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Causal relationship between Baff-R expression and normal pressure hydrocephalus: insights from Mendelian randomization analysis

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Abstract

Objectives Previous studies have suggested a possible link between normal pressure hydrocephalus (NPH) and immune factors, but the causal relationship between NPH and Baff-R expression on immune cells remains enigmatic. This study used a Mendelian randomization (MR) method to elucidate this association.

Methods The study used data from the Finngen genome-wide association study (GWAS) and included a large European cohort of 767 patients with NPH and 375,610 controls. Baff-R genetic results in 3,757 individuals of European ancestry had 22 Baff-R-related traits. Different MR techniques were used, and efficacy was assessed using heterogeneity and sensitivity analyses.

Results and conclusion Among the 22 traits, 8 Baff-R-related traits were causally related to NPH. The genetic prediction indicates that Baff-R, particularly in the area of BAFF – R on unswitched memory B cell, BAFF – R on IgD + CD38 – B cell, BAFF – R on CD24 + CD27 + B cell, BAFF – R on IgD – CD38 – B cell, BAFF – R on IgD + CD38dim B cell, BAFF – R on IgD + CD24 + B cell, BAFF – R on IgD + CD38 – naive B cell, BAFF – R on memory B cell may decrease risks on the development of NPH. These findings may help us to understand the immune mechanisms associated with NPH and help to develop future biomarkers related to the disease.

Keywords Mendelian randomization, Normal pressure hydrocephalus, GWAS, BAFF – R, Immune inflammation, Angiogenesis, Fibrosis

Introduction

Normal pressure hydrocephalus (NPH), characterized by ventricular enlargement and normal cerebrospinal fluid (CSF) pressure, presents with the clinical triad of gait disturbance, incontinence, and cognitive decline [1]. Depending on whether there is a clear cause, NPH can be divided into secondary normal pressure hydrocephalus (SNPH) and idiopathic normal pressure hydrocephalus (INPH) [2]. Given the significant economic burden NPH imposes on patients and society, a comprehensive understanding of its pathogenesis is clinically crucial [3]. However, the underlying cause of NPH remains unclear for many patients [4]. In recent years, people have paid more and more attention to the relationship between immune inflammation and NPH.

B-cell activating factor (BAFF), a tumor necrosis factor(TNF) family member [5], is up-regulated in response to genetic alterations and viral infections, strongly associated with autoimmunity, and appears involved in neuroinflammatory processes [6]. BAFF-R,

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one of three known receptors for BAFF [7], binds specifically to BAFF, controlling B cell survival [8]. Abnormal BAFF-R expression can be observed in neurological diseases such as multiple sclerosis and Alzheimer's disease [9, 10]. In addition, these neurological disorders often co-occur with NPH, prompting investigation of the link between BAFF-R and its pathogenesis. The pathophysiology of NPH involves arachnoid fibrosis, pathological angiogenesis, and neuroinflammation [11, 12]. Although immune-inflammatory molecules like TGF-β, TNF-α, IL-1β, and IL-6 are closely associated with these mechanisms, the relationship between BAFF-R and NPH remains unclear.

Traditional observational studies are prone to biases arising from confounding variables and reverse causality, which can undermine their overall credibility. In contrast, Mendelian randomization (MR), which leverages data from genome-wide association studies (GWAS), has become a powerful method for exploring causal relationships. This study employs MR to investigate the genetic variants of BAFF-R on immune cells as instrumental variables (IVs), with the goal of determining the causal link between BAFF-R expression on immune cells and the development of NPH.

Material and method

In this study, a MR approach was employed to analyze the cause-and-effect relationship. The exposure variables consisted of BAFF-R expression on immune cells, while the IVs were single nucleotide polymorphisms (SNPs) strongly associated with BAFF-R on immune cells. The primary outcome of interest was NPH. To ensure the robustness of the results, heterogeneity and sensitivity analyses were conducted.

Data sources

The exposures and outcomes were obtained from publicly available databases, and secondary analyses were conducted. Therefore, ethical approval was not required for this study, which focused on European populations for both the exposure and outcome samples.

