·数据库研究·

炎症因子与强直性脊柱炎及血液代谢物因果关系的孟德尔随机化分析

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摘　要　目的:探讨炎症因子与强直性脊柱炎(ankylosing spondylitis,AS)及血液代谢物的因果关系。**方法:**从全基因组关联研究(genome-wide association study,GWAS)Catalog数据库中获取炎症因子表达水平和血液代谢物指标(代谢物水平或代谢物比率)的GWAS数据,从FinnGen数据库中获取AS的GWAS数据。基于工具变量筛选标准,筛选符合要求的炎症因子表达水平的单核苷酸多态性(single nucleotide polymorphism,SNP)位点。将筛选出的炎症因子表达水平的SNP位点作为工具变量,以AS为结局进行孟德尔随机化(Mendelian randomization,MR)分析,并进行敏感性分析;将确定的与AS具有可靠因果关系的炎症因子表达水平的SNP位点作为工具变量,以血液代谢物指标为结局进行MR分析,并进行敏感性分析。**结果:**①炎症因子表达水平与AS的因果关系分析结果。CD244、成纤维细胞生长因子(fibroblast growth factor,FGF)-23、FMS样酪氨酸激酶3配体(FMS-like tyrosine kinase 3 ligand,FIt3L)、白细胞介素(interleukin,IL)-7表达水平与AS存在可靠的因果关系,其中CD244、FIt3L表达水平与AS呈负相关,FGF-23、IL-7表达水平与AS呈正相关。②炎症因子表达水平与血液代谢物指标的因果关系分析结果。CD244、FGF-23、FIt3L、IL-7表达水平分别与61项、62项、37项、68项血液代谢物指标存在可靠的因果关系。**结论:**FGF-23、IL-7、CD244、FIt3L表达水平与AS存在可靠的因果关系,这4种炎症因子表达水平分别与多项血液代谢物指标存在可靠的因果关系;这为探索AS的发生机制和治疗AS的药物靶点提供了参考。

关键词　脊柱炎,强直性;炎症介导素类;代谢物;孟德尔随机化分析

The causal relationships of inflammatory factors with ankylosing spondylitis and blood metabolites:a mendelian randomization analysis

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ABSTRACT　Objective: To explore the causal relationships of inflammatory factors with ankylosing spondylitis(AS)and blood metabolites. **Methods:**The genome-wide association study(GWAS)data about the expression levels of inflammatory factors and blood metabolite indicators(metabolite levels or metabolite ratios)were retrieved and extracted from the GWAS Catalog database,and that about AS from the FinnGen database. According to the instrumental variable screening criteria,the eligible single nucleotide polymorphism(SNP)loci for the expression levels of inflammatory factors were screened as the instrumental variable,and then a mendelian randomization(MR)analysis was conducted with AS as the outcome variable to assess the causality between the expression levels of inflammatory factors and AS,and the sensitivity was examined. Furthermore,another MR analysis was conducted by taking the SNP loci of the expression levels of inflammatory factor having a reliable causality with AS as the instrumental variable,and the blood metabolite indicators as the outcome variable to assess the causality between the expression levels of inflammatory factors and blood metabolite indicators,and the sensitivity was examined. **Results:**①The causality between the expression levels of inflammatory factors and AS. The expression levels of CD244,fibroblast growth factor(FGF)-23,FMS-like tyrosine kinase 3 ligand(FIt3L)and interleukin(IL)-7 exhibited a reliable causal relationship with AS,among which,the expression levels of CD244 and FIt3L showed a inverse causal relationship with AS,while the expression levels of FGF-23 and IL-7 presented a positive causal relationship with AS. ②The causality between the expression levels of inflammatory factors and blood metabolite indicators. The expression levels of CD244,FGF-23,FIt3L and IL-7 exhibited a reliable causal relationship with 61,62,37 and 68 blood metabolite indicators,respectively. **Conclusion:** The expression levels of FGF-23,IL-7,CD244 and FIt3L exhibit a reliable causal

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relationship with AS,and they also have a reliable causal relationship with multiterm blood metabolite indicators,respectively,which provides a reference for exploring the pathogenesis of AS and the potential drug targets in treating AS.

Keywords spondylitis,ankylosing;inflammation mediators;metabolites;Mendelian randomization analysis

强直性脊柱炎(ankylosing spondylitis,AS)是一种慢性进行性炎症性疾病,主要表现为进行性的脊柱和骶髂关节炎症,可导致关节疼痛、僵硬和功能障碍,严重者可出现脊柱畸形[1]。AS多见于30~40岁男性,其患病率地区差异较大,为0.1%~1.4%[2-3]。目前,AS的发病机制尚不清楚。相关研究表明[4-6],多种炎症因子的异常表达是AS患者的主要病理特征,也是引起关节疼痛和组织损伤的主要原因。此外,AS的发生与机体代谢异常也存在密切联系[7]。然而,由于样本量限制和混杂因素影响,炎症因子、代谢物与AS的因果关系难以通过临床试验予以验证。孟德尔随机化(Mendelian randomization,MR)基于大样本基因型和表型数据,将与暴露因素具有强相关性的单核苷酸多态性位点(single nucleotide polymorphism,SNP)作为工具变量,进而确定暴露因素与结局间的因果关系。MR分析不受样本量的限制,能够避免传统观察性研究中混杂因素和反向因果关系的影响,进而获得可靠的因果关系分析结果[8]。本研究采用两样本MR评估了炎症因子与AS及血液代谢物的因果关系,现总结报告如下。

1 资料与方法

1.1 数据来源

炎症因子表达水平和血液代谢物指标(代谢物水平或代谢物比率)的全基因组关联研究(genome-wide association study,GWAS)数据来自GWAS Catalog数据库(https://www.ebi.ac.uk/gwas/)。炎症因子的GWAS数据ID为GCST90274758至GCST90274848,来自Zhao等[9]的研究;该研究涉及了91种炎症因子表达水平的遗传信息,数据源自14 824名欧洲人。血液代谢物指标的GWAS数据ID为GCST90199621至GCST90204063,来自Chen等[10]的研究;该研究涉及了1400项血液代谢物指标,包含了1091项血液代谢物水平(850种已知的血液代谢物和241种未知的血液代谢物)和309项血液代谢物比率的遗传信息;数据源自8299名欧洲人。

AS的GWAS数据来自FinnGen数据库(https://www.finngen.fi/en),数据ID为M13_ANKYLOSPON;数据源自297 932名欧洲人,其中AS患者3162例,健康人294 770名。

1.2 工具变量筛选

1.2.1 筛选标准 ①工具变量与暴露因素之间强相关;②工具变量与和暴露因素、结局变量有关联的混杂因素之间是独立的;③工具变量只能通过暴露因素对结局产生影响[11-12]。

1.2.2 筛选方法 基于工具变量筛选标准筛选符合要求的SNP位点。将91种炎症因子表达水平的遗传数据导入分析工具R包,以$P<5\times10^{-5}$为条件筛选达到全基因组显著水平的SNP位点[13]。以$r^2=0.001$、连锁不平衡的区域长度为10 000 kb为条件进行连锁不平衡分析,选择独立的工具变量。计算SNP位点的F值,剔除$F<10$的弱工具变量[14]。剔除中等等位基因频率的回文SNP[15]。

1.3 MR分析及敏感性分析

将筛选出的炎症因子表达水平的SNP位点作为工具变量,以AS为结局进行MR分析,并进行敏感性分析;将确定的与AS具有因果关系的炎症因子表达水平的SNP位点作为工具变量,以血液代谢物指标为结局,进行MR分析,并进行敏感性分析。

1.3.1 MR分析方法 采用TwoSampleMR、MR-PRESSO等软件包进行MR分析。MR分析方法包括逆方差加权法(inverse variance weighted,IVW)、MR-Egger、加权中位数、简单模式和加权模式等,其中以IVW为主要分析方法,其他方法作为补充。炎症因子表达水平与AS的具体因果关系采用$OR(95\%CI)$表示,$OR>1$提示炎症因子表达水平与AS呈正相关,$OR<1$提示炎症因子表达水平与AS呈负相关;炎症因子表达水平与血液代谢物/代谢物比率的具体因果关系采用$\beta(95\%CI)$表示,$\beta>0$提示炎症因子表达水平与AS呈正相关,$\beta<0$提示炎症因子表达水平与AS呈负相关。检验水准$\alpha=0.05$。

1.3.2 敏感性分析方法 采用Cochran's Q检验对IVW和MR Egger法结果进行异质性检验,采用MR Egger检验进行水平多效性检验。采用留一法评价MR分析结果的稳定性。检验水准$\alpha=0.05$。

