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银屑病与非酒精性脂肪性肝病之间因果关系：双向双样本孟德尔随机化研究

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摘　要

目的：采用孟德尔随机化(MR)研究银屑病与非酒精性脂肪性肝病之间的双向因果关系。方法：我们使用来自银屑病和NAFLD的汇总GWAS数据进行了双样本孟德尔随机化(TSMR)分析。选择满足孟德尔随机化三个核心假设的工具变量(IV)。TSMR分析采用逆方差加权(IVW)法为主要分析方法进行分析，辅以MR-Egger回归法和加权中位数(WM)法进行。为确保研究结果的准确性和稳定性，进行了异质性检验、多重有效性检验和敏感性分析。结果：IVW方法提示银屑病与非酒精性脂肪性肝病之间有因果关系(OR 1.20；95%可信区间：1.10~1.32；$P = 9.58 \times 10^{-5}$)。MR-Egger回归未显示有水平多效性。Cochran-Q检验结果表明纳入分析的SNP之间不存在异质性，MR-PRESSO检验未发现离群的SNP，“留一法”敏感性分析显示，因果估计不太可能受到某些SNP效应的影响，反向MR分析的结果表明非酒精性脂肪性肝病增加银屑病患病率。结论：银屑病与非酒精性脂肪性肝病之间存在因果关系。

关键词

银屑病，非酒精性脂肪性肝病，孟德尔随机化，因果关系

Causal Relationship between Psoriasis and Non-Alcoholic Fatty Liver Disease: A Bidirectional Two-Sample Mendelian Randomization Study

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Abstract

Objective: Mendelian randomization (MR) was used to investigate the bidirectional causal relationship between psoriasis and non-alcoholic fatty liver disease (NAFLD). Method: We performed a two-sample Mendelian randomization (TSMR) analysis using pooled GWAS data from psoriasis and NAFLD. Instrumental variables (IVs) were selected to satisfy the three core assumptions of Mendelian randomization. TSMR analyses were performed using the inverse variance weighting (IVW) method as the primary analytical method for the analyses, supplemented by MR-Egger regression and weighted median (WM) methods. Heterogeneity test, multiple validity test and sensitivity analysis were conducted to ensure the accuracy and stability of the findings. Results: The IVW method suggested a causal association between psoriasis and non-alcoholic fatty liver disease (OR 1.20; 95% confidence interval: 1.10~1.32; P = 9.58 × 10^{-5}). MR-Egger regression did not show horizontal pleiotropy. The results of Cochran's Q-test showed no heterogeneity between the SNPs included in the analysis, MR-PRESSO found no outlier SNPs, leave-one-out sensitivity analyses showed that causal estimates were unlikely to be affected by certain SNP effects, and the results of inverse MR analyses showed that NAFLD increased the prevalence of psoriasis. Conclusion: There is a causal relationship between psoriasis and non-alcoholic fatty liver disease.

Keywords

Psoriasis, NAFLD, Mendelian Randomization, Causal Relationship

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1. 引言

银屑病是一种由免疫系统介导的皮肤炎症性疾病，在不同的国家和地区其发病率不同，从东亚的0.14%到澳大拉西亚的 1.99%。西欧为 0.92%，中欧 1.83%、北美 1.50%和高收入拉丁美洲南部 1.10%，其发病率在各个地区都很高[1]。主要表现为皮肤上出现边界清楚的红色、椭圆形斑块，黏附有银白色鳞片[2]。牛皮癣很大程度上可能是由遗传多态性介导的，有研究表明单卵双胞胎银屑病的患病率是双卵双胞胎的 2~3 倍，此外银屑病患者一级和二级亲属的发病率高于普通人群[3]。银屑病是与全身多种疾病相关，2014 年 WHO 通过提议认为银屑病是一种无法治愈的慢性、非传染性、疼痛、毁容和致残性疾病[4]。

