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ORIGINAL RESEARCH

Causal Effects of Diet on Atopic Dermatitis: A Mendelian Randomization Study Implicating Lipid Pathways and Clinical Implications

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Background: Dietary fat quality and carbohydrate processing shape lipid and lipoprotein profiles involved in skin barrier integrity and cutaneous inflammation relevant to atopic dermatitis (AD). We assessed the causal relevance of dietary patterns and food items to AD and mapped lipid-lipoprotein mediators.

Methods: We conducted a two-sample Mendelian randomization using genome-wide significant instruments for 83 UK Biobank diet traits and 241 serum lipid/lipoprotein measures, with AD cases from FinnGen R10 (European ancestry). Primary analyses used inverse-variance weighted MR with extensive sensitivity analyses, false discovery rate control, reverse MR, and multivariable MR. Mediation was assessed using the product-of-coefficients approach. Instrument strength was adequate (median $F > 10$).

Results: Using two-step Mendelian randomization, we identified specific dietary items with causal effects on AD risk. Notably, a dietary pattern characterized by higher unsaturated fats—exemplified by the protective effect of "other oil-based spreads"—was associated with lower AD risk (OR = 0.56, 95% CI 0.34–0.93, $P = 0.023$). Conversely, a pattern reflecting refined-grain intake, represented by the risk-increasing effect of "brown bread", was associated with higher AD risk (OR = 1.78, 95% CI 1.10–2.89, $P = 0.01$). Mediation analyses mapped the underlying lipid pathways: sphingomyelin SM C20:2 mediated 15.9% of the protective effect of oil-based spreads ($\beta_{\text{mediation}} = -0.09$, $P = 0.003$), and VLDL particle measures mediated 8.9% of the risk associated with brown bread ($\beta_{\text{mediation}} = 0.05$, $P = 0.003$). A complex antagonistic mediation was observed for muesli via phosphatidylcholine PC aa C36:0 (proportion mediated: −13.6%, $P < 0.001$). Reverse MR analyses supported the proposed direction of causality (all $P > 0.05$), and findings were robust across sensitivity analyses.

Conclusion: Dietary patterns high in unsaturated fats, particularly oil-based spreads, appear protective against AD, while refined-grain intake, especially brown bread and black bread, increases AD risk. These effects are mediated through lipid pathways involving sphingomyelins and VLDL metabolism, highlighting modifiable nutritional targets for AD prevention and adjunctive management.

Keywords: atopic dermatitis, diet, fat quality, Mendelian randomization, lipids, mediation analysis

Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin disorder of increasing global prevalence, affecting up to 20% of children and 10% of adults, and represents a major contributor to the global burden of skin diseases.[1,2] It severely impairs quality of life and imposes substantial socioeconomic costs.[3,4] Diet is a key modifiable factor that influences systemic lipid metabolism, which in turn regulates immune responses and skin barrier function.[5,6] However, causal evidence directly linking holistic dietary patterns to AD via lipid intermediates remains limited.[7,8]

Mechanistic studies indicate that obesogenic diets disrupt lipid homeostasis and fuel inflammation.[9,10] Dysregulated lipid metabolism is a hallmark of various inflammatory skin diseases. For instance, elevated sphingolipids in psoriasis[11] and aberrant sebaceous lipid synthesis in rosacea[12] underscore the broader relevance of lipid pathways in cutaneous

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inflammation. Key lipids such as sphingomyelins and free fatty acids—implicated in these conditions—modulate immune activation and barrier integrity,[13] and clinical observations link dyslipidemia to AD severity.[14,15] Nonetheless, prior research has predominantly focused on isolated nutrients (eg., ω-3 fatty acids), overlooking the complex effects of dietary patterns. Furthermore, establishing a causal diet-AD pathway presents a high-dimensional computational challenge, requiring modeling of complex exposure-mediator networks while controlling for confounding.

Mendelian randomization (MR) has emerged as a powerful tool for causal inference by using genetic variants as instrumental variables to mitigate confounding.[16,17] While MR has linked specific lipids (eg., LDL-C, PUFAs) to AD risk,[18,19] a critical gap persists: no study has systematically investigated the broad lipid metabolome as a mediator between dietary patterns and AD. Applying MR to this high-dimensional mediation context also requires robust methods to handle multiple testing and potential biases like horizontal pleiotropy.

To address this gap, we implement a two-step, high-dimensional MR framework. Using genetic instruments for high-fat/high-sugar dietary patterns. Our study aims to causally identify key lipid mediators, moving beyond associations to extract actionable mechanistic insights for AD prevention.

Methods

Study Design

This study adopted a two-step MR framework to investigate how genetically influenced dietary habits affect AD risk through circulating lipid metabolism, using genome-wide association study (GWAS) summary data (Figure 1). In the first step, we evaluated the cause-and-effect link between dietary behaviors (including high-fat and high-sugar intake, and ω-3 fatty acids) and circulating lipids (cholesterol, triglycerides, and lipoprotein components). During the second stage, we evaluated the causal effect of lipid profiles on AD risk and quantified the mediation proportion using the product method. To confirm the validity and independence of the IVs, we employed rigorous genetic screening criteria, including linkage disequilibrium (LD) clumping and F-statistics, which help minimize confounding. Ethical review for this study was formally waived by the Ethics Committee of Shenzhen Hospital (Fu Tian) of Guangzhou University of Chinese Medicine. This decision was based on the use of de-identified, public GWAS summary data and is in accordance with Article 32, Items 1/2 of the "Measures for Ethical Review of Life Science and Medical Research Involving Human Subjects" (2023, China). An official exemption certificate has been provided as Supplementary Material. All original GWASs obtained ethical approval and participant consent in their primary studies.

