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·临床研究·

# 牙周炎与哮喘的因果关系:一项两样本孟德尔随机化研究

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**【摘要】　目的**　通过双样本孟德尔随机化法(Mendelian randomization,MR)探究牙周炎与哮喘的双向因果关系,为牙周炎和哮喘的病因探索和防治措施制定提供基础。**方法**　使用公开发布的欧洲人种的牙周炎($n$ = 34 615)与哮喘($n$ = 408 422)的全基因组关联研究(genome-wide association studies,GWAS)统计数据进行了两样本双向孟德尔随机化分析。以逆方差加权法(inverse variance weighted,IVW)作为主要MR分析方法来估计牙周炎与哮喘之间的双向因果效应,同时采用加权中位数法(weighted median,WM)、MR-Egger回归法、最大似然法(maximum likelihood)和孟德尔随机化稳健调整特征评分法(Mendelian randomization robust adjusted profile score,MR-RAPS)作为补充分析,并通过Cochran's $Q$检验、孟德尔随机化多效性残差与离群值检测(Mendelian randomization pleiotropy residual sum and outlier,MR-PRESSO)和留一法进行敏感性分析。**结果**　最终分别有12个和43个单核苷酸多态性(single nucleotide polymorphism,SNP)被纳入作为牙周炎和哮喘的工具变量。IVW、WM、MR-Egger回归、最大似然法和MR-RAPS的结果表明,在欧洲人群中,牙周炎对哮喘发病无因果关系(IVW:$OR$=1.003,95%$CI$=0.973-1.035,$P$ = 0.828;WM:$OR$=0.990,95%$CI$=0.951-1.031,$P$ = 0.641;MR-Egger回归:$OR$=0.988,95%$CI$=0.960-1.028,$P$ = 0.573;最大似然法:$OR$=1.003,95%$CI$=0.972-1.035,$P$ = 0.834;MR-RAPS:$OR$=1.002,95%$CI$=0.970-1.036,$P$ = 0.890);哮喘对牙周炎也无因果关系(IVW:$OR$=1.021,95%$CI$=0.938-1.111,$P$=0.633;WM:$OR$=1.011,95%$CI$=0.894-1.142,$P$ = 0.866;MR-Egger回归:$OR$=1.042,95%$CI$=0.824-1.319,$P$ = 0.731;最大似然法:$OR$=1.021,95%$CI$=0.938-1.112,$P$ = 0.631;MR-RAPS:$OR$=1.017,95%$CI$=0.931-1.110,$P$ = 0.713)。Cochran's $Q$检验表明纳入的工具变量之间不具有异质性,MR-PRESSO检验显示不存在水平多效性,留一法也未发现离群SNP。**结论**　基于欧洲人群遗传数据的MR研究表明,牙周炎与哮喘发病之间不存在双向的因果关系。

**【关键词】**　牙周炎；　哮喘；　孟德尔随机化；　全基因组关联分析；　单核苷酸多态性；　因果关联；　双向因果；　工具变量；　敏感性分析
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**Causal relationship between periodontitis and asthma: a two-sample Mendelian randomization study**

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**【Abstract】　Objective**　To explore the bidirectional causal relationships between periodontitis and asthma using the

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two-sample Mendelian randomization (MR) method to provide a basis for exploring the etiology and formulating preventive and therapeutic measures of periodontitis and asthma. **Methods** We performed two-sample bidirectional Mendelian randomization analysis using publicly released European genome-wide association studies (GWAS) statistics for periodontitis ($n$ = 34 615) and asthma ($n$ = 408 422). The inverse variance weighted (IVW) method was employed as the main approach to estimate the bidirectional causal relationships between periodontitis and asthma. In addition, weighted median (WM), MR-Egger regression, maximum likelihood, and Mendelian randomization robust adjusted profile score (MR-RAPS) were used as supplementary analyses. Sensitivity analyses were conducted using Cochran's $Q$ test, Mendelian randomization pleiotropy residual sum and outlier (MR-PRESSO), and leave-one-out analysis. **Results** A total of 12 and 43 single-nucleotide polymorphisms (SNPs) were included as instrumental variables for periodontitis and asthma, respectively. The results of IVW, WM, MR-Egger regression, maximum likelihood, and MR-RAPS showed that periodontitis was not causally related to the risk of asthma (IVW: *OR*: 1.003, 95% *CI*: 0.973-1.035, $P$ = 0.828, WM: *OR*: 0.990, 95% *CI*: 0.951-1.031, $P$ = 0.641; MR-Egger regression: *OR*: 0.988, 95% *CI*: 0.960-1.028, $P$ = 0.573; maximum likelihood: *OR*: 1.003, 95% *CI*: 0.972-1.035, $P$ = 0.834; MR-RAPS: *OR*: 1.002, 95% *CI*: 0.970-1.036, $P$ = 0.890) among the European population, and no causal effect of asthma on periodontitis was found (IVW: *OR*: 1.021, 95% *CI*: 0.938-1.111, $P$ = 0.633, WM: *OR*: 1.011, 95% *CI*: 0.894-1.142, $P$ = 0.866; MR-Egger regression: *OR*: 1.042, 95% *CI*: 0.824-1.319, $P$ = 0.731; maximum likelihood: *OR*: 1.021, 95% *CI*: 0.938-1.112, $P$ = 0.631; MR-RAPS: *OR*: 1.017, 95% *CI*: 0.931-1.110, $P$ = 0.713) among the European population. Cochran's $Q$ test showed no heterogeneity among the included instrumental variables, MR-PRESSO test found no horizontal pleiotropy, and the leave-one-out method did not identify outlier SNPs. **Conclusion** The results of this study, based on European genetic data, do not support a bidirectional causal association between periodontitis and asthma in the European population.

