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ORIGINAL RESEARCH

The Causal Relationship Between Circulating Metabolites and the Risk of Atopic Dermatitis: A Two-Sample Mendelian Randomization Study

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Background: Previous research has shown that metabolites (especially lipid-related metabolites) have a significant influence in the development of atopic dermatitis (AD). However, there is no evidence of a causal connection between metabolites and AD risk. The specific mechanisms require further elucidation. Our study employed a two-sample Mendelian randomization (TSMR) strategy to investigate how metabolite traits affect AD.

Methods: Utilizing publicly accessible GWAS data, we conducted TSMR studies to investigate the relationship between 233 metabolites traits (213 lipid-related traits and 20 no lipid-related traits) and AD. Our TSMR study primarily employed the Inverse-variance weighted method and four ancillary methods to analyze causation. Sensitivity analysis was performed to guarantee the TSMR results were trustworthy. Reverse MR analysis was used for investigating reverse causality.

Results: After analyzing GWAS datasets for metabolites and AD, 13 metabolites were identified as positive. The MR analysis result indicates that total cholesterol in very small VLDL, cholesterol esters in very small VLDL, free cholesterol in IDL, concentration of medium LDL particles, concentration of large LDL particle, concentration of chylomicrons and extremely large VLDL particles, triglyceride levels in chylomicrons and extremely large VLDL, total lipid levels in chylomicrons and extremely large VLD, phospholipid levels in chylomicrons and extremely large VLDL, phospholipids in medium LDL, phospholipids in large LDL, phospholipids in small LDL, ratio of 18:2 linoleic acid to total fatty acids exhibited negative effects on AD. Reverse MR result analysis found that ratio of 18:2 linoleic acid to total fatty acids in serum was decreased in patients with AD. Sensitivity analyses ensure the stability of our results.

Conclusion: These findings highlight a definite correlation between metabolite and AD, demonstrating the significant role of 13 lipid-related metabolite traits. Our results significantly reduced the influence of unavoidable confounders and reverse causality. Our findings may set the framework for prospective therapeutic approaches and call for further investigation to validate them.

Keywords: Mendelian randomization, causal connection, atopic dermatitis, metabolite, lipid

Introduction

Atopic dermatitis (AD) is a common, inflammatory skin disease condition with a predominant type 2 immune response.[1] The global prevalence of AD is estimated at 2. 62%, affecting approximately 204.05 million people. It impacts approximately 101.27 million adults and 102.78 million children globally, with prevalence rates of 1.95% and 3.96%, respectively.[2] AD also imposes a significant financial burden on individuals and their families.[3] Therefore, it is vital to understand the causes of AD.

Metabolites are the downstream products of genes and proteins that reflect the current state of an individual.[4] Notably, previous studies have identified possible metabolite changes and influences in patients or models of AD.[5,6] In particular, the relationship between serum lipid-related metabolites and AD has recently received significant attention. Kim et al showed that serum triglyceride (TG) and total cholesterol (TC) levels were significantly elevated in children with AD,

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and that the SCORing Atopic Dermatitis (SCORAD) index had significant associations with high levels of TG and TC, and a low level of HDL-C.[7] There is evidence that dyslipidemia is linked to altered adaptive immunological responses of Th2 cells and the occurrence of allergy disorders.[8] Furthermore, obese children and adults have a much higher risk of developing AD.[9,10] Studying metabolites related with the development of AD not only aids in the early detection and prevention of the condition, but also provides insights into the molecular mechanisms underlying disease therapy. However, while these investigations have found a link between metabolites and AD, the causal association between lipid metabolites and AD is uncertain. And these studies have only examined a limited selection of metabolites and are constrained by inherent biases in traditional epidemiological research, such as possible confounders, small sample sizes, and reverse causality.

Mendelian randomization (MR) is an emerging epidemiological approach that utilizes genetic variations as instrumental variables (IVs) to make causal inferences about exposures and outcomes.[11] Compared to traditional observational research, it has the advantage of reducing factors that cause confusion and reverse causality, resulting in solid causal relationships.[12] Our study meticulously collected the most recent genome-wide association studies (GWAS) data on 233 metabolite traits (mainly lipid, fatty acid, and lipoprotein parameters) and AD in individuals of European descent. Using summary statistics data from GWAS described above, We conducted a thorough two-sample MR analysis (TSMR) to investigate the relationship between 233 metabolite traits and AD. Our research offers a novel perspective and theoretical framework for the prevention and therapy of AD.

