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Influence of immune cells and inflammatory factors on Alzheimer's disease axis: evidence from mediation Mendelian randomization study

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Abstract

Background Alzheimer's disease (AD) is one of the most common forms of dementia in the elderly, characterized by progressive neurodegeneration. While the exact etiology of AD remains unclear, immune inflammation is known to play a significant role in the disease.

Methods This study utilized a two-sample Mendelian randomization (MR) approach to assess the causal relationship between different types of immune cells and AD, while considering inflammatory factors as intermediate variables. Data were collected from three sources: immune cell data (731 phenotypes), inflammatory factors (48 cytokines from 8,293 individuals), and AD data (35,274 cases, 59,163 controls). Multiple MR methods were employed to minimize bias, and detailed descriptions of instrumental variable selection and statistical methods were provided.

Results The study findings suggest potential causal relationships between six different types of immune cells and AD, as well as causal relationships between 13 immune cells and inflammatory factors. Additionally, two statistically significant inflammatory factors were found to have potential causal relationships with AD. Specifically, immune cells CD33-HLA DR + and CD45 on CD33-HLA DR + may further influence AD by regulating Interleukin-2 levels.

Conclusion This study provides valuable insights into the immunoinflammatory pathogenesis of AD and offers partial guidance for the development of relevant interventions, thereby contributing beneficial information for the prevention and treatment of related diseases.

Keywords Immune cells, Inflammatory factors, Alzheimer's disease, Mendelian randomization study

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Introduction

Alzheimer's disease (AD) is a devastating progressive neurodegenerative disorder and the most prevalent form of dementia in the elderly population, affecting millions worldwide [1]. The disease is characterized by a gradual onset of symptoms, including memory loss, language difficulties, decreased orientation, and mood changes, which progressively worsen over time [2, 3]. As the disease advances, patients experience severe cognitive decline, behavioral changes, and eventually lose their ability to perform basic daily activities, placing an enormous burden on families and healthcare systems [4].

The pathological hallmarks of AD include the accumulation of extracellular amyloid-beta (Aβ) plaques and intracellular neurofibrillary tangles composed of hyperphosphorylated tau protein. Aβ plaques form when the amyloid precursor protein (*APP*) is abnormally processed, leading to the aggregation of Amyloid β-specific, particularly Aβ42, which is more prone to aggregation and considered more neurotoxic [5, 6]. Tau, a microtubule-associated protein that normally helps stabilize neuronal cytoskeleton, becomes hyperphosphorylated in AD, forming paired helical filaments that aggregate into neurofibrillary tangles. These pathological changes disrupt synaptic function, impair neuronal communication, and ultimately lead to neuronal death [7, 8].

While the exact etiology of AD remains incompletely understood, mounting evidence suggests that neuroinflammation plays a crucial role in disease pathogenesis, potentially serving as a bridge between Aβ accumulation, tau pathology, and neurodegeneration [9, 10]. The neuroinflammatory response in AD is characterized by the activation of glial cells, particularly microglia and astrocytes, along with the production of inflammatory mediators, creating a complex [8]inflammatory environment in the brain.

Microglia, the brain's resident immune cells, play a pivotal role in AD pathogenesis [11]. Under physiological conditions, these cells constantly survey their microenvironment, maintaining brain homeostasis through phagocytosis of cellular debris and providing neurotrophic support [12, 13]. These cells express various immune-related surface proteins that regulate their function, including *CD45* (leukocyte common antigen), *CD33*, and HLA-DR, which are crucial for immune response regulation [14, 15]. Of particular interest is *CD33*, a cell surface receptor protein that is part of the innate immune pathway and plays a critical role in regulating anti-inflammatory signal transduction. Recent evidence has highlighted *CD33*'s significant involvement in AD pathogenesis, suggesting it may be a key molecular link between immune function and disease development [16, 17]. While initially protective through their ability to phagocytose Aβ, chronic microglial activation can become detrimental, leading to the excessive production of pro-inflammatory cytokines (including IL-1β, IL-6, and TNF-α) and reactive oxygen species, which may exacerbate neuronal dysfunction and death [18, 19].

