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基于孟德尔随机化探讨风湿系统疾病与胰腺癌风险的因果关系

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摘　要

目的：通过两样本孟德尔随机化的方法探究风湿系统疾病(类风湿性关节炎、骨关节炎、系统性红斑狼疮、强直性脊柱炎、痛风)与胰腺癌发病之间的因果关系，为胰腺癌的早期发现提供依据。方法：从全基因组关联分析研究的数据中分别筛出与上述5种风湿系统疾病具有强相关的独立遗传变异作为工具变量，通过孟德尔随机化分析中的逆方差加权法、MR-Egger回归分析和加权中位数法三种方法进行探讨上述5种风湿系统疾病与胰腺癌发病的因果关联。结果：逆方差加权分析法结果：类风湿性关节炎(OR = 1.182, P = 0.013)、骨关节炎(OR = 2.434, P = 0.009)、系统性红斑狼疮(OR = 1.018, P = 0.469)、强直性脊柱炎(OR = 19951683.481, P = 0.040)、痛风(OR = 23.705, P = 0.189)。MR-Egger回归分析结果：类风湿性关节炎(OR = 1.329, P = 0.018)，其余四组结果P > 0.05，统计结果无统计学意义；加权中位数法结果：类风湿性关节炎(OR = 1.265, P = 0.007)，其余四组结果P > 0.05，统计结果无统计学意义。敏感性分析显示研究结果稳健，异质性检验表明不存在异质性。结论：类风湿性关节炎、骨关节炎、强直性脊柱炎与胰腺癌发病存在正向因果关联，在此类患者中定期进行胰腺癌的相关筛查可有利于胰腺癌的早期发现与及时干预。

关键词

胰腺癌，类风湿性关节炎，骨性关节炎，系统性红斑狼疮，强直性脊柱炎，痛风，孟德尔随机化

To Investigate the Causal Relationship between Rheumatological Diseases and Pancreatic Cancer Risk Based on Mendelian Randomization

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Abstract

Objective: Two sample Mendelian randomization method was used to explore the causal relationship between rheumatoid arthritis, osteoarthritis, systemic lupus erythematosus, ankylosing spondylitis, gout and the incidence of pancreatic cancer, so as to provide the basis for the early detection of pancreatic cancer. Methods: From the data of genome-wide association analysis studies, independent genetic variants strongly associated with the above five rheumatic diseases were screened as instrumental variables. The causal relationship between rheumatoid arthritis, osteoarthritis, systemic lupus erythematosus, ankylosing spondylitis, gout and pancreatic cancer was investigated by using the inverse variance weighting method, MR-Egger regression analysis and weighted median method in Mendelian randomized analysis. Results: Inverse variance weighted analysis results: Rheumatoid arthritis (OR = 1.182, P = 0.013), osteoarthritis (OR = 2.434, P = 0.009), systemic lupus erythematosus (OR = 1.018, P = 0.469), ankylosing spondylitis (OR = 19951683.481, P = 0.040), gout (OR = 23.705, P = 0.189). The result of MR-Egger regression analysis: rheumatoid arthritis (OR = 1.329, P = 0.018); the results of the other four groups P > 0.05; the statistical results were not statistically significant. Weighted median method results: rheumatoid arthritis (OR = 1.265, P = 0.007); the results of the other four groups P > 0.05; statistical results were not statistically significant. Sensitivity analysis showed robust results, and heterogeneity test showed no heterogeneity. Conclusion: Rheumatoid arthritis, osteoarthritis, ankylosing spondylitis and pancreatic cancer have a positive causal association, and regular screening of pancreatic cancer in these patients can be conducive to early detection and timely intervention of pancreatic cancer.