2 结 果

2.1 炎症因子与AS的因果关系分析结果

2.1.1 工具变量筛选结果 共筛选24 207个炎症因子表达水平的SNP位点作为工具变量。

2.1.2　MR 分析及敏感性分析结果　MR 分析结果显示,CCL19、CD244、成纤维细胞生长因子(fibroblast growth factor, FGF)-23、FMS 样酪氨酸激酶 3 配体(FMS-like tyrosine kinase 3 ligand,FIt3L)、白细胞介素(interleukin,IL)-18R1、IL-6、IL-7 表达水平与 AS 存在因果关系。水平多效性检验和异质性检验结果显示,CCL19、IL-18R1、IL-6 表达水平存在异质性,CCL19 表达水平存在水平多效性,均予以剔除(表 1)。其余炎症因子表达水平留一法检验结果显示,无明显离群值,MR 分析结果稳健。因此,CD244、FGF-23、FIt3L、IL-7 表达水平与 AS 存在可靠的因果关系,其中 CD244、FIt3L 表达水平与 AS 呈负相关,FGF-23、IL-7 表达水平与 AS 呈正相关(图 1、图 2)。

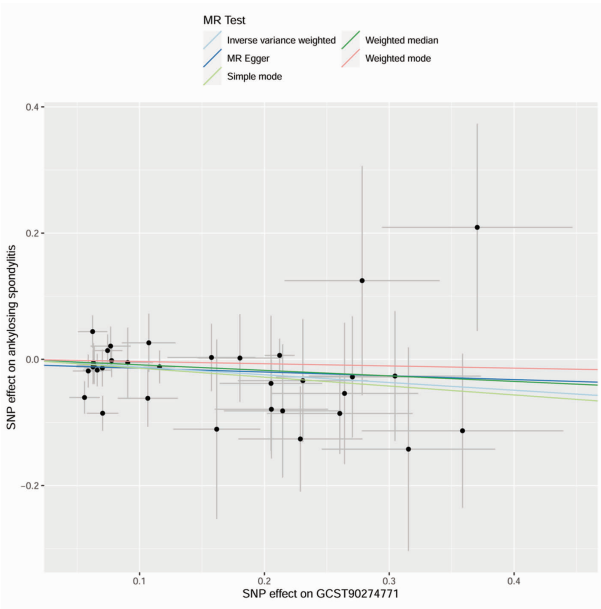
2.2　炎症因子表达水平与血液代谢物指标的因果关系分析结果

2.2.1　工具变量筛选结果　共有 33 个 CD244 表达水平的 SNP 位点、28 个 FGF-23 表达水平的 SNP 位点、46 个 FIt3L 表达水平的 SNP 位点、22 个 IL-7 表达水平的 SNP 位点作为工具变量,F 值范围为 19.53 ~ 442.14。

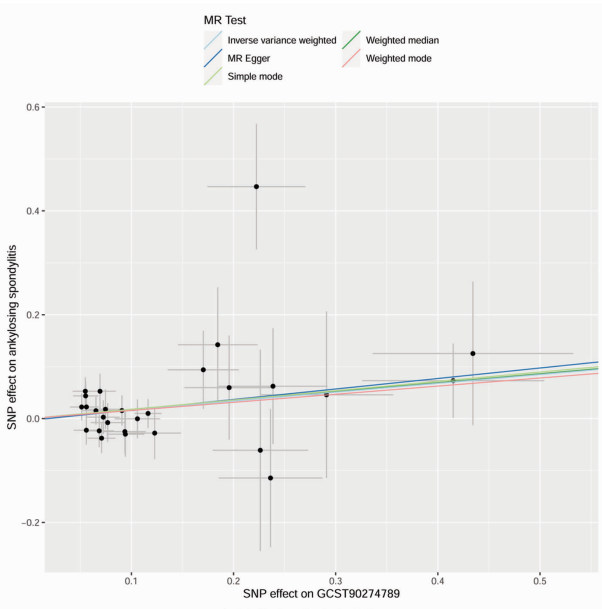
2.2.2　MR 分析及敏感性分析结果　MR 分析结果显示,CD244 表达水平与 68 项血液代谢物指标存在因果关系。水平多效性检验和异质性检验结果显示,6 项血液代谢物指标存在异质性,1 项血液代谢物指标存在水平多效性,均予以剔除(表 2)。其余血液代谢物指标留一法检验结果显示,无明显离群值,MR 分析结果稳健。因此,CD244 表达水平与 61 项血液代谢物指标存在可靠的因果关系,其中已知血液代谢物指标 51 项,未知血液代谢物指标 10 项。已知血液代谢物指标中,CD244 表达水平与 18 项血液代谢物指标呈正相关,与 33 项血液代谢物指标呈负相关;未知血液代谢物指标中,CD244 表达水平与 9 项血液代谢物指标呈负相关,与 1 项血液代谢物指标呈正相关(图 3)。

表 1　炎症因子表达水平与强直性脊柱炎之间因果关系的孟德尔随机化敏感性分析结果

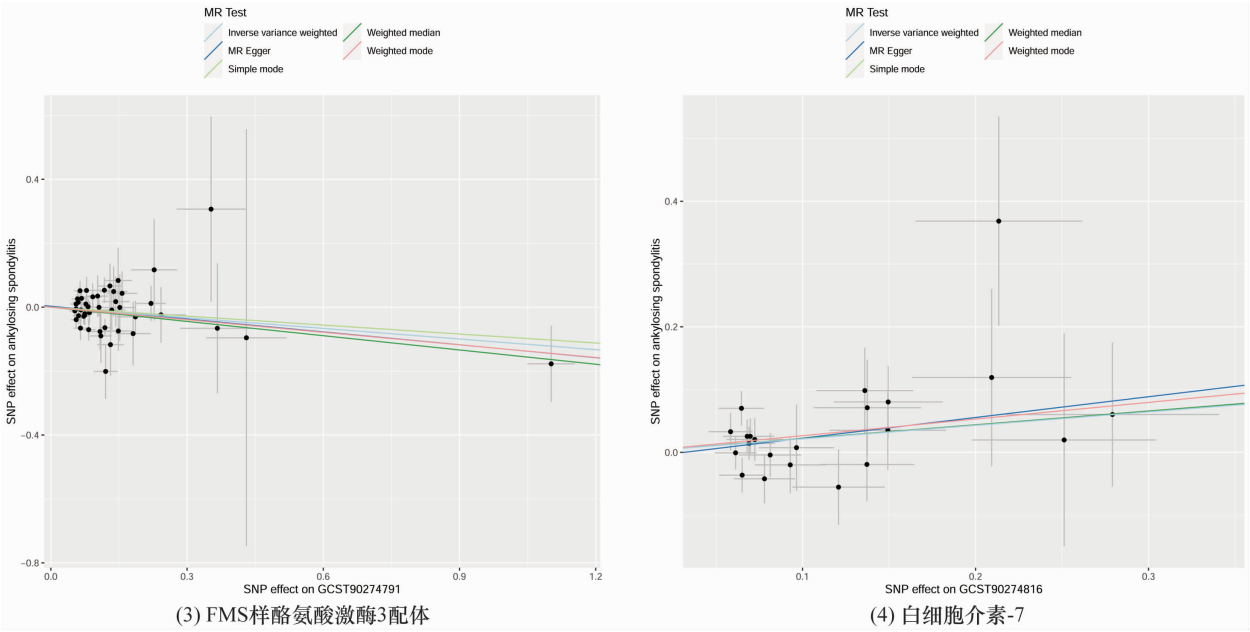
炎症因子	数据 ID	Cochran's Q 检验 P 值		MR Egger 检验	
		逆方差加权法	MR Egger	截距值	P 值
CCL19	GCST90274765	0.000	0.000	-0.100	0.001
CD244	GCST90274771	0.617	0.587	-0.008	0.537
成纤维细胞生长因子-23	GCST90274789	0.286	0.244	-0.004	0.812
FMS 样酪氨酸激酶 3 配体	GCST90274791	0.487	0.448	0.003	0.769
白细胞介素-18R1	GCST90274805	0.000	0.000	0.138	0.104
白细胞介素-6	GCST90274815	0.025	0.016	-0.001	0.974
白细胞介素-7	GCST90274816	0.475	0.425	-0.011	0.663



(1) CD244



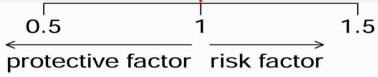
(2) 成纤维细胞生长因子-23



(3) FMS样酪氨酸激酶3配体　　(4) 白细胞介素-7

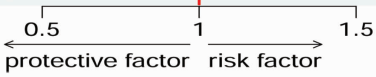
图 1　炎症因子表达水平与强直性脊柱炎的因果关系散点图

Method	SNP	β	SE	P	OR(95%CI)
MR Egger	33	−0.060	0.117	0.612	0.94(0.75-1.18)
Weighted median	33	−0.087	0.089	0.324	0.92(0.77-1.09)
Inverse variance weighted	33	−0.122	0.060	0.043	0.88(0.79-1.00)
Simple mode	33	−0.141	0.155	0.368	0.87(0.64-1.18)
Weighted mode	33	−0.035	0.108	0.748	0.97(0.78-1.19)



