Clin. Lab. 2026;72:XXX-XXX

ORIGINAL ARTICLE

Genetic Evidence Linking Circulating Epidermal Growth Factor to Sjögren's Syndrome Risk

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ABSTRACT

Background: **This study aimed to explore the potential causal correlations between circulating expression levels of six growth factors - epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), transforming growth factor-beta (TGF-β), platelet-derived growth factor (PDGF), and nerve growth factor (NGF) - and the risk of developing Sjögren's syndrome (SS), from the perspective of genetic variation, using a Mendelian Randomization (MR) approach.**

Methods: **Genetic data related to SS and the six growth factors were obtained from the IEU OpenGWAS project [GWAS IDs: "finn-b-M13_SJOGREN" (SS), "ebi-a-GCST90010212" (EGF), "ebi-a-GCST90011995" (VEGF), "ebi-a-GCST004459" (FGF), "ebi-a-GCST90000481" (TGF-β), "ebi-a-GCST004432" (PDGF), and "prot-b-40" (NGF)]. A two-sample MR analysis was conducted to estimate the causal effect of each growth factor on SS risk. Five complementary MR methods were employed to ensure robustness: Inverse Variance Weighted (IVW), MR-Egger, Weighted Median, Simple Mode, and MR-PRESSO. We further assessed heterogeneity and horizontal pleiotropy using Cochran's Q test and MR-Egger intercept, and performed leave-one-out analyses to test the sensitivity and reliability of the results.**

Results: **The MR analysis provided evidence supporting a causal association between elevated EGF levels and increased SS risk. Both IVW (p = 0.0485, OR [95%] = 1.0696 [1.0004 - 1.1436]) and MR-PRESSO (p = 0.0406, OR [95% CI] = 1.0684 [1.0080 - 1.1325]) yielded statistically significant results. No significant causal associations were observed between SS and the other five growth factors across all MR methods. Sensitivity analyses supported the robustness of the observed association between EGF and SS.**

Conclusions: **The findings suggest that elevated circulating EGF levels may play a causal role in the development of Sjögren's syndrome, supporting EGF as a potential biomarker for early diagnosis and risk prediction. These results provide novel insights into the pathogenesis of SS and highlight EGF as a potential target for future diagnostic and therapeutic strategies. Further research is needed to explore the clinical utility of growth factor-targeted approaches for SS prevention and treatment.**

(Clin. Lab. 2026;72:xx-xx. DOI: 10.7754/Clin.Lab.2025.251104)

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Manuscript accepted November 23, 2025

KEYWORDS

Sjögren's syndrome, epidermal growth factor, Mendelian randomization, GWAS

INTRODUCTION

Sjögren's Syndrome (SS) is a chronic autoimmune disorder primarily affecting exocrine glands, with the Salivary and lacrimal glands being the most commonly involved. Clinically, patients present with diminished

glandular secretion, leading to hallmark symptoms such as xerostomia (dry mouth) and xerophthalmia (dry eyes) [1,2]. The syndrome was first described in 1933 by Danish ophthalmologist Henrik Sjögren, who reported 19 female patients with dry eyes and mouth. To differentiate it from xerophthalmia associated with vitamin A deficiency, Sjögren coined the term keratoconjunctivitis sicca [3].

A global epidemiological study based on data from PubMed and Embase reports that the annual incidence of SS is 6.92 cases per 100,000 people, while the prevalence stands at 60.82 per 100,000 [4]. In SS pathogenesis, exocrine gland cells may secrete growth factors during tissue repair processes to facilitate local healing. Fibroblast growth factors (FGFs) play a critical role not only in maintaining the pluripotency and dedifferentiation of stem cells, but also in mediating tissue repair during regeneration. Hepatocyte growth factor-like epidermal growth factor (HB-EGF), a member of the EGF family, is widely expressed across various organs and plays a pivotal role in tissue repair and regeneration. Furthermore, the transforming growth factor-beta (TGF-β) superfamily, key mediators in tissue repair, includes TGF-β1, which is associated with fibrosis in adult wound healing, and TGF-β3, which has been shown to reduce scar formation [5-7]. These findings suggest that abnormalities in the secretion of specific growth factors may contribute to the pathogenesis of SS, making it clinically relevant to investigate the relationship between growth factor levels and SS onset.