**【Key words】** periodontitis; asthma; Mendelian randomization; genome-wide-association study; single nucleotide polymorphism; causal association; bidirectional casual association; instrumental variable; sensitivity analysis

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牙周炎是一种以牙齿支持组织的炎症为特征的疾病，可导致牙周膜和牙槽骨的破坏，甚至牙齿脱落。据统计，全球范围内，重度牙周炎的患病率高达11.2%，已成为世界第六大流行疾病[1]。这种由厌氧菌为主要致病菌引起的炎性感染性疾病，与心血管疾病、糖尿病、类风湿性关节炎、呼吸系统疾病、肾脏疾病和癌症等多种全身性疾病密切相关[2-3]。尽管哮喘被认为是一种具有类似于慢性炎症性质的全身性疾病，但其与牙周炎的联系尚不明确。然而，越来越多的研究揭示了牙周炎与哮喘之间存在一定的关联性[4-8]。

哮喘（asthma）是一种以炎症和支气管收缩为特征的慢性气道疾病，可影响各年龄段的人群[9]。据估计，欧洲目前有超过2 500万哮喘患者，且哮喘的发生与社会经济状况无关[10]。近期一项涉及457例患者的病例对照研究证实，牙周炎致病菌中的中间普氏菌与哮喘相关[4]。研究发现，哮喘患者同时伴发牙周炎的概率比没有这种呼吸系统疾病的对照组高3倍以上[11]。然而，Rivera等[12]的研究指出，牙周炎患者患哮喘的可能性较低，并且在使用哮喘药物作为结果变量时，发现了更明显的逆相关证据。尽管哮喘和牙周炎之间的关系已在多项研究中得到了探讨，但结论并不一致。许多研究在样本量、个体对治疗的反应调查以及分析模型中对混杂因素的控制方面存在局限性。哮喘和牙周炎之间的因果关系可能受到多种混杂因素的影响，例如长期使用药物的哮喘患者可能增加对牙周病的易感性[13]。由于观察性研究可能因方法学限制而产生偏倚，包括潜在未知混杂因素的影响、反向因果关系的干扰以及测量误差，因此牙周炎与哮喘之间的确切联系需要进一步的研究来证实。

孟德尔随机化（Mendelian randomization，MR）是一种基于遗传变异的因果推断方法，旨在利用遗传变异作为目标暴露的工具变量来推断暴露因素与研究结果之间的因果关系[14-15]，从而克服观察

流行病学的局限性。最常用的MR方法是基于全基因组关联研究(genome-wide association study, GWAS)鉴定的单核苷酸多态性(single nucleotide polymorphism, SNP)的推断[16]。可供公众查阅的全球GWAS汇总统计数据的增加为这一方法的应用提供了便利。本研究通过在欧洲血统人群中使用双向双样本MR方法调查牙周炎和哮喘之间的潜在因果关系。

## 1　资料和方法

### 1.1　研究设计

本研究选择代表遗传变异的SNP作为工具变量,进行双向双样本MR分析。此分析基于3个关键假设[17]:①工具变量与暴露因素直接相关;②工具变量独立于任何混杂因素;③工具变量仅通过暴露因素影响结果(图1)。本研究使用GWAS的汇总统计数据进行两次MR分析,探究牙周炎和哮喘之间的双向关联。在正向MR分析中,将牙周炎作为暴露因素,哮喘作为结局;在反向MR分析中,将哮喘作为暴露因素,牙周炎作为结局。

### 1.2　工具变量的筛选

本研究从两个不同的GWAS汇总统计数据中选择合适的工具变量。通过设置$P<5\times10^{-8}$作为筛选标准,并使用$r^2<0.001$和遗传距离>10 000 kb为阈值去除连锁不平衡,从而确定合适的SNP,其中连锁不平衡根据欧洲人群的千人基因组计划参考面板估算得到。然后,本研究在整合暴露和结局数据的过程中,依次去除等位基因不一致的以及不能判断等位基因方向的回文SNP(A/T, C/G等位基因的SNP)[18]。此外,为了评估工具变量的强度并避免弱工具变量偏差,计算每个工具变量的$F$统计量:$F=\beta^2/SE^2$[19]。$F$值越高,说明发生弱工具偏倚的可能性越小,$F>10$认为工具变量没有弱变量偏移[20]。

