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ORIGINAL ARTICLE

Associations between Immune Cell Traits and Tonsil and Adenoid Hypertrophy in Children: a Bidirectional Two-Sample Mendelian Randomization Study

Xiaoyu Wen, Jiarou Zhong, Yunyun Luo, Chaojie Yang

The Second Affiliated Hospital of Guangzhou University of Traditional Chinese Medicine, Guangzhou, China

ABSTRACT

Background: **Mounting evidence indicates associations between immune cells and chronic diseases of the tonsils and adenoids (CDTA). Whether these observational links reflect underlying causality has yet to be determined. To elucidate causal links between immune cell traits and CDTA we used two-sample Mendelian randomization (MR).**
Methods: **Summary data of 731 immune cell traits were acquired from the OPEN GWAS repository, encompassing absolute cell counts (n = 118), morphological parameters (MP; n = 32), relative cell counts (n = 192), and median fluorescence intensity of surface antigens (n = 389). Causality was investigated using forward MR analyses (immune cell traits as exposures, CDTA as outcomes) and reverse MR analyses (CDTA as exposures, immune cell traits as outcomes) and the inverse-variance weighting (IVW) method, complemented by sensitivity analyses to assess robustness.**
Results: **Forward MR by IVW identified 14 immune cell traits that were positively associated with CDTA ($p < 0.05$, odds ratio [OR] > 1) and 12 immune cell traits that were negatively associated with CDTA ($p < 0.05$, OR < 1). Five of the immune cell traits exhibited heterogeneity ($p < 0.05$), but no horizontal pleiotropy ($p > 0.05$). Reverse MR revealed 3 immune cell traits that were positively associated with CDTA ($p < 0.05$, OR > 1), demonstrating bidirectional causality, with no heterogeneity or horizontal pleiotropy ($p > 0.05$).**
Conclusions: **This study used bidirectional two-sample MR to identify intricate causal links between multiple immune cell traits and CDTA, underscoring complex interactions between immunology and pathology in CDTA.**
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Correspondence:
Chaojie Yang
The Second Affiliated Hospital of Guangzhou University of Traditional Chinese Medicine
No. 111, Dade Road, Yuexiu District
Guangzhou City
Guangzhou, 510000
China
Phone: + 86 8613570490140
Email: 407672818@qq.com

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INTRODUCTION

Tonsillar hypertrophy (TH) and adenoid hypertrophy (AH) represent prevalent pediatric conditions affecting 10 - 30% of children worldwide, with significant associations to obstructive sleep apnea syndrome (OSAS), abnormal craniofacial development, and recurrent respiretory infections [1]. While environmental factors such as recurrent infections, allergic rhinitis, and obesity are known to influence the development of TH and AH [2], immunological mechanisms underlying lymphoid tissue hyperplasia are poorly characterized. Emerging evidence suggests that hypertrophic tonsils and adenoids exhibit distinct immune microenvironments compared to healthy tissues, particularly in cytokine profiles (e.g. IL-1, IL-10) and immune cell activation markers (CD25, CD69) [3]. Immune cell phenotypes, specifically those mediating type 2 inflammation such as Th2 lymphocytes and group 2 innate lymphoid cells (ILC2s), may drive mucosal hyperplasia through cytokine cascades involving IL-25, IL-33, and thymic stromal lymphopoietin (TSLP) [4]. A previous study [5] exploring the interplay between alterations of the gut microbiome and enlarged adenoids found that children with AH had significantly more immune cells and a lower Th17/Treg ratio in peripheral blood and nasal-associated lymphoid tissue than healthy controls, implying a connection between AH and immunological imbalance. Another study [6] evaluating the composition of the lymphocyte subset in hypertrophic adenoids with multicolor flow cytometry revealed an increase in immature lymphocytes and a decrease in effector cells in children with severe AH compared to mild to moderate AH, implying that aberrant lymphocyte migration or differentiation may contribute to the development of AH. Despite these associations, observational studies cannot disentangle causation from confounding factors (e.g. genetic predisposition, environmental triggers) or reverse causality (e.g. whether immune changes precede or follow TH or AH) [7].

By leveraging genetic variants as instrumental variables (IVs), Mendelian randomization (MR) is an effective methodology for establishing causal relationships in complex diseases, reducing confounding effects [8-10]. Recent MR studies have identified genetic associations between immune-related single nucleotide polymorphisms (SNPs) and risk of tonsillectomy [11], while others demonstrate bidirectional relationships between allergic diseases and chronic adenotonsillar disorders [8,12]. Notably, immune cell traits that reflect immune cell differentiation and function have been implicated in various pediatric inflammatory conditions using MR analyses [10,13,14]. A critical evidence gap persists regarding whether specific immune cell subsets drive the pathogenesis of TH and AH or merely reflect secondary immune activation.

