Lipids in Health and Disease

RESEARCH

Open Access

Causal and mediating effects of lipid and facial aging: association study integrating GWAS, eQTL, mQTL, and pQTL data

Mingjian Zhao[1†], Zhanchen He[1†], Lukuan Liu[2], Yichen Wang[1], LinQi Gao[3], Yuxuan Shang[1*] and Mengru Zhu[1*]

Abstract

Background Increasing evidence suggests a potential causal association between lipid levels and facial aging. The aim of this study was to investigate the relationship between levels of specific lipids and facial aging via Mendelian randomization methods. Additionally, this study aimed to identify mediators and explore relevant genes and drug targets.

Methods In this study, genome-wide association data on plasma lipids from 7,174 Finnish individuals in the UK Biobank were used. Two-sample Mendelian randomization was applied to assess the causal effects of specific lipids on facial aging. Sensitivity and pleiotropy analyses were conducted to ensure the robustness and reliability of the results. Multivariate Mendelian randomization was conducted to account for the potential impact of confounding factors. Furthermore, summary-data-based Mendelian randomization was used to identify relevant genes, which were validated through multiomics data. Finally, drug–gene interactions were explored via molecular docking techniques.

Results Two-sample Mendelian randomization analysis revealed a causal relationship between lipid levels and facial aging. According to the multivariate Mendelian randomization results, smoking was found to mediate this association, and these lipids remained significantly associated with facial aging, even after accounting for environmental confounders. Using summary-data-based Mendelian randomization, CYP21A2, CCND1, PSMA4, and MED1 were identified as potential gene targets, with MED1 further validated through pQTL and mQTL data. Additionally, the MED1 protein was found to bind spontaneously with astragalin, fenofibrate, and ginsenoside.

Conclusions The results revealed a causal relationship between lipid levels and facial aging, revealing key gene targets that were still significantly associated with facial aging after controlling for environmental confounders. Additionally, the interactions between MED1 and certain drugs may indicate potential pathways for therapeutic interventions related to facial aging.

Keywords Facial aging, Lipids, Multivariate mendelian randomization, Mediation analysis, Gene target

†Mingjian Zhao and Zhanchen He are co-first author.

*Correspondence:
Yuxuan Shang
18267801813@163.com
Mengru Zhu
drzhumengru@163.com

[1]Department of Plastic Surgery, The First Affiliated Hospital of Dalian Medical University, 222 Zhongshan Road, Dalian 116011, China
[2]Stem Cell Clinical Research Center, The First Affiliated Hospital of Dalian Medical University, Dalian 116011, China
[3]Department of Gastrointestinal Surgery, The First Affiliated Hospital of Dalian Medical University, Dalian 116011, China

Background

Facial aging (FA) is a natural and gradual process involving changes in facial tissues and is influenced by both internal and external factors. It is characterized primarily by cellular and molecular damage [1], which subsequently leads to a series of visible changes, such as increased wrinkles, tissue laxity, and a reduction in the barrier function of the skin [2]. This not only negatively affects normal interpersonal interactions [3] but also increases the risk of developing skin diseases [4, 5]. As a phenomenon of global aging, FA has received increasing attention. A better understanding of the biological mechanisms of FA can help develop early prevention strategies to reduce the negative effects of FA. However, the underlying mechanisms still need to be further clarified.

Lipids are an important and highly diverse class of molecules, and with recent advances in lipidomics research, the effects of lipids on the human aging process have been gradually revealed [6–8]. Lipids play an important role in chronic diseases associated with human aging, especially in the process of skin aging [9–11]. For example, the peroxidation of lipids induced by inflammation and infection during human aging leads to DNA damage in cells [12]. Although a potential causal relationship between lipid levels and FA has been demonstrated, this correlation still lacks the support of extensive data analysis, and the subclasses of lipids and the pathways of action that exert an effect are still not fully explored.

Mendelian randomization (MR) has emerged as an important method for investigating the causal relationship between exposure and disease, particularly because of its large sample size and ability to minimize bias from confounding factors in causal effect assessments [13, 14]. This research, which involved data from a large genome-wide association study (GWAS), primarily employed inverse-variance weighting (IVW) analysis to investigate the relationships between lipid levels and FA. To ensure the robustness of our findings, IVW analysis was supplemented with secondary methods, including weighted mode, weighted median, MR–Egger, and simple mode. To minimize the impact of potential confounders, multivariate Mendelian randomization (MVMR) was applied. Confounders such as smoking status, alcohol consumption status, and blood pressure were accounted for in the analysis [15–22], and potential mediating effects were explored on the basis of this framework [23]. Additionally, to uncover the underlying molecular mechanisms, summary-data-based Mendelian randomization (SMR) and colocalization analyses were conducted using pooled data from expression quantitative trait loci (eQTLs), protein quantitative trait loci (pQTLs), and methylation quantitative trait loci (mQTLs) for the relevant lipids. These analyses identified potential links between specific genes and FA. Furthermore, molecular docking techniques were applied to explore the interactions between these genes and potential antiaging drugs, including Astragalin, fenofibrate and ginsenoside, enhancing the clinical relevance of the findings [24–26].

Methods

Research design

This study is based on the 3 assumptions of MR [27], which are shown in Fig. 1a. Specifically, genetic variations used as instrumental variables (IVs) are called single nucleotide polymorphisms (SNPs), and IVs should be (1) strongly correlated with exposure, (2) only correlated with outcomes through exposure, and (3) not associated with any confounding factors associated with exposure outcomes. The flowchart of this study is shown in Fig. 1b and c. The Strengthening the Reporting of Observational Studies in Epidemiology using Mendelian Randomization (STROBE-MR) checklist was completed [28, 29].

Data sources

Detailed information on the GWASs used in the present study can be found in Supplementary Table 1. The lipid data came from a study of 7174 Finnish individuals [30], which included 179 lipid types and belonged to 13 lipid categories, covering 4 main lipid categories: glycerolipids, glycerophospholipids, sphingolipids, and sterols. The lipid species are named in the following notation: class name<sum of carbon atoms>:< sum of double bonds>;< sum of hydroxyl groups>. The annotation of lipid subspecies includes information on their acyl moieties and, if available, their sn-position. The acyl chains are separated either by "_" if the sn-position on the glycerol cannot be resolved or otherwise by "/".

FA data were sourced from the publicly available GWAS database, which includes phenotype and biological samples from 432,999 participants in the UK. The FA data in the UK Biobank were obtained through questionnaires and can be accessed on the open GWAS database website of the Integrated Epidemiological Unit (IEU).

On the basis of previous studies, we identified several confounding factors for lipids, such as smoking status, alcohol consumption status, duration of strenuous exercise participation, type of special diet followed: (low-calorie, vegetarian), and blood pressure. The data on the duration of strenuous exercise participation and type of special diet followed: (low-calorie, vegetarian) were obtained from the IEU OPEN GWAS database, which included biological samples and phenotypes from 64,949 participants and 9,851,867 SNPs. Alcohol intake and smoking frequency data can be accessed from the IEU OPEN GWAS database website. The data for systolic and diastolic blood pressure were obtained from the International Consortium of Blood Pressure, which includes 757,601 samples and 7,160,619 SNPs.