Keywords

Pancreatic Cancer, Rheumatoid Arthritis, Osteoarthritis, Systemic Lupus Erythematosus, Ankylosing Spondylitis, Gout, Mendelian Randomization

1. 引言

胰腺癌是消化系统中常见的恶性肿瘤，由于缺乏敏感的诊断标志物、转移能力强、抗癌药物耐药，胰腺癌预后较差[1]，被称为“癌中之王”。全世界被诊断患有胰腺癌的患者数量正在上升，全球癌症数据表明，2020 年全球估计有 495,773 名胰腺癌患者新诊断为胰腺癌，在所有恶性肿瘤中排名第 12 位[2]。胰腺癌患者的 5 年生存率非常低[3]，其中一个重要原因在于胰腺癌的诊断往往发生在晚期阶段，从而限制了治疗选择并降低了治愈的前景[4]。由于胰腺癌起病隐匿，病理生理未知，预后不良，即使采用手术、放疗、生物治疗和靶向治疗等广泛的治疗方法，胰腺癌患者的总生存率也没有显著提高[5]。因此，深入研究胰腺癌的危险因素，对早期诊断和预防、干预进行探索，将带来巨大的收益。

风湿性疾病是一系列自身免疫性和炎症性疾病[6]，该类疾病可累及患者全身多个脏器组织[7]，具有病程迁延、治疗难度大的特点[8]。常见的风湿病有痛风、类风湿关节炎、系统性红斑狼疮、干燥综合征、

系统性硬化症、强直性脊柱炎及骨关节炎等[9]。有研究表明免疫反应的失衡是某些类型癌症的危险因素[10]。但目前尚无风湿系统疾病与胰腺癌之间因果关联的系统性研究，因此我们将采用孟德尔随机化分析的研究方法去探讨这一问题。

孟德尔随机化(Mendelian randomization, MR)是确定暴露对结果的因果效应的有用工具[11]。MR使用遗传变异作为工具变量，在减数分裂过程中平等、随机和独立分布[12]，有效地避免了混杂因素和反向因果的影响[13]。全基因组关联研究(Genome-wide association study, GWASs)已经确定了数千种与各种复杂疾病相关的遗传变异，这将 MR 的使用推向了一个更高的阶段[14]。在上述知识的基础上，我们借助近期大规模 GWASs，运用 MR 分析的方法来研究上述 5 种风湿系统疾病与胰腺癌之间的因果关系。

2 材料与方法

2.1. 数据来源与工具变量的选择

5 种风湿系统疾病及胰腺癌的数据均来自 IEU OPen GWAS Project (https://gwas.mrcieu.ac.uk/)。详见表 1，为了符合孟德尔随机化的要求，我们需要确保所选的工具变量分别与上述 5 种风湿系统疾病之间存在强相关，筛选条件为 $P < 5 \times 10^{8}$。为保证各个 SNP 之间互相独立，连锁不平衡系数设置为 $r^2 = 0.001$，区域宽度设定为 kb = 10,000。我们将 F > 10 定义为无弱工具偏倚的标准。通过 Phenosanner 平台筛查进行排除与混杂因素相关的 SNPs，就得到了我们所需要的工具变量。为了减少异质性，同一组暴露与结局的数据我们选择了来自同一地区人群的数据。

Table 1. Brief information in the GWAS database for two sample MR studies
表 1. 两样本 MR 研究中 GWAS 数据库中的简要信息

	GWAS ID	Trait	Sample size	Number of SNPs	Population
Pancreatic cancer	ebi-a-GCST90018893	Pancreatic cancer	476,245	24,195,229	European
Pancreatic cancer	ebi-a-GCST90018673	Pancreatic cancer	159,700	12,452,059	East Asia
Rheumatoid arthritis	ebi-a-GCST90018690	Rheumatoid arthritis	178,616	12,454,695	East Asia
Osteoarthritis	ebi-a-GCST90013881	Osteoarthritis (Firth correction)	407,746	11,039,204	European
Systemic lupus rythematosus	ebi-a-GCST003156	Systemic lupus rythematosus	14,267	7,071,163	European
Ankylosing spondylitis	ukb-b-18194	Ankylosing spondylitis	462,933	9,851,867	European
Gout	ebi-a-GCST90038687	Gout	484,598	9,587,836	European

