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TNFSF14 mediates the impact of docosahexaenoic acid on atopic dermatitis: a Mendelian randomization study

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Abstract. – OBJECTIVE: While current research suggests potential value for docosahexaenoic acid (DHA) in the prevention and management of atopic dermatitis (AD), the causal relationship between DHA and AD remains unclear, and the underlying mechanisms are not well understood.

MATERIALS AND METHODS: To investigate the potential causal relationship between DHA and AD, as well as to explore potential mediating mechanisms, we employed the Mendelian randomization (MR) methods. To study these potential relationships, we conducted MR analysis using publicly available Genome-Wide Association Studies (GWAS) data. Effect estimates were computed using the random-effects inverse-variance weighted method.

RESULTS: Our study demonstrates a negative correlation between DHA levels and AD risk (OR: 0.915, 95% CI: 0.858-0.975, *p*=0.007). Furthermore, in MR analysis using tumor necrosis factor ligand superfamily member 14 (TNFSF14) levels as an outcome, DHA levels also show a negative association with TNFSF14 levels (OR: 0.933, 95% CI: 0.879-0.990, *p*=0.022). Subsequently, we performed further analysis to explore the relationship between TNFSF14 and AD risk, revealing a positive correlation (OR: 1.069, 95% CI: 1.005-1.137, *p*=0.033). This suggests a potential mediating role of TNFSF14 in the impact of DHA on AD risk.

CONCLUSIONS: In summary, our study employs MR analysis to offer genetic evidence indicating a potential role of DHA in reducing the risk of AD, as well as opening avenues for further in-depth investigation into potential mechanisms. These findings emphasize the importance of ongoing research in this field.

Key Words:
TNFSF14, Atopic dermatitis, Mendelian randomization.

Abbreviations
DHA = Docosahexaenoic acid, AD = Atopic Dermatitis, MR = Mendelian Randomization, GWAS = Genome-Wide Association Study, TNFSF14 = Tumor necrosis factor ligand superfamily member 14.

Introduction

Atopic dermatitis (AD), also known as atopic eczema, is a chronic and recurrent inflammatory skin condition that affects approximately one in every ten individuals during their lifetime[1].

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The development of AD is the result of a complex interplay involving genetic mutations in the epidermis, dysregulation of the immune system, and environmental influences[2]. These multifaceted interactions lead to the disruption of the skin's barrier function, ultimately resulting in the formation of intensely pruritic dermatological lesions[2]. The incessant itch-scratch cycle triggered by repetitive scratching significantly impairs the quality of life for those afflicted by AD[3].

Docosahexaenoic acid (DHA), an omega-3 polyunsaturated fatty acid, has gained prominence in recent research4 due to its potential to modulate the skin's epidermal ecosystem. It aids in maintaining normal keratinocyte differentiation and supports the structural integrity of the epidermal layers, thereby enhancing skin barrier function[4]. In addition to these benefits, DHA exhibits anti-inflammatory potential, helping to balance immune system activity and mitigate excessive immune responses[5]. While primarily acknowledged as a dietary supplement beneficial for cardiovascular health[6], DHA has been explored for its therapeutic applications in AD[7]. Several select clinical trials have examined the potential of DHA in preventing and treating AD. Furuhjelm et al[8] conducted a study focusing on the effects of prenatal and postnatal supplementation with eicosapentaenoic acid (EPA) and DHA on allergic diseases in infants up to 2 years of age. Their findings indicated a significant reduction in AD associated with IgE levels among infants in the group receiving EPA/DHA supplementation. However, another clinical trial initiated by Gunaratne et al[9] found that, compared to standard-dose DHA, high-dose DHA supplementation did not significantly reduce the incidence and severity of AD in infants from birth to 7 years. Consequently, the cause-and-effect connection between DHA and AD remains inconclusive, and its application in the prevention and treatment of AD remains a subject of ongoing and enduring scientific discussion.

Regarding causality, Mendelian Randomization (MR) has become an increasingly employed method, utilizing data from recent Genome-Wide Association Studies (GWAS). Genetic variation within a phenotype can serve as an instrumental variable (IV) to clarify the causal relationship between exposure and outcome, concurrently mitigating the potential impact of confounding factors and the issue of reverse causation often encountered in observational studies[10]. A recent comprehensive systematic review[7], which aggregates findings from seven distinct studies, has put forth the proposition that omega-3 fatty acid supplementation may potentially mitigate the incidence of AD and ameliorate associated clinical symptoms, conceivably through its anti-inflammatory properties. In this study, our aim is to employ MR analysis to investigate the potential causal relationship between DHA and AD while exploring potential mediating mechanisms[11].

Materials and Methods

Study Design

The study design meets the three crucial assumptions of MR analysis[10], as follows: (A) Single Nucleotide Polymorphisms (SNPs) are strongly associated with the exposure, (B) SNPs are independent of known confounding factors, and (C) SNPs only influence the outcome through exposure.