We obtained GWAS data for BAFF-R on immune cells from the ieu open GWAS project website (https://gwas.mrcieu.ac.uk/datasets) to explore the potential effects of BAFF-R on immune cells in NPH [13]. And GWAS data for NPH was obtained at the Finngen GWAS summary statistics website (https://r9.finngen.fi/). A group of 3,757 Europeans were tested for the genetic variation in BAFF-R on immune cells [14]. All data used in the analysis were collected by flow cytometry, and 22 BAFF-R-related features were collected from this cohort. All 22 traits were median fluorescence intensity (MFI). The expression levels of the BAFF-R protein in different cell subgroups are indirectly reflected in the MFI group. Increasing the number of cells expressing BAFF-R or the level of BAFF-R expression in specific cell subsets can enhance the intensity of BAFF-R fluorescence, even when the total cell count remains consistent. Supplementary Table S1 presents the GWAS IDs, names, and trait type information for BAFF-R-related traits. Furthermore, genetic data about NPH was acquired from the Finngen initiative for a substantial European sample set comprising 767 cases and 375,610 controls [15].

Selection of IVs

To function successfully as IVs, SNPs must fulfill three essential assumptions. Firstly, it is crucial to establish a strong correlation between SNPs and the exposure of interest. Additionally, it is necessary to set a minimum threshold of ≥ 10 for the strength of IVs as determined by F-values to mitigate potential bias in estimates of causal effects. Any value below this threshold may pose a significant risk of introducing bias [16]. Afterward, the principle of exclusiveness requires that IVs are not directly associated with the outcome. Their impact ought to be moderated only by exposure, guaranteeing the absence of genetic pleiotropy. Finally, independence: Independence means that IVs are not subject to confounders that influence both exposure and outcome [17]. MR simulates the random distribution process in the population by utilizing the random segregation and recombination of genetic variation during gamete formation. Notably, the integrity of the MR analysis is enhanced as the technique is usually not related to external environmental confounders [18–20].

The following parameters were implemented to ensure the authenticity and reliability of the causal relationship between BAFF-R on immune cells and NPH. First, we meticulously selected significant SNPs from the GWAS database of BAFF-R-associated traits. The power was set to F ≥ 10 (Supplementary Table S1), corresponding to the association significance level for "IVs" which is widely regarded as a robust screening threshold for IVs. Additionally, we applied a screening threshold of $P < 5 \times 10^{-6}$ to ensure an adequate number of SNPs. Second, the coefficient of linkage disequilibrium (LD) was set at $r^2 = 0.001$, with a maximum LD region span of 10,000 kb. Third, SNPs associated with BAFF-R were extracted from the NPH GWAS database. Finally, the data from the two relevant datasets were combined, and SNPs with palindromic structures were excluded.

Statistical analyses

R software version R-4.3.1 conducted a statistical analysis of all data. All estimates were considered significant at the level of ≤ 0.05. This study utilized multiple methodologies to deduce the potential causal impacts of BAFF-R-related traits on NPH. The employed methods comprise

the MR-Egger, Inverse Variance Weighted (IVW), Simple Mode, Weighted Mode, and Wald Ratio approaches. For instances where three or more SNPs were present, the MR-Egger and IVW methods were utilized. SNP heterogeneity was assessed using Cochran's Q test, deemed significant with a P-value of < 0.05. If no pleiotropy and heterogeneity were present, preference was granted to the outcomes obtained from the IVW method. To prevent errors caused by multiple hypothesis testing, we used the False Discovery Rate (FDR) method created by Benjamini and Hochberg to regulate the p-value and manage the total error rate. In the MR analysis, we used the odds ratio (OR) to determine the link between outcome and exposure. If OR = 1, it indicates that the exposure has no impact on the outcome. If OR > 1, it implies that the exposure is linked to an increased likelihood of the outcome. On the other hand, if OR < 1, the exposure is associated with a decreased outcome probability.

The MR-Egger regression analysis was used to assess potential horizontal pleiotropy effects associated with the included SNPs. A significant deviation from zero in the intercept term of the MR-Egger method would suggest the presence of horizontal pleiotropy. Additionally, we performed sensitivity analysis using the Leave-one-out sensitivity test, where the results were reanalyzed by systematically excluding individual SNPs. The goal was to determine whether the exclusion of any single SNP caused a significant change in the findings. The reliability of the MR results was considered validated if the exclusion of any SNP did not notably affect the overall outcomes.

Furthermore, the selected SNPs underwent a thorough cross-validation procedure utilizing the website: http://www.phenoscanner.medschl.cam.ac.uk/ can to identify additional characteristics that could potentially impact the study outcomes. Any SNPs that showed correlations with these traits were subsequently removed, successfully reducing the likelihood of confounding factors influencing the results.

