a Open Access Full Text Article

Risk of Facial Aging

Zhanyi Zhang¹, Mengyuan Li², Yujia Geng¹, Wangshu Wang¹, Weihao Wang¹, Ying Shao¹

¹Department of Plastic and Reconstructive Surgery, the First Hospital of Jilin University, Changchun, Jilin Province, 130000, People's Republic of China; ²College of Chinese Medicinal Materials, Jilin Agricultural University, Changchun, Jilin Province, 130118, People's Republic of China

Correspondence: Ying Shao, Department of Plastic and Reconstructive Surgery, the First Hospital of Jilin University, Changchun, Jilin Province, 130000, People's Republic of China, Email shao_ying@jlu.edu.cn

Purpose: Previous studies have suggested a relationship between autoimmune diseases and the risk of facial skin aging. However, evidence from population-based studies on this topic is limited, leaving the causal association between these factors unknown. This study aimed to systematically evaluate the causal effects of 18 autoimmune diseases on the risk of facial skin aging, aim of providing strategies to mitigate early facial aging in patients with autoimmune diseases.

Patients and Methods: We conducted univariate Mendelian randomization (UVMR) analyses to examine the causal relationship between 18 autoimmune diseases and facial aging using publicly available summary data from genome-wide association studies (GWASs). We also conducted multivariate Mendelian randomization (MVMR) analyses to adjust for confounding factors, including smoking, alcohol consumption, and body mass index (BMI).

Results: The main inverse variance weighted (IVW) method revealed that genetically proxied ankylosing spondylitis (AS) (OR 1.017; 95% CI: 1.003–1.031; P=0.018), sicca syndrome (SS) (OR 1.008; 95% CI: 1.005–1.011; P= 2.66×10⁻⁶), systemic lupus erythematosus (SLE) (OR 1.006; 95% 1.001–1.011; P=0.014), multiple sclerosis (MS) (OR 1.004; 95% CI: 1.001–1.007; P=0.021), primary sclerosing cholangitis (PSC) (OR 1.002; 95% CI: 1.000-1.004; P=0.023), and celiac disease (CeD) (OR 1.002; 95% CI: 1.001-1.004; P=0.009) were significantly associated with higher risk of facial aging. After adjusting for potential confounding factors, the association persisted between AS, SLE, and CeD.

Conclusion: These findings indicated that autoimmune diseases play a causal role in facial skin aging. Therefore, patients with autoimmune diseases should take appropriate measures to prevent early facial aging.

Keywords: autoimmune disease, facial aging, Mendelian randomization, ankylosing spondylitis, systemic lupus erythematosus, celiac disease

Introduction

Autoimmune diseases encompass a group of highly heterogeneous disorders characterized by immune system disturbances.¹ These conditions affect approximately 5% of the global population.^{2,3} Autoimmune diseases can affect various organ systems and cause diverse clinical manifestations across individuals of any age. Systemic inflammation in autoimmune diseases can lead to oxidative stress, which can contribute to skin aging through multiple biochemical processes.⁴ Several autoimmune diseases are associated with premature skin senescence. For instance, skin aging is related to the disappearance of melanocytes in vitiligo patients,⁵ while skin fibroblasts in multiple sclerosis patients display an underlying stress phenotype, which leads to reduced resiliency of these cells when exposed to hydrogen peroxide.⁶ Skin, as the largest organ covering the surface of the human body, not only serves as a protective barrier against the external environment but also defines our outward appearance.^{7–9} Facial skin acts as a socially meaningful interface with unique psychological importance compared to other areas of the skin. In the context of an aging society and the consequent paradigm shift in medical research focus, facial rejuvenation and early intervention for skin aging are attracting growing attention.^{10,11} However, to date, observational studies focusing on the association between autoimmune diseases and facial aging remain rare. Moreover, conventional observational studies cannot establish causation

owing to potential confounding factors. Therefore, more reliable approaches are needed to establish the etiological link between autoimmune diseases and facial aging.

Mendelian randomization (MR) is a statistical analysis method that employs genetic variants (generally singlenucleotide polymorphisms, SNPs) as instrumental variables (IVs) to infer the epidemiological etiology based on genomewide association studies (GWASs).¹² Following the Mendelian inheritance rule, SNPs are randomly assigned during the formation of a fertilized ovum and are not associated with random errors. Thus, the fundamental principle of MR investigation is equivalent to that of randomized controlled trials (RCTs).¹³ Compared with traditional observational studies, MR can reveal a genuine causal relationship between exposure and outcome, since SNPs cannot be modified by acquired factors such as exposures, confounders, and outcomes. In this study, we conducted an MR investigation to systematically evaluate the relationship between 18 autoimmune diseases and the risk of facial aging, thereby contributing to the prevention of early facial aging in patients with autoimmune diseases. Additionally, we also performed multivariable Mendelian randomization (MVMR) to adjust for potential confounding factors, including smoking, alcohol consumption, and body mass index (BMI), which may increase the risk of facial skin aging.^{10,14,15}

Materials and Methods

Study Design

In this study, MR analyses were conducted to investigate the causal effects of autoimmune diseases on the risk of facial aging. MR analysis is based on three critical assumptions: (1) IVs are strongly associated with the exposure of interest (relevance assumption); (2) Confounders of the exposure-outcome association should not affect IVs (independence assumption); (3) IVs only affect the outcome via the exposure (exclusion-restriction assumption).¹⁶ As the present study is based on publicly available GWAS data, and all original studies had already met ethical requirements; therefore no additional ethics approvals or informed consent was required. An overview of the MR study is illustrated in Figure 1.