In addition to growth factor abnormalities, genetic factors are implicated in the development of SS [8]. Single nucleotide polymorphisms (SNPs) are one of the most common forms of genetic variation associated with autoimmune diseases. For example, the rs2069705 SNP in the IFN-γ gene has been identified as a key susceptibility factor for SS. Carriers of this SNP exhibit increased transcription of IFN-γ, which activates the JAK/STAT1 pathway and results in B lymphocyte infiltration into exocrine glands [9]. Similarly, elevated expression of the PCSK3 gene has been linked to SS, with certain SNP variants showing a strong association with both gene expression levels and SS susceptibility [10]. Furthermore, significant associations have been observed between SNPs in the BLK gene and primary SS, as well as between the rs3733197 SNP and SS susceptibility in different genetic models [11].

Recently, Mendelian Randomization (MR) has gained widespread application in biomedical research, offering valuable insights into the causal relationships underlying various diseases. By using SNPs as instrumental variables, MR allows for the statistical exploration of causal links between exposure factors and outcomes [12,13]. This study, leveraging the MR methodology, investigates the causal relationship between growth factor levels and the development of SS, providing statistical support for the potential use of growth factors in early disease screening and clinical treatment.

MATERIALS AND METHODS

Sources of outcome data

To obtain outcome data related to SS, a comprehensive search was conducted in the IEU OpenGWAS Project (https://gwas.mrcieu.ac.uk/) using relevant keywords for retrieval and screening. The GWAS dataset with ID "finn-b-M13_SJOGREN" was identified, which includes SS-related data [14]. This dataset encompasses a total of 214,435 European adults (1,290 patients and 213,145 healthy controls), providing information on 16,380,454 SNPs (Table 1).

Selection of instrumental variables

For the selection of instrumental variables related to growth factors, six key growth factors were included in the analysis: epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), transforming growth factor-beta (TGF-β), platelet-derived growth factor (PDGF), and nerve growth factor (NGF). Corresponding GWAS datasets were retrieved with the following IDs: "ebi-a-GCST 90010212" for EGF [15], "ebi-a-GCST90011995" for VEGF [16], "ebi-a-GCST004459" for FGF [17], "ebi-a-GCST90000481" for TGF-β [18], "ebi-a-GCST004432" for PDGF [17], and "prot-b-40: for NGF [19] (Table 1). Subsequently, phenotypic-associated SNPs were extracted based on the genome-wide statistical significance threshold, and the SNP screening threshold was set at $p < 1 \times 10^{-5}$. To address potential bias arising from linkage disequilibrium (LD), the PLINK clustering method was employed with a clustering threshold of $r^2 < 0.001$ and a distance of 10,000 kb.

MR analysis

In this study, two-sample MR was performed to assess the causal relationship between six growth factors and the development of SS. The analysis utilized multiple MR methods, including MR-Egger, Inverse Variance Weighted (IVW), Weighted Median, Simple Mode, and the MR-PRESSO algorithms. These methods were selected to ensure robust and comprehensive estimation of causal effects. To assess the heterogeneity of the selected instrumental variables, Cochran's Q statistic test was applied. Furthermore, to evaluate potential horizontal pleiotropy, which could bias the results, a horizontal pleiotropy test was conducted using the MR-Egger method. All statistical analyses were conducted using R software (Version: 4.3.2), with the relevant packages: "TwoSampleMR" (Version: 0.5.8) and "MRPRESSO" (Version: 1.0). To further assess the robustness of the findings, sensitivity analysis was performed using the Leave-one-out method, which involves systematically excluding each instrumental variable to check for any undue influence on the results.