Data Sources

The analysis was conducted using publicly available summary-level data from GWAS (https://gwas.mrcieu.ac.uk/), focusing on the traits of interest. These studies predominantly featured European populations and were published between 2020 and 2022. In our study, the diagnosis of AD adhered to the diagnostic criteria of the American Academy of Dermatology[12]. Quantitative variables within the dataset, including key metrics such as DHA and tumor necrosis factor ligand superfamily member 14 (TNFSF14) levels, were measured using their respective standard units. Genetic association estimates for DHA were derived from the GWAS database reported by Richardson et al[13], primarily focusing on European populations and involving 115,006 study subjects and 11,590,399 SNPs. Genetic association estimates for TNFSF14 were obtained from the GWAS database reported by Folkersen et al[14], primarily focusing on European populations and involving 21,758 study subjects and 12,601,513 SNPs. Genetic association estimates for AD were extracted from the GWAS database reported by Sliz et al[15], predominantly concentrating on European populations and encompassing 16,121,213 SNPs and 796,661 study subjects, including 22,474 cases and 774,187 controls. The data used in this work are publicly available, and we have used and cited the data from these studies. All these studies[13-15] obtained consent and ethical approval from the relevant participants. The analysis results conducted in this work are provided in the main manuscript or its supplementary files. All code used for this

work is available upon reasonable request from the respective authors. This study is reported in accordance with the STrengthening the Reporting of OBservational studies in Epidemiology-Mendelian Randomization (STROBE-MR) guidelines[16].

Statistical Analysis

Selection and validation of SNPs

Compliance with three standard guidelines directed the selection of suitable SNPs[10]. Firstly, we identified SNPs associated with DHA/TNFSF14 above a genome-wide significance threshold ($p<5\times10^{-5}$)[10,17]. To ensure the independence of the chosen SNPs, we assessed pairwise linkage disequilibrium. Any SNP showing a high correlation ($r^2>0.001$) with other SNPs or having a higher p-value within a 10,000 kb aggregate window was excluded. Subsequently, we calculated the F-statistic to assess the strength of individual SNPs. SNPs with an F-statistic greater than 10 were considered robust enough to mitigate potential bias. Before conducting MR analysis, data harmonization steps were taken to ensure that SNPs affecting exposure and outcomes corresponded to the same alleles. To prevent IVs from being correlated with potential confounders that could influence exposure and outcomes, we systematically searched each selected SNP and its proxies in the Phenoscanner (http://www.phenoscanner.medschl.cam.ac.uk/)[18] and GWAS Catalog (https://www.ebi.ac.uk/gwas/)[19] databases. We removed SNPs associated with exposure and outcomes to avoid potential pleiotropic effects. Subsequently, we conducted the MR analysis as described above. This comprehensive approach ensures the reliability and robustness of MR analysis.

MR and Statistical Analysis

We employed the random-effects model for Inverse Variance Weighting (IVW) as our primary MR analysis method[10]. Regarding missing values, we used imputation methods. Additionally, two sensitivity analyses were conducted: the Weighted Median method and the MR-Egger method. The Weighted Median method can provide reliable estimates when more than 50% of the information originates from valid IVs[20]. MR-Egger method was used to assess the presence of horizontal pleiotropy among the selected IVs[21]. Heterogeneity among the chosen IVs was indicated by Cochrane's Q statistic[10]. Furthermore, we performed a leave-one-out sensitivity analysis to evaluate whether individual SNPs disproportionately influenced the overall estimates. These analysis methods were employed to ensure the reliability and robustness of our MR study. All statistical analyses were conducted using the "TwoSampleMR" package in R version 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria). The results were considered statistically significant with a threshold set at $p<0.05$. The research protocol and details were not pre-registered.

Results

SNP Selection and Validation

In summary, the studies included in our analysis were published between 2020 and 2022 and primarily focused on European populations (Table I). Based on the selection criteria mentioned earlier, we extracted 95 and 108 independent SNPs without linkage disequilibrium from a total of 115,006 samples for MR analysis to investigate their associations with AD and TNFSF14, respectively. Additionally, we extracted 20 independent SNPs without linkage disequilibrium from 21,758 samples for MR analysis to estimate the genetic association of TNFSF14 with AD (Table II). **Supplementary Tables I-III** provide information about SNPs significantly associated with the exposure factors, including SNP ID codes, effect alleles, other alleles, estimated allele frequencies (EAF) values, Beta values, and standard errors (SE).

Mendelian Randomization Analysis

As shown in Table II, the IVW analysis results indicate that DHA levels are inversely associated

Table I. Details of the GWAS datasets included in this mendelian randomization.

GWAS ID	Traits	Author	Year	Sample size	Number of SNPs	Population
ebi-a-GCST90027161	AD	Sliz et al[15]	2021	796,661	16,121,213	European
ebi-a-GCST90092816	DHA	Richardson et al[13]	2022	115,006	11,590,399	European
ebi-a-GCST90012029	TNFSF14	Folkersen et al[14]	2020	21,758	12,601,513	European

GWAS: Genome-Wide Association Studies, TNFSF14: Tumor necrosis factor ligand superfamily member 14, DHA: Docosahexaenoic acid, AD: Atopic dermatitis.

Table II. The causal association of exposure with outcome in Mendelian randomization analysis.