非酒精性脂肪性肝病(NAFLD)是全球肝病的主要原因，在普通人群中的发病率为 25% [5]。银屑病作为一种免疫介导的全身性炎症疾病，其与非酒精性脂肪性肝病之间的联系一直以来都被广泛关注。一项荟萃分析证实与非银屑病对照组相比，银屑病患者的 NAFLD 患病率增加了 2 倍，并且原发疾病越严重，风险越高[6]。同时有队列研究指出对于年轻的 NAFLD 患者，患银屑病的风险高出 1.3 倍[7]。然而，由于混杂因素和反向因果关系是观察性研究的固有局限性，NAFLD 与银屑病之间的因果关系仍不清楚。

孟德尔随机化(MR)研究使用与表型密切相关的单核苷酸多态性(SNP)作为工具变量(IV)来研究暴露与疾病的相关性，可以有效解决与传统观察性研究相关的混淆和反向因果关系的问题[8]。由于遗传变异是在怀孕期间从父母随机遗传给后代的，所以这些遗传变异不太可能受到潜在的混杂因素和反向因果关系的影[9]。本篇文章中，我们旨在进行双样本 MR 研究，以评估银屑病和 NAFLD 风险之间的

可能因果关联。

2. 材料和数据方法

数据源：暴露和结局相关的全基因组关联分析数据全部来自 IEU OpenGWAS project (https://gwas.mrcieu.ac.uk/)公开可获得的数据库。银屑病的汇总数据库来自 4510 名银屑病患者和 212,242 名对照者的 16,380,464 个 SNPs；非酒精性脂肪肝的数据来自 894 名非酒精性脂肪性肝病患者和 217,898 对照者的 16,380,466 个 SNPs。

2.1. 研究设计与统计分析方法

MR 分析主要在三个假设下进行：1) 遗传变异与暴露因素密切相关；2) 遗传变异不应与任何可能介导从暴露到结果的潜在混杂因素相关联；3) 遗传变异对结局没有影响，除了可能通过它们与暴露的关联[10] [11]。

首先，我们评估了 SNPs 与银屑病的独立相关性，且去除了连锁不平衡($P < 5 \times 10^{-8}$，$R^2 = 0.001$, kb = 10,000)。其次，我们研究了每个 SNP 与 NAFLD 风险之间的关系。第三，我们将这些发现结合起来，使用 MR 分析来估计银屑病与 NAFLD 风险之间的不可分割的因果关系。逆方差加权(IVW)法被用作主要的统计分析方法。辅以逆方差加权 MR-Egger 和加权中位法[12]。IVW 法使用荟萃分析方法来组合从不同 SNP 获得的因果效应的 Wald 比率估计。如果存在异质性，则使用随机效应模型，无异质性则采用固定效应模型[13]。为了检测潜在的水平多效性我们进行 MR-Egger 回归。我们还使用孟德尔随机化多效性残差和异常值(MR-PRESSO)分析来检验离群的 SNP [14]。此外我们还进行了反向因果关系的分析，反向因果关系分析以 IVW 方法为主要分析方法。

2.2. 异质性和敏感性分析

我们使的 Cochran Q 检验评估了 SNP 之间的异质性，检验的 P 值 > 0.05 被认为异质性较底[15]。我们还进行了“留一法敏感性”分析，以调查因果关系由单个 SNP 驱动的可能性，从而保证 MR 结果的可靠性[15] [16]。

3. 结果

3.1. 工具变量的选择

为了满足 MR 的假设，所有用于分析的工具变量都是和暴露因素强相关且独立的，并且去除了连锁不平衡($P < 5 \times 10^{-8}$, $R^2 = 0.001$)；我们使用每个 SNP 的 F 统计量($F = beta^2/se^2$)评估每个 SNP 的功效，F < 10 被认为是弱工具变量，所有用于本 MR 分析的工具变量 F 统计量均大于 20 (表 1) [17]。

Table 1. Causal relationship instrumental variables between psoriasis and non-alcoholic fatty liver disease
表 1. 银屑病与非酒精性脂肪性肝病因果关系工具变量