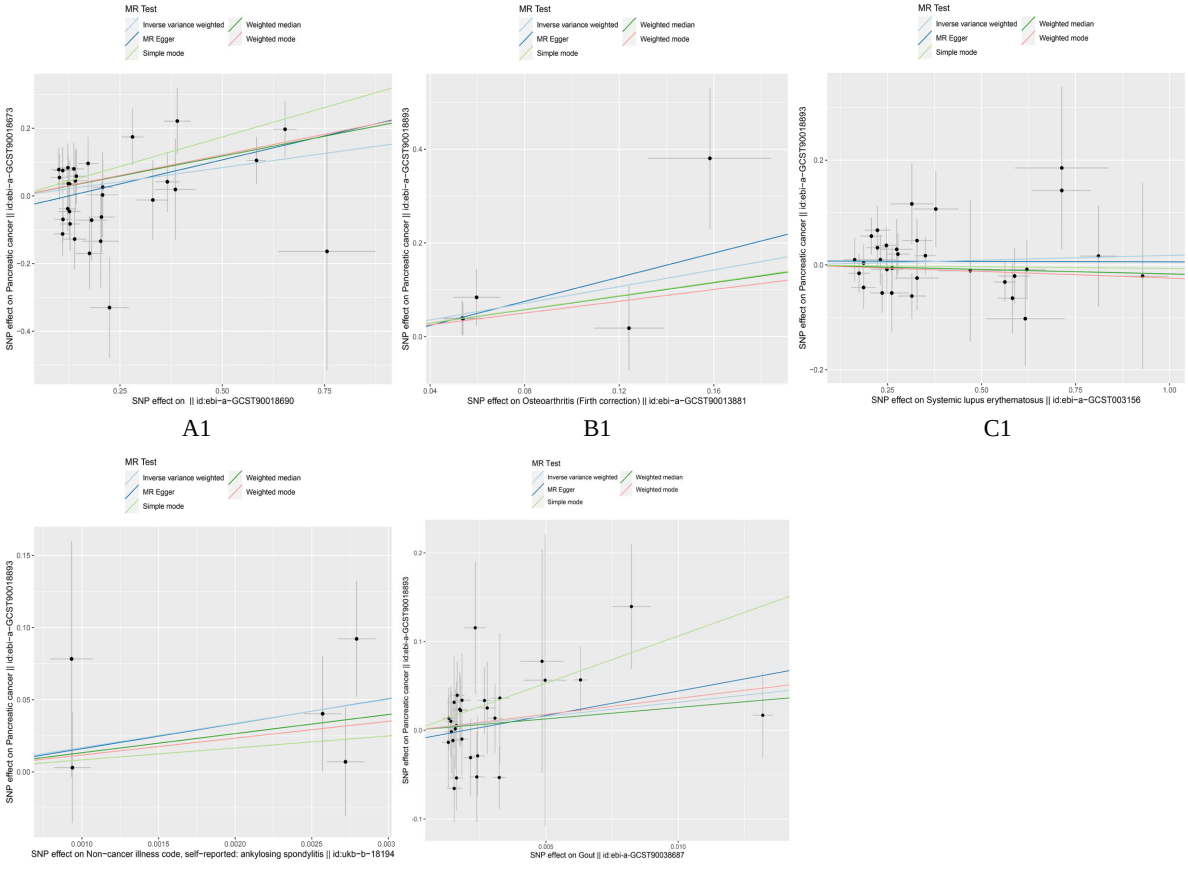
2.2. MR 分析

本研究使用双样本孟德尔随机化分析的方法评估 5 种风湿系统疾病与胰腺癌发病风险之间的因果关系。MR 研究包含三个主要假设[15]：1) 工具变量与暴露(所所筛选出的 5 组 SNPs 分别于所研究的 5 种风湿系统疾病)具有强相关。2) 工具变量与混杂因素无关。3) 工具变量只能通过暴露(5 种风湿系统疾病)影响结局(胰腺癌)。逆方差加权法(IVW)作为本研究的主要结局指标，MR-Egger 回归、加权中位数法(Weighted median method, WME) 2 种方法进行补充分析。当三种结果不一致时，以 IVW 方法为主。