Materials and Methods

The Assumptions of MR

The research basis for TSMR stems from the following three key assumptions:[1,13] The selected Single nucleotide polymorphisms (SNPs) must exhibit a robust and significant association with the variable of exposure, ensuring its efficacy as IVs.[2] The IVs should be uncorrelated with confounding factors that simultaneously influence the exposure and the outcome, maintaining the assumption of independence from confounders.[3] The influence of the IVs on the outcome should be mediated exclusively through the exposure in question, with no alternative pathways affecting the outcome, adhering to the exclusion restriction criterion.[14]

Data Source

The exposure GWAS dataset included 233 metabolite traits, including 213 lipid-related traits (including lipid, lipoprotein parameters or fatty acids) and 20 non-lipid-related traits (including amino acids, gluconeogenesis/glycolysis, ketone bodies, fluid balance and inflammation-related metabolites) updated in March 2024. After variant filtering and quality control, a total of 136, 016 samples from up to 33 cohorts (27 European cohorts) were included in the Metabolite GWAS study.[15] Through the NHGRI-EBI GWAS catalogue (GCST90301941–GCST90302173), complete GWAS summary statistics are accessible to the public viewers.

SNPs of AD have been identified in the most comprehensive GWAS meta-analysis undertaken by the EArly Genetics & Lifecourse Epidemiology (EAGLE) eczema consortium, which included 21399 cases (diagnosed by doctors and self-reported) and 95464 controls of European source.[16] We can find specific information in GWAS catalogue GCST003184.

Instrumental Variables (IVs)

Single nucleotide polymorphisms (SNPs) were utilized as IVs in this study to ascertain the causal relationships between distinct metabolite traits and the risk of AD. For screening IVs, the following criteria were established:[1] For each metabolite traits assessed, SNPs that exhibited significant associations at a rigorous threshold of $P < 5\times10^{-8}$ were selected.[2] SNPs exhibiting linkage disequilibrium (LD) were excluded (r^2<0. 001within10000kb), to ensure the independence of IVs.[3] Through the LDtrait database (https://ldlink.nih.gov/?tab=ldtrait), SNPs associated with confounders or outcomes were thoroughly evaluated from positive results (allergic rhinitis, asthma, C-reactive protein). Additionally, palindromic variants were deleted and omitted.[4] In order to mitigate the impact of weak instrument bias on causal

inference, the strength of the IVs was calculated using the formula F = b2 exposure/SE2 exposure, and IVs with F < 10 were excluded.[17]

Statistical Analysis

The principle design of the whole study is shown in Figure 1. We performed a bidirectional analysis and used five different methods to examine the causal connection between 233 metabolite traits and AD. The Inverse-variance weighted (IVW) method was used as our main MR analysis method. IVW method, which assume no horizontal pleiotropy across all SNPs, is based on a detailed examination of Wald ratios for all genetic variations.[18] We also used the MR-Egger, weighted median, weighted mode, and simple mode as complementary analysis methods. In addition, if the results of forward MR analysis were positive, we performed reverse MR analysis to determine the direction of causality.

To bolster the validity of this findings, several sensitivity analyses were conducted. Heterogeneity of IVs was assessed using Cochran's Q test. MR-Egger regression intercept analysis and MR-PRESSO global test were utilized to assess the impact of horizontal pleiotropy. The leave-one-out analysis was used to ensure data robustness. Finally, we performed an additional steiger test to ensure that exposure was the most directionally responsible for the results.

The analyses were accomplished using R version 4. 3. 1, utilizing the "TwoSampleMR" and "MRPRESSO" software packages.