MR utilizes genetic variants, usually SNPs, which satisfy the assumptions of an IV. A valid IV must be associated with the risk factor of interest, such that it is not associated with confounders of the risk factor-outcome association and it does not affect the outcome directly (only potentially indirectly via its effect on the risk factor of interest) [15,16]. Confounding variables have no effect on the IVs because they are genetically based [17]. Conventionally, MR analyses adopt a unidirectional approach, moving from a defined exposure to a specific outcome to assess potential causal effects. In complex settings, exposure-outcome associations may be bidirectional, particularly when feedback mechanisms operate. Consequently, the outcome may reciprocally impact the exposure. Employing bidirectional MR methodology enhances the discernment of primary from secondary effects, addressing confounding arising from reverse causation.

The objective of this bidirectional MR analysis was to examine the potential causal relationships between 731 immune cell traits and chronic diseases of the tonsils and adenoids (CDTA). In forward MR analyses, SNPs demonstrating a strong association with CDTA ($p < 10^{-8}$) were designated as exposure variables, and CDTA constituted the outcome. In reverse MR analyses, CDTA was the exposure, and immune cell traits were the outcomes. Causal relationships between immune cell traits and CDTA were disentangled while accounting for horizontal pleiotropy through sensitivity analyses, overcoming the limitations of previous cross-sectional studies [18,19]. Key confounding variables encompassing multiple domains were considered, including: 1) nutritional parameters, particularly dietary patterns linked to increased risk of TH and AH; 2) history of infectious disease, as recurrent upper respiratory infections have been associated with AH; 3) exposure to environmental tobacco, which elevates susceptibility to AH in children; 4) anthropometric measures, as there are documented correlations between body mass index (BMI) and AH development; 5) gastroesophageal reflux disease (GERD), recognized as a risk factor for AH; and 6) atopic conditions, notably allergic rhinitis constituting an independent risk factor for AH [20-23]. By overcoming the limitations of randomized controlled trials and elucidating confounding factors in observational studies, MR provides compelling avenues for research. Therefore, we chose a bidirectional MR study to evaluate the intricate causal relationships between immune cell traits and CDTA.

MATERIALS AND METHODS

This study was conducted and reported in accordance with the STROBE-MR checklist [24].

Study design

A bidirectional two-sample MR framework was implemented leveraging SNPs derived from summary-level data as IVs to investigate potential causal interdependencies between 731 immune cell traits and CDTA (Figure 1). The IVs satisfied three core assumptions: 1) relevance assumption: selected IVs must exhibit robust associations with the exposure trait; 2) independence assumption: IVs should be uncorrelated with confounding variables; and 3) exclusion-restriction assumption: IVs must affect outcomes exclusively via the exposure pathway without evidence of horizontal pleiotropy.

Data sources

Data sources included public repositories (OPEN GWAS and FinnGen). Data were publicly available and not identifiable; therefore, this research qualified for institutional review board exemption.

Summary data of 731 immune cell traits were acquired from the OPEN GWAS repository (accession IDs: GCST90001391 to GCST90002121), including 3,757 individuals of European ancestry [25]. The 731 immune cell traits contained 118 absolute cell counts, 192 relative cell counts, 389 median fluorescence intensities that reflect surface antigen levels, and 32 morphological parameters. The traits were stratified across seven cell types, including 43 monocytes, 64 CD cells, 64 myeloid cells, 79 mature T cells, 124 TBNK cells, 167 Treg cells, and 190 B cells (Supplementary Table 1).

Summary data for CDTAs were extracted from the FinnGen consortium's R12 public data repository (accessible at https://www.finngen.fi/fi), including 431,220 individuals of European ancestry (59,700 cases and 371,520 controls).

As the OPEN GWAS and FinnGen datasets originated from distinct consortia and all individuals were of European ancestry, no sample overlap existed.