Table 1 The MR analysis results of BAFF-R related traits on NPH

Exposure	Methods	nSNPs	OR (95%CI)	*P*
BAFF-R on unswitched memory B cell	IVW	12	0.90 (0.82, 0.98)	0.021
	MR Egger	12	0.89 (0.79, 1.01)	0.107
	Weighted median	12	0.92 (0.82, 1.02)	0.111
	Weighted mode	12	0.91 (0.82, 1.01)	0.095
	Simple mode	12	0.83 (0.68, 0.99)	0.069
BAFF-R on IgD + CD38- B cell	IVW	13	0.90 (0.82, 0.98)	0.021
	MR Egger	13	0.92 (0.81, 1.03)	0.189
	Weighted median	13	0.91 (0.82, 1.02)	0.092
	Weighted mode	13	0.91 (0.81, 1.01)	0.104
	Simple mode	13	0.87 (0.70, 1.07)	0.214
BAFF-R on CD24 + CD27 + B cell	IVW	15	0.90 (0.82, 0.99)	0.024
	MR Egger	15	0.89 (0.78, 1.01)	0.087
	Weighted median	15	0.92 (0.82, 1.02)	0.116
	Weighted mode	15	0.90 (0.81, 1.00)	0.079
	Simple mode	15	0.84 (0.69, 1.02)	0.099
BAFF-R on IgD- CD38- B cell	IVW	11	0.90 (0.82, 0.99)	0.028
	MR Egger	11	0.88 (0.78, 1.01)	0.093
	Weighted median	11	0.92 (0.82, 1.03)	0.137
	Weighted mode	11	0.91 (0.81, 1.02)	0.125
	Simple mode	11	0.88 (0.74, 1.04)	0.160
BAFF-R on IgD + CD38dim B cell	IVW	17	0.91 (0.83, 0.99)	0.030
	MR Egger	17	0.89 (0.79, 1.01)	0.085
	Weighted median	17	0.91 (0.82, 1.02)	0.098
	Weighted mode	17	0.91 (0.81, 1.01)	0.097
	Simple mode	17	0.87 (0.71, 1.06)	0.192
BAFF-R on IgD + CD24 + B cell	IVW	12	0.90 (0.82, 0.99)	0.031
	MR Egger	12	0.89 (0.78, 1.01)	0.095
	Weighted median	12	0.92 (0.82, 1.03)	0.128
	Weighted mode	12	0.90 (0.81, 1.00)	0.074
	Simple mode	12	0.84 (0.70, 1.01)	0.095
BAFF-R on IgD + CD38- naive B cell	IVW	17	0.91 (0.84, 1.00)	0.039
	MR Egger	17	0.97 (0.84, 1.11)	0.635
	Weighted median	17	0.92 (0.82, 1.03)	0.139
	Weighted mode	17	0.92 (0.82, 1.03)	0.160
	Simple mode	17	0.77 (0.59, 1.00)	0.070
BAFF-R on memory B cell	IVW	13	0.91 (0.83, 1.00)	0.043
	MR Egger	13	0.87 (0.77, 0.98)	0.045
	Weighted median	13	0.92 (0.82, 1.02)	0.113
	Weighted mode	13	0.90 (0.80, 1.00)	0.084
	Simple mode	13	0.85 (0.71, 1.03)	0.123

Results

Selection of IVs

After strict quality control, we finally found SNPs that were consistent with 22 BAFF-R-related traits and NPH GWAS. The SNP's ID, P-value, β-value, effect allele (EA), other alleles and standard error (SE) were comprehensively merged for later analysis and presented in Supplementary Table S1. Finally, we found that only 8 BAFF-R-related traits showed significant correlation with NPH (Supplementary Figure S1).

Exploration of the causation of Baff-R on immune cells on NPH

As demonstrated in Table 1, a significant correlation suggests that eight traits related to BAFF-R are closely connected to the vulnerability of NPH, acting as protective measures against its onset. All 8 BAFF-R-related trait types were MFI and B cell panels. MFI indicates the degree to which BAFF-R is expressed within

a specific cellular subset of B cells. After adjusting for FDR (P-FDR < 0.20), protective effects of eight traits related to BAFF-R were detected on NPH: BAFF – R on unswitched memory B cell, BAFF – R on IgD + CD38 – B cell, BAFF – R on CD24 + CD27 + B cell, BAFF – R on IgD – CD38 – B cell, BAFF – R on IgD + CD38dim B cell, BAFF – R on IgD + CD24 + B cell, BAFF – R on IgD + CD38 – naive B cell, BAFF – R on memory B cell (Figs. 1 and 2). In addition, the robustness of the negative correlation results between the eight traits associated with BAFF-R and NPH was ensured by MR-Egger intercept and MR-PRESSO overall tests (Table 2). The scatter plots, funnel plots and leave-one-out plots (Figs. 3 and 4, Supplementary Figure S2) also indicated the stability of the results.