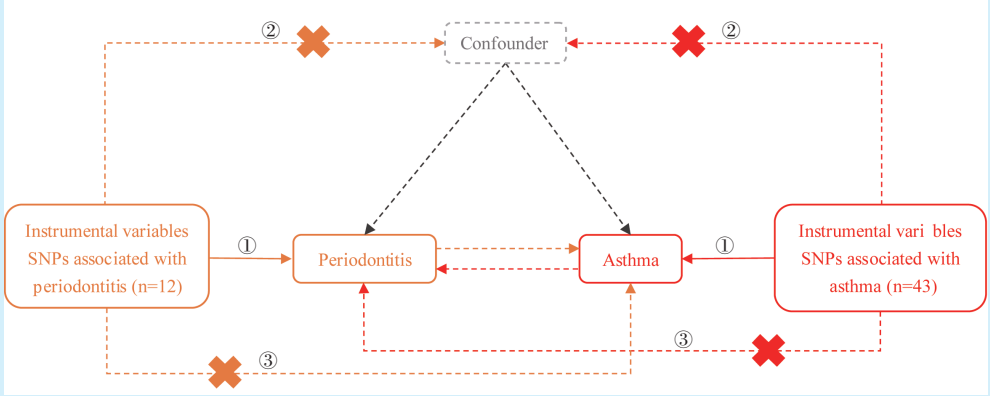
### 1.3　数据来源

牙周炎的汇总统计数据来自英国的Gene-Lifestyle Interactions in Dental Endpoints(GLIDE)联盟,该数据库是现有样本量最大的牙周炎GWAS数据库,其中包括17 353例临床诊断病例和28 210例对照[21]。由于人群中排除西班牙裔和拉丁裔背景,本研究最终分析了12 289例临床诊断病例与22 326例对照。哮喘数据的结果汇总统计量来自Valette等[22]的一项GWAS(56 167例病例和352 255例对照)。在MR-Base NHGRI-EBI GWAS目录(https://gwas.mrcieu.ac.uk/)能够获取到可用的GWAS汇总统计信息。从仅包括欧洲血统人群的研究中检索了随附的汇总数据。

### 1.4　MR分析

本研究采用逆方差加权(inverse variance weighted, IVW)法作为主要MR分析方法来估计暴露和结局之间的因果效应[23-24]。同时,采用加权中位数(weighted median, WM)法[25]、MR-Egger回归法[26]、最大似然法(maximum likelihood)[27]和孟德尔随机化稳健调整特征评分(Mendelian randomization robust adjusted profile score, MR-RAPS)作为补充分析。

IVW法的基本原理是利用Wald比值法估计每个遗传工具变量针对暴露因素和结局变量的因果效应,并使用荟萃分析方法将每个工具变量的Wald效应估计值进行合并得到因果效应估计量[23]。WM法在无效工具变量比例高达50%的情况下,仍能提供稳健且准确的结论[24];与IVW相




Mendelian randomization requires valid genetic instrumental variants that satisfy three assumptions: ① genetic variants are related to exposure; ② genetic variants are independent of confounders; ③ genetic variants affect the risk of outcome completely through exposure, rather than alternative pathways. SNP: single nucleotide polymorphism

Figure 1　Schematic of the bidirectional Mendelian randomization design

**图1**　双向孟德尔随机化设计示意图

比，MR-Egger回归法在回归分析中纳入了截距项，允许通过截距项对水平多效性进行量化，若截距检验的*P*值小于0.05，则表明存在水平多效性[26]；最大似然法在SNP暴露效应存在测量误差时，能够提供更为可靠的估计[27]；而MR-RAPS法即使在某些违反MR研究假设的情况下（例如水平多效性和弱工具变量），也能得出稳健的分析结果[28]。

### 1.5　敏感性分析

采用Cochran's *Q*检验、孟德尔随机化多效性残差与离群值检测方法（Mendelian randomization pleiotropy residual sum and outlier，MR-PRESSO）[28]和留一法进行敏感性分析。Cochran's *Q*检验判断SNP的异质性[24]，若*P* > 0.05，表明结果不存在异质性，采用固定效应IVW法，反之采用随机效应IVW法；使用MR-PRESSO全局检验来评估是否存在总体水平多效性[29]；利用留一法逐个剔除每个工具变量SNP，进而计算剩余SNP的因果效应估计值，从而检验单个工具SNP是否对总的因果效应估计具有驱动作用。

### 1.6　统计学分析

本研究使用MR研究计算平台（http://cnsgenomics.com/shiny/mRnd/）进行功效计算，以验证任何阳性结果[30]。所有统计分析均在R软件（版本4.1.2）中使用“TwoSampleMR”、“MR-RAPS”和“MRPRESSO”软件包进行。检验水准α=0.05。

