Clinical, Cosmetic and Investigational Dermatology

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

Association Between Genetically Elevated Omega-3 Polyunsaturated Fatty Acids and Skin Disease Risk: A Mendelian Randomization Study

Jia Min Chen[1,*], Yan Wang[2,*], Yan Shi[3]

[1]The Fourth School of Clinical Medicine, Zhejiang Chinese Medical University, Hangzhou, Zhejiang, People's Republic of China; [2]Department of Reproductive Medicine, Hangzhou Red Cross Hospital, Hangzhou, Zhejiang, People's Republic of China; [3]Department of Acupuncture, Hangzhou First People's Hospital, Hangzhou, Zhejiang, People's Republic of China

*These authors contributed equally to this work

Correspondence: Yan Shi, Email zjshane40@163.com

Background: Omega-3 polyunsaturated fatty acids (PUFAs) are potential targets for the treatment of skin diseases due to their anti-inflammatory and immunomodulatory effects. By leveraging a genetic approach known as Mendelian randomization (MR), we sought to determine the causal impact of PUFAs on the likelihood of developing skin diseases among individuals of European ancestry.

Methods: We integrated GWAS data from the CHARGE consortium and UK Biobank to identify genetic instruments for omega-3 PUFAs and desaturase activity, using two-sample MR to assess their associations with six skin diseases.

Results: Elevated levels of omega-3 fatty acids were found to substantially lower the probability of experiencing atopic dermatitis (0.92, [0.85,0.98]), while increased DPA levels correlated with a substantial increase in the probability of squamous cell carcinoma occurrence (2.25, [1.29,3.92]). Increased DHA levels were also associated with a reduced risk of atopic dermatitis (0.90, [0.84,0.96]) but increased the risk of solar dermatitis (1.38, [1.09,1.73]). In addition, tissue-type specific MR analysis revealed that elevated FADS1 expression in fibroblasts significantly inhibited atopic dermatitis development (β = −0.181, [−0.276,-0.0853]), while elevated FADS2 expression in non-sun-exposed skin tissues was associated with a reduced risk of squamous cell carcinoma (β = −0.562, [−0.833,-0.029]). Conversely, heightened FADS2 expression was strongly linked to a greater likelihood of developing atopic dermatitis in both sun-exposed and sun-protected skin areas (β = 0.107, [0.0348,0.179]; β = 0.192, [0.114,0.0270], respectively).

Conclusion: This study reveals the causal role of omega-3 PUFAs and FADS expression in specific tissues and blood in skin diseases. These findings underscore the potential of PUFA biosynthesis pathways as therapeutic targets for skin disease interventions.

Keywords: Mendelian randomization, ω3 polyunsaturated fatty acids, delta-5 desaturase, delta-6 desaturase, atopic dermatitis, squamous cell carcinoma

Skin diseases are a major global health concern, significantly impacting the health and quality of life of 30–70% of the population.[1] Despite their prevalence, the absence of safe and effective treatments for many skin conditions not only prolongs patient suffering but also imposes a substantial burden on health-care systems. Identifying and investigating potential interventions and therapeutic targets to prevent or treat these conditions is essential for improving patient outcomes and advancing dermatological research and care.

Food intake is essential for sustaining vital functions and building the body's organs. Among the nutrients obtained from food, Fatty acids, as one of the key nutrients derived from food, significantly contribute to the development of cellular structures and the proper functioning of cells. Omega-3 polyunsaturated fatty acids (PUFAs) are characterized by a carbon chain of 18 or more atoms, featuring a distinctive double bond near the terminal methyl group, include three key types: alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA).[2] In the liver, ALA undergoes enzymatic processes (including desaturases, elongases, etc.) that in turn converts it to EPA and subsequently

Received: 26 February 2025
Accepted: 1 August 2025
Published: 26 September 2025

into DHA. However, the efficiency of this conversion is extremely low due to limited enzyme availability, highlighting the importance of omega-3 supplementation through fish oil-rich foods or dietary supplements.[3]

Omega-3 PUFAs have demonstrated anti-inflammatory effects in systemic diseases. Through their metabolites, omega-3 PUFAs modulate various immune and structural cells in the skin, including dendritic cells, CD4+ T cell, NK-Cell, neutrophils, and epithelial cells.[4,5] Despite the importance of this topic, large-scale observational studies and clinical trials in humans, particularly regarding malignant tumors, are lacking. Existing observational studies are further limited by inter-study heterogeneity and methodological issues. The relationship between dietary intake, as assessed through recall methods, and the levels of fatty acid biomarkers in the body has been shown to be weak to moderate. These gaps highlight the need for additional evidence to clarify whether omega-3 PUFAs have a causal role in skin diseases.[6,7] Given that fatty acid composition is influenced by genetic factors, particularly in blood fractions, we conducted an MR study focused on evaluating the relevance of omega-3 PUFAs to specific skin diseases. Delta-5 desaturase (D5D) and delta-6 desaturase (D6D) are crucial enzymes that play a central role in the production of polyunsaturated fatty acids, which require multiple metabolic steps. D6D catalyzes the desaturation of linoleic acid (LA) and alpha-linolenic acid (ALA) into gamma-linolenic acid (GLA) and stearidonic acid (SDA), respectively. Similarly, D5D catalyzes the desaturation of dihomo-gamma-linolenic acid (DGLA) and eicosatetraenoic acid (ETA) to produce arachidonic acid (AA) and eicosapentaenoic acid (EPA).[8] To minimize the effects of horizontal pleiotropy, we used protein-level exposures for MR analysis. The primary focus was placed on the functional roles of delta-5 and delta-6 desaturase enzymes, governed by genetic regions associated with fatty acid metabolism, specifically involving the FADS1 and FADS2 loci.[9,10] By integrating expression quantitative trait loci (eQTLs) data from various tissues and cell types, MR analysis provides a robust framework for predicting the functional implications of these genes and their variants in the context of skin diseases(See Supplementary Table 1 for details).[11]

The central aim of this study was to apply Mendelian randomization (MR) techniques to investigate the potential causal effects that omega-3 fatty acids may have on the occurrence of skin diseases. We focused on six skin diseases. Their prevalence in the European population is more than 20%, and there has been controversy in observational studies on the relationship between PUFAs and diseases. To identify potential genetic targets, we employed a cis-eQTL-based MR approach to assess the tissue type-specific and cell-type specific causal impact of FADS1 and FADS2 genetic expression on six distinct skin diseases.

