

· 论著 ·

肠道菌群与丛集性头痛的因果关系： 两样本孟德尔随机化分析

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【摘要】 目的 采用两样本孟德尔随机化(MR)分析探讨肠道菌群与丛集性头痛(CH)的因果关系。**方法** 肠道菌群数据集来自MiBioGen联盟的汇总数据,共涉及1 053 032 560个单核苷酸多态性(SNP);CH数据集来自R9版本的芬兰数据库,共涉及20 167 676个SNP。本研究主要采用逆方差加权法(IVW)进行MR分析,以探讨肠道菌群与CH的潜在因果关系,并采用错误发现率(FDR)校正P值;其次,以MR-Egger回归、加权中位数法(WME)、加权众数法(WM)、简单众数法(SM)作为IVW的补充方法。采用IVW、MR-Egger回归分析肠道菌群与CH的反向因果关系。**结果** IVW分析结果显示,放线菌门是CH的危险因素[OR=1.786, 95%CI(1.154~2.764), P=0.009, P_{FDR}=0.046],粪球菌属1是CH的保护因素[OR=0.563, 95%CI(0.355~0.894), P=0.015, P_{FDR}=0.074],副拟杆菌属、普雷沃氏菌属9、瘤胃球菌属UCG003组与CH具有潜在关联(P<0.05, P_{FDR}>0.10)。且MR-Egger回归、WME、WM、SM的β值与IVW的β值方向一致。反向MR分析结果显示,CH与放线菌门、粪球菌属1、副拟杆菌属、普雷沃氏菌属9、瘤胃球菌属UCG003组不存在反向因果关系(P>0.05)。**结论** 放线菌门是CH的危险因素,粪球菌属1是CH的保护因素,副拟杆菌属、普雷沃氏菌属9、瘤胃球菌属UCG003组与CH具有潜在关联。

【关键词】 丛集性头痛;胃肠道微生物组;肠道菌群;孟德尔随机化分析;因果关系**【中图分类号】** R 741.041 **【文献标识码】** A DOI: 10.12114/j.issn.1008-5971.2024.00.061

Causal Relationship between Intestinal Flora and Cluster Headache: Two-Sample Mendelian Randomization Analysis

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【Abstract】 Objective To analyze the causal relationship between intestinal flora and cluster headache (CH) by two-sample Mendelian randomization (MR) analysis. **Methods** The intestinal flora dataset was from the MiBioGen consortium, involving 1 053 032 560 single nucleotide polymorphisms (SNPs). The CH dataset was from the R9 version of the Finnish database, involving 20 167 676 SNPs. In this study, inverse variance weighting (IVW) was used for MR analysis to investigate the potential causal relationship between intestinal flora and CH, and the P value was corrected with false discovery rate (FDR). Secondly, MR-Egger regression, weighted median estimator (WME), weighted mode (WM), and simple mode (SM) were used as supplementary methods for IVW. IVW and MR-Egger regression were used to analyze the reverse causal relationship between intestinal flora and CH. **Results** IVW analysis results showed that, Actinobacteria was a risk factor for CH [OR=1.786, 95%CI (1.154-2.764), P=0.009, P_{FDR}=0.046], Coprococcus 1 was a protective factor for CH [OR=0.563, 95%CI (0.355-0.894), P=0.015, P_{FDR}=0.074], Parabacteroides, Prevotella 9 and Ruminococcus UCG003 group were potentially associated with CH (P<0.05, P_{FDR}>0.10). The β values of MR-Egger regression, WME, WM and SM were consistent with the β values of IVW. The results of reverse MR analysis showed that there was no causal relationship between CH and Actinobacteria, Enterococcus 1, Parabacteroides, Prevotella 9, Ruminococcus UCG003 group (P>0.05). **Conclusion** Actinobacteria is a risk factor for CH, Enterococcus 1 is a protective factor for CH, and Parabacteroides, Prevotella 9, Ruminococcus UCG003 group are potentially associated with CH.

【Key words】 Cluster headache; Gastrointestinal microbiome; Intestinal flora; Mendelian randomization analysis; Causation

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丛集性头痛 (cluster headache, CH) 是最严重的原发性头痛类型, 常单侧发作并出现严重的头面部疼痛^[1], 通常伴有同侧自主神经症状, 如上睑下垂、瞳孔缩小、面部发红或潮红、鼻塞、流涕、眶周肿胀、烦躁不安或激越等, 但其病理生理学机制复杂^[2]。研究表明, 约55%的CH患者发作期出现自杀倾向, 故其又被称为“自杀性头痛”^[3]。既往研究表明, CH与偏头痛具有部分相同的临床特征, 包括前驱症状、发作性视觉超敏反应、发作性异常性疼痛和自主神经症状^[4]。全基因组关联研究荟萃分析结果显示, CH与偏头痛至少共享1个遗传位点, 故两者具有部分相同的解剖结构和病理生理学机制^[5]。研究表明, 肠道菌群与偏头痛的发病相关^[5-6], 如TANG等^[7]研究发现, 肠道菌群紊乱可能通过上调TNF- α 表达而导致偏头痛的发生。基于CH与偏头痛存在相似性, 笔者提出肠道菌群也是诱发CH的病理因素的假设。基于此, 本研究采用两样本孟德尔随机化 (Mendelian randomization, MR) 分析探讨肠道菌群与CH的因果关系, 现报道如下。