Exposures	Outcomes	nSNPs	β	SE	p	OR	95% CI	
							Lower	Upper
DHA	AD	95						
MR Egger			-0.101	0.046	0.032	0.904	0.826	0.990
Weighted median			-0.121	0.037	0.001	0.886	0.825	0.952
Inverse variance weighted			-0.089	0.033	0.007	0.915	0.858	0.975
Simple mode			-0.119	0.112	0.287	0.887	0.713	1.104
Weighted mode			-0.100	0.032	0.002	0.905	0.850	0.963
DHA	TNFSF14	108						
MR Egger			-0.080	0.043	0.068	0.923	0.848	1.005
Weighted median			-0.120	0.042	0.004	0.887	0.817	0.963
Inverse variance weighted			-0.070	0.030	0.022	0.933	0.879	0.990
Simple mode			-0.021	0.129	0.870	0.979	0.760	1.261
Weighted mode			-0.102	0.036	0.006	0.903	0.841	0.969
TNFSF14	AD	20						
MR Egger			0.111	0.041	0.016	1.117	1.030	1.211
Weighted median			0.084	0.032	0.010	1.087	1.020	1.159
Inverse variance weighted			0.067	0.031	0.033	1.069	1.005	1.137
Simple mode			0.038	0.103	0.715	1.039	0.849	1.272
Weighted mode			0.086	0.033	0.017	1.089	1.022	1.161

SNP: Single nucleotide polymorphism, SE: Standard error, OR: Odd ratio, Cl: Confidence interval, MR: Mendelian randomization, TNFSF14: Tumor necrosis factor ligand superfamily member 14, DHA: Docosahexaenoic acid, AD: Atopic dermatitis.

with the risk of AD, with an Odds Ratio (OR) of 0.915 [95% Confidence Interval (CI): 0.858-0.975, p=0.007]. Furthermore, in the MR analysis with TNFSF14 as the outcome, DHA levels also exhibit a negative correlation with TNFSF14 levels, with an OR of 0.933 (95% CI: 0.879-0.990, p=0.022). Consequently, we conducted further analysis to explore the relationship between TNFSF14 and the risk of AD. Using the same analytical approach, we found that TNFSF14 levels are positively associated with the risk of AD, with an OR of 1.069 (95% CI: 1.005-1.137, p=0.033). Additionally, we calculated the F-values for the IVs, and all the exposure F-values exceeded 10, indicating the robust strength of the SNPs (**Supplementary Tables I-III**). We defined the causal effect of DHA on the risk of AD as *β1*, representing the total effect. The causal effect of DHA on TNFSF14 was represented as *β2*. The causal effect of TNFSF14 on the risk of AD was defined as *β3*, and the mediating effect was expressed as *β2×β3*. *β2×β3/β1* quantifying the percentage of the mediating effect. The calculated mediating effect was -0.005, accounting for 5.27% of the total effect. Furthermore, the majority of weighted median and MR-Egger analyses yielded consistent estimates.

Sensitivity Analysis

As indicated in Table III, our sensitivity analysis examined the genetic estimates of the causal relationship between DHA and AD. It revealed

Table III. Pleiotropy and heterogeneity test of exposure IVs in outcome GWAS.

		Pleiotropy test			Heterogeneity test					
		MR-Egger			MR-Egger			Inverse-variance weighted		
Exposures	Outcomes	Intercept	SE	p	Q	Q_df	Q_p-value	Q	Q_df	Q_p-value
DHA	AD	0.001	0.003	0.724	148	93	<0.001	148	94	<0.001
DHA	TNFSF14	0.001	0.002	0.731	115	106	0.259	115	107	0.279
TNFSF14	AD	-0.009	0.006	0.136	22	17	0.172	26	18	0.110

IVs: Independent Variables, GWAS: Genome-Wide Association Studies, MR: Mendelian randomization, Q: heterogeneity statistic Q, df: degree of freedom, TNFSF14: Tumor necrosis factor ligand superfamily member 14, DHA: Docosahexaenoic acid, AD: Atopic dermatitis.

significant heterogeneity according to Cochran's Q test (p<0.001). However, other sensitivity analyses did not show substantial heterogeneity (p>0.05). Importantly, the MR Egger regression did not indicate any signs of horizontal pleiotropy (Table III). Figure 1 presents a scatterplot illustrating individual estimates of the exposure's causal effect on the outcome. Notably, as the impact of SNPs on the exposure strengthens, their effect on the outcome also becomes more pronounced, implying an overall positive association between genetic exposure and the outcome. Additionally, Figure 2 offers a forest plot of SNPs associated with the outcome's risk, providing an intuitive overview of the Beta values for each SNP after IVW calculation. These visual aids deepen our understanding of result consistency. Moreover, we conducted a leave-one-out sensitivity analysis, depicted in Figure 3, to assess how individual SNPs influence the overall estimate. Importantly, this analysis demonstrated the stability of the overall estimate, suggesting it was not unduly influenced by any specific SNP, and no evidence of reverse causality was found. Furthermore, we used funnel plots to investigate potential horizontal pleiotropy, as shown in Figure 4. The absence of asymmetry in this plot suggests no evidence of horizontal pleiotropy, further strengthening the reliability of our study results. Finally, a reverse MR analysis did not reveal any evidence of a reverse causal association between the exposure and the outcome. In summary, these additional analyses bolster the accuracy and robustness of our study.

Discussion

In this study, we employed MR analysis to investigate the causal relationship between DHA and the risk of AD. Our findings revealed a significant inverse causal association between DHA levels and AD risk, suggesting the potential of DHA in reducing the risk of AD. These results align with prior studies conducted by Lin et al[11] and Li et al[22]. However, the precise underlying mechanisms merit further exploration.