2.3. 敏感性分析

采用 Cochran's Q 检验和漏斗图检测异质性。如果 Cochran Q 检验的值 $P < 0.05$，则认为存在异质性[16]。采用 MR-Egger 截距检验和“留一法”分析评估结果的水平多效性和稳定性。如果 MR-Egger 截距

检验的值 P < 0.05，则认为存在水平多效性[17]。使用“留一法”判断单个 SNP 对因果关系的影响程度。评估和校正水平多效性的指标采用离群值(MR-PRESSO)方法[18]。本研究采用 R4.3.1 软件中用“Mendelian Randomization”和“Two SamPle MR”的 R 包进行两样本孟德尔随机化分析。

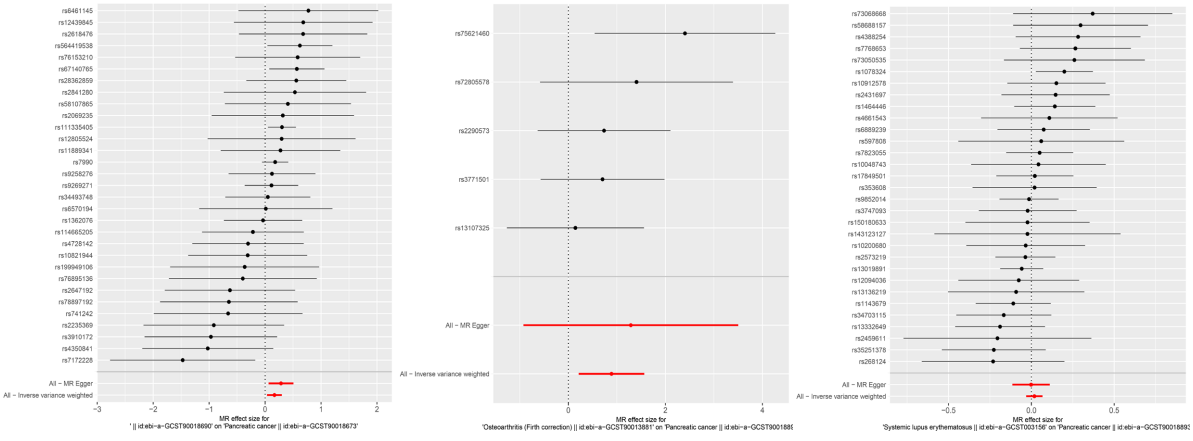


A1 B1 C1

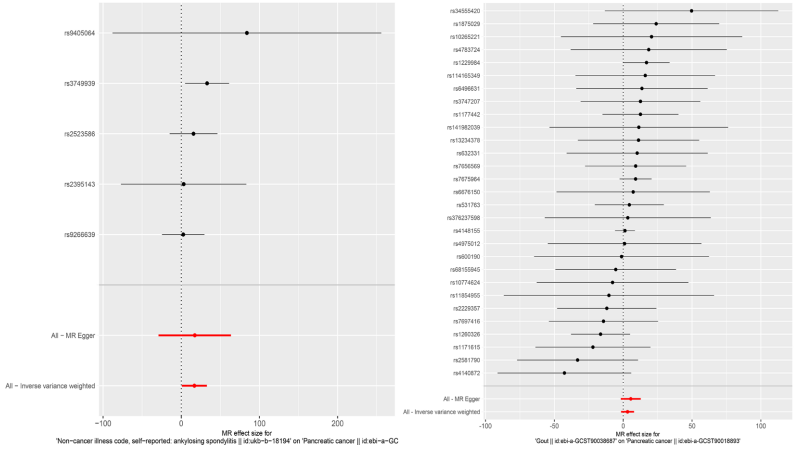
D1 E1

Figure 1. A scatter plot (A1, B1, C1, D1, E1 represent rheumatoid arthritis, osteoarthritis, systemic lupus erythematosus, ankylosing spondylitis, and gout, respectively)