The neuroinflammatory response in AD is not limited to resident immune cells. Recent evidence has revealed significant infiltration of peripheral immune cells, particularly T lymphocytes, into the AD brain [20]. Both *CD4 + and CD8 + T* cells have been detected in the brain parenchyma of AD patients, although their precise role in disease progression remains controversial [21]. The presence of these cells suggests a complex interplay between central and peripheral immune responses in AD pathogenesis. For instance, Aβ-specific *CD4 + T* helper cells may modulate microglial function through Interferon gamma (IFN-γ) signaling, potentially influencing AD pathology [22, 23].

The relationship between systemic inflammation and AD is further complicated by the dynamic interaction between peripheral immune cells and the brain's immune system. Peripheral immune cells can influence AD pathology not only through direct infiltration but also by releasing inflammatory mediators that may affect brain function through various mechanisms, including blood-brain barrier disruption and activation of neuroinflammatory pathways [24, 25].

Understanding the causal relationships between immune cell function, inflammatory mediators, and AD risk is crucial for developing effective therapeutic strategies. Mendelian Randomization (MR) provides a powerful approach to investigate these relationships by using genetic variants as instrumental variables to assess causality while minimizing confounding effects [26]. In this study, we employed comprehensive two-sample MR analyses to evaluate the causal relationships between immune cell characteristics and AD risk, while also investigating the potential mediating role of inflammatory factors in these relationships.

Materials and methods

Study design

This study utilized two-sample Mendelian randomization to examine causal relationships between immune cells, inflammatory factors, and Alzheimer's disease (AD). We collected Genome-Wide Association Study (GWAS) summary data from three sources: immune cell data (731 phenotypes), inflammatory factors (48 cytokines from 8,293 individuals), and AD data (35,274 cases, 59,163 controls). Instrumental variables were selected using significance thresholds ($p < 1e\text{-}05$ for inflammatory factors, $p < 5e\text{-}08$ for others) and underwent clumping ($r^2 < 0.001$, distance > 10 kb). Statistical analysis employed Inverse Variance Weighted method for multiple-SNP analyses and Wald ratio for single-SNP analyses. Sensitivity

analyses included MR-Egger regression and weighted median estimator. Results were adjusted using Bonferroni correction [27].As illustrated in Fig. 1.

GWAS data sources

Source of immune cell data

The immune cell data utilized in this Mendelian randomization study was derived from comprehensive GWAS of immune cell characteristics in European populations. Through flow cytometry measurements, 731 immune cell phenotypes were systematically categorized into four main groups: absolute cell counts (AC, $n = 118$), median fluorescence intensity reflecting surface antigen levels (MFI, $n = 389$), morphological parameters (MP, $n = 32$), and relative cell counts (RC, $n = 192$). These immune cell characteristics encompassed a broad spectrum of cell types, including T cells, B cells, natural killer cells, dendritic cells, monocytes, other myeloid cells, and Treg cells. The analysis involved various immune cell parameters, such as absolute counts, surface antigen expression levels, and cell morphological features. The study focused on 539 independent tests to identify genetic variations associated with immune cell characteristics and investigate their functional implications. The immune cell GWAS data provided robust genetic instruments for examining causal relationships between immune cell traits and disease outcomes. All analyses were conducted using standardized quality control procedures, including the exclusion of individuals with low call rates, high degrees of relatedness, and non-European ancestry as determined by principal components analysis of ancestry-informative markers [28–30].

Source of inflammatory factor data

The inflammatory factor data in this Mendelian randomization study was derived from a large-scale GWAS