DHA, a long-chain ω-3 fatty acid, belongs to the family of unsaturated fatty acids. It plays a pivotal role in the normal development of the brain, retina, and nervous system[8,9]. Moreover, DHA is considered beneficial for cardiovascular health, anti-inflammatory effects, and immune system regulation[5,6]. Given that the human body cannot independently synthesize an adequate amount of DHA, it is typically acquired through dietary sources or dietary supplements to maintain overall health[23]. TNFSF14, a protein within the Tumor Necrosis Factor (TNF) superfamily, plays a critical role in regulating immune responses and inflammation[24]. Current research[24] indicates that TNFSF14 expression levels increase during infections, immune stimulation, or inflammatory processes. Typically expressed on the surfaces of immune cells, including T lymphocytes, B lymphocytes, dendritic cells, and others, TNFSF14 interacts with its receptors, Herpesvirus Entry Mediator (HVEM) or Lymphotoxin β receptor (LTβR), triggering the regulation of immune and inflammatory responses[25]. Upon binding to its respective receptors, TNFSF14 initiates a series of signaling pathways, including Nuclear Factor-κB (NF-κB), Mitochondrial Protein Kinase (MAPK), and Protein Kinase B (Akt), leading to immune cell activation and the production of cytokines[26]. Activation of immune cells like T and B lymphocytes results in their participation in specific antigen immune responses, leading to the release of cytokines such as Interferon-γ (IFN-γ) and Interleukin-2 (IL-2), thereby enhancing the immune response[24,25]. Furthermore, TNFSF14 can modulate inflammatory responses by influencing macrophage activation, directing them to respond to infections or injuries, thus aiding in pathogen clearance and tissue repair, effectively regulating the inflammatory response[24,26]. Studies[5,27] have revealed that DHA possesses anti-inflammatory properties, with elevated levels capable of suppressing immune cell functions and reducing the production of inflammatory cytokines, potentially achieved through the reduction of TNFSF14 production or release. It is our hypothesis that the impact of DHA on AD risk is associated with the downregulation of TNFSF14 expression and the inhibition of the inflammatory response. However, it is essential to note that in MR analysis, TNFSF14 levels represent the overall inflammation status of the organism. Consequently, our analysis suggests a negative causal relationship between DHA levels and AD risk, implying that DHA acts to inhibit the inflammatory response.

AD is a chronic and recurrent inflammatory skin condition, where various cytokines, including TNFSF14, are believed to potentially mediate its pathogenesis[28]. In the plasma of AD patients, there is a significant upregulation of various cytokines, including TNFSF14[28]. Inflammatory cells are activated and release numerous cytokines. Elevated levels of TNFSF14 are indicative of a potentially

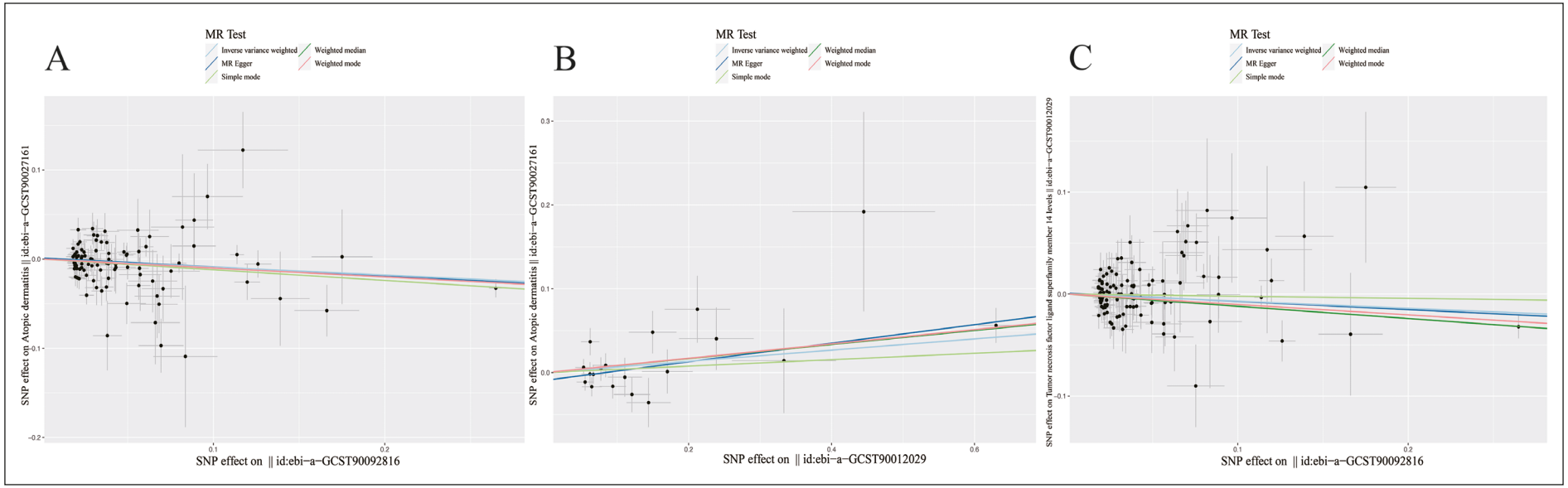

Figure 1. Scatter plots. **A**, Exposure: Docosahexaenoic acid. Outcome: Atopic dermatitis. **B**, Exposure: Tumor necrosis factor ligand superfamily member 14. Outcome: Atopic dermatitis. **C**, Exposure: Docosahexaenoic acid. Outcome: Tumor necrosis factor ligand superfamily member 14. Each black dot represents a single nucleotide polymorphism (SNP), positioned according to the SNPs impact on the risk of outcomes, along with their respective standard error bars. The slopes of the lines correspond to causal estimates derived from various methods.