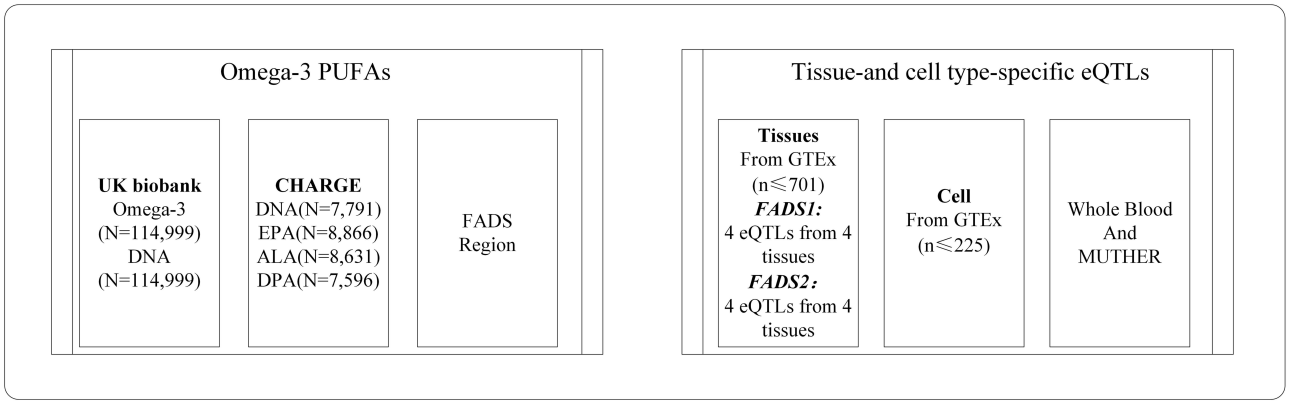
Methodologies

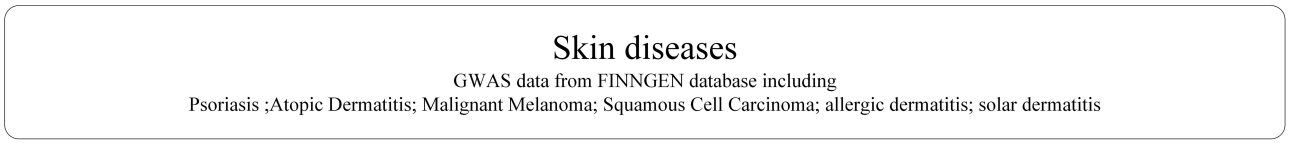
General Study Design

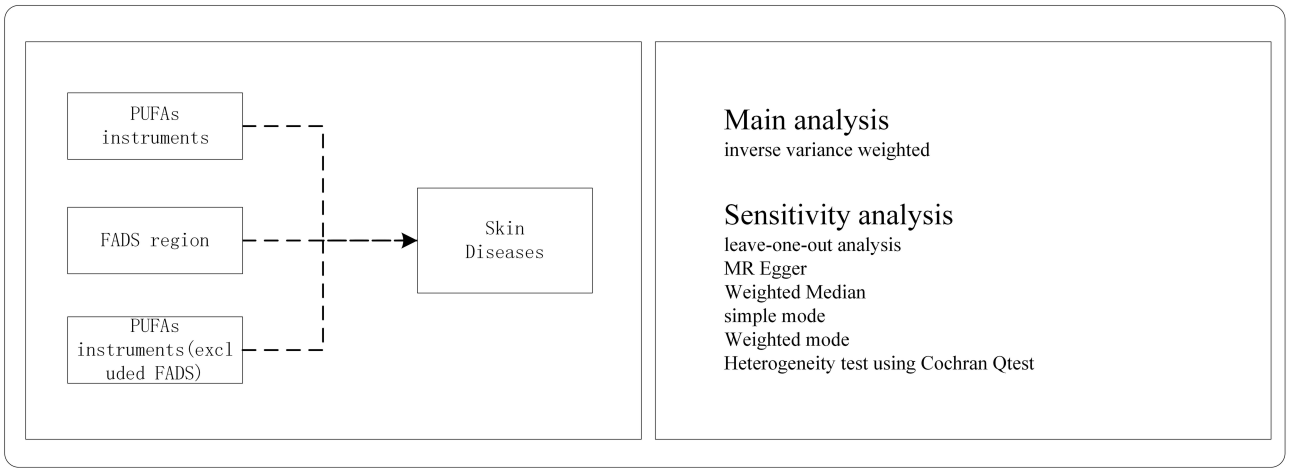
Figure 1 illustrates the overall study design. The study consisted of three main components: (i) the definition of PUFA and the design of exposure tools (ii) two-sample MR analysis was applied to investigate the potential causal effects of omega-3 fatty acids on six skin diseases. (iii) Conducting specific MR analysis using tissue-type specific and cell-type specific eQTLs as instruments to assess the effects of functional genes (FADS1 and FADS2) in skin tissues, cells, and blood on six skin diseases. The necessary ethical clearances were acquired for each of the initial research studies.

Genome-wide association study (GWAS) summary statistics for omega-3 PUFAs—including those like ALA, EPA, DPA, and DHA—were sourced from the CHARGE consortium and the UK Biobank. Although minimal sample overlap exists between the data sources, the cis-eQTL data and the outcome datasets share no common genetic variants, thereby minimizing the impact of sample overlap on the majority of the MR results. To ensure robust instrumental variables, we performed linkage disequilibrium (LD) clumping on omega-3 PUFAs (EPA, DHA, DPA and ALA) and excluded SNPs with minor allele frequencies (MAF) <0.01 or those that did not meet the whole-genome level significance threshold ($P \leq 5 \times 10^{-8}$).

For the primary exposure instrument (focused on omega-3 PUFAs), we selected the pooled data of 6 polyunsaturated fatty acids from 2 studies for LD clumping and selected the resulting variants as instruments. For omega-3 fatty acids, 43 SNPs were identified for omega-3 PUFA, and 34 SNPs were selected specifically for DHA from the UK Biobank. A meta-analysis using inverse-variance weighting was performed on data from 114,999 participants of European descent as part of the UK Biobank's genome-wide association study. The CHARGE consortium analyzed the associations of plasma phospholipid levels of four types of omega-3 PUFAs in approximately 8,000 individuals of







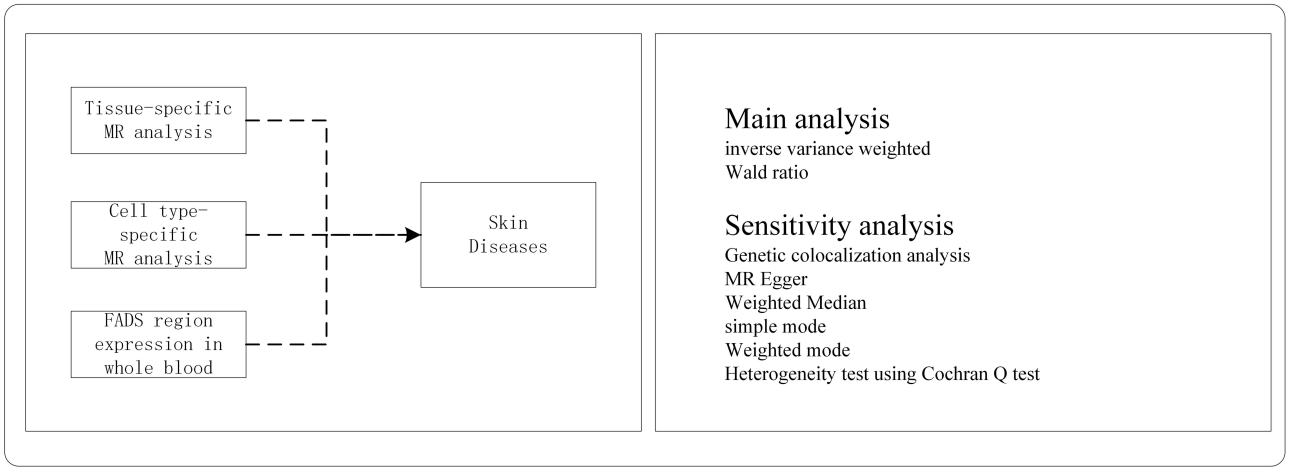


Figure 1 Flow chart of the entire study design.

https://doi.org/10.2147/CCID.S524519

European ancestry. From this dataset, instrumental variables were identified as follows: 8 SNPs for alpha-linolenic acid (ALA), 6 SNPs for docosahexaenoic acid (DHA), 26 SNPs for eicosapentaenoic acid (EPA), and 12 SNPs for docosapentaenoic acid (DPA).