Data Sources and Variable Definitions

Genetic instruments for 83 dietary habits were derived from the UK Biobank study, with summary statistics via the GWAS Catalog (https://www.ebi.ac.uk/gwas/).[20] Instrumental variables were selected following a standardized procedure, including single-nucleotide polymorphism (SNP) filtering ($P < 5\times10^{-5}$), linkage disequilibrium (LD) pruning ($r^2 < 0.001$ within 10 Mb), data normalization, and bias correction using the TwoSampleMR R package. Circulating lipid profiles, serving as mediator variables, comprised 241 serum lipid markers sourced from the following:

1. Omicscience database: provided 139 lipid species (eg., triglycerides, sphingomyelins) (N = 9,363).[21]
2. Johannes et al: provided 98 lipoprotein subfractions, including Very Low-Density Lipoprotein/Low-Density Lipoprotein (VLDL/LDL) particle size distributions (N = 24,925).[22]
3. Global Lipids Genetics Consortium (GLGC): provided conventional lipid measures, including total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) (N = 1,320,016).[23]

Outcome data for atopic dermatitis were obtained from the IEU Open GWAS platform (ID: ebi-a-GCST90027161), based on the FinnGen R10 cohort. Cases were defined according to ICD-10 code L20 and further verified through dermatologist-reviewed electronic medical records. The total sample size of 796,661 individuals (22,474 cases).

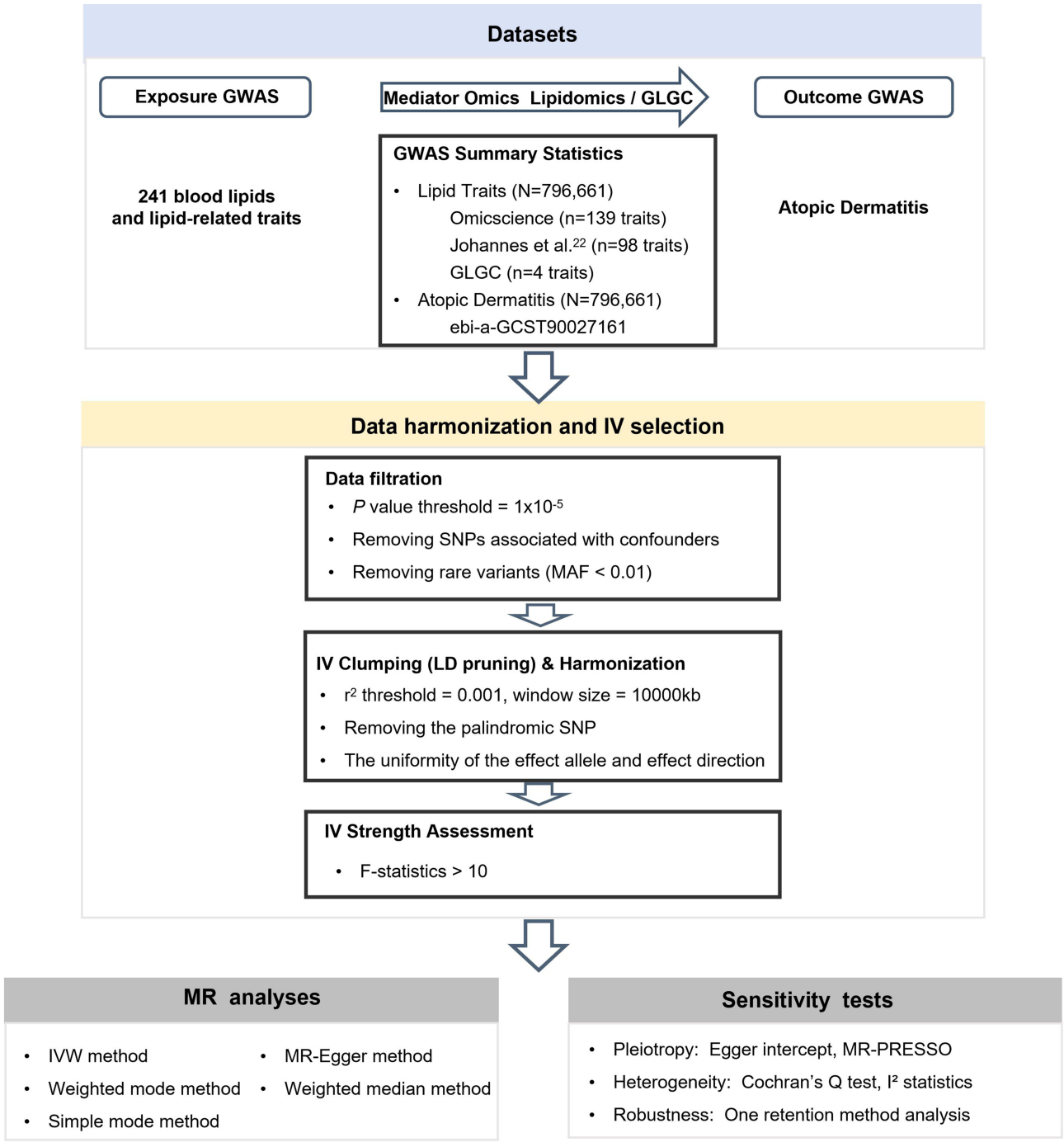

Figure 1 Causal pathway from dietary habits through lipid metabolism to AD risk. Bold text indicates main sections (Datasets, Data harmonization and IV selection, MR analyses, Sensitivity tests) and key methods (IVW method, MR-Egger method, Cochran's Q test).
Abbreviations: GWAS, genome-wide association study; GLGC, Global Lipid Genetics Consortium; IV, instrumental variable; MR, Mendelian randomization.