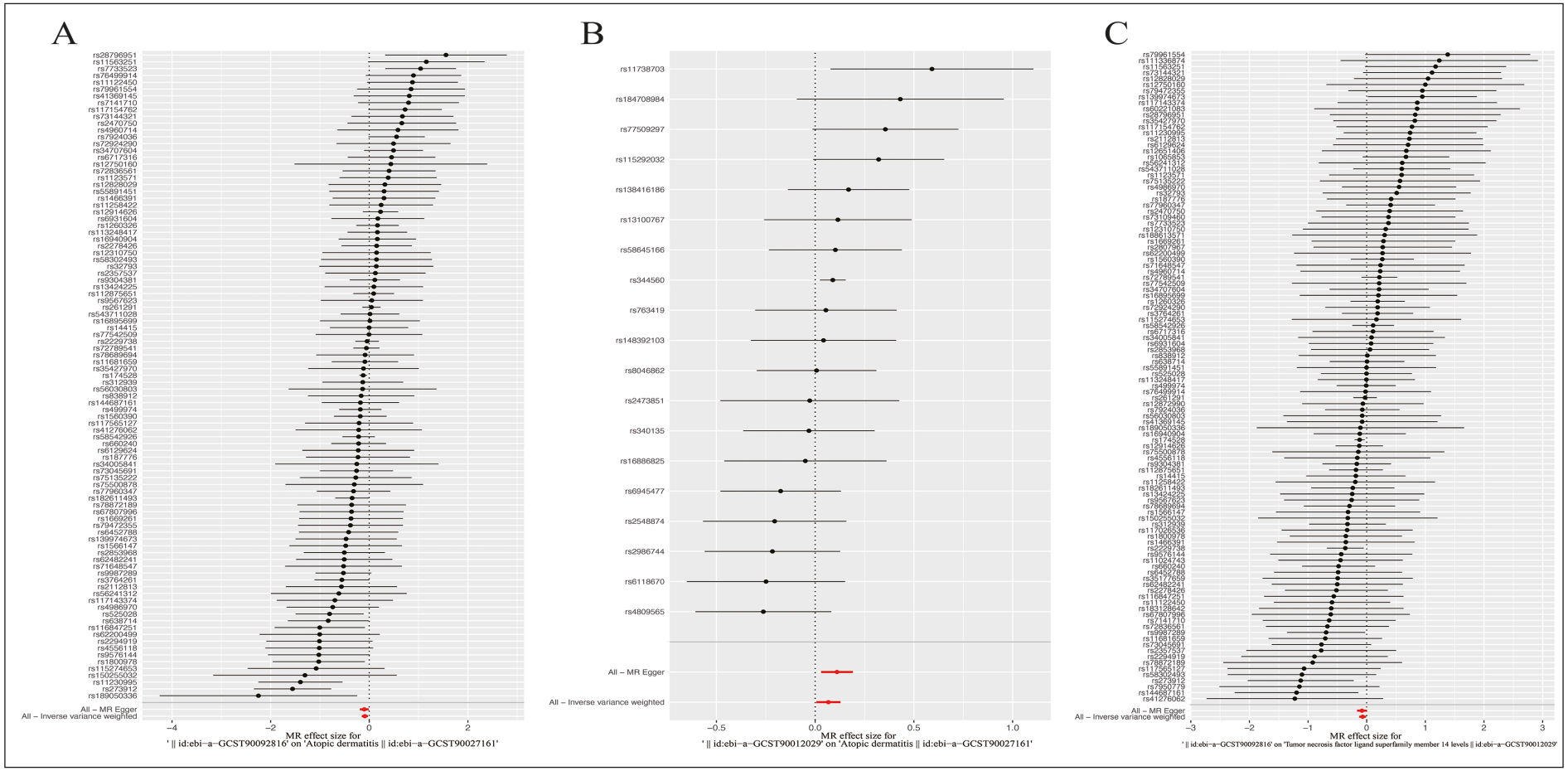

Figure 3. Forest plots. **A**, Exposure: Docosahexaenoic acid. Outcome: Atopic dermatitis. **B**, Exposure: Tumor necrosis factor ligand superfamily member 14. Outcome: Atopic dermatitis. **C**, Exposure: Docosahexaenoic acid. Outcome: Tumor necrosis factor ligand superfamily member 14. The dot and bar represent the causal estimate for outcomes (forest plots).