## 2　结　果

### 2.1　工具变量的特点

在牙周炎对哮喘的MR分析中，由于没有*P*值小于$5\times10^{-8}$的SNP，将阈值扩大到$1\times10^{-5}$，共纳入12个SNP作为牙周炎的工具变量，具体信息如表1所示。12个SNP的*F*值范围在19.717～24.304，均大于10，表明弱工具变量偏倚存在的可能性较小。

在哮喘对牙周炎的MR分析中，共纳入了43个SNP作为哮喘的工具变量，具体信息如表2所示。43个SNP的*F*值范围在29.858～251.458，均大于10，表明弱工具变量偏倚存在的可能性较小。

### 2.2　牙周炎与哮喘的双向因果效应分析

使用不同MR方法对牙周炎与哮喘之间的双向因果关系的分析结果如表3所示。Cochran's *Q*检验表明，牙周炎的工具变量之间不存在异质性（*Q* = 10.99，*P* = 0.444），因此本研究采用固定效应模型的IVW计算MR效应值。固定效应IVW主要分析结果显示，遗传预测牙周炎对哮喘的发生没有显著影响（*OR* = 1.003，95%*CI* = 0.973-1.035，*P* = 0.828）。此外，WM（*OR* = 0.990，95%*CI* = 0.951-1.031，*P* = 0.641）、MR-Egger回归（*OR* = 0.988，95%*CI* = 0.960-1.028，*P* = 0.573）、最大似然法（*OR* = 1.003，95%*CI* = 0.972-1.035，*P* = 0.834）和MR-RAPS（*OR* = 1.002，95%*CI* = 0.970-1.036，*P* = 0.890）的分析结果也表明，遗传预测牙周炎对哮喘的发生没有显著影响，与IVW主要分析的结果一致。SNPs对牙周炎和哮喘的因果估计影响大小的散点图结果显示，牙周炎的总效应和哮喘的发生风险之间不存在显著的因果关系（图2）。

**表1**　牙周炎作为暴露工具变量时所纳入的SNP信息

Table 1　Information on SNPs selected as instrumental variables of exposure to periodontitis

| SNPs | EA | OA | Exposure(periodontitis) | | | Outcome(asthma) | | | *F* |
|---|---|---|---|---|---|---|---|---|---|
| | | | *β* | *SE* | *P* | *β* | *SE* | *P* | |
| rs10143801 | A | G | −0.084 | 0.017 | < 0.001 | −0.002 | 0.007 | 0.794 | 24.131 |
| rs12438274 | T | G | −0.088 | 0.020 | < 0.001 | −0.010 | 0.009 | 0.239 | 20.227 |
| rs13220384 | A | C | 0.108 | 0.024 | < 0.001 | −0.009 | 0.010 | 0.361 | 20.100 |
| rs138868497 | T | C | 1.639 | 0.332 | < 0.001 | −0.016 | 0.038 | 0.676 | 24.304 |
| rs139182625 | T | C | 0.102 | 0.023 | < 0.001 | 0.001 | 0.009 | 0.929 | 19.762 |
| rs151226594 | T | G | −0.367 | 0.077 | < 0.001 | −0.051 | 0.026 | 0.055 | 22.848 |
| rs184267209 | A | G | 0.246 | 0.055 | < 0.001 | 0.026 | 0.023 | 0.254 | 19.717 |
| rs3779291 | T | C | −0.098 | 0.022 | < 0.001 | 0.001 | 0.009 | 0.920 | 20.106 |
| rs72712882 | A | G | −0.131 | 0.029 | < 0.001 | −0.002 | 0.011 | 0.861 | 20.564 |
| rs73155039 | A | G | 0.832 | 0.176 | < 0.001 | −0.037 | 0.028 | 0.191 | 22.402 |
| rs76734229 | A | G | −0.176 | 0.037 | < 0.001 | −0.014 | 0.011 | 0.224 | 22.652 |
| rs9954920 | T | C | 0.077 | 0.016 | < 0.001 | 0.004 | 0.007 | 0.562 | 22.258 |

SNP: single nucleotide polymorphism; EA: effect allele; OA: other allele; *SE*: standard error. *F* value for these 12 SNPs ranged from 19.717 to 24.304, with all the values greater than 10, indicating a low likelihood of weak instrument variable biases

Cochran's *Q*检验表明哮喘的工具变量之间不存在异质性（*Q* = 47.11，*P* = 0.272），因此本研究采用固定效应模型的IVW计算MR效应值。固定效应IVW主要分析结果显示，遗传预测哮喘对牙周炎的发生没有显著影响（*OR* = 1.021，95%*CI* = 0.938-1.111，*P* = 0.633）。此外，WM（*OR* = 1.011，95%*CI* = 0.894-1.142，*P* = 0.866）、MR-Egger回归（*OR* = 1.042，95%*CI* = 0.824-1.319，*P* = 0.731）、最大似然法（*OR* = 1.021，95%*CI* = 0.938-1.112，*P* = 0.631）和MR-RAPS（*OR* = 1.017，95%*CI* = 0.931-1.110，*P* = 0.713）的分析结果也表明遗传预测哮喘对牙周炎的发生没有显著影响，与IVW主要分析结果一致。SNPs对哮喘和牙周炎的因果估计影响大小的散点图显示，哮喘的总效应和牙周炎的发生风险之间不存在显著的因果关系（图3）。

