participants were analyzed [19,20]. Therefore, a total of 760 blood BMTs were selected from the relevant summary statistics of GWAS through the integrative epidemiology unit (IEU) Open GWAS project (Supp A Table S1) (https://gwas.mrcieu.ac.uk/).

2.3. AD datasets

Genetic variants were obtained from GWAS meta-analysis of participants of European descent clinically diagnosed with AD and proxy-ADD (proxy AD and related dementia), which included 111,326 cases and 677,663 controls in total [21].

2.4. MR analysis

The MR method uses single nucleotide polymorphisms (SNPs) strongly associated with the exposure as instrumental variables (IVs) to evaluate the causal effect of exposure on the outcome. Three assumptions must be met for the eligible IVs [22]: (1) IVs are directly related to exposure; (2) IVs are independent of any confounding factor; and (3) IVs should be independent of the outcome. To meet assumption 1, we adopted the genome-wide significance threshold ($p < 5 \times 10^{-8}$) and F-statistics≥10 to include the strong IVs, as weak IVs can introduce bias into MR results [23]. Next, to ensure that each selected significant SNP was independent of each other and to exclude the influence of gene pleiotropy, we set the linkage disequilibrium coefficient r^2 to 0.001 and the width of the linkage disequilibrium region to 10 Mb [24,25]. Then, we used the inverse variance weighting (IVW) method to perform the main MR analysis under the multiplicative random effect model (REM) [26]. Briefly, the Wald ratio was used to estimate the impact of exposure on the results of each IV, and then IVW analysis was performed on each Wald ratio to obtain MR estimates [27]. We also conducted sensitivity analysis using MR Egger and weighted median methods to avoid horizontal pleiotropy [28,29]. Assumptions 2 and 3 can be calculated as horizontal pleitropy, which was detected by MR Egger intercept. If the MR Egger intercept is less than 0.05, IVs are considered to be seriously affected by horizontal pleiotropy [28]. Then, we use the MR-PRESSO global test to detect outliers. If significant SNP outliers ($p < 0.05$) were detected, they were removed from the analysis to return the unbiased causal estimate [30]. Furthermore, using a random effect model, Cochran's Q test was used to test the heterogeneity of IVW estimates [31]. $P < 0.05$ indicated the existence of heterogeneity, which was visually displayed in the forest plot. In addition, the visual inspection of funnel plots and leave-one-out plots

Table 1
The results of two-step/mediation MR analysis.

Exposure (BMTs)	Mediator (IDPs)	outcome	Step 1				Step 2				Do mediation?	Mediation effect (beta)	Proportion mediated(%)
			effect	sensitivity	F-stats	duplicate SNPs	effect	sensitivity	F-stats	duplicate SNPs			
IDL_PL_pct	Superior parietal lobe	AD	1	1	1	1	1	1	1	1	yes	−0.009	61.37
	Lh Accumbns	AD	1	0	1	1	1	1	1	1	yes	0.015	8.1
XXL_VLDL_C_pct	Rh hippocampal-fissure	AD	1	1	1	1	1	0	1	1	yes	0.014	8.7
XXL_VLDL_CE_pct		AD	1	1	1	1	1	0	1	1	yes	0.019	13.07
Aspartylphenylalanine	Frontal pole	AD	1	0	1	1	1	0	1	1	no	–	–
1-PGPE		AD	1	0	1	1	1	0	0	1	no	–	–

Notes: We identified 3 brain IDPs mediated the causative association between 3 blood BMTs and AD. In the first step, we estimated the effect of candidate blood BMTs on mediators (candidate brain IDPs). In the second step, we verified the effect of the mediator (candidate brain IDPs) on AD. When there was evidence indidating that blood BMTs affect mediators, and then the mediators further affect AD. "Effect" is evidence of a causal effect in the analysis (1-present, 0-not); "Sensitivity/F-state" indicates consistent and satisfactory performance in the sensitivity analyses (1-yes, 0-no); "duplicate SNPs" indicates whether there are duplicate SNPs between exposure and mediator (1-no, 0-present). Intermediary analysis will be conducted if the evaluation score is ≥ 7. AD, Alzheimer's disease;.lh, left; rh, right; IVW, inverse variance weighting; SNP, single nucleotide polymorphism; 1-PGPE, 1-palmitoyl-*glycero*-phosphoethanolamine; IDL_PL_pct, phospholipids to total lipids ratio in IDL; XXL_VLDL_C_pct, cholesterol to total lipids ratio in chylomicrons and extremely large VLDL; XXL_VLDL_CE_pct, cholesteryl esters to total lipids ratio in chylomicrons and extremely large VLDL.

