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The Impact of Immune Cells, Metabolites, Inflammatory Factors, and Circulating Proteins on Atopic Dermatitis: Insights from a Mendelian Randomization Study

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Background: The onset of atopic dermatitis (AD) is complex, and its specific pathological mechanisms have not yet been fully elucidated.

Methods: Using circulating multi-omics as the exposure factors and AD as the outcome, we conducted univariable MR analysis. The circulating multi-omics data included immunomics (731 immune cell types), proteomics (4907 plasma proteins), metabolomics (1400 metabolites and 486 additional metabolites), and 91 inflammatory factors. MR analysis was conducted using IVW, WM, Simple Mode, Weighted Mode, and MR-Egger methods, with IVW as the primary analysis tool. To address horizontal pleiotropy, we utilized MR-Egger intercept tests and MR-PRESSO for correction, alongside the Cochrane Q statistic for heterogeneity assessment. Sensitivity analysis was performed using a leave-one-out strategy. To control for false positives due to multiple testing, we set a standard of a 5% false discovery rate. Additionally, we conducted F-statistics on the included SNPs to eliminate the impact of weak instrumental variables.

Results: IL-18R1 on AD (OR = 1.12, 95% CI: 1.08–1.17, $P_{FDR} < 0.01$). Mannonate levels on AD (OR = 0.88, 95% CI: 0.83–0.94, $P_{FDR} = 0.03$). Retinol (Vitamin A) to linoleoyl-arachidonoyl-glycerol (18:2 to 20:4) on AD (OR = 1.12, 95% CI: 1.06–1.18, *P*FDR = 0.03). HVEM on CM CD4+ cells on AD (OR = 0.81, 95% CI: 0.75–0.88, $P_{FDR} < 0.01$). CR2 on AD (OR = 0.81, 95% CI: 0.72–0.90, $P_{FDR} = 0.04$). MANSC1 on AD (OR = 0.87, 95% CI: 0.81–0.93, $P_{FDR} = 0.04$). IL18R1 (4097 inflammatory markers) on AD (OR = 1.11, 95% CI: 1.06–1.17, $P_{FDR} = 0.01$). HNRNPAB on AD (OR = 1.44, 95% CI: 1.23–1.70, $P_{FDR} < 0.01$).

Conclusion: This study further explored the correlations between multi-omics data and AD. We identified seven previously unreported circulating substances with causal relationships to AD, filling a current theoretical gap.

Keywords: multi-omics, immunomics, metabolomics, proteomics, Mendelian randomization, atopic dermatitis

Background

Atopic dermatitis (AD), a chronic and relapsing immune-related skin disease, is marked by persistent itching, dryness, and erythema.[1] It affects over 15% of children and approximately 10% of adults worldwide.[2,3] Environment, Genetics, stress, and the immune system are considered factors related to the onset of AD, while skin barrier dysfunction and immune dysregulation are regarded as key pathological factors in AD.[4] The treatment of AD includes topical and systemic therapies, biologics, phototherapy, and supportive care.[5] Due to individual patient differences, not all achieve satisfactory clinical outcomes. Specifically, corticosteroids can alleviate itching and rashes by inhibiting antigen processing in immune cells and reducing the production of inflammatory factors. As a result, they are currently used as first-line treatment for AD in clinical practice. However, long-term use of corticosteroids and other immunosuppressants can lead to side effects such as skin atrophy, wrinkles, and thinning, which can limit their efficacy.[6] Calcineurin inhibitors like tacrolimus and pimecrolimus serve as second-line treatments for AD and help avoid the side effects associated with long-term glucocorticoid use. Nevertheless, their drawbacks include systemic absorption, which can cause gastrointestinal side

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effects, headaches, and unsuitability for prolonged use.[7] Medications such as mycophenolate mofetil, cyclosporine, and methotrexate are typically used for moderate to severe AD that is unresponsive to conventional treatments. These drugs can potentially cause liver and kidney damage, which requires close monitoring.[8] Despite research into the mechanisms and treatment of AD, its periodic relapse nature and multiple triggering factors continue to challenge the long-term stability of patient conditions. Particularly in the development of more precise personalized treatment plans and the identification of specific biomarkers, many issues remain unresolved. Hence, further exploration of specific diagnostic and therapeutic factors for AD is of notable clinical and research importance.