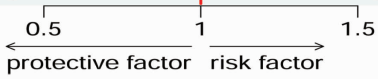
(1) CD244

Method	SNP	β	SE	P	OR(95%CI)
MR Egger	28	0.202	0.157	0.210	1.22(0.90-1.67)
Weighted median	28	0.173	0.116	0.137	1.19(0.95-1.49)
Inverse variance weighted	28	0.170	0.080	0.034	1.18(1.01-1.39)
Simple mode	28	0.179	0.183	0.336	1.20(0.84-1.71)
Weighted mode	28	0.156	0.142	0.280	1.17(0.89-1.54)



(2) 成纤维细胞生长因子-23

Method	SNP	β	SE	P	OR(95%CI)
MR Egger	45	−0.134	0.096	0.171	0.87(0.72-1.06)
Weighted median	45	−0.149	0.092	0.106	0.86(0.72-1.03)
Inverse variance weighted	45	−0.111	0.055	0.045	0.90(0.80-1.00)
Simple mode	45	−0.093	0.175	0.596	0.91(0.65-1.28)
Weighted mode	45	−0.131	0.097	0.185	0.88(0.72-1.06)



(3) FMS样酪氨酸激酶3配体

Method	SNP	β	SE	P	OR(95%CI)
MR Egger	22	0.330	0.279	0.250	1.39(0.81-2.40)
Weighted median	22	0.220	0.146	0.131	1.25(0.94-1.66)
Inverse variance weighted	22	0.215	0.099	0.030	1.24(1.02-1.51)
Simple mode	22	0.265	0.258	0.315	1.30(0.79-2.16)
Weighted mode	22	0.265	0.239	0.279	1.30(0.82-2.08)

(4) 白细胞介素-7

图 2　炎症因子表达水平与强直性脊柱炎的因果关系森林图

表 2　CD244 表达水平与血液代谢物指标之间因果关系的孟德尔随机化敏感性分析结果

序号	血液代谢物水平/代谢物比率	Cochran's Q 检验 P 值		MR Egger 检验	
		逆方差加权法	MR Egger	截距值	P 值
1	1-(1-enyl-stearoyl)-GPE (p-18:0)	0.966	0.955	-0.002	0.840
2	13-HODE + 9-HODE	0.653	0.635	0.007	0.439
3	17alpha-hydroxypregnanolone glucuronide	0.823	0.848	0.011	0.226
4	1-arachidonoyl-gpc (20:04n6)	0.891	0.886	0.007	0.421
5	1-arachidonoyl-GPE (20:04n6)	0.978	0.970	-0.003	0.746
6	1-palmitoyl-2-stearoyl-gpc (16:00/18:00)	0.692	0.648	-0.002	0.790
7	1-palmitoyl-GPE (16:00)	0.590	0.543	-0.002	0.788
8	1-stearoyl-GPE (18:00)	0.734	0.694	-0.003	0.746
9	21-hydroxypregnenolone disulfate	0.798	0.758	-0.001	0.942
10	3-methylxanthine	0.323	0.283	-0.003	0.774
11	3-phenylpropionate hydrocinnamate	0.136	0.122	-0.006	0.536
12	5alpha-androstan-3alpha,17beta-diol disulfate	0.015	0.020	-0.014	0.217
13	5alpha-pregnan-3beta,20beta-diol monosulfate (1)	0.177	0.148	-0.002	0.837
14	7-methylxanthine	0.889	0.861	-0.001	0.932
15	alpha-ketoglutarate to aspartate	0.300	0.258	-0.001	0.950
16	alpha-ketoglutarate to kynurenine	0.109	0.090	-0.003	0.727
17	androstenediol (3alpha,17alpha) monosulfate (3)	0.760	0.748	0.006	0.425
18	aspartate to citrate	0.040	0.031	0.001	0.928
19	aspartate to N-acetylglucosamine to N-acetylgalactosamine	0.069	0.062	-0.007	0.503
20	aspartate to phosphate	0.026	0.024	0.007	0.465
21	caprylate (8:00)	0.359	0.326	-0.005	0.592
22	carotenoid (cryptoxanthin)	0.978	0.971	-0.002	0.796
23	cortisol (plasma)	0.452	0.407	-0.003	0.741
24	cys-gly,oxidized	0.869	0.851	-0.005	0.556
25	etiocholanolone glucuronide	0.466	0.423	0.003	0.699
26	glucuronate to etiocholanolone glucuronide	0.352	0.311	-0.003	0.748
27	glutarate (C5-DC) to caprylate (8:00)	0.850	0.885	0.012	0.178
28	glycerophosphorylcholine (GPC)	0.631	0.582	-0.001	0.873
29	glycosyl ceramide (d18:02/24:01,d18:01/24:02)	0.788	0.755	-0.003	0.701
30	glycosyl-N-(2-hydroxynervonoyl)-sphingosine (d18:01/24:01(2OH))	0.385	0.377	-0.008	0.370
31	glycosyl-N-behenoyl-sphingadienine (d18:02/22:00)	0.281	0.528	-0.021	0.018
32	glycosyl-N-tricosanoyl-sphingadienine (d18:02/23:00)	0.637	0.668	-0.011	0.221
33	glycoursodeoxycholate	0.624	0.579	-0.003	0.764
34	glycoursodeoxycholic acid sulfate (1)	0.625	0.588	0.005	0.615
35	lignoceroyl sphingomyelin (d18:01/24:00)	0.482	0.436	-0.003	0.758
36	N-carbamoylalanine	0.262	0.234	0.005	0.598
37	oleoyl ethanolamide	0.972	0.990	-0.014	0.098
38	ornithine to glutamate	0.181	0.150	0.000	0.980
39	pipecolate	0.130	0.131	0.009	0.345
40	pregnanediol-3-glucuronide	0.336	0.312	0.006	0.508
41	pregnenediol disulfate (C21H34O8S2)	0.784	0.752	0.003	0.663
42	pregnenediol sulfate (C21H34O5S)	0.026	0.020	-0.001	0.948
43	pregnenetriol disulfate	0.954	0.939	0.001	0.919
44	pregnenetriol sulfate	0.361	0.345	-0.006	0.430
45	pregnenolone sulfate	0.032	0.024	-0.001	0.959
46	S-1-pyrroline-5-carboxylate	0.399	0.366	0.005	0.574
47	salicylate to caprylate (8:00)	0.579	0.529	-0.002	0.845
48	sphingomyelin (d18:01/20:02,d18:02/20:01,d16:01/22:02)	0.470	0.497	0.010	0.228
49	sphingomyelin (d18:01/22:01,d18:02/22:00,d16:01/24:01)	0.609	0.568	-0.003	0.679
50	sphingomyelin (d18:02/18:01)	0.073	0.061	-0.004	0.652
51	sphingomyelin (d18:02/21:00,d16:02/23:00)	0.951	0.936	0.000	0.963
52	sphingomyelin (d18:02/23:00,d18:01/23:01,d17:01/24:01)	0.318	0.276	0.001	0.875
53	sphingomyelin (d18:02/23:01)	0.803	0.770	0.003	0.727
54	sphingomyelin (d18:02/24:01,d18:01/24:02)	0.708	0.666	0.002	0.755
55	sphingomyelin (d18:02/24:02)	0.226	0.231	0.009	0.311
56	tauro-beta-muricholate	0.021	0.017	-0.006	0.699

续表 2

序号	血液代谢物水平/代谢物比率	Cochran's Q 检验 P 值		MR Egger 检验	
		逆方差加权法	MR Egger	截距值	P 值
57	theobromine	0.784	0.743	0.000	0.964
58	theophylline to EDTA	0.300	0.258	−0.001	0.957
59	X-12822	0.936	0.923	0.004	0.631
60	X-13553	0.670	0.629	0.003	0.700
61	X-13728	0.555	0.518	−0.005	0.598
62	X-16397	0.283	0.245	−0.002	0.794
63	X-16580	0.686	0.639	−0.001	0.928
64	X-21470	0.627	0.577	0.000	0.971
65	X-21845	0.879	0.853	0.003	0.763
66	X-23636	0.684	0.636	0.001	0.913
67	X-24306	0.683	0.645	0.004	0.649
68	X-24970	0.917	0.896	0.002	0.840