Genetic Tools for FADS1 and FADS2 Expression in Specialized Tissues

The cis-eQTL data for FADS1 and FADS2 expression genes were sourced from the GTEx project (v8) and include various tissue types, such as skin from the suprapubic area (not exposed to sunlight), skin from the lower leg (sun-exposed), fibroblasts, and lymphocytes (See Supplementary Table 2 for details).

For these four tissues, the original study applied a threshold of a false discovery rate (FDR) below 5% to select independent cis-eQTLs, which were then used as instruments for tissue-type specific MR analysis. Finally, four cis-e QTLs for FADS1 gene and four cis-e QTLs for FADS2 gene were generated in four tissues.

Data related to cis-eQTL analysis at the single-cell level for the genes FADS1 and FADS2 were derived from the cell-type-specific research conducted by GTEx. This dataset included epithelial cells and keratinocytes derived from suprapubic skin (sunlight-unexposed) and lower-extremity skin (sunlight-exposed) (See Supplementary Table 3 for details). One FADS1 and one FADS2 expressing cis-eQTLs were detected in both types of cells, respectively (FDR < 0.05).

The eQTLGen Consortium provided cis-eQTL data for *FADS1* and *FADS2* expression across 31,470 individuals, identifying four and three cis-eQTLs, respectively.

Outcome Data

The genetic association data for genome-wide association studies concerning both skin diseases were sourced from the R10 dataset provided by the FinnGen consortium. We focused on six dermatologic conditions, and the specific inclusion data are listed below: Psoriasis (including 11,479 case and 437,420 control), Atopic Dermatitis (including 26,905 case and 394,476 control), Malignant melanoma of skin (including 3,932 case and 345,118 control), squamous cell carcinoma (including 4,078 case and 345,118 control), Allergic dermatitis (including 5,331 case and 394,476 control) and Solar Dermatitis (including 1,175 case and 438,369 control) (See Supplementary Table 4 for details). Individuals were excluded if they had undetermined gender, a high genotypic failure rate (>5%), or non-Finnish descent. Disease diagnoses were based on the International Classification of Diseases (ICD) codes from the 8th, 9th, and 10th revisions.

Statistical Analyses

After harmonizing the SNPs across exposure tools and six skin diseases, including psoriasis and squamous cell carcinoma, associations were estimated by inverse variance weighting (IVW) using the TwosampleMR R package (version 0.6.6).

A random effects framework was employed to calculate the variability of IVW estimates, except when analysis relied only on two or less separate SNP tools.[12] To assess the robustness of the results, a leave-one analysis was performed to examine the effect of removing individual SNPs on association. An alpha threshold of 0.0083 (Bonferroni correction: 0.05/6 skin diseases) was applied to identify statistically significant associations.[12]

MR Analysis of FADS1 and FADS2 expression in Whole Blood on Skin Diseases

The IVW method was applied to assess the influence of individual SNPs on the associations between FADS1 and FADS2 expression in whole blood and skin diseases (See Supplementary Table 5 for details).

MR Analyses Tailored to Specific Tissues and Cell Types

In tissue-type specific MR analyses, data from GTEx were used to estimate the expression of FADS1 and FADS2 in four skin tissues, aiming to infer their causal effects on skin diseases. Given the availability of only one instrumental variable per tissue, the Wald ratio method was employed to estimate these causal effects.[13]

In cell type-specific MR analyses, the Wald ratio method was similarly used to evaluate the potential causal effect of FADS1 and FADS2 expression in two epithelial and two keratinocyte cell types. This analysis provided further insights into the role of these genes in specific cell types related to skin diseases (See Supplementary Table 6 for details).

Leave-One-Out Analysis

Biomarkers of Enzyme Activity and Genetic Tools

To assess enzyme activity, the following product-to-substrate ratios were used as biomarkers:

D5D activity: The proportion of arachidonic acid relative to dihomo-gamma-linolenic acid (AA:DGLA) is used as a metric for analysis.

D6D activity: The proportion of gamma-linolenic acid relative to linoleic acid (GLA:LA) is used as a metric for analysis.

In the analysis of populations of European ancestry, we utilized Genome-Wide Inferential Statistics for Multiple Phenotypic Functions (GWIS) to examine pooled data for AA, DGLA, GLA, and LA from the CHARGE (sample size N = 8631).[14] Genetic variations associated with D5D and D6D enzyme activity were identified by analyzing genome-wide data using statistical significance criteria, along with linkage disequilibrium (LD) clustering.

The SNP rs174546, located within the FADS gene region, was identified as the genetic variant most strongly associated with the AA:DGLA ratio trait. It was used as a genetic tool to infer the causal effect of PUFA desaturase activity via the Wald ratio method. To evaluate the broader genetic contributions, we excluded rs174546 and other FADS-related variations to assess the effects of genetic variants outside the FADS region (See Supplementary Table 7 for details).

Sensitivity Analysis Concerning Potential Violations of Assumptions

The derivation of causal effects from our estimations necessitates that a genetic variant be qualified as an instrumental variable, which is contingent upon its compliance with the following three methodological assumptions: 1. There is a strong association between the genetic variant and the exposure factor. 2. The genetic marker is independent of any confounding variables, including but not limited to BMI, social factors, ethnicity, gender, or age. 3. The genetic marker does not have a direct effect on the outcome but rather exerts influence solely via its relationship with the factor under study.

Genetic Colocalization Analysis

Co-localization analyses were conducted to determine whether the observed associations between FADS1 and FADS2 expression and six skin diseases shared the same causal genetic variants. This approach enabled the calculation of posterior probabilities, providing evidence to distinguish true causal relationships from spurious genomic confounding. By integrating this evidence, co-localization analysis helped validate the robustness of the observed associations and clarify the causal links between gene expression signals and disease phenotypes.