1 资料与方法

1.1 研究设计

采用两样本MR分析方法, 以肠道菌群为暴露因素, CH为结局, 分析肠道菌群与CH的因果关系。

1.2 数据来源

1.2.1 肠道菌群数据集

肠道菌群数据集来自MiBioGen联盟 (<https://gwas.mrcieu.ac.uk/>) 的汇总数据, 该数据集包括18 340例不同种族和国籍的参与者的16S rRNA基因测序数据 (72.3%为欧洲人, 27.7%为中东、东亚、美国西班牙裔/拉丁裔和非裔美国人)^[8], 共涉及1 053 032 560个单核苷酸多态性 (single nucleotide polymorphism, SNP)。

1.2.2 CH数据集

CH数据集来自R9版本的芬兰数据库 (<https://r9.finngen.fi/>), 该数据集包括288 944例参与者, 其中CH患者1 107例、健康对照者287 837例, 共涉及20 167 676个SNP。

1.3 筛选工具变量

剔除15种未知菌属后, 本研究共纳入196种肠道微生物。各肠道微生物工具变量应满足以下条件: (1) 在基因位点范围内存在显著性阈值 ($P < 1.0 \times 10^{-5}$) 的SNP被作为潜在工具变量^[9]; (2) 排除连锁不平衡的SNP, 即 $r^2 < 0.001$; (3) 区域宽度为10 000 kD, 以确保各SNP间相互独立; (4) 选取 $F > 10$ 的SNP, 以排除弱工具变量^[10]。F值计算公式如下: $F = \beta^2 / se^2$ ^[11], 其中 β 为效应值、 se 为标准误。

1.4 两样本MR分析过程

1.4.1 正向MR分析

(1) MR分析方法: 本研究主要采用逆方差加权法 (inverse variance weighting, IVW) 进行MR分析, 以探讨肠道菌群与CH的潜在因果关系, 并采用错误发现率 (false discovery rate, FDR) 校正P值, 以 $P < 0.05$ 且 $P_{FDR} < 0.10$ 为存在因果关系, $P < 0.05$ 且 $P_{FDR} \geq 0.10$ 为可能存在潜在关联^[12-13]。其次, 以MR-Egger回归、加权中位数法 (weighted median estimator, WME)、加权众数法 (weighted mode, WM)、简单众数法 (simple mode, SM) 作为IVW的补充方法, 当MR-Egger回归、WME、WM、SM的 β 值与IVW的 β 值方向一致时, 提示IVW结果稳定可靠^[14]。(2) 统计学异质性: 应用Cochran Q检验评估SNP间是否存在统计学异质性, $P < 0.05$ 提示SNP间存在统计学异质性。(3) 水平多效性: 采用MR-Egger回归的截距项评估SNP的水平多效性, 若截距项与0相比无统计学意义, 表明SNP不存在水平多效性^[15]。(4) 离群值: 采用MR-PRESSO法识别SNP的离群值, 并剔除离群值后重新进行MR分析^[16]。(5) 敏感性分析: 采用留一法进行敏感性分析, 以判断单个SNP对MR分析结果的影响^[17]。

1.4.2 反向MR分析

以CH为暴露因素, 肠道菌群为结局, 仅采用IVW、MR-Egger回归分析肠道菌群与CH的反向因果关系。

2 结果

2.1 工具变量

196种肠道微生物包括9门、16纲、20目、32科、119属, 共得到2 774个与肠道微生物高度相关的SNP。

2.2 正向MR分析

IVW分析结果显示, 放线菌门是CH的危险因素 [$OR = 1.786$, 95%CI (1.154 ~ 2.764), $P = 0.009$, $P_{FDR} = 0.046$], 粪球菌属1是CH的保护因素 [$OR = 0.563$, 95%CI (0.355 ~ 0.894), $P = 0.015$, $P_{FDR} = 0.074$], 副拟杆菌属、普雷沃氏菌属9、瘤胃球菌属UCG003组与CH具有潜在关联 (P 值分别为0.036、0.036、0.048, P_{FDR} 值分别为0.180、0.180、0.240)。且MR-Egger回归、WME、WM、SM的 β 值与IVW的 β 值方向一致, 见表1、图1。