图 1. 散点图(A1、B1、C1、D1、E1 分别为类风湿性关节炎、骨关节炎、系统性红斑狼疮、强直性脊柱炎、痛风)



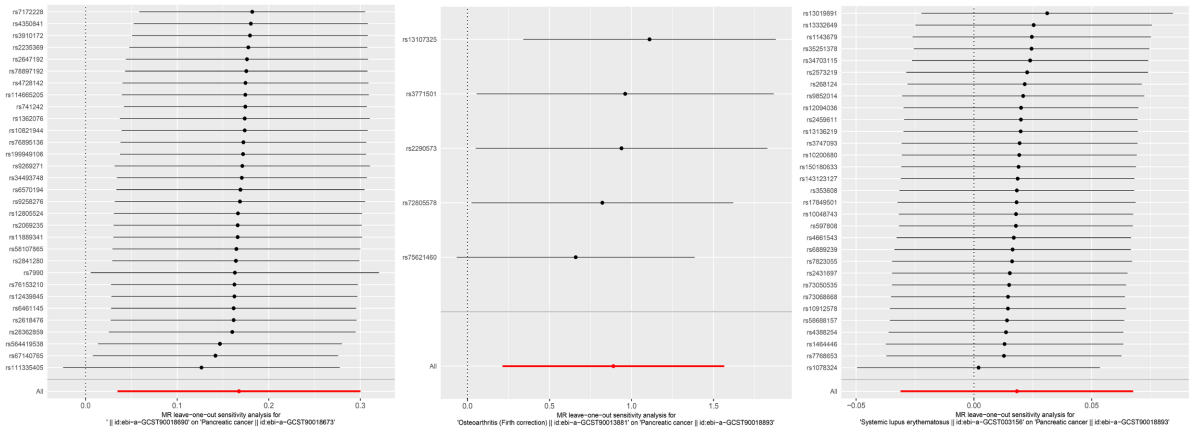
A2 B2 C2



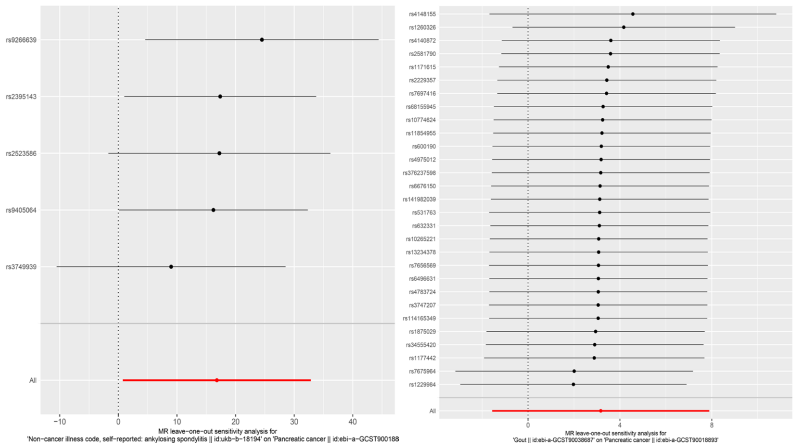
D2 E2

Figure 2. Forest map (A2, B2, C2, D2, E2 represent rheumatoid arthritis, osteoarthritis, systemic lupus erythematosus, ankylosing spondylitis, and gout, respectively)

图 2. 森林图(A2、B2、C2、D2、E2 分别为类风湿性关节炎、骨关节炎、系统性红斑狼疮、强直性脊柱炎、痛风)



A3 B3 C3



D3 E3

Figure 3. The leave-one-out graph (A3, B3, C3, D3, and E3 respectively represent rheumatoid arthritis, osteoarthritis, systemic lupus erythematosus, ankylosing spondylitis, and gout, respectively)

图 3. 留一法图(A3、B3、C3、D3、E3 分别为类风湿性关节炎、骨关节炎、系统性红斑狼疮、强直性脊柱炎、痛风)