Exploration of the causation of NPH on Baff-R on immune cells

We conducted a reverse MR to examine if NPH causally affects Baff-R on immune cells. Nevertheless, we found no causative link between NPH and Baff-R on immune cells. Therefore, this is an indication that there is no reverse causal association between NPH and Baff-R on immune cells (Table 3).

Discussion

Using comprehensive publicly available genetic data, we explored causal associations between 22 Baff-R-related immune cell traits and NPH. The causal association between Baff-R-related immunophenotypes and NPH was investigated for the first time. The study determined that NPH had no causal effects on Baff-R-related immunophenotypes, and eight Baff-R-related immunophenotypes showed a potential causal effect on NPH (FDR < 0.20) [21].

The three widely accepted pathophysiological mechanisms of NPH are arachnoid fibrosis [22, 23], pathological angiogenesis [24, 25], and neuroinflammation [11, 26]. Baff is strongly associated with fibrosis, angiogenesis, and neuroinflammation. In our study, BAFF-R was negatively correlated with NPH. Therefore, we hypothesize that BAFF and its receptor BAFF-R may be involved in all three primary mechanisms of NPH.

The involvement of BAFF in fibrosis, demonstrated in previous studies including liver fibrosis [27, 28], multiple sclerosis [29], and interstitial fibrosis [30], contradicts our finding where the level of BAFF-R expressed on immune cells was inversely correlated with the occurrence of NPH. Subarachnoid fibrosis is a crucial mechanism in forming NPH and may be related to the production of inflammatory factors in chronic inflammatory response. In NPH subarachnoid fibrosis, TGF-β emerges as a critical molecule. Previous studies have shown that the BAFF binding to BAFF-R decreases TGF-β levels [31]. Therefore, we hypothesize that BAFF specifically binds to BAFF-R, activating B cells, promoting Treg cell apoptosis, reducing TGF-β, inhibiting the TGF-β pathway, and thus inhibiting subarachnoid fibrosis.

The tumor necrosis factor (TNF) family is vital in the process of angiogenesis [32, 33]. BAFF, also a member of the TNF family, binds explicitly to BAFF-R, increasing TNF-α levels, activating the NF-kb pathway, elevating angiogenic factors, and promoting angiogenesis [34]. Additionally, BAFF specifically binding to BAFF-R activates B cells to produce various cytokines, such as IFN-γ [35, 36]. IFN-γ acts to inhibit angiogenesis [37, 38]. Furthermore, BAFF binding specifically to BAFF-R modulates B and T cells, reducing TGF-β levels [31]. TGF-β negatively correlates with VEGFA expression through TGF-β signaling and can inhibit angiogenesis [39, 40]. The combined effect of these mechanisms may confirm our conclusion that BAFF-R levels are inversely related to NPH.

Neuroinflammation is one of the essential mechanisms in the pathogenesis of NPH, mainly involving glial cell activation [41], the secretion of inflammatory cytokines [42], and alterations to the blood-brain barrier [43]. When BAFF binds to BAFF-R, it can also promote neuronal survival through the JAK-STAT signaling pathway activated by IFN-γ and IL-10 [44, 45]. This aligns precisely with the results of our study.

This research conducted a two-sample MR analysis of the largest published NPH GWAS cohort results. Conclusions are drawn based on genetic instrumental variables using various MR analysis methods. Nevertheless, our research has limitations. Firstly, the small sample size of the current NPH may lead to some false positives in our results. Secondly, additional stratified analysis of the population cannot be performed due to insufficient individual information. Thirdly, because the study used a European database and did not apply to other ethnic groups, the generalizability of our findings is limited. Fourthly, we used a less stringent threshold to evaluate the results. This may increase false-positive results but allows a more comprehensive evaluation of the robust correlation between BAFF-R-related immunophenotypes and NPH. Finally, although we have adopted a variety of methods to detect and adjust horizontal pleiotropy, we still need to pay attention to that certain tool variables may be affected by pleiotropy. Therefore, the stability of the result may still need to be further verified.