IV selection

SNPs strongly associated with exposure were extracted. The screening criterion for SNPs when immune cell traits were considered was low, at $p < 1 \times 10^{-5}$, as immune cell traits in GWAS infrequently reach the conventional genome-wide significance benchmark ($p < 5 \times 10^{-8}$). This lower standard has been broadly accepted in many MR studies [26-28] and enabled incorporation of a broad spectrum of variants. To minimize linkage disequilibrium (LD), the cluster data function from the TwoSampleM package in R was implemented. This procedure, filtering SNPs for a window size of 10,000 kb and a LD level of $r^2 < 0.001$, ensured SNP independence. The “harmonize data” function (action = 2) was applied to remove palindromic or duplicate SNPs. The F-statistic was derived for each SNP using the formula $F = (\beta/SE)^2$ [29,30], where β represents the effects of the SNP on the exposure and SE represents the standard error of β. To minimize the potential for estimates susceptible to weak instrument bias, SNPs with an F-statistic below 10 were removed.

Statistical analysis

MR analyses were conducted using the TwoSampleM package in R (version 4.4.1). IVs were evaluated for MR using the inverse variance weighted (IVW) method, implemented using a random-effects model to address heterogeneity, capturing balanced pleiotropic effects [31]. Findings were confirmed by sensitivity analyses using 1) Cochran's Q statistic to quantify heterogeneity (significant association: $p < 0.05$) and 2) MR-Egger regression to assess horizontal pleiotropy. Leave-one-out analyses sequentially excluding SNPs were used to determine the influence of individual SNPs on the causal relationships. Outcomes were presented as odds ratios (ORs) with 95% confidence intervals (CIs). A p-value < 0.05 indicated statistical significance.

RESULTS

Causal effects of immune cell traits on CDTA

Forward MR analysis

IV screening was performed on GWAS data for 731 immune cell traits. All selected IVs exhibited F-statistics > 10, and no weak instrument bias was detected (Supplementary Table 2).

The IVW showed 26 immune cell traits had significant causal relationships with CDTA (Figure 2). Among these, 14 exhibited positive associations with CDTA (OR > 1, $p < 0.05$) (B cell panel: IgD- CD38dim B cell %lymphocyte, BAFF-R on CD20- B cell, CD24 on IgD+ CD24+ B cell, and Switched memory B cell %B cell; Myeloid cell panel: Hematopoietic stem cell absolute count, CD33 on CD66b++ myeloid cell, CD33 on monocytic myeloid-derived suppressor cells, CD33 on CD33+ HLA DR+, CD33 on granulocytic myeloid-derived suppressor cells, and CD33 on CD33+ HLA DR+ CD14-; Monocyte panel: CD14+ CD16- monocyte %monocyte; TBNK panel: CD45 on B cell and CD45 on CD8+ T cell; Treg panel: CD28- CD25++ CD8+ T cell absolute count), and 12 exhibited negative associations with CDTA (OR < 1, $p < 0.05$) (B cell panel: IgD+ CD38- B cell absolute count, CD20 on memory B cell, and BAFF-R on IgD+ CD24- B cell; Maturation stages of T cell panel: CD45RA on terminally differentiated CD8+ T cell; Monocyte panel: HLA DR on CD14+ monocyte and HLA DR on CD14+ CD16- monocyte; Myeloid cell panel: HLA DR on CD33+ HLA DR+ CD14-; TBNK panel: CD3 on HLA DR+ CD4+ T cell; Treg panel: Activated & resting CD4 regulatory T cell absolute count, CD25 on CD39+ resting CD4 regulatory T cell, CD3 on CD39+ activated CD4 regulatory T cell, and CD25++ CD45RA+ CD4 not regulatory T cell %CD4+ T cell).

Sensitivity analyses revealed that five of the 26 immune cell traits showed heterogeneity (Q-test $p < 0.05$, random-effects model applied) (HLA-DR expression on CD33+ HLA- DR+ CD14-, IgD- CD38dim B cells, CD33 expression on monocytic myeloid-derived suppressor cells [MDSCs], CD20 expression on memory B cells, and CD33 expression on granulocytic MDSCs). There was no evidence of horizontal pleiotropy (MR-Egger intercept $p > 0.05$), confirming the robustness of the causal inferences (Table 1). Both leave-one-out analysis and funnel plots indicated data reliability (Supplementary Material 1).

Reverse MR

Bidirectional two-sample MR analyses demonstrated positive correlations (OR > 1, $p < 0.05$) between three immune cell traits and CDTA: B cell panel: CD20 on memory B cell; Monocyte panel: HLA DR on CD14+ monocyte and HLA DR on CD14+ CD16- monocyte (Figure 3).

