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·临床研究·

牙周炎与干燥综合征的因果关系:一项孟德尔随机化研究

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【摘要】　目的　利用孟德尔随机化方法(Mendelian randomization,MR)探索牙周炎与干燥综合征(Sjögren's syndrome,SS)的双向因果关系。**方法**　选取符合同一人种且来自不同地区的牙周炎(*N* = 45 563)及SS(*N* = 214 435)的全基因组关联研究(genome-wide association study,GWAS)数据。采用逆方差加权(inverse variance weighted,IVW)、MR-Egger回归、加权中位数(weighted median,WM)法评估因果效应;采用Cochran's *Q*检验、MR-Egger回归截距项、MR-PRESSO、留一法进行敏感性分析,评估结果的稳定性和可靠性。**结果**　筛选后的SS和牙周炎GWAS数据分别来自芬兰、英国,且均为欧洲人种数据。采用IVW(*OR* = 1.017,95%*CI* = 0.956~1.082)、MR-Egger(*OR* = 0.985,95%*CI* = 0.956 ~ 1.082)、WM(*OR* =1.021, 95%*CI* = 0.948 ~ 1.099)三种方法均未发现SS对牙周炎存在的效应;反之,三种方法(IVW,*OR* = 1.024, 95%*CI* = 0.852~1.230;MR-Egger,*OR* = 0.978, 95% *CI* = 0.789~1.212;WM,*OR* = 1.024,95% *CI* = 0.846 ~ 1.260)亦未发现牙周炎对SS的因果效应。各项敏感性分析表明结果稳定可靠。Cochran's *Q*检验、MR-PRESSO表明纳入的工具变量——单核苷酸多态性(single nucleotide polymorphism,SNP)之间无显著异质性;MR-Egger回归截距项显示纳入的SNP不存在多效性;留一法未发现显著影响结果的SNP。**结论**　MR分析不支持牙周炎与SS之间存在双向因果关联。

【关键词】　牙周炎;　干燥综合征;　孟德尔随机化;　全基因组关联分析;　因果关联;　双向因果;　混杂因素;　逆方差加权
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Bidirectional casual effects between periodontitis and Sjögren's syndrome: a Mendelian randomization study

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【Abstract】　Objective　To evaluate the bidirectional association between periodontitis and Sjögren's syndrome using the Mendelian randomization (MR) method. **Methods**　Genome-wide association study (GWAS) data of periodontitis (*N* = 45 563) and Sjögren's syndrome (*N* = 214 435) were selected to meet the requirements of the same ethnicity and different regions. Inverse variance-weighted (IVW), MR-Egger, and weighted median (WM) tests were used to evaluate the causal effect. Cochran´s *Q* statistics, MR-Egger intercept, MR-PRESSO and leave-one-out analysis were used as sensitivity analyses to assess the stability and reliability of the results. **Results**　After screening, the GWAS data of Sjögren's syndrome were based on the Finnish region, and the periodontitis GWAS data were based on the UK region, both of which originated from European ancestry. Using IVW (*OR* = 1.017, 95% *CI* = 0.956-1.082), MR-Egger (*OR* =

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0.985, 95% *CI*= 0.956-1.082), and WM (*OR* =1.021, 95% *CI* = 0.948-1.099), no causal effect of Sjögren's syndrome on periodontitis was found using any of the three methods. Conversely, no causal effect of periodontitis on Sjögren's syndrome was found (IVW, *OR* = 1.024, 95% *CI* = 0.852-1.230; MR-Egger, *OR* = 0.978, 95% *CI* = 0.789-1.212; WM, *OR* = 1.024, 95% *CI* = 0.846-1.260). The sensitivity analyses indicated that the results were stable and reliable. Cochran's *Q* test and MR-PRESSO revealed that there was no significant heterogeneity among the instrumental variables, which included single nucleotide polymorphisms (SNPs). The intercept of MR-Egger regression indicated no pleiotropy in the included SNPs. No individual SNP was found that significantly affected the results using the leave-one-out method. **Conclusion**　This study does not support a bidirectional causal effect between periodontitis and Sjögren's syndrome.