There are complex interactions between the immune system and the skin barrier, and since inflammation, lipids, and metabolism are all related to the occurrence and development of AD, the understanding that AD is a systemic disease has gained further support.[9] In reality, abnormalities in the skin barrier can be broadly classified into three aspects: structural defects of the skin barrier, abnormal skin lipid metabolism, and functional abnormalities of the skin barrier. Elucidated aspects include filaggrin deficiency impairing the stratum corneum structure in AD patients,[10] and abnormalities in ceramides and free fatty acids leading to imbalances in epidermal barrier permeability.[11,12] Nonetheless, numerous detailed biological processes are still not fully understood. Additionally, there is well-documented evidence regarding the relationship between the immune system and AD. The imbalance among helper T cells 1(Th1), helper T cells (Th2), and regulatory T cells (Treg cells) triggers immune responses and IgE-mediated hypersensitivity, both of which exacerbate the progression of AD.[13] However, no study has comprehensively elucidated the correlation between human immune cells and AD. Traditional randomized controlled trials (RCTs) are unable to design protocols that sufficiently meet the requirements for exploring the detailed mechanisms of circulating substances and AD. Similarly, basic research is limited by compensatory mechanisms and confounding influence, making it difficult to uncover how various immune, metabolic, and lipid substances interact with AD. Thus, identifying suitable methods to comprehensively supplement the potential evidence and key targets of AD is a direction worth exploring.

Mendelian randomization (MR) is a methodological approach used to assess causal relationships by exploiting the natural random allocation of genotypes. MR employs genetic variations to evaluate the effect of a risk factor, aiming to determine if this exposure contributes to the development of a specific disease.[14] Due to the natural random distribution of alleles being unaffected by gender, age, disease, social status, and other factors, MR can effectively mitigate biases from confounding factors and reverse causation more efficiently than traditional RCTs and observational studies.[15] Multi-omics refers to the method of integrating various omics data (such as genomics, transcriptomics, proteomics, metabolomics, etc) for comprehensive analysis. It can reveal complex mechanisms within specific disease areas through comprehensive and systematic research. Multi-omics technology has been widely applied in the fields of cardiovascular diseases, metabolic diseases, cancer, and more. In the field of AD, nearly 30 studies have reported correlations between different exposure factors and AD to date.[16] Research involving the causal relationships between AD and omics, including gut microbiota and lipidomics, has already been reported.[17,18] To further supplement the evidence on AD, our study integrates information on circulating substances related to metabolomics, immunomics, proteomics, and inflammatory markers. The correlation between above circulating multi-omics data and AD has not been reported so far, making this study significant in filling the current evidence gap and providing more insights for further exploration of AD.

Materials and Methods

Study Design

This study employed univariate MR analysis to explore the causal connection between circulating multi-omics and AD. Circulating multi-omics encompasses a variety of components, including 731 immune cells, 91 inflammation markers, 4907 plasma proteins, 486 metabolites (released in 2014), and 1400 circulating metabolites (made public in 2023). The MR analysis framework utilized here rests on three pivotal premises:[19] firstly, there's a notable link between the instrumental variables (IVs) and circulating multi-omics; secondly, these IVs maintain no association with any confounders that might influence the relationship between circulating multi-omics and AD; and thirdly, the impact of IVs on AD is mediated exclusively through multi-omics. The data for this study were obtained from publicly accessible databases with no associated costs, and informed consent was not applicable to this study. This study involves human

data, which have been ethically reviewed by the Sichuan Taikang Hospital Ethics Committee, with the ethical approval number being SCTK-IRB-2024-046.

Circular Multi-Omics and Atopic Dermatitis Data Sources

Table 1 shows the data sources for the study's exposures and outcomes. Data on inflammatory proteins was derived from an extensive Genome-Wide Association Study (GWAS) published in August 2023, which provided details on 91 inflammatory proteins across 11 cohorts, involving a total of 14,824 participants with European ancestry.[20] For each immune trait, the GWAS Catalog offers summary statistics, bearing accession numbers from GCST0001391 to GCST0002121.[21,22] The data cover a wide array of immune cell types, such as B cells, CDCs, mature T cells, monocytes, myeloid cells, and TBNK cells. The GWAS summary data for 486 metabolites were obtained from a large-scale study conducted by Shin et al in 2014,[23] comprising 309 identified metabolites and 177 metabolites whose identities remain undisclosed. These 309 metabolites are meticulously categorized into eight distinct biochemical groups: lipids, compounds associated with energy metabolism, nucleotides, peptides, amino acids, cofactors and vitamins and carbohydrates.[24] From the Canadian Longitudinal Study on Aging (CLSA) cohort, we have obtained data encompassing 1400 metabolic markers. This dataset comprises 1091 individual metabolites and 309 ratios, collected from a group of 8299 participants.[25] The GWAS data for plasma proteins was sourced from a study published by Egil Ferkingstad et al in 2021.[26] This GWAS includes information on 4907 protein quantitative trait loci (pQTL) from 35,559 Icelandic individuals. To reduce biases introduced by using MR across different populations, the AD used in this study comes from the Finnish database, which represents a European population.[27] The GWAS summary data includes 15,208 cases of AD and 367,046 controls. The data can be downloaded from the following link: gs://finngen-public-data-r10/summary_stats/finngen_R10_L12_ATOPIC.gz.