was also used to evaluate the hypothesis of "no horizontal pleiotropy" of MR. To correct multiple comparisons, the false discovery rate (FDR) of the causal relationship between blood BMTs and AD <0.05 was considered significant. However, to obtain more potential causative markers from brain IDPs, $p < 0.05$ was considered suggestive. All data analysis was performed using R software (version 4.1.2) and R packages (TwoSampleMR, MR-PRESSO and Rmmediation).

2.5. Two-step/Mediation MR design

Two-step/mediation MR is a specialized form of MR designed to assess the causal pathway of one or more mediator variables between an exposure and an outcome. The central premise of this method is to use genetic variants as IVs to separately estimate the causal effects of the exposure on the mediator and the mediator on the outcome [32]. In our study, if two-sample MR analysis found a causal relationship between blood BMTs and AD and between brain IDPs and AD, a two-step/mediation MR analysis was conducted to explore the possible mediating effects of candidate brain IDPs [33]. In the first step, we estimated the effect of candidate blood BMTs on mediators (candidate brain IDPs) (Fig. 1, beta2). In the second step, we verified the effect of the mediator (candidate brain IDPs) on AD (Fig. 1, beta3). When there was evidence indicating that blood BMTs affect mediators and that the mediators further affect AD, we used the "product of coefficients approach" to evaluate the indirect impact of blood BMTs on AD through each potential mediator [34]. The indirect effect and proportion were obtained by the delta method [35]. The premise of this mediated analysis includes [36] the following: (1) The MR analysis in all steps is statistically significant; (2) There are no repetitive SNPs between the mediator and exposure, and IVs should be strong IVs (F-statistics≥10); and (3) The results of three methods (including IVW, MR−Egger and weighted median) should be consistent. To make the results of the intermediary analysis more robust, we evaluated the score from four aspects (causal effect, sensitivity analysis, F statistic and whether there are duplicate SNPs) in the two-step MR analysis, with a total score of 8 points. Here, we regarded the analysis as intermediary if the evaluation score was ≥7; otherwise, it was excluded (Table 1 and Supp B Appendix 6 - Fig. S1).

3. Results

3.1. The causal effect of blood BMTs on AD

A total of 12 significant blood BMTs, including 5 lipoproteins, 2 amino acids and their derivatives, 1 carbohydrate derivative, 1 amino acid and lipid compound, and 3 unknown metabolites, were identified to be causally associated with the risk of AD (Fig. 2). Specifically, we observed that S_HDL_CE (OR:1.14, 95%CI: 1.06–1.03, P_{FDR} = 2.30e-02) and erythronate (OR: 5.93, 95%CI: 2.00–17.55, P_{FDR} = 0.0477) were associated with an increased risk of AD, while the remaining 10 traits were associated with the