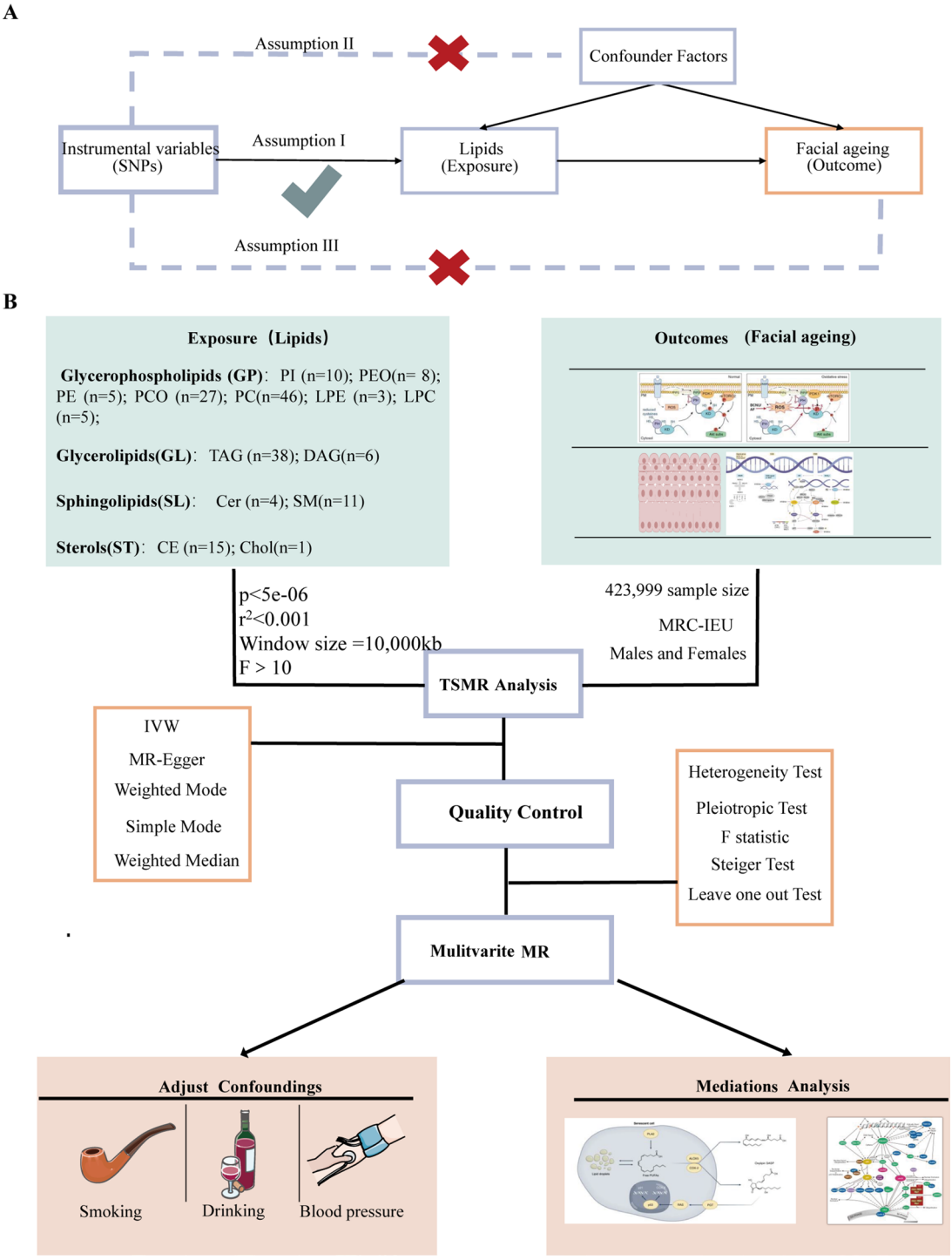

Fig. 1 This is the flowchart of this study

Lipid-associated genes were sourced from the GeneCards database, with duplicates meticulously removed. To increase the reliability of our dataset, we specifically selected genes that encode proteins and have correlation scores exceeding 1. The eQTL dataset encompasses 10,317 traits from 31,684 individuals, including SNP information [31]. The pQTL data were sourced from the decode database, which features 35,559 Icelanders and encompasses 4,907 proteins [32]. The mQTL data were derived from two distinct comprehensive meta-analyses, including a total of 1,980 individuals [33, 34].

This study is based on publicly available data. Individual studies within each GWAS received approval from the relevant Institutional Review Board, and informed

consent was obtained from the participants or a caregiver, legal guardian, or other proxy.

IVs selected

Statistical analyses were conducted via R software (version 4.3.1). For MR analysis of the causal links between FA and lipid levels, we utilized the "TwoSampleMR" package in R. We selected SNPs on the basis of lipid data, applying a significance threshold of $p<5E-06$. To adhere to the MR assumptions (r2<0.001, aggregation distance=10,000 kb), we undertook quality control measures and linkage disequilibrium (LD) analysis to exclude palindromic SNPs. Given that weak SNPs can bias two-sample Mendelian randomization (TSMR) results toward the null, we excluded such SNPs using an F-statistic threshold of greater than 10.

The F statistic was calculated to evaluate the strength of the instrumental variables. This calculation involved assessing the proportion of phenotype variance explained by the genetic variants. The calculations included the minor allele frequency (MAF), explained genetic variance (R^2), sample size (N), and number of instrumental variables (k) via the following formula: F = (N-k-1/k)*(R^2/1-R^2), where R^2=2(1-MAF)*MAFβ^2.

Mendelian analysis

In the initial phase of our analysis, TSMR was employed to assess the influence of lipid species on FA. We used the random-effects IVW method as the primary estimator for this MR analysis [35]. Owing to the presence of heterogeneity in our data, we chose between fixed-/random-effects models for the IVW method. Importantly, the IVW method operates under the assumption that all selected SNPs are valid IVs. This method is widely acknowledged for its robust statistical power. To increase the robustness of our findings, we conducted supplementary analyses via the weighted median approach [36], MR Egger regression [37], and both simple and weighted mode methods. We presented the results as odds ratios (ORs) and 95% confidence intervals (CIs) to quantify the effect strength.

In the MVMR analysis, we integrated several factors (primarily based on past research, including the number of cigarettes smoked daily, alcohol intake frequency, systolic blood pressure, diastolic blood pressure, vegetarian diet status, low-calorie diet status, and duration of strenuous exercise participation) in the analysis for adjustment. The IVW method was used for MVMR.

Following MVMR, a mediation analysis was conducted to estimate the potential proportion of the variance explained by mediators using MVMR. The calculation of the proportion of the mediating effect was based on the formula β(A)* β(B)/β(Total), where β(A) is the effect value of the mediating factors and lipids, β(B) is the effect of the mediator and outcome, and β(Total) is the effect of the lipids and outcomes.

SMR software was utilized for causal analysis of genes associated with lipids [33, 38], employing the 1000 Genomes European reference to compute LD. The SMR analysis framework included (1) the use of SNPs as instrumental variables with blood gene expression as the exposure and FA as the outcome and (2) the use of SNPs as instrumental variables with blood gene methylation data as the exposure and FA as the outcome. The β coefficient was determined by the ratio βSMR=βGene/βFA, and the odds ratio (OR) was calculated as OR=exp(βSMR). pQTL analysis was subsequently conducted via the "TwoSampleMR" package, where SNPs serve as instrumental variables, protein expression of genes in blood as the exposure, and blood gene expression as the outcome. Colocalization analysis, a technique used to identify shared causal variants of two traits within the same genomic region, is applied to investigate the potential interactions between lipid-related genes and FA [39, 40]. The foundational hypotheses for colocalization are as follows: H0, neither trait possesses a causal genetic variant; H1, only trait 1 has a causal variant; H2, only trait 2 has a causal variant; H3, both traits have causal variants, but they are not identical; and H4, both traits share the same causal variant. This analysis was executed via the "coloc" R package, with PH4>0.5 considered to indicate a shared genetic effect between two traits [41].

Molecular docking results

The receptor protein was imported into PyMOL 2.4.0 software for dehydration, and then AutoDockTools 1.5.7 software was used for merging, hydrogenation, and removal of nonpolar hydrogen atoms before converting into PDBQT format. The Grid function in AutoDockTools 1.5.7 software was employed to identify the protein receptor regions that can bind to ligands, namely, the active pocket. The ligand small molecules in mol2 format were imported into AutoDockTools, where settings such as hydrogenation and charge calculation were applied. On the basis of the docking pocket obtained in the previous step and the processed receptor and ligand, molecular docking was performed via AutoDock Vina 1.1.2 software, and PyMOL 2.4.0 was used to analyze the affinity and hydrogen bonds of amino acid residues.

Statistical analysis

Analyses were conducted via R (version 4.3.1), SMR (version 1.3.1) and PLINK (version 1.9) software, with packages such as "TwoSampleMR", "Tidyverse", "ggplot2", and "data.table" for analysis. Heterogeneity was tested with the Cochran Q test. Q<0.05 was considered to indicate the presence of heterogeneity. Horizontal pleiotropy was evaluated on the basis of the MR Egger intercept, with

$p<0.05$ considered to indicate the presence of horizontal pleiotropy. A leave-one-out test was used for outliers. The Steiger test was used to verify the directionality of the results. The heterogeneity in the dependent instrument (HEIDI) test was employed to assess result heterogeneity, considering outcomes reliable when P-SMR < 0.05 and P-HEIDI > 0.05. Multiple corrections were made to the P value via the Benjamini–Hochberg (BH) method.