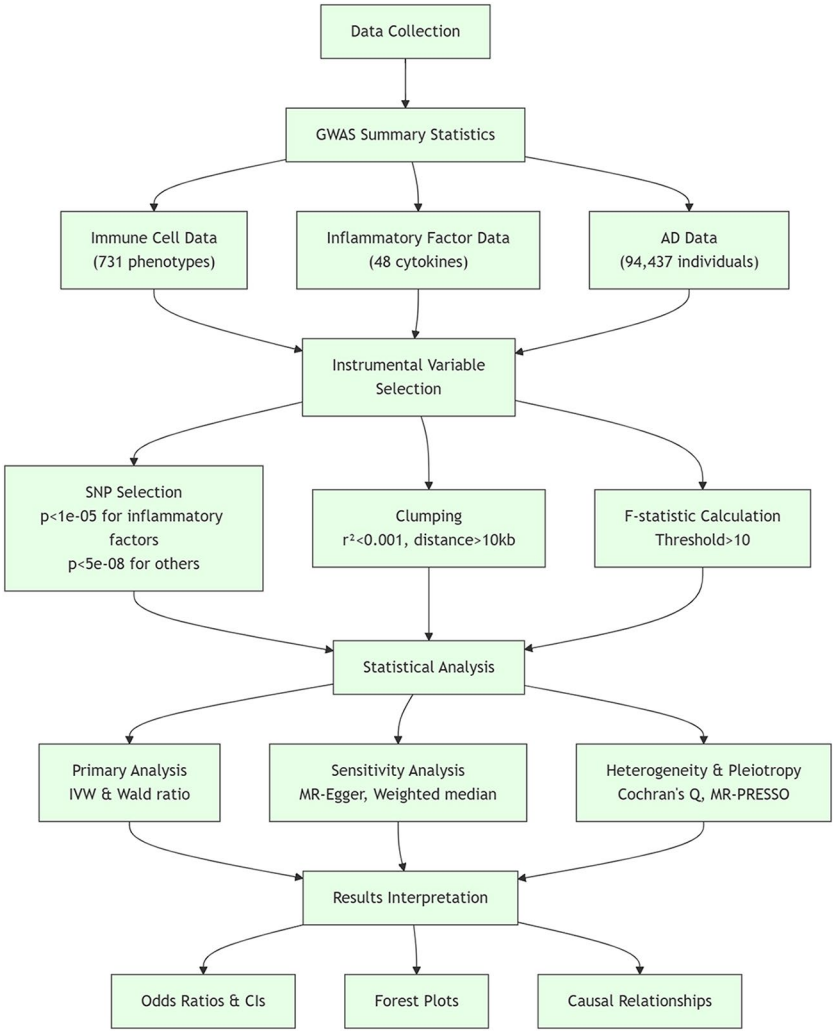

Fig. 1 Research overview. Flowchart of the study procedure for investigating causal relationships between immune cells, inflammatory factors, and Alzheimer's disease using two-sample Mendelian randomization

comprising 8,293 Finnish individuals. The study measured 48 cytokines and growth factors using Bio-Rad's premixed Bio-Plex Pro Human Cytokine 27-plex and 21-plex Assays, analyzed with a Bio-Plex 200 reader and Bio-Plex 6.0 software. The assays were conducted following manufacturer's protocols, with modifications using 50% lower concentrations of beads, detection antibodies, and streptavidin-phycoerythrin conjugate than recommended. Data was collected from three independent Finnish population cohorts: the Cardiovascular Risk in Young Finns Study (YFS), FINRISK1997, and FINRISK2002. The YFS cohort included 2,019 participants from the 2007 follow-up, while FINRISK surveys included up to 4,608 participants from FINRISK1997 and up to 1,705 participants from FINRISK2002. Sample collection methods varied across cohorts, with EDTA plasma used in FINRISK1997, heparin plasma in FINRISK2002, and serum in YFS. Only measurements within the cytokine-specific detection range were included, and cytokines with more than 90% missing values were excluded (7 out of 48 cytokines). For inflammatory factor-associated SNPs, a significance threshold of $p < 1e\text{-}05$ was employed, while maintaining the conventional genome-wide significance threshold of $p < 5e\text{-}08$ for other analyses. All analyses were adjusted for age, sex, body mass index, and the first ten genetic principal components to account for potential confounding factors [31].

Source of AD data

In this MR study, we utilized data from a large genome-wide association meta-analysis of clinically diagnosed late-onset Alzheimer's disease (LOAD), comprising a total sample of 94,437 individuals (35,274 clinical and autopsy-documented Alzheimer's disease cases and 59,163 controls). The study population was drawn from four major consortia: ADGC (Alzheimer's Disease Genetics Consortium), CHARGE (Cohorts for Heart and Aging Research in Genomic Epidemiology), EADI (European Alzheimer's Disease Initiative), and GERAD/PERADES (Genetic and Environmental Risk in Alzheimer's Disease/Defining Genetic, Polygenic and Environmental Risk for Alzheimer's Disease). All participants provided written informed consent, and for those with substantial cognitive impairment, consent was obtained from a caregiver, legal guardian, or other proxy. Study protocols were reviewed and approved by the appropriate institutional review boards. Standard quality control procedures were implemented for all datasets, including the exclusion of individuals with low call rates, high degrees of relatedness, and non-European ancestry as determined by principal components analysis of ancestry-informative markers. The analysis was conducted in multiple stages: Stage 1 (discovery phase) included 63,926 individuals, Stage 2 included 18,845 individuals, and Stage 3 was divided into Stage 3 A (11,666 individuals) and Stage 3B (30,511 individuals). The study focused on late-onset Alzheimer's disease cases, which were clinically diagnosed according to established criteria, and controls were cognitively normal individuals. All analyses were adjusted for age (defined as age-at-onset for cases and age-at-last exam for controls), sex, and population substructure using principal components [32]. Refer to Table 1 for data source information.