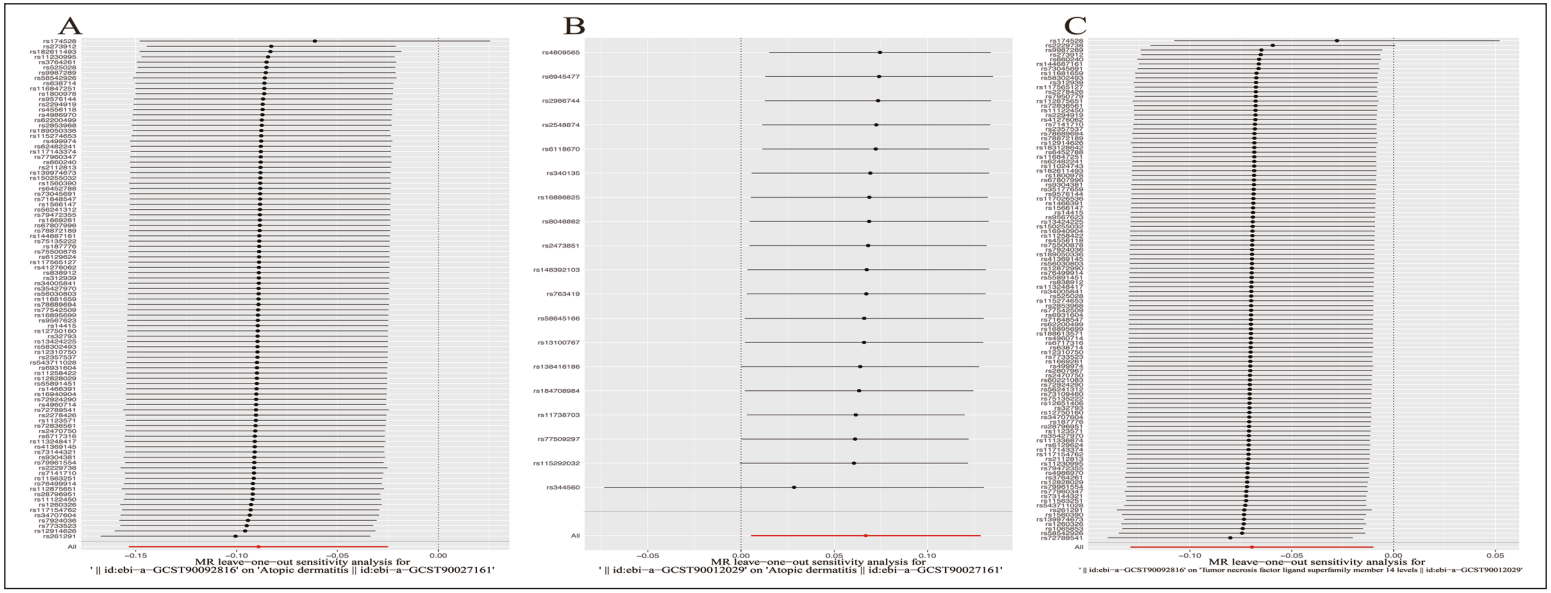

Figure 3. Leave-one-out sensitivity analysis plots. **A**, Exposure: Docosahexaenoic acid. Outcome: Atopic dermatitis. **B**, Exposure: Tumor necrosis factor ligand superfamily member 14. Outcome: Atopic dermatitis. **C**, Exposure: Docosahexaenoic acid. Outcome: Tumor necrosis factor ligand superfamily member 14. The dot and bar indicate the estimates and 95% confidence interval when the specific single nucleotide polymorphism is removed.

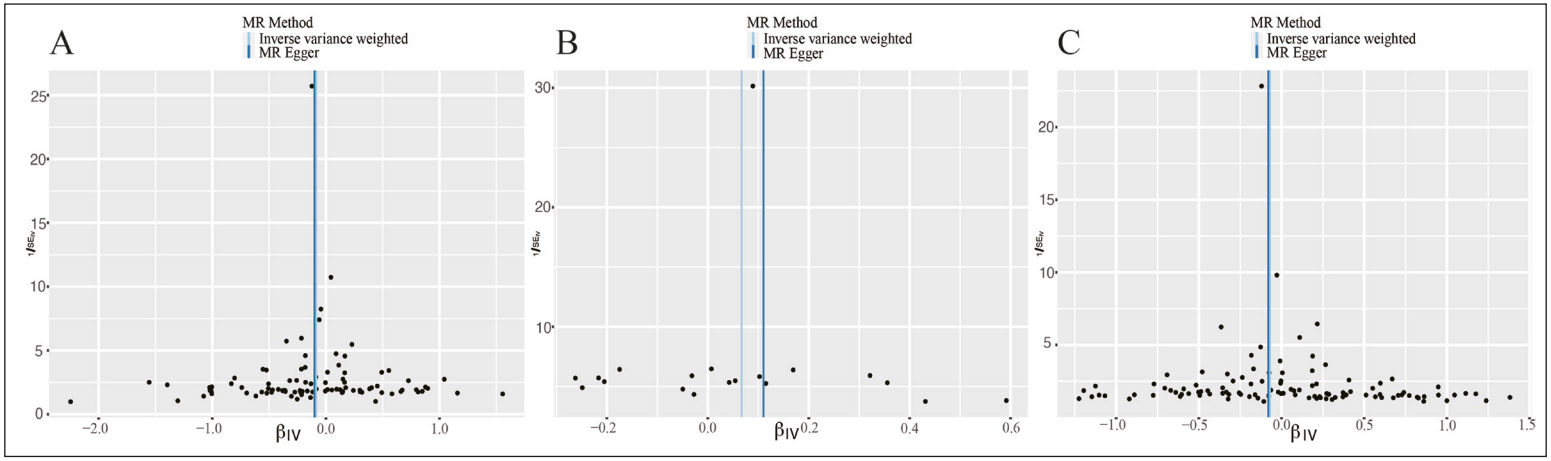

Figure 4. Funnel plot. **A**, Exposure: Docosahexaenoic acid. Outcome: Atopic dermatitis. **B**, Exposure: Tumor necrosis factor ligand superfamily member 14. Outcome: Atopic dermatitis, **C**, Exposure: Docosahexaenoic acid. Outcome: Tumor necrosis factor ligand superfamily member 14. Each black dot indicates a single nucleotide polymorphism.

higher risk of AD. Therefore, there is a causal relationship between TNFSF14 and the risk of AD. Inflammatory cells and related cytokines are considered to be associated with the occurrence and exacerbation of AD. Thus, inhibiting the inflammatory response, particularly the key cytokines within it, is a crucial aspect of preventing and treating AD. In summary, our study provides genetic evidence for the adjunctive role of DHA in reducing the risk of AD and offers potential mechanisms that warrant further in-depth analysis.