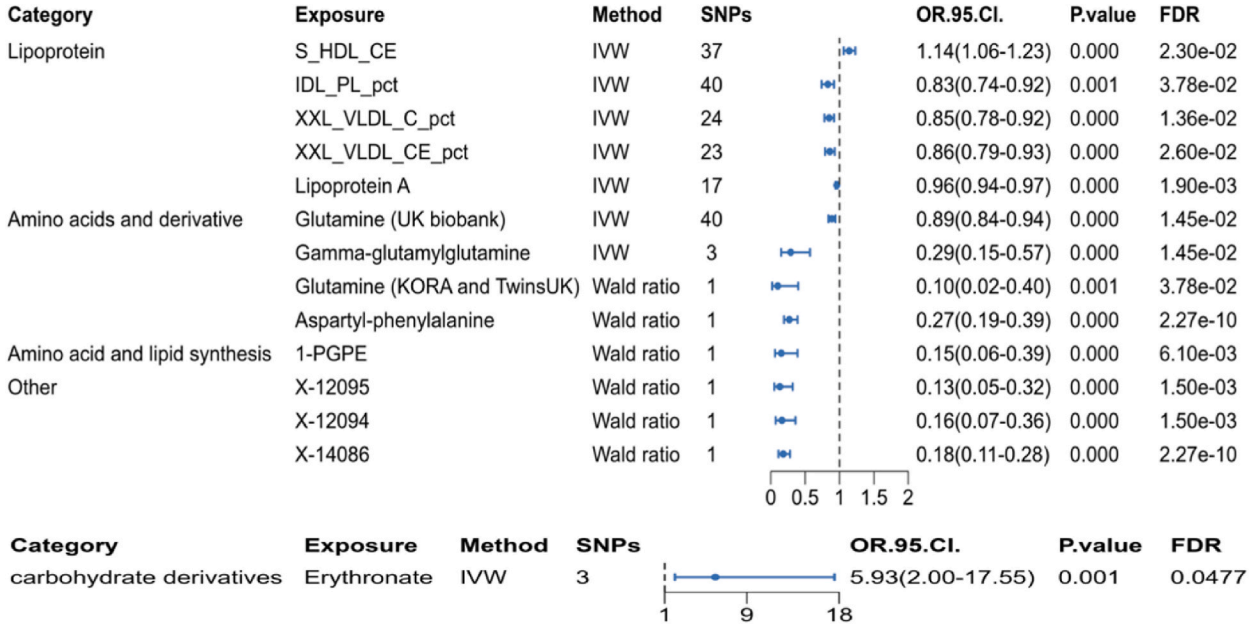

Fig. 2. Mendelian randomization analysis of blood BMTs (IVW or Wald ratio FDR < 0.05) and AD. Glutamine from three data aggregations with different sources was classified as a type of trait in this study. We identified 12 blood BMTs that support a causal association with AD. AD, Alzheimer's disease; 1-PGPE, 1-palmitoyl-*glycero*-phosphoethanolamine; S_HDL_CE, cholesteryl esters in small high density lipoprotein; IDL_PL_pct, Phospholipids to total lipids ratio in intermediate density lipoprotein; XXL_VLDL_C_pct, cholesterol to total lipids ratio in chylomicrons and extremely large very low density lipoprotein; XXL_VLDL_CE_pct, cholesteryl esters to total lipids ratio in chylomicrons and extremely large very low density lipoprotein; IVW, inverse variance weighting; SNP, single nucleotide polymorphism.

reduced risk of AD, including1-palmitoyl-*glycero*-phosphoethanolamine (1-PGPE, OR: 0.15, 95%CI: 0.06–0.39, P_{FDR} = 6.10e-03), aspartyl-phenylalanine (OR: 0.27, 95%CI: 0.19–0.39, P_{FDR} = 2.27e-10), IDL_PL_pct (OR: 0.83, 95%CI: 0.74–0.92, P_{FDR} = 3.78e-02), XXL_VLDL_C_pct (OR: 0.85, 95%CI: 0.78–0.92, P_{FDR} = 1.36e-02), XXL_VLDL_CE_pct (OR: 0.86, 95%CI: 0.79–0.93, P_{FDR} = 2.60e-02), lipoprotein A (OR: 0.96, 95%CI: 0.94–0.97, P_{FDR} = 1.90e-03), glutamine [UK biobank (OR 0.89, 95%CI: 0.84–0.94, P_{FDR} = 1.45e-02), KORA and TwinsUK (OR 0.10, 95%CI: 0.02–0.40, P_{FDR} = 3.78e-02), Gamma-glutamylglutamine (OR 0.29, 95%CI: 0.15–0.57, P_{FDR} = 1.45e-02)] and 3 unknown metabolites. Importantly, glutamine from all 3 datasets showed a significant correlation with the reduction