Sensitivity analysis revealed that the three immune cell traits showed no heterogeneity (Q-test $p > 0.05$) or horizontal pleiotropy (MR-Egger intercept $p > 0.05$), confirming the credibility of robust causal estimates (Table

Table 1. Forward MR: Sensitivity analysis.

Panel	Immune traits	Inverse variance weighted		MR-Egger	
		Q	p	Intercept	p
B cell	IgD- CD38dim B cell %lymphocyte	49.60	0.001	0.005	0.233
B cell	BAFF-R on CD20- B cell	12.07	0.522	0.002	0.69
B cell	IgD+ CD38- B cell absolute count	20.58	0.195	0.006	0.368
B cell	CD24 on IgD+ CD24+ B cell	29.22	0.212	-0.0004	0.873
B cell	Switched memory B cell %B cell	4.48	0.923	0.001	0.867
B cell	CD20 on memory B cell	46.19	0.012	-0.001	0.697
B cell	BAFF-R on IgD+ CD24- B cell	26.21	0.159	-0.006	0.111
Maturation stages of T cell	CD45RA on terminally differentiated CD8+ T cell	9.82	0.709	0.002	0.781
Monocyte	HLA DR on CD14+ monocyte	20.24	0.380	0.004	0.464
Monocyte	HLA DR on CD14+ CD16- monocyte	25.66	0.177	0.003	0.562
Monocyte	CD14+ CD16- monocyte %monocyte	24.17	0.394	0.002	0.491
Myeloid cell	Hematopoietic stem cell absolute count	18.52	0.422	0.001	0.846
Myeloid cell	CD33 on CD66b++ myeloid cell	15.56	0.555	0.001	0.801
Myeloid cell	CD33 on monocytic myeloid-derived suppressor cells	37.78	0.009	-0.003	0.511
Myeloid cell	HLA DR on CD33+ HLA DR+ CD14-	45.69	0.003	0.007	0.133
Myeloid cell	CD33 on CD33+ HLA DR+	21.00	0.521	-0.003	0.387
Myeloid cell	CD33 on granulocytic myeloid-derived suppressor cells	39.30	0.004	-0.00002	0.998
Myeloid cell	CD33 on CD33+ HLA DR+ CD14-	21.09	0.392	-0.004	0.307
TBNK	CD45 on B cell	19.18	0.206	-0.005	0.144
TBNK	CD3 on HLA DR+ CD4+ T cell	29.28	0.252	0.001	0.71
TBNK	CD45 on CD8+ T cell	26.04	0.351	-0.001	0.827
Treg	CD28- CD25++ CD8+ T cell absolute count	33.16	0.078	-0.003	0.423
Treg	Activated & resting CD4 regulatory T cell absolute count	21.95	0.234	-0.002	0.695
Treg	CD25 on CD39+ resting CD4 regulatory T cell	16.43	0.288	0.004	0.463
Treg	CD3 on CD39+ activated CD4 regulatory T cell	23.71	0.536	0.001	0.699
Treg	CD25++ CD45RA+ CD4 not regulatory T cell %CD4+ T cell	32.76	0.381	-0.001	0.603

Table 2. Reverse MR: Sensitivity analysis.

Panel	Immune traits	Inverse variance weighted		MR-Egger	
		Q	p	Intercept	p
B cell	Plasma blast-plasma cell %B cell	66.63	0.657	0.0003	0.982
Monocyte	HLA DR on CD14+ monocyte	57.79	0.871	-0.004	0.728
Monocyte	HLA DR on CD14+ monocyte	55.64	0.910	-0.002	0.903