表2　哮喘作为暴露工具变量时所纳入的SNP信息

Table 2　Information on SNPs selected as instrumental variables of exposure to asthma

| SNPs | EA | OA | Exposure (asthma) | | | Outcome (periodontitis) | | | *F* |
|---|---|---|---|---|---|---|---|---|---|
| | | | *β* | *SE* | *P* | *β* | *SE* | *P* | |
| rs10477741 | G | T | 0.074 | 0.010 | < 0.001 | −0.029 | 0.025 | 0.247 | 57.467 |
| rs10486391 | G | A | −0.039 | 0.007 | < 0.001 | −0.031 | 0.016 | 0.049 | 34.141 |
| rs11042902 | T | C | 0.041 | 0.007 | < 0.001 | 0.019 | 0.018 | 0.291 | 33.780 |
| rs11071559 | T | C | −0.085 | 0.010 | < 0.001 | −0.005 | 0.022 | 0.818 | 75.219 |
| rs11178649 | T | G | −0.043 | 0.007 | < 0.001 | −0.004 | 0.016 | 0.795 | 41.704 |
| rs112119265 | G | T | −0.078 | 0.014 | < 0.001 | 0.004 | 0.034 | 0.899 | 31.747 |
| rs112267124 | A | G | 0.043 | 0.008 | < 0.001 | 0.007 | 0.019 | 0.727 | 31.023 |
| rs113981909 | A | G | −0.061 | 0.011 | < 0.001 | 0.040 | 0.026 | 0.121 | 34.023 |
| rs117552144 | T | C | 0.079 | 0.014 | < 0.001 | 0.149 | 0.062 | 0.016 | 33.155 |
| rs117710327 | A | C | −0.126 | 0.013 | < 0.001 | −0.085 | 0.045 | 0.056 | 89.053 |
| rs11816044 | A | G | −0.047 | 0.007 | < 0.001 | −0.023 | 0.016 | 0.158 | 45.964 |
| rs12165508 | C | T | −0.045 | 0.008 | < 0.001 | 0.028 | 0.018 | 0.118 | 31.127 |
| rs12365699 | A | G | −0.054 | 0.009 | < 0.001 | 0.002 | 0.022 | 0.916 | 37.043 |
| rs12964116 | G | A | 0.108 | 0.018 | < 0.001 | 0.020 | 0.050 | 0.683 | 37.169 |
| rs13277355 | G | A | −0.041 | 0.007 | < 0.001 | 0.015 | 0.018 | 0.408 | 30.648 |
| rs1444782 | A | G | −0.095 | 0.007 | < 0.001 | 0.002 | 0.016 | 0.906 | 209.120 |
| rs1608555 | T | C | 0.038 | 0.007 | < 0.001 | −0.015 | 0.017 | 0.355 | 30.618 |
| rs1837253 | C | T | 0.108 | 0.007 | < 0.001 | 0.001 | 0.017 | 0.948 | 209.845 |
| rs1870140 | G | A | −0.050 | 0.009 | < 0.001 | −0.055 | 0.022 | 0.013 | 30.169 |
| rs2412099 | A | G | −0.051 | 0.007 | < 0.001 | −0.007 | 0.016 | 0.640 | 59.919 |
| rs2477923 | C | T | −0.036 | 0.007 | < 0.001 | 0.011 | 0.016 | 0.500 | 30.334 |
| rs2800040 | A | G | −0.038 | 0.007 | < 0.001 | 0.017 | 0.018 | 0.355 | 30.016 |
| rs28498223 | T | C | 0.050 | 0.007 | < 0.001 | −0.001 | 0.017 | 0.944 | 46.226 |
| rs3024971 | G | T | −0.112 | 0.011 | < 0.001 | −0.010 | 0.026 | 0.710 | 111.470 |
| rs35225972 | A | G | 0.044 | 0.007 | < 0.001 | −0.001 | 0.018 | 0.973 | 38.918 |
| rs35621564 | G | A | −0.044 | 0.007 | < 0.001 | 0.004 | 0.016 | 0.831 | 42.384 |
| rs3785356 | T | C | 0.056 | 0.007 | < 0.001 | 0.004 | 0.017 | 0.821 | 61.774 |
| rs3827780 | A | G | −0.037 | 0.007 | < 0.001 | −0.007 | 0.016 | 0.659 | 31.478 |
| rs413214 | A | G | 0.047 | 0.007 | < 0.001 | 0.014 | 0.016 | 0.388 | 48.909 |
| rs4739738 | A | G | −0.068 | 0.007 | < 0.001 | 0.001 | 0.016 | 0.951 | 99.605 |
| rs4795401 | G | A | −0.103 | 0.007 | < 0.001 | −0.002 | 0.016 | 0.924 | 247.028 |
| rs479844 | G | A | 0.040 | 0.007 | < 0.001 | 0.011 | 0.016 | 0.501 | 37.834 |
| rs4842921 | A | G | −0.041 | 0.007 | < 0.001 | −0.001 | 0.016 | 0.947 | 37.019 |
| rs56375023 | A | G | 0.103 | 0.008 | < 0.001 | 0.020 | 0.019 | 0.284 | 180.838 |
| rs7734635 | G | A | 0.077 | 0.009 | < 0.001 | −0.013 | 0.020 | 0.520 | 71.722 |
| rs7770794 | A | G | 0.042 | 0.007 | < 0.001 | −0.016 | 0.017 | 0.349 | 33.087 |
| rs7936312 | T | G | 0.084 | 0.007 | < 0.001 | 0.026 | 0.016 | 0.100 | 164.916 |
| rs7961712 | A | G | 0.056 | 0.009 | < 0.001 | −0.051 | 0.022 | 0.020 | 37.925 |
| rs848 | C | A | −0.096 | 0.008 | < 0.001 | 0.004 | 0.018 | 0.844 | 129.311 |
| rs912131 | G | A | 0.058 | 0.007 | < 0.001 | −0.001 | 0.017 | 0.956 | 66.218 |
| rs919826 | C | T | −0.036 | 0.007 | < 0.001 | 0.012 | 0.016 | 0.455 | 29.858 |
| rs9272226 | T | C | −0.090 | 0.009 | < 0.001 | −0.008 | 0.024 | 0.747 | 90.011 |
| rs992969 | G | A | −0.120 | 0.008 | < 0.001 | 0.026 | 0.018 | 0.151 | 251.458 |