RESULTS

Three key assumptions in MR analysis

To investigate the potential causal relationship between growth factors and the development of SS, this study is based on three key assumptions: 1) The SNPs selected as instrumental variables are strongly associated with the growth factors and meet the genome-wide significance threshold; 2) The instrumental variables are independent of confounding factors; 3) The instrumental variables affect Sjögren's Syndrome exclusively through their effect on the growth factors, without influencing the disease through any other pathways. In line with these assumptions, we performed a comprehensive search using relevant keywords related to both growth factors and SS in the IEU OpenGWAS Project (https://gwas.mrcieu.ac.uk/). From this, we retrieved the following GWAS datasets: "ebi-a-GCST90010212" for EGF, "ebi-a-GCST90011995" for VEGF, "ebi-a-GCST004459" for FGF, "ebi-a-GCST90000481" for TGF-β, "ebi-a-GCST004432" for PDGF, "prot-b-40" for NGF, and "finn-b-M13_SJOGREN" for SS. The datasets were utilized to designate growth factors as the exposure variables, with SS as the outcome in the subsequent analyses (Figure 1).

Extraction of instrumental variables

For the EGF-related GWAS data, a total of 19 SNPs were initially selected based on a genome-wide significance threshold of $p < 1 \times 10^{-5}$. These SNPs were further refined using the PLINK clustering method, with a threshold of $r^2 < 0.001$ and a distance parameter of 10,000 kb. Subsequently, the R^2 and *F*-statistics for each SNP were calculated. SNPs with an *F*-statistic less than 10 were excluded, although no SNPs were removed in this analysis. The median R^2 [interquartile range (IQR)] was 0.1256 [0.1236 - 0.1287], and the median *F*-statistic [IQR] was 21.8500 [21.5400 - 22.0500]. Similarly, using the same selection criteria, 27 SNPs for VEGF, 18 SNPs for FGF, 19 SNPs for TGF-β, 18 SNPs for PDGF, and 44 SNPs for NGF were identified as associated SNPs (Table 2).

EGF increases the risk of developing SS

To explore the potential causal role of EGF in the development of SS, a total of 17 EGF-related SNPs were initially identified from the SS-associated GWAS data. After applying quality control measures, including the removal of 2 low-quality SNPs (rs10835730, rs3858800) based on allele frequency and LD effects, 15 SNPs were retained as instrumental variables for subsequent analysis (Figure 2A). The results of the MR analysis indicated that the IVW and MR-PRESSO methods produced statistically significant p-values of 0.0485 and 0.0406, respectively. The odds ratios (OR) [95% CI] for these methods were 1.0696 [1.0004 - 1.1436] and 1.0684 [1.0080 - 1.1325], suggesting that EGF may increase the risk of developing SS (Table 3 and Figure 2B). The MR scatter plot visualization of EGF is shown in Figure 2C.

Additionally, a total of 26 VEGF-related SNPs were identified, and after excluding 1 low-quality SNP (rs6475938), 25 SNPs were retained for downstream analysis (Table 3). Similar analyses were conducted for FGF (13 SNPs), TGF-β (14 SNPs), PDGF (15 SNPs), and NGF (39 SNPs), with low-quality SNPs excluded in each case (Table 3). The MR scatter plot visualization of VEGF, FGF, TGF-β, PDGF and NGF is shown in Figure 3B, C, D, E, and F. However, for all these growth factors, the two-sample MR analysis revealed no significant associations with SS, with all p-values exceeding 0.05 for all MR methods, indicating the absence of a statistically significant causal relationship (Table 3).

Sensitivity analysis

Furthermore, Cochran's Q test was performed to assess the heterogeneity among the selected instrumental variables. The results demonstrated that both the MR-Egger and IVW methods yielded p-values exceeding 0.05, indicating no substantial heterogeneity in the analysis. Additionally, horizontal pleiotropy was evaluated using the MR-Egger method, with all p-values surpassing 0.05, suggesting that the selected SNPs do not exhibit pleiotropic effects. Sensitivity analysis using the leave-one-out method further corroborated the robustness and consistency of the results (Figure 2D).