Figure I An overview of this MR study.

Data Sources

We used publicly available summary-level statistics obtained from the IEU OpenGWAS Project database (<u>https://gwas.mrcieu.ac.uk</u>) to perform the MR study. The 18 most common autoimmune diseases were included as exposures: (1) inflammatory bowel disease (IBD), (2) vitiligo, (3) alopecia areata (AA), (4) multiple sclerosis (MS), (5) sicca syndrome (SS), (6) hypothyroidism, (7) sarcoidosis, (8) rheumatoid arthritis (RA), (9) ankylosing spondylitis (AS), (10) celiac disease (CeD), (11) systemic lupus erythematosus (SLE), (12) systemic sclerosis (SSc) (13) type 1 diabetes (T1D), (14) psoriasis, (15) juvenile idiopathic arthritis (JIA), (16) primary biliary cirrhosis (PBC), (17) primary sclerosing cholangitis (PSC), and (18) myasthenia gravis (MG). Details of these GWAS are shown in Table 1.

Facial aging was assessed using publicly available summary statistics from the population-based UK Biobank. A total of 423,999 eligible European individuals were recruited to participate in baseline assessments, which encompassed the completion of questionnaires, undergoing physical measurements, providing biological samples, and undergoing follow-up procedures. The approach of this domain to evaluate perceived age through questionnaire-based assessments has been described previously.^{27,28} Subjective perceptions of facial aging were determined by the following question: Do people say that you look (1) about your age, (2) younger than you are, (3) older than you are, (4) do not know, or (5) prefer not to answer? Eligible participants were selected from health records within the UK National Health Service (NHS) and invited to participate in one of the 22 assessment centers situated in densely populated regions of Great Britain. Participants who responded with "do not know" or "prefer not to answer" were excluded from the analysis.

Genetic Instrumental Variable Selection

SNPs with genome-wide significance are required to identify IVs strongly associated with autoimmune diseases. Except for vitiligo, AA, MG, and SSc, we selected SNPs related to each autoimmune disease with a significance threshold of $P < 5 \times 10^{-8}$. However, for vitiligo, AA, MG, and SSc, SNPs at a lower threshold ($P < 5 \times 10^{-6}$) were selected because there were not sufficient SNPs identified at the $P < 5 \times 10^{-8}$ level to perform MR analysis. During the clumping process, SNPs

Traits	Number of	Number of	Datasets in the GWAS	References
	Cases	Controls		
IBD	4101	480,497	ebi-a-GCST90038683	[17]
Vitiligo	131	207,482	finn-b-L12_VITILIGO	NA
AA	289	211,139	finn-b-L12_ALOPECAREATA	NA
MS	9722	17,376	ieu-a-1024	[18]
SS	1290	213,145	finn-b-M13_SJOGREN	NA
Hypothyroidism	26,306	187,684	finn-b-E4_HYTHYNAS	NA
Sarcoidosis	1718	484,955	ebi-a-GCST90018918	[19]
RA	5427	479,171	ebi-a-GCST90038685	[17]
AS	9069	1550	ebi-a-GCST005529	[20]
CeD	12,041	12,228	ieu-a-1058	[21]
SLE	1311	1783	ieu-a-815	[22]
SSc	302	213,145	finn-b-MI3_SYSTSLCE	NA
TID	18,942	501,638	ebi-a-GCST90014023	[23]
Psoriasis	5072	478,102	ebi-a-GCST90018907	[19]
JIA	2816	13,056	ebi-a-GCST005528	[24]
PBC	2861	8514	ebi-a-GCST005581	[25]
PSC	2871	12,019	ieu-a-1112	[26]
MG	197	354,945	ebi-a-GCST90018876	[19]

Table	L	The	Detailed	Data	Information	of the	Selected	Autoimmune	Diseases	in	the
Present	t S	Study									

Abbreviations: IBD, inflammatory bowel disease; AA, alopecia areata; MS, multiple sclerosis; SS, sicca syndrome; RA, rheumatoid arthritis; AS, ankylosing spondylitis; CeD, celiac disease; SLE, systemic lupus erythematosus; SSc, systemic sclerosis; TID, type I diabetes; JIA, juvenile idiopathic arthritis; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; MG, myasthenia gravis; NA, not applicable.

were clumped using a strict linkage disequilibrium (LD) threshold ($R^2 > 0.001$, window size = 10,000 kb) to ensure that all SNPs were independent. Subsequently, we used variants in linkage disequilibrium ($R^2 > 0.8$) to identify proxies for SNPs that were not available in the outcome GWAS. Ambiguous or palindromic SNPs were removed during harmonization. Additionally, to avoid bias caused by weak IVs, we calculated the *F*-statistic for each SNP and found no IV with an *F*-statistic <10 (Supplementary Table 1).

Statistical Analysis

First, we conducted a univariate Mendelian randomization (UVMR). The inverse-variance weighted (IVW) approach was applied as the principal estimator to evaluate the causal effects of autoimmune diseases on the risk of facial aging. The IVW method has dramatically high statistical power with the assumption that all IVs are valid.²⁹ In addition, we used MR-Egger regression, weighted median (WM), simple mode, and weighted mode as complementary methods to enhance the reliability of causal results. The MVMR analysis was conducted only for significant MR relationships in the primary analysis. Specifically, each selected autoimmune disease, smoking, alcohol consumption, and BMI were considered exposures, with facial aging as the outcome.