【Key words】 periodontitis; Sjögren's syndrome; Mendelian randomization; genome-wide association study; causal association; bidirectional casual association; confounder; inverse variance-weighted

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牙周炎是一种菌斑微生态失调与宿主免疫反应异常相互强化导致的慢性系统性感染性炎症性疾病，可导致失牙并影响生活质量[1]。全球重度牙周炎患病率为23.6%[2]，我国重度牙周炎患病率超30%[3]。牙周炎与五十多种系统性疾病相关联，包括炎症性疾病、自身免疫病、肿瘤等，一般通过系统性炎症和感染性转染与系统性疾病产生联系[4]。

干燥综合征（Sjögren's syndrome，SS）是一种以外分泌腺体功能障碍为特征的系统性自身免疫病，可导致口腔干燥、进食障碍、味觉减退等[5]，常与类风湿性关节炎、系统性红斑狼疮等自身免疫病共发。SS在中国和欧洲的患病率分别为0.33%~0.77%[6]，0.04%[7]。近年，SS与牙周炎的关联性研究逐渐增多。一项纳入五项研究的荟萃分析显示，SS患者的牙周炎患病风险较非SS组高1.12倍[8]。另一项系统评价则显示，SS患者的菌斑指数、探诊深度、附着丧失等指标与非SS组无显著性差异[9]。目前，SS是否是牙周炎的风险指标，仍不明确。一些研究表明，牙周炎可能加重某些自身免疫病的风险，如类风湿性关节炎[10]、系统性红斑狼疮[11]。然而，牙周炎是否与SS的患病风险相关，则研究极少。一项回顾性队列研究发现，牙周炎患者后续发生SS的风险增加约50%，在调整吸烟、饮酒等协变量后该风险水平下降[12]。总之，探究二者双向关系的研究较少，证据级别不高，或研究之间存在较大异质性。探索这一问题，有助于为牙周炎与SS等自身免疫病共发的患者的临床诊治提供参考。

既往探索牙周炎与SS的关联性研究均采用传统临床研究设计方法，大部分为观察性研究，存在样本量小、混杂因素不可控、无法随机分配疾病等问题。孟德尔随机化（Mendelian randomization，MR）分析是一种探索疾病间因果关系的新方法，使用全基因组关联研究（genome-wide association study，GWAS）数据，以单核苷酸多态性（single nucleotide polymorphism，SNP）等遗传变异作为工具变量（instrumental variable，Ⅳ），利用配子形成时的随机分配以模拟疾病的随机分配过程。而且，该方法基于的GWAS数据样本量一般较大，可进行双向因果关联分析。本文拟通过MR分析，探究牙周炎和SS的双向因果关系。

1　资料和方法

1.1　GWAS数据源

为避免人群分层（即SNP与表型的关联在不同种族之间存在异质性）引起的偏倚，应选取不同地区的同种族GWAS数据，以获得不重叠的样本。据此，对牙周炎和SS相关的GWAS开放数据进行全面检索（表1），最终纳入两份无样本重叠的欧洲人种数据。

牙周炎的GWAS数据来自英国的Gene-Lifestyle Interactions in Dental Endpoints（GLIDE）联盟，共45 563例样本，包括17 353例牙周炎病例和28 210例对照[13]。牙周炎的诊断主要采用了CDC/AAP标准，包括社区牙周指数、探诊深度等指标[14]。SS的GWAS数据来自芬兰的FinnGen数据库，含214 435例样本，包括1 290例SS患者和213 145例对照[15]。