DISCUSSION

SS is a chronic inflammatory autoimmune disorder primarily characterized by the infiltration of the lacrimal and salivary glands. While these glands are the primary sites of involvement, the disease can also affect other exocrine glands and various organ systems, leading to widespread systemic manifestations. SS predominantly affects older women, with typical clinical features including dry mouth, dry eyes, parotid gland enlargement, rampant caries, and multi-organ damage [20]. In addition, due to the immune dysregulation, individuals with SS have an increased risk of developing lymphoma and other malignancies, highlighting the importance of early detection and management [21]. The complex interactions between growth factors and the immune system play a pivotal role in the pathogenesis of SS, significantly influencing the progression and severity of the disease. Given that immune dysregulation is central to SS, understanding how growth factors such as VEGF-A interact with key immune components - such as platelets and complement proteins - is essential for developing targeted therapeutic strategies aimed at modulating these pathways [22]. This understanding can potentially lead to more effective treatments that address both the underlying immune mechanisms and the associated glandular dysfunction.

Therefore, in this study, we investigated the causal relationship between six common growth factors and the development of SS from the genetic variation perspec-

Table 1. Information on data related to SS and six growth factors.

GWAS ID	Trait	Population	Sample size	Case (n)	Control (n)	SNPs
finn-b-M13_SJOGREN	Sjögren's syndrome	European	214,435	1,290	213,145	16,380,454
ebi-a-GCST90010212	epidermal growth factor levels	European	1,323	-	-	18,221,903
ebi-a-GCST90011995	vascular endothelial growth factor levels	European	21,758	-	-	12,717,927
ebi-a-GCST004459	fibroblast growth factor basic levels	European	7,565	-	-	9,790,946
ebi-a-GCST90000481	transforming growth factor-beta levels	European	982	-	-	7,883,830
ebi-a-GCST004432	platelet-derived growth factor BB levels	European	8,293	-	-	9,800,009
prot-b-40	nerve growth factor	European	3,394	-	-	5,270,646

Table 2. Statistics on data of instrumental variables.

Instrumental variables	SNPs	R^2 Median [IQR]	*F* Median [IQR]
Epidermal growth factor (EGF)	19	0.1256 [0.1236 - 0.1287]	21.8500 [21.5400 - 22.0500]
Vascular endothelial growth factor (VEGF)	27	0.0319 [0.0309 - 0.0361]	256.3000 [146.6100 - 161.2900]
Fibroblast growth factor (FGF)	18	0.0529 [0.0513 - 0.0537]	87.3900 [85.9700 - 88.1000]
Transforming growth factor-beta (TGF-β)	19	0.1448 [0.1423 - 0.1466]	17.2900 [17.1700 - 17.4700]
Platelet-derived growth factor (PDGF)	18	0.0524 [0.0503 - 0.0580]	91.1100 [86.3900 - 93.1400]
Nerve growth factor (NGF)	44	0.0816 [0.0774 - 0.0866]	29.7000 [28.7600 - 30.5700]

tive, utilizing MR analysis. Our findings demonstrated a significant causal association between EGF levels and the occurrence of SS. Several related studies provide strong support for these findings. For instance, Mougeot et al. [23] explored the effects of EGF and interferons on a cell culture model of SS, revealing that the EGF/interferon signaling pathway may regulate the expression of STAT1 and STAT4 genes in salivary gland epithelial cells. Similarly, Azuma et al. investigated the role of EGF in activating the PI3K-Akt pathway and NF-kB in primary cultured salivary gland epithelial cells from patients with primary SS, demonstrating that EGF effectively inhibits apoptosis in these cells [24]. However, a study by Błochowiak et al. [25] reported no significant difference in EGF levels between SS patients and healthy controls, although salivary EGF levels were found to be significantly higher than serum levels. These studies lend substantial weight to our own results. By employing MR analysis, this study provides statistical evidence supporting the causal link between growth factors and the development of SS. Furthermore, our findings offer new insights into the potential application of growth factors, particularly EGF, in the early detection and clinical management of SS. In addition, with the ongoing expansion of biobank initiatives across multiple countries, researchers now have access to vast GWAS data sets encompassing diverse populations, diseases, and biomarkers. In this context, Mendelian randomization analysis, with its ability to process high volumes of SNPs, large sample sizes, and enhanced test stability, offers significant advantages over traditional small-sample approaches. As a result, it has found wide application in numerous biomedical fields. Nonetheless, this study has several limitations. First, due to constraints in the available GWAS data and the scope of the analysis, we were unable to include a comprehensive set of growth factors. As a result, our findings may not fully capture the complex interactions between all potential growth factors and SS. Additionally, for some growth factors, such as TGF-β the associated genetic instruments had relatively low F-statistics. This raises the potential for weak instrument bias, which could affect the accuracy of the causal estimates. Future studies should address this limitation by incorporating stronger instruments or utilizing larger datasets. Second, the study sample was restricted to individuals of European ancestry, which may limit the generalizability of the findings to other populations. Ethnic and population-specific genetic variations could influence the causal relationship between growth factors and SS, and there-