SNP: single nucleotide polymorphism; EA: effect allele; OA: other allele; *SE*: standard error. The *F* value for these 43 SNPs ranged from 29.858 to 251.458, with all the values greater than 10, indicating a low likelihood of weak instrument variable biases

表3　牙周炎与哮喘相关性分析的孟德尔随机化结果

Table 3　Mendelian randomization results for the association between periodontitis and asthma

| Method | Periodontitis on asthma | | | | Asthma on periodontitis | | | |
|---|---|---|---|---|---|---|---|---|
| | *SE* | *β* | *OR* (95%*CI*) | *P* | *SE* | *β* | *OR* (95%*CI*) | *P* |
| Inverse variance weighted | 0.016 | 0.003 | 1.003 (0.973-1.035) | 0.828 | 0.043 | 0.021 | 1.021 (0.938-1.111) | 0.633 |
| Weighted median | 0.021 | −0.010 | 0.990 (0.951-1.031) | 0.641 | 0.062 | 0.011 | 1.011 (0.894-1.142) | 0.866 |
| MR-Egger | 0.020 | −0.012 | 0.988 (0.960-1.028) | 0.573 | 0.120 | 0.042 | 1.042 (0.824-1.319) | 0.731 |
| Maximum likelihood | 0.016 | 0.003 | 1.003 (0.972-1.035) | 0.834 | 0.044 | 0.021 | 1.021 (0.938-1.112) | 0.631 |
| MR-RAPS | 0.017 | 0.002 | 1.002 (0.970-1.036) | 0.890 | 0.045 | 0.017 | 1.017 (0.931-1.110) | 0.713 |

RAPS: robust adjusted profile score. 12 SNPs were used as instrumental variables for periodontitis. 43 SNPs were used as instrumental variables for asthma. Inverse variance weighted, weighted median, MR-Egger regression, maximum likelihood and MR-RAPS results showed that periodontitis was not causally related with the risk of asthma among European population, and no causal effect of asthma on periodontitis was found. MR: Mendelian randomization; *SE*: standard error; SNP: single nucleotide polymorphism

### 2.3　敏感性分析

对本研究所纳入的工具变量进行异质性和多效性分析。当以牙周炎作为暴露因素，哮喘作为结局时，Cochran's *Q*检验表明，牙周炎相关的工具变量之间没有显著的异质性（$Q = 10.99$，$P = 0.444$）。MR-PRESSO全局检验的结果也显示，纳入的工具变量之间不存在水平多效性（$P = 0.266$）。此外，留一法分析的结果也未发现本研究存在会对MR结果产生显著影响的离群SNP（图2）。

当以哮喘作为暴露因素，牙周炎作为结局时，Cochran's *Q*检验表明，哮喘相关的工具变量之间没有显著的异质性（$Q = 47.11$，$P = 0.272$）。MR-PRESSO全局检验的结果也显示，纳入的工具变量之间不存在水平多效性（$P = 0.851$）。此外，留一法分析的结果也未发现本研究存在会对MR结果产生显著影响的离群SNP（图3）。