Conclusions

In conclusion, our comprehensive bidirectional MR analysis has shown the causal relationships between numerous BAFF-R-related immunophenotypes and NPH. This has highlighted the intricate interaction patterns between these immunophenotypes and NPH, emphasizing their

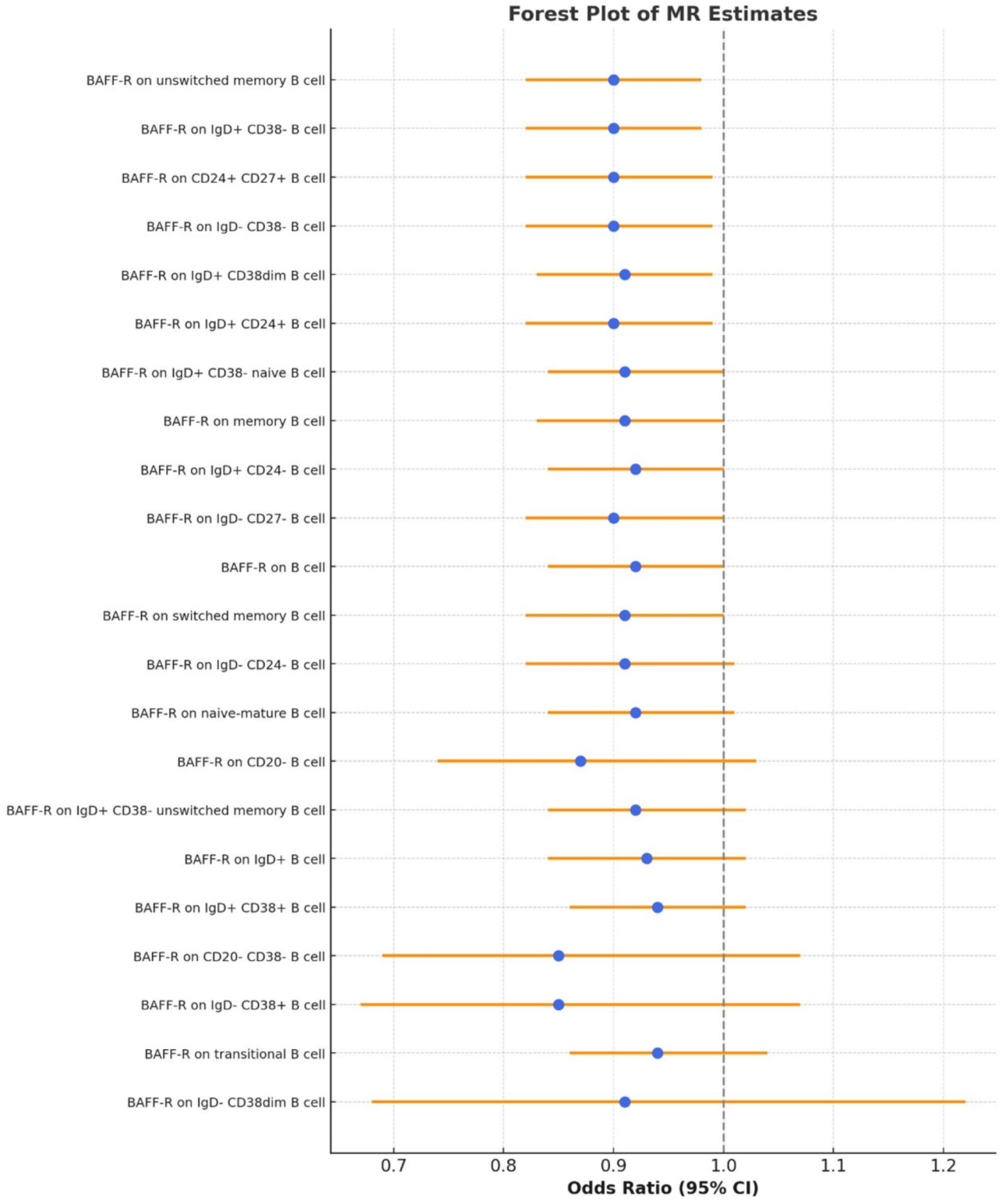

Fig. 1 The forest plot of the causation of Baff-R on immune cells on NPH

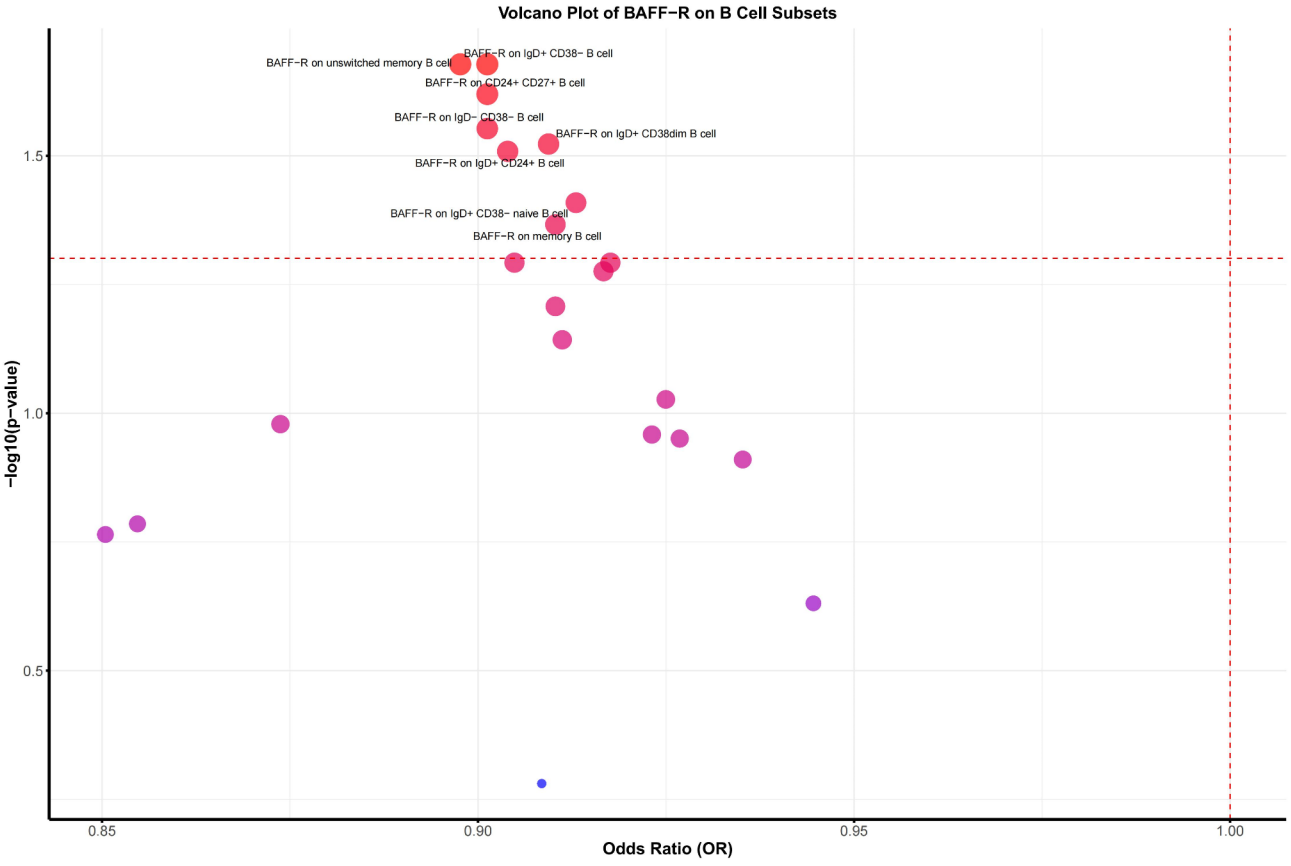

Fig. 2 The volcano plot of the causation of Baff-R on immune cells on NPH

Table 2 The sensitivity analysis results of BAFF-R related traits on NPH

Exposure	Outcome	Het.*p*	Ple.*p*	MR.prosso
BAFF-R on unswitched memory B cell	NPH	0.979	0.896	0.975
BAFF-R on IgD + CD38- B cell	NPH	0.631	0.658	0.706
BAFF-R on CD24 + CD27 + B cell	NPH	0.974	0.743	0.975
BAFF-R on IgD- CD38- B cell	NPH	0.970	0.690	0.974
BAFF-R on IgD + CD38dim B cell	NPH	0.834	0.693	0.867
BAFF-R on IgD + CD24 + B cell	NPH	0.930	0.712	0.942
BAFF-R on IgD + CD38- naive B cell	NPH	0.490	0.313	0.570
BAFF-R on memory B cell	NPH	0.900	0.279	0.932

complexity. Moreover, our study has minimized the effect of inescapable confounding variables, reverse causation and other factors. This discovery could pave the way for researchers to investigate the biological mechanisms of NPH further, potentially resulting in earlier interventions and treatment. Our findings augment the existing immunological evidence, offering essential insights into the prevention of NPH.