Results

TSMR results

In this study, the number of SNPs for all lipid types was confirmed to be above 4, and the F value fluctuated between 20.8700 and 1945.6043 (Supplementary Table 2). Through the TSMR, a total of 27 types of lipids were found to have causal effects on FA (Fig. 2, Supplementary Tables 2 and Supplementary Figs. 1–3), of which 16 were protective factors and 11 were risk factors. After adjusting for p values via the BH method, a total of 6 types of lipids were retained, and all were risk factors (Fig. 3 and Supplementary Table 4), namely, the sterol ester (SE) (27:1/20:4) level (Pval: 3.32E-09, OR: 1.0104 (1.0069–1.0139)), the phosphatidylcholine (PC) (20:4:0) level (Pval: 1.1682E-04, OR: 1.0122 (1.0060–1.0185)), the PC (16:0_20:5) level (Pval: 1.34E-05, OR: 1.015785113 (1.0086–1.0230)), the PC (17:0_20:4) level (Pval: 8.49E-07, OR: 1.0140 (1.0084–1.0196)), the PC (18:0_20:4) level (Pval: 3.01E-05, OR: 1.0103 (1.0054–1.0151)), and the PC (18:1_20:4level (Pval: 2.51E-08, OR: 1.0138 (1.0089–1.0187); all of these variables belonged to 2 species: sterols and glycerophospholipids. Among them, 5 species were glycerophospholipids and 1 species was a sterol. After further tests for heterogeneity, pleiotropy and sensitivity analysis, we did not detect horizontal pleiotropy. Except for the (27:1/20:4) levels, the levels of the other 5 variables exhibited heterogeneity (Supplementary Tables 3 and 4 and Supplementary Figs. 4–6). We used the IVW random-effects model to reduce the error in the results.

MVMR results

MVMR was used to further estimate the associations between lipid types and FA (Fig. 4 and Supplementary Table 5). The P values of the 6 lipids were all less than 0.05 after controlling for smoking status, drinking status, blood pressure, vegetarian diet status, low-calorie diet status, and duration of strenuous exercise participation,

Characteristics	nSNPs	OR (95% CI)	P value
Sterol ester (27:1/20:4) levels	21	1.0104(1.0069−1.0139)	3.32e−09
Phosphatidylcholine (20:4_0:0) levels	13	1.0122(1.0060−1.0185)	0.000116816
Phosphatidylethanolamine (18:2_0:0) levels	17	0.9880(0.9797−0.9964)	0.005163864
Phosphatidylcholine (15:0_18:2) levels	24	0.9914(0.9850−0.9978)	0.008345962
Phosphatidylcholine (16:0_18:2) levels	21	0.9901(0.9840−0.9962)	0.00147109
Phosphatidylcholine (16:0_20:2) levels	23	0.9920(0.9846−0.9994)	0.03342345
Phosphatidylcholine (16:0_20:4) levels	15	1.0110(1.0048−1.0171)	0.000432928
Phosphatidylcholine (16:0_20:5) levels	12	1.0158(1.0086−1.0230)	1.34e−05
Phosphatidylcholine (16:0_22:4) levels	18	1.0132(1.0049−1.0215)	0.001763287
Phosphatidylcholine (16:1_18:1) levels	17	0.9892(0.9789−0.9997)	0.04324096
Phosphatidylcholine (17:0_20:4) levels	23	1.0140(1.0084−1.0196)	8.49e−07
Phosphatidylcholine (18:0_18:2) levels	21	0.9914(0.9840−0.9989)	0.02393503
Phosphatidylcholine (18:0_20:2) levels	8	0.9819(0.9689−0.9952)	0.007619094
Phosphatidylcholine (18:0_20:4) levels	21	1.0103(1.0054−1.0151)	3.01e−05
Phosphatidylcholine (18:1_20:2) levels	17	0.9899(0.9835−0.9963)	0.002129339
Phosphatidylcholine (18:1_20:4) levels	18	1.0138(1.0089−1.0187)	2.51e−08
Phosphatidylcholine (18:2_18:2) levels	17	0.9861(0.9768−0.9956)	0.003971026
Phosphatidylcholine (O−18:2_18:2) levels	11	0.9835(0.9685−0.9987)	0.0334999
Phosphatidylethanolamine (16:0_18:2) levels	14	0.9888(0.9816−0.9960)	0.002370356
Phosphatidylethanolamine (18:0_18:2) levels	22	0.9914(0.9857−0.9971)	0.003309502
Phosphatidylethanolamine (O−18:1_20:4) levels	15	1.0160(1.0049−1.0272)	0.004487119
Phosphatidylethanolamine (O−18:2_20:4) levels	11	1.0202(1.0038−1.0368)	0.01528711
Sphingomyelin (d36:2) levels	13	1.0153(1.0023−1.0285)	0.02115289
Triacylglycerol (52:4) levels	14	0.9944(0.9889−0.99997)	0.04906573
Triacylglycerol (52:5) levels	18	0.9935(0.9871−0.9999)	0.0454834
Triacylglycerol (53:2) levels	14	0.9824(0.9704−0.9946)	0.004760833
Triacylglycerol (54:4) levels	19	0.9913(0.9838−0.9989)	0.02461051