In this study, we used a Bayesian co-localization method called COLOC for gene co-localization analysis.[15]

Result

Effects of Omega-3 Fatty Acids on Six Skin Diseases

We evaluated the potential effects of omega-3 PUFAs with six skin diseases by MR analysis, which showed that certain omega-3 PUFAs were linked to the risk of some selected skin diseases ($P < 0.0083$): the omega-3 group exhibited a reduced likelihood of developing atopic dermatitis (OR = 0.92, 95% CI [0.86,0.98]); the DPA group was correlated with an increased risk of squamous cell carcinoma (OR = 2.25, 95% CI [1.29, 3.92]); The DHA group in the UK Biobank cohort demonstrated an increased likelihood of developing solar dermatitis. (OR = 1.38, 95% CI [1.09, 1.73]) and a lower risk of atopic dermatitis (OR = 0.90, 95% CI [0.84, 0.96]). Omega-3 PUFAs did not show any relevant impact on the other skin conditions studied. Previous studies have demonstrated that long-chain polyunsaturated fatty acids (PUFAs) potentiate ultraviolet radiation-induced oxidative stress in cutaneous cells.[16] (Further significant results of the study can be found in Figure 2).

Additionally, MR analysis excluding instrumental variables within the FADS region showed no evidence of causal associations between omega-3 PUFAs and skin diseases ($P > 0.0083$).

Tissue type-specific and cell type-specific effect of FADS1 and FADS2 expression on skin diseases

Given the well-established importance of FADS in the development of six skin diseases, we carried out an in-depth analysis to investigate the gene expression effects of FADS1 and FADS2 across different tissues and cell types. We focused on five tissues containing FADS1 and four tissues containing FADS2. MR analysis results showed that in fibroblasts, elevated expression levels of FADS1 were associated with a reduced risk of atopic dermatitis ($\beta = -0.181$,95% CI (−0.276,-0.0853),$P = 2.04 \times 10^{-4}$). No

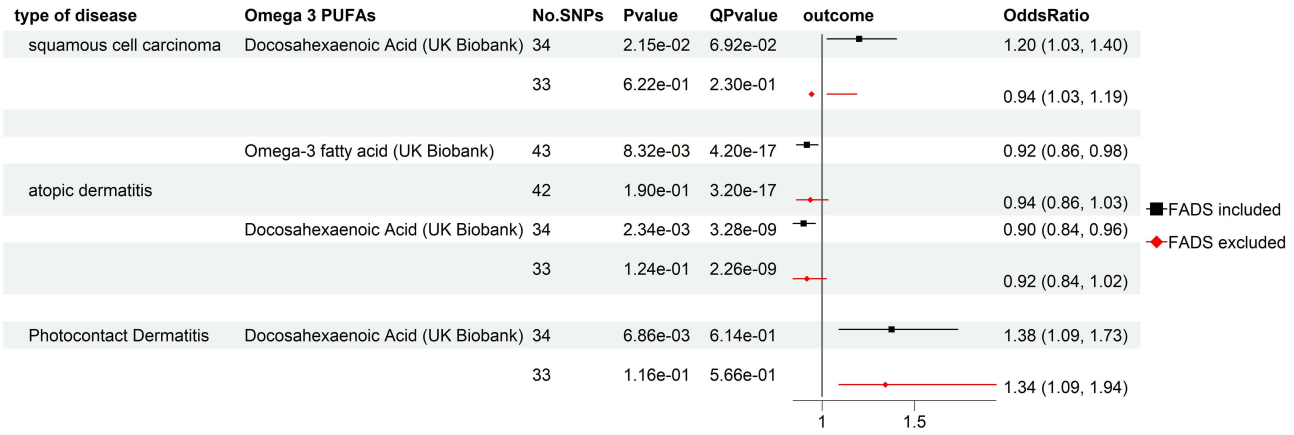


Figure 2 Association between genetically proxied polyunsaturated fatty acid and risk of skin diseases. Summary data on outcomes for skin disorders are from the FinnGen study.Summary data on fatty acid exposure were obtained from the CHARGE consortium or the UK Biobank.QP values were derived from Cochran's Q test for heterogeneity between MR results for SNPs in genetic instruments.The p-value column represents the p-value for the association between PUFA and skin disease, derived from inverse variance-weighted linear regression.The Number of SNPs column represents the number of SNPs present in the genetic tool.FADS regions are either included (black data points) or excluded (red data points).
Abbreviation: PUFA, polyunsaturated fatty acids.

significant associations were observed for FADS gene expression levels in lymphocytes. In addition, no relationship between FADS expression levels and skin diseases was observed in skin tissues from the MUTHER experiment (See Figures 3 and 4 further details).

In non-sun-exposed skin tissues (suprapubic), increased FADS2 expression suppressed the development of squamous cell carcinoma (β = −0.562, 95% CI [−0.833, −0.029], $P = 4.97 \times 10^{-5}$), whereas decreased FADS2 expression suppressed the development of atopic dermatitis (β = 0.192, 95% CI [0.114, 0.027], $P = 1.30 \times 10^{-6}$). In sun-exposed skin tissues (leg), elevated FADS2 expression was significantly and positively associated with increased atopic dermatitis occurrence (β = 0.107, 95% CI [0.0348, 0.179], $P = 3.64 \times 10^{-3}$) (See Supplementary Table 8 for details).

Mendelian Randomization analyses specific to different cell types, using cis-eQTL data from skin cells, indicated that FADS1 and FADS2 expression levels in these cells do not have a causal impact on the six skin diseases ($P > 0.0083$).

We then estimated the potential causal relationship between FADS1 and FADS2 expression in whole blood with six skin diseases, incorporating four cis-eQTL of FADS1 and three cis-eQTL of FADS2. MR analysis showed no significant associations with the six skin diseases. No signs of heterogeneity were found in any of the trials, with the exception of the causal link between FADS2 and psoriasis. The representative results selected based on colocalization analysis are shown in Figure 5; additional supporting images can be found in the supplementary material.

Discussions

This study revealed how the expression levels of FADS1 and FADS2 in different tissue types and cells influence the development of skin diseases, using genetic analysis techniques. Expression data in whole blood further confirmed the link between PUFA desaturase activity and disease.

Possible Mechanism

Our results suggest that heightened activity of PUFA desaturases may have a causal link to the risk of atopic dermatitis and cutaneous squamous cell carcinoma. This aligns with existing studies and reveals multiple mechanisms of PUFA metabolites in inflammatory and neoplastic diseases.