Category	Exposure	Method	SNPs	OR.95.CI.	P.value
Cortical thickness	Frontal polar	Wald ratio	1	0.25(0.07-0.83)	0.025
	Insula	IVW	2	0.1(0.01-0.93)	0.044
	Superior parietal lobe	IVW	4	7.46(1.35-40.96)	0.021
Subcortical volume	lh molecular-layer-hippocampal-head	IVW	3	1.2(1.04-1.37)	0.010
	lh CA3-body	IVW	6	1.13(1.01-1.25)	0.020
	Rh CA1-body	IVW	5	1.16(1.03-1.3)	0.009
	Rh hippocampal-fissure	IVW	2	1.22(1.03-1.43)	0.015
	Rh hippocampus	IVW	6	1.1(1.01-1.2)	0.019
	Global 4th-Ventricle	IVW	13	1.16(1.05-1.28)	0.003
	lh Cerebral White Matter	IVW	11	0.83(0.71-0.96)	0.014
	Rh Cerebral White Matter	IVW	11	0.84(0.72-0.97)	0.024
	lh accumbens-area	IVW	2	1.25(1.07-1.46)	0.004
	lh choroid-plexus	IVW	4	1.24(1.02-1.51)	0.031

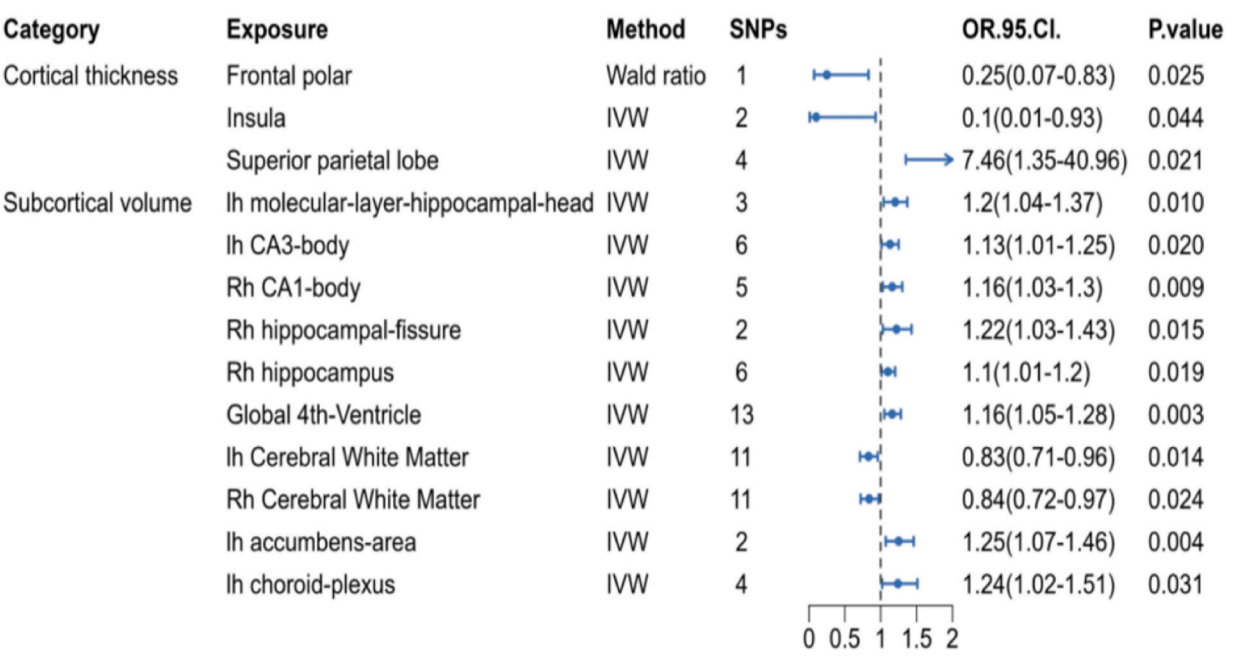

Fig. 3. Mendelian randomization analysis of brain IDPs (IVW or Wald ratio p-value < 0.05) and AD. We identified 13 brain IDPs that support a causal association with AD. Cortical thickness: odds ratio per one standard deviation increase of cortical thickness. Subcortical volume: odds ratio per one standard deviation decrease of volume. AD, Alzheimer's disease; lh, left; rh, right; IVW, inverse variance weighting; SNP, single nucleotide polymorphism. We visualized the alteration of IDPs based on the anatomical automatic labeling (AAL) brain atlas [63]. However, some IDPs (left choroid plexus, bilateral white matter, fourth ventricle, and hippocampus subarea) are not included in the AAL brain atlas, so we didn't show them.

in AD risk (Fig. 2).