Table 1 Summary of Circulating Multi-Omics Data and Atopic Dermatitis Sources

Circulating Multi-omics Data					
Traits	**Data Sources**	**Publishing Years**	**Descriptions**		**Population**
486 human serum metabolites	Shin et al	2014	Peptides, Nucleotides, Amino acids, Energy, Co-factors, Vitamins, Lipids, Carbohydrates.		European
1400 human serum metabolites	Yiheng Chen et al	2023	1091 blood metabolites and 309 metabolite ratios		Canadian CLSA Cohort
731 circulating immune cells	Valeria Orrù et al	2020	Absolute cell counts for 118 traits, median fluorescence intensity of surface antigen levels for 389 traits, morphological parameters for 32 traits, and relative cell counts for 192 traits		European
91 Circulating inflammatory proteins	Jing Hua Zhao et al	2023	91 plasma proteins associated with inflammation		European
4907 Plasma proteins	Egil Ferkingstad et al	2021	Genome-wide association study analyzed the plasma protein levels of 4907 protein quantitative trait loci (pQTL) in a cohort of 35,559 individuals.		European
Atopic Dermatitis					
Traits	Cases	Controls	Sample size	Dataset	Population
Atopic Dermatitis	152,08	367,046	382,254	FinnGen ID: L12_ATOPIC	European

Selection of IVs

The significance threshold for associations between IVs and 91 inflammatory markers was established with a *p*-value under 5 ×.10−6[28] Similarly, the criteria for significant associations between IVs and 731 types of immune cells were set with a *p*-value below 5 ×.10−6[29] The selection benchmarks for 486 and 1400 metabolites IVs were both positioned at 1 ×.10−5 [24,30] The selection criterion for IVs of 4907 plasma protein pQTLs was *p*-value below 5×.10–8[31] To enhance the accuracy of these IVs and reduce the effects of linkage disequilibrium (LD), the clumping method was utilized, employing the setting `clump=TRUE`. Furthermore, the threshold for LD was fixed at r^2=0.001, with the extent of the clumping window set to kb=10000. In scenarios where r^2 is 1, this indicates a condition of complete linkage disequilibrium, showing that SNPs are inherited collectively. The kb metric specifies the genomic length considered in LD assessments. As SNPs that are closely located on a chromosome are more likely to be inherited together, the parameters r^2=0.001 and kb=10000[32] were chosen to address such linkage possibilities and enhance the integrity of our findings. To minimize the risk of skewed outcomes stemming from frail IVs, we computed the F-statistic for each SNP and discarded those with values under 10, securing stability and reliability in our findings.[33]

MR Analysis

In our research, we utilized a suite of methods including the Inverse Variance Weighted (IVW), Weighted Median (WM), Simple Mode, Weighted Mode, and the Mendelian Randomization Egger (MR-Egger) techniques, with IVW positioned as the foundational tool for analysis. The IVW method is particularly beneficial for processing large datasets, delivering straightforward and precise estimates under the condition that all genetic variants function as effective IVs. This implies a direct association with circular multi-omics without being influenced by external variables. Nonetheless, in scenarios where certain IVs deviate from MR principles, for example, influencing outcomes via pathways not related to circular multi-omics, IVW's reliability might be compromised, leading to potential bias. On the other hand, the WM approach offers more robust estimates when faced with pleiotropic IVs, providing a layer of reliability absent in IVW.[34] Additionally, the MR-Egger method supplements our analytical arsenal, offering a mechanism to detect directional pleiotropy through its regression intercept,[35] thus illuminating possible biases in MR findings and enhancing the overall understanding of the data.

Sensitivity Analysis

In the exploration of horizontal pleiotropy's effects, our research deployed the MR-Egger intercept test to systematically address such biases. We tackled horizontal pleiotropy by implementing corrections through MR-PRESSO and meticulously evaluating outliers that might distort our findings.[36,37] To identify heterogeneity within our dataset, the Cochrane Q statistic was applied. Our investigation's integrity was further bolstered by conducting a sensitivity analysis, utilizing a leave-one-out strategy to determine the impact of single instrumental variables on the overall causal conclusions. The analysis quantified the causal association for a dichotomous outcome, detailing regression coefficients, odds ratios, and their 95% confidence intervals for comprehensive understanding. In an effort to control for potential errors stemming from multiple testing, we adhered to a 5% false discovery rate (FDR) criterion. The primary analytical tool used was the TwoSampleMR package within the R version 4.3.1 software environment. For access to all R packages, one can contact the corresponding author.