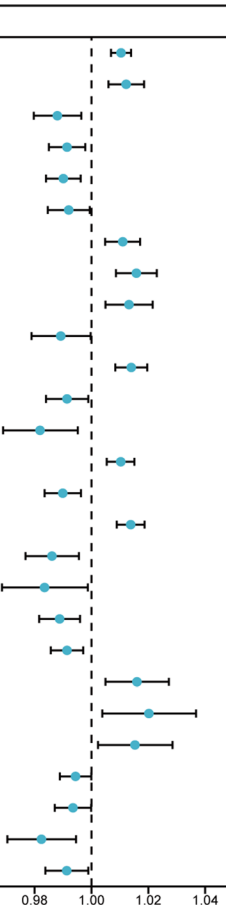

Fig. 2 Preliminary TSMR analysis results analysis

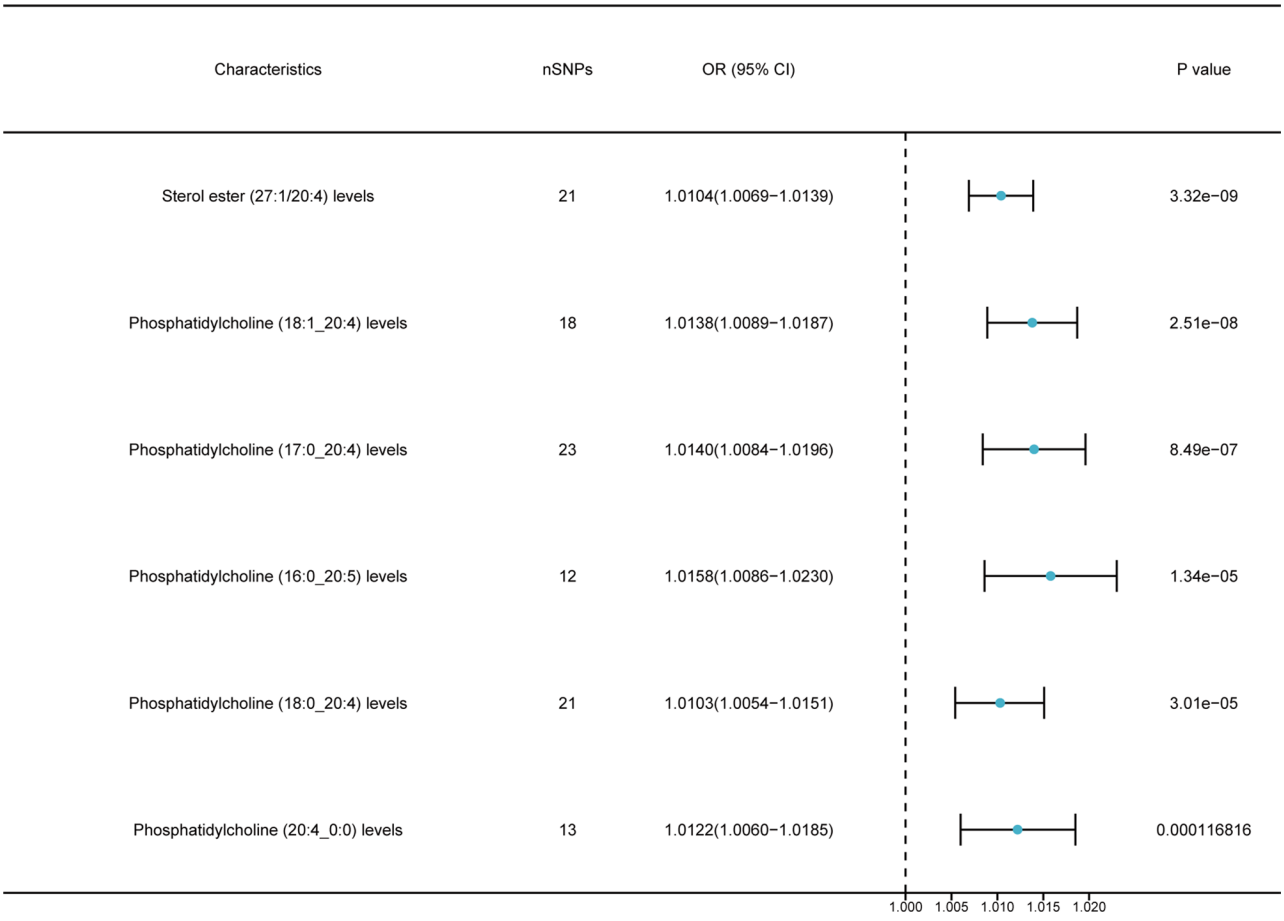

Fig. 3 Adjusted TSMR analysis results

and all lipids remained risk factors after correction, with an OR value ranging from 1.0074 to 1.0176.

Results of the mediation analysis

On the basis of the MVMR, we identified a potential causal relationship between smoking status and lipid levels, and the TSMR identified a potential mediating effect between the 2 lipid species and smoking status (Fig. 5 and Supplementary Tables 6 and 7). Further mediation analysis revealed that smoking mediated approximately 8.1% and 7.3% of the effects of lipid species and FA, respectively (Table 1).

eQTL analysis of PC- and SE-related genes

PC- and SE-related genes were searched through the GeneCards database, and after nonprotein-coding genes and genes with correlation scores less than 1 were removed, 2053 related genes were ultimately obtained (Supplementary Table 8), and a total of 1471 genes were included in the analysis. SMR analysis revealed that 166 genes were initially analyzed ($p<0.05$, p_HEIDI>0.05), and 4 genes were retained after "BH" multiple correction (0.05/1471): CYP21A2 (OR=1.0146, P=2.41 E-05), CCND1 (OR=1.0282, P=7.05E-06), PSMA4 (OR=1.0350, P=4.99E-08), and MED1 (OR=1.0350, P=5.90E-06) (Supplementary Table 9). All four genes are risk factors for FA, which is consistent with our previous study. In addition, the TSMR analysis results for MED1 (P=2.90E-06, OR=1.0234) were consistent with the SMR results. Additionally, the TSMR analysis indicated that MED1 (P=2.90E-06, OR=1.0234) was a significant risk factor for FA, with the results being consistent between the SMR and TSMR analyses (Supplementary Table 10).

mQTL and pQTL analysis of PC- and SE-related genes

A search of mQTL and pQTL data revealed that only MED1 presented complete mQTL and pQTL data, for which mQTL and pQTL analyses were ultimately performed. mQTL analysis revealed that MED1 possessed two probes that were causally associated with FA (cg15445000, p=7.36E-06, OR=0.9926; cg03013999, p=1.05E-05, OR=0.9888), and both were risk factors (Supplementary Table 11). pQTL analysis revealed that MED1 (OR=1.0387, P=0.0482) was a risk factor for FA (Supplementary Table 12).

Fig. 4 MVMR analysis results

Colocalization analysis and TSMR analysis of genes and confounders

The eQTL colocalization analysis indicated that PP.H4=58.4% (H4>50%), suggesting a shared causal variant locus between MED1 and FA (Supplementary Table 13). Additionally, TSMR analysis investigating the link between confounders and selected genes (Supplementary Table 14) revealed that MED1 may be associated with alcohol intake frequency and acts as a risk factor for this trait (OR=1.0524, *P*=2.98E-04). CCND1 was strongly associated with both diastolic (OR=1.378, *P*=1.91E-06) and systolic (OR=1.650, *P*=0.00176) blood pressure. PSMA4 and CYP21A2 were both linked to the number of cigarettes previously smoked daily and identified as

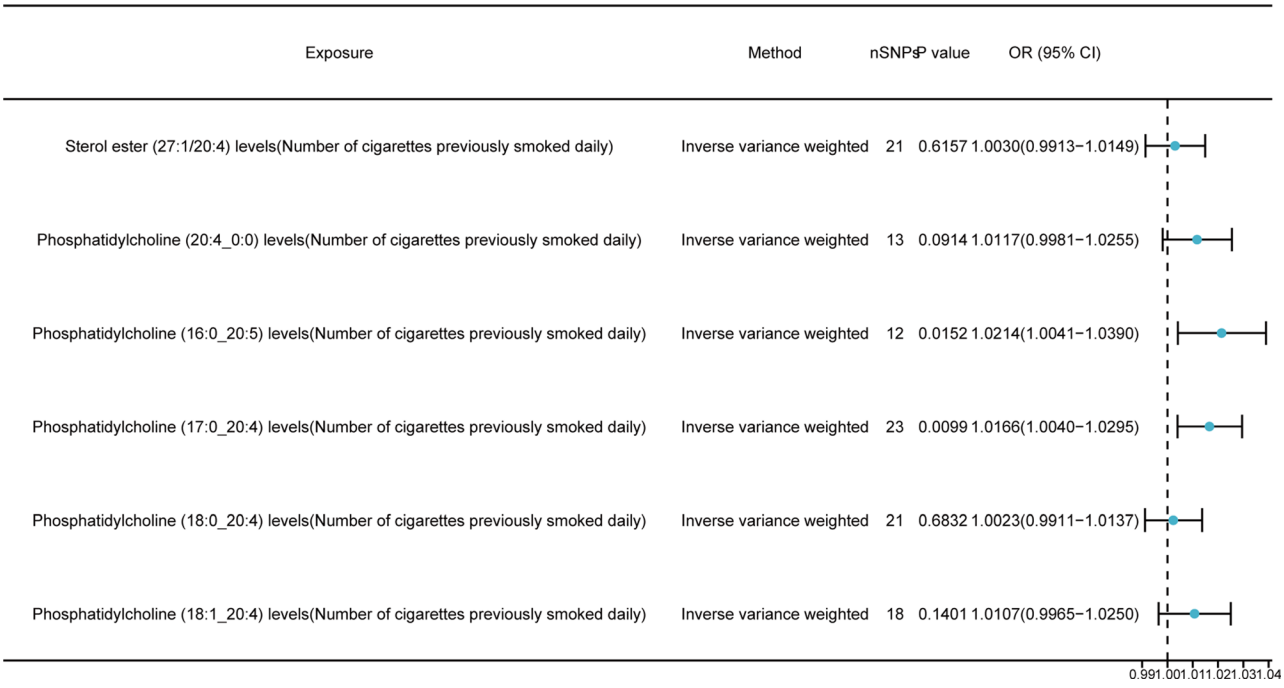

Fig. 5 TSMR analysis results of lipids and smoking

Table 1 The results of mediation analysis

Exposure	Mediator	Total effect (Beta)	A (Beta)	B (Beta)	Indirect effect (Beta)	Mediation effect/ Total effect
Phosphatidylcholine (16:0_20:5) levels	Number of cigarettes previously smoked daily	0.0157	0.0212	0.0599	0.0013	0.0810
Phosphatidylcholine (17:0_20:4) levels	Number of cigarettes previously smoked daily	0.0139	0.0165	0.0617	0.0010	0.0734

Table 2 Binding energy of molecular docking result

Macromolecule	Ligand	Binding Energy(kal/mol)
MED1	Astragalin	-7.6
	Fenofibrate	-7.2
	Ginsenoside	-8.0

risk factors (PSMA4, $P=0.047$, OR=1.247; CYP21A2, $P=0.0337$, OR=1.0177). Additionally, CYP21A2 was associated with following a low-calorie diet ($P=0.0252$, OR=0.9901).

Molecular docking results

A review of the relevant literature revealed that astragalin, fenofibrate, and ginsenoside are commonly used to treat FA, although their mechanisms of action in FA are not yet fully understood. The aim of this study was to explore the relationships between MED1 status and the use of these drugs. The molecular docking results revealed that the minimum binding energy of all three active compounds with the MED1 protein target was less than −5 kcal/mol, indicating that the ligand and receptor can bind spontaneously. Among these compounds, ginsenoside had the lowest binding energy at -8.0 kcal/mol, suggesting that it has the strongest binding affinity. The detailed docking results for the other molecules are presented in Table 2. The lower the minimum binding energy is, the stronger the binding between the small molecule and the target protein. Interactions such as hydrogen bonds, π-π stacking, and other molecular interactions contribute to tight binding between the active ingredients and the target protein, further stabilizing their conformation and enhancing their binding affinity. For each docking, three conformations were generated, and the one with the best binding energy was selected for visualization (Fig. 6a-f).