Atopic dermatitis (AD) is a T helper 2 cell (Th2)-mediated chronic inflammatory dermatosis characterized by inflammation and itching of the skin. The Th2-mediated inflammatory response is driven by factors such as skin barrier damage[17] and prostaglandin activity.[18]

Among the omega-3 fatty acid metabolites, resolvin E1 (RvE1) exhibits significant anti-inflammatory properties, effectively attenuating AD-like lesions by inhibiting immune cell infiltration and inflammatory factor production. In the

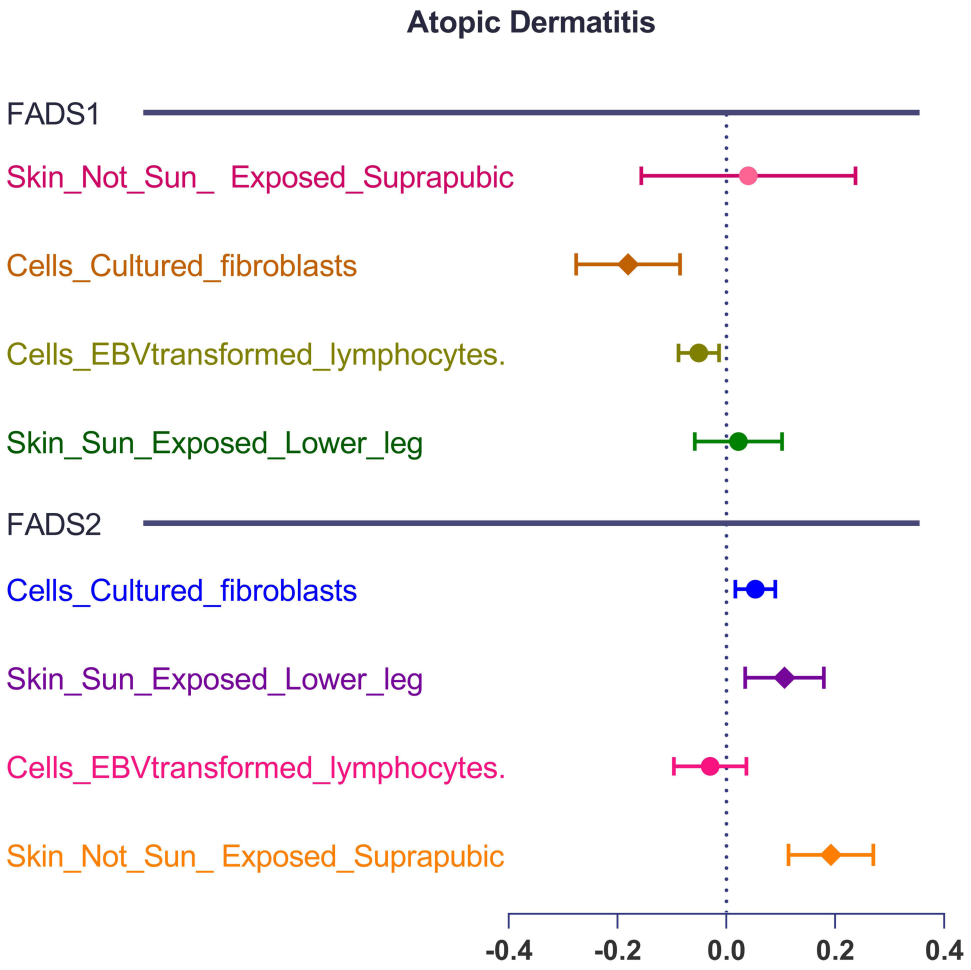


Figure 3 Forest plot illustrating the skin tissue-dependent association for *FADS1* and *FADS2* expression on atopic dermatitis. The dashed vertical lines represent null values for beta = 0, and the error bars correspond to 95% confidence intervals. Squares represent significant results, circles represent significant results.

DNFB-induced atopic dermatitis model in NC/Nga mice, RvE1 alleviated ear swelling and lesions on the dorsal skin through intraperitoneal administration. This treatment also inhibited the secretion of inflammatory cytokines IFN-γ and IL-4 from CD4(+) T cells, decreased IgE levels in the serum, and minimized the presence of immune cells, including eosinophils, mast cells, and T cells, in the skin lesions.[19]

In squamous cell carcinoma (SCC) of the skin, high FADS2 expression correlates with improved SCC outcomes. Epithelial-mesenchymal transition (EMT) represents a biological mechanism by which cells transition from epithelial traits to mesenchymal characteristics, a process that plays a significant role in tumor invasion and metastasis.[20] Annemarie Schwab et al demonstrated that FADS2 is highly expressed in less differentiated tumors, with high expression linked to increased sensitivity of cancer cells to ferroptosis inducers. FADS2 facilitates PUFA metabolism, enhancing ferroptosis in cancer cells and thereby improving patient outcomes. Additionally, RvD2, an omega-3 fatty acid metabolite derived from DHA, plays a critical role in combating squamous cell carcinoma (SCC). RvD2 reduces neutrophil infiltration, inhibits myeloperoxidase (MPO) activity, enhances phagocytosis by M2-type macrophages, and suppresses various pro-inflammatory signaling molecules, including chemokines and cytokines (eg, CXCL10, IL-6, MCP-1, and TNF-α), ultimately resulting in a significant inhibition of SCC development.[21]

However, increased D6D activity in skin tissues exacerbated atopic dermatitis risk. This may be due to LA metabolism via FADS2 and elongases, producing GLA and DLA metabolites, which enhance AA synthesis and cyclooxygenase analogs. Arachidonic acid is further converted by COX-2 into prostaglandin E2 and leukotrienes, promoting inflammation. Experimental studies demonstrate that docosahexaenoic acid (DHA) supplementation