Sensitivity analyses were conducted to assess the robustness of the results. Cochrane's Q test was used to detect heterogeneity among the estimates of SNPs. Horizontal pleiotropy occurs when the instruments also affect the outcomes through pathways that are independent of the exposure itself.¹² Potential horizontal pleiotropic effects were evaluated using the MR-Egger regression intercept. The MR-PRESSO framework was used to identify the outlier SNPs with pleiotropic effects (*NbDistribution* was set at 10,000). Leave-one-out sensitivity analyses were performed to determine whether the results were driven by a single SNP. All analyses were performed using the statistical software R (version 4.3.1) with TwoSampleMR package (version 0.5.7) and Mendelian Randomization package (version 0.9.0). P < 0.05 was considered as the statistical significance threshold.

Results

Genetic Instrumental Variable Selection

After a series of quality control steps, an appropriate number of SNPs was identified as IVs for each analysis. We identified 17 independent SNPs in IBD, 25 independent SNPs for AS, 3 independent SNPs for SS, 3 independent SNPs for SLE, 26 independent SNPs for MS, 18 independent SNPs for PSC, 15 independent SNPs for CeD, 76 independent SNPs for T1D, 10 independent SNPs for psoriasis, 45 independent SNPs for hypothyroidism, 11 independent SNPs for AA, 7 independent SNPs for SSc, 5 independent SNPs for sarcoidosis, 4 independent SNPs for vitiligo, 12 independent SNPs for MG, 22 independent SNPs for PBC, 4 independent SNPs for JIA, and 8 independent SNPs for RA. In addition, 1 proxy SNP for IBD (rs112749594 targeted by rs181159261), 1 proxy SNP for SS (rs35407265 targeted by rs34518860), 1 proxy SNP for sarcoidosis (rs77527755 targeted by rs72845795), 1 proxy SNP for MG (rs6995908 targeted by rs6996371), 2 proxy SNPs for PSC (rs139010734 and rs41316239 targeted by rs1790932, rs685810, and rs9276180, respectively), and 1 proxy SNP for hypothyroidism (rs62073975 targeted by rs41444548) were found as the original SNPs were not present in the selected outcome.

Causal Effects of Autoimmune Diseases on the Risk of Facial Aging

In UVMR, the IVW method demonstrated that six out of 18 autoimmune diseases showed statistically significant effects on the risk of facial aging (Figure 2). In detail, a genetic predisposition to AS (OR 1.017; 95% CI: 1.003–1.031; P=0.018), genetic predisposition to SS (OR 1.008; 95% CI: 1.005–1.011; P= 2.66×10⁻⁶), genetic predisposition to SLE (OR 1.006; 95% 1.001–1.011; P=0.014), genetic predisposition to MS (OR 1.004; 95% CI: 1.001–1.007; P=0.021), genetic predisposition to PSC (OR 1.002; 95% CI: 1.000–1.004; P=0.023), and genetic predisposition to CeD (OR 1.002; 95% CI: 1.001–1.004; P=0.009) was associated with higher odds of facial aging. Conversely, genetic liability to IBD (OR 1.277; 95% CI: 0.895–1.823; P=0.178), genetic liability to T1D (OR 1.001; 95% CI: 0.998–1.004; P=0.708), genetic liability to psoriasis (OR 1.001; 95% CI: 0.995–1.006; P=0.843), genetic liability to hypothyroidism (OR 1.000;

Exposure	nSNP			OR(95%CI)	p-value
IBD	17	←	1	→ 1.277(0.895, 1.823)	0.178
AS	25		•	→ 1.017(1.003, 1.031)	0.018
SS	3			1.008(1.005, 1.011)	0.000
SLE	3			1.006(1.001, 1.011)	0.014
MS	26		_	1.004(1.001, 1.007)	0.021
PSC	18		 	1.002(1.000, 1.004)	0.023
CeD	15		-	1.002(1.001, 1.004)	0.009
T1D	76	_	—	1.001(0.998, 1.004)	0.708
Psoriasis	10		—	1.001(0.995, 1.006)	0.843
Hypothyroidism	45			1.000(0.996, 1.005)	0.838
AA	11	-	 - @	1.000(0.999, 1.002)	0.599
SSc	7	-	-	1.000(0.999, 1.001)	0.884
Sarcoidosis	5		-	1.000(0.997, 1.003)	0.991
Vitiligo	4	-	•	1.000(0.998, 1.002)	0.785
MG	12	-	 	0.999(0.998, 1.001)	0.365
PBC	22	•	 	0.999(0.996, 1.002)	0.568
JIA	4	-•		0.999(0.997, 1.001)	0.269
RA	8 C	< .99	1	→ 0.812(0.544, 1.211) 1.02	0.307

Figure 2 Associations of liability to autoimmune diseases with facial skin aging. AS, SS, SLE, MS, PSC, and CeD was positively associated with the risk of facial aging. The red line and bold text represents the OR, 95% CI, and p-value of the statistically significant results.