Discussion

FA is a complex physiological process that is considered irreversible, but various interventions, such as dietary modifications and lifestyle improvements [42], are considered to be meaningful in delaying FA [43]. With the expansion of studies on lipidomics, the relationship

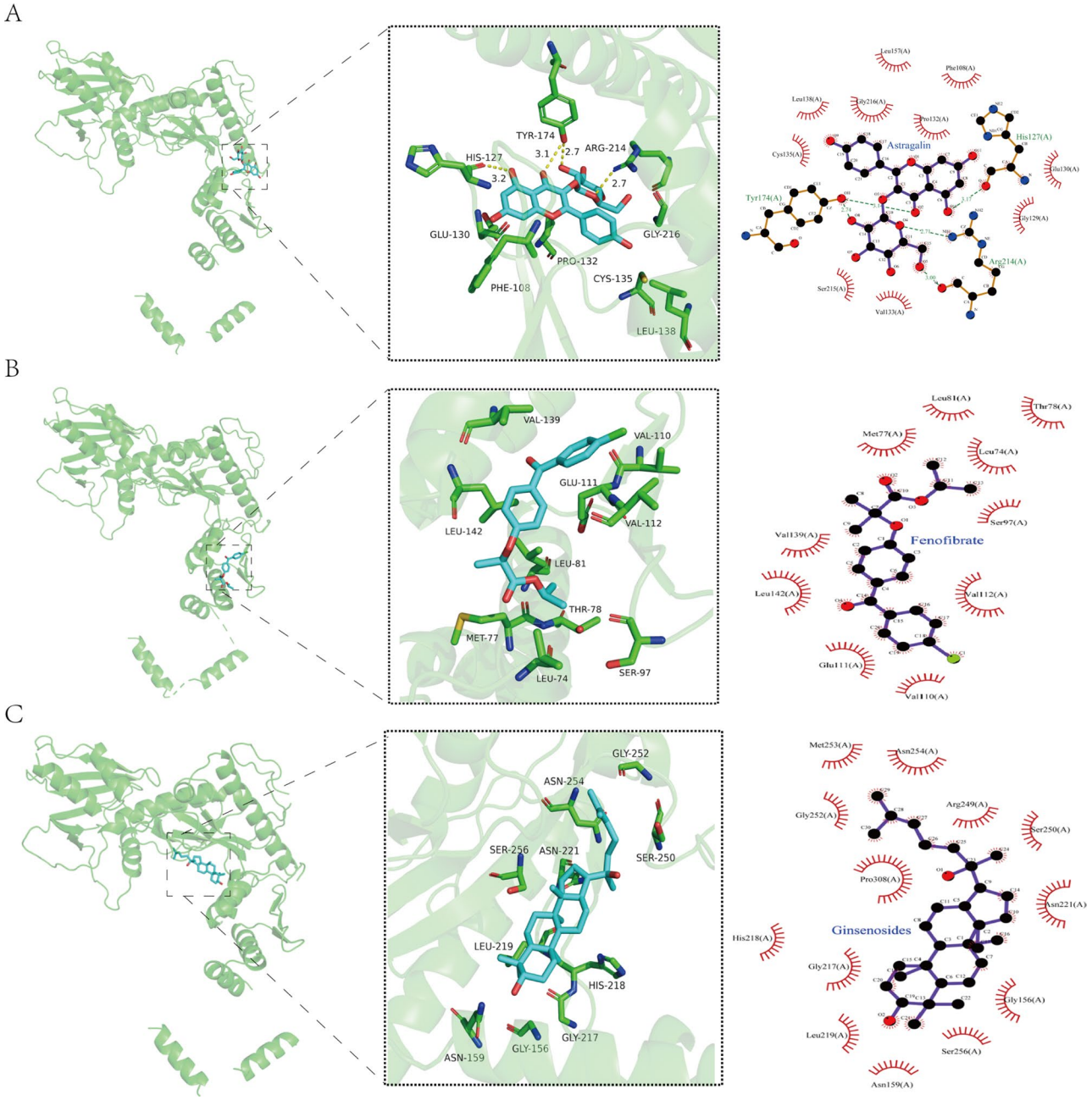

Fig. 6 Molecular docking results. **(A)** Astragalin. **(B)** Fenofibrate. **(C)** Ginsenoside

between lipid levels and FA has been noted [44–47]. Several related mechanisms have been emphasized in the FA process, and oxidative stress, which can directly or indirectly mediate skin aging, is thought to play a crucial role in the aging process [48]. On the one hand, lipid peroxidation products are thought to be involved in the formation of exocyclic DNA adducts, which cause DNA damage; on the other hand, lipids in membrane proteins can combine with reactive oxygen species (ROS) in tissues, damaging animal cell membranes, which can cause chronic inflammation and disease, leading to aging [12, 49–51]. In addition, the breakdown of elastin fibers, which are essential for maintaining skin elasticity and firmness, is also an important factor in aging [52], and cholesterol and polyunsaturated fatty acid oxidation products bind to elastin, which in turn leads to impaired or loss of elastin fiber function [53]. Although previous studies have revealed a link between lipid levels and FA, the physiological processes involved remain to be elucidated.

In this study, which was based on a large sample of GWAS data, TSMR analysis detected 27 specific lipids

(16 risk factors and 11 protective factors) as potential causative factors for FA. To minimize bias, the BH method was used to adjust the P value, and the results revealed that all 6 corrected lipids (1 sterol ester and 5 phosphatidylcholines) were risk factors for FA. Steiger's test confirmed the correct direction of causality. To further refine the analysis and account for confounders, factors known to be associated with lipids or FA, such as smoking status, alcohol consumption status, vegetarian diet status, low-calorie diet status, duration of strenuous exercise, and blood pressure, were adjusted for via MVMR. After adjustment, the causal relationships between the six lipids and FA remained significant. In addition, mediation analyses confirmed the mediating effect of daily smoking status on certain lipids. To explore the potential molecular mechanisms, four FA-associated genes (CYP21A2, CCND1, PSMA4 and MED1) were identified by SMR via eQTL data of phosphatidylcholine and sterol esters, and the associations of these genes with the above confounders were explored. On this basis, we focused on the MED1 gene and confirmed its significant causal relationship with FA via mQTL and pQTL data. Colocalization analyses further demonstrated the interaction between MED1 and FA. In molecular docking, the MED1 gene spontaneously binds to astragalin, fenofibrate and ginsenosides. According to the TSMR results, 1 SE subclass and 5 PC subclasses were significantly associated with FA and were risk factors for FA. SE is an important organic compound involved in the composition of cellular membranes, which are formed by esterification of Sterol, and in mammals, the cholesterol ester is the main form of SE present [54]. Atherosclerosis is considered an important manifestation of aging in the cardiovascular system [55], and SE and related oxidation products, such as oxidized LDL, are thought to accelerate this process by triggering chronic inflammation and oxidative stress [56, 57]. Modified LDL, such as oxidized LDL, exacerbates atherosclerosis by accelerating the uptake and accumulation of lipids, including cholesterol esters, by vascular smooth muscle cells and macrophages [56].

PC is a glycerophospholipid that also serves as an important component of animal cell membranes [59, 60], and previous studies have suggested that PC may be associated with delayed hepatic and neurological aging [61–63]. Interestingly, a total of 16 PCs were considered to be associated with FA in this study, of which 9 were protective factors and 7 were risk factors, although only 5 risk factors were retained after multiple corrections, which still suggests that the role of PCs in the aging process of the human body is complex. PCs are associated with the production of tissue-derived ROS to form oxidized phosphatidylcholine (oxPC). The accumulation of oxPCs can affect the physicochemical properties of cytoplasmic membranes, potentially increasing membrane permeability while inducing apoptosis, and is considered to be a deleterious substance [65, 66]. In addition, PCs are involved in the human skin barrier [67], and when the normal lipid components of the skin, including PCs, are dysregulated, the risk of impaired skin barrier function increases, which in turn leads to the development of chronic inflammatory skin diseases, such as psoriasis [68–70]. Previous studies have shown that elevated levels of specific PC molecules (particularly those containing stearic acid (C18:0) and arachidonic acid (C20:4)) are associated with cellular senescence in human dermal fibroblasts cultured in vitro, which may affect the normal structure of cell membranes. This finding is consistent with some of our findings [69]. In addition, extrinsic factors such as ultraviolet light promote the accumulation of oxidative products such as oxPCs and ROS in human dermal fibroblasts cultured in vitro, accelerating FA [72, 73]. Although the present study explored a possible mechanistic explanation for the influence of related lipids on FA, more clinical studies and basic experiments are needed to confirm and refine this mechanism.