All datasets were confined to individuals of European ancestry to minimize bias from population stratification. Detailed characteristics of the data sources are provided in Table 1 (accessed March 25, 2025).

Dietary Exposure Assessment

The key exposure variable "Other oil-based spread" was derived from the UK Biobank touchscreen questionnaire item "Spread type" (Field ID 1428; https://biobank.ndph.ox.ac.uk/showcase/field.cgi?id=1428). This variable represents a mutually exclusive category that includes generic, non-branded spreads predominantly composed of vegetable oils

Table 1 Summary of GWAS Sources, Sample Sizes, and Traits for Exposure, Mediator, and Outcome Variables

Type	Data Source	Phenotype	Sample Size	Cases	Population	Unit
Exposure	GWAS CatLog	83 Dietary habit	–	–	European	–
Mediator	Omicscience	139 lipid and lipid-related traits	9,363	–	European	mmol/L
	Johannes Data	98 lipid and lipid-related traits	24,925	–	European	
	GLGC	HDL-C	1,320,016	–	European	mmol/L
		LDL-C				
		TC				
		TG				
Outcome	ebi-a-GCST90027161	Atopic dermatitis	796,661	22,474	European	–

Notes: "–" indicates that this field is not applicable.

(eg., sunflower, rapeseed, or olive oil blends), distinct from butter, branded functional margarines (eg., Flora Pro-activ /Benecol), or low-fat spreads. This classification aligns with nutritional surveillance studies of UK spread consumption and prior methodological work utilizing UK Biobank dietary data.[20,24]

Construction and Assumption Validation of Instrumental Variables

Instrumental variables (IVs) were constructed following the core assumptions of Mendelian randomization. The relevance assumption required all SNPs to show significant associations with the exposure variable—dietary traits or lipid phenotypes—at a threshold of $P < 1\times10^{-5}$, and an F-statistic >10 to minimize weak instrument bias. The independence assumption mandated that the selected SNPs be independent of known confounders, verified using PhenoScanner v2 with the same significance threshold ($P < 1\times10^{-5}$). The exclusion restriction assumption stipulated that SNP effects on the outcome should occur solely through the exposure, excluding horizontal pleiotropic effects.

SNP selection involved LD clumping with an $r^2 < 0.001$ within a 10,000 kb window. SNPs exhibiting an allele frequency (MAF) ≤0.01 were excluded, and palindromic SNPs with MAF values ranging from 0.42 to 0.58 were removed to prevent strand ambiguity. Additionally, SNPs that were directly linked to the outcome ($P < 1\times10^{-5}$) were discarded. Pleiotropy was controlled using the MR-PRESSO global test ($P < 0.05$) to identify and exclude outlier SNPs. Detailed methodological steps, including specific tools used for SNP selection and bias correction, are described in the Supplementary Methods section.

Mendelian Randomization Analysis

To investigate the potential mediating role of lipid traits (mediator) in the causal pathway from dietary habits (exposure) to AD (outcome), We employed a two-stage MR design. In the first stage, the effects of dietary habits on 241 lipid traits were estimated, followed by evaluation of the impact of these lipid traits on AD in the second stage. The primary statistical method used was inverse-variance weighted (IVW) regression. Sensitivity analyses included MR-Egger, weighted median, weighted mode, and simple mode approaches, along with leave-one-out analyses. Heterogeneity was assessed via Cochran's Q test and I^2 statistic, and horizontal pleiotropy was evaluated using the MR-Egger intercept. Multivariable MR (MVMR) was applied if I^2 statistic >50% to account for potential confounding.

Mediation Effect Assessment

Mediation effects were assessed within the two-stage MR framework using the product-of-coefficients method. For each lipid trait, the indirect effect ($\beta_{\text{mediation}}$) was calculated as the product of β_1 (dietary habit → lipid trait) and β_2 (lipid trait → AD), and the total effect of dietary habits on AD was denoted β_3. The proportion mediated was calculated as: Proportion mediated $= \frac{\beta_{\text{mediation}}}{\beta_3} \times 100\%$. A mediation effect was considered significant if (1) the indirect and total effects were in the same direction ($\beta_{mediation} > 0$) and (2) $P < 0.05$ with an absolute proportion mediated >5%, minimizing false positives from weak mediation.

Reverse MR Analysis

We conducted a reverse MR analysis to examine the direction of causality. This tested whether lipid levels influenced dietary habits (lipid trait → dietary habits) or whether AD affected lipid levels (AD → lipid trait). The "diet → lipids → AD" causal pathway was considered more plausible if effect estimates for all reverse directions were statistically non-significant ($P > 0.05$).

Software Implementation

The analyses were conducted with R software (version 4.1.0), utilizing key packages such as "TwoSampleMR" (v0.5.6), "MRPRESSO" (v1.0), and "MendelianRandomization" (v0.5.1). Figures were generated using "ggplot2" (v3.3.5) and "forestplot" (v2.0.1). The tests were two-sided, and a P value under 0.05 was regarded as statistically significant.

Reporting Guidelines

This study was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology using Mendelian Randomization (STROBE-MR) guidelines. The completed checklist is provided as Supplementary Material.