Results

MR results

This study identified several circulating substances that exhibit significant causal relationships with AD through MR analysis, following FDR correction. Among 91 inflammation markers, IL-18R1 was identified as a risk factor for AD, with an OR of 1.12 (95% CI: 1.08–1.17, $P_{FDR} < 0.01$). Additionally, when analyzing 4097 circulating plasma proteins, IL-18R1 again exhibited a significant risk association with AD, with an OR of 1.11 (95% CI: 1.06–1.17, $P_{FDR} = 0.01$). HNRNPAB emerged as a strong risk factor (OR = 1.44, 95% CI: 1.23–1.70, $P_{FDR} < 0.01$), while CR2 (OR = 0.81, 95% CI: 0.72–0.90, $P_{FDR} = 0.04$) and MANSC1 (OR = 0.87, 95% CI: 0.81–0.93, $P_{FDR} = 0.04$) were identified as protective

factors. From a pool of 1400 circulating metabolites, two were found to have significant associations with AD: Mannonate levels were identified as a protective factor (OR = 0.88, 95% CI: 0.83–0.94, P_{FDR} = 0.03). The ratio of Retinol (Vitamin A) to linoleoyl-arachidonoyl-glycerol (18:2 to 20:4) was identified as a risk factor (OR = 1.12, 95% CI: 1.06–1.18, P_{FDR} = 0.03). In the analysis of 731 immune cell phenotype, HVEM on CM $CD4^+$ cells was found to be a significant protective factor for AD (OR = 0.81, 95% CI: 0.75–0.88, $P_{FDR} < 0.01$). Table 2 shows the MR IVW FDR results. Figure 1 presents an intuitive summary of the MR analysis results for the seven substances found to have causal relationships with AD. Additional circulating multi-omics data that did not show significant causal relationships with AD are provided in Supplementary Table 1 for reference.

F-Values of SNPs

Table 3 presents the F-statistics of the SNPs for the exposure data. As shown in the table, all SNPs in this study have F-statistics greater than 10, indicating high instrument strength. This suggests that the study's conclusions are less likely to be biased by weak IVs. More detailed information on SNPs is provided in Supplementary table 2.

MR Sensitivity, Pleiotropy, and Heterogeneity Results

The sensitivity results show that all SNPs of the seven circulating substances did not cross the null line after leave-one-out analysis, indicating a very low potential bias in this study. Sensitivity results can be found in Supplementary Figure 1. Horizontal pleiotropy was assessed using the MR-Egger test. Supplementary table 3 summarizes all results, showing that none of the seven circulating substances exhibited horizontal pleiotropy ($p > 0.05$). This further supports the reliability of the study findings. Heterogeneity was assessed using the Cochrane Q statistic. In fact, heterogeneity is permissible in MR studies because different SNPs may influence the same outcome variable through different biological pathways. The heterogeneity test results for this study can be found in Supplementary table 4. No outliers were detected for IL-18R1 (91 inflammation), IL-18R1 (4907 protein), HNRNPAB, MANSC1, mannonate levels, and the ratio of retinol (Vitamin A) to linoleoyl-arachidonoyl-glycerol (18:2 to 20:4) during the MR analysis. After removing outliers, CR2 and HVEM on CM CD4 remained significantly associated with AD ($P < 0.05$). Detailed information can be found in Supplementary table 5. The funnel plot indicates that the IVs in this study are symmetrically distributed. The funnel plot and scatter plot are provided in Supplementary Figure 2.

Discussion

This study comprehensively explores the potential causal relationships between circulating multi-omics substances such as plasma proteins, immune cells, metabolites, and inflammatory factors on AD based on MR analysis. Previous studies have reported the relationships between the gut microbiome, lipidomics, and AD, and therefore, these were not repeated in this study. In total, three circulating substances were found to be positively associated with AD, while four were negatively associated. Interestingly, IL-18R1 appeared as a risk factor for AD in both the inflammatory factor dataset and the circulating proteomics dataset, affirming the credibility of our results and highlighting IL-18R1's potential role in AD. CR2 and MANSC1 were identified as protective factors against AD, which has not been previously reported.