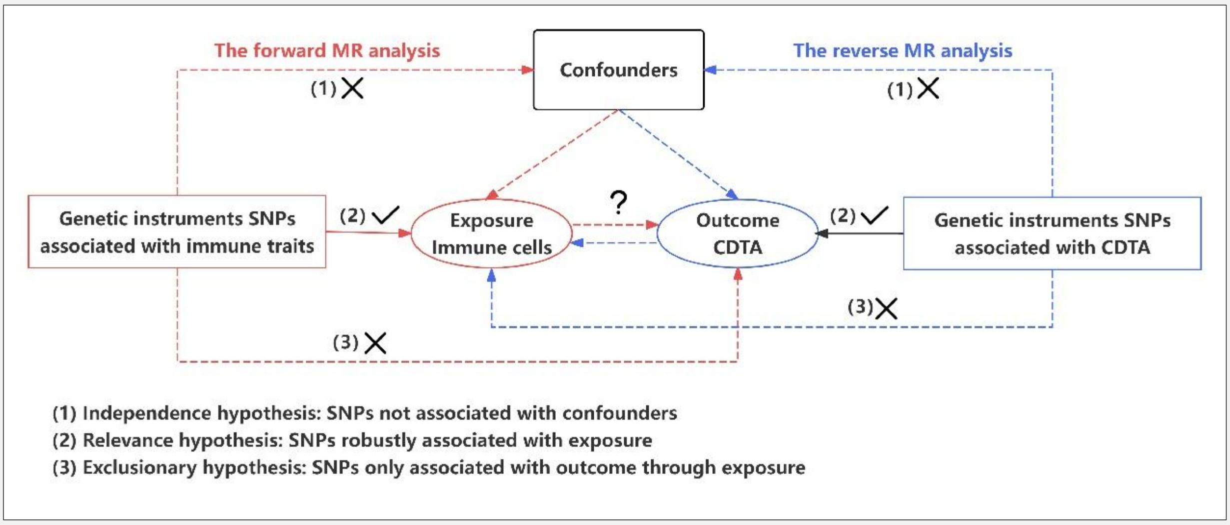
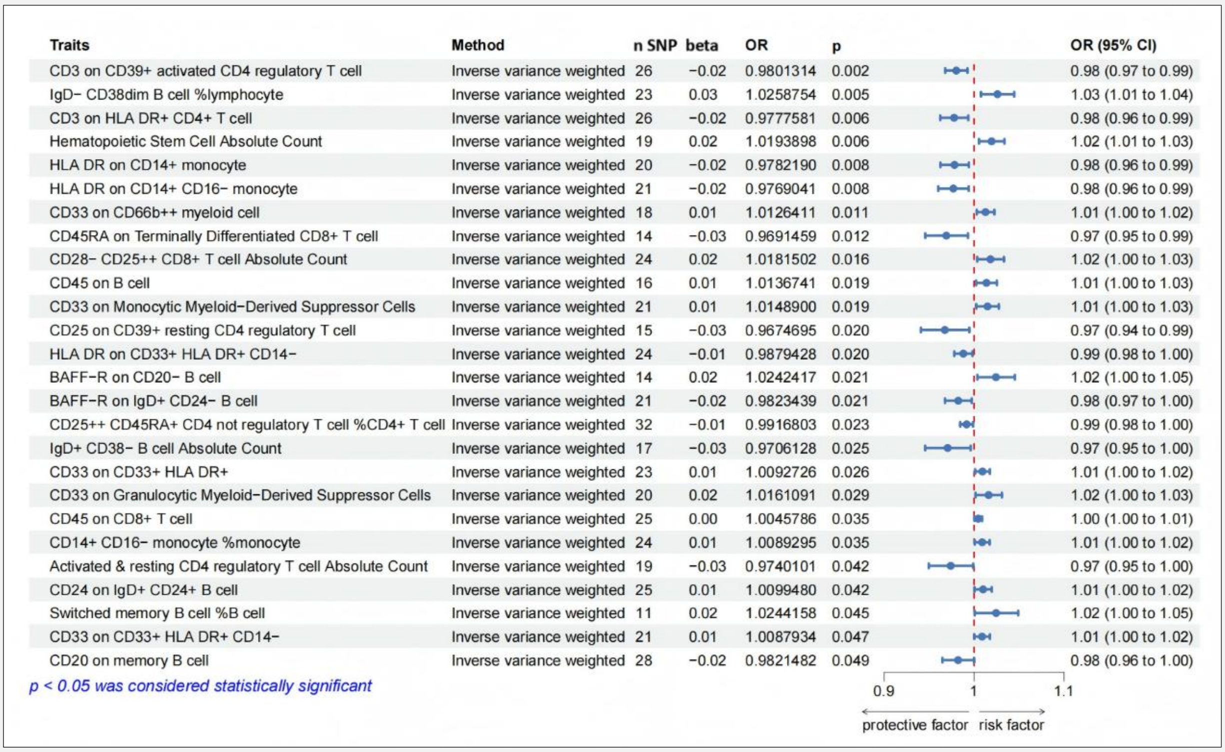