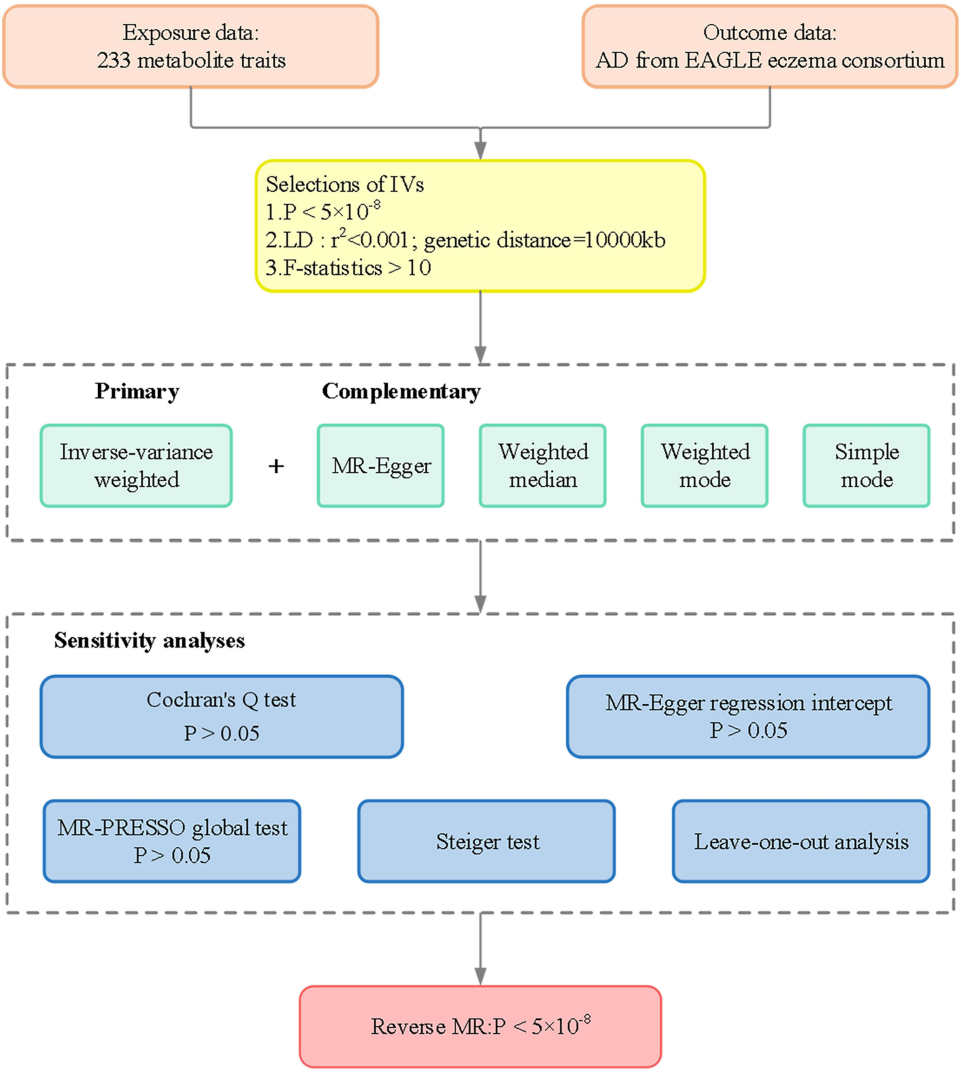

Figure 1 The flow chart of the study. The whole workflow of MR analysis.

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Results

Instrumental Variables Selection

As a result of searching from https://ldlink.nih.gov/?tab=ldtrait, deleting SNPS associated with confounders, Supplementary Table 1 contained 10655 SNPS for further MR analysis. Supplementary Table 2 lists SNPs that have been eliminated and confounded. Since the F-statistics of all instrumental SNPs were larger than 10, it was clear that the IVs were powerful enough. The results of all MR analysis and sensitivity analysis results are detailed in Figure 2 and Supplementary Table 3.

In the end, a substantial relationship between 233 metabolite traits and AD was judged confident if it matched the following strict criteria:[1] IVW methods showed a significant relationship ($P < 0.05$) (Supplementary Table 4).[2] The five MR approaches (IVW, MR-Egger, weighted median, weighted mode, and simple mode) showed consistent direction.[3] All IVs achieved a standard of F>10 and each metabolite trait contains at least 3 IVs.[4] There was no significant heterogeneity among IVs (Cochran's Q test $P > 0.05$).[5] There was no evidence of horizontal pleiotropy (MR-Egger regression intercept $P > 0.05$ and MR-PRESSO global test P >0.05).[6] MR analysis result was not affected by a single IV in leave-one-out analyses.[7] The Steiger test findings showed no inverse causal relationship.