Abbreviations: IBD, inflammatory bowel disease; AA, alopecia areata; MS, multiple sclerosis; SS, sicca syndrome; RA, rheumatoid arthritis; AS, ankylosing spondylitis; CeD, celiac disease; SLE, systemic lupus erythematosus; SSc, systemic sclerosis; TID, type I diabetes; JIA, juvenile idiopathic arthritis; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; MG, myasthenia gravis.

95% CI: 0.996–1.005; P=0.838), genetic liability to AA (OR 1.000; 95% CI: 0.999–1.002; P=0.599), genetic liability to SSc (OR 1.000; 95% CI: 0.999–1.001; P=0.884), genetic liability to sarcoidosis (OR 1.000; 95% CI: 0.997–1.003; P=0.991), genetic liability to vitiligo (OR 1.000; 95% CI: 0.998–1.002; P=0.785), genetic liability to MG (OR 0.999; 95% CI: 0.998–1.001; P=0.365), genetic liability to PBC (OR 0.999; 95% CI: 0.996–1.002; P=0.568), genetic liability to JIA (OR 0.999; 95% CI: 0.997–1.001; P=0.269), and genetic liability to RA (OR 0.812; 95% CI: 0.544–1.211; P=0.307) showed no causal relationships with the risk of facial aging. Details of the results of other complementary methods are presented in <u>Supplementary Table 2</u>. Details of the SNPs effects are shown in <u>Supplementary Figure 1</u>.

In the MVMR analysis adjusted for alcohol consumption, genetic liability for AS, SS, SLE, MS, PSC, and CeD remained significantly associated with facial aging. After adjusting for smoking, alcohol consumption, and BMI, genetic liability to AS (OR 1.026; 95% CI: 1.005–1.048; P=0.016), SLE (OR 1.005; 95% CI: 1.001–1.009; P=0.006), and CeD (OR 1.002; 95% CI: 1.000–1.005; P=0.044) were still significantly associated with higher risk of facial aging, while genetic liability to SS (OR 0.996; 95% CI: 0.991–1.001; P=0.118), MS (OR 1.002; 95% CI: 0.997–1.007; P=0.391), and PSC (OR 1.002; 95% CI: 0.998–1.005; P=0.378) were no longer associated with facial skin aging (Figure 3).

Sensitivity Analysis

We conducted a series of sensitivity analyses to test the stability of the primary results. MR-Egger regression for pleiotropy and Cochrane's Q test for heterogeneity were performed (Table 2). Heterogeneity was observed when the causal effects of MS, AS, T1D, psoriasis, and JIA were analyzed. We detected several outliers for AS (rs1041926 and rs1128905), T1D (rs1050979, rs1574285, rs2188962, and rs57209021), psoriasis (rs10040411, rs12188300, rs2312786, and rs2735008), hypothyroidism (rs4409785), and PBC (rs2523882 and rs8067378). After removing these SNPs, heterogeneity was no longer detected in AS or PBC. The IVW results persisted even after removing the outliers. None

Exposure	Confounders			OR(95%CI)	p-value
AS	Smoking, alcohol, and BMI	i	>	1.026(1.005, 1.048)	0.016
AS	Smoking			1.020(1.003, 1.036)	0.018
AS	Alcohol consumption		•>	1.018(1.002, 1.034)	0.027
AS	BMI			1.025(1.004, 1.047)	0.020
SS	Smoking, alcohol, and BMI			0.996(0.991, 1.001)	0.118
SS	Smoking	-		1.004(0.999, 1.010)	0.099
SS	Alcohol consumption			1.007(1.000, 1.013)	0.040
SS	BMI	• ¦	_	0.999(0.994, 1.003)	0.550
SLE	Smoking, alcohol, and BMI	-	—	1.005(1.001, 1.009)	0.006
SLE	Smoking		-	1.005(0.998, 1.011)	0.145
SLE	Alcohol consumption	-		1.007(1.001, 1.012)	0.023
SLE	BMI	-	—	1.005(1.001, 1.009)	0.009
MS	Smoking, alcohol, and BMI			1.002(0.997, 1.007)	0.391
MS	Smoking	-		1.004(1.000, 1.009)	0.038
MS	Alcohol consumption	-	•	1.004(1.000, 1.008)	0.027
MS	BMI		—	1.002(0.998, 1.007)	0.333
PSC	Smoking, alcohol, and BMI			1.002(0.998, 1.005)	0.378
PSC	Smoking	H	-	1.002(1.000, 1.005)	0.084
PSC	Alcohol consumption	-	-	1.002(1.000, 1.004)	0.028
PSC	BMI			1.001(0.998, 1.005)	0.408
CeD	Smoking, alcohol, and BMI	4	-	1.002(1.000, 1.005)	0.044
CeD	Smoking	H	-	1.002(1.000, 1.005)	0.047
CeD	Alcohol consumption	-	-	1.002(1.001, 1.004)	0.011
CeD	BMI		-	1.002(1.000, 1.005)	0.045
	0.9	9 1	1.0)2	

Figure 3 Multivariable MR analysis adjusting for potential confounding variables. After adjusting for smoking, alcohol consumption, and BMI, AS, SLE, and CeD remained positively associated with the risk of facial aging. The red line and bold text represents the OR, 95% Cl, and p-value of the statistically significant results. **Abbreviations:** MS, multiple sclerosis; SS, sicca syndrome; AS, ankylosing spondylitis; CeD, celiac disease; SLE, systemic lupus erythematosus; SSc, systemic sclerosis; PSC, primary sclerosing cholangitis; BMI, body mass index.

of the MR-Egger intercepts was statistically different from zero, suggesting that the heterogeneity of SNPs did not cause any horizontal pleiotropic bias. <u>Supplementary Figure 2</u> shows the results of the leave-one-out analysis. <u>Supplementary</u> <u>Figure 3</u> shows the effects of instrumental SNPs on each autoimmune disease and the risk of facial aging. <u>Supplementary</u> <u>Figure 4</u> shows the distribution of the effects of the individual SNP.