Results

SNP Selection

Following cluster analysis and application of exclusion criteria, we selected three SNP sets: 6,290 SNPs associated with dietary habits (Supplementary Table 1-1), 7,703 SNPs associated with both lipid traits and AD (Supplementary Table 1-2), and 11,575 SNPs associated with both dietary habits and lipid traits (Supplementary Table 1-3). All GWAS data for exposures, mediators, and outcomes were obtained from independent cohorts with no sample overlap.

Direct Causal Effects of Dietary Habits on AD

Based on IVs for 83 dietary habits, IVW analysis identified five dietary habits significantly associated with AD risk ($P < 0.05$; Table 2 and Figure 2). High intake of brown bread (OR = 1.78, 95% CI 1.10–2.89) and wholemeal bread (OR = 1.23, 95% CI 1.06–1.43) increased AD risk, whereas muesli (OR = 0.814, 95% CI 0.67–0.99), lamb or mutton (OR = 0.80, 95% CI 0.67–0.95), and other oil-based spread (OR = 0.56, 95% CI 0.34–0.93) was protective. Heterogeneity was low (Cochran's Q $P > 0.05$; $I^2 < 25\%$) and no horizontal pleiotropy was detected. Sensitivity analyses (leave-one-out, funnel, scatter plots) revealed no influential outliers, supported by Supplementary Dataset 1.

Table 2 IVW Estimates of Dietary Exposures on AD Risk

Outcome	Exposure	Nsnp	OR (95% CI)	P value	F-Statistic	Heterogeneity Tests (I^2(%)/Q-P)	Pleiotropy Tests (Egger/PRESSO P)
Atopic dermatitis	Brown Bread	33	1.78 (1.10–2.89)	0.02	22.04	22/0.135	0.62/0.15
	Wholemeal or wholegrain Bread	121	1.23 (1.06–1.43)	0.01	25.40	0/0.676	0.71/0.68
	Muesli	82	0.81 (0.67–0.99)	0.04	22.81	0/0.66	0.76/0.69
	Lamb or mutton consumption	123	0.80 (0.67–0.95)	0.01	23.50	9/0.21	0.24/0.20
	Other oil-based spread	24	0.56 (0.34–0.93)	0.03	21.77	18/0.21	0.89/0.23

Abbreviations: AD, atopic dermatitis; OR, odds ratio; CI, confidence interval; Nsnp, number of single nucleotide polymorphisms; IVW, inverse-variance weighted; PRESSO, Pleiotropy RESidual Sum and Outlier test.

Exposure	Nsnp	OR(95%CI)	P-value	I2	Cochran's Q	Heterogeneity	Horizontal pleiotropy	MR-PRESSO
Bread type: Brown	33	1.783(1.101-2.889)	0.019	22	40.893	0.135	0.619	0.147
Bread type: Wholemeal or wholegrain	121	1.231(1.062-1.428)	0.006	0	112.429	0.676	0.706	0.681
Cereal type: Muesli	82	0.814(0.665-0.995)	0.045	0	75.296	0.658	0.764	0.690
Lamb or mutton consumption	123	0.795(0.665-0.951)	0.012	9	134.629	0.205	0.238	0.198
Spread type: Other oil-based spread	24	0.563(0.340-0.933)	0.026	18	28.184	0.209	0.885	0.234

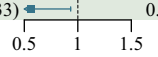

Figure 2 MR forest plot: Causal effects of dietary exposures on AD risk.

Two-Stage MR Analysis of Lipid Traits Mediating the Diet–AD Relationship

To explore whether lipid traits mediate the relationship between dietary patterns and AD, we performed a two-stage MR analysis.

Causal Relationship Between Lipid Traits and AD

In the first stage, we assessed 241 lipid traits as candidate mediators and examined their causal associations with AD.

The IVW method identified 37 lipid traits significantly associated with AD risk ($P < 0.05$), 28 of which remained consistent after sensitivity analyses (Table 3 and Figure 3). Fourteen traits were positively associated (eg., SM C20:2, OR = 1.13), while 14 were associated with a reduced risk (eg., phosphatidylcholine aa C36:4, OR = 0.96). Omega-6 fatty acids emerged as a significant risk factor (OR = 1.06, 95% CI 1.01–1.11, $P = 0.03$). Heterogeneity was low ($I^2 = 12\%$, Cochran's Q = 32.97, $P = 0.28$) and no horizontal pleiotropy was observed (MR-PRESSO $P = 0.26$). Sensitivity analyses (leave-one-out, funnel, scatter plots) revealed no influential outliers, supported by Supplementary Dataset 2.

Causal Relationships Between Dietary Habits and Lipid Traits

In the initial stage of the two-sample Mendelian randomization analysis, 28 lipid traits demonstrated significant associations with AD. Using the IVW method, we identified four significant causal relationships between dietary exposures and lipid traits.

Specifically, consumption of other oil-based spreads was negatively associated with sphingomyelin SM C20:2 levels (OR = 0.47, 95% CI 0.25–0.87, $P = 0.02$). Brown bread intake exhibited negative associations with both the concentration of very large VLDL particles (OR = 0.56, 95% CI 0.37–0.85, $P = 0.01$) and total lipids in large VLDL (OR = 0.63, 95% CI 0.42–0.94, $P = 0.03$). Muesli intake was also negatively associated with phosphatidylcholine PC aa C36:0 levels (OR = 0.73, 95% CI 0.56–0.95, $P = 0.02$) (Figure 4 and Table 4).

No significant heterogeneity ($I^2 = 0$–7%, Cochran's Q test $P > 0.35$) or horizontal pleiotropy (MR-Egger intercept test $P > 0.18$; MR-PRESSO global test $P > 0.43$) was detected. Sensitivity analyses (leave-one-out, funnel, scatter plots) revealed no influential outliers, supported by Supplementary Dataset 3.