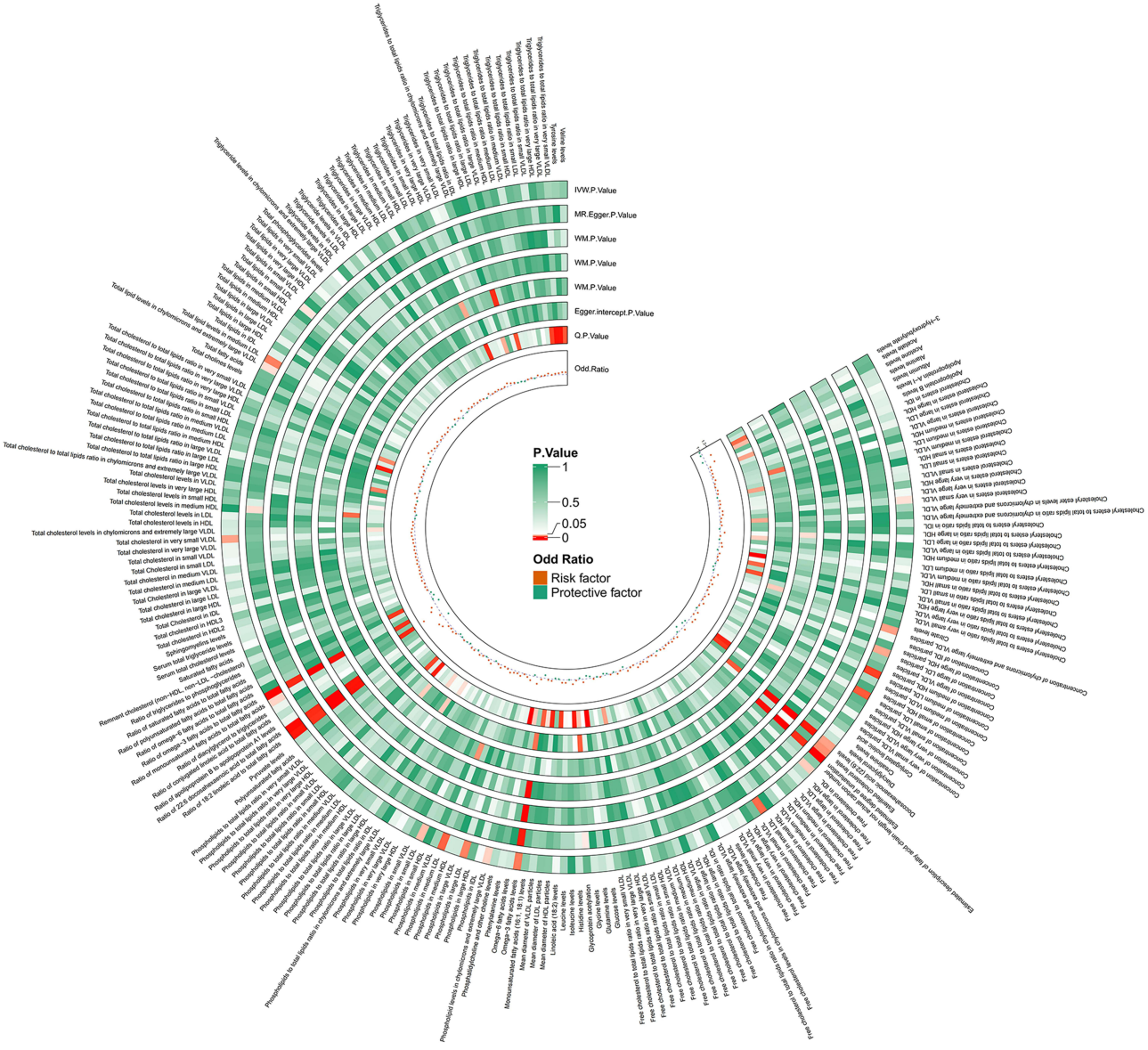

Figure 2 Results of all MR analysis and sensitivity analyses result between 233 metabolite traits and AD.

Two-Sample MR Analysis

After analyzing GWAS datasets for metabolites and AD, 13 metabolites were identified as positive by the IVW methods and had a consistent direction across four methods.

Specifically, the MR estimates indicated that total cholesterol in very small VLDL (OR = 1.130, 95% CI = 1.014–1.260, P = 0.026), cholesterol esters in very small VLDL (OR = 1.118, 95% CI = 1.004–1.245, P = 0.042), concentration of medium LDL particles (OR = 1.138, 95% CI = 1.039–1.246, P = 0.005), total lipid levels in chylomicrons and extremely large VLDL (OR = 1.179, 95% CI = 1.006–1.380, P = 0.041), concentration of chylomicrons and extremely large VLDL particles (OR = 1.194, 95% CI = 1.022–1.395, P = 0.025), phospholipid levels in chylomicrons and extremely large VLDL (OR = 1.179, 95% CI = 1.009–1.378, P = 0. 038), triglyceride levels in chylomicrons and extremely large VLDL (OR = 1.181, 95% CI = 1.000–1.394, P = 0. 050), phospholipids in medium LDL (OR = 1.134, 95% CI = 1.029–1.250, P = 0.012), free cholesterol in IDL (OR = 1.100, 95% CI = 1.006–1.203, P = 0.037), ratio of 18:2 linoleic acid to total fatty acids (OR = 1.311, 95% CI = 1.117–1.538, P = 0.001), concentration of large LDL particles (OR = 1.112, 95% CI = 1.012–1.223, P = 0.028), phospholipids in large LDL (OR = 1.122, 95% CI = 1.020–1.235, P = 0.018), phospholipids in small LDL (OR = 1.108, 95% CI = 1.008–1.219, P = 0.033) were associated with an increased risk of developing AD (Figure 3 and Supplementary Table 5).

Reverse MR Analysis

To fully investigate the direction of causality, we conducted a reverse MR study with AD as the exposure and 13 positive metabolite traits as the outcome. Using a P value of <0.05 for IVW as a threshold, we found that ratio of 18:2 linoleic acid to total fatty acids in serum were decreased in patients with AD (Supplementary Table 6).

Sensitivity Analysis

Our study was robust, as demonstrated by heterogeneity and horizontal pleiotropy analyses. Cochran's Q test (P > 0.05) found no significant heterogeneity among the IVs. Furthermore, no horizontal pleiotropy was detected in the MR-Egger regression intercept analysis (P > 0.05), while no significant exceptions were discovered in the MR-PRESSO global test (P > 0.05). The leave-one-out analysis supported these findings (Figure 4). Last but not least, the steiger test findings showed no inverse causal relationship between the previously indicated metabolite traits and AD (Supplementary Tables 7–11).