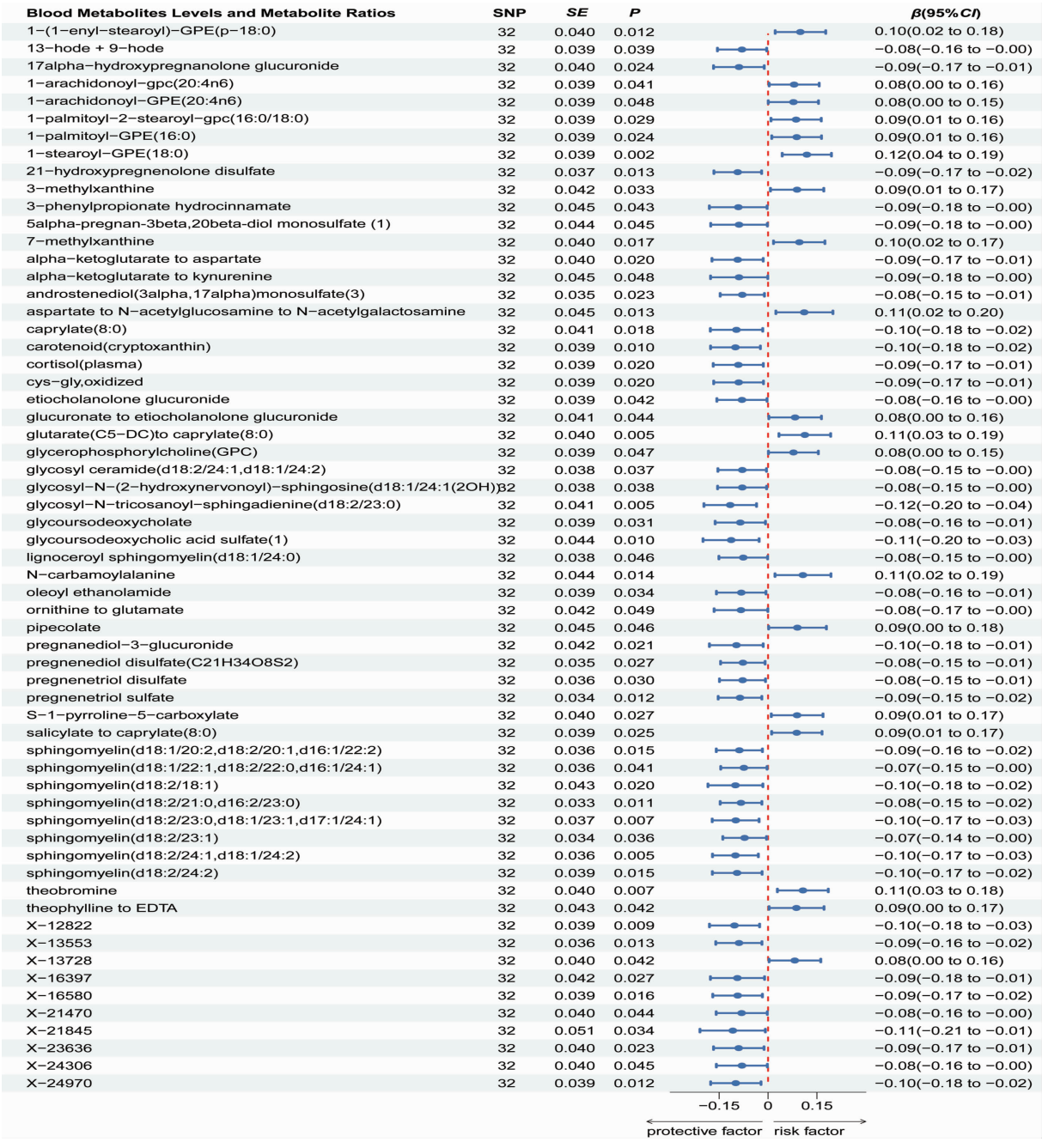


图 3　CD244 表达水平与血液代谢物指标的因果关系森林图

FGF-23 表达水平与 67 项血液代谢物指标存在因果关系。水平多效性检验和异质性检验结果显示，1 项血液代谢物指标存在异质性，4 项血液代谢物指标存在水平多效性，均予以剔除(表 3)。其余血液代谢物指标留一法检验结果显示，无明显离群值，MR 分析结果稳健。因此，FGF-23 表达水平与 62 项血液代谢物指标存在可靠的因果关系，其中已知血液代谢物指标 55 项，未知血液代谢物指标 7 项。已知血液代谢物指标中，FGF-23 表达水平与 18 项血液代谢物指标呈正相关，与 37 项血液代谢物指标呈负相关；未知血液代谢物指标中，FGF-23 表达水平与 7 项血液代谢物指标呈负相关(图 4)。

表 3　成纤维细胞生长因子-23 表达水平与血液代谢物指标之间因果关系的孟德尔随机化敏感性分析结果

序号	血液代谢物水平/代谢物比率	Cochran's Q 检验 P 值		MR Egger 检验	
		逆方差加权法	MR Egger	截距值	P 值
1	(2,4 or 2,5)-dimethylphenol sulfate	0.808	0.796	-0.010	0.435
2	1,3,7-trimethylurate	0.840	0.833	-0.009	0.409
3	1-methylnicotinamide	0.620	0.675	0.014	0.188
4	1-palmitoyl-2-docosahexaenoyl-GPE (16:0/22:6)	0.389	0.343	0.004	0.673
5	2-piperidinone	0.565	0.716	0.019	0.077
6	2s,3R-dihydroxybutyrate	0.582	0.528	-0.003	0.742
7	3-acetylphenol sulfate	0.492	0.453	-0.007	0.565
8	3-hydroxyphenylacetoylglutamine	0.208	0.169	0.000	0.977
9	5alpha-androstan-3beta,17beta-diol disulfate	0.952	0.972	0.012	0.191
10	aconitate [cis or trans]	0.912	0.883	0.001	0.948
11	adenosine 5′-diphosphate (ADP) to arginine	0.127	0.165	-0.022	0.178
12	adenosine 5′-diphosphate (ADP) to aspartate	0.419	0.365	-0.004	0.810
13	adenosine 5′-diphosphate (ADP) to EDTA	0.144	0.139	-0.014	0.402
14	adenosine 5′-diphosphate (ADP) to flavin adenine dinucleotide (FAD)	0.167	0.209	-0.025	0.179
15	adenosine 5′-diphosphate (ADP) to glutamate	0.635	0.648	-0.015	0.290
16	adenosine 5′-diphosphate (ADP) to glutamine	0.076	0.083	-0.018	0.298
17	adenosine 5′-diphosphate (ADP) to glycine	0.166	0.164	-0.015	0.367
18	adenosine 5′-diphosphate (ADP) to N-palmitoyl-sphingosine (d18:1 to 16:0)	0.045	0.051	-0.019	0.284
19	adenosine 5′-diphosphate (ADP) to uridine	0.184	0.218	-0.020	0.208
20	adenosine 5′-diphosphate (ADP) to valine	0.177	0.212	-0.020	0.203
21	alpha-hydroxyisovalerate	0.198	0.794	0.034	0.002
22	alpha-ketoglutarate to trans-4-hydroxyproline	0.643	0.618	0.008	0.469
23	androsterone glucuronide to etiocholanolone glucuronide	0.414	0.406	-0.009	0.364
24	behenoyl sphingomyelin (d18:1/22:0)	0.439	0.412	0.007	0.473
25	branched chain 14:0 dicarboxylic acid	0.514	0.495	0.009	0.415
26	catechol sulfate	0.924	0.929	-0.010	0.333
27	choline	0.586	0.526	-0.001	0.922
28	cinnamoylglycine	0.740	0.688	-0.001	0.905
29	citrate	0.722	0.691	-0.006	0.542
30	gamma-CEHC glucuronide	0.097	0.094	-0.012	0.406
31	gamma-glutamyl-2-aminobutyrate	0.780	0.736	0.003	0.758
32	glyco-beta-muricholate	0.255	0.492	-0.026	0.028
33	glycolithocholate sulfate	0.888	0.870	-0.006	0.555
34	glycosyl-N-palmitoyl-sphingosine (d18:1/16:0)	0.445	0.506	-0.015	0.170
35	glycoursodeoxycholic acid sulfate (1)	0.135	0.124	0.010	0.466
36	guaiacol sulfate	0.738	0.716	-0.007	0.476
37	histidine betaine (hercynine)	0.634	0.731	0.017	0.124
38	isoursodeoxycholate	0.162	0.442	0.028	0.014
39	malonylcarnitine	0.437	0.554	-0.020	0.100
40	mannose to trans-4-hydroxyproline	0.657	0.615	0.005	0.621
41	myristoyl dihydrosphingomyelin (d18:0/14:0)	0.325	0.314	0.009	0.389

续表3

序号	血液代谢物水平/代谢物比率	Cochran's Q检验P值		MR Egger检验	
		逆方差加权法	MR Egger	截距值	P值
42	nicotinamide	0.349	0.378	0.013	0.234
43	nisinate (24:6n3)	0.297	0.285	0.012	0.405
44	nonanoylcarnitine (C9)	0.855	0.858	0.010	0.350
45	palmitoyl sphingomyelin (d18:1/16:0)	0.856	0.840	-0.007	0.500
46	perfluorooctanesulfonate (PFOS)	0.253	0.209	0.000	0.981
47	salicylate	0.134	0.107	-0.003	0.828
48	salicylate to caprylate (8:0)	0.313	0.263	-0.001	0.967
49	salicyluric glucuronide	0.219	0.192	-0.008	0.577
50	sphingomyelin (d17:1/14:0,d16:1/15:0)	0.781	0.733	-0.001	0.912
51	sphingomyelin (d17:1/16:0,d18:1/15:0,d16:1/17:0)	0.739	0.690	0.003	0.789
52	sphingomyelin (d18:1/14:0,d16:1/16:0)	0.263	0.244	0.008	0.466
53	sphingomyelin (d18:1/17:0,d17:1/18:0,d19:1/16:0)	0.983	0.978	-0.005	0.654
54	sphingomyelin (d18:1/22:2,d18:2/22:1,d16:1/24:2)	0.924	0.908	-0.005	0.597
55	sphingomyelin (d18:2/23:0,d18:1/23:1,d17:1/24:1)	0.884	0.866	0.006	0.542
56	sphingomyelin (d18:2/23:1)	0.945	0.943	-0.007	0.421
57	tartarate	0.179	0.170	0.010	0.416
58	trans-4-hydroxyproline	0.500	0.467	-0.007	0.507
59	tricosanoyl sphingomyelin (d18:1/23:0)	0.746	0.701	0.003	0.740
60	X-11381	0.587	0.799	0.022	0.044
61	X-12306	0.727	0.674	-0.001	0.925
62	X-21312	0.193	0.166	-0.008	0.625
63	X-21845	0.448	0.525	0.020	0.144
64	X-22162	0.685	0.631	0.002	0.837
65	X-23593	0.299	0.280	-0.008	0.455
66	X-25520	0.437	0.391	-0.005	0.657
67	X-26111	0.689	0.657	0.007	0.533