We performed sensitivity analysis on 8 BMTs (SNPs≥3) identified by the IVW method (Supp B Appendix 3 and 7), and MR Egger and weighted media showed the same point estimation direction as IVW. Except for four traits (S_HDL_CE, IDL_PL_pct, XXL_VLDL_C_pct, XXL_VLDL_CE_pct), no heterogeneity was found in the other four traits by the Q test of MR Egger and IVW. To make the research results more reliable, we used the REM to weighted average the overall effects of each study to correct the heterogeneity. In addition, the MR Egger intercept test did not show evidence of pleiotropy of eight BMTs.

3.2. The causal effect of brain IDPs on AD

A total of 13 brain IDPs were identified to have potential causal effects on AD risk, as shown in Fig. 3. We observed that 4 traits, including cortical TH of frontal pole (OR: 0.25, 95%CI: 0.07–0.83, P = 0.025, per SD increase) and insula (OR 0.1, 95%CI: 0.01–0.93, P = 0.044, per SD increase), bilateral white matter volume (WMV, per SD decrease; left OR 0.83, 95%CI: 0.71–0.96, P = 0.014; right OR 0.84, 95%CI: 0.72–0.97, P = 0.024) were associated with the reduced risk of AD. The other 9 brain IDPs were associated with the increased risk of AD (Fig. 3), including the increased thickness of the superior parietal cortex (OR 7.46, 95%CI: 1.35–40.96, P = 0.021, per SD increase), the atrophy of five hippocampal subgroups [left molecular-layer-hippocampal-head (OR 1.2, 95%CI: 1.04–1.37, P = 0.010), left CA3-body (OR 1.13, 95%CI: 1.01–1.25, P = 0.020), right CA1-body (OR 1.16, 95%CI: 1.03–1.3, P = 0.009), right hippocampal-fissure (OR 1.22, 95%CI: 1.03–1.43, P = 0.015) and right hippocampal (OR 1.10, 95%CI: 1.01–1.20, P = 0.019)] and the decreased volume of three other subcortical structures [global 4th-ventricle (OR 1.16, 95%CI: 1.05–1.28, P = 0.003), left accumbens-area (OR 1.25, 95%CI: 1.07–1.46, P = 0.004) and left choroid-plexus (OR 1.24, 95%CI: 1.02–1.51, P = 0.031)].

We also conducted sensitivity analysis on 9 brain IDPs (SNPs≥3) identified by IVW (Supp B Appendix 4 and 8). Except for the left choroid plexus, MR Egger and weighted medium of other traits showed the same estimation direction as IVW. The Q test found heterogeneity in the fourth ventricle, the left WMV and the right hippocampus. As above, we use the REM to correct the heterogeneity. No evidence of horizontal pleiotropy was found in the MR Egger intercept test.

3.3. Two-step/Mediation MR analysis

To explore the mediating effects and the proportion of brain IDPs between blood BMTs and AD risk, a two-step/mediation MR analysis was performed. In the first step, based on the results of the two-sample MR, we used the 12 blood BMTs associated with AD as the exposure and evaluated their causal relationship with 13 brain IDPs (Supp A Table S4 and Fig. 4). The results showed that there was a causal relationship between 5 blood BMTs and 4 brain IDPs ($p < 0.05$, Fig. 4). We conducted sensitivity analysis on the traits identified by the IVW method (SNPs≥3) (Supp B Appendix 5 and 9). Except for potential heterogeneity and horizontal pleiotropy between IDL_PL_pct and the left accumbens tested by the Q and MR-PRESSO tests, no heterogeneity or horizontal pleiotropy was detected in other traits. In the second step, based on the identified causal relationship between 4 brain IDPs (candidate mediators) and AD by the two-sample MR analysis, we calculated the mediating effects from 4 brain IDPs (candidate mediators) between blood BMTs