CHR	SNP	Position	EA	OA	Beta	SE	P 值	F 统计量
2	rs12713428	61118113	C	A	0.1694	0.0261	8.11E−11	42.12557068
5	rs17728338	150478318	A	G	0.3092	0.0439	1.76E−12	49.60779573
5	rs12188300	158829527	T	A	0.4331	0.0495	2.24E−18	76.55366187
6	rs674451	138216788	C	T	0.1307	0.0235	2.82E−08	30.93253056
6	rs13210419	31266977	A	G	1.1157	0.0511	1.10E−105	476.7086868

续表

6	rs28752856	31298418	G	C	0.833	0.0393	5.90E−100	449.2673957
6	rs4947309	31302328	T	A	0.5524	0.0274	3.86E−90	406.4491449
6	rs4713605	32985992	A	T	0.1526	0.0241	2.35E−10	40.09359343
6	rs9481169	111929862	T	G	0.2515	0.0422	2.47E−09	35.51821051
6	rs1611309	29902063	T	C	0.241	0.0267	1.60E−19	81.47259746
7	rs60600003	37382465	G	T	0.2128	0.0372	1.03E−08	32.72332062
7	rs181316459	5473610	C	G	0.3544	0.0553	1.50E−10	41.07117842
10	rs10829130	27174346	A	G	0.1965	0.0359	4.24E−08	29.95961391
16	rs138009430	27302897	A	C	0.2538	0.0423	1.94E−09	36
16	rs2021511	11344903	T	C	−0.1387	0.0254	4.75E−08	29.81847914
17	rs28998802	26124908	A	G	0.1672	0.0289	7.41E−09	33.47162989

3.1.1. 银屑病对非酒精性脂肪肝 MR 结果

IVW 分析显示有证据支持牛皮癣可增加非酒精性脂肪性肝病的风险(OR 1.20；95%可信区间：1.10~1.32；P = 9.58 × 10^{-5}) (图 1，图 2)。MR-Egger 回归截距显示结果不受水平多效性的影响(P = 0.60)；MR-PRESSO 检验未发现有影响水平多效性的异常值存在。留一法敏感性分析的结果表明，没有单个 SNP 在因果推断中起决定性作用，从而保证了结果的可靠性(图 3)。漏斗图中的不对称性表明定向水平多效性，结果的漏斗图基本对称(图 4)。

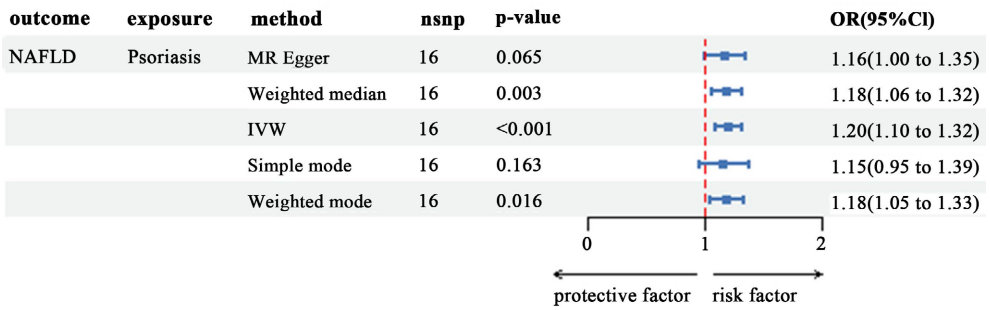

Figure 1. Mendelian randomization results for psoriasis versus non-alcoholic fatty liver disease
图 1. 银屑病与非酒精性脂肪性肝病孟德尔随机化结果图

3.1.2. 非酒精性脂肪肝对银屑病 MR 结果

反向 MR 结果提示非酒精性脂肪性肝病增加银屑病的患病风险(OR 1.11；95%可信区间：1.03~1.19；P = 0.006)。

4. 讨论

本研究通过 MR 分析，从基因的角度讨论了银屑病和非酒精性脂肪性肝病之间双向因果关系。我们的结果提示银屑病增加非酒精性脂肪性肝病风险，同时非酒精性脂肪性肝病也增加银屑病的风险。但我们用于反向因果关系验证的 SNP 数量较少，此外 Näslund 等人既往的 MR 研究也指出非酒精性脂肪性肝病不是银屑病的危险因素[18]，所以我们使用由 IEU 平台获得的其余两个汇总数据进行了 MR 分析