Smoking status, alcohol consumption status, vegetarian diet status, blood pressure, low calorie diet status and duration of strenuous exercise participation were summarized as possible confounders that were included in the MVMR due to their possible potential impact on FA [74]. The MVMR results revealed that the causal effect of lipid levels on FA was strong. In addition, in a further mediation analysis, we identified daily smoking status as a mediator. Cigarette smoke (CS) is a well-recognized risk factor for skin aging, and its effects are multifaceted. CS extracts not only increase the accumulation of ROS in tissues and promote tissue oxidative damage [75] but also decrease the biosynthesis of collagen types I and III in human skin fibroblasts. In addition, owing to the toxic effects of CS, the normal function of the extracellular matrix is also negatively affected, accelerating the process of FA [76]. Lipid levels and smoking status are strongly associated, and a clinical trial has shown that CS rapidly affects reverse lipid transport in the lungs and circulation of mice and promotes the accumulation of certain lipids, such as cholesterol, in peripheral tissues [77]. Moreover, further experiments are needed to validate the molecular mechanisms underlying the interaction between these two proteins.

To further investigate the underlying mechanisms, four key upstream genes regulating PC and SE were identified as potential risk factors for facial aging (FA). These genes were found to be associated with various confounders, suggesting that their effects on FA may not operate through a single, direct pathway.

Instead, multiple environmental confounding factors may influence these causal relationships. The direct impact of CYP21A2, CCND1, and PSMA4 on lipid regulation and FA remains underexplored in the existing clinical literature. The MED1 gene, a component of the Mediator complex encoding Mediator complex subunit 1 [78], has a significant effect on lipid autophagy and fatty acid oxidation in mouse hepatocytes [79]. Moreover, MED1 is present in keratinocytes and participates in numerous pathways that regulate keratinocyte proliferation. Its physiological activation reduces Hedgehog signaling, thereby inhibiting keratinocyte proliferation and inducing a dormant phase in hair follicle tissues [80, 81], which is likely characterized by senescence [82]. Conversely, MED1 knockdown activates pathways, including the activin A/follistatin and JNK/c-Jun pathways, enhancing keratinocyte proliferation and collagen synthesis [83]. MiR-146a, a human microRNA, targets MED1 in hepatocytes and has been shown to promote oxidative stress-induced senescence in human primary fibroblasts [84], suggesting its anti-aging potential [85]. Although the results of molecular docking illustrated the potential of MED1 for applications, its actual clinical input still requires further validation in more clinical trials.

Strengths and limitations

In this study, we clarified the causal relationship between lipid levels and FA through TSMR analysis and applied MVMR to further explore the interaction between lipid levels and confounders. On the basis of the results of MVMR, we further used mediation analysis to discover the mediating role of daily smoking in this causal relationship. Furthermore, we utilized pQTL, eQTL, and mQTL data to identify potential regulatory genes and investigate the regulation of FA at the molecular level. Sensitivity analyses confirmed the robustness of our methodology, indicating that our results were not influenced by pleiotropy. To our knowledge, this study is the first to amalgamate various Mendelian randomization analyses with eQTL, pQTL, and mQTL data to investigate the relationships between lipid levels and FA.

Several limitations should be noted in this study. First, the main participants in our study were of European origin, and although this limits the bias caused by population heterogeneity, it remains to be determined whether the results of this study are still applicable to other populations. Second, heterogeneity remained in the MR analyses of the present study, although we used a random-effects model to circumvent it, and no horizontal pleiotropy was detected. Third, while direct clinical trials validating our findings are currently lacking, preliminary experimental studies align with some of our results. Nonetheless, these observations require confirmation through additional experimentation.

Conclusions

In summary, this study reveals the causal relevance of lipids in FA processes and the mediating effects of smoking status on this relationship, broadens the scope of global lipidomics research, enhances our understanding of relevant lipids, and unveils the underlying molecular mechanisms. Furthermore, modulating lipid metabolism through the regulation of specific gene expression could mitigate FA, providing a theoretical foundation for future investigations.

Abbreviations

FA	Facial aging
MR	Mendelian randomization
TSMR	Two-sample mendelian randomization
MVMR	Multivariate mendelian randomization
IVW	Inverse variance weighting
SE	Sterol ester
PC	Phosphatidylcholine
IVs	Instrumental variables
SNPs	Single nucleotide polymorphisms
GWAS	Genome-wide association study
IEU	Integrated Epidemiological Unit
OR	Odds ratios
CI	Confidence intervals
BH	Benjamini-hochberg
ROS	Reactive oxygen species
oxPC	Oxidized phosphatidylcholine
CS	Cigarette smoke
SMR	Summary-data-based Mendelian Randomization
eQTL	Expression quantitative trait loci
mQTL	Methylation quantitative trait loci
pQTL	Protein quantitative trait loci

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12944-024-02328-1.

Supplementary Material 1: STROBE-MR-checklist of this research.

Supplementary Material 2: Figs. 1–3 Scatter plots of 27 lipids obtained through Mendelian randomization analysis.

Supplementary Material 3: Figs. 4–6 Leave-one-out test of 27 lipids obtained through Mendelian randomization analysis.

Supplementary Material 4: Table 1-Data sources and related information. Table 2-MR analysis results of 27 types of lipids and facial ageing. Table 3-SNPs used in MR analysis of 27 types of lipids and facial aging. Table 4-MR analysis results of 6 types of lipids and facial aging (adjusted). Table 5-The causal relationship between 6 types of lipids and smoking. Table 6-Multivariate Mendelian analysis correcting confounding factors. Table 7-Mediation analysis results of lipids and smoking. Table 8-PC and SE related genes from GeneCards. Table 9-The Result of eQTL analysis. Table 10-The MR Result of MED1 and Facial ageing. Table 11-The Result of mQTL analysis. Table 12-The Result of pQTL analysis. Table 13-Colocalization Results of MED1 and Facial ageing. Supplementary Table 14-The MR Result of Genes and Environment.

Acknowledgements

We are grateful to the patients for their contributions to this study.

Author contributions
Mingjian Zhao: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. Zhanchen He: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing. Lukuan Liu: Conceptualization, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing – original draft, Writing – review & editing. Yichen Wang: Conceptualization, Data curation, Investigation, Methodology, Supervision, Validation, Writing – original draft. Gaolin Qi: Conceptualization, Data curation, Investigation, Supervision, Writing – original draft. Yuxuan Shang: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing – original draft, Writing – review & editing. Mengru Zhu: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

Funding
This study was supported by the National Natural Science Foundation of China (Grant No. 22004012).

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
This manuscript has not been published or presented elsewhere in part or in entirety and is not under consideration by another journal. We have read and understood your journal's policies, and we believe that neither the manuscript nor the study violates any of these. All co-authors approved publication.

Competing interests
The authors declare no competing interests.