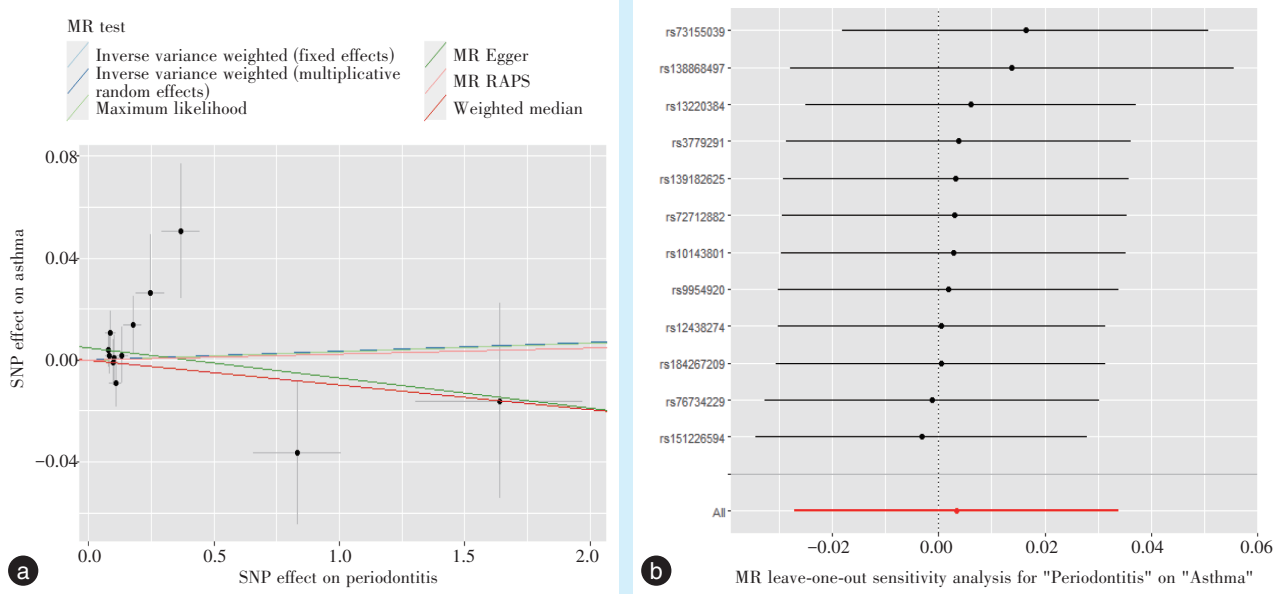
## 3　讨　论

本研究通过多种互补MR方法来探讨牙周炎和哮喘之间双向因果关系，但结果并未显示这两

种疾病之间存在显著的双向关联。尽管如此，鉴于目前关于这两种疾病的GWAS数据有限，对这些结果应谨慎解释。先前的一些流行病学研究已经指出了牙周炎可能对哮喘产生影响[4, 31]。例如，一项包含220例哮喘患者和237例对照的病例对照研究发现，牙周炎与重度哮喘的发生呈现显著正相关[4]。Molina等[31]基于75项研究开展的荟萃分析也表明，牙周炎与哮喘的发生存在正向关。此外，多项研究发现，牙周炎患者的哮喘患病率高于健康人群[5-6]。Gomes-Filho等[5]通过系统回顾和荟萃分析证实了牙周炎与哮喘、慢性阻塞性肺疾病和肺炎之间的正相关性。然而，美国一项以人群为基础的观察性流行病学研究发现，与从未患过哮喘的成年人相比，目前患有哮喘的成年人患重度牙周炎的可能性更小[6]。由于观察性研究固有的局限性，很难确定牙周炎和哮喘之间的因果关系。其他可能的混杂因素，如肥胖和吸烟[5]，可能导致结果不准确。在本研究中，基于严格的工具变量筛选和多种MR分析方法，数据并不支持牙周炎和哮喘之间的双向因果关系。

哮喘是一种具有类似于慢性炎症性质的全身性疾病[32]，但其与牙周炎的确切联系尚未明确。在观察性研究中，牙周炎和哮喘之间的关联可能由几个因素解释。首先，哮喘患者频繁使用抗哮喘药物，如含糖止咳糖浆、镇静剂和皮质类固醇，这可能增加了他们对牙周病的易感性[33]；其次，由于被诊断为哮喘后患者健康意识的提高和饮食的改变，它促使患者进行更仔细的口腔护理，减少了牙菌斑在口内的聚集，降低了患牙周炎的机率；此外，牙周炎炎症细胞释放的基质金属蛋白酶可能降解呼吸道组织内的结构蛋白，导致慢性支气管炎症和哮喘的形成[34-35]。