(NAFLDid：ebi-a-GCST90054782，银屑病 ID：finn-b-L12_PSORIASIS)结果显示非酒精性脂肪性肝病增加银屑病风险(OR 1.10；95%可信区间：1.01~1.21；P = 0.03)。

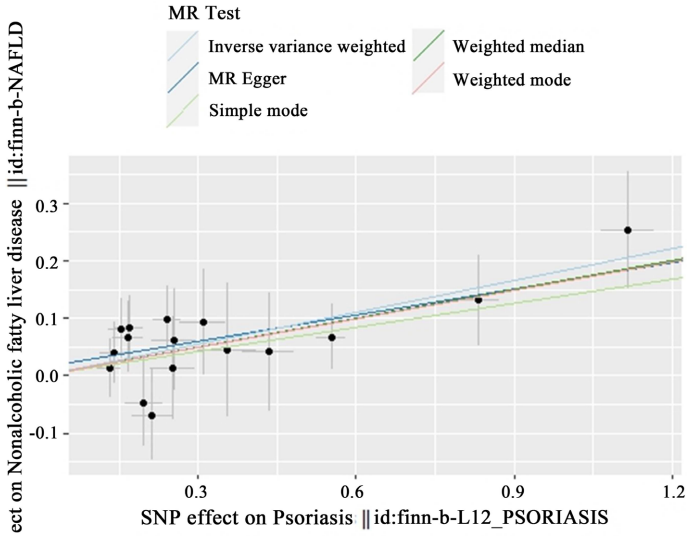

Figure 2. Scatter plot of causality between psoriasis and non-alcoholic fatty liver disease
图 2. 银屑病与非酒精性脂肪性肝病因果关系散点图

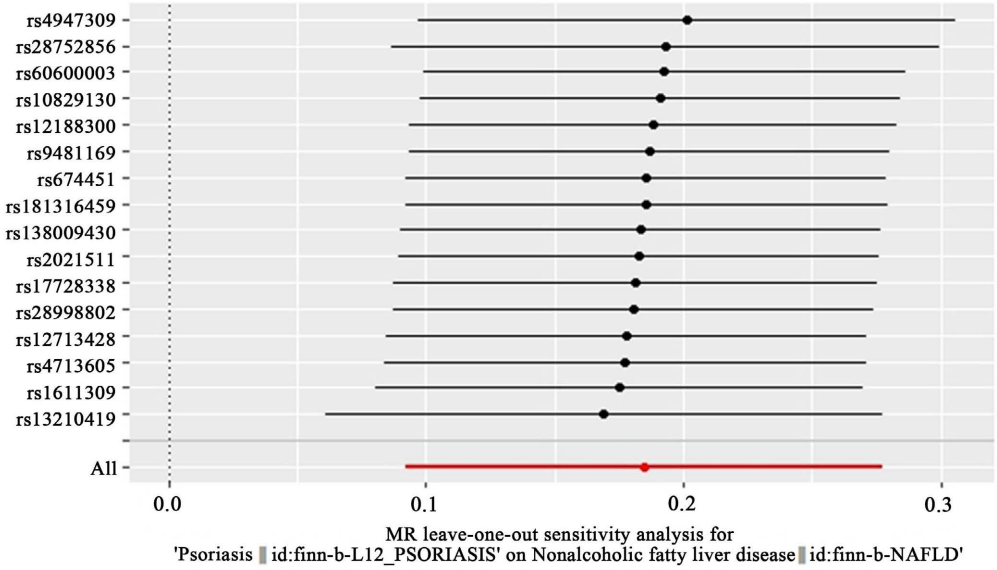

Figure 3. Leave-one-out sensitivity analysis chart of the causal relationship between psoriasis and non-alcoholic fatty liver disease
图 3. 银屑病与非酒精性脂肪性肝病因果关系留一法敏感性分析图