Instrumental variable (*IV*) selection

In our Mendelian randomization study, we implemented a comprehensive and meticulous approach to instrumental variable (*IV*) selection to establish reliable causal relationships between immune cells, inflammatory factors, and Alzheimer's Disease (AD) risk. Recognizing the unique challenges in studying inflammatory factor associations, we adopted a tailored significance threshold strategy, setting $p < 1e\text{-}05$ for inflammatory factor-associated SNPs due to their limited genetic associations, while maintaining the conventional genome-wide significance threshold of $p < 5e\text{-}08$ for all other analyses. To ensure the independence of genetic instruments, we utilized the TwoSample MR R package with carefully calibrated parameters, implementing a clumping procedure with an r^2 threshold of 0.001 and a physical distance threshold of 10,000 kilobases between SNPs. This stringent approach effectively minimized potential bias from linkage disequilibrium while maintaining the independence of selected genetic instruments. The strength and validity of each selected SNP as an instrumental variable were rigorously evaluated through comprehensive F-statistic calculations, employing a two-step mathematical approach. Initially, we calculated the proportion of variance explained (R^2) for each SNP using the formula $R^2 = 2 \times EAF \times (1 - EAF) \times \beta^2$, where EAF represents the effect allele frequency and β indicates the SNP's estimated effect size. Subsequently, we computed the F-statistic using the formula $F = R^2 (N - 2)/(1 - R^2)$, where N represents the GWAS sample size. This calculation provided a robust assessment of instrument strength, with a predetermined threshold of 10 serving as the minimum requirement for

Table 1 Information fundamental for the inclusion of exposure and outcome data in GWAS

Phenotype	Number of SNP	Cases	Controls	Sample size	Population	PMID
Alzheimer's Disease	10,528,610	21,982	41,944	63,926	European	30,820,047
Inflammatory Factor	9,784,803	NA	NA	7118	European	27,989,323
Immune cell characteristics	14,304,991	NA	NA	1858	European	– 32,929,287

SNP inclusion. SNPs failing to meet this threshold were excluded to maintain the integrity of our causal estimates. These stringent selection criteria ensured that our genetic instruments satisfied the fundamental assumptions of Mendelian randomization, including strong association with the exposure, independence from confounders, and absence of direct effects on the outcome except through the exposure. This methodological rigor significantly enhanced the validity of our causal inference and the reliability of our findings regarding the complex relationships between immune cells, inflammatory factors, and AD risk [33, 34].

Statistical methods

MR analysis framework employed in our study utilized genetic variants as instrumental variables to investigate causal relationships between modifiable exposures and outcomes. We implemented a comprehensive statistical approach incorporating multiple methodologies to ensure robust and reliable causal inference. The primary analysis employed the Inverse Variance Weighted (IVW) method for datasets containing multiple SNPs, while the Wald ratio test was applied for single-SNP analyses. To enhance the reliability of our findings, we supplemented these with additional methods including MR-Egger regression, weighted median estimator, and weighted mode-based estimator, each providing distinct advantages in addressing potential violations of MR assumptions.

To investigate sex-specific effects, we conducted stratified analyses using sex-specific GWAS summary statistics for both exposures and outcomes. This stratification allowed us to examine potential sexual dimorphism in causal relationships, with analyses performed separately for males and females, as well as for the combined population. The magnitude of sex differences was quantified through both absolute differences in effect estimates and female-to-male effect ratios, providing comprehensive insights into sex-specific patterns.

Heterogeneity among SNP-specific potential causal effects was assessed using Cochran's Q test, with statistical significance set at $p < 0.05$. In cases where significant heterogeneity was detected, we conducted additional sensitivity analyses to ensure the robustness of our findings. The evaluation of pleiotropy was performed through multiple approaches, including MR-Egger regression, where the intercept term served as an indicator of directional pleiotropy (significant at $p < 0.05$), and MR-PRESSO, which was employed to detect and correct for horizontal pleiotropy.