Table 2 MR Circulating Multi-Omics Data IVW Results

Exposures	Method	OR	95% CI	β	SE	P_{FDR}
IL-18R1 (91 inflammatory markers)	Inverse variance weighted	1.12	1.08~1.17	0.116	0.021	<0.01
Mannonate levels (1400 circulating metabolites)		0.88	0.83~0.94	−0.127	0.031	0.03
Retinol (Vitamin A) to linoleoyl-arachidonoyl-glycerol (18:2 to 20:4) ratio		1.12	1.06~1.18	0.109	0.027	0.03
HVEM on CM CD4+ (731 immune cells)		0.81	0.75~0.88	−0.207	0.041	<0.01
IL18R1 (4907 plasma proteins)		1.11	1.06~1.17	0.108	0.025	0.01
CR2 (4907 plasma proteins)		0.81	0.72~0.90	−0.215	0.056	0.04
HNRNPAB (4907 plasma proteins)		1.44	1.23~1.70	0.368	0.082	<0.01
MANSC1 (4907 plasma proteins)		0.87	0.81~0.93	−0.138	0.035	0.04

Analysis	Method	N SNPs	OR (95% CI)	P value
Mannonate levels (1,400 circulating metabolites)				
	MR Egger	22	0.98 (0.87 , 1.11)	0.780
	Weighted median	22	0.85 (0.77 , 0.93)	0.010
	Inverse variance weighted	22	0.88 (0.83 , 0.94)	0.010
	Simple mode	22	0.89 (0.75 , 1.05)	0.170
	Weighted mode	22	0.85 (0.77 , 0.94)	0.010
Retinol (Vitamin A) to linoleoyl arachidonoyl glycerol ratio				
	MR Egger	26	1.13 (1.02 , 1.26)	0.030
	Weighted median	26	1.12 (1.04 , 1.20)	0.010
	Inverse variance weighted	26	1.12 (1.06 , 1.08)	0.010
	Simple mode	26	1.19 (1.06 , 1.34)	0.010
	Weighted mode	26	1.13 (1.06 , 1.21)	0.010
HVEM on CM CD4+ (731 immune cells)				
	MR Egger	3	1.53 (0.80 , 2.92)	0.420
	Weighted median	3	0.83 (0.77 , 0.91)	0.010
	Inverse variance weighted	3	0.81 (0.75 , 0.88)	0.010
	Simple mode	3	0.85 (0.76 , 0.94)	0.090
	Weighted mode	3	0.84 (0.76 , 0.93)	0.070
IL-18R1 (91 inflammatory markers)				
	MR Egger	22	1.11 (1.04 , 1.19)	0.010
	Weighted median	22	1.14 (1.08 , 1.20)	0.010
	Inverse variance weighted	22	1.12 (1.08 , 1.17)	0.010
	Simple mode	22	1.06 (0.95 , 1.18)	0.310
	Weighted mode	22	1.12 (1.07 , 1.17)	0.010
IL18R1 (4907 plasma proteins)				
	MR Egger	20	1.11 (1.03 , 1.19)	0.010
	Weighted median	20	1.14 (1.08 , 1.20)	0.010
	Inverse variance weighted	20	1.11 (1.06 , 1.17)	0.010
	Simple mode	20	1.05 (0.94 , 1.18)	0.410
	Weighted mode	20	1.12 (1.08 , 1.18)	0.010
CR2 (4907 plasma proteins)				
	MR Egger	31	0.75 (0.57 , 0.98)	0.040
	Weighted median	31	0.86 (0.77 , 0.96)	0.010
	Inverse variance weighted	31	0.81 (0.72 , 0.90)	0.010
	Simple mode	31	0.92 (0.74 , 1.14)	0.470
	Weighted mode	31	0.88 (0.73 , 1.06)	0.170
HNRNPAB (4907 plasma proteins)				
	MR Egger	6	1.51 (1.01 , 2.25)	0.110
	Weighted median	6	1.40 (1.16 , 1.70)	0.010
	Inverse variance weighted	6	1.44 (1.23 , 1.70)	0.010
	Simple mode	6	1.43 (1.09 , 1.87)	0.040
	Weighted mode	6	1.40 (1.14 , 1.73)	0.020
MANSC1 (4907 plasma proteins)				
	MR Egger	18	0.93 (0.83 , 1.03)	0.190
	Weighted median	18	0.89 (0.81 , 0.97)	0.010
	Inverse variance weighted	18	0.87 (0.41 , 0.93)	0.010
	Simple mode	18	0.87 (0.73 , 1.04)	0.150
	Weighted mode	18	0.89 (0.81 , 0.98)	0.020

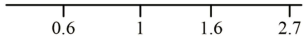

Figure 1 MR results for 7 cyclic substances with potential causal links to AD. **Figure 1** Shows the MR results for seven circulating substances with potential causal relationships with AD. IVW is used as the primary reference result. Among these substances, four exhibit protective effects, while three are identified as risk factors. IL18R1, derived from different circulating databases, shows consistent results across all sources.

Mannonate levels is a protective factor, while the Retinol (Vitamin A) to linoleoyl-arachidonoyl-glycerol (18:2 to 20:4) ratio is a risk factor. Next, we will discuss the significance of these findings.