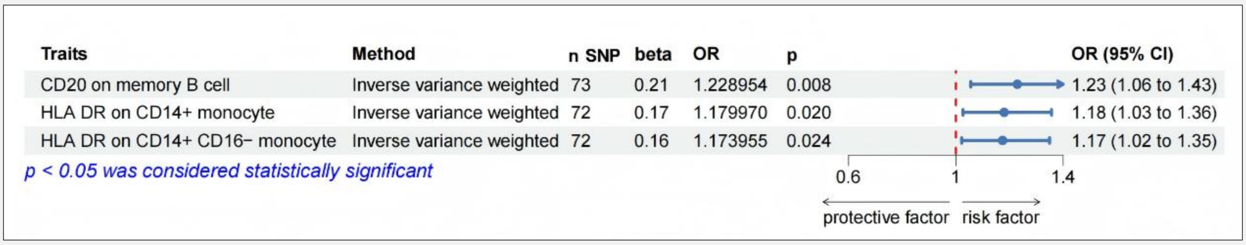
Figure 1. Study design.



Traits	Method	n SNP	beta	OR	p	OR (95% CI)
CD3 on CD39+ activated CD4 regulatory T cell	Inverse variance weighted	26	−0.02	0.9801314	0.002	0.98 (0.97 to 0.99)
IgD− CD38dim B cell %lymphocyte	Inverse variance weighted	23	0.03	1.0258754	0.005	1.03 (1.01 to 1.04)
CD3 on HLA DR+ CD4+ T cell	Inverse variance weighted	26	−0.02	0.9777581	0.006	0.98 (0.96 to 0.99)
Hematopoietic Stem Cell Absolute Count	Inverse variance weighted	19	0.02	1.0193898	0.006	1.02 (1.01 to 1.03)
HLA DR on CD14+ monocyte	Inverse variance weighted	20	−0.02	0.9782190	0.008	0.98 (0.96 to 0.99)
HLA DR on CD14+ CD16− monocyte	Inverse variance weighted	21	−0.02	0.9769041	0.008	0.98 (0.96 to 0.99)
CD33 on CD66b++ myeloid cell	Inverse variance weighted	18	0.01	1.0126411	0.011	1.01 (1.00 to 1.02)
CD45RA on Terminally Differentiated CD8+ T cell	Inverse variance weighted	14	−0.03	0.9691459	0.012	0.97 (0.95 to 0.99)
CD28− CD25++ CD8+ T cell Absolute Count	Inverse variance weighted	24	0.02	1.0181502	0.016	1.02 (1.00 to 1.03)
CD45 on B cell	Inverse variance weighted	16	0.01	1.0136741	0.019	1.01 (1.00 to 1.03)
CD33 on Monocytic Myeloid−Derived Suppressor Cells	Inverse variance weighted	21	0.01	1.0148900	0.019	1.01 (1.00 to 1.03)
CD25 on CD39+ resting CD4 regulatory T cell	Inverse variance weighted	15	−0.03	0.9674695	0.020	0.97 (0.94 to 0.99)
HLA DR on CD33+ HLA DR+ CD14−	Inverse variance weighted	24	−0.01	0.9879428	0.020	0.99 (0.98 to 1.00)
BAFF−R on CD20− B cell	Inverse variance weighted	14	0.02	1.0242417	0.021	1.02 (1.00 to 1.05)
BAFF−R on IgD+ CD24− B cell	Inverse variance weighted	21	−0.02	0.9823439	0.021	0.98 (0.97 to 1.00)
CD25++ CD45RA+ CD4 not regulatory T cell %CD4+ T cell	Inverse variance weighted	32	−0.01	0.9916803	0.023	0.99 (0.98 to 1.00)
IgD+ CD38− B cell Absolute Count	Inverse variance weighted	17	−0.03	0.9706128	0.025	0.97 (0.95 to 1.00)
CD33 on CD33+ HLA DR+	Inverse variance weighted	23	0.01	1.0092726	0.026	1.01 (1.00 to 1.02)
CD33 on Granulocytic Myeloid−Derived Suppressor Cells	Inverse variance weighted	20	0.02	1.0161091	0.029	1.02 (1.00 to 1.03)
CD45 on CD8+ T cell	Inverse variance weighted	25	0.00	1.0045786	0.035	1.00 (1.00 to 1.01)
CD14+ CD16− monocyte %monocyte	Inverse variance weighted	24	0.01	1.0089295	0.035	1.01 (1.00 to 1.02)
Activated & resting CD4 regulatory T cell Absolute Count	Inverse variance weighted	19	−0.03	0.9740101	0.042	0.97 (0.95 to 1.00)
CD24 on IgD+ CD24+ B cell	Inverse variance weighted	25	0.01	1.0099480	0.042	1.01 (1.00 to 1.02)
Switched memory B cell %B cell	Inverse variance weighted	11	0.02	1.0244158	0.045	1.02 (1.00 to 1.05)
CD33 on CD33+ HLA DR+ CD14−	Inverse variance weighted	21	0.01	1.0087934	0.047	1.01 (1.00 to 1.02)
CD20 on memory B cell	Inverse variance weighted	28	−0.02	0.9821482	0.049	0.98 (0.96 to 1.00)

$p < 0.05$ was considered statistically significant

Figure 2. Forward MR: IVW method.