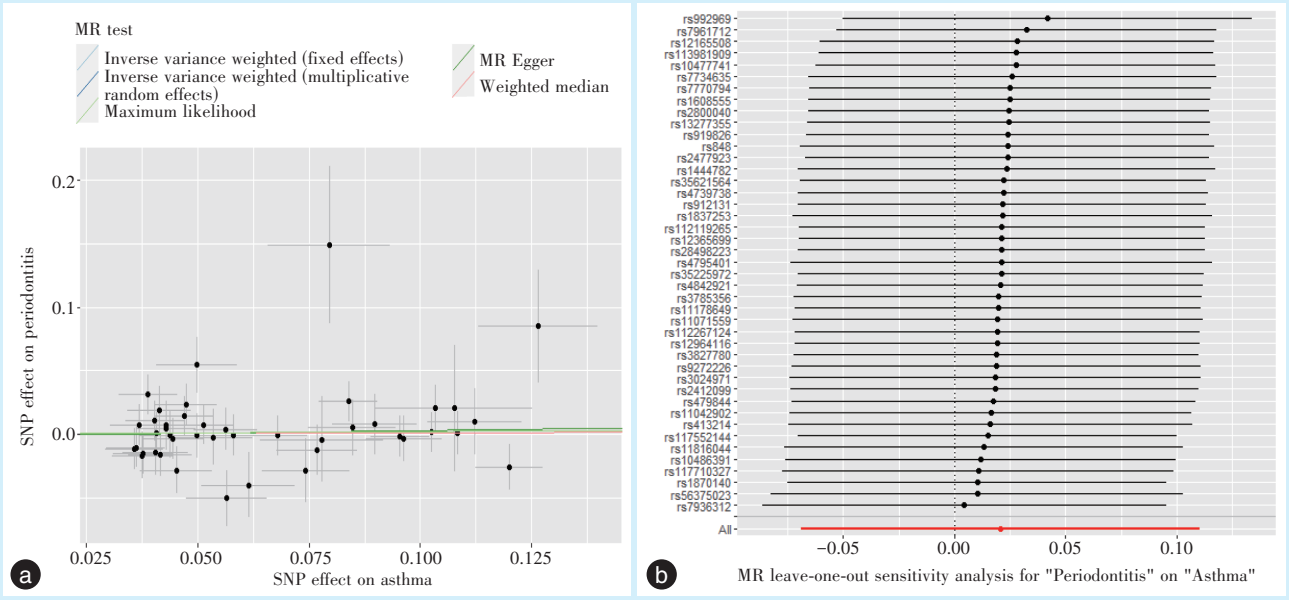
本研究基于欧洲人群遗传数据的双向MR分析表明，在欧洲人群中，牙周炎与哮喘发病之间可能不存在双向的因果关系。本研究也存在一些局限性。首先，亚洲人群GWAS数据较少，本研究纳入的MR分析人群均为欧洲血统，这限制了研究结果的普遍性。其次，作为遗传工具的SNP与牙周炎的相关性较弱，使用的临界$P$值为$1\times10^{-5}$而不是$5\times10^{-8}$。在全基因组显著性水平上，只有12个与临床定义的牙周炎相关的独立SNPs被纳入。此外，大多数与牙周炎相关的SNP的生物学机制尚不明确。由于不同研究中使用的牙周炎定义不一致，GWAS研究很难识别出一致的SNP。未来还需要




a: scatter plots of MR analysis. Black dots denote the genetic instruments included in the primary MR analysis. The slope of each line corresponding to the estimated MR effect in different models. b: leave-one-out analysis. Each black point represents the IVW MR method applied to estimate the causal effect of periodontitis on asthma, excluding that particular variant from the analysis. The red point represents the IVW estimate using all SNPs. MR: Mendelian randomization; IVW: inverse variance weighted

Figure 2　Results of sensitivity and MR analysis for the causal relationship between periodontitis and asthma

**图2**　牙周炎和哮喘因果关系的孟德尔随机化分析与敏感性检验




a: scatter plots of the MR analysis. Black dots denote the genetic instruments used in the primary MR analysis. The slope of each line corresponds to the estimated MR effect in different models. b: leave-one-out analysis. Each black point represents the IVW MR method applied to estimate the causal effect of periodontitis on asthma, excluding that particular variant from the analysis. The red point represents the IVW estimate using all SNPs. MR: Mendelian randomization; IVW: inverse variance weighted

Figure 3　Sensitivity and MR analysis for the causal relationship between asthma and periodontitis

**图3**　哮喘和牙周炎因果关系的孟德尔随机化分析与敏感性检验

基于更大规模的GWAS总结数据和更多遗传工具进行MR分析，以验证本研究的结果。

**【Author contributions】** Chen QW collected, analyzed the data, and wrote the article. Liu T collected, analyzed the data. Cai Y designed the study, guided and critically reviewed the article structures. All authors read and approved the final manuscript as submitted.

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