FIt3L表达水平与37项血液代谢物指标存在因果关系。水平多效性检验和异质性检验结果显示,无血液代谢物指标存在异质性和水平多效性(表4)。留一法检验结果显示,无明显离群值,MR分析结果稳健。因此,FIt3L表达水平与37项血液代谢物指标存在可靠的因果关系,其中已知血液代谢物指标32项,未知血液代谢物指标5项。已知血液代谢物指标中,FIt3L表达水平与13项血液代谢物指标呈正相关,与19项血液代谢物指标呈负相关;未知血液代谢物指标中,Fit3L表达水平与4项血液代谢物指标呈正相关,与1种血液代谢物指标呈负相关(图5)。

IL-7表达水平与70项血液代谢物指标存在因果关系。水平多效性检验和异质性检验结果显示,2项血液代谢物指标存在水平多效性,均予以剔除(表5)。其余血液代谢物指标留一法检验结果显示,无明显离群值,MR分析结果稳健。因此,IL-7表达水平与68项血液代谢物指标存在可靠的因果关系,其中已知血液代谢物指标57项,未知血液代谢物指标11项。已知血液代谢物指标中,IL-7表达水平与42项血液代谢物指标呈正相关,与15项血液代谢物指标呈负相关;未知血液代谢物指标中,IL-7表达水平与11项血液代谢物指标呈正相关(图6)。

3 讨 论

AS的具体发生机制尚不清楚,机体的免疫、代谢过程都与其发生关系密切。相关研究[16-17]结果表明,炎症因子的异常表达是导致AS发生的重要因素。然而,具体哪些炎症因子和代谢物与AS存在因果关系,目前尚不清楚。因此,我们采用MR分析了91种炎症因子的表达水平与AS的因果关系,进而又分析了与AS具有可靠因果关系的炎症因子表达水平与1400项血液代谢物指标的因果关系,以期为AS发生机制的探索和药物靶点的选择提供参考。

Blood Metabolites Levels and Metabolite Ratios	SNP	*SE*	*P*	*β*(95%*CI*)
(2,4 or 2,5)−dimethylphenol sulfate	24	0.065	0.002	0.20(0.07 to 0.33)
1,3,7−trimethylurate	24	0.055	0.011	−0.14(−0.25 to −0.03)
1−methylnicotinamide	24	0.052	0.022	−0.12(−0.22 to −0.02)
1−palmitoyl−2−docosahexaenoyl−GPE(16:0/22:6)	24	0.052	0.021	−0.12(−0.22 to−0.02)
2−piperidinone	24	0.051	0.035	0.11(0.01 to 0.21)
2s,3R−dihydroxybutyrate	24	0.047	0.049	−0.09(−0.18 to −0.00)
3−acetylphenol sulfate	24	0.057	0.024	−0.13(−0.24 to −0.02)
3−hydroxyphenylacetoylglutamine	24	0.070	0.011	−0.18(−0.31 to −0.04)
5alpha−androstan−3beta,17beta−diol disulfate	24	0.044	0.012	−0.11(−0.20 to −0.02)
Aconitate [cis or trans]	24	0.049	0.041	−0.10(−0.20 to −0.00)
adenosine 5'−diphosphate(ADP)to arginine	24	0.081	0.009	−0.21(−0.37 to −0.05)
adenosine 5'−diphosphate(ADP)to aspartate	24	0.070	0.015	−0.17(−0.31 to −0.03)
adenosine 5'−diphosphate(ADP)to EDTA	24	0.079	0.041	−0.16(−0.32 to −0.01)
adenosine 5'−diphosphate(ADP)to flavin adenine dinucleotide(FAD)	24	0.091	0.021	−0.21(−0.39 to −0.03)
adenosine 5'−diphosphate(ADP)to glutamate	24	0.068	0.023	−0.15(−0.29 to −0.02)
adenosine 5'−diphosphate(ADP)to glutamine	24	0.084	0.031	−0.18(−0.35 to −0.02)
adenosine 5'−diphosphate(ADP)to glycine	24	0.079	0.028	−0.17(−0.33 to −0.02)
adenosine 5'−diphosphate(ADP)to uridine	24	0.078	0.046	−0.16(−0.31 to −0.00)
adenosine 5'−diphosphate(ADP)to valine	24	0.078	0.030	−0.17(−0.32 to −0.02)
alpha−ketoglutarate to trans−4−hydroxyproline	24	0.051	0.014	−0.13(−0.23 to −0.03)
androsterone glucuronide to etiocholanolone glucuronide	24	0.051	0.007	0.14(0.04 to 0.24)
behenoyl sphingomyelin(d18:1/22:0)	24	0.051	0.050	0.10(0.00 to 0.20)
branched chain 14:0 dicarboxylic acid	24	0.053	0.039	−0.11(−0.21 to −0.01)
catechol sulfate	24	0.052	0.027	−0.12(−0.22 to −0.01)
choline	24	0.050	0.040	−0.10(−0.20 to −0.00)
cinnamoylglycine	24	0.052	0.002	−0.16(−0.26 to −0.06)
citrate	24	0.050	0.018	−0.12(−0.22 to −0.02)
gamma−CEHC glucuronide	24	0.069	0.046	−0.14(−0.27 to −0.00)
gamma−glutamyl−2−aminobutyrate	24	0.054	0.029	−0.12(−0.22 to −0.01)
glycolithocholate sulfate	24	0.052	0.019	−0.12(−0.22 to −0.02)
glycosyl−N−palmitoyl−sphingosine(d18:1/16:0)	24	0.052	0.021	0.12(0.02 to 0.22)
glycoursodeoxycholic acid sulfate(1)	24	0.067	0.035	0.14(0.01 to 0.27)
guaiacol sulfate	24	0.052	0.016	−0.12(−0.23 to −0.02)
histidine betaine(hercynine)	24	0.055	0.006	−0.15(−0.26 to −0.04)
malonylcarnitine	24	0.060	0.017	−0.14(−0.26 to −0.03)
mannose to trans−4−hydroxyproline	24	0.052	0.011	−0.13(−0.23 to −0.03)
myristoyl dihydrosphingomyelin(d18:0/14:0)	24	0.052	0.014	0.13(0.03 to 0.23)
nicotinamide	24	0.054	0.034	−0.12(−0.22 to −0.01)
nisinate(24:6n3)	24	0.072	0.042	−0.15(−0.29 to −0.00)
nonanoylcarnitine(C9)	24	0.053	0.028	0.12(0.01 to 0.22)
palmitoyl sphingomyelin(d18:1/16:0)	24	0.051	0.018	0.12(0.02 to 0.22)
perfluorooctanesulfonate(PFOS)	24	0.052	0.036	−0.11(−0.21 to −0.01)
salicylate	24	0.059	0.046	−0.12(−0.23 to −0.00)
salicylate to caprylate(8:0)	24	0.055	0.025	−0.12(−0.23 to −0.02)
salicyluric glucuronide	24	0.070	0.003	−0.21(−0.34 to −0.07)
sphingomyelin(d17:1/14:0,d16:1/15:0)	24	0.047	0.025	0.11(0.01 to 0.20)
sphingomyelin(d17:1/16:0,d18:1/15:0,d16:1/17:0)	24	0.050	0.004	0.14(0.05 to 0.24)
sphingomyelin(d18:1/14:0,d16:1/16:0)	24	0.054	0.039	0.11(0.01 to 0.22)
sphingomyelin(d18:1/17:0,d17:1/18:0,d19:1/16:0)	24	0.050	0.009	0.13(0.03 to 0.23)
sphingomyelin(d18:1/22:2,d18:2/22:1,d16:1/24:2)	24	0.047	0.006	0.13(0.04 to 0.22)
sphingomyelin(d18:2/23:0,d18:1/23:1,d17:1/24:1)	24	0.046	0.048	0.09(0.00 to 0.18)
sphingomyelin(d18:2/23:1)	24	0.045	0.014	0.11(0.02 to 0.20)
tartarate	24	0.063	0.020	−0.15(−0.27 to −0.02)
trans−4−hydroxyproline	24	0.051	0.032	0.11(0.01 to 0.21)
tricosanoyl sphingomyelin(d18:1/23:0)	24	0.048	0.010	0.12(0.03 to 0.22)
X−12306	24	0.061	0.015	−0.15(−0.27 to −0.03)
X−21312	24	0.075	0.007	−0.20(−0.35 to −0.05)
X−21845	24	0.067	0.042	−0.14(−0.27 to −0.01)
X−22162	24	0.049	0.035	−0.10(−0.20 to −0.01)
X−23593	24	0.053	0.030	−0.12(−0.22 to −0.01)
X−25520	24	0.053	0.024	−0.12(−0.23 to −0.02)
X−26111	24	0.052	0.021	−0.12(−0.22 to −0.02)