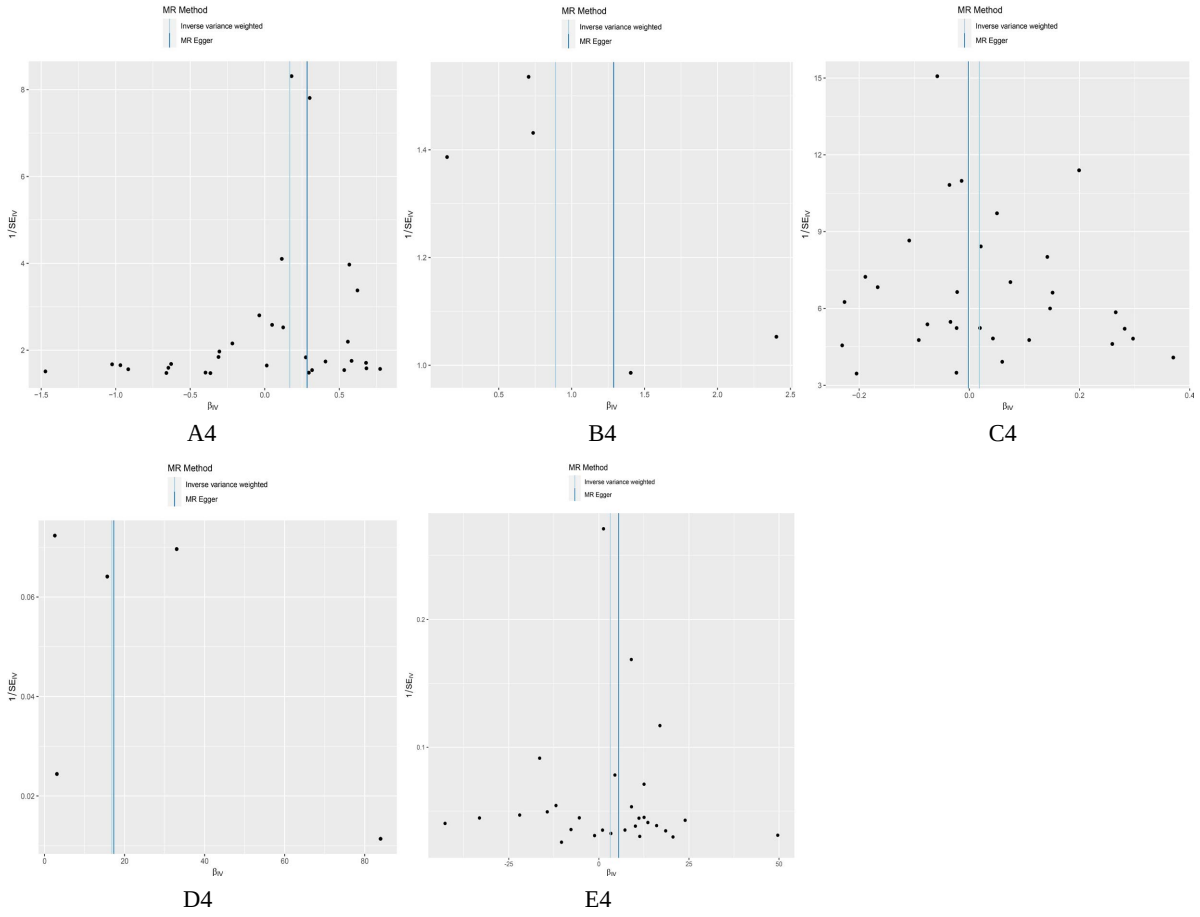


Figure 4. Funnel plot (A4, B4, C4, D4, and E4 respectively represent rheumatoid arthritis, osteoarthritis, systemic lupus erythematosus, ankylosing spondylitis, and gout, respectively)
图 4. 漏斗图(A4、B4、C4、D4、E4 分别为类风湿性关节炎、骨关节炎、系统性红斑狼疮、强直性脊柱炎、痛风)