表1　相关表型的全基因组关联研究数据信息汇总

Table 1　Summary information of GWAS data for relevant phenotypes

Target phenotype	Database	Term	Data source/Phenotype code	Race	Region	Used
Periodontitis	GWAS Catalog	Periodontitis	Exome sequencing and analysis of 454 787 UK Biobank participants	EU	UK	×
			A generalized linear mixed model association tool for biobank-scale data	EU	UK	×
	PubMed	Periodontitis & genome-wide association	Genome-wide analysis of dental caries and periodontitis combining clinical and self-reported data	EU	UK	√
Sjogren syndrome	GWAS Catalog	Sjogren syndrome	A generalized linear mixed model association tool for biobank-scale data	EU	UK	×
			Computationally efficient whole-genome regression for quantitative and binary traits	EU	UK	×
	IEU Open GWAS project	Sicca syndrome	https://www.finngen.fi/en/access_results	EU	FIN	√

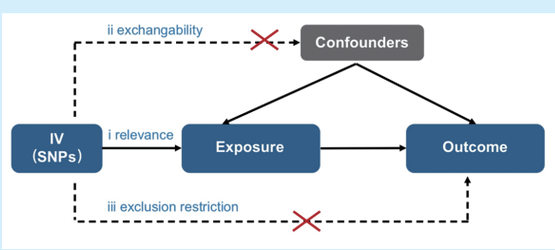
GWAS: genome-wide association study. IEU: integrative epidemiology unit. EU: European. UK: the United Kingdom. FIN: Republic of Finland

1.2　工具变量的筛选

为建立稳健的MR模型，被选为工具变量的SNP需满足三个假设（图1）：①关联性，所选SNP须与暴露存在一定的关联强度；②独立性，SNP与任何参与“暴露→结局”通路的混杂因素无关联；③排他性，SNP仅通过作用于暴露而影响研究结局，即SNP无显著的水平多效性[16]。

为满足关联性假设并获取分析所需数量的SNP，纳入的SNP有全基因组意义（$P<5\times10^{-6}$）。为保证工具变量强度，采用以下列公式计算F值，纳入$F>10$的SNP：$F=\left(\frac{\hat{\beta}x}{SE(\hat{\beta}x)}\right)$[17]。$\hat{\beta}x$（SNP与暴露的关联强度估计值），SE（标准误）。

为确保SNP的独立性，筛选$r^2<0.01$的SNP，且要求每两个SNP之间的物理距离>10 000 kb，以避免SNP之间物理位置临近所致的连锁不平衡。采用MR-Egger回归的截距项评估SNP的排他性，并剔除有显著水平多效性的SNP。



SNP: single nucleotide polymorphism. Ⅳ: instrumental variable

Figure 1　Three basic assumptions to be satisfied by instrumental variables selected

图1　工具变量需满足的三个假设

1.3　MR分析

采用逆方差加权（inverse variance weighted，IVW）、MR-Egger回归、加权中位数（weighted median，WM）3种方法评估牙周炎与SS之间的因果效应。IVW法对每个IV的Wald比值加权，要求使用的SNP均满足MR的三个假设，较MR Egger回归、WM法有较高的统计效力[18]。

为确保所选用的SNP符合MR的三个假设，进行多种敏感性分析，包括异质性检验、多效性检验和留一法（leave-one-out）分析；其中异质性检验包括Cochran's Q检验及多效性残差和异常值法（MR-pleiotropy residual sum and outlier，MR-PRESSO）；Cochran's Q统计量是IVW估计值的方差加权，$P>0.05$说明SNP之间不存在显著的异质性；MR-PRESSO检测到造成异质性的SNP离群值时（$P<0.05$），则剔除该离群值后再次分析。多效性检验以MR-Egger回归的截距项评估，若截距项的95% CI包括原点，即认为没有水平多效性[19]。留一法通过逐一去除各个SNP并计算剩余SNP的合并效应，分别评估每个SNP对总因果效应的影响。

1.4　统计学分析

使用R软件（version 4.1.1）中的Two Sample MR工具包（version 0.5.6）和MR-PRESSO工具包（version 1.0）进行统计学分析。使用比值比（odds ratio，OR）描述因果效应。除特殊说明，统计学检验水准为$\alpha=0.05$。