Interleukin-18 Receptor 1 (IL-18R1) is a cell surface receptor primarily involved in regulating the immune system. When IL-18R1 binds to Interleukin-18 (IL-18), it initiates a series of intracellular signaling pathways, activating immune cells and promoting inflammatory responses.[38,39] The upregulation of IL-18R1 expression, although not directly increasing IL-18 levels, may enhance the efficiency of IL-18 signaling. It is well known that IL-18 is a pro-inflammatory cytokine that can enhance the activity, cytotoxicity, and proliferation of natural killer (NK) cells.[40] NK cells and Keratinocytes are principal producers of antimicrobial peptides (AMPs), which protect the skin from infections

Table 3 F-Values of Circulating Multi-Omics SNPs

Exposure	F-statistics	
	Min	Max
IL-18R1 (91 inflammatory markers)	21.40	797.36
Mannonate levels (1400 circulating metabolites)	19.71	200.24
Retinol (Vitamin A) to linoleoyl-arachidonoyl-glycerol (18:2 to 20:4) ratio	19.53	353.86
HVEM on CM CD4+ (731 immune cells)	22.21	55.24
IL18R1 (4907 plasma proteins)	31.43	3399.96
CR2 (4907 plasma proteins)	29.98	424.13
HNRNPAB (4907 plasma proteins)	30.43	125.25
MANSC1 (4907 plasma proteins)	29.94	755.40

and inflammation by creating a chemically stable barrier.[41] Patients with AD exhibit reduced AMP levels and a greater risk of Staphylococcus aureus infection.[42] A study found that highly activated NK cells are present in patients with AD, and NK cells extracted from lesion sites can produce large amounts of pro-inflammatory cytokines such as interferon-γ.[43] Furthermore, the proportion of NK cells that produce cytokines like IL-5 and IL-13 is notably higher in AD patients compared to healthy individuals.[44] Considering the study's results that IL-18R1 is a risk factor for AD, increased IL-18R1 expression may trigger excessive cytotoxic activity of NK cells, worsening AD symptoms. As previously mentioned, AD is associated with an imbalance between Th1, Th2, and Treg cells.[45,46] The dermis, the deeper layer of skin, actually houses most of the skin's adaptive immune cells. Typically, damage to the epidermal barrier is seen as the initial trigger for AD.[7] One theory suggests that this damage results from the immune system reacting to irritants and allergens.[47] It has been reported that Treg cells in the epidermis can act on B lymphocytes through cytokines, with the differentiation of mature B lymphocytes into plasma cells producing IgE antibodies being strictly regulated by Th2 cells.[48] Recent research shows that IL-18 promotes Th1 responses and can also affect the function of Treg cells in the lungs. Additionally, Treg cells located in the skin express IL-18R1 and require IL-18 signaling to perform their immune functions.[49] Therefore, the IL-18R1/IL-18 signaling axis may be involved in the adaptive immune response within AD dermal cells. A highly worthwhile direction for exploration is to target and investigate whether IL-18R1/IL-18 in AD affects the proportion of different CD4+ T cells (Th1, Th2, and Treg cells) and whether it is related to the IgE immune response in AD. For AD and IL-18R1, the solid evidence comes from an MR report. This study discovered that the levels of IL-18R1 in the bloodstream can mediate the development of AD induced by dyslipidemia, indicating that the occurrence of AD due to dyslipidemia might be linked to IL-18R1.[50] In this study, IL-18R1 identified from various GWAS datasets was also found to be a risk factor for AD, consistent with previous finding. Given the existing evidence, it is reasonable to define IL-18R1 as a new risk factor for AD. However, the correlation between IL-18R1 and abnormal skin lipid metabolism still requires further investigation.

Heterogeneous nuclear ribonucleoprotein A/B (HNRNPAB) functions as an RNA-binding molecule integral to RNA metabolism and biological activities. Recent studies have focused on the role of HNRNPAB in various tumor carcinogenesis processes.[51,52] However, the earliest research on this molecule was more focused on autoimmune diseases. Back in 1996, scientists found that the HNRNPAB protein gets targeted by autoantibodies in patients with mixed connective tissue disease (MCTD), systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) because of its structure, leading to immune reactions.[53] Toll-like receptors (TLRs) are a category of pattern recognition receptors that detect specific molecular motifs of pathogens including bacteria, viruses, and fungi, thus activating immune responses. The autoimmune response induced by HNRNPAB is believed to occur through its nucleic acids binding to TLR7 and TLR9, thereby mediating antigenic properties.[54] A MR study has established a connection between AD and autoimmune diseases like RA,[55] but the exact mechanisms remain unclear. In fact, excessive activation of TLRs in the pathogenesis of AD can exacerbate T lymphocyte-mediated autoimmunity, triggering AD. Langerhans cells, a special type of dendritic cell in the skin epidermis, can exacerbate AD by producing pro-inflammatory cytokines and chemokines through TLR2

and TLR7.[56] Although there is currently no direct evidence proving the correlation between HNRNPAB and AD, there is a potential link between HNRNPAB-driven autoimmunity through TLR7 binding and AD.