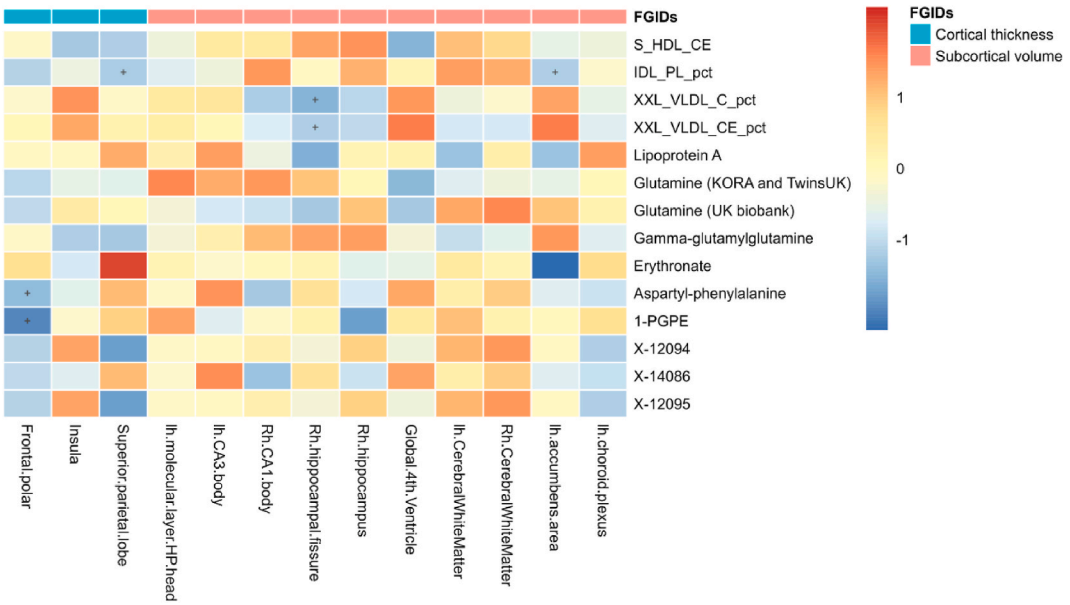

Fig. 4. Mendelian randomization analysis of 12 blood BMTs and 13 brain IDPs. "+" indicates that there is a causal effect between the two traits (IVW or Wald ratio P-value < 0.05). Glutamine from three data aggregations with different sources was classified as a type of trait in this study. Our results revealed a causal relationship between 5 blood BMTs and 4 brain IDPs.

and AD (supp B Appendix 6). According to the preset criteria, we identified 3 brain IDPs that mediated the causative association between 3 blood BMTs and AD (Table 1): (1) superior parietal lobe thickness (61.37%) and left accumbens volume (8.1%) mediated the causative relationship between IDL_PL_pct and AD; (2) right hippocampal-fissure mediated the causative relationship between XXL_VLDL_C_pct (8.7%) and XXL_VLDL_CE_pct (13.07%) and AD.

4. Discussion

Using genetic variation as IVs, we analyzed the causal relationship between blood BMTs, brain IDPs and AD and clarified the intermediate effect of brain IDPs mediating between blood BMTs and AD. We identified 25 traits related to AD risk, including 12 blood BMTs and 13 brain IDPs. Notably, frontal lobe atrophy and specific subcortical volume changes (especially in the hippocampal subarea) can be used as warning signs of AD; however, glutamine has a protective effect on AD. Moreover, the superior parietal lobe, left accumbens and right hippocampal fissure act as mediators between blood BMTs and AD risk.

Plasma is a readily available biological fluid, and the metabolites in plasma have been widely used as biomarkers for AD. Our study found that glutamine from three datasets showed a significant correlation with reduced AD risk. The consistency and validity of the three MR analysis methods provided sufficient evidence. Consistent with our results, two published MR studies have drawn similar conclusions about the causal relationship between glutamine and AD [37,38]. Previous studies found that glutamine has a protective effect on oxidative stress-induced injury in an AD mouse model [39]; however, the relevant mechanism between glutamine and AD is not clarified. Currently, there is a consensus that blood lipids and their metabolites are related to AD risk. Most studies have found that there is a link between higher lipoprotein A concentrations and cognitive decline [40,41]. However, some studies found that a high level of lipoprotein A was related to an increased risk of vascular dementia but a reduced incidence of AD [42]. Kunutsor et al. reported evidence that lipoprotein A has a protective effect on cognitive decline [43]. These studies are observational, with reverse causality and confusion bias, so MR analysis with balanced horizontal pleiotropy is more reliable [44]. Our MR study has observed that lipoprotein A is negatively correlated with AD risk, but its mechanism needs further study.