Autoimmune Diseases	P for Cochrane's Q test (MR Egger Method)	P for Cochrane's Q test (IVW Method)	MR-Egger Intercept	P for MR-Egger Intercept
IBD	0.696	0.752	0.000	0.755
Vitiligo	0.120	0.224	-0.002	0.823
AA	0.203	0.100	0.002	0.129
MS	0.014	0.017	-0.000	0.685
SS	0.541	0.446	-0.002	0.466
Hypothyroidism	0.003	0.002	0.001	0.313
Sarcoidosis	0.714	0.655	-0.002	0.376
RA	0.068	0.060	-0.001	0.375

Tabla	2	Soncitivity	Analy	sos of	the	Procont	Study
rable	4	Sensitivity	Analy	ses or	une	rresent	SLUDY

(Continued)

Autoimmune Diseases	P for Cochrane's Q test (MR Egger Method)	P for Cochrane's Q test (IVW Method)	MR-Egger Intercept	P for MR-Egger Intercept
AS	<0.001	<0.001	-0.001	0.400
CeD	0.293	0.268	-0.00 I	0.272
SLE	0.100	0.104	-0.006	0.562
SSc	0.705	0.809	0.000	0.860
TID	<0.001	<0.001	-0.000	0.835
Psoriasis	<0.001	<0.001	-0.000	0.933
JIA	0.168	0.310	-0.000	0.942
PBC	<0.001	<0.001	-0.002	0.091
PSC	0.038	0.048	0.000	0.658
MG	0.321	0.371	-0.000	0.561

Table	2	(Contini	ied).

Note: The bold text indicates that the P value is less than 0.05.

Abbreviations: IBD, inflammatory bowel disease; AA, alopecia areata; MS, multiple sclerosis; SS, sicca syndrome; RA, rheumatoid arthritis; AS, ankylosing spondylitis; CeD, celiac disease; SLE, systemic lupus erythematosus; SSc, systemic sclerosis; TID, type I diabetes; JIA, juvenile idiopathic arthritis; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; MG, myasthenia gravis.

Discussion

Autoimmune diseases constitute a group of inflammatory conditions that affect diverse organ systems.³⁰ Skin, the largest organ covering the human body, is generally affected by the systemic inflammation of autoimmune diseases. Oxidative stress in autoimmune diseases may accelerate the skin aging process.⁴ Previous studies have demonstrated a potential association between autoimmune diseases and skin aging. As a special part of the skin, facial skin plays a vital aesthetic role, prompting increasing interest in early intervention against facial skin aging. However, studies on the association between autoimmune diseases and facial skin aging are limited. The lack of research on this topic at the population level may be attributed to difficulties in measuring facial aging. For instance, although artificial intelligence (AI) technology can deliver comprehensive characteristics of facial aging, it has not been widely used owing to considerable errors and biases.^{31,32} The use of questionnaire-based tools can help overcome the challenges associated with facial aging assessment.³³ The large sample size of the IEU OpenGWAS project may alleviate concerns about measurement errors when evaluating facial skin aging using questionnaires, highlighting the benefits of such data. In the present study, we examined the relationship between genetically predicted autoimmune diseases and facial aging by applying an MR approach based on the IEU OpenGWAS project database. Our study may help in developing strategies to prevent premature facial skin aging in patients with autoimmune diseases.

To our knowledge, this is the first study to systematically investigate the causality between diverse autoimmune diseases and the risk of facial aging. Using UV-MR statistical approaches, genetically predicted AS, SS, SLE, MS, PSC, and CeD are associated with a more severe likelihood of facial skin aging. Previous studies have suggested that tobacco smoking, alcohol intake, and adiposity can affect facial skin health.^{10,14,15} Therefore, we performed MVMR analyses after adjusting for these potential confounding factors. The MVMR results demonstrated the robustness of the relationship between genetically predicted AS, SLE, and CeD, and a higher risk of facial skin aging. Our study adds to the evidence supporting the causal role of autoimmune diseases in facial aging. Autoimmune diseases affect diverse organ systems, including the skin, via multiple biochemical processes. AS patients with systemic inflammation presented with a reduced vasodilator capacity of the skin microvasculature, which was positively correlated with inflammatory parameters.³⁴ Cutaneous vasculitis was observed in CeD patients.³⁵ Maintaining normal vascular activities is crucial in preserving skin health. The reduced vasodilator capacity in the skin microvasculature leads to decreased microvessel blood flow, which plays a key role in skin aging.³⁶ The microvasculature is responsible for delivering oxygen and epidermal cells, thus determining the cell environment and papillae.^{37,38} Subcutaneous fat also needs adequate support of the capillaries. Loss of subcutaneous fat generally causes skin swelling and contraction. Therefore, a disrupted skin microvascular function may be an important