Traits	Method	n SNP	beta	OR	p	OR (95% CI)
CD20 on memory B cell	Inverse variance weighted	73	0.21	1.228954	0.008	1.23 (1.06 to 1.43)
HLA DR on CD14+ monocyte	Inverse variance weighted	72	0.17	1.179970	0.020	1.18 (1.03 to 1.36)
HLA DR on CD14+ CD16− monocyte	Inverse variance weighted	72	0.16	1.173955	0.024	1.17 (1.02 to 1.35)

$p < 0.05$ was considered statistically significant

Figure 3. Reverse MR: IVW method.

2). Leave-one-out analysis and funnel plots verified data reliability (Supplementary Material 2).

DISCUSSION

This bidirectional two-sample MR analysis offers comprehensive insights into the immune system and aids in identifying immune characteristics that may influence the risk of CDTA. The analysis leveraged genetic variants as IVs to substantially mitigate confounding, thereby serving as an essential strategy for addressing prevalent challenges in observational studies [32]. Such insights are invaluable for the development of targeted therapies. Consequently, this investigation is well-positioned to facilitate timely advancement of precision medicine strategies for CDTA prophylaxis and treatment.

This bidirectional two-sample MR analysis found 14 immune cell traits that were positively associated with CDTA (OR > 1, $p < 0.05$). These findings highlight the critical role of B cells, myeloid cells, and T-cell subsets in driving lymphoid hyperplasia.

In the B-cell panel, elevated IgD-CD38dim B cells and BAFF-R on CD20- B cells were causally linked to CDTA. BAFF-R, a key regulator of B-cell survival and maturation, may promote hyperplasia by sustaining autoreactive B-cells in inflamed tissues [6]. This aligns with a previous study that showed children with severe AH exhibit increased CD27+ naive B-cells in the tonsils, indicative of impaired differentiation rather than proliferation [33]. Similarly, the positive association of switched memory B-cell %B cell with CDTA suggests chronic antigen exposure drives repeated B-cell activation, a hallmark of hypertrophy in pediatric obstructive sleep apnea [33]. Myeloid cell traits, particularly CD33 expression on granulocytic/monocytic myeloid-derived suppressor cells (MDSCs), also showed strong positive associations with CDTA. CD33 is a sialic acid-binding receptor implicated in amplifying pro-inflammatory myeloid cell responses [34]. Enhanced activation of myeloid cells is involved in severe AH, reflected in elevated CD64+ monocyte levels [34]. Previous studies have reported a positive correlation between bone marrow-derived immune phenotypes (e.g., hematopoietic stem cell absolute counts) and OSAS [35], suggesting that bone marrow-derived immune cells may play a role in pediatric upper airway lymphoid hyperplasia.

Some findings (e.g. the positive association between absolute counts of CD28- CD25++ CD8+ T cells with CDTA) cannot be explained by published evidence. These may represent unique immune regulatory networks in pediatric CDTA, although their specific mechanisms require elucidation through integration with single-cell sequencing technologies. Other findings, such as the negative associations between CD45 expression in B cells and CD8+ T cells with CDTA require further validation. In particular, a previous study reported that the CD45 participates in asthma pathogenesis via regulation of lymphocyte activation [36].