Mediating Effect of Dietary Habits on AD and Validation of Causal Direction

Following the two-stage MR mediation framework outlined in Section 2.5, we applied the product method to identify significant diet–lipid–AD pathways. Mediation was deemed significant if (1) the indirect and total effects were in the same direction ($\beta_{mediation} > 0$) and (2) $P < 0.05$ with an absolute proportion mediated >5%.

The total effect of "other oil-based spread" on AD was $\beta_3 = -0.54$ ($P < 0.01$), with 15.9% mediated by SM C20:2 ($\beta_{\text{mediation}} = -0.091$, $P < 0.01$). For "brown bread", a total effect of $\beta_3 = 0.58$ ($P < 0.05$) was partially mediated by VLDL particles, (8.9%; $\beta_{\text{mediation}} = 0.05$, $P < 0.01$). "muesli" showed a negative mediation via PC aa C36:0, accounting for −13.6% of the total effect, indicating that this lipid may attenuate the protective effect of muesli (Table 5).

All instrumental variables were robust (F-statistic > 10), with no evidence of heterogeneity or pleiotropy detected. Figure 5 illustrates the causal pathways through which dietary habits influence AD risk via specific lipid profiles (Spread → SM C20:2, Bread → VLDL traits, Cereal → PC aa C36:0), with key mediation statistics—$\beta_{\text{mediation}}$, proportion mediated, and P value—provided. To validate the causal direction, reverse MR analysis was conducted. No significant causal effects of AD on either dietary habits or lipid traits were observed (all $P > 0.05$; Supplementary Table 2), supporting the proposed directionality in the primary model.

Table 3 IVW Estimates of Lipid Traits on AD Risk

Class	Lipid Mediator	Nsnp	OR (95% CI)	P value	F-Statistic	Heterogeneity Tests (I^2 (%)/Q-P)	Pleiotropy Tests (Egger/ PRESSO P)
Sphingomyelin	SM C24:0	22	1.11 (1.04–1.18)	< 0.01	21.87	0/0.50	0.61/0.54
	SM C20:2	16	1.13 (1.03–1.24)	0.01	23.23	40/0.05	0.43/0.07
Lysophosphatidylcholine	lysoPC a C26:0	17	1.12 (1.028–1.21)	0.01	23.09	37/0.06	0.78/0.07
Glycerophospholipids	PC aa C32:2	19	1.11 (1.039–1.19)	< 0.01	20.92	26/0.15	0.44/0.17
	PC aa C38:3	21	1.09 (1.02–1.16)	0.01	29.86	14/0.28	0.55/0.29
	PC ae C34:2	20	1.10 (1.03–1.17)	< 0.01	25.42	12 / 0.30	0.29/0.27
	PC ae C36:2	17	1.09 (1.02–1.16)	0.01	25.72	6/0.38	0.07/0.32
	PC aa C32:3	11	1.10 (1.00–1.20)	0.04	21.48	12/0.33	0.78/0.39
	Total phosphoglycerides	33	1.05 (1.00–1.10)	< 0.05	23.61	0/0.75	0.90/0.77
Fatty acid	Hydroxybutyrylcarnitine	17	1.08 (1.01–1.16)	0.02	21.80	4/0.41	0.43/0.41
	Omega-6 fatty acids	30	1.06 (1.01–1.11)	0.03	28.88	12/0.28	0.24/0.26
	18:2, linoleic acid (LA)	27	1.07 (1.01–1.13)	0.02	31.48	23/0.14	0.08/0.12
Lipoprotein-associated	Total lipids in small LDL	41	1.05 (1.00–1.10)	< 0.05	27.42	24/0.09	0.15/0.09
Cholesteryl ester	Cholesterol esters in large LDL	35	1.05 (1.01–1.09)	0.022	33.03	1/0.45	0.42/0.39
Lysophospholipid	LysoPC a C20:4	23	0.92 (0.88–0.95)	<0.001	30.54	0/0.77	0.99/0.79
Glycerophospholipids	PC aa C24:0	22	0.91 (0.86–0.97)	0.001	21.17	28/0.11	0.27/0.15
	PC ae C40:6	16	0.88 (0.83–0.93)	<0.001	26.51	5/0.40	0.95/0.49
	PC aa C42:2	16	0.88 (0.81–0.96)	0.01	20.92	25/0.17	0.43/0.20
	PC aa C36:0	18	0.91 (0.86–0.98)	0.01	21.52	0/0.96	0.83/0.96
	PC aa C38:6	21	0.91 (0.86–0.97)	0.01	23.39	11/0.31	0.58/0.35
	PC aa C42:6	17	0.92 (0.85–0.98)	0.02	20.24	21/0.21	0.25/0.22
	PC ae C40:5	34	0.96 (0.93–0.99)	0.01	24.45	0/0.61	0.06/0.46
	PC aa C36:4	26	0.96 (0.93–0.99)	0.03	23.30	22/0.16	0.52/0.18
	PC aa C38:4	19	0.95 (0.91–0.99)	0.02	37.10	23/0.18	0.50/0.25
	PC aa C40:4	18	0.94 (0.81–0.99)	0.03	22.41	0/0.66	0.21/0.47
Lipoprotein-associated	Total lipids in large VLDL	31	0.94 (0.89–0.99)	< 0.05	25.48	0/0.91	0.31/0.91
	Concentration of very large VLDL particles	29	0.92 (0.85–0.98)	0.02	29.55	13/0.27	0.78/0.30
Lysophospholipid	Lysopc a C28:1	22	0.91 (0.86–0.97)	0.01	21.20	14/0.28	0.45/0.28