Erythronate is a carbohydrate derivative synthesized from glucose in vivo and in vitro [45]. Our study found that erythritol was associated with an increased risk of AD, and the results of the three analysis methods (IVW, MR Egger and weighted median) showed consistency. There is no research on the relationship between erythronate and AD. However, some studies have pointed out that erythronate is endogenously synthesized from glucose through the pentose phosphate pathway (PPP), which is related to body obesity [45]. Previous studies have shown that obesity is significantly and independently related to the risk of AD development, especially middle-aged obesity, which is a risk factor for the development of dementia [46,47]. Therefore, the effect of erythronate on the risk of AD identified in this study could be understood. In addition, we found that 1 IDL subcomponent (IDL_PL_pct), 1 HDL subcomponent (S_HDL_CE) and 2 VLDL subcomponents (XXL_VLDL_C_pct and XXL_VLDL_CE_pct) can decrease AD risk. Lipoproteins are strongly associated with the risk of AD. For example, increased VLDL levels are associated with a higher risk of developing AD [48], but higher HDL levels are associated with a lower risk of AD [49]. However, to explore the relationship between lipoproteins and AD from a microscopic perspective (such as particle size and the composition ratio of lipoproteins), further studies are needed to fully understand their pathogenesis in AD.

Brain structural changes in AD patients are common and may occur in the preclinical stage [50]. Our study focused on three aspects: cortical thickness, cortical surface area and subcortical volume. We identified specific alterations in cortical thickness and subcortical volume that are vulnerable to AD. For cortical thickness, we found that the increased thickness of the frontal pole and insular cortex reduced AD risk. Previous studies have shown that frontal pole and insular lobe atrophy are correlated with cognitive impairment [51,52]. Frontal lobe atrophy, especially bilateral frontal poles, is associated with emotional processing deficits and impaired consciousness [51], while insular lobe atrophy can lead to emotional disorders and decreased social cognitive function [52]. In addition, the parietal lobe plays an important role in cognition. Studies have found that changes in the structure and function of the parietal lobe in AD patients may precede clinical symptoms, and cerebral glucose metabolism in the parietal cortex region is significantly reduced [53,54]. However, our study found that the increased thickness of the superior parietal cortex was correlated with AD risk. More evidence is needed to determine whether the compensatory mechanism is involved.

The subcortical structure also plays an important role in the pathogenesis of AD. Observational studies have found that the volume of subcortical structures in AD patients has decreased [55]. Here, using the MR method, genetically predicted atrophy in the hippocampus and its subgroups was associated with increased AD risk. Many previous studies have shown that atrophy in the hippocampus is closely related to cognitive impairment (especially memory ability) and even changes before the decline in cognition, which can predict overall cognitive changes [56,57]. The hippocampus is a complex composed of multiple regions with different functions and structures. Compared to the hippocampus, changes in the hippocampus subarea may reflect the trajectory of AD [58]. Additionally, our research indicated which hippocampal subgroup should be the more specific predictive indicator for AD diagnosis. Other subcortical structural changes (such as the fourth ventricle, the accumbens, the choroid plexus and the white matter) are also associated with AD risk. A previous study found a negative correlation between the volume of the choroid plexus and cerebrospinal fluid (CSF) protein [59]. Our study also found that a decreased volume of the choroid plexus was associated with increased AD risk, supporting the possible role of the choroid plexus in CSF protein clearance [59]. We found that accumbens atrophy may lead to cognitive impairment, which may be related to the accumulation of tau protein and the decrease in dopaminergic projection [60]. and that the decreased volume of the fourth ventricle is related to the risk of AD.

Some MR studies have focused on the potential causal relationship between some blood BMTs and brain IDPs [7,15,61]. However, whether genetically predicted alterations in BMTs cause brain IDPs to change, leading to AD, is largely unknown. Hence, we conducted an intermediate MR analysis to evaluate the indirect effect of brain IDPs between blood BMTs and AD. The results showed that three

brain IDPs mediate the causative relationship between three blood BMTs and AD. Our study suggested that alterations in BMTs partially affect brain structure and then cause AD, which might play an important role in future research. However, the application of the identified biomarkers in clinical practice and future management of AD requires further empirical evidence. For instance, validation in independent patient cohorts is essential to assess the real-world utility of these biomarkers in diagnosis, prognosis, and treatment. Therefore, by combining blood BMTs and brain IDPs, we could determine the early prediction index for AD diagnosis and explore the pathogenesis of AD from the perspective of metabolic and brain structure pathways. Furthermore, there are currently no effective therapeutics for AD, and the joint study of multiomics may be a promising direction for the development of AD drugs in the future [62].