3. 结果

3.1. 工具变量选择的结果

本研究工具变量筛选标准均是通过提取强相关、去除连锁不平衡、去除弱工具变量，剔除混杂因素，并且在胰腺癌的 GWAS 数据库中匹配上述暴露的工具表变量，数据统一化处理后，得到最终纳入研究的类风湿性关节炎 SNPs31 个、骨关节炎 SNPs5 个、系统性红斑狼疮 SNPs31 个、强直性脊柱炎 SNPs5 个、痛风 SNPs29 个工具变量。

3.2. MR 分析的结果

Table 2. Three MR results of five rheumatic diseases and pancreatic cancer
表 2. 5 种风湿系统疾病与胰腺癌的三种 MR 结果

	method	nsnP	β	SE	OR (95%CI)	P
Rheumatoid arthritis	IVW	31	0.167	0.067	1.182 (1.035~1.350)	0.013
	MR-Egger 回归	31	0.284	0.113	1.329 (1.063~1.660)	0.018
	WME	31	0.235	0.087	1.265 (1.066~1.502)	0.007

续表

Osteoarthritis	IVW	5	0.889	0.344	2.434 (1.238~4.784)	0.009
	MR-Egger 回归	5	1.287	1.128	3.624 (0.396~33.133)	0.336
	WME	5	0.719	0.434	2.052 (2.052~4.806)	0.097
Systemic lupus rythematosus	IVW	31	0.018	0.025	1.0184 (0.969~1.069)	0.469
	MR-Egger 回归	31	−0.001	0.057	0.998 (0.891~1.117)	0.977
	WME	31	−0.017	0.035	0.982 (0.916~1.053)	0.627
Ankylosing spondulicks	IVW	5	16.808	8.187	19951683.481 (2.141990e+00~1.858411e+14)	0.040
	MR-Egger 回归	5	17.304	23.632	32759757.532 (2.506349e−13~4.281932e+27)	0.517
	WME	5	13.258	10.542	572684.467 (6.081380e−04~5.392978e+14)	0.208
Gout	IVW	29	3.165	2.411	23.705 (0.210~2674.995)	0.189
	MR-Egger 回归	29	5.493	3.679	243.015 (0.179~329052.412)	0.147
	WME	29	2.575	3.445	13.139 (0.015~11252.824)	0.454

3 种方法的结果见表 2，由表可知，逆方差加权分析法结果：类风湿性关节炎(OR = 1.182, P = 0.013)、骨关节炎(OR = 2.434, P = 0.009)、系统性红斑狼疮(OR = 1.018, P = 0.469)、强直性脊柱炎(OR = 19951683.481, P = 0.040)、痛风(OR = 23.705, P = 0.189)。MR-Egger 回归分析结果：类风湿性关节炎(OR = 1.329, P = 0.018)，其余四组结果 P > 0.05，统计结果无统计学意义；加权中位数法结果：类风湿性关节炎(OR = 1.265, P = 0.007)，其余四组结果 P > 0.05，统计结果无统计学意义。

3.3. 敏感性分析的结果

Table 3. Horizontal pleiotropy
表 3. 水平多效性

	egger_intercept	P
Rheumatoid arthritis	−0.035	0.212
Osteoarthritis	−0.027	0.732
Systemic lupus rythematosus	0.007	0.704
Ankylosing spondylitis	−0.001	0.983
Gout	−0.010	0.409

Table 4. Heterogeneity results
表 4. 异质性结果

	Q	P
Rheumatoid arthritis	35.871	0.212
Osteoarthritis	3.990	0.407
Systemic lupus rythematosus	27.979	0.571
Ankylosing spondylitis	3.038	0.551
Gout	21.225	0.815