Table 3. MR analysis of growth factors in the development of SS.

Exposures	MR info						Cochran's Q			Horizontal pleiotropy		
	SNP (n)	Methods	Beta	SE	OR [95% CI]	p	Q	Q_ df	Q_ p-val	Inter-cept	SE	p
Epidermal growth factor	15	MR-Egger	0.0678	0.0487	1.0701 [0.9727 - 1.1773]	0.1873	12.1618	13	0.5144	-0.0003	0.0205	0.9898
		IVW	0.0673	0.0341	1.0696 [1.0004 - 1.1436]	0.0485	12.1620	14	0.5933	-	-	-
		Weighted median	0.0477	0.0432	1.0488 [0.9636 - 1.1415]	0.2700	-	-	-	-	-	-
		Simple mode	0.1724	0.0879	1.1881 [1.0002 - 1.4114]	0.0700	-	-	-	-	-	-
		MR-PRESSO	0.0662	0.0297	1.0684 [1.0080 - 1.1325]	0.0406	-	-	-	-	-	-
Vascular endothelial growth factor	25	MR-Egger	-0.1920	0.1080	0.8253 [0.6679 - 1.0198]	0.0886	23.9729	23	0.4053	0.0208	0.0175	0.2458
		IVW	-0.0965	0.0729	0.9080 [0.7871 - 1.0475]	0.1858	25.4515	24	0.3816	-	-	-
		Weighted median	-0.1429	0.0881	0.8669 [0.7294 - 1.0302]	0.1047	-	-	-	-	-	-
		Simple mode	-0.3245	0.2200	0.7229 [0.4697 - 1.1127]	0.1533	-	-	-	-	-	-
		MR-PRESSO	-0.0770	0.0711	0.9259 [0.8054 - 1.0644]	0.2895	-	-	-	-	-	-
Fibroblast growth factor	13	MR-Egger	-0.1226	0.4378	0.8846 [0.375 - 2.0864]	0.7846	6.3280	11	0.8506	0.0186	0.0452	0.6889
		IVW	0.0469	0.1468	1.0480 [0.786 - 1.3974]	0.7492	6.4969	12	0.8890	-	-	-
		Weighted median	-0.0095	0.1855	0.9906 [0.6886 - 1.4249]	0.9593	-	-	-	-	-	-
		Simple mode	-0.0306	0.3233	0.9698 [0.5147 - 1.8276]	0.9261	-	-	-	-	-	-
		MR-PRESSO	-0.0068	0.0967	0.9932 [0.8218 - 1.2005]	0.9450	-	-	-	-	-	-
Transform-ing growth factor-beta	14	MR-Egger	-0.0139	0.0106	0.9862 [0.9659 - 1.0068]	0.1923	6.4559	12	0.8914	0.0021	0.0257	0.9350
		IVW	0.0033	0.0029	1.0033 [0.9976 - 1.009]	0.2545	6.4629	13	0.9277	-	-	-
		Weighted median	0.0050	0.0043	1.005 [0.9965 - 1.0135]	0.2477	-	-	-	-	-	-

Table 3. MR analysis of growth factors in the development of SS (continued).