https://doi.org/10.2147/CCID.S524519

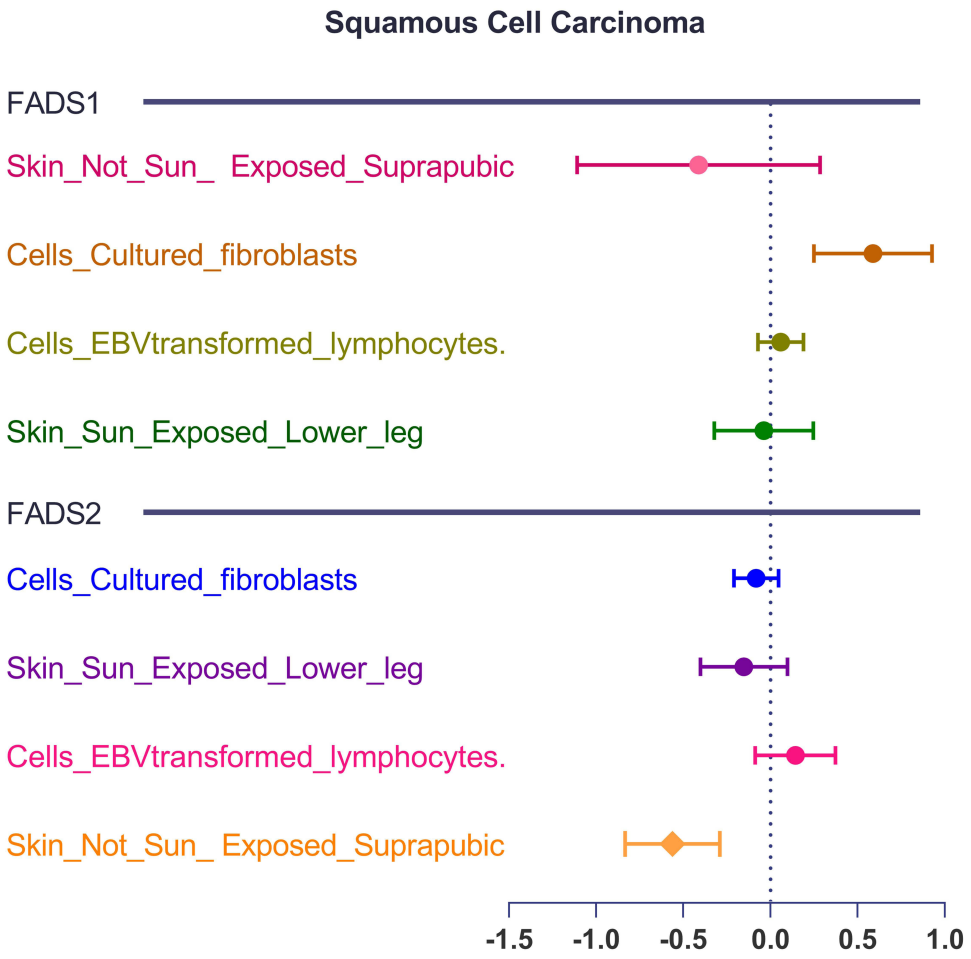


Figure 4 Forest plot illustrating the skin tissue-dependent association for *FADS1* and *FADS2* expression on squamous cell carcinoma. The dashed vertical lines represent null values for beta = 0, and the error bars correspond to 95% confidence intervals. Squares represent significant results, circles represent significant results.

effectively reduces levels of the proinflammatory mediator prostaglandin E_2 (PGE_2) in cutaneous inflammation models. This occurs primarily through the generation of prostaglandin E_3 (PGE_3) and specialized pro-resolving mediators (SPMs): anti-inflammatory lipid molecules that counterbalance proinflammatory prostaglandins derived from arachidonic acid (AA).[22] In psoriasis models, elevated levels of two proinflammatory mediators (5-lipoxygenase activity and leukotriene B_4 [LTB_4]) are observed, which correlate strongly with T helper 17 (Th17) cell activation and neutrophil infiltration in the skin.[23,24] Conversely, the atopic dermatitis samples exhibit increased levels of specific metabolites (9-HETE, 11-HETE, and LTB_4), which are associated with immunoglobulin E (IgE)-related impairment of the skin barrier function.[25,26] Collectively, these findings indicate that ω-3 polyunsaturated fatty acids (PUFAs) alleviate chronic skin inflammation by generating anti-inflammatory mediators while suppressing proinflammatory lipid production. Similarly, studies utilizing cellular assays and diverse animal models substantiate the anti-cancer potential of ω-3 PUFA derivatives. For instance, a metabolite of eicosapentaenoic acid (EPA), 17,18-epoxide, activates the p38 mitogen-activated protein kinase (MAPK) signaling pathway and downregulates the key cell cycle protein Cyclin D1, thereby inducing cancer cell cycle arrest and death.[27] Another class of compounds, alkylphospholipids (ALPs), diminishes leukemic cell viability by disrupting specialized structures in cancer cell membranes, inhibiting the critical survival pathway PI3K/Akt, and triggering intracellular stress responses (endoplasmic reticulum stress). These mechanistically observed effects in preclinical models align with the anti-tumor efficacy of ALPs demonstrated in clinical trials involving skin cancer and leukemia patients,[14] highlighting the translational potential of ω-3 PUFAs and their derivatives in multi-faceted anti-cancer strategies.

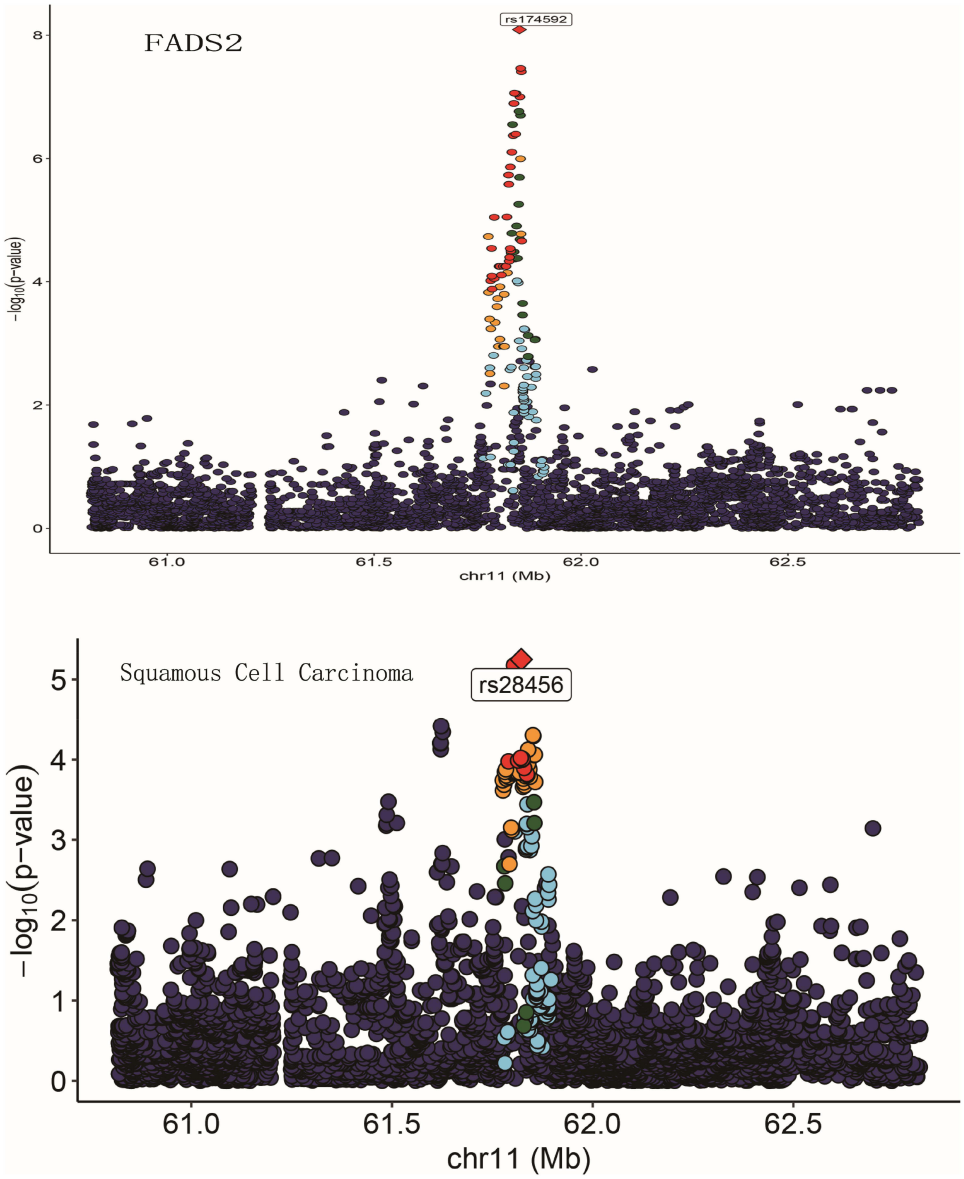


Figure 5 Regional association plots of FADS2 expression in suprapubic skin (non-sun-exposed) on squamous cell carcinoma in the FADS region.