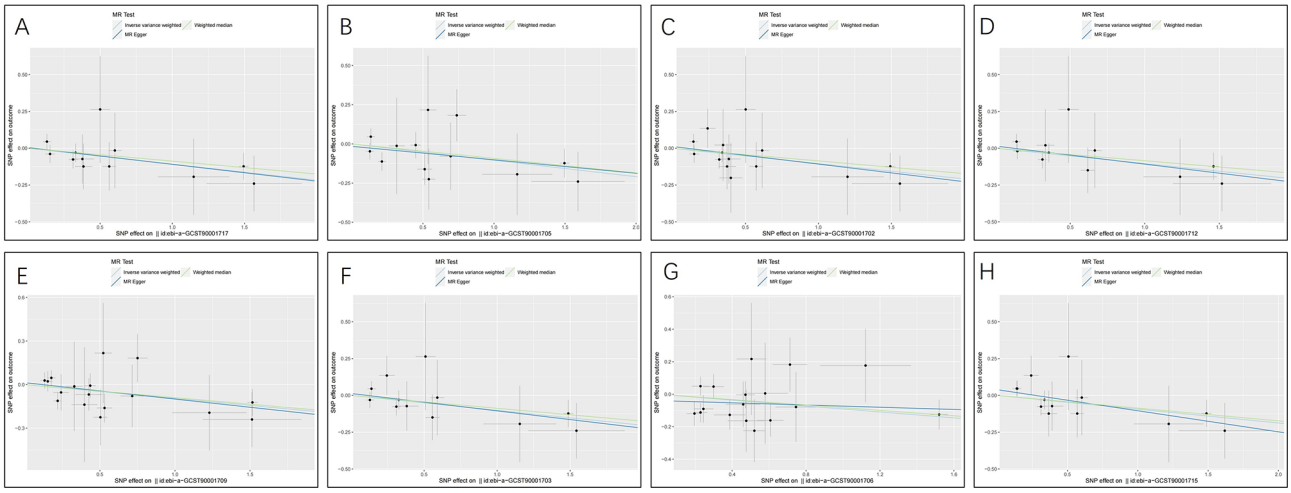

Fig. 3 The scatter plot of the causation of Baff-R on immune cells on NPH. (**A**) scatter plots for BAFF – R on unswitched memory B cell on NPH. (**B**) scatter plots for BAFF – R on IgD + CD38 – B cell on NPH. (**C**) scatter plots for BAFF – R on CD24 + CD27 + B cell on NPH. (**D**) scatter plots for BAFF – R on IgD – CD38 – B cell on NPH. (**E**) scatter plots for BAFF – R on IgD + CD38dim B cell on NPH. (**F**) scatter plots for BAFF – R on IgD + CD24 + B cell on NPH. (**G**) scatter plots for BAFF – R on IgD + CD38 – naive B cell on NPH. (**H**) scatter plots for BAFF – R on memory B cell on NPH