Exposures	MR info						Cochran's Q			Horizontal pleiotropy		
	SNP (n)	Methods	Beta	SE	OR [95% CI]	p	Q	Q_ df	Q_ p-val	Inter-cept	SE	p
Transform-ing growth factor-beta	14	Simple mode	0.0054	0.0108	1.0054 [0.9843 - 1.0269]	0.6207	-	-	-	-	-	-
		MR-PRESSO	0.0038	0.0028	1.0038 [0.9984 - 1.0093]	0.1731	-	-	-	-	-	-
Platelet-derived growth factor	15	MR-Egger	-0.0139	0.0106	0.9862 [0.9659 - 1.0068]	0.1923	13.5053	13	0.4096	0.0149	0.0267	0.5877
		IVW	0.0033	0.0029	1.0033 [0.9976 - 1.0090]	0.2545	13.8265	14	0.4627	-	-	-
		Weighted median	0.0050	0.0043	1.005 [0.9965 - 1.0135]	0.2477	-	-	-	-	-	-
		Simple mode	0.0054	0.0108	1.0054 [0.9843 - 1.0269]	0.6207	-	-	-	-	-	-
		MR-PRESSO	0.0038	0.0028	1.0038 [0.9984 - 1.0093]	0.1731	-	-	-	-	-	-
Nerve growth factor	39	MR Egger	-0.0139	0.0106	0.9862 [0.9659 - 1.0068]	0.1923	25.9361	37	0.9136	-0.0222	0.0250	0.3804
		IVW	0.0033	0.0029	1.0033 [0.9976 - 1.0090]	0.2545	26.7244	38	0.9148	-	-	-
		Weighted median	0.0050	0.0043	1.005 [0.9965 - 1.0135]	0.2477	-	-	-	-	-	-
		Simple mode	0.0054	0.0108	1.0054 [0.9843 - 1.0269]	0.6207	-	-	-	-	-	-
		MR-PRESSO	0.0038	0.0028	1.0038 [0.9984 - 1.0093]	0.1731	-	-	-	-	-	-

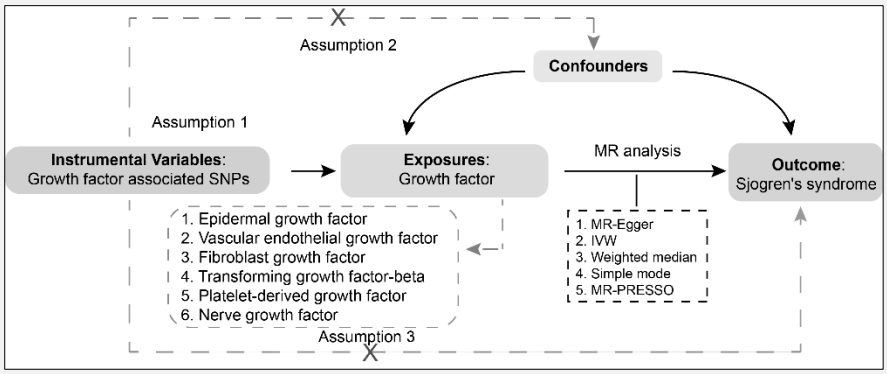

Figure 1. The three key assumptions of MR analysis for six growth factors in the development of SS.