2　结　果

2.1　工具变量筛选结果

根据工具变量筛选标准，以SS作为暴露工具

变量时提取到9个SNP;以牙周炎作为暴露工具变量时共获取6个SNP作为工具变量(表2、表3)。

2.2　SS与牙周炎的双向因果效应分析

IVW结果显示,SS对牙周炎无因果效应(*OR* = 1.017, 95% *CI* = 0.956 ~ 1.082, *P* = 0.592)。反之,牙周炎对SS的因果效应亦无显著性(*OR* = 1.024, 95% *CI* = 0.852 ~ 1.230, *P* = 0.802)。MR Egger、WM法进行双向分析所得结果与IVW法一致(表4)。

表2　SS作为暴露工具变量时所纳入的SNP信息

Table 2　Information of SNPs selected as instrumental variable of exposure from Sjögren's syndrome

SNP	EA	OA	*F*	Sjögren's syndrome			Periodontitis		
				β	*SE*	*P*	*β*	*SE*	*P*
rs116898071	G	A	22.1	0.999	0.212	2.57×10^{-6}	−0.013	0.117	0.909
rs12888138	T	C	22.5	−0.246	0.052	2.09×10^{-6}	0.033	0.020	0.101
rs13289503	C	T	25.9	−0.224	0.044	3.67×10^{-7}	−0.019	0.020	0.347
rs2307308	T	C	21.5	0.423	0.091	3.48×10^{-6}	−0.078	0.056	0.163
rs2853986	C	T	109.2	0.775	0.074	1.43×10^{-25}	0.028	0.040	0.493
rs34831921	A	C	36.8	−0.372	0.061	1.31×10^{-9}	−0.026	0.036	0.469
rs4630834	T	C	21.9	0.191	0.041	2.97×10^{-6}	0.002	0.018	0.905
rs496315	C	T	30.5	0.225	0.041	3.21×10^{-8}	−0.001	0.024	0.971
rs76882717	T	C	21.2	0.430	0.093	4.05×10^{-6}	−0.017	0.031	0.586

SS: Sjögren's syndrome. SNP: single nucleotide polymorphism. EA: effect allele. OA: other allele. *β*: effect size. *SE*: standard error

表3　牙周炎作为暴露工具变量时所纳入的SNP信息

Table 3　Information of SNPs selected as instrumental variable of exposure from periodontitis

SNP	EA	OA	*F*	Periodontitis			Sjögren's syndrome		
				β	*SE*	*P*	*β*	*SE*	*P*
rs116898071	A	G	24.1	−0.084	0.017	8.66×10^{-7}	−0.001	0.042	0.983
rs12888138	T	C	24.3	1.639	0.332	8.20×10^{-7}	0.055	0.178	0.760
rs13289503	T	C	22.8	−0.367	0.077	1.75×10^{-6}	−0.010	0.141	0.944
rs2307308	A	G	22.4	0.832	0.176	2.22×10^{-6}	−0.174	0.276	0.527
rs496315	A	G	22.7	−0.176	0.037	1.94×10^{-6}	0.041	0.071	0.565
rs76882717	T	C	22.2	0.077	0.016	2.37×10^{-6}	0.071	0.043	0.097

SNP: single nucleotide polymorphism. EA: effect allele. OA: other allele. *β*: effect size. *SE*: standard error

表4　SS与牙周炎的双向因果效应分析结果

Table 4　The results of bidirectional casual association analysis between Sjögren's syndrome and periodontitis

Exposure	Outcome	Methods	*OR*	95%*CI*	*P*
Sjögren's syndrome	Periodontitis	IVW	1.017	0.956-1.082	0.592
		MR Egger	0.985	0.850-1.141	0.841
		Weighted Median	1.021	0.948-1.099	0.586
Periodontitis	Sjögren's syndrome	IVW	1.024	0.852-1.230	0.802
		MR Egger	0.978	0.789-1.212	0.848
		Weighted Median	1.032	0.846-1.260	0.756