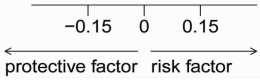


图 4　成纤维细胞生长因子-23 表达水平与血液代谢物指标的因果关系森林图

表4 FMS样酪氨酸激酶3配体表达水平与血液代谢物指标之间因果关系的孟德尔随机化敏感性分析结果

序号	血液代谢物水平/代谢物比率	Cochran's Q 检验 P 值		MR Egger 检验	
		逆方差加权法	MR Egger	截距值	P 值
1	1-palmitoleoyl-2-linolenoyl-GPC (16:1/18:3)	0.809	0.777	0.000	0.952
2	1-stearoyl-2-arachidonoyl-GPI (18:0/20:4)	0.748	0.750	0.006	0.333
3	2-methylserine	0.926	0.911	0.002	0.699
4	3b-hydroxy-5-cholenoic acid	0.424	0.384	-0.001	0.853
5	3-bromo-5-chloro-2,6-dihydroxybenzoic acid	0.416	0.484	0.009	0.112
6	4-ethylphenylsulfate	0.595	0.662	0.009	0.119
7	4-methyl-2-oxopentanoate to 3-methyl-2-oxobutyrate	0.887	0.872	0.003	0.583
8	5-hydroxyhexanoate	0.810	0.793	0.004	0.533
9	adenosine 5′-diphosphate (ADP) to EDTA	0.309	0.278	-0.003	0.702
10	adenosine 5′-diphosphate (ADP) to glycerol	0.265	0.232	0.000	0.987
11	adenosine 5′-diphosphate (ADP) to uridine	0.364	0.328	-0.002	0.791
12	alpha-tocopherol to glycerol	0.156	0.135	-0.002	0.763
13	carnitine to ergothioneine	0.130	0.152	-0.008	0.194
14	ceramide (d18:1/16:0)	0.420	0.379	-0.001	0.886
15	eicosenedioate (C20:1-DC)	0.536	0.534	-0.006	0.336
16	fructose to sucrose	0.376	0.372	0.006	0.355
17	glucose to sucrose	0.360	0.332	0.003	0.604
18	glycerol to palmitoylcarnitine (C16)	0.278	0.255	0.003	0.577
19	glyco-beta-muricholate	0.294	0.259	-0.001	0.910
20	mannose to glycerol	0.305	0.295	-0.004	0.412
21	methylsuccinate	0.943	0.939	0.004	0.448
22	N6,N6-dimethyllysine	0.835	0.825	-0.004	0.450
23	N6-methyllysine	0.824	0.817	-0.005	0.408
24	N-lactoyl tyrosine	0.788	0.789	0.006	0.338
25	N-palmitoyl-sphinganine (d18:0/16:0)	0.568	0.526	-0.001	0.854
26	N-stearoyl-sphingadienine (d18:2/18:0)	0.892	0.871	0.001	0.830
27	N-stearoyl-sphingosine (d18:1/18:0)	0.738	0.733	-0.005	0.375
28	spermidine to adenosine 5′-diphosphate (ADP)	0.980	0.974	0.000	0.999
29	succinate	0.917	0.903	-0.002	0.678
30	succinate to proline	0.797	0.770	-0.002	0.696
31	succinate to trans-4-hydroxyproline	0.870	0.858	-0.004	0.516
32	X-12013	0.915	0.897	0.002	0.803
33	X-12112	0.534	0.561	-0.007	0.210
34	X-12306	0.731	0.699	0.003	0.705
35	X-12851	0.279	0.264	-0.005	0.464
36	X-23648	0.455	0.413	0.001	0.910
37	Xylose	0.920	0.912	0.004	0.503

本研究结果表明,CD244、FGF-23、FIt3L、IL-7表达水平与AS存在可靠的因果关系,其中FGF-23、IL-7表达水平与AS呈正相关,CD244、FIt3L表达水平与AS呈负相关。FGF-23是一种由长骨的骨细胞和成骨细胞表达的具有调节磷和维生素D代谢的激素,其参与血清磷酸盐和骨化三醇水平的调节[11],与慢性肾脏病相关代谢性骨病、骨质疏松症等疾病存在联系[18-19]。Gercik等[20]研究发现,AS患者中血清FGF-23水平明显高于健康成年人。IL-7是维持免疫系统稳态的多功能细胞因子,广泛分布于骨髓、胸腺、淋巴结、脾脏等器官以及皮肤、肺、肠、肝等部位[21-22]。Meyer等[23]研究发现,关节滑膜组织和滑膜液中IL-7水平升高与类风湿关节炎等自身免疫性疾病密切相关。Ciccia等[24]研究表明,AS患者中以$Lyn^-RORc^-Tbet^+NKp44^+$细胞为特征的3型固有淋巴细胞在肠道、滑膜液和骨髓中显著扩增,并引起血清中IL-17和IL-22水平升高,IL-7在这个过程中起关键作用。因此,FGF-23、IL-7可能参与了AS的发