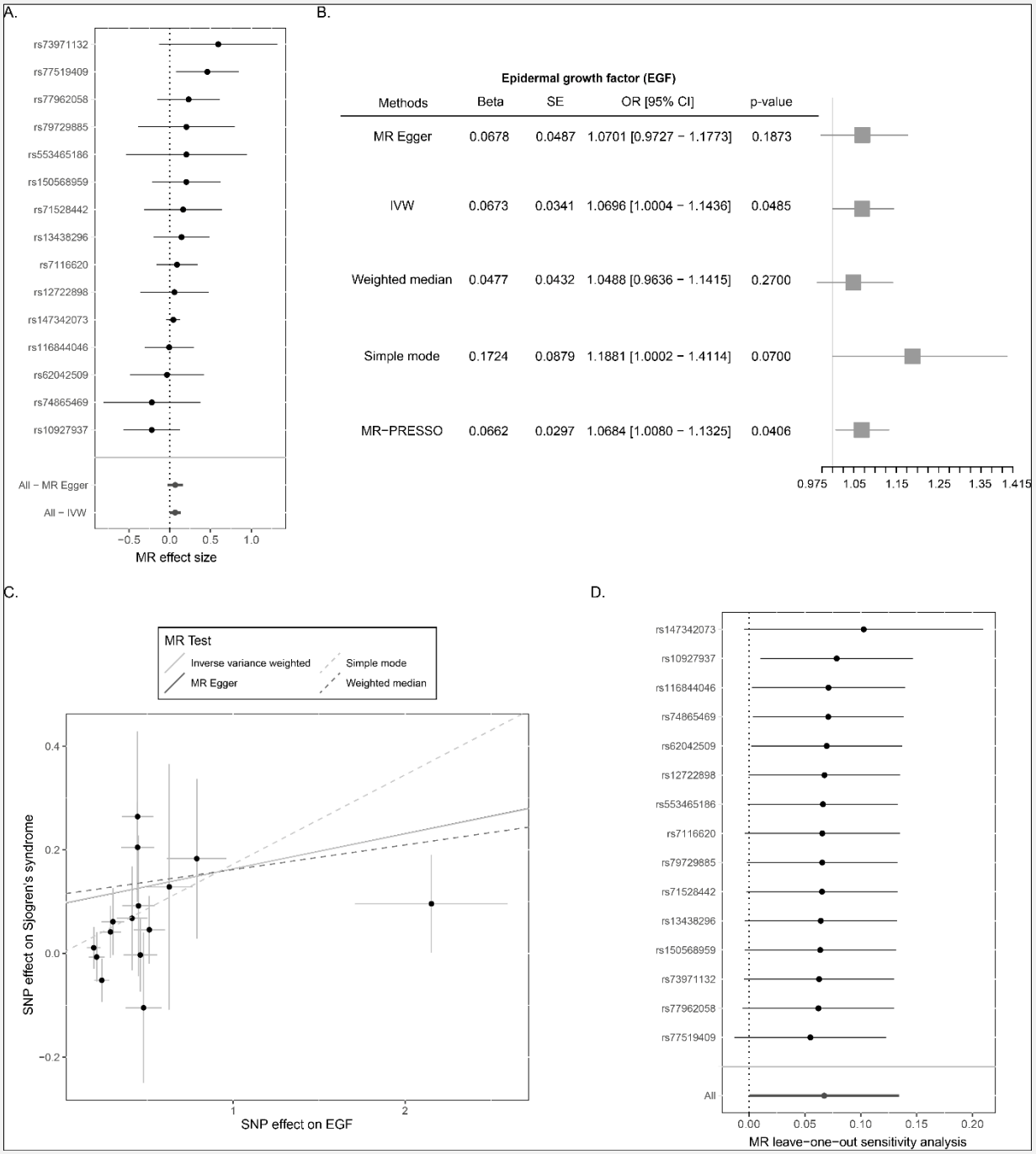

Figure 2. The MR analysis results for EGF.

A: Effect sizes of the SNPs used in the MR analysis, B: results of the five MR methods, C: scatter plots illustrating the causal estimates, and D: results of the leave-one-out sensitivity analysis.

fore, future research should aim to validate these findings in diverse populations to minimize potential biases. In conclusion, this study employed MR analysis to identify EGF levels as a potential significant risk factor for the development of SS. Future research should focus on further statistical comparisons between EGF levels in

saliva and serum from both SS patients and healthy controls. Moreover, further investigation into the underlying biological and molecular mechanisms by which EGF contributes to SS pathogenesis is essential. Such efforts will provide new perspectives for the development of therapeutic strategies targeting EGF in SS treatment.

Declaration of Generative AI in Scientific Writing:
No generative AI tools were used in the writing, editing, or data analysis of this manuscript.

Declaration of Interest:
Both of two authors declared that they have no conflict of interests.

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