Our research has several advantages. First, we conducted a two-sample MR analysis, overcoming the limitations of traditional observational studies, including environmental confounding factors, reverse causality, insufficient sample size and so on. Second, the summary data from GWAS with a large sample size significantly improved the ability to detect causal effects. Third, for the first time, we performed a two-step MR design to conduct an intermediary analysis and showed that specific brain IDPs were involved in mediating the causal relationship between blood BMTs and AD. However, this study also has some limitations. First, as with all MR investigations, despite employing various methods in our MR analysis, potential biases, such as horizontal pleiotropy, could still permeate the results. To further ensure robustness, future studies might require validation in independent samples or integration with other research methodologies. Second, the GWAS database used was primarily based on European populations, potentially limiting the applicability of our findings to other ethnic groups. Consequently, future studies should conduct GWAS in populations from diverse regions, including Asia, Africa, and others. Moreover, considering AD complexity, our focus on specific biomarkers and brain structures may not capture the full spectrum of etiological factors involved in AD. Finally, while our MR study revealed certain causal relationships, it did not delve into how specific blood biochemical characteristics directly influence brain structures or AD risk. Additionally, this study may not have fully accounted for all potential external factors, such as lifestyle, environmental influences, or comorbidities, which could impact AD risk.

5. Conclusion

Using genetic IVs, we found that frontal lobe atrophy and specific subcortical changes (especially hippocampal subareas) can be used as warning signs of AD; however, glutamine plays a protective effect on AD. More importantly, for the first time, we discovered that three brain IDPs (superior parietal lobe thickness, left ventricular volume, and right hippocampal fissure) mediate the causal relationships among three blood BMTs (IDL_PL_PCT, XXL_VLDL_C_PCT, and XXL_VLDL_CE_PCT) and AD; this provides a list of biomarkers that precede changes in brain IDPs and suggests new potential preventive measures. In the future, the joint study of multiomics may be a promising direction for AD research.

Ethics approval and consent to participate

Not applicable.

Consent for publication

All the authors have consented for publication.

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Data availability statement

Any data generated in the analysis process can be requested from the corresponding author. Our data are sourced from publicly accessible summary statistics. The data related to cortical sub-volume and hippocampal volume were obtained from the BIG40 website (https://open.win.ox.ac.uk/ukbiobank/big40/) or from the publication by Stephen M Smith et al. (PMID: 33875891). Information concerning cortical surface area and cortical thickness is available through the ENIGMA Consortium (https://enigma.ini.usc.edu/research/download-enigma-gwas-results). Biochemical summary statistics from blood samples were procured from the UK Biobank (http://www.nealelab.is/uk). Additionally, GWAS datasets specific to AD can be accessed from the GWAS Catalog (https://www.ebi.ac.uk/gwas/) or from the publication by Céline Bellenguez et al. (PMID: 35379992).

CRediT authorship contribution statement

Kang-Fu Yin: Writing – original draft, Software, Methodology, Investigation, Formal analysis, Data curation. **Xiao-Jing Gu:** Writing – review & editing, Conceptualization. **Wei-Ming Su:** Methodology, Investigation, Formal analysis. **Ting Chen:** Formal

analysis, Conceptualization. **Jiang Long:** Methodology. **Li Gong:** Methodology. **Zhi-Ye Ying:** Software, Methodology. **Meng Dou:** Software, Formal analysis. **Zheng Jiang:** Software, Methodology, Formal analysis. **Qing-Qing Duan:** Methodology, Formal analysis. **Bei Cao:** Funding acquisition, Conceptualization. **Xia Gao:** Methodology, Data curation. **Li-Yi Chi:** Software, Resources. **Yong-Ping Chen:** Writing – review & editing, Project administration, Funding acquisition, 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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e27422.

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