factor in facial skin aging in patients with AS or CeD. As an autoimmune enteropathy primarily involving the small intestine, CeD is characterized by intestinal villi atrophy and consequent malabsorption. Nutritional factors play important roles in preserving normal skin function. In patients with CeD, the balance of serum lipids is dramatically disrupted,³⁹ which may promote skin aging. Triglycerides are crucial for moisturizing the human skin, and their deficiency can lead to skin dryness. Maintaining water content in the stratum corneum is crucial for the mechanical properties and normal desquamation of the skin. Low water content in the stratum corneum can inhibit the activities of proteinases responsible for the orderly degradation of skin structures, leading to abnormal desquamation and dysfunction of the stratum corneum.⁴⁰ In such conditions, the skin becomes rough and scaly, resulting in reduced flexibility and premature aging of facial skin. A high degree of unsaturated fatty acids also affects skin health, as increased fat unsaturation in tissue membranes accelerates aging by generating free radicals. Cutaneous inflammation is quite common in patients with SLE.⁴¹ The activation of the innate and adaptive immune systems promotes skin tissue inflammation, thus resulting in cytotoxic damage. Accumulated damage resulting from chronic inflammation leads to the inability of keratinocytes and fibroblasts to produce crucial cellular components compared to their younger counterparts. Fibroblasts, the dominant dermal cells, are responsible for the turnover of the extracellular matrix (ECM). Changes in the dermal compartments, such as reduced synthesis or heightened degradation of the ECM, can result in wrinkles and sagging of the facial skin.⁴² The present study, conducted at the population level, supported the association between autoimmune diseases and facial skin aging. The clinical relevance of facial aging in autoimmune diseases is shown in Figure 4.

Previous studies have also revealed a potential association between vitiligo and skin aging.⁵ However, our study did not observe such a relationship. The discrepancy may be attributed to undetected biases caused by extracting SNPs associated with vitiligo at a relatively relaxed threshold ($P < 5 \times 10^{-6}$). In addition, after adjusting for alcohol consumption, SS, MS, and PSC remained significantly associated with facial aging, whereas this relationship no longer existed after adjusting for all three confounding factors. This indicates that alcohol consumption might be merely a minor confounding factor compared to smoking and adiposity. As alcohol is known to be a risk factor for autoimmune diseases,⁴³ patients with autoimmune diseases are more likely to refrain from alcohol consumption, thereby mitigating the impact of alcohol on facial aging.



Figure 4 The clinical relevance of facial aging in autoimmune diseases.

Based on this evidence, potential strategies for the prevention of premature facial aging can be developed. Patients with AS, CeD, or SLE should receive proactive treatment to control disease progression and reduce systemic inflammation. Improving the skin microcirculation perfusion function is also necessary in patients with AS and CeD. Patients with CeD and severe intestinal manifestations should pay more attention to their serum lipid levels and receive appropriate medical intervention if necessary. For SLE patients with poor fibroblast function, oral collagen peptide or hyaluronan may be an option to supply the ECM and maintain dermis health. Additionally, patients with SS, MS, or PSC should avoid excessive smoking, alcohol consumption, and adiposity, as these factors contribute to accelerated facial aging in individuals with SS, MS, and PSC.

We acknowledge several limitations to our study. A major limitation is that the leave-one-out method observed single genetic markers driving associations in several MR analyses. However, these SNPs, including rs2596501, rs2853986, rs3134954, rs3131781, and rs13198474, were not linked to any confounding phenotypes below the threshold of $P < 5 \times 10^{-8}$ according to the PhenoScanner database (www.phenoscanner.medschl.cam.ac.uk/), suggesting the robustness of the present results. Other sensitivity analyses also confirmed the stability of our results. Another limitation is that the present research was confined to the epidemiological level and did not investigate the specific mechanisms of the associations between autoimmune diseases and facial aging, owing to the limitations of the datasets. In addition, our study primarily involved Europeans, which may have limited the applicability of our findings to other populations. Finally, we were unable to detail the inclusion and exclusion criteria, which is a common limitation of MR analyses using publicly available summary-level data. However, the data derived from high-quality GWAS studies ensure the robustness of the present study.

Conclusion

This MR study provides evidence that genetically proxied AS, SS, SLE, MS, PSC, and CeD are associated with a higher risk of facial skin aging. After adjusting for confounding factors, the relationships between AS, SLE, and CeD remained unchanged. Further investigations should focus on the underlying mechanisms of these associations. Moreover, individuals of different ancestries should be included in future research to expand generalizability.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

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

Acknowledgments

The authors extend their thanks to the participants and investigators of the GWAS analyses. The authors extend their thanks to Smart (<u>https://smart.servier.com/</u>) and Pinclipart (<u>https://www.pinclipart.com/</u>) for the icons they provided for the Figure 4. We would like to thank Editage (<u>www.editage.cn</u>) for English language editing.

Funding

Funding ID: 20210204154YY, Source: Science and technology department of Jilin Province, Project Title: Mechanism on mesenchymal stem cells in preventing skin photoaging.

Disclosure

The authors report no conflicts of interest in this work.