These findings highlight the dual role of PUFA metabolism in inflammatory skin diseases and tumors, offering critical clues for targeting lipid metabolism in future interventions.[28]

These results emphasize the dual functions of PUFA metabolism in controlling inflammatory skin conditions and skin cancers, and provide important clues for future intervention in skin diseases by regulating lipid metabolism. Future studies employing tissue-type specific metabolomics and interventional trials are warranted to validate these mechanistically plausible targets.

Clinical Relevance

Our findings underscore omega-3 PUFAs as potential intervention targets for preventing and treating squamous cell carcinoma and AD via dietary intake or chemical synthesis.

Preventing and treating atopic dermatitis and squamous cell carcinoma is possible through the inclusion of omega-3-rich nutrients, either from dietary sources or additional supplementation. A clinical study explored the impact of omega-3 PUFAs on the treatment of atopic dermatitis, participants experienced an improvement of over 50% in the average severity scoring of

atopic dermatitis after 8 to 16 weeks of treatment.[29] Another double-blind trial demonstrated that individuals suffering from moderate to severe forms of atopic dermatitis who received n-3 fatty acid in unions exhibited significant improvements in disease severity, along with alterations in plasma and cell membrane fatty acid composition.[30] Another study revealed that plasma DHA levels were significantly lower in patients with atopic dermatitis (AD), and the study also suggested that elevated plasma DHA concentrations were linked to a decreased likelihood of developing AD.[31]

In a subsequent investigation involving organ transplant recipients, administering high doses of omega-3 fatty acids demonstrated a positive effect in lowering the likelihood of squamous cell carcinoma.[32]

Advantages and Limitations

Several limitations of this study should be acknowledged. First, the genetic analyses were primarily conducted in European-ancestry populations, limiting generalizability to other ethnic groups. Genetic variations influencing PUFA metabolism (eg, in the *Fatty Acid Desaturase (FADS)* gene cluster) and disease susceptibility differ substantially across populations. Second, our assessment of PUFA metabolic activity relies on genetic variants as proxies for enzyme function and PUFA levels, rather than direct biochemical measurements (eg, tissue-type specific quantification of PUFA species or enzyme activities). While useful, these proxies may not capture dietary influences, post-translational regulation, or localized tissue metabolism, constraining mechanistic interpretations. Third, regarding data sources: omega-3 measurements and a subset of samples originated from the UK Biobank, introducing potential sample overlap; however, the cis-eQTL and outcome datasets did not share genetic variants, minimizing bias in most MR analyses. Additionally, the limited number of cis-eQTL instruments restricted sensitivity analyses (eg, MR-Egger), though co-localization supported shared causal variants. Finally, cell-type-specific eQTL instruments showed F-statistics <10, indicating possible weak instrument bias; nevertheless, primary findings relied on tissue-level eQTLs with robust instruments ($F > 10$). Future large-scale single-cell eQTL studies are needed to enhance statistical power for cellular analyses.

Abbreviations

PUFA, polyunsaturated fatty acids; MR, Mendelian randomization; CHARGE, The Cohorts for Heart and Aging Research in Genomic Epidemiology; ALA, α-Linolenic acid; DHA, Docosahexaenoic Acid; EPA, Eicosapentaenoic Acid; DPA, docosapentaenoic acid; Cis-eQTL, cis-Expression Quantitative Trait Loci; FDR, false discovery rate; D5D, Delta-5 desaturase; D6D, Delta-6 desaturase; LA, linoleic acid; GLA, gamma-linolenic acid; SDA, stearidonic acid; DGLA, dihomo-gamma-linolenic acid; ETA, eicosatetraenoic acid; FADS1, fatty acid desaturase 1; FADS2, fatty acid desaturase 2; IVW, Inverse Variance Weighting; Th2, T helper 2 cell; RvE1, resolvin E1; EMT, Epithelial-Mesenchymal Transition.

Availability of Data and Materials

The datasets generated and/or analyzed during the current study are available in UK BioBank (https://www.ukbiobank.ac.uk/), CHARGE consortium (https://www.hgsc.bcm.edu/human/charge-consortium), the FinnGen Database (https://www.finngen.fi/en), the GTEx project (v8; https://gtexportal.org/home), MUTHER project (http://www.muther.ac.uk/) and the IEU OPEN GWAS PROJECT repository (https://gwas.mrcieu.ac.uk/).

Ethics Approval and Consent to Participate

The data involved in this study are from public summary data. According to the local legislation and the requirements of the ethics committee of HANGZHOU FIRST PEOPLE'S HOSPITAL, ethical review and approval were not required for this study on human participants. This study used publicly available summary-level data from the UK Biobank, CHARGE consortium, FinnGen, the GTEx project (v8), and the IEU Open GWAS Project. This study used publicly available summary-level data from the UK Biobank (Application 299116), FinnGen (Approval Nr HUS/990/2017 by The Coordinating Ethics Committee of the Hospital District of Helsinki and Uusimaa), CHARGE consortium, the GTEx project (v8), and the IEU Open GWAS Project. Ethical approvals for all datasets were obtained by the original investigators, and no additional ethics review was required for this secondary analysis under the guidelines of these databases. All data use complied with institutional policies and participant consents.

Acknowledgments

We thank UK BioBank, CHARGE consortium, IEU OPEN GWAS PROJECT repository and FinnGen database and all the researchers who share research data.

Disclosure

The authors declare no competing interests for this work.