Nine immune cell traits demonstrated protective effects against CDTA (OR < 1, $p < 0.05$), potentially disrupting pathways in hypertrophy. The negative associations between IgD+ CD38- B-cell absolute counts and BAFF-R on IgD+ CD24- B cells with CDTA suggest disturbances in transitional B-cell homeostasis. Prior work identified diminished IgA+ plasmablasts in hypertrophic tonsils, reflecting defective mucosal B-cell maturation [33]. Notably, our MR results extend these observations by implicating BAFF-R dysregulation in this process, a novel mechanistic insight. Similarly, the negative association between CD45RA on terminally differentiated CD8+ T cells with CDTA aligns with evidence that chronic inflammation depletes naive T-cell reserves, as seen in AH with recurrent infections [37]. For Treg subsets, the negative associations between activated & resting CD4 regulatory T-cell counts and CD25 on CD39+ resting Tregs with CDTA indicate compromised immune tolerance. A previous study found that children with AH exhibit Th17/Treg imbalance, favoring pro-inflammatory responses [37]. The specific role of CD39+ Tregs in this context has not been previously reported, highlighting the novelty of our findings. In contrast, the negative association between HLA DR on CD33+ HLA DR+ CD14- cells with CDTA contradicts earlier reports of HLA DR upregulation in myeloid cell activation [34]. This discrepancy may reflect tissue-specific differences, as systemic HLA DR levels may be negatively associated with myeloid cell exhaustion in chronic hypertrophy.

A previous study reported a significant increase in naive B cells (CD27- CD21+) and a relative reduction in memory B cells (CD27+) in patients with TH, with this aberration linked to defects in the local immune microenvironment [33]. Reduced expression of CD20, a maturation marker for B cells, may reflect impaired memory B cell function, potentially leading to insufficient antibody secretion or abnormal antigen presentation. Such defects could render children more susceptible to recurrent upper respiratory tract infections, thereby inducing adenoidal/tonsillar hypertrophy through chronic inflammation [38].

HLA-DR CD14+ and CD14+ CD16- monocytes may reduce chronic infection risk by enhancing antigen-presenting capacity and anti-pathogen responses. One study showed that HLA-DR on CD14+ CD16- monocytes exert protective effects against juvenile idiopathic arthritis (OR = 0.63 - 0.88) [13]. Similar mechanisms might lower the risk of adenoidal/tonsillar hypertrophy by suppressing excessive inflammatory responses. Furthermore, as a classic monocyte subset, high HLA-DR expression on CD14+ CD16- monocytes correlates with efficient phagocytic clearance of pathogens [39], potentially reducing lymphoid hyperplasia caused by persistent local tissue infections [3].

Another study showed significantly elevated HLA-DR density on intermediate monocytes (CD14++ CD16+) in inflammatory states, which positively correlated with plasma sCD163 levels. This suggests that inflammation-driven monocyte activation may exacerbate local immune responses through a positive feedback loop [40]. The chronic inflammatory microenvironment in patients with adenoidal/tonsillar hypertrophy may potentially upregulate HLA-DR expression on monocytes via cytokines (e.g., IFN-γ, IL-6).

This exploratory study provides novel evidence on the causal relationships between immune cell traits and CDTA. A wide range of immune cell traits that might play a role in the pathogenesis of CDTA were examined, thereby establishing a foundation for future research; however, this study was associated with some initiations. Forward causal assessments employed lenient thresholds to maximize detection of immune cell-CDTA relationships, potentially compromising specificity but enabling broader exploration. The MR methodology utilized summary-level SNP datasets from GWAS repositories. The aggregate nature of these data resources, devoid of individual participant data, may account for variances between certain findings and prior studies. Despite this, the substantial genetic heterogeneity captured in the analysis provides a framework for examining population-level immune determinants of CDTA pathogenesis. The applicability of this study's findings to populations beyond European ancestry is questionable due to its reliance on a European database, potentially restricting the generalizability of our results. To assess heterogeneity and horizontal pleiotropy, we employed Cochran's Q test and Egger's intercept. While statistically non-significant, these analyses cannot completely rule out residual heterogeneity or pleiotropy in a clinical setting. A significant constraint of the two-sample MR approach is its difficulty in managing multiple exposures, especially correlations among them, which can bias causal estimates. Exploring alternative analytical methods is thus warranted. Ultimately, robust clinical conclusions demand validation via comprehensive clinical trials. Hence, to clarify the association of specific immune cell traits with childhood adenotonsillar hypertrophy and their mechanistic pathways, broader GWAS databases coupled with either methodological refinements or experimental validation are required.

CONCLUSION

In summary, this investigation established evidence for a causal link between specific immune cell traits and CDTA, uncovering multifaceted immune cell trait-CDTA interactions and evidencing profound immunological entanglement. These results identify novel investigative pathways regarding immunological contributions to CDTA etiology that may inform the design of immunotherapies targeting these disorders. This work motivates deeper examination of disease-specific immune microenvironments. Subsequent investigations should focus on validating the causal associations and uncovering the underlying biological mechanisms.

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Declaration of Interest:
The authors declare no competing interests.

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