Received: 28 July 2024 / Accepted: 7 October 2024
Published online: 21 October 2024

References

1. Lim MY, Nam YD. Gut microbiome in healthy aging versus those associated with frailty. Gut Microbes. 2023;15:2278225.
2. Jenkins G. Molecular mechanisms of skin ageing. Mech Ageing Dev. 2002;123:801–10.
3. Swift A, Liew S, Weinkle S, Garcia JK, Silberberg MB. The facial aging process from the inside out. Aesthet Surg J. 2021;41:1107–19.
4. Rittié L, Fisher GJ. Natural and sun-induced aging of human skin. Cold Spring Harb Perspect Med. 2015;5:a015370.
5. Sreedhar A, Aguilera-Aguirre L, Singh KK. Mitochondria in skin health, aging, and disease. Cell Death Dis. 2020;11:444.
6. Hornburg D, Wu S, Moqri M, Zhou X, Contrepois K, Bararpour N, et al. Dynamic lipidome alterations associated with human health, disease and ageing. Nat Metab. 2023;5:1578–94.
7. Johnson AA, Stolzing A. The role of lipid metabolism in aging, lifespan regulation, and age-related disease. Aging Cell. 2019;18:e13048.
8. Mutlu AS, Duffy J, Wang MC. Lipid metabolism and lipid signals in aging and longevity. Dev Cell. 2021;56:1394–407.
9. Gu Y, Han J, Jiang C, Zhang Y. Biomarkers, oxidative stress and autophagy in skin aging. Ageing Res Rev. 2020;59:101036.
10. Rinnerthaler M, Bischof J, Streubel MK, Trost A, Richter K. Oxidative stress in aging human skin. Biomolecules. 2015;5:545–89.
11. Liu Z, Mi J, Wu H. Relationships between circulating metabolites and facial skin aging: a mendelian randomization study. Hum Genomics. 2023;17:23.
12. Tudek B, Zdżalik-Bielecka D, Tudek A, Kosicki K, Fabisiewicz A, Speina E. Lipid peroxidation in face of DNA damage, DNA repair and other cellular processes. Free Radic Biol Med. 2017;107:77–89.
13. Yoon S, Kim YA. Cosmetic surgery and self-esteem in South Korea: a systematic review and meta-analysis. Aesthetic Plast Surg. 2020;44:229–38.
14. Chen Y, Ouyang Y, Chen X, Chen R, Ruan Q, Farag MA, et al. Hypoglycaemic and anti-ageing activities of green alga Ulva lactuca polysaccharide via gut microbiota in ageing-associated diabetic mice. Int J Biol Macromol. 2022;212:97–110.
15. Bourassa KJ, Moffitt TE, Ambler A, Hariri AR, Harrington H, Houts RM, et al. Association of treatable health conditions during adolescence with accelerated aging at midlife. JAMA Pediatr. 2022;176:392–9.
16. Surugiu R, Iancu MA, Vintilescu ȘB, Stepan MD, Burdusel D, Genunche-Dumitrescu AV, et al. Molecular mechanisms of healthy aging: the role of caloric restriction, intermittent fasting, Mediterranean Diet, and ketogenic Diet-A Scoping Review. Nutrients. 2024;16(17):2878.
17. Rungratanawanich W, Qu Y, Wang X, Essa MM, Song BJ. Advanced glycation end products (AGEs) and other adducts in aging-related diseases and alcohol-mediated tissue injury. Exp Mol Med. 2021;53:168–88.
18. Bencivenga L, Barreto PDS, Rolland Y, Hanon O, Vidal JS, Cestac P, et al. Blood pressure variability: a potential marker of aging. Ageing Res Rev. 2022;80:101677.
19. Lacolley P, Regnault V, Segers P, Laurent S. Vascular smooth muscle cells and arterial stiffening: relevance in development, aging, and disease. Physiol Rev. 2017;97:1555–617.
20. Di Francescomarino S, Sciartilli A, Di Valerio V, Di Baldassarre A, Gallina S. The effect of physical exercise on endothelial function. Sports Med. 2009;39(10):797–812.
21. Aleksandrova K, Koelman L, Rodrigues CE. Dietary patterns and biomarkers of oxidative stress and inflammation: a systematic review of observational and intervention studies. Redox Biol. 2021;42:101869.
22. Sturmlechner I, Durik M, Sieben CJ, Baker DJ, Van Deursen JM. Cellular senescence in renal ageing and disease. Nat Rev Nephrol. 2017;13:77–89.
23. Sanderson E. Multivariable mendelian randomization and mediation. Cold Spring Harb Perspect Med. 2021;11:a038984.
24. Wang R, Ding A, Wang J, Wang J, Zhou Y, Chen M, Ju S, Tan M, Xiang Z. Astragalin from Thesium chinense: a novel anti-aging and antioxidant Agent Targeting IGFR/CD38/Sirtuins. Antioxid (Basel). 2024;13(7):859.
25. Walker AE, Kaplon RE, Lucking SM, Russell-Nowlan MJ, Eckel RH, Seals DR. Fenofibrate improves vascular endothelial function by reducing oxidative stress while increasing endothelial nitric oxide synthase in healthy normolipidemic older adults. Hypertension. 2012;60(6):1517–23.
26. Cong L, Ma J, Zhang Y, Zhou Y, Cong X, Hao M. Effect of anti-skin disorders of ginsenosides- A systematic review. J Ginseng Res. 2023;47(5):605–14.
27. Bowden J, Holmes MV. Meta-analysis and mendelian randomization: a review. Res Synth Methods. 2019;10:486–96.
28. Skrivankova VW, Richmond RC, Woolf BAR, Yarmolinsky J, Davies NM, Swanson SA, et al. Strengthening the reporting of observational studies in epidemiology using mendelian randomization: the STROBE-MR statement. JAMA. 2021;326:1614–21.
29. Skrivankova VW, Richmond RC, Woolf BAR, Davies NM, Swanson SA, VanderWeele TJ, et al. Strengthening the reporting of observational studies in epidemiology using mendelian randomisation (STROBE-MR): explanation and elaboration. BMJ. 2021;375:n2233.
30. Ottensmann L, Tabassum R, Ruotsalainen SE, Gerl MJ, Klose C, Widén E, et al. Genome-wide association analysis of plasma lipidome identifies 495 genetic associations. Nat Commun. 2023;14:6934.
31. Võsa U, Claringbould A, Westra HJ, Bonder MJ, Deelen P, Zeng B, et al. Large-scale cis- and trans-eQTL analyses identify thousands of genetic loci and polygenic scores that regulate blood gene expression. Nat Genet. 2021;53:1300–10.
32. Ferkingstad E, Sulem P, Atlason BA, Sveinbjornsson G, Magnusson MI, Styrmisdottir EL, et al. Large-scale integration of the plasma proteome with genetics and disease. Nat Genet. 2021;53:1712–21.
33. McRae AF, Marioni RE, Shah S, Yang J, Powell JE, Harris SE, et al. Identification of 55,000 replicated DNA methylation QTL. Sci Rep. 2018;8:17605.
34. Wu Y, Zeng J, Zhang F, Zhu Z, Qi T, Zheng Z, et al. Integrative analysis of omics summary data reveals putative mechanisms underlying complex traits. Nat Commun. 2018;9:918.
35. Burgess S, Scott RA, Timpson NJ, Smith GD, Thompson SG. Using published data in mendelian randomization: a blueprint for efficient identification of causal risk factors. Eur J Epidemiol. 2015;30:543–52.