SS: Sjögren's syndrome. IVW: inverse variance weighted

2.3　敏感性分析

对纳入的工具变量(SNP)进行异质性检验及多效性分析。以SS为暴露,牙周炎为结局时,使用Cochran's Q进行异质性检验,结果显示纳入的SNP之间没有异质性(*P* > 0.05)。MR-PRESSO全局检验显示,纳入的SNP不存在显著异质性(*P* > 0.05)。MR-Egger回归截距项检验表明,水平多效性不会造成MR分析效应量的偏倚(*P* > 0.05)。以牙周炎为暴露,SS为结局,进行以上敏感性分析,均未发现显著异质性及水平多效性(表5)。留一法分析(即逐个剔除纳入的SNP再分析)发现,没有单个SNP可对MR分析的效应量产生显著影响(图2)。

3　讨　论

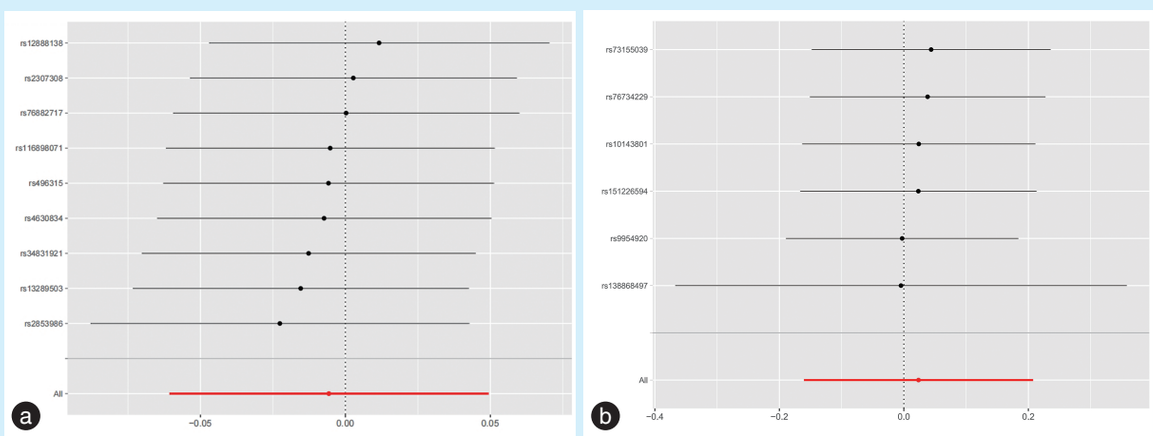
基于公开的大样本GWAS数据,首次采用孟德尔随机化分析方法,探索牙周炎与SS的双向因果关联,以较严格的系列标准筛选满足MR三项假

表5　双向孟德尔随机化分析敏感性检验结果

Table 5　The results of sensitivity analyses of MR analysis

Exposure	Outcome	Heterogeneity		Pleiotropy
		Cochran's Q(*P*)	MR-PRESSO-*P*	MR Egger(*P*)
Sjögren's syndrome	Periodontitis	12.685 (0.177)	0.207	−0.006 (0.756)
Periodontitis	Sjögren's syndrome	3.521 (0.620)	0.771	0.025 (0.460)

MR: Mendelian randomization



a: Sjögren's syndrome as exposure. b: periodontitis as exposure. The column represents each included SNP. The abscissa represents the confidence interval for causal effects obtained after removing the SNP. All represents the causal effect confidence interval obtained by integrating all SNPs. SNP: single nucleotide polymorphism

Figure 2　Leave-one-out tests for the sensitivity of Mendelian randomization analysis