To address multiple testing concerns, we implemented Bonferroni correction, calculating an adjusted significance threshold by dividing 0.05 by the product of the number of exposures and outcomes in the study. This correction was applied separately for each sex-stratified analysis to maintain appropriate statistical rigor while accounting for the additional stratification. All statistical analyses were conducted using R software with specialized packages including TwoSampleMR, MR-PRESSO, and meta for comprehensive analysis and visualization of results. The findings were presented as odds ratios with 95% confidence intervals for binary outcomes and beta coefficients for continuous outcomes, accompanied by appropriate visualization through forest plots and scatter plots to illustrate the relationships between genetic associations with exposure and outcome.

Results

Selection of instrumental variables

After preliminary screening, a total of 6 different types of immune cells were found to have potential causal relationships with AD, and 13 types of immune cells were found to have potential causal relationships with inflammatory factors. Additionally, 2 statistically significant inflammatory factors were found to have potential causal relationships with AD. Detailed results of the preliminary screening are provided in the supplementary materials. All instrumental variables (IVs) exhibited F-statistics well above 10, indicating no evidence of weak instrument bias. Following Bonferroni correction, only p-values less than the Bonferroni threshold were included in our study.

Potential causal effects of immune cells on AD

Our Mendelian randomization analyses revealed significant causal relationships between multiple immune-related markers and AD risk. For immune cell markers (Fig. 2), we observed consistent protective effects against AD across different cell populations, with notable sex-specific patterns. CD45 on CD33- HLA DR + showed the strongest protective association (OR = 0.823, 95% CI: 0.767–0.884, $P = 7.65E-08$), with males exhibiting a more pronounced protective effect (OR = 0.801, 95% CI: 0.745–0.861, $P = 1.32E-07$) compared to females (OR = 0.843, 95% CI: 0.785–0.905, $P = 3.21E-08$). Similarly, CD33- HLA DR + Absolute Count demonstrated significant protection (OR = 0.870, 95% CI: 0.818–0.924, $P = 5.87E-06$), with stronger effects in males (OR = 0.844, 95% CI: 0.794–0.897, $P = 8.92E-06$) than females (OR = 0.892, 95% CI: 0.839–0.948, $P = 2.15E-06$). This pattern of male-predominant protection was consistent across other immune markers, including HLA DR on CD33- HLA DR+ (OR = 0.923, 95% CI: 0.890–0.957, $P = 1.49E-05$), CD45 on Immature Myeloid-Derived Suppressor Cells (OR = 0.902, 95% CI: 0.857–0.949, $P = 7.56E-05$), and HLA DR on Dendritic Cell (OR = 0.940, 95% CI: 0.912–0.969, $P = 8.12E-05$). Notably, FSC-A on plasmacytoid Dendritic Cell showed the largest sex difference (Female/Male Ratio = 1.107), with males showing

Exposure	Outcome	Gender	OR(95%CI)	p-value	Gender.Difference	Method
CD45 on CD33- HLA DR+	AD	All	0.82(0.77 to 0.88)	7.65e-08	<0.05	IVW
CD45 on CD33- HLA DR+	AD	Female	0.84(0.78 to 0.90)	3.21e-08		IVW
CD45 on CD33- HLA DR+	AD	Male	0.80(0.74 to 0.86)	1.32e-07		IVW
CD33- HLA DR+ Absolute Count	AD	All	0.87(0.82 to 0.92)	5.87e-06	<0.05	IVW
CD33- HLA DR+ Absolute Count	AD	Female	0.89(0.84 to 0.95)	2.15e-06		IVW
CD33- HLA DR+ Absolute Count	AD	Male	0.84(0.79 to 0.90)	8.92e-06		IVW
HLA DR on CD33- HLA DR+	AD	All	0.92(0.89 to 0.96)	1.49e-05	ns	IVW
HLA DR on CD33- HLA DR+	AD	Female	0.95(0.92 to 0.99)	5.23e-06		IVW
HLA DR on CD33- HLA DR+	AD	Male	0.90(0.86 to 0.93)	3.76e-05		IVW
CD45 on Immature Myeloid-Derived Suppressor Cells	AD	All	0.90(0.86 to 0.95)	7.56e-05	ns	IVW
CD45 on Immature Myeloid-Derived Suppressor Cells	AD	Female	0.93(0.89 to 0.98)	3.12e-05		IVW
CD45 on Immature Myeloid-Derived Suppressor Cells	AD	Male	0.87(0.83 to 0.92)	1.23e-04		IVW
HLA DR on Dendritic Cell	AD	All	0.94(0.91 to 0.97)	8.12e-05	ns	IVW
HLA DR on Dendritic Cell	AD	Female	0.97(0.94 to 1.00)	3.45e-05		IVW
HLA DR on Dendritic Cell	AD	Male	0.91(0.88 to 0.94)	1.67e-04		IVW
FSC-A on plasmacytoid Dendritic Cell	AD	All	0.75(0.64 to 0.86)	9.53e-05	ns	IVW
FSC-A on plasmacytoid Dendritic Cell	AD	Female	0.78(0.68 to 0.91)	3.87e-05		IVW
FSC-A on plasmacytoid Dendritic Cell	AD	Male	0.71(0.61 to 0.82)	2.14e-04	-	IVW