36. Bowden J, Smith GD, Haycock PC, Burgess S. Consistent estimation in mendelian randomization with some invalid instruments using a weighted median estimator. Genet Epidemiol. 2016;40:304–14.
37. Bowden J, Smith GD, Burgess S. Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression. Int J Epidemiol. 2015;44:512–25.
38. Zhu Z, Zhang F, Hu H, Bakshi A, Robinson MR, Powell JE, et al. Integration of summary data from GWAS and eQTL studies predicts complex trait gene targets. Nat Genet. 2016;48:481–7.
39. Huang Y, Shan Y, Zhang W, Lee AM, Li F, Stranger BE, et al. Deciphering genetic causes for sex differences in human health through drug metabolism and transporter genes. Nat Commun. 2023;14:175.
40. Arvanitis M, Tayeb K, Strober BJ, Battle A. Redefining tissue specificity of genetic regulation of gene expression in the presence of allelic heterogeneity. Am J Hum Genet. 2022;109:223–39.
41. Al-Naamani N, Sagliani KD, Dolnikowski GG, Warburton RR, Toksoz D, Kayyali U, et al. Plasma 12- and 15-hydroxyeicosanoids are predictors of survival in pulmonary arterial hypertension. Pulm Circ. 2016;6:224–33.
42. Weyh C, Krüger K, Strasser B. Physical activity and diet shape the immune system during aging. Nutrients. 2020;12:622.
43. Langille MG, Meehan CJ, Koenig JE, Dhanani AS, Rose RA, Howlett SE, et al. Microbial shifts in the aging mouse gut. Microbiome. 2014;2:50.
44. Wambier CG, Lee KC, Soon SL, Sterling JB, Rullan PP, Landau M, et al. Advanced chemical peels: phenol-croton oil peel. J Am Acad Dermatol. 2019;81:327–36.
45. Haftek M. Memory' of the stratum corneum: exploration of the epidermis' past. Br J Dermatol. 2014;171:6–9.
46. Foolad N, Vaughn AR, Rybak I, Burney WA, Chodur GM, Newman JW, et al. Prospective randomized controlled pilot study on the effects of almond consumption on skin lipids and wrinkles. Phytother Res. 2019;33:3212–7.
47. Binder CJ, Papac-Milicevic N, Witztum JL. Innate sensing of oxidation-specific epitopes in health and disease. Nat Rev Immunol. 2016;16:485–97.
48. Kammeyer A, Luiten RM. Oxidation events and skin aging. Ageing Res Rev. 2015;21:16–29.
49. Seo E, Kang H, Choi H, Choi W, Jun HS. Reactive oxygen species-induced changes in glucose and lipid metabolism contribute to the accumulation of cholesterol in the liver during aging. Aging Cell. 2019;18:e12895.
50. Wang L, Yang T, Pan Y, Shi L, Jin Y, Huang X. The metabolism of reactive oxygen species and their effects on lipid biosynthesis of microalgae. Int J Mol Sci. 2023;24:11041.
51. Zhang S, He Y, Sen B, Wang G. Reactive oxygen species and their applications toward enhanced lipid accumulation in oleaginous microorganisms. Bioresour Technol. 2020;307:123234.
52. Shin JW, Kwon SH, Choi JY, Na JI, Huh CH, Choi HR, et al. Molecular mechanisms of dermal aging and antiaging approaches. Int J Mol Sci. 2019;20:2126.
53. Heinz A. Elastic fibers during aging and disease. Ageing Res Rev. 2021;66:101255.
54. Korber M, Klein I, Daum G. Steryl Ester synthesis, storage and hydrolysis: a contribution to sterol homeostasis. Biochim Biophys Acta Mol Cell Biol Lipids. 2017;1862:1534–45.
55. Wang JC, Bennett M. Aging and atherosclerosis: mechanisms, functional consequences, and potential therapeutics for cellular senescence. Circ Res. 2012;111:245–59.
56. Choi SH, Sviridov D, Miller YI. Oxidized cholesteryl esters and inflammation. Biochim Biophys Acta Mol Cell Biol Lipids. 2017;1862:393–7.
57. Duan Y, Gong K, Xu S, Zhang F, Meng X, Han J. Regulation of cholesterol homeostasis in health and diseases: from mechanisms to targeted therapeutics. Signal Transduct Target Ther. 2022;7:265.
58. Wang D, Yang Y, Lei Y, Tzvetkov NT, Liu X, Yeung AWK, et al. Targeting foam cell formation in atherosclerosis: therapeutic potential of natural products. Pharmacol Rev. 2019;71:596–670.
59. Van Der Veen JN, Kennelly JP, Wan S, Vance JE, Vance DE, Jacobs RL. The critical role of phosphatidylcholine and phosphatidylethanolamine metabolism in health and disease. Biochim Biophys Acta Biomembr. 2017;1859:1558–72.
60. Ousley AH, Morell P. Individual molecular species of phosphatidylcholine and phosphatidylethanolamine in myelin turn over at different rates. J Biol Chem. 1992;267:10362–9.
61. Proitsi P, Kim M, Whiley L, Simmons A, Sattlecker M, Velayudhan L, et al. Association of blood lipids with Alzheimer's disease: a comprehensive lipidomics analysis. Alzheimers Dement. 2017;13:140–51.
62. Garcia-Ruiz C, Mato JM, Vance D, Kaplowitz N, Fernández-Checa JC. Acid sphingomyelinase-ceramide system in steatohepatitis: a novel target regulating multiple pathways. J Hepatol. 2015;62:219–33.
63. Wang B, Tontonoz P. Phospholipid remodeling in physiology and disease. Annu Rev Physiol. 2019;81:165–88.
64. Simpson BN, Kim M, Chuang YF, Beason-Held L, Kitner-Triolo M, Kraut M, et al. Blood metabolite markers of cognitive performance and brain function in aging. J Cereb Blood Flow Metab. 2016;36:1212–23.
65. Dong Y, Yong VW. Oxidized phospholipids as novel mediators of neurodegeneration. Trends Neurosci. 2022;45:419–29.
66. Dong Y, Jain RW, Lozinski BM, D'Mello C, Visser F, Ghorbani S, et al. Single-cell and spatial RNA sequencing identify perturbators of microglial functions with aging. Nat Aging. 2022;2:508–25.
67. Essa EA, Bonner MC, Barry BW. Electroporation and ultradeformable liposomes; human skin barrier repair by phospholipid. J Control Release. 2003;92:163–72.
68. Uche LE, Gooris GS, Bouwstra JA, Beddoes CM. Barrier capability of skin lipid models: effect of ceramides and free fatty acid composition. Langmuir. 2019;35:15376–88.
69. Janssens M, Van Smeden J, Gooris GS, Bras W, Portale G, Caspers PJ, et al. Increase in short-chain ceramides correlates with an altered lipid organization and decreased barrier function in atopic eczema patients. J Lipid Res. 2012;53:2755–66.
70. Ilves L, Ottas A, Kaldvee B, Abram K, Soomets U, Zilmer M, et al. Metabolomic differences between the skin and blood sera of atopic dermatitis and psoriasis. Int J Mol Sci. 2022;23:13001.
71. Naru E, Takanezawa Y, Kobayashi M, Misaki Y, Kaji K, Arakane K. Increased levels of a particular phosphatidylcholine species in senescent human dermal fibroblasts in vitro. Hum Cell. 2008;21:70–8.
72. Gruber F, Marchetti-Deschmann M, Kremslehner C, Schosserer M. The skin epilipidome in stress, aging, and inflammation. Front Endocrinol (Lausanne). 2020;11:607076.
73. Zi Y, Wang X, Zi Y, Yu H, Lan Y, Fan Y, et al. Cigarette smoke induces the ROS accumulation and iNOS activation through deactivation of Nrf-2/SIRT3 axis to mediate the human bronchial epithelium ferroptosis. Free Radic Biol Med. 2023;200:73–86.
74. López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. The hallmarks of aging. Cell. 2013;153:1194–217.
75. Birch-Machin MA, Bowman A. Oxidative stress and ageing. Br J Dermatol. 2016;175:26–9.
76. Knuutinen A, Kokkonen N, Risteli J, Vähäkangas K, Kallioinen M, Salo T, et al. Smoking affects collagen synthesis and extracellular matrix turnover in human skin. Br J Dermatol. 2002;146:588–94.
77. Jubinville É, Talbot M, Bérubé JC, Hamel-Auger M, Maranda-Robitaille M, Beaulieu MJ, et al. Interplay between cigarette smoking and pulmonary reverse lipid transport. Eur Respir J. 2017;50:1700681.
78. Wang C, Xing Y, Zhang J, He M, Dong J, Chen S, et al. MED1 regulates BMP/TGF-β in endothelium: implication for pulmonary hypertension. Circ Res. 2022;131:828–41.
79. Zhou J, Singh BK, Ho JP, Lim A, Bruinstroop E, Ohba K, et al. MED1 mediator subunit is a key regulator of hepatic autophagy and lipid metabolism. Autophagy. 2021;17:4043–61.
80. Oda Y, Hu L, Bul V, Elalieh H, Reddy JK, Bikle DD. Coactivator MED1 ablation in keratinocytes results in hair-cycling defects and epidermal alterations. J Invest Dermatol. 2012;132:1075–83.
81. Nakajima T, Inui S, Fushimi T, Noguchi F, Kitagawa Y, Reddy JK, et al. Roles of MED1 in quiescence of hair follicle stem cells and maintenance of normal hair cycling. J Invest Dermatol. 2013;133:354–60.
82. Zou Z, Long X, Zhao Q, Zheng Y, Song M, Ma S et al. A single-cell transcriptomic atlas of human skin aging. Dev Cell. 2021;56:383 – 97.e8.
83. Meng Z, Li Z, Guo S, Wu D, Wei R, Liu J, et al. MED1 ablation promotes oral mucosal wound healing via JNK signaling pathway. Int J Mol Sci. 2022;23:13414.
84. Li K, Zhao B, Wei D, Wang W, Cui Y, Qian L, et al. miR–146a improves hepatic lipid and glucose metabolism by targeting MED1. Int J Mol Med. 2020;45:543–55.

85. Abbas H, Kamel R, El-Sayed N. Dermal anti-oxidant, anti-inflammatory and anti-aging effects of compritol ATO-based resveratrol colloidal carriers prepared using mixed surfactants. Int J Pharm. 2018;541:37–47.

Publisher's note