References

- 1. Illescas-Montes R, Melguizo-Rodriguez L, Ruiz C, Costela-Ruiz VJ. Vitamin D and autoimmune diseases. *Life Sci.* 2019;233:116744. doi:10.1016/j.lfs.2019.116744
- Eaton WW, Pedersen MG, Atladottir HO, Gregory PE, Rose NR, Mortensen PB. The prevalence of 30 ICD-10 autoimmune diseases in Denmark. Immunol Res. 2010;47(1-3):228–231. doi:10.1007/s12026-009-8153-2
- 3. Sardu C, Cocco E, Mereu A, et al. Population based study of 12 autoimmune diseases in Sardinia, Italy: prevalence and comorbidity. *PLoS One*. 2012;7(3):e32487. doi:10.1371/journal.pone.0032487
- 4. Papaccio F, Da A, Caputo S, Bellei B. Focus on the Contribution of Oxidative Stress in Skin Aging. Antioxidants. 2022;11(6):56.
- 5. Bellei B, Picardo M. Premature cell senescence in human skin: dual face in chronic acquired pigmentary disorders. *Ageing Res Rev.* 2020;57:100981. doi:10.1016/j.arr.2019.100981
- 6. Wilkins JM, Gakh O, Kabiraj P, et al. Signatures of cell stress and altered bioenergetics in skin fibroblasts from patients with multiple sclerosis. *Aging*. 2020;12(14):15134–15156. doi:10.18632/aging.103612
- Harris-Tryon TA, Grice EA. Microbiota and maintenance of skin barrier function. *Science*. 2022;376(6596):940–945. doi:10.1126/science.abo0693
 Liu Z, Mi J, Wu H. Relationships between circulating metabolites and facial skin aging: a Mendelian randomization study. *Hum Genomics*. 2023;17 (1):23. doi:10.1186/s40246-023-00470-y
- 9. Liang Y, Su W, Wang F. Skin Ageing: a Progressive, Multi-Factorial Condition Demanding an Integrated, Multilayer-Targeted Remedy. Clin Cosmet Invest Dermatol. 2023;16:1215-1229. doi:10.2147/CCID.S408765
- 10. Liu M, Feng J. Association between adiposity and facial aging: results from a Mendelian randomization study. *Eur J Med Res.* 2023;28(1):350. doi:10.1186/s40001-023-01236-x
- 11. Bourassa KJ, Moffitt TE, Ambler A, et al. Association of Treatable Health Conditions During Adolescence With Accelerated Aging at Midlife. *JAMA Pediatr.* 2022;176(4):392–399. doi:10.1001/jamapediatrics.2021.6417
- 12. Davey Smith G, Hemani G. Mendelian randomization: genetic anchors for causal inference in epidemiological studies. *Hum Mol Genet*. 2014;23 (R1):R89–98. doi:10.1093/hmg/ddu328
- Smith GD, Ebrahim S. 'Mendelian randomization': can genetic epidemiology contribute to understanding environmental determinants of disease? Int J Epidemiol. 2003;32(1):1–22. doi:10.1093/ije/dyg070
- Goodman GD, Kaufman J, Day D, et al. Impact of Smoking and Alcohol Use on Facial Aging in Women: results of a Large Multinational, Multiracial, Cross-sectional Survey. J Clin Aesthet Dermatol. 2019;12(8):28–39.
- Okada HC, Alleyne B, Varghai K, Kinder K, Guyuron B. Facial changes caused by smoking: a comparison between smoking and nonsmoking identical twins. *Plast Reconstr Surg.* 2013;132(5):1085–1092. doi:10.1097/PRS.0b013e3182a4c20a
- 16. Davies NM, Holmes MV, Davey Smith G. Reading Mendelian randomisation studies: a guide, glossary, and checklist for clinicians. *BMJ*. 2018;362:k601. doi:10.1136/bmj.k601
- 17. Donertas HM, Fabian DK, Valenzuela MF, Partridge L, Thornton JM. Common genetic associations between age-related diseases. *Nat Aging*. 2021;1(4):400–412. doi:10.1038/s43587-021-00051-5
- Sawcer S. Genetic risk and a primary role for cell-mediated immune mechanisms in multiple sclerosis. *Nature*. 2011;476(7359):214–219. doi:10.1038/nature10251
- 19. Sakaue S, Kanai M, Tanigawa Y, et al. A cross-population atlas of genetic associations for 220 human phenotypes. *Nat Genet.* 2021;53 (10):1415–1424. doi:10.1038/s41588-021-00931-x
- 20. Spondylitis C, Cortes A, Hadler J, et al.; International Genetics of Ankylosing. Identification of multiple risk variants for ankylosing spondylitis through high-density genotyping of immune-related loci. *Nat Genet.* 2013;45(7):730–738. doi:10.1038/ng.2667
- Trynka G, Hunt KA, Bockett NA, et al. Dense genotyping identifies and localizes multiple common and rare variant association signals in celiac disease. Nat Genet. 2011;43(12):1193–1201. doi:10.1038/ng.998
- 22. Hom G, Graham RR, Modrek B, et al. Association of systemic lupus erythematosus with C8orf13-BLK and ITGAM-ITGAX. N Engl J Med. 2008;358(9):900–909. doi:10.1056/NEJMoa0707865
- Chiou J, Geusz RJ, Okino ML, et al. Interpreting type 1 diabetes risk with genetics and single-cell epigenomics. *Nature*. 2021;594(7863):398–402. doi:10.1038/s41586-021-03552-w
- 24. Hinks A, Cobb J, Marion MC, et al. Dense genotyping of immune-related disease regions identifies 14 new susceptibility loci for juvenile idiopathic arthritis. *Nat Genet.* 2013;45(6):664–669. doi:10.1038/ng.2614
- 25. Liu JZ, Almarri MA, Gaffney DJ, et al. Dense fine-mapping study identifies new susceptibility loci for primary biliary cirrhosis. *Nat Genet*. 2012;44(10):1137–1141. doi:10.1038/ng.2395
- 26. Ji SG, Juran BD, Mucha S, et al. Genome-wide association study of primary sclerosing cholangitis identifies new risk loci and quantifies the genetic relationship with inflammatory bowel disease. Nat Genet. 2017;49(2):269–273. doi:10.1038/ng.3745
- 27. Zhan Y, Hagg S. Association between genetically predicted telomere length and facial skin aging in the UK Biobank: a Mendelian randomization study. *Geroscience*. 2021;43(3):1519–1525. doi:10.1007/s11357-020-00283-0
- 28. Jiang L, Zheng Z, Fang H, Yang J. A generalized linear mixed model association tool for biobank-scale data. Nat Genet. 2021;53(11):1616–1621. doi:10.1038/s41588-021-00954-4
- 29. Burgess S, Scott RA, Timpson NJ, Davey Smith G, Thompson SG, Consortium E-I. Using published data in Mendelian randomization: a blueprint for efficient identification of causal risk factors. *Eur J Epidemiol.* 2015;30(7):543–552. doi:10.1007/s10654-015-0011-z
- 30. Borsky P, Chmelarova M, Fiala Z, et al. Aging in psoriasis vulgaris: female patients are epigenetically older than healthy controls. *Immun Ageing*. 2021;18(1):10. doi:10.1186/s12979-021-00220-5
- 31. Flament F, Jacquet L, Ye C, et al. Artificial Intelligence analysis of over half a million European and Chinese women reveals striking differences in the facial skin ageing process. J Eur Acad Dermatol Venereol. 2022;36(7):1136–1142. doi:10.1111/jdv.18073
- 32. Ganel T, Sofer C, Goodale MA. Biases in human perception of facial age are present and more exaggerated in current AI technology. *Sci Rep.* 2022;12(1):22519. doi:10.1038/s41598-022-27009-w
- Dykiert D, Bates TC, Gow AJ, Penke L, Starr JM, Deary IJ. Predicting mortality from human faces. Psychosom Med. 2012;74(6):560–566. doi:10.1097/PSY.0b013e318259c33f