Notes: All analyses used the IVW method with random effects, selecting IVs at genome-wide significance ($P < 5 \times 10^{-8}$) and ensuring LD clumping ($r^2 < 0.001$, 10,000 kb) with *F*-statistic > 10. Heterogeneity was assessed with I^2 (≥50% indicates significant heterogeneity), and pleiotropy was evaluated using the MR-PRESSO global test for outlier removal. Lipid nomenclature: SM, sphingomyelin; lysoPC a, 1-acyl-lysophosphatidylcholine; PC aa, diacyl-phosphatidylcholine; PC ae, acyl-alkyl-phosphatidylcholine; lysoPC, lysophosphatidylcholine; CXX:Y denoting carbon atoms and double bonds.

Discussion

Employing a two-step Mendelian randomization framework, this study establishes causal links between dietary patterns and AD through distinct pathways of food processing and lipid metabolism. Our genetic analysis revealed that ultra-processed brown bread (OR = 1.78) and wholemeal bread (OR = 1.23) increased AD risk, whereas minimally processed muesli, lamb, and other oil-based spreads conferred protection. By providing novel genetic evidence and mechanistic clarification, these findings advance nutritional epidemiology. They not only support the known principle that processed grains elevate systemic inflammation while nutrient-dense foods attenuate it,[25,26] but further identify specific lipid mediators—such as VLDL particles and sphingomyelins—which underlie these causal relationships.

Our MR results both align with and extend prior evidence. The protective association of unsaturated fat-rich spreads aligns with dietary guidelines and observational studies linking n-3 PUFAs to lower inflammation. However, our finding that genetic predisposition to higher brown and wholemeal bread intake increases AD risk appears counterintuitive and

Exposure	Nsnp	OR(95%CI)	P-value	I2	Cochran's Q	Heterogeneity	Horizontal pleiotropy	MR-PRESSO
SM C20:2	16	1.128(1.030-1.235)	0.010	40	24.839	0.052	0.431	0.065
lysoPC a C26:0	17	1.117(1.028-1.213)	0.009	37	25.336	0.064	0.785	0.070
PC aa C32:2	19	1.113(1.039-1.194)	0.002	26	24.207	0.148	0.444	0.167
SM C24:0	22	1.106(1.038-1.178)	0.002	0	20.285	0.503	0.613	0.535
PC aa C32:3	11	1.098(1.003-1.203)	0.044	12	11.332	0.332	0.783	0.394
PC ae C34:2	20	1.098(1.030-1.169)	0.004	12	21.605	0.304	0.286	0.271
PC ae C36:2	17	1.090(1.020-1.164)	0.010	6	17.064	0.381	0.065	0.324
PC aa C38:3	21	1.088(1.022-1.157)	0.008	14	23.124	0.283	0.547	0.292
Hydroxybutyrylcarnitine	17	1.084(1.013-1.161)	0.020	4	16.710	0.405	0.429	0.413
18:2, linoleic acid (LA)	27	1.070(1.012-1.131)	0.017	23	33.864	0.138	0.082	0.121
Omega-6 fatty acids	30	1.057(1.005-1.112)	0.032	12	32.967	0.279	0.237	0.255
Total phosphoglycerides	33	1.049(1.000-1.101)	0.049	0	26.362	0.747	0.896	0.769
Total lipids in small LDL	41	1.049(1.001-1.099)	0.046	24	52.592	0.088	0.147	0.089
Cholesterol esters in large LDL	35	1.045(1.006-1.086)	0.022	1	34.294	0.454	0.415	0.385
PC aa C36:4	26	0.960(0.926-0.996)	0.031	22	31.906	0.161	0.519	0.178
PC ae C40:5	34	0.958(0.926-0.992)	0.014	0	30.113	0.612	0.059	0.460
PC aa C38:4	19	0.951(0.911-0.992)	0.020	23	23.403	0.176	0.500	0.245
PC aa C40:4	18	0.942(0.891-0.995)	0.033	0	14.167	0.655	0.211	0.473
Total lipids in large VLDL	31	0.941(0.886-0.999)	0.047	0	20.364	0.907	0.313	0.912
lysoPC a C20:4	23	0.916(0.883-0.950)	<0.001	0	16.933	0.767	0.985	0.791
Concentration of very large VLDL particles	29	0.915(0.852-0.983)	0.015	13	32.026	0.273	0.784	0.298
PC aa C42:6	17	0.915(0.851-0.983)	0.015	21	20.161	0.213	0.249	0.217
PC aa C36:0	18	0.914(0.855-0.977)	0.009	0	8.418	0.957	0.829	0.963
PC aa C24:0	22	0.913(0.863-0.965)	0.001	28	29.192	0.109	0.269	0.152
lysoPC a C28:1	22	0.913(0.857-0.973)	0.005	14	24.307	0.278	0.454	0.281
PC aa C38:6	21	0.912(0.855-0.973)	0.005	11	22.529	0.313	0.579	0.350
PC aa C42:2	16	0.883(0.810-0.963)	0.005	25	19.955	0.174	0.428	0.200
PC ae C40:6	16	0.877(0.826-0.932)	<0.001	5	15.771	0.397	0.953	0.493

Figure 3 MR forest plot: Causal effects of Lipid Traits on AD risk.