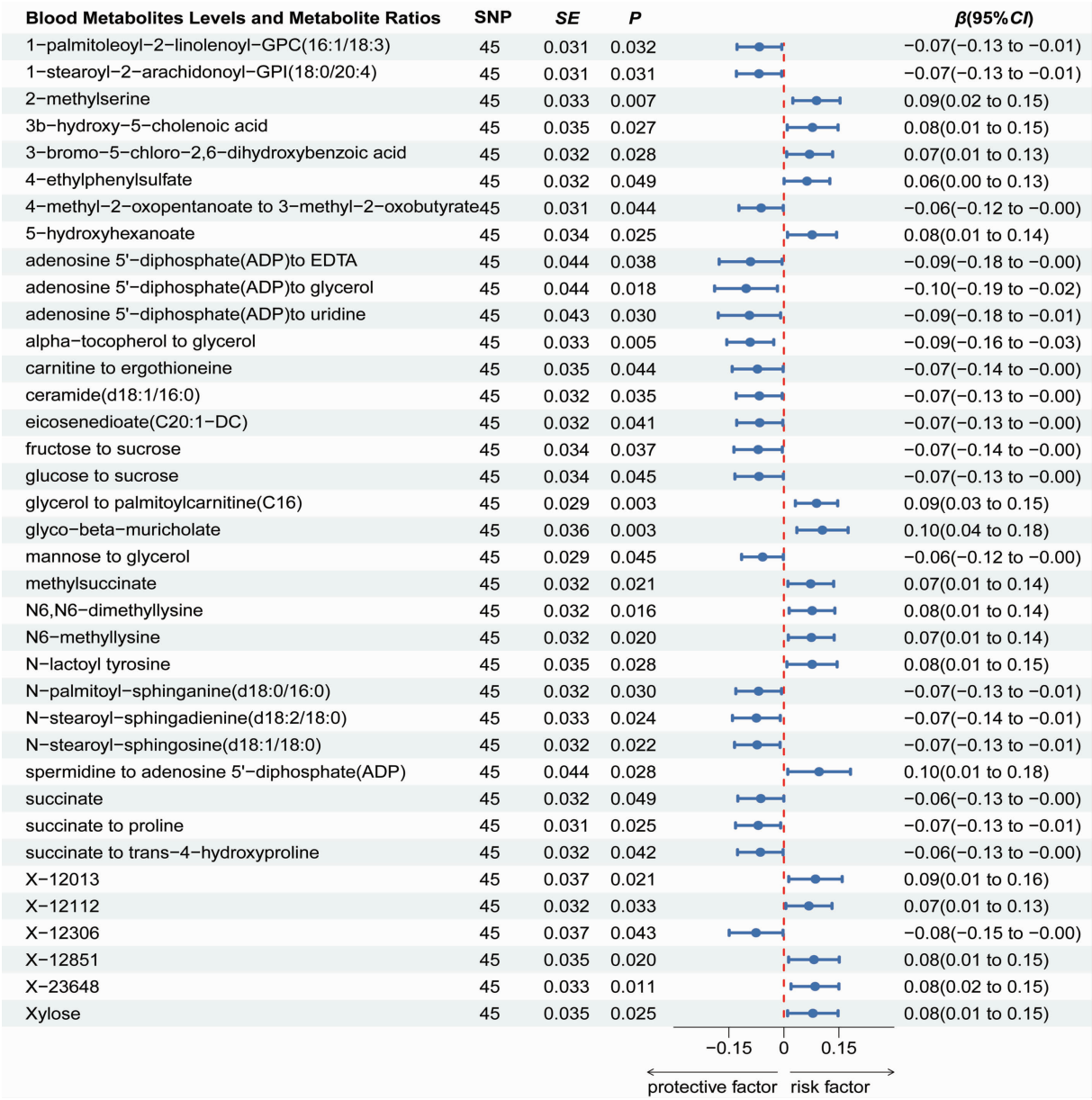


图 5　FMS 样酪氨酸激酶 3 配体表达水平与血液代谢物指标的因果关系森林图

表 5　白细胞介素-7 表达水平与血液代谢物指标之间因果关系的孟德尔随机化敏感性分析结果

序号	血液代谢物水平/代谢物比率	Cochran's Q 检验 P 值		MR Egger 检验	
		逆方差加权法	MR Egger	截距值	P 值
1	(S)-a-amino-omega-caprolactam	0.666	0.608	0.003	0.790
2	2-methoxyresorcinol sulfate	0.286	0.297	-0.018	0.297
3	2-oxoarginine	0.527	0.623	-0.020	0.137
4	3-formylindole	0.659	0.649	-0.011	0.386
5	3-methylglutarylcarnitine (2)	0.794	0.751	0.005	0.702
6	4-hydroxyphenylacetate	0.875	0.837	-0.002	0.905
7	5,6-dihydrouridine	0.398	0.340	-0.003	0.847
8	5-hydroxyhexanoate	0.979	0.968	0.002	0.901
9	5-hydroxymethyl-2-furoylcarnitine	0.961	0.987	-0.026	0.140
10	6-hydroxyindole sulfate	0.824	0.779	0.003	0.831
11	adenosine 3′,5′-cyclic monophosphate (cAMP) to taurocholate	0.285	0.399	0.027	0.099
12	adenosine 5′-diphosphate (ADP) to N-palmitoyl-sphingosine (d18: to 16:0)	0.344	0.311	0.012	0.530
13	anthranilate	0.886	0.914	0.019	0.233

续表 5

序号	血液代谢物水平/代谢物比率	Cochran's Q 检验 P 值		MR Egger 检验	
		逆方差加权法	MR Egger	截距值	P 值
14	aspartate to glutamate	0.779	0.730	0.003	0.798
15	bilirubin (Z,Z) to taurocholate	0.258	0.256	0.014	0.356
16	caffeine to theophylline	0.988	0.981	-0.003	0.809
17	caproate (6:0)	0.697	0.645	-0.005	0.727
18	caprylate (8:0)	0.905	0.872	0.002	0.907
19	cholesterol to linoleoyl-arachidonoyl-glycerol (18:2 to 20:4)[2]	0.294	0.600	0.034	0.024
20	cholesterol to taurocholate	0.120	0.125	0.016	0.329
21	choline to taurocholate	0.449	0.418	0.010	0.484
22	citrate to taurocholate	0.316	0.339	0.017	0.259
23	cortisol to taurocholate	0.619	0.596	0.011	0.444
24	cys-gly,oxidized	0.524	0.538	0.014	0.286
25	delta-CEHC	0.509	0.499	0.014	0.370
26	docosatrienoate (22:3n6)	0.345	0.414	0.025	0.159
27	ferulic acid 4-sulfate	0.401	0.372	0.010	0.482
28	glyco-beta-muricholate	0.785	0.769	-0.011	0.449
29	glycocholate	0.123	0.097	-0.004	0.804
30	glycodeoxycholate	0.078	0.059	0.005	0.807
31	glycohyocholate	0.472	0.454	0.012	0.404
32	glycolithocholate sulfate	0.965	0.965	0.011	0.404
33	indoleacetate	0.571	0.593	-0.015	0.270
34	indoleacetylglutamine	0.688	0.665	-0.011	0.457
35	indolebutyrate	0.886	0.865	-0.010	0.578
36	leucine to phosphate	0.848	0.919	-0.019	0.130
37	mannose to glycerol	0.886	0.861	-0.006	0.623
38	methionine sulfone	0.608	0.543	0.000	0.983
39	methionine sulfoxide	0.513	0.662	-0.024	0.089
40	N-lactoyl phenylalanine	0.504	0.489	-0.011	0.388
41	N-palmitoyl-sphingosine (d18:1 to 16:0) to N-palmitoyl-sphinganine (d18:0 to 16:0)	0.682	0.766	0.020	0.150
42	oleoyl-linoleoyl-glycerol (18:1 to 18:2)[2] to linoleoyl-arachidonoyl-glycerol (18:2 to 20:4)[2]	0.205	0.614	0.039	0.010
43	phosphate to glutamine	0.392	0.349	0.007	0.604
44	propionylcarnitine (c3)	0.217	0.178	0.005	0.755
45	retinol (Vitamin A) to linoleoyl-arachidonoyl-glycerol (18:2 to 20:4)[2]	0.325	0.362	0.018	0.220
46	spermidine to taurocholate	0.325	0.282	0.007	0.651
47	sphingomyelin (d17:2/16:0,d18:2/15:0)	0.420	0.541	0.020	0.106
48	sphingomyelin (d18:1/24:1,d18:2/24:0)	0.099	0.093	0.012	0.437
49	tauro-beta-muricholate	0.706	0.646	0.000	0.989
50	taurochenodeoxycholate	0.279	0.233	-0.004	0.772
51	taurochenodeoxycholic acid 3-sulfate	0.755	0.721	-0.009	0.562
52	taurocholate to oxalate (ethanedioate)	0.276	0.229	0.004	0.819
53	taurocholenate sulfate	0.540	0.512	0.010	0.460
54	taurocholic acid	0.376	0.365	-0.013	0.380
55	taurodeoxycholate	0.076	0.062	-0.009	0.628
56	taurolithocholate 3-sulfate	0.148	0.116	0.001	0.930
57	thyroxine to taurocholate	0.120	0.115	0.014	0.409
58	vanillic acid glycine	0.726	0.689	-0.008	0.577
59	vanillic alcohol sulfate	0.694	0.663	-0.011	0.518

续表 5

序号	血液代谢物水平/代谢物比率	Cochran's Q 检验 P 值		MR Egger 检验	
		逆方差加权法	MR Egger	截距值	P 值
60	X-11315	0.561	0.564	-0.013	0.326
61	X-12544	0.091	0.086	0.014	0.427
62	X-13695	0.631	0.614	0.012	0.413
63	X-13723	0.083	0.099	0.023	0.251
64	X-17438	0.292	0.242	0.003	0.862
65	X-21286	0.592	0.706	0.021	0.119
66	X-21310	0.878	0.883	-0.013	0.351
67	X-21471	0.403	0.384	-0.011	0.421
68	X-24418	0.641	0.628	-0.013	0.400
69	X-24588	0.972	0.958	0.000	0.988
70	X-25520	0.987	0.983	0.007	0.632