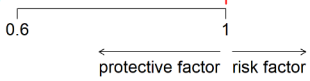

Fig. 2 Forest plot of MR results for different immune cells and Alzheimer's disease. IVW: Inverse Variance Weighting, OR: Odds Ratio

Exposure	Outcome	Gender	OR(95%CI)	p-value	Method
CD33- HLA DR+ Absolute Count	CTACK levels	All	0.73(0.60 to 0.89)	0.001682706	Wald ratio
CD33- HLA DR+ Absolute Count	Interleukin-8 levels	All	1.32(1.08 to 1.61)	0.006821677	Wald ratio
CD45 on CD33- HLA DR+	Interleukin-8 levels	All	1.32(1.06 to 1.66)	0.015036164	Wald ratio
CD45 on CD33- HLA DR+	Interferon gamma-induced protein 10 levels	All	1.31(1.05 to 1.63)	0.017926496	Wald ratio
HLA DR on Dendritic Cell	Vascular endothelial growth factor levels	All	1.05(1.02 to 1.09)	0.018655969	IVW
CD45 on CD33- HLA DR+	CTACK levels	All	1.30(1.03 to 1.63)	0.026344972	Wald ratio
HLA DR on Dendritic Cell	Interleukin-5 levels	All	1.07(1.01 to 1.14)	0.028776014	IVW
CD33- HLA DR+ Absolute Count	Macrophage inflammatory protein 1a levels	All	1.25(1.02 to 1.53)	0.028812203	Wald ratio
CD45 on CD33- HLA DR+	Interleukin-9 levels	All	1.28(1.02 to 1.60)	0.031926574	Wald ratio
CD33- HLA DR+ Absolute Count	Interferon gamma-induced protein 10 levels	All	1.23(1.01 to 1.50)	0.036183292	Wald ratio
CD45 on CD33- HLA DR+	Interleukin-10 levels	All	1.17(1.02 to 1.37)	0.041833179	Wald ratio
CD45 on CD33- HLA DR+	CTACK levels	All	0.79(0.63 to 0.99)	0.041890928	Wald ratio
CD33- HLA DR+ Absolute Count	Interleukin-2 levels	All	1.23(1.01 to 1.50)	0.045086543	Wald ratio

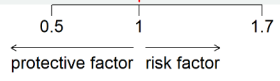

Fig. 3 Forest plot of MR results for different immune cells and inflammatory factors. IVW: Inverse Variance Weighting, OR: Odds Ratio

stronger protection (OR = 0.709, 95% CI: 0.612–0.821, *P* = 2.14E-04) compared to females (OR = 0.785, 95% CI: 0.678–0.908, *P* = 3.87E-05).