Exposure	Outcome	Nsnp	OR(95%CI)	P-value	I2	Cochran's Q	Heterogeneity	Horizontal pleiotropy	MR-PRESSO
Cereal type: Muesli	PC aa C36:0	94	0.732(0.563-0.952)	0.020	0	81.798	0.790	0.182	0.822
Bread type: Brown	Total lipids in large VLDL || id:met-c-889	37	0.626(0.415-0.944)	0.025	0	26.264	0.883	0.860	0.913
Bread type: Brown	Concentration of very large VLDL particles || id:met-c-950	37	0.558(0.365-0.852)	0.007	5	37.749	0.389	0.719	0.445
Spread type: Other oil-based spread	SM C20:2	26	0.468(0.252-0.868)	0.016	7	26.979	0.357	0.553	0.430

Figure 4 MR forest plot: Dietary exposures → Lipid traits.

contrasts with some epidemiological studies promoting whole grains. This discrepancy may be reconciled by considering food processing. Most MR and large cohort studies classify "whole grain" as a beneficial category. Our instrument, derived from UK Biobank's specific "bread type" questions, likely captures consumption of commercially produced breads, which even when labeled "brown" or "wholemeal," can undergo significant processing, containing additives, high glycemic index flours, and added sugars—factors linked to inflammation. This distinction highlights a key novelty of our work: moving beyond broad food groups to reveal how commercial processing may alter the health effects of nominally healthy foods, a nuance crucial for dermatological nutrition. This interpretation is reinforced by the mediation analysis. The link between brown bread and AD was partly mediated (8.9%) by VLDL traits. This likely reflects the pro-

Table 4 IVW Estimates of Dietary Exposures on Lipid Traits

Outcome	Exposure	Nsnp	OR (95% CI)	P value	F-Statistic	Heterogeneity Tests (I^2(%)/Q-P)	Pleiotropy Tests (Egger/PRESSO P)
Concentration of very large VLDL particles	Brown Bread	37	0.56 (0.37–0.85)	0.01	21.49	5 / 0.39	0.72 / 0.45
PC aa C36:0	Muesli	94	0.73 (0.56–0.95)	0.02	22.64	0 / 0.79	0.18 / 0.82
SM C20:2	Other oil-based spread	26	0.47 (0.25–0.87)	0.02	20.78	7 / 0.36	0.55 / 0.43
Total lipids in large VLDL	Brown Bread	37	0.63 (0.42–0.94)	0.03	20.90	0 / 0.88	0.86 / 0.92

Abbreviations: VLDL, very low-density lipoprotein; PC, phosphatidylcholine; SM, sphingomyelin; OR, odds ratio; CI, confidence interval; Nsnp, number of single nucleotide polymorphisms; IVW, inverse-variance weighted.

Table 5 Mediation Analysis of Dietary Exposures on AD Risk via Lipid Traits

Exposure	Mediator	$\beta_{mediation}$ ($\beta_1 \times \beta_2$)	Mediation Proportion (%)	Total Effect (β_3)	P§
Other oil-based spread	SM C20:2	−0.09	15.9 (5.4–26.4)	−0.57	0.003
Brown Bread	VLDL-related traits†			0.58	
↳Sub-item 1	Total lipids in large VLDL	0.03	5.0 (1.0–8.9)	–	0.015
↳Sub-item 2	Concentration of very large VLDL particles	0.05	8.9 (3.1–14.7)	–	0.003
Muesli	PC aa C36:0	0.03	−13.6 (−16.9–-10.3)	−0.21	<0.001

Notes: $\beta_{mediation}$: Mediation effect (calculated as $\beta_1 \times \beta_2$); β_3: Total effect of exposure on outcome; Proportion mediated = ($\beta_{mediation}$ / β_3) × 100%; ↳indicates sub-items under the main exposure category. † VLDL traits include total lipids and concentration of very large VLDL; § Negative values indicate that the mediation effect is opposite in direction to the total effect; Data sources: GCST90132961, GCST90132965, GCST90132972, ebi-a-GCST90027161.

inflammatory impact of processing-associated components like added sugars and high glycemic index flours—which promote hepatic VLDL secretion—rather than the intrinsic properties of whole-grain fiber.

Mechanistically, food processing alters the food matrix, affecting bioactive components and gut microbiota. High-temperature baking and mechanical grinding degrade compounds, such as β-glucan and polyphenols, promote pro-inflammatory bacteria (eg., *Prevotella* spp.), and reduce short-chain fatty acid (SCFA) production.[27,28] These alterations activate TLR4/NF-κB signaling via LPS, downregulate Claudin-1, increase intestinal permeability, and impair skin barrier function.[29,30] In contrast, minimally processed whole grains and n-3 polyunsaturated fatty acids (n-3 PUFAs) in lamb enrich beneficial gut microbiota, elevate SCFAs, suppress NF-κB activation, and reinforce skin barrier integrity.[31,32] Specifically for highly processed grains, this gut dysbiosis and increased permeability can stimulate hepatic secretion of large, triglyceride-rich VLDL particles. These VLDL particles, in turn, can activate inflammatory pathways such as TLR2/4-NF-κB, releasing IL-6 and IL-1β, thereby creating a direct "gut-liver-skin" axis that propagates dietary inflammation to AD pathogenesis.[19]

These findings outline a mechanistic model where the gut-skin axis and neuro-skin axis jointly regulate AD pathogenesis. Intestinal pro-inflammatory mediators, such as IL-6, activate vagal afferent fibers, prompting sensory neurons to release calcitonin gene-related peptide (CGRP) and substance P (SP).[33] These neuropeptides stimulate keratinocytes to secrete thymic stromal lymphopoietin (TSLP), which drives a Th2/Th22-dominant immune response and