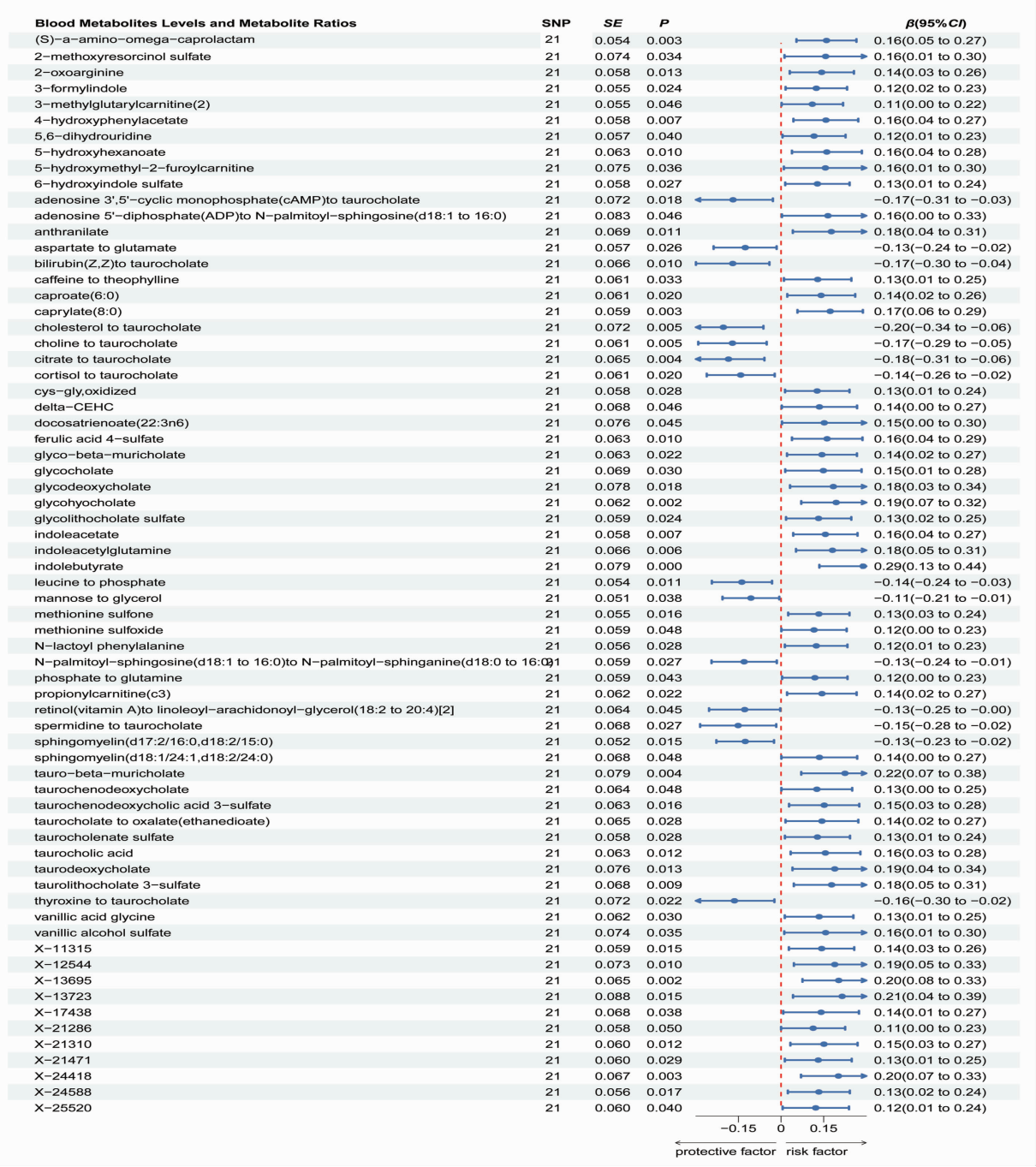


图 6　白细胞介素-7 表达水平与血液代谢物指标的因果关系森林图

生,但其具体的作用机制仍有待进一步研究。CD244 是一种存在于 NK 细胞、T 细胞等免疫细胞中的一种跨膜蛋白,在系统性红斑狼疮、类风湿关节炎、Ⅰ型糖尿病等多种免疫相关疾病的发生发展中起作用[25]。Ramos 等[26]研究发现,类风湿关节炎患者的血清、关节滑液、滑膜组织中 Flt3L 水平显著升高。然而,CD244 和 Flt3L 在 AS 中的作用尚缺乏实证研究,CD244、Flt3L 表达水平与 AS 呈负相关的结论尚需进一步研究予以验证。

炎症反应与代谢过程密切相关,炎症因子的异常表达会影响血液代谢物的合成和分解。FGF-23 表达水平与 62 项血液代谢物指标存在可靠的因果关系。Li 等[27]研究发现,AS 患者组血清中 5α-雄甾-3β,17β-二醇重硫酸盐(5α-androstan-3β,17β-diol disulfate)、枸橼酸(citrate)、胆碱(choline)水平低于健康对照组。本研究结果显示,FGF-23 表达水平与这 3 项血液代谢物指标均呈负相关。我们推测,FGF-23 通过下调血清中 5α-雄甾-3β,17β-二醇重硫酸盐、枸橼酸、胆碱这 3 种代谢物的血清水平增加 AS 的患病风险。Vittimberga 等[28]研究发现,水杨酸盐(salicylate)能够抑制大鼠巨噬细胞肿瘤坏死因子-α 的表达。Zu 等[29]研究发现,水杨酸盐能够抑制由肿瘤坏死因子-α 刺激引起的大鼠原代细胞的脂肪分解,进而抑制大鼠原代细胞释放游离脂肪酸。此外,水杨酸盐还是非甾体抗炎药的主要有效成分,在 AS 的治疗中发挥重要作用。本研究结果显示,FGF-23 表达水平与水杨酸盐呈负相关。我们推测 FGF-23 可能通过下调血液中水杨酸盐水平增加 AS 的患病风险。此外,在与 FGF-23 表达水平存在可靠的因果关系的血液代谢物指标中,多种代谢物与 AS 的相关性缺少实证研究。但部分代谢物与其他炎症性疾病或癌症存在相关性。Paine 等[30]研究表明,以血清甘氨熊去氧胆酸硫酸酯(glycoursodeoxycholic acid sulfate)水平预测银屑病向银屑病性关节炎发展,具有较高的敏感度和特异度。Nystrom 等[31]研究发现,患有炎症性肠病新生儿血浆中山嵛酰鞘磷脂(d18:1/22:0)[behenoyl sphingomyelin(d18:1/22:0)]水平增高,提示其与炎症反应关系密切。全氟辛烷磺酸(perfluorooctanesulfonate)是一种具有毒性和致癌作用的有机污染物,能够诱导免疫细胞凋亡,破坏免疫系统[32]。Zhang 等[33]研究发现,乳腺癌患者血液中丙二酰肉碱(malonylcarnitine)水平低于健康成年人,是乳腺癌的保护因素。Liu 等[34]研究发现,肝癌患者血清中 1-甲基烟酰胺(1-methylnicotinamide)的水平明显高于健康成年人,是肝癌的危险因素。Sidor 等[35]研究发现,1-甲基烟酰胺通过活性氧依赖途径降低了人巨噬细胞 NOD 样受体蛋白 3 炎症小体的激活,减少 NOD 样受体蛋白 3 相关的炎症性疾病的发生。这些研究成果以及本研究的结果,可为探索 AS 的发生机制提供思路和参考。

IL-7 表达水平与 68 项血液代谢物指标存在可靠的因果关系。Li 等[27]研究发现,AS 患者组邻氨基苯甲酸(anthranilate)水平低于健康对照组。然而,本研究结果显示,IL-7 表达水平与血液邻氨基苯甲酸水平呈正相关,而 IL-7 表达水平与 AS 呈正相关。因此,IL-7、邻氨基苯甲酸在 AS 发生中的具体作用机制尚需进一步探究。此外,在与 IL-7 表达水平存在可靠的因果关系的血液代谢物指标中,一些实证研究结果表明,部分血液代谢物与其他炎症性疾病或癌症存在相关性。硫酸牛磺胆酸酯(taurocholenate sulfate)是肝癌早期血清诊断的新候选标志物[36]。人体血清中 3-甲基戊二酰肉碱(3-methylglutarylcarnitine)水平与侵袭性乳腺癌和雌激素受体阳性乳腺癌具有相关性[37]。

CD244 表达水平与 61 项血液代谢物指标存在可靠的因果关系。Li 等[27]研究发现,AS 患者血清中 1-硬脂酰-GPE(18:0)[1-stearoyl-GPE(18:0)]、孕烯二醇重硫酸盐(pregnenediol disulfate)的水平显著低于健康成年人,1-(1-烯基-硬脂酰基)-GPE(p-18:0)[1-(1-enyl-stearoyl)-GPE(p-18:0)]水平高于健康成年人。本研究显示,CD244 表达水平与血清 1-硬脂酰-GPE(18:0)、1-(1-烯基-硬脂酰基)-GPE(p-18:0)水平成正相关,与血清孕烯二醇重硫酸盐水平呈负相关。我们推测 CD244 可能通过上调 1-硬脂酰-GPE(18:0)和下调 1-(1-烯基-硬脂酰基)-GPE(p-18:0)的血清水平来降低 AS 的发生风险。但 1-(1-烯基-硬脂酰基)-GPE(p-18:0)与 AS 发生的具体机制有待进一步研究。此外,Imrich 等研究[38-39]发现,AS 患者血清中的皮质醇(cortisol)水平与健康成年人比较,差异无统计学意义。然而本研究结果表明,CD244 表达水平与血清皮质醇水平呈负相关,而 CD244 表达水平与 AS 呈正相关。因此,CD244、皮质醇在 AS 发生中的具体作用机制尚需进一步探究。

本研究采用 MR 分析了炎症因子表达水平与 AS 及与血液代谢物指标的因果关系,具有以下优势:①方法优势。本研究先以炎症因子表达水平为暴露因素,以 AS 为结局分析了炎症因子表达水平与 AS 间的因果关系,再以与 AS 具有因果关系的炎症因子表达水平为暴露因素,以血液代谢物指标为结局,分析炎症因子表达水平与血液代谢物指标的因果关系,方法具有较强的理论依据;且 MR 能够避免混杂因素和反向因果关系的影响,进而获得可靠的因果关系分析结果。②数量优势。本研究涉及 91 种炎症因子和 1400 项血液代谢物指标,相较于 Fang 等[40] 关于 41 种炎症因子与 AS 因果关系的研究,本研究能够更加全面地评估炎症因子与 AS 的因果关系。然而,本研究也存在一定的局限性:①GWAS 数据源自欧洲人,研究结论在其他人群是否具有适应性尚需进一步验证;②多种血液代谢物与 AS 的关系缺少实证研究,本研究的结论尚需更多动物实验、临床试验予以验证。

本研究结果显示,FGF-23、IL-7、CD244、FIt3L 表达水平与 AS 存在可靠的因果关系,这 4 种炎症因子表达水平分别与多项血液代谢物指标存在可靠的因果关系;这为探索 AS 的发生机制和治疗 AS 的药物靶点提供了参考。

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