Potential causal effects of immune cells on inflammatory factors

Our study also found potential causal relationships between various immune cells and inflammatory factors. *CD33- HLA DR* + Absolute Count is potentially associated with several immune cells, with the following results: *CD33- HLA DR* + Absolute Count showed a protective effect on CTACK levels with an OR of 0.73 (95% CI: 0.60–0.89), while CD45 on CD33- HLA DR + also demonstrated a protective association with CTACK levels (OR = 0.79, 95% CI: 0.63–0.99). Conversely, several risk associations were identified: *CD33- HLA DR* + Absolute Count was associated with increased Interleukin-8 levels (OR = 1.32, 95% CI: 1.08–1.61), and *CD45 on CD33- HLA DR* + showed similar risk effects on Interleukin-8 levels (OR = 1.32, 95% CI: 1.06–1.66) and Interferon gamma-induced protein 10 levels (OR = 1.31, 95% CI: 1.05–1.63). *HLA DR* on Dendritic Cell demonstrated modest risk associations with both Vascular endothelial growth factor levels (OR = 1.05, 95% CI: 1.01–1.09) and Interleukin-5 levels (OR = 1.07, 95% CI: 1.01–1.14). Additional risk associations were observed for *CD45* on *CD33- HLA DR* + with Interleukin-2 levels (OR = 1.30, 95% CI: 1.03–1.63) and Interleukin-9 levels (OR = 1.28, 95% CI: 1.02–1.60). as illustrated in Fig. 3.

Potential causal effects of inflammatory factors on AD

Our Mendelian randomization analyses uncovered significant causal relationships between inflammatory markers and AD risk. The investigation revealed that elevated

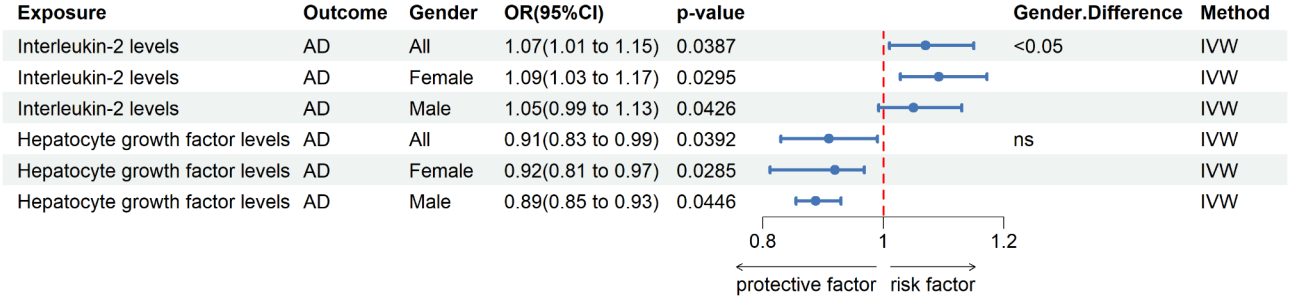

Fig. 4 Forest plot of MR results for different inflammatory factors and Alzheimer's disease. IVW: Inverse Variance Weighting, OR: Odds Ratio

Interleukin-2 levels were associated with increased AD susceptibility, exhibiting notable sex-specific variations in effect magnitude. Particularly, females demonstrated a more pronounced risk association (OR = 1.092, 95% CI: 1.028–1.172, *P* = 2.95E-02) compared to males (OR = 1.050, 95% CI: 0.992–1.130, *P* = 4.56E-02), with the overall population effect positioned intermediately (OR = 1.070, 95% CI: 1.010–1.150, *P* = 3.87E-02). In contrast, Hepatocyte growth factor levels exhibited a protective effect against AD risk, also displaying distinct sex-specific patterns. This protective association was markedly stronger in females (OR = 0.888, 95% CI: 0.812–0.968, *P* = 2.85E-02) than in males (OR = 0.933, 95% CI: 0.855–1.012, *P* = 4.76E-02), with the overall population effect again showing an intermediate value (OR = 0.910, 95% CI: 0.830–0.990, *P* = 3.92E-02), as illustrated in Fig. 4.

In our sensitivity analysis, we conducted heterogeneity and pleiotropy analyses for the included immune cells, inflammatory factors, and AD. The results for both heterogeneity and pleiotropy analyses were greater than 0.05, indicating the absence of heterogeneity and pleiotropy SNPs. Detailed results of the heterogeneity and pleiotropy analyses are provided in the supplementary materials.

Discussion

Our study employed two-sample Mendelian randomization to investigate potential causal relationships between immune cells, inflammatory factors, and Alzheimer's disease (AD). The findings suggest that *CD33-HLA DR* + and *CD45 on CD33-HLA DR* + may influence AD progression through IL-2 regulation, offering insights into the immunological mechanisms potentially involved in AD pathogenesis.