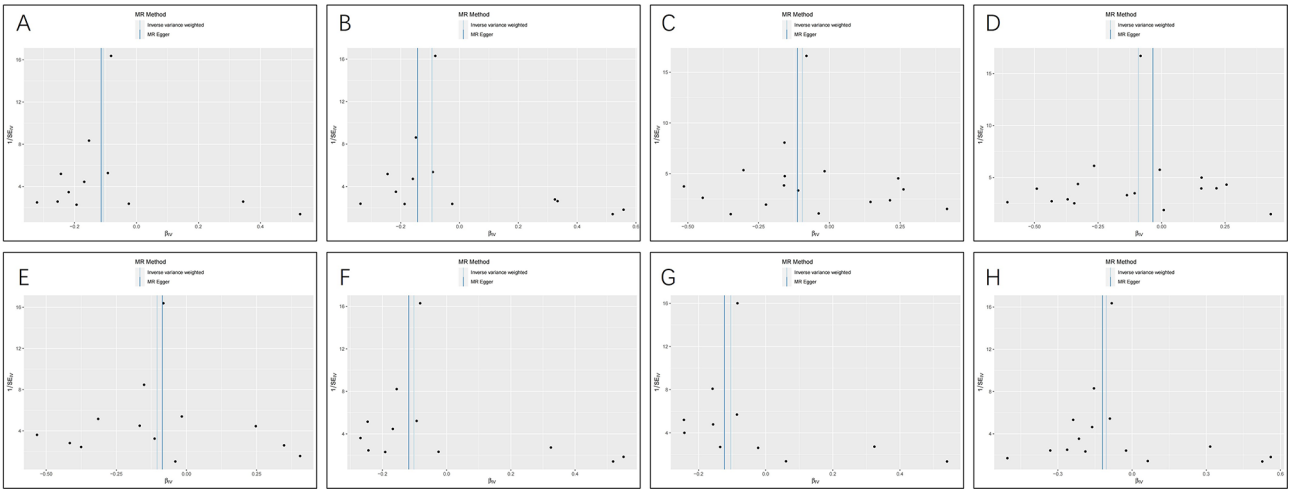

Fig. 4 The funnel plots for Baff-R on immune cells on NPH. (**A**) funnel plots for BAFF – R on unswitched memory B cell on NPH. (**B**) funnel plots for BAFF – R on IgD + CD38 – B cell on NPH. (**C**) funnel plots for BAFF – R on CD24 + CD27 + B cell on NPH. (**D**) funnel plots for BAFF – R on IgD – CD38 – B cell on NPH. (**E**) funnel plots for BAFF – R on IgD + CD38dim B cell on NPH. (**F**) funnel plots for BAFF – R on IgD + CD24 + B cell on NPH. (**G**) funnel plots for BAFF – R on IgD + CD38 – naive B cell on NPH. (**H**) funnel plots for BAFF – R on memory B cell on NPH

Table 3 Exploration of the causation of NPH on Baff-R on immune cells

Outcomes	Trait type	Panel	Methods	nSNPs	*P*-unadj	*P*-adj
BAFF-R on IgD + CD38- naive B cell	MFI	B cell	IVW	21	0.182	0.942
BAFF-R on IgD + CD38- unswitched memory B cell	MFI	B cell	IVW	21	0.200	0.942
BAFF-R on CD20- B cell	MFI	B cell	IVW	20	0.294	0.942
BAFF-R on IgD- CD38 + B cell	MFI	B cell	IVW	21	0.607	0.942
BAFF-R on CD20- CD38- B cell	MFI	B cell	IVW	21	0.641	0.942
BAFF-R on IgD + CD24- B cell	MFI	B cell	IVW	21	0.684	0.942
BAFF-R on B cell	MFI	B cell	IVW	21	0.704	0.942
BAFF-R on IgD + B cell	MFI	B cell	IVW	21	0.717	0.942
BAFF-R on naive-mature B cell	MFI	B cell	IVW	21	0.725	0.942
BAFF-R on IgD + CD38dim B cell	MFI	B cell	IVW	21	0.748	0.942
BAFF-R on transitional B cell	MFI	B cell	IVW	21	0.768	0.942
BAFF-R on IgD + CD38 + B cell	MFI	B cell	IVW	21	0.807	0.942
BAFF-R on IgD- CD38dim B cell	MFI	B cell	IVW	9	0.812	0.942
BAFF-R on unswitched memory B cell	MFI	B cell	IVW	21	0.814	0.942
BAFF-R on IgD- CD27- B cell	MFI	B cell	IVW	21	0.823	0.942
BAFF-R on IgD + CD24 + B cell	MFI	B cell	IVW	21	0.826	0.942
BAFF-R on IgD- CD24- B cell	MFI	B cell	IVW	21	0.858	0.942
BAFF-R on IgD + CD38- B cell	MFI	B cell	IVW	21	0.861	0.942
BAFF-R on switched memory B cell	MFI	B cell	IVW	21	0.884	0.942
BAFF-R on CD24 + CD27 + B cell	MFI	B cell	IVW	21	0.894	0.942
BAFF-R on memory B cell	MFI	B cell	IVW	21	0.899	0.942
BAFF-R on IgD- CD38- B cell	MFI	B cell	IVW	21	0.978	0.978

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12883-025-04098-4 .

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

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Not applicable.

Author contributions
Conceptualization: Wencai Wang, Luyao Ma, Menghao Liu, Yongqiang Zhao, and Wei Ye; acquisition, analysis, or interpretation of data: Wencai Wang and Luyao Ma; drafting of the manuscript: Wencai Wang; critical revision and editing of the manuscript: Wencai Wang, Luyao Ma, and Xianfeng Li. All authors read and approved the final version of the manuscript.

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

Declarations

Ethical approval
All data in the manuscript were obtained from public databases, GWAS data for BAFF-R on immune cells from the ieu open GWAS project website (https://gwas.mrcieu.ac.uk/datasets). GWAS data for NPH was obtained at the Finngen GWAS summary statistics website (https://r9.finngen.fi/).

Consent to participate
All studies used in the analysis received ethical approval from their respective institutional review boar.

Consent for publication
Not Applicable.

Competing interests
The authors declare no competing interests.

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