Discussion

This TSMR analysis is the first to establish a causal connection between 233 metabolites and AD utilizing a European genetic database. We utilize rigorous screening methods in our MR analysis, which can yield reliable results. Notably, following a thorough sensitivity analysis, our findings indicate that thirteen metabolite traits are causally related with AD when probed using genetic variants. All of the above metabolite traits are risk factors for AD. Total cholesterol in very small VLDL, cholesterol esters in very small VLDL, free cholesterol in IDL, concentration of medium LDL particles, concentration of large LDL particle, concentration of chylomicrons and extremely large VLDL particles, triglyceride levels in chylomicrons and extremely large VLDL, total lipid levels in chylomicrons and extremely large VLD, phospholipid levels in chylomicrons and extremely large VLDL, phospholipids in medium LDL, phospholipids in large LDL, phospholipids in small LDL, ratio of 18:2 linoleic acid to total fatty acids exhibited negative effects on AD. It is worth noting that all of the above positive results were lipid-associated traits, and none of the non-lipid-associated traits demonstrated a reliable effect on AD. This phenomenon is partly indicative of the strong association of lipids with AD and partly related to the low number of non-lipid traits in this GWAS database.

Serum lipid-related metabolites, such as triglycerides, cholesterol, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol, are crucial for signal transduction, cellular structure, material transport and energy metabolism.[19] Dyslipidemia is frequently observed in human with obesity, and many obese individuals also have lipid metabolism disorders. TC, TG and non-HDL-C levels were significantly higher in the obese population than in the non-obese population, while HDL levels were lower than in the non-obese population.[20] Obesity (especially abdominal obesity) is associated with an increased risk of cardiovascular-related diseases due to the presence of atherogenic dyslipidaemia.[21] Chylomicrons are principally responsible for transporting dietary fat. Chylomicrons do not directly

Oucome	Exposure	Method	nsnp	OR(95%CI)	*pval*
Atopic dermatitis	Total cholesterol in very small VLDL	Inverse variance weighted	61	1.130(1.014 to 1.260)	0.026
		MR Egger	61	1.045(0.871 to 1.253)	0.638
		Weighted median	61	1.129(0.976 to 1.306)	0.103
		Simple mode	61	1.292(0.962 to 1.735)	0.094
		Weighted mode	61	1.098(0.948 to 1.271)	0.219
Atopic dermatitis	Cholesterol esters in very small VLDL	Inverse variance weighted	55	1.118(1.004 to 1.245)	0.042
		MR Egger	55	1.083(0.904 to 1.298)	0.390
		Weighted median	55	1.115(0.952 to 1.307)	0.177
		Simple mode	55	1.227(0.919 to 1.637)	0.171
		Weighted mode	55	1.096(0.938 to 1.280)	0.253
Atopic dermatitis	Concentration of medium LDL particles	Inverse variance weighted	68	1.138(1.039 to 1.246)	0.005
		MR Egger	68	1.088(0.950 to 1.247)	0.226
		Weighted median	68	1.117(0.976 to 1.279)	0.107
		Simple mode	68	1.038(0.798 to 1.350)	0.781
		Weighted mode	68	1.090(0.953 to 1.247)	0.215
Atopic dermatitis	Total lipid levels in chylomicrons and extremely large VLDL	Inverse variance weighted	40	1.179(1.006 to 1.380)	0.041
		MR Egger	40	1.023(0.756 to 1.384)	0.886
		Weighted median	40	1.114(0.907 to 1.369)	0.303
		Simple mode	40	1.077(0.771 to 1.503)	0.666
		Weighted mode	40	1.077(0.869 to 1.334)	0.502
Atopic dermatitis	Concentration of chylomicrons and extremely large VLDL particles	Inverse variance weighted	41	1.194(1.022 to 1.395)	0.025
		MR Egger	41	1.078(0.796 to 1.460)	0.630
		Weighted median	41	1.117(0.914 to 1.364)	0.280
		Simple mode	41	1.100(0.790 to 1.531)	0.577
		Weighted mode	41	1.090(0.884 to 1.344)	0.426
Atopic dermatitis	Phospholipid levels in chylomicrons and extremely large VLDL	Inverse variance weighted	40	1.179(1.009 to 1.378)	0.038
		MR Egger	40	1.061(0.785 to 1.433)	0.704
		Weighted median	40	1.113(0.914 to 1.355)	0.287
		Simple mode	40	1.059(0.741 to 1.512)	0.756
		Weighted mode	40	1.078(0.860 to 1.351)	0.520
Atopic dermatitis	Triglyceride levels in chylomicrons and extremely large VLDL	Inverse variance weighted	36	1.181(1.000 to 1.394)	0.050
		MR Egger	36	1.093(0.784 to 1.524)	0.602
		Weighted median	36	1.121(0.913 to 1.376)	0.277
		Simple mode	36	1.120(0.797 to 1.573)	0.518
		Weighted mode	36	1.091(0.874 to 1.361)	0.448
Atopic dermatitis	Phospholipids in medium LDL	Inverse variance weighted	66	1.134(1.029 to 1.250)	0.012
		MR Egger	66	1.061(0.913 to 1.233)	0.444
		Weighted median	66	1.121(0.970 to 1.296)	0.122
		Simple mode	66	1.404(1.058 to 1.864)	0.022
		Weighted mode	66	1.096(0.951 to 1.263)	0.210
Atopic dermatitis	Free cholesterol in IDL	Inverse variance weighted	81	1.100(1.006 to 1.203)	0.037
		MR Egger	81	1.075(0.936 to 1.235)	0.306
		Weighted median	81	1.114(0.964 to 1.287)	0.144
		Simple mode	81	1.103(0.855 to 1.421)	0.453
		Weighted mode	81	1.092(0.953 to 1.251)	0.207
Atopic dermatitis	Ratio of 18:2 linoleic acid to total fatty acids	Inverse variance weighted	28	1.311(1.117 to 1.538)	0.001
		MR Egger	28	1.461(1.159 to 1.840)	0.003
		Weighted median	28	1.594(1.286 to 1.977)	2.16E-05
		Simple mode	28	1.307(0.833 to 2.049)	0.254
		Weighted mode	28	1.471(1.214 to 1.782)	0.001
Atopic dermatitis	Concentration of large LDL particles	Inverse variance weighted	69	1.112(1.012 to 1.223)	0.028
		MR Egger	69	1.088(0.942 to 1.258)	0.256
		Weighted median	69	1.116(0.973 to 1.279)	0.117
		Simple mode	69	1.206(0.939 to 1.551)	0.147
		Weighted mode	69	1.093(0.962 to 1.243)	0.177
Atopic dermatitis	Phospholipids in large LDL	Inverse variance weighted	71	1.122(1.020 to 1.235)	0.018
		MR Egger	71	1.087(0.941 to 1.255)	0.261
		Weighted median	71	1.119(0.976 to 1.283)	0.107
		Simple mode	71	1.068(0.833 to 1.368)	0.606
		Weighted mode	71	1.090(0.967 to 1.228)	0.164
Atopic dermatitis	Phospholipids in small LDL	Inverse variance weighted	67	1.108(1.008 to 1.219)	0.033
		MR Egger	67	1.068(0.922 to 1.236)	0.385
		Weighted median	67	1.131(0.974 to 1.313)	0.108
		Simple mode	67	1.104(0.833 to 1.463)	0.494
		Weighted mode	67	1.065(0.922 to 1.232)	0.394