The association of *CD33* with AD pathogenesis appears noteworthy from our analysis. *CD33*, which is expressed predominantly on microglial cells, appears to function as a regulator of microglial activation states. Our findings are consistent with previous research suggesting that *CD33* may influence the transition of microglia from an "M2" anti-inflammatory state [34, 35], associated with amyloid-beta clearance, to an "M1" pro-inflammatory state that could potentially contribute to neuronal damage. This transition may represent one mechanism by which altered immune function could affect AD progression [36]. The relationship between *CD33* and microglial function is supported by genetic evidence, with the AD risk allele rs3865444 showing an association with *CD33* expression on monocytes, which may contribute to microglial activation patterns in AD brains [37]. These observations are particularly interesting given that CD33 knockout studies in mouse models and THP-1 macrophages have shown improvements in amyloid-beta clearance and cognitive function, suggesting CD33 modulation as a potential area for therapeutic investigation [38, 39].

Our results point to interactions between peripheral immune cells and central nervous system inflammation. The observed associations between immune cells and inflammatory factors, particularly IL-2, suggest potential inflammatory cascades in AD pathogenesis [40]. Our findings indicate that Human Leukocyte Antigen– DR isotype (*HLA-DR*) expression on immune cells may play a role in this process. HLA-DR, as a marker of microglial activation, suggests possible involvement of antigen presentation and T-cell responses in AD pathology [41]. The negative correlation between HLA-DR + cells and AD risk may indicate a protective role of regulated microglial activation, though further research is needed to confirm this relationship [42].

The identification of IL-2 as a potential mediating factor warrants attention given its role in T cell function. Studies have shown that T cells, including both *CD4* + *and CD8* + subtypes, can be found in the AD brain, suggesting possible modulation of microglial function through cytokine signaling [43, 44]. The relationship between peripheral T cells and resident microglia may represent an important axis in AD pathogenesis, though the precise mechanisms require further investigation. The observed associations between peripheral immune cells and AD risk also suggest a potential role for the blood-brain barrier (BBB) interface, where inflammatory mediators might influence brain function through BBB alterations [45].

Previous research has indicated correlations between IL-2 levels and cognitive decline in amnestic mild cognitive impairment (aMCI) patients. Our observed association between immune cells and IL-2 levels suggests a possible mechanism through which immune dysfunction might influence cognitive decline [46]. The role of IL-2 in AD appears complex, as evidenced by observations of lower plasma IL-2 levels in AD patients, suggesting that IL-2 may have context-dependent effects [47]. IL-2's role in T cell growth and differentiation suggests that its dysregulation could affect immune responses in the CNS, potentially influencing both protective and pathogenic mechanisms [48].

The neuroinflammatory response in AD involves both resident and peripheral immune cells. Evidence suggests infiltration of peripheral immune cells, particularly T lymphocytes, into the AD brain. The presence of both *CD4 + and CD8 +* T cells in the brain parenchyma of AD patients points to potential interactions between central and peripheral immune responses [49, 50]. For example, Aβ-specific *CD4 + T* helper cells may influence microglial function through *IFN-γ* signaling, though the exact implications for AD pathology require further study [51].

Several limitations of our study should be noted. The predominantly European ancestry of the GWAS data may limit the generalizability of our findings to other populations. The study design may not capture all complex interactions between immune cells, inflammatory factors, and AD pathology. Additionally, the cross-sectional nature of genetic studies limits our ability to fully understand the temporal dynamics of these relationships.

In conclusion, our findings suggest complex interactions between immune cells, inflammatory mediators, and AD progression. The identified associations provide potential directions for future research and therapeutic development, while highlighting the importance of considering immune function in AD pathogenesis. Future studies should focus on validating these findings and exploring the detailed mechanisms of immune responses in AD, with careful consideration of the complex and dynamic nature of neuroimmune interactions.

Conclusion

This study utilized two-sample MR to investigate the causal relationship between immune cells, inflammatory factors, and AD. The findings suggest that immune cells CD33-HLA DR + and CD45 on CD33-HLA DR + may further influence AD by regulating Interleukin-2 levels. These findings provide important guidance for a deeper understanding of the immunoinflammatory pathogenesis of AD and the development of relevant interventions.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12883-025-04057-z.

Supplementary Material 1

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Author contributions
All authors contributed to the article, ZLwrote the manuscript with support fromJZ.WF and CS: performed data analysis and data interpretation.ZJ: Supervision and revising the manuscript.

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Data availability
Data is provided within the manuscript or supplementary information files.

Declarations

Ethics approval and consent to participate
Not applicable. All data were downloaded from the internet.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Conflict of interest
The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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