- Klimek E, Sulicka J, Gryglewska B, et al. Alterations in skin microvascular function in patients with rheumatoid arthritis and ankylosing spondylitis. *Clin Hemorheol Microcirc*. 2017;65(1):77–91. doi:10.3233/CH-15112
- 35. Abenavoli L, Dastoli S, Bennardo L, et al. The Skin in Celiac Disease Patients: the Other Side of the Coin. Medicina. 2019;55(9):578. doi:10.3390/ medicina55090578
- 36. Balint AR, Puskas T, Menyhart A, et al. Aging Impairs Cerebrovascular Reactivity at Preserved Resting Cerebral Arteriolar Tone and Vascular Density in the Laboratory Rat. Front Aging Neurosci. 2019;11:301. doi:10.3389/fnagi.2019.00301
- 37. Wang W. Oxygen partial pressure in outer layers of skin: simulation using three-dimensional multilayered models. *Microcirculation*. 2005;12 (2):195–207. doi:10.1080/10739680590905062
- 38. Li J, Zeng X, Yang X, Ding H. Lycopene ameliorates skin aging by regulating the insulin resistance pathway and activating SIRT1. *Food Funct*. 2022;13(21):11307–11320. doi:10.1039/d2fo01111e
- 39. Sen P, Carlsson C, Virtanen SM, et al. Persistent Alterations in Plasma Lipid Profiles Before Introduction of Gluten in the Diet Associated With Progression to Celiac Disease. *Clin Transl Gastroenterol*. 2019;10(5):1–10. doi:10.14309/ctg.0000000000044
- 40. Hashizume H. Skin aging and dry skin. J Dermatol. 2004;31(8):603-609. doi:10.1111/j.1346-8138.2004.tb00565.x
- 41. Vale E, Garcia LC. Cutaneous lupus erythematosus: a review of etiopathogenic, clinical, diagnostic and therapeutic aspects. *An Bras Dermatol.* 2023;98(3):355–372. doi:10.1016/j.abd.2022.09.005
- 42. Gruber F, Kremslehner C, Eckhart L, Tschachler E. Cell aging and cellular senescence in skin aging Recent advances in fibroblast and keratinocyte biology. *Exp Gerontol.* 2020;130:110780. doi:10.1016/j.exger.2019.110780
- 43. Caslin B, Mohler K, Thiagarajan S, Melamed E. Alcohol as friend or foe in autoimmune diseases: a role for gut microbiome? *Gut Microbes*. 2021;13(1):1916278. doi:10.1080/19490976.2021.1916278

Clinical, Cosmetic and Investigational Dermatology

Dovepress

DovePress

Publish your work in this journal

Clinical, Cosmetic and Investigational Dermatology is an international, peer-reviewed, open access, online journal that focuses on the latest clinical and experimental research in all aspects of skin disease and cosmetic interventions. This journal is indexed on CAS. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit http://www. dovepress.com/testimonials.php to read real quotes from published authors.

Submit your manuscript here: https://www.dovepress.com/clinical-cosmetic-and-investigational-dermatology-journal

🖬 🔰 in 🗖