P<0.05 was considered statistically significant

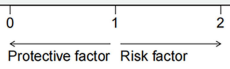

Figure 3 Forest plot showed MR analysis result between positive 13 metabolite traits and AD.

lead to obesity, however their metabolism is abnormal in obese individuals.[22,23] Obesity-related and cardiovascular-related lipid traits accounted for the majority of our positive findings (including LDL-cholesterol, VLDL-cholesterol, IDL-cholesterol, LDL, VLDL, chylomicrons, and triglyceride-related traits). The links between serum lipid-related

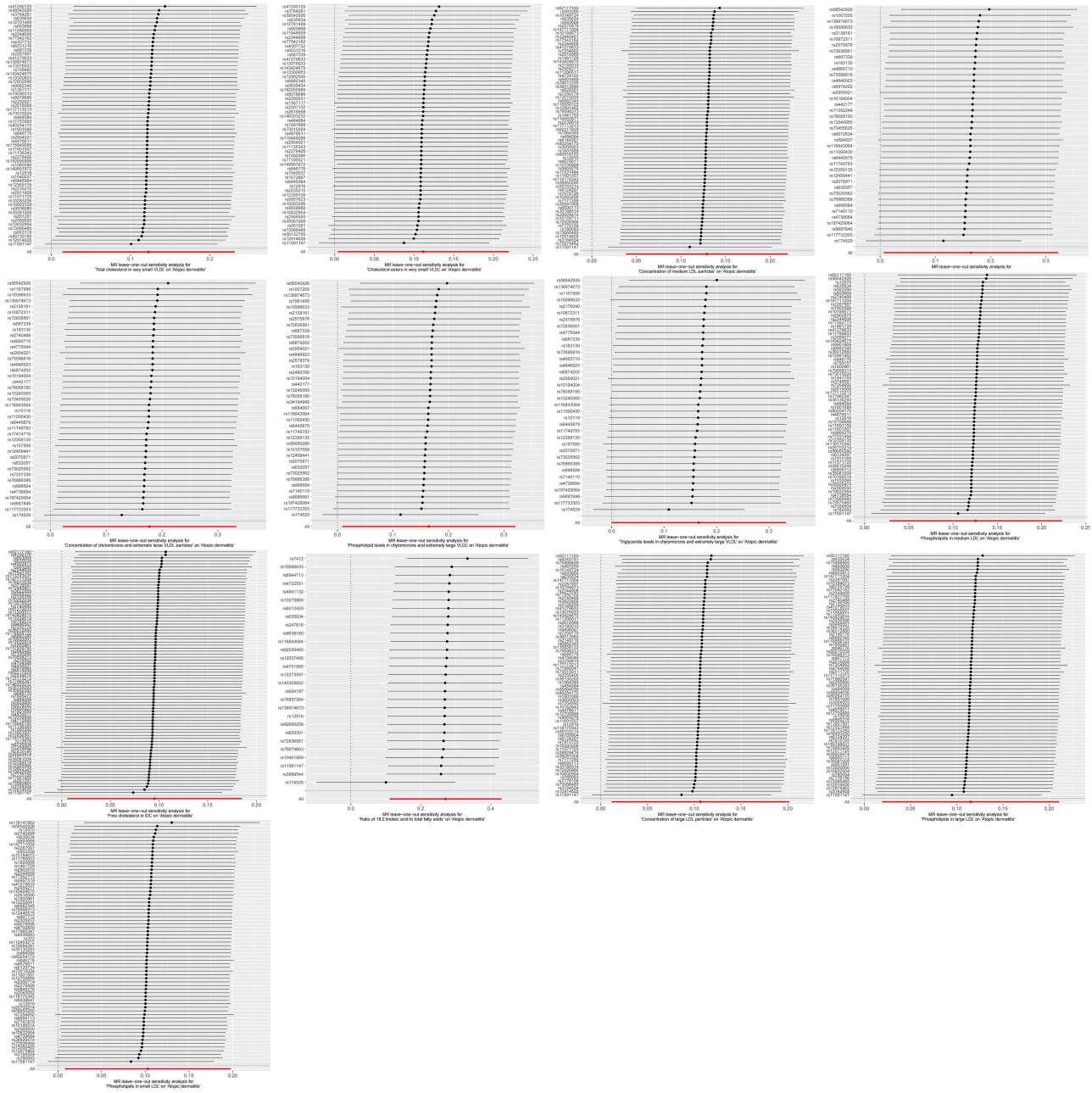

Figure 4 The results of leave-one-out analysis.

metabolites levels, obesity and AD have been erratic, and the underlying mechanism has yet to be identified. According to studies, obese adults and children are more prone to develop AD. Chronic childhood obesity is a risk factor for AD. Weight reduction may be an essential method for preventing and treating AD in children.[10] Cross-sectional studies of obese adults have reached similar conclusions.[24] The majority of current research on the involvement of lipid metabolism in AD has focused on the oxidative stress mechanisms and immune-inflammatory response. AD in both adults and children is associated with heightened oxidative damage and impaired antioxidant defenses. Serum lipid peroxide levels in AD are much greater.[25–27] Cholesterol enhances the production of IgE in AD patients with latex allergy in a dose-dependent manner. Cholesterol exacerbates allergic symptoms by biasing the cytokine pattern towards the TH2 type.[28] In addition, obesity and hyperlipidemia may stimulate pro-inflammatory immunological responses.[29,30] There are studies that hypercholesterolaemia, LDL-triglycerides, VLDL promotes systemic and vascular inflammation.[31–33] A recent

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research found a link between AD and cardiovascular disease,[34] which supports this concept. Obese mice had significantly different immune responses than lean mice; obesity may have transformed the conventional type-2 T helper-predominant illness related to AD into a more serious illness with considerable T helper-17 inflammation.[35] Actually, Th17 might be the most crucial factor in obesity-related AD. This study challenges the Th2-dominant etiology of AD. In summary, it is reasonable to conclude that serum lipids-related metabolites and obesity influence the development of AD. This impact is thought to be linked to lipid-mediated inflammation. These assertions also explain why individuals who have AD are more inclined to comorbid cardiovascular problems.