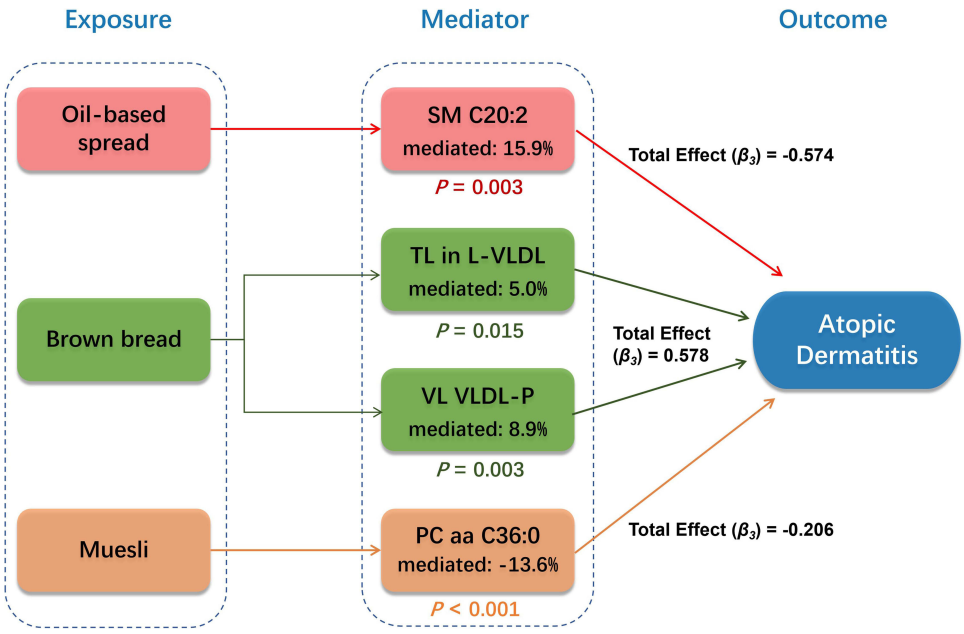

Figure 5 Mediation pathways from dietary habits to atopic dermatitis.
Abbreviations: L-VLDL, large very-low-density lipoprotein; PC, phosphatidylcholine; TL, total lipids; VL-VLDL-P, very large very-low-density lipoprotein particles.

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perpetuates the itch–scratch cycle. This integrated cascade illustrates how dietary modulation of lipid metabolism can influence AD progression, highlighting the combined systemic and neural contributions to disease pathophysiology.

Beyond the damaging VLDL pathway, mediation analysis revealed protective and antagonistic lipid mechanisms.

1. Sphingomyelin-PPARγ Protective Pathway: The observed protective effect of "Other oil-based spread" (OR = 0.56) likely reflects the predominance of unsaturated fats in generic vegetable oil spreads (eg., sunflower, rapeseed, or olive oil blends), as opposed to the saturated fats in butter, aligning with dietary guidelines to mitigate inflammation. Mechanistically, these unsaturated fats promote PPARγ activation and upregulate barrier-associated proteins, attenuating inflammation and reducing AD risk.[34] This pathway mediated 15.9% of the protective effect ($\beta = -0.09$, $P = 0.003$), underscoring the role of optimized lipid composition in barrier repair.

2. Phosphatidylcholine Antagonistic Network: Conversely, certain lipids such as oat-derived phosphatidylcholine PC aa C36:0 may partially counteract protective effects by modulating keratinocyte metabolism and immune responses,[34] revealing complex interactions within the lipid network. Collectively, these pathways delineate a multi-faceted "diet-lipid metabolism-AD" axis.

In summary, this study establishes lipid metabolism as a central mediator linking diet to atopic dermatitis, delineating specific pro-inflammatory (VLDL particles), protective (sphingomyelin-PPARγ), and antagonistic (phosphatidylcholine) pathways within the "diet→lipid metabolism→AD" axis. This framework provides a mechanistic basis for dietary interventions: reducing highly processed grains to lower inflammatory triggers, while increasing intake of n-3 PUFA-rich foods and minimally processed whole grains to support skin barrier function.

The key strength of this work is its two-step Mendelian randomization mediation design, providing novel genetic evidence for these causal pathways beyond observational associations. Limitations include potential residual pleiotropy, limited generalizability from European-centric data, and an inability to capture life-stage-specific dietary effects. Future studies should validate these findings in trans-ethnic populations and employ more complex models to further elucidate dietary impacts on AD.

Conclusion

This Mendelian randomization study establishes lipid metabolism as a key mediator linking dietary factors to atopic dermatitis. A lipid regulatory network, including ceramide homeostasis, pro-inflammatory VLDL signaling, and barrier-protective sphingolipid pathways, underlies this relationship. The identified lipid species represent promising candidate biomarkers that mechanistically link diet to AD pathogenesis. Prioritizing these lipid pathways in future epidemiological studies could pave the way for validating targeted nutritional strategies.

Data Sharing Statement

All GWAS summary statistics are publicly available from UK Biobank (https://www.ukbiobank.ac.uk), FinnGen R10 (https://www.finngen.fi/en), and curated lipid GWAS datasets (https://omicscience.org/apps/crossplatform). Analysis code is available from the corresponding author upon reasonable request.

Ethics Approval and Consent to Participate

Not applicable. No individual-level participant data were accessed; all original studies had obtained appropriate ethical approval and informed consent.

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 declare no competing interests.

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