Among 4907 plasma proteins, two protective factors for AD were observed. Complement receptor 2 (CR2), also known as CD21, is a receptor expressed on the surface of B cells and some epithelial cells. It primarily participates in the complement system, promoting B cell activation and antibody production. Downregulation or deficiency of CD21 on B cells has been observed in several immune system diseases, such as SLE and RA.[57] In the context of AD, a lower percentage of CD21-expressing cells in the peripheral blood of patients has been noted,[58] aligning with this study's result that there is a negative correlation between CD21 and AD. Motif at N terminus with seven cysteine (MANSC) is a novel domain characterized by a well-conserved set of seven cysteine residues. This domain is found at the N-terminus of membrane and extracellular proteins, including low-density lipoprotein receptor-related protein 11 (LRP-11) and hepatocyte growth factor activator inhibitor 1.[59] LRP-11 is a membrane protein involved in lipid metabolism.[60] Although lipid metabolism impacts the skin barrier function in patients with AD, there is currently no direct evidence linking the MANSC1 to AD. This study is the first to define and report the potential roles of CR2 and MANSC1 in AD through MR method, providing enlightening insights.

Four different potential circulating biomarkers for AD, including IL-18R1, HNRNPAB, CR2, and MANSC1, were revealed through GWAS data of inflammatory factors and plasma circulating proteins. The identification of these biomarkers provides new tools for laboratory research. High-throughput sequencing and proteomics analyses enable laboratories to more accurately detect changes in the levels of these markers, thereby enhancing the understanding of the biological basis of AD. Furthermore, measuring the levels of IL-18R1, HNRNPAB, CR2, and MANSC1 in patients' plasma may help in the early identification of high-risk individuals for AD and support early intervention measures, such as anti-inflammatory treatments targeting the IL-18R1 pathway.

Herpesvirus Entry Mediator (HVEM) is a transmembrane protein that belongs to the tumor necrosis factor receptor superfamily. HVEM is expressed on various immune cells, including T cells, B cells, and NK cells.[61] It interacts with ligands such as BTLA and LIGHT to regulate multiple immune responses.[62] Study has indicated that HVEM may have diagnostic significance for immunological conditions, including AD.[63] The upregulation of LIGHT is believed to be associated with AD, with HVEM being highly expressed in keratinocytes from skin samples of AD patients.[64] It has been established that LIGHT-induced expression and competitive binding to HVEM are essential for the development of experimental AD and are directly related to keratinocyte proliferation and the production of periostin.[65] In circulating immune cells, HVEM on CM CD4+ was found to have a correlation with AD in this study. The term "HVEM on CM CD4+" indicates the expression of HVEM on Central Memory CD4+ T cells. The LIGHT-HVEM signaling acting on keratinocytes is a widely reported pathogenic mechanism in AD. However, the exact role of immune cells in this process remains unclear. This study identified that Central Memory CD4+ T cells may be involved. Nevertheless, only three SNPs were deemed suitable for the MR analysis after screening. While this meets the minimum criterion for MR analysis, such a limited number of SNPs may not adequately represent the genetic underpinnings of the exposure variable, limiting the result's broader applicability and representativeness. Hence, further observation is necessary to validate this finding.

Mannonate levels and the retinol (vitamin A) to linoleoyl-arachidonoyl-glycerol (18:2 to 20:4) ratio are two substances defined in metabolomics as having a causal relationship with AD. Mannonate is a type of aldonic acid and an oxidation product of mannose, which can be produced through oxidation processes in the body. Currently, research on Mannonate in humans is relatively limited, with some evidence linking Mannonate to type 2 diabetes and neurodegenerative diseases.[66,67] Retinol, retinal, and retinoic acid are forms of vitamin A present in human body. Vitamin A is deemed critical for supporting immune function and maintaining skin health.[68] Current evidence suggests that vitamin A is related to AD in several ways. Firstly, vitamin A promotes the expression of FOXP3, a signature transcription factor of Treg cells, thereby influencing Treg cell function. Secondly, vitamin A inhibits the release of mediators from eosinophils and mast cells, effectively reducing inflammatory reactions and allergic.[69] Lastly, vitamin A generally tends to promote Th2-type immune responses while inhibiting Th1-type responses. A deficiency in vitamin A results in an increase in Th1 cells and the release of interferon-γ,[70] thus worsening AD symptoms. The deficiency of retinoic acid promotes an increase in Th2-associated interferon-γ and leads to elevated production of IgE antibodies,[71] which, as