Circulating phospholipids were recently proposed as indicators and targets for therapy for a variety of conditions. However, previous research on AD has mostly focused on phospholipid alterations in the stratum corneum, but limited is known about circulating phospholipids. Our findings identify four phospholipid-related traits as risk factors for the development of AD. The influence of circulating phospholipids on the development of AD is likely to be associated with an inflammatory response and ferroptosis. Que's study found that oxidized phospholipids had pro-inflammatory and pro-atherosclerotic effects in hypercholesterolemic mice.[36] It is crucial to emphasize the strong connection between phospholipids and ferroptosis. Ferroptosis has been recognised as a non-apoptotic programmed cell death pathway promoted by excess phospholipid peroxidation. The accumulation of large amounts of lipid peroxides is a hallmark of ferroptosis.[37] Recent studies have shown that ferroptosis plays an important role in inflammatory skin diseases. Ferroptosis can affect skin barrier function and differentially exacerbate the inflammatory response through mediators of some ferroptosis regulators (eg ROS, GPX4).[38] Inhibitors of ferroptosis have the potential to mitigate inhibit psoriatic inflammation.[39] Ferroptosis also induces an inflammatory response in allergy-related complications of AD (such as allergic rhinitis, asthma).[40–42] We speculate that the way in which phospholipids affect AD is probably closely linked to ferroptosis. Additionally, Sphingosine-1-phosphate (S1P) is a bioactive lipid mediator that affects immune processes. Serum S1P levels are elevated in AD patients and related to disease severity. S1P receptors (S1PRs) are potential therapeutic targets for several illnesses, including AD.[43] However, Keller discovered that supplementation with milk phospholipids had no positive impact on skin parameters in AD. The SCORAD index and plasma sphingomyelin ratio showed no significant effect as compared to usual whole milk supplementation.[44] The specific role of phospholipids in AD needs to be further investigated.