MR-Egger 回归截距项分别为类风湿性关节炎 b = −0.035 (P = 0.212)、骨关节炎 b = −0.027 (P = 0.732)、系统性红斑狼疮 b = 0.007 (P = 0.704)、强直性脊柱炎 b = −0.001 (P = 0.983)、痛风 b = −0.010 (P = 0.409)，即筛选出的 SNPs 与胰腺癌不存在水平多效性，见表 3，因此孟德尔随机化方法在本研究中为因果推断的有效方法。Q 检验中 P 值均大于 0.05，提示各个 SNP 之间不存在异质性，见表 4。另外，MR-PRESSO 分析显示，本研究中包含的 SNPs 没有显著的异常值。各种暴露因素的散点图见图 1，可以直观看到，类风湿性关节炎、骨关节炎、强直性脊柱炎与胰腺癌成正相关，见图 2。图 3 留一法图表明，没有单一 SNP 对总体评估有主导作用。此外，图 4 漏斗图的结果表明，潜在偏倚对因果关联的影响较小。通过这些分析方法，我们能够更加可靠地评估暴露对结局的影响，并确认研究结果的稳健性。

4. 讨论

这项研究利用 GWAS 数据库，使用两样本进行孟德尔随机化研究去探讨了 5 种风湿系统疾病与胰腺癌之间的因果关联。以上数据结果表明，类风湿性关节炎、骨关节炎、强直性脊柱炎会增加胰腺癌的发生风险，系统性红斑狼疮和痛风与胰腺癌不存在因果关联。类风湿性关节炎本身可能导致肿瘤形成风险增加，其机制可能为慢性免疫刺激、慢性炎症所致[19]。另一种机制可能为类风湿性关节炎导致抑制 T 淋巴细胞的数量和功能减少，这可能损害 T 淋巴细胞对抗促癌病毒的能力[20]。另一种间接机制是类风湿性关节炎患者联合使用甲氨蝶呤会使得体内 TNF-α 拮抗剂增多[21]，TNF-α 是一种有效的细胞因子，参与许多细胞生理活动过程，包括调节和维持免疫系统以及激发炎症，从而促进癌症的发生与发展[22] [23]。骨关节炎是一种慢性炎症性疾病[24]，而慢性炎症与癌症的发展和进展有关。慢性炎症可能通过诱导 DNA 损伤和突变等方式[25]，慢性炎症过程会诱发氧化应激并降低细胞抗氧化能力，自由基可导致 DNA 损伤和突变[26]，从而增加胰腺癌的风险。强直性脊柱炎(AS)是一种全身性的自身免疫疾病，长期存在炎症状态，慢性炎症可增加胰腺癌发生的风险，AS 患者免疫系统功能异常，如 T 细胞和细胞因子水平改变，这可能导致监视和清除癌细胞的能力下降。AS 与 HLA-B27 基因相关[27]，HLA-B27 可能影响免疫监视功能[28]。且有研究证明 AS 是胰腺癌的危险因素[29]。

本文所研究的 5 种风湿系统疾病是否与胰腺癌的发病具有因果关系在观察性研究很难得出确定性结论。而孟德尔随机化分析是一种广泛使用的评估因果关系的统计学方法，具有显著优势。首先，可以解决影响观察性研究的许多问题，例如反向因果关系和混杂偏差[30]。其次，研究基于公共数据库，具有巨大的样本量，同时也节省了大量研究成本和研究时间。

然而，本研究也存在一些不足。第一，目前的研究是专门针对欧洲血统或东亚血统的人进行的，未来需要进一步的在国内人群中再次研究加以验证。第二，单一遗传变异可能无法完全反映特定生物指标的复杂性。第三，本研究基于公共数据库，无法对患者一般情况资料进行更详细的亚组分析[31]。

5. 结论

综上所述，本研究采用双样本孟德尔随机化的分析方法，以类风湿性关节炎、骨关节炎、系统性红斑狼疮、强直性脊柱炎、痛风为暴露因素，与其具有强相关的 SNPs 为工具变量，研究证明类风湿性关节炎、骨关节炎、强直性脊柱炎可导致胰腺癌发病风险增加。因此，如果患有以上三种疾病的患者，应该积极治疗和控制炎症，以减少胰腺癌风险。同时，定期进行体检和筛查。

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