However, it is essential to acknowledge that this study has several limitations that warrant consideration. Firstly, while the MR-Egger intercept test did not reveal evidence of pleiotropy effects, it is important to acknowledge that fully ruling out the possibility of directional pleiotropy in any MR study remains challenging[10]. Secondly, our study population primarily consisted of individuals of European descent, which may introduce some limitations in terms of the generalizability of the results. Thirdly, it must be acknowledged that the calculated percentage of mediated effect was relatively low, underscoring the potential need for further research and data to gain a more comprehensive understanding of the causal relationship between DHA and AD risk. Finally, it is essential to recognize that our assessment of causality is based on MR, which leverages the genetic information for each trait and, therefore, requires cautious interpretation, as the occurrence and development of AD are inherently multifactorial.

Conclusions

In summary, our study employs MR analysis to offer genetic evidence indicating a potential role of DHA in reducing the risk of AD, as well as opening avenues for further in-depth investigation into potential mechanisms. These findings emphasize the importance of ongoing research in this field.

Supplementary Materials

The datasets used in this study are accessible to online repositories. The names of these repositories and their corresponding identification numbers can be located within the article and supplementary material.

Authors' Contributions

X.-W. Huang, S.-W. Pang and L.-Z. Yang conceived of and designed the study. X.-W. Huang, S.-W. Pang and L.-Z. Yang drafted the paper. X.-W. Huang, J.-M. Chen and C.-W. Huang collected data. X.-W. Huang, T. Han, L. Liao and P.-J. Xie analyzed and interpreted the data. S.-W. Pang, L.-Z. Yang, J.-M. Chen and C.-W. Huang consulted the literature and helped with language.

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Ethics Approval

Not appplicable.

Informed Consent

Not appplicable.

Data Availability

Data is available in a publicly accessible repository that does not issue DOIs. Publicly available datasets were analyzed in this study. This data can be found here: [https://gwas.mrcieu.ac.uk/].

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Conflict of Interest

The authors declare no conflict of interest.

References

1) Frazier W, Bhardwaj N. Atopic Dermatitis: Diagnosis and Treatment. Am Fam Physician 2020; 101: 590-598.
2) Bieber T, Paller AS, Kabashima K, Feely M, Rueda MJ, Ross Terres JA, Wollenberg A. Atopic dermatitis: pathomechanisms and lessons learned from novel systemic therapeutic options. J Eur Acad Dermatol Venereol JEADV 2022; 36: 1432-1449.
3) Reszke R, Szepietowski JC. Itch and Psyche: Bilateral Associations. Acta Derm Venereol 2020; 100: adv00026.