牛皮癣被认为是一种慢性，全身炎症性疾病，其增加非酒精性脂肪性肝病的风险可能与内脏脂肪组织的紊乱和过度促炎细胞因子释放有关[19] [20]。银屑病患者表现出脂肪因子谱紊乱(瘦素水平升高和脂联素水平降低) [21] [22]。脂联素是一种可以抑制脂肪酸摄取、增加线粒体对脂肪酸氧化的脂肪因子，刺激甘油三酯输出并提高肝脏胰岛素敏感性[23]。在牛皮癣患者的皮肤中角质形成细胞和淋巴细胞分泌大量

促炎症细胞因子，例如 IL-6、IL-17、TNF-α。促炎因子以及失衡的脂肪因子谱加重肝脏胰岛素抵抗，诱导肝细胞脂肪变性，使肝脏容易受到进一步的炎症损伤[24]。

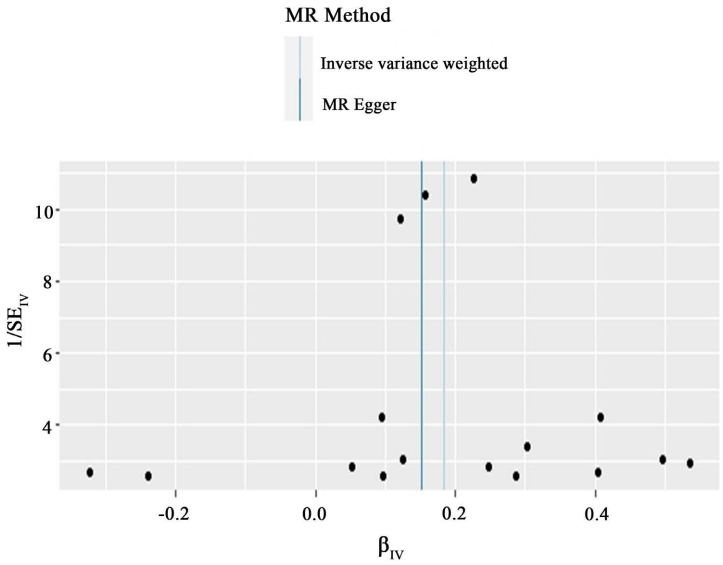

Figure 4. Funnel plot of causality between psoriasis and non-alcoholic fatty liver disease
图 4. 银屑病与非酒精性脂肪性肝病因果关系漏斗图

非酒精性脂肪性肝病也被证明是一种多系统疾病，目前认为非酒精性脂肪性肝病与心血管系统、女性生殖系统、内分泌系统等多个系统有关[25]。脂肪变性的肝细胞会释放大量促炎、促凝血、促氧化和促纤维化介质以及游离脂肪酸(例如，C 反应蛋白、IL-6、纤维蛋白原、纤溶酶原激活物抑制剂-1、转化生长因子-β)这些物质释放后会促进皮肤角质形成细胞增生、皮肤炎症反应增强和各种血管粘附分子上调，增加非酒精性脂肪性肝病患者牛皮癣的发病风险[26] [27]。对于银屑病患者，抗炎和促炎细胞因子的紊乱(IL-6、IL-17、TNF-α、瘦素水平增高以及脂联素水平的降低)会通过自身的炎症级联放大肝损伤，促进肝病的进展，反过来肝脏的炎症过程又会加重银屑病严重程度，造成恶性循环[28] [29]。

我们的研究有几个优点。目前尚未有研究进行 MR 来评估银屑病与 NAFLD 之间双向因果的关系。我们的研究通过两样本 MR 验证了银屑病和非酒精性脂肪性肝病之间因果关系。此外，我们还进行了重要的敏感性分析，以验证 MR 模型的假设。在解释我们的结果时需要考虑局限性。首先我们的分析是使用欧洲人群进行的，这限制了其普遍性。由于因果关系可能取决于种族和选择偏见，因此需要对其他人群进行进一步的 MR 研究。其次我们的研究使用的汇总 GWAS 数据样本量有限，未来需要更大的样本量来验证因果关系。

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