References

1. Hay RJ, Johns NE, Williams HC, et al. The global burden of skin disease in 2010: an analysis of the prevalence and impact of skin conditions. *J Investigative Dermatol*. 2014;134(6):1527–1534. doi:10.1038/jid.2013.446
2. de Carvalho C, Caramujo MJ. The various roles of fatty acids. *Molecules*. 2018;23(10). doi:10.3390/molecules23102583
3. Nguyen P, Leray V, Diez M, et al. Liver lipid metabolism. *J Animal Physiol Animal Nutr*. 2008;92(3):272–283. doi:10.1111/j.1439-0396.2007.00752.x
4. Gutiérrez S, Svahn SL, Johansson ME. Effects of omega-3 fatty acids on immune cells. *Int J Mol Sci*. 2019;20(20). doi:10.3390/ijms20205028
5. Cucchi D, Camacho-Muñoz D, Certo M, et al. Omega-3 polyunsaturated fatty acids impinge on CD4+ T cell motility and adipose tissue distribution via direct and lipid mediator-dependent effects. *Cardiovascular Res*. 2020;116(5):1006–1020. doi:10.1093/cvr/cvz208
6. Kobayashi M, Sasaki S, Kawabata T, Hasegawa K, Tsugane S. Validity of a self-administered food frequency questionnaire used in the 5-year follow-up survey of the JPHC study cohort I to assess fatty acid intake: comparison with dietary records and serum phospholipid level. *J Epidemiol*. 2003;13(1 Suppl):S64–81. doi:10.2188/jea.13.1sup_64
7. Di Angelantonio E, Chowdhury R, Forouhi NG, Danesh J. Association of dietary, circulating, and supplement fatty acids with coronary risk. *Annals Internal Med*. 2014;161(6):458–459. doi:10.7326/l14-5018-11
8. Liu Y, Xia YY, Zhang T, et al. Complex interactions between circulating fatty acid levels, desaturase activities, and the risk of gestational diabetes mellitus: a prospective cohort study. *Front Nutrition*. 2022;9:919357. doi:10.3389/fnut.2022.919357
9. Tosi F, Sartori F, Guarini P, Olivieri O, Martinelli N. Delta-5 and delta-6 desaturases: crucial enzymes in polyunsaturated fatty acid-related pathways with pleiotropic influences in health and disease. *Adv Exp Med Biol*. 2014;824:61–81. doi:10.1007/978-3-319-07320-0_7
10. Glaser C, Heinrich J, Koletzko B. Role of FADS1 and FADS2 polymorphisms in polyunsaturated fatty acid metabolism. *Metabolism*. 2010;59 (7):993–999. doi:10.1016/j.metabol.2009.10.022
11. Zhang J, Zhao H. eQTL studies: from bulk tissues to single cells. *ArXiv*. 2023;50(12):925–933. doi:10.1016/j.jgg.2023.05.003
12. Burgess S, Thompson SG. Interpreting findings from mendelian randomization using the MR-Egger method. *Eur J Epidemiol*. 2017;32(5):377–389. doi:10.1007/s10654-017-0255-x
13. Lawlor DA, Harbord RM, Sterne JA, Timpson N, Davey Smith G. Mendelian randomization: using genes as instruments for making causal inferences in epidemiology. *Stat Med*. 2008;27(8):1133–1163. doi:10.1002/sim.3034
14. Biernacki M, Skrzydlewska E. Metabolic pathways of eicosanoids-derivatives of arachidonic acid and their significance in skin. *Cell Mol Biol Lett*. 2025;30(1):7. doi:10.1186/s11658-025-00685-y
15. Ding R, Zou X, Qin Y, et al. xQTLbiolinks: a comprehensive and scalable tool for integrative analysis of molecular QTLs. *Briefings Bioinf*. 2023;25(1). doi:10.1093/bib/bbad440
16. Gruber F, Ornelas CM, Karner S, et al. Nrf2 deficiency causes lipid oxidation, inflammation, and matrix-protease expression in DHA-supplemented and UVA-irradiated skin fibroblasts. *Free Radic Biol Med*. 2015;88(Pt B):439–451. doi:10.1016/j.freeradbiomed.2015.05.006
17. Palmer CN, Irvine AD, Terron-Kwiatkowski A, et al. Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. *Nature Genet*. 2006;38(4):441–446. doi:10.1038/ng1767
18. Sawada Y, Honda T, Nakamizo S, et al. Prostaglandin E(2) (PGE(2))-EP2 signaling negatively regulates murine atopic dermatitis-like skin inflammation by suppressing thymic stromal lymphopoietin expression. *J Allergy Clin Immunol*. 2019;144(5):1265–1273.e9. doi:10.1016/j.jaci.2019.06.036
19. Kim TH, Kim GD, Jin YH. Park YS, Park CS. Omega-3 fatty acid-derived mediator, Resolvin E1, ameliorates 2,4-dinitrofluorobenzene-induced atopic dermatitis in NC/Nga mice. *Int Immunopharmacol*. 2012;14(4):384–391. doi:10.1016/j.intimp.2012.08.005
20. Brabletz S, Schuhwerk H, Brabletz T, Stemmler MP. Dynamic EMT: a multi-tool for tumor progression. *EMBO J*. 2021;40(18):e108647. doi:10.15252/embj.2021108647
21. Schwab A, Rao Z, Zhang J, et al. Zeb1 mediates EMT/plasticity-associated ferroptosis sensitivity in cancer cells by regulating lipogenic enzyme expression and phospholipid composition. *Nat Cell Biol*. 2024;26(9):1470–1481. doi:10.1038/s41556-024-01464-1
22. Kendall AC, Pilkington SM, Massey KA, Sassano G, Rhodes LE, Nicolaou A. Distribution of bioactive lipid mediators in human skin. *J Investigative Dermatol*. 2015;135(6):1510–1520. doi:10.1038/jid.2015.41
23. Cook-Moreau JM, El-Makhour Hojeij Y, Barrière G, et al. Expression of 5-lipoxygenase (5-LOX) in T lymphocytes. *Immunology*. 2007;122 (2):157–166. doi:10.1111/j.1365-2567.2007.02621.x
24. Sawada Y, Honda T, Nakamizo S, et al. Resolvin E1 attenuates murine psoriatic dermatitis. *Sci Rep*. 2018;8(1):11873. doi:10.1038/s41598-018-30373-1
25. Fogh K, Herlin T, Kragballe K. Eicosanoids in acute and chronic psoriatic lesions: leukotriene B4, but not 12-hydroxy-eicosatetraenoic acid, is present in biologically active amounts in acute guttate lesions. *J Investigative Dermatol*. 1989;92(6):837–841. doi:10.1111/1523-1747.ep12696858
26. Töröcsik D, Weise C, Gericke J, et al. Transcriptomic and lipidomic profiling of eicosanoid/docosanoid signalling in affected and non-affected skin of human atopic dermatitis patients. *Exp Dermatol*. 2019;28(2):177–189. doi:10.1111/exd.13867
27. Cui L, Jia Y, Cheng ZW, et al. Advancements in the maintenance of skin barrier/skin lipid composition and the involvement of metabolic enzymes. *J Cosmet Dermatol*. 2016;15(4):549–558. doi:10.1111/jocd.12245
28. Korbecki J, Rębacz-Maron E, Kupnicka P, Chlubek D, Baranowska-Bosiacka I. Synthesis and significance of arachidonic acid, a substrate for cyclooxygenases, lipoxygenases, and cytochrome P450 pathways in the tumorigenesis of glioblastoma multiforme, including a pan-cancer comparative analysis. *Cancers*. 2023;15(3). doi:10.3390/cancers15030946

29. Eriksen BB, Kåre DL. Open trial of supplements of omega 3 and 6 fatty acids, vitamins and minerals in atopic dermatitis. *J Dermatolog Treat*. 2006;17(2):82–85. doi:10.1080/09546630600621946
30. Mayser P, Mayer K, Mahloudjian M, et al. A double-blind, randomized, placebo-controlled trial of n-3 versus n-6 fatty acid-based lipid infusion in atopic dermatitis. *JPEN J Parenteral Enteral Nutri*. 2002;26(3):151–158. doi:10.1177/0148607102026003151
31. Hammouda S, Ghzaiel I, Khamlaoui W, et al. Genetic variants in FADS1 and ELOVL2 increase level of arachidonic acid and the risk of alzheimer's disease in the Tunisian population. *Prostaglandins Leukotrienes Essent Fatty Acids*. 2020;160:102159. doi:10.1016/j.plefa.2020.102159
32. Miura K, Way M, Jiyad Z, et al. Omega-3 fatty acid intake and decreased risk of skin cancer in organ transplant recipients. *Eur J Nutr*. 2021;60 (4):1897–1905. doi:10.1007/s00394-020-02378-y