4) Kuzina O, Nives P. The Role of Probiotics, Vitamin D and Omega-3 Fatty Acids in Pathophysiology, Prevention and Treatment of Atopic Dermatitis. Repository of Faculty of Pharmacy and Biochemistry University of Zagreb [Internet]. 2022 [cited 2023 Oct 8]; Available from: https://urn.nsk.hr/urn:nbn:hr:163:124936.
5) Gutiérrez S, Svahn SL, Johansson ME. Effects of Omega-3 Fatty Acids on Immune Cells. Int J Mol Sci 2019; 20: 5028.
6) Yamagata K. Docosahexaenoic acid regulates vascular endothelial cell function and prevents cardiovascular disease. Lipids Health Dis 2017; 16: 118.
7) Abdelnour AM, Shareef SJ, Kreuser K, Ashack K. 319 Effects of omega-3 fatty acid supplementation on atopic dermatitis. Br J Dermatol 2023; 188: ljac140.015.
8) Furuhjelm C, Warstedt K, Fagerås M, Fälth-Magnusson K, Larsson J, Fredriksson M, Duchén K. Allergic disease in infants up to 2 years of age in relation to plasma omega-3 fatty acids and maternal fish oil supplementation in pregnancy and lactation. Pediatr Allergy Immunol Off Publ Eur Soc Pediatr Allergy Immunol 2011; 22: 505-514.
9) Gunaratne AW, Makrides M, Collins CT, Gibson RA, McPhee AJ, Sullivan TR, Gould JF, Green TJ, Doyle LW, Davis PG, French NP, Colditz PB, Simmer K, Morris SA, Best KP. Docosahexaenoic acid supplementation of preterm infants and parent-reported symptoms of allergic disease at 7 years corrected age: follow-up of a randomized controlled trial. Am J Clin Nutr 2019; 109: 1600-1610.
10) Boehm FJ, Zhou X. Statistical methods for Mendelian randomization in genome-wide association studies: A review. Comput Struct Biotechnol J 2022; 20: 2338-2351.
11) Lin JY, Ma LJ, Yuan JP, Yu P, Bai BX. Causal effects of fatty acids on atopic dermatitis: A Mendelian randomization study. Front Nutr 2023; 10: 1083455.
12) Davis DMR, Drucker AM, Alikhan A, Bercovitch L, Cohen DE, Darr JM, Eichenfield LF, Frazer-Green L, Paller AS, Silverberg JI, Singh AM, Sidbury R. American Academy of Dermatology Guidelines: Awareness of comorbidities associated with atopic dermatitis in adults. J Am Acad Dermatol 2022; 86: 1335-1336.e18.
13) Richardson TG, Leyden GM, Wang Q, Bell JA, Elsworth B, Davey Smith G, Holmes MV. Characterising metabolomic signatures of lipid-modifying therapies thr ough drug target mendelian randomisation. PLoS Biol 2022; 20: e3001547.
14) Folkersen L, Gustafsson S, Wang Q, Hansen DH, Hedman ÅK, Schork A, Page K, Zhernakova DV, Wu Y, Peters J, Eriksson N, Bergen SE, Boutin TS, Bretherick AD, Enroth S, Kalnapenkis A, Gådin JR, Suur BE, Chen Y, Matic L, Gale JD, Lee J, Zhang W, Quazi A, Ala-Korpela M, Choi SH, Claringbould A, Danesh J, Davey Smith G, de Masi F, Elmståhl S, Engström G, Fauman E, Fernandez C, Franke L, Franks PW, Giedraitis V, Haley C, Hamsten A, Ingason A, Johansson Å, Joshi PK, Lind L, Lindgren CM, Lubitz S, Palmer T, Macdonald-Dunlop E, Magnusson M, Melander O, Michaelsson K, Morris AP, Mägi R, Nagle MW, Nilsson PM, Nilsson J, Orho-Melander M, Polasek O, Prins B, Pålsson E, Qi T, Sjögren M, Sundström J, Surendran P, Võsa U, Werge T, Wernersson R, Westra HJ, Yang J, Zhernakova A, Ärnlöv J, Fu J, Smith JG, Esko T, Hayward C, Gyllensten U, Landen M, Siegbahn A, Wilson JF, Wallentin L, Butterworth AS, Holmes MV, Ingelsson E, Mälarstig A. Genomic and drug target evaluation of 90 cardiovascular proteins in 30,931 individuals. Nat Metab 2020; 2: 1135-1148.
15) Sliz E, Huilaja L, Pasanen A, Laisk T, Reimann E, Mägi R, FinnGen, Estonian Biobank Research Team, Hannula-Jouppi K, Peltonen S, Salmi T, Koulu L, Tasanen K, Kettunen J. Uniting biobank resources reveals novel genetic pathways modulating su sceptibility for atopic dermatitis. J Allergy Clin Immunol 2022; 149: 1105-1112.e9.
16) Skrivankova VW, Richmond RC, Woolf BAR, Yarmolinsky J, Davies NM, Swanson SA, VanderWeele TJ, Higgins JPT, Timpson NJ, Dimou N, Langenberg C, Golub RM, Loder EW, Gallo V, Tybjaerg-Hansen A, Davey Smith G, Egger M, Richards JB. Strengthening the Reporting of Observational Studies in Epidemiology Using Mendelian Randomization: The STROBE-MR Statement. JAMA 2021; 326: 1614-1621.
17) Kwok MK, Kawachi I, Rehkopf D, Schooling CM. The role of cortisol in ischemic heart disease, ischemic stroke, type 2 diabetes, and cardiovascular disease risk factors: a bi-directional Mendelian randomization study. BMC Med 2020; 18: 1-14.
18) Kamat MA, Blackshaw JA, Young R, Surendran P, Burgess S, Danesh J, Butterworth AS, Staley JR. PhenoScanner V2: an expanded tool for searching human genotype-phenoty pe associations. Bioinforma Oxf Engl 2019; 35: 4851-4853.
19) Buniello A, MacArthur JAL, Cerezo M, Harris LW, Hayhurst J, Malangone C, McMahon A, Morales J, Mountjoy E, Sollis E, Suveges D, Vrousgou O, Whetzel PL, Amode R, Guillen JA, Riat HS, Trevanion SJ, Hall P, Junkins H, Flicek P, Burdett T, Hindorff LA, Cunningham F, Parkinson H. The NHGRI-EBI GWAS Catalog of published genome-wide association studie s, targeted arrays and summary statistics 2019. Nucleic Acids Res 2019; 47: D1005-D1012.
20) Burgess S, Bowden J, Fall T, Ingelsson E, Thompson SG. Sensitivity Analyses for Robust Causal Inference from Mendelian Random ization Analyses with Multiple Genetic Variants. Epidemiol Camb Mass 2017; 28: 30-42.
21) Lin Z, Pan I, Pan W. A practical problem with Egger regression in Mendelian randomization. PLoS Genet 2022; 18: e1010166.
22) Li Y, Li Q, Cao Z, Wu J. The causal association of polyunsaturated fatty acids with allergic disease: A two-sample Mendelian randomization study. Front Nutr 2022; 9: 962787.

23) Li J, Pora BLR, Dong K, Hasjim J. Health benefits of docosahexaenoic acid and its bioavailability: A review. Food Sci Nutr 2021; 9: 5229-5243.

24) Ware CF, Croft M, Neil GA. Realigning the LIGHT signaling network to control dysregulated inflammation. J Exp Med 2022; 219: e20220236.

25) Bechill J, Muller WJ. Herpesvirus entry mediator (HVEM) attenuates signals mediated by the lymphotoxin β receptor (LTβR) in human cells stimulated by the shared ligand LIGHT. Mol Immunol 2014; 62: 96-103.

26) Shi JH, Sun SC. Tumor Necrosis Factor Receptor-Associated Factor Regulation of Nuclear Factor κB and Mitogen-Activated Protein Kinase Pathways. Front Immunol 2018; 9: 1849.

27) Honda KL, Lamon-Fava S, Matthan NR, Wu D, Lichtenstein AH. Docosahexaenoic acid differentially affects TNFα and IL-6 expression in LPS-stimulated RAW 264.7 murine macrophages. Prostaglandins Leukot Essent Fatty Acids 2015; 97: 27-34.

28) Herro R, Croft M. The control of tissue fibrosis by the inflammatory molecule LIGHT (TNF Superfamily member 14). Pharmacol Res 2016; 104: 151-155.