previously mentioned, are directly related to the immune response in AD. Among the three forms of vitamin A, retinol is the primary circulating form in the blood. The absence of retinol has been distinctly noted to worsen AD.[72] A study in India also reported decreased retinol levels in AD patients, suggesting that it could serve as a diagnostic marker for AD.[73] Research on mice showed that when retinol metabolism and absorption pathways are activated, the skin's mucosal barrier gets stronger, and certain anti-AD bacteria in the cecum become more abundant.[74] Despite these findings, the exact details of how retinol metabolism works are still not fully understood. Linoleoyl-arachidonoyl-glycerol (LAG) is part of triglyceride metabolism, composed of linoleic acid and arachidonic acid, which can form esterified forms of these two fatty acids in the human body. On the one hand, serum linoleic acid levels are elevated in children with AD,[75] and intestinal linoleic acid levels are associated with the severity of AD in infants.[76] On the other hand, Arachidonic acid is considered clinically significant in allergy sensitization and improvement in allergic manifestations during infant immune development.[77] Increased levels of arachidonic acid-related metabolites have been observed in the urine of AD patients.[78] Therefore, combining the above evidence and the findings of this study, the balance between vitamin A metabolism and fatty acid metabolism may be a potential direction for further research into the metabolic pathways of AD. Although studies support linoleic acid and arachidonic acid as biomarkers for AD, the specific metabolic and mechanistic roles of linoleic and arachidonic acids in AD remain unknown and warrant further exploration. For clinical applications, focusing on the dietary structure of AD patients may be beneficial for disease control. Further optimizing the intake levels or ratios of mannonate, retinol (Vitamin A), and LAG may improve the management and prevention of AD.

Conclusions

This study presents seven significant new findings that enhance our understanding of AD and offer potential avenues for practical applications. One promising area for further exploration is the pathological mechanisms of IL-18R1, which could serve as a potential target for AD diagnostics or therapeutic interventions. Additionally, IL-18R1, CR2, MANSC1, and HNRNPAB show promise in personalized medicine and precision therapy for AD. HVEM on CM CD4+ cells acts as a protective factor against AD, presenting a new therapeutic angle for immune modulation. Developing pharmacological agents that modulate HVEM-LIGHT interactions may become an essential strategy for symptom relief in AD. Our study also identifies mannonate, retinol (Vitamin A), and LAG as metabolites influential in AD, highlighting the potential role of diet in managing the disease. Therefore, the development of targeted nutritional supplements, dietary guideline adjustments, and personalized nutritional strategies for AD patients represents a promising field of research and application.

Advantages and Limitations

This study is notable for comprehensively analyzing the correlation between several circulating multi-omics data and AD through MR research. Extensive data analysis helps fill the current gaps in AD theories. The MR method employed and the selected IVs adhered to the strictest current methodologies. Additionally, only positive results with FDR-adjusted p-values were reported, avoiding the false discovery rate due to multiple testing. However, the study has some limitations. Firstly, it assumes the exposure factors (such as 4907 plasma proteins) have a lifelong effect on the outcome AD, which may introduce bias due to changes in exposure duration and intensity in real-world scenarios. Additionally, since the study only reports results with FDR-adjusted p-values, some potentially significant findings might have been overlooked.

Abbreviations

MR, Mendelian randomization; OR, odds ratio; CI, confidence interval; SE, standard error; FDR, false discovery rate; IVs, Instrumental variables; Min, Minimum; Max, Maximum; AD, atopic dermatitis; Th1, helper T cells 1; Th2, helper T cells 2; Treg, regulatory T cells; RCTs, Traditional randomized controlled trials; GWAS, Genome-Wide Association Study; CLSA, Canadian Longitudinal Study on Aging; pQTL, protein quantitative trait loci; LD, linkage disequilibrium; SNPs, single nucleotide polymorphisms; IVW, Inverse Variance Weighted; WM, Weighted Median; MR-Egger, Mendelian Randomization Egger; IL-18R1, Interleukin-18 Receptor 1; IL-18, Interleukin-18; HNRNPAB, Heterogeneous nuclear ribonucleoprotein A/B; TLRs, Toll-like receptors; CR2, Complement receptor 2; MANSC,

Motif at N terminus with seven cysteine; LRP-11, low-density lipoprotein receptor-related protein 11; HVEM, Herpesvirus Entry Mediator; AMPs, antimicrobial peptides (; NK, natural killer cells; MCTD, mixed connective tissue disease; SLE, systemic lupus erythematosus; RA, rheumatoid arthritis.

Data Sharing Statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Ethical Approval

This study does not involve human or animal subjects. All data sources are from publicly accessible databases, hence not applicable.

Author Contributions

All authors made a significant contribution to the work reported, whether in the conception, study design, execution, acquisition of data, analysis and interpretation, or all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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