Linoleic acid is a polyunsaturated fatty acid that belongs to the omega-6 family of fatty acids. The influence of fatty acids on the development of AD was previously controversial. The consumption of omega-6 fatty acids may contribute to the onset of infantile AD.[45,46] Biochemical and immunological alterations in AD were related to a deficiency in the conversion of omega-6 fatty acids (such as linoleic acid and gamma-linolenic acid) to prostaglandin (PG) E1.[47] Another research discovered that a long-chain saturated fatty acid milk diet caused eczema and an increase in intestine type 3 intrinsic lymphoid cells.[48] However, Lee's studies at the mice level have shown that conjugated linoleic acid ameliorates AD by simultaneously inhibiting the TLR4/NFκB and COX-2, 5-LOX signalling pathways.[49] Interestingly, in the above reverse MR results, we found that ratio of 18:2 linoleic acid to total fatty acids in serum was decreased in patients with AD. We speculate that this phenomenon is due to the negative feedback regulation mechanism of the human body. The specific causes and mechanisms need to be further studied.

Our MR studies also help to guide the protective effects of drugs or dietary supplements. The lipid-lowering drug PCSK9 inhibitors are effective and safe in lowering serum LDL-cholesterol levels. Recent studies have found that PCSK9 has a potential protective effect in AD and that this protective effect is related to their anti-inflammatory properties.[50,51] In addition, dupilumab is one of the most often utilized biologics for treating AD. Studies have found that the metabolic profile of AD patients treated with dupilumab changes dramatically, particularly in terms of lipids. The post-treatment group had considerably greater levels of triacylglycerol and phosphatidylcholine.[52] Our results confirm the preceding findings. In the future, researchers may need to investigate the impact of lipid management in lowering the prevalence of AD. More importantly, a high-fat diet has the potential to worsen or trigger AD.[53,54] Our findings are useful for future dietary treatment of AD patients.

This study has several strengths. The effectiveness of the IVs is highly related to the size of the GWAS sample. A larger dataset could boost accuracy.[55] The GWAS dataset we used provided an adequate number of sample sizes. Even with a rigorous criterion of $P < 5\times10^{-8}$, there were still enough IVs to analyze. This improved the dependability of the results. Our study reveals potential clinical implications. Regular lipid profiling for patients

with AD may become a component of future health assessments. Knowledge of the lipid profile of specific patients could provide a reference model for personalised medication. For several metabolites, serum levels indicate tissue aggregation.[56] Thus, our research reflects, at least in part, the involvement of metabolites in tissues like skin. Our MR studies also help to guide the protective effects of drugs or supplements.

However, our research has several limitations. Firstly, the exposed samples originated from a mixed population of predominantly European origin, which could lead to the presence of potential heterogeneity. Secondly, this study is relatively preliminary, and the effect of serum lipid-related metabolites on AD has to be examined further. Clinical cohort studies are required to validate our findings. Thirdly, while our results indicated possible causal associations between specific 13 metabolite traits and AD, future research ought to employ more strict statistical correction procedures, including the False Discovery Rate (FDR) adaptation, to address the problem of multiple testing.

Conclusion

In conclusion, we identified 13 lipid-related metabolite traits with strong putative causal associations with AD. Our findings considerably decreased the effects of unavoidable confounders, reverse causality, and other variables. Our findings might impact AD treatment and offer insights into the processes underlying the disease's onset and development.

Data Sharing Statement

The datasets analyzed in this study are available in the GWAS repository https://www.ebi.ac.uk/gwas/ and https://www.phpc.cam.ac.uk/ceu/lipids-and-metabolites/.

Ethics Approval and Consent to Participate

According to Article 32 of the Measures for Ethical Review of Life Science and Medical Research Involving Human Beings adopted by the National Science and Technology Ethics Committee of the People's Republic of China, ethical review can be exempted because the data used in this study do not cause any harm to human beings, do not involve any sensitive personal information or commercial interests, and the databases selected are open and legal.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in 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

The authors report no conflicts of interest in this work.

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