图2　Leave-one-out法检验孟德尔随机化分析的敏感性

设的工具变量，多种敏感性测试表明分析结果可靠。结果显示，牙周炎与SS不存在显著的双向因果关联。

目前，SS并非牙周炎的危险因素这一观点得到较多研究支持。有临床研究发现，SS患者的探诊深度、附着丧失等指标与非SS组无显著差异[9]；另有干预性研究发现，经毛果芸香碱治疗后，SS患者唾液流速及流量增加，但牙周指标并未改善[20]。亦有研究支持SS为牙周炎的风险因素。一项纳入五项研究的荟萃分析显示，SS患者的牙周炎患病风险较健康对照组高1.12倍（*OR* = 2.12, 95% *CI* = 1.43 ~ 3.17）。然而，该证据的可靠性较低，牙周炎的关键指标探诊深度在两组间无明显差异，附着丧失合并值的95% *CI*下限为0[8]。另一方面，尚少有研究调查牙周炎是否为SS的风险因素。一项回顾性队列研究发现，牙周炎患者后续发生SS风险增加了约50%，但在调整吸烟、饮酒等协变量后该风险水平下降[12]。

总体而言，牙周炎与SS之间的关联尚未有明确定论，主要存在以下问题。① SS和牙周炎存在共同的风险因素（如吸烟、高脂血症等）[21]，这些风险因素作为混杂变量可造成结果偏倚[12]；②牙周炎和SS均为系统性疾病，常与其他疾病共发[22-25]，这些共发病可能使两者产生间接关联[26]。例如，4% ~ 31%的SS患者伴发类风湿关节炎，后者又是牙周炎的风险因素[27]；③针对牙周炎和SS的关联性研究大多是横断面调查及病例对照研究[9]，样本量受限，难以排除混杂因素，存在反向因果效应等影响；④二者均为系统性慢性疾病，从伦理角度考虑，不适合开展长期随访的队列研究；⑤模拟两种疾病共发的动物模型研究和体外实验很少，缺乏机制性研究支持。

基于本MR分析得出的牙周炎与SS缺乏双向因果联系的发现，除了印证现有临床研究的整体性结论，至少有如下启示。①牙周炎与SS的患病率存在明显差距[28]，牙周炎患者伴发SS的概率明显小于SS患者伴发牙周炎的概率。对于SS患者伴发牙周炎的情况，临床层面尚不能认为前者是后者的潜在风险，两种疾病以分别防治为主。即便如此，由于SS患者的治疗药物多为糖皮质激素、

免疫抑制剂等[28]，这类免疫抑制剂可能增加牙周炎的风险或对牙周治疗预后造成影响；② SS与牙周炎均为宿主免疫反应异常导致的疾病[29]，两者缺乏因果效应暗示其背后的异常免疫反应缺乏直接联系；③ SS和牙周炎均有一定的遗传易感性，两种疾病在遗传变异方面可能有明显异质性。而且，相对于传统的临床研究，MR分析存在不少优势。①能够有效避免反向因果效应。既往病例对照中所观察到的现象仅能提供二者的潜在关联性，无法确定两种疾病的先后顺序，因此可能导致反向因果；②由于遗传变异在配子形成时既已决定，先于混杂因素对个体的作用，因此MR分析理论上能有效避免各种混杂因素的干扰；③从配子形成到慢性病发生本身就是一种长期的“观察”，MR分析所采用的工具变量不受干预性研究的影响，此种回溯性规避了长期随访的伦理风险。；④MR分析是基于遗传变异的随机分配原则之上的，因此其证据级别高于观察性研究。

本研究存在一些局限性。首先，SS患病率与性别相关，本研究受限于数据集，无法对牙周炎和SS分别进行性别分层分析。然而，SS在女性中的患病率远高于男性（9∶1），说明性别因素对结果造成的偏倚可能很小[20]，使用性别分层数据或能取得更为稳健的阴性结果。其次，亚洲人群GWAS数据较少，本研究采用的GWAS数据库均源自欧洲人群。一项基于中国人群的横断面调查结果显示，SS患者的牙周及无牙颌情况与无系统性疾病的健康人群相比无显著差异（$P>0.05$），SS并未增加牙周炎的患病风险[30]，与本研究基于欧洲人种的分析结果一致。然而，本研究结论是否可向欧洲种族以外的人群推广仍待验证。

综上，MR分析不支持牙周炎与SS之间存在双向的因果关联，该结论是否可向欧洲种族以外的人群推广仍待验证。

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