Cochran Q检验分析结果显示, 与上述5种肠道微生物高度相关的SNP间不存在统计学异质性 ($P > 0.05$); MR-Egger回归的截距项分析显示, 与上述5种肠道微生物高度相关的SNP不存在水平多效性 ($P > 0.05$); MR-PRESSO法分析结果显示, 与上述5种肠道微生物高度相关的SNP不存在离群值 ($P > 0.05$), 见表2。留一法分析结果显示, 剔除单个SNP后, MR分析结果无明显改

变, 见图2。

2.3 反向MR分析

反向MR分析结果显示, CH与放线菌门、粪球菌属

表1 肠道菌群与CH因果关系的5种MR分析方法分析结果

Table 1 Results of five MR analysis methods for causal relationship between intestinal flora and CH

暴露因素	SNP数量 (个)	方法	β	OR值	95%CI	P值	P_{FDR} 值
放线菌门	14	IVW	0.580	1.786	1.154 ~ 2.764	0.009	0.046
		MR-Egger回归	1.403	4.067	0.663 ~ 24.960	0.155	
		WME	0.657	1.930	1.069 ~ 3.484	0.029	
		WM	0.671	1.957	0.708 ~ 5.407	0.218	
		SM	0.646	1.907	0.662 ~ 5.496	0.253	
粪球菌属1	11	IVW	-0.574	0.563	0.355 ~ 0.894	0.015	0.074
		MR-Egger回归	-0.779	0.459	0.139 ~ 1.521	0.235	
		WME	-0.649	0.523	0.280 ~ 0.977	0.042	
		WM	-0.492	0.611	0.258 ~ 1.447	0.289	
		SM	-0.323	0.724	0.290 ~ 1.809	0.505	
副拟杆菌属	5	IVW	0.780	2.182	1.053 ~ 4.521	0.036	0.180
		MR-Egger回归	0.780	2.181	0.012 ~ 408.442	0.789	
		WME	0.717	2.049	0.807 ~ 5.200	0.131	
		WM	0.377	1.458	0.362 ~ 5.874	0.624	
		SM	0.886	2.426	0.567 ~ 10.386	0.298	
普雷沃氏菌属9	15	IVW	-0.322	0.725	0.536 ~ 0.979	0.036	0.180
		MR-Egger回归	-0.058	0.944	0.392 ~ 2.270	0.899	
		WME	-0.215	0.806	0.538 ~ 1.207	0.295	
		WM	-0.193	0.825	0.460 ~ 1.479	0.528	
		SM	-0.200	0.819	0.410 ~ 1.635	0.580	
瘤胃球菌属UCG003组	12	IVW	-0.413	0.662	0.439 ~ 0.996	0.048	0.240
		MR-Egger回归	-0.008	0.992	0.260 ~ 3.794	0.991	
		WME	-0.408	0.665	0.381 ~ 1.160	0.151	
		WM	-0.507	0.603	0.248 ~ 1.464	0.287	
		SM	-0.310	0.733	0.291 ~ 1.850	0.525	

注: SNP=单核苷酸多态性, FDR=错误发现率, IVW=逆方差加权法, WME=加权中位数法, WM=加权众数法, SM=简单众数法。

1、副拟杆菌属、普雷沃氏菌属9、瘤胃球菌属UCG003组不存在反向因果关系($P>0.05$), 见表3。

3 讨论

研究表明, CH的疼痛机制是三叉神经源性炎症^[18], 炎症可引起三叉神经-副交感神经反射^[19], 而三叉神经血管系统激活可诱导神经递质与促炎递质的分泌, 如降钙素基因相关肽、一氧化氮和神经激肽^[20], 进而加剧疼痛; 此外, 上述物质也可以影响三叉神经系统, 诱导相关疾病发作^[21], 如降钙素基因相关肽会引发肥大细胞脱颗粒, 并与P物质一起导致神经源性炎症^[22-23], 促进一氧化氮合成及三叉神经致敏, 从而驱动CH并加剧疼痛^[24]。5-羟色胺是一种存在于周围神经的神经递质, 其分泌增多会刺激脑血管, 诱发三叉神经核活动, 进而引发CH^[25-26]。另有研究发现, 白介素1 β 可调节三叉神经中伤害性感觉神经元总电压依赖性钠电流, 进而引发炎症相关性痛觉过敏^[27-28]。上述物质不仅与CH关系密切, 还与肠道菌群相关。研究表明, 肠道菌群可影响背根神经节中降钙素基因相关肽的产生^[29]。XIANG等^[30]研究发现, 双歧杆菌与辣椒素诱导的胃肠道炎症模型小鼠血清降钙素基因相关肽水平呈正相关。5-羟色胺又称为血清素, 90%来自胃肠道, 由肠嗜铬细胞分泌^[31]。ZHANG等^[32]研究发现, 长双

表2 与肠道菌群高度相关的SNPs的Cochran Q检验、MR-Egger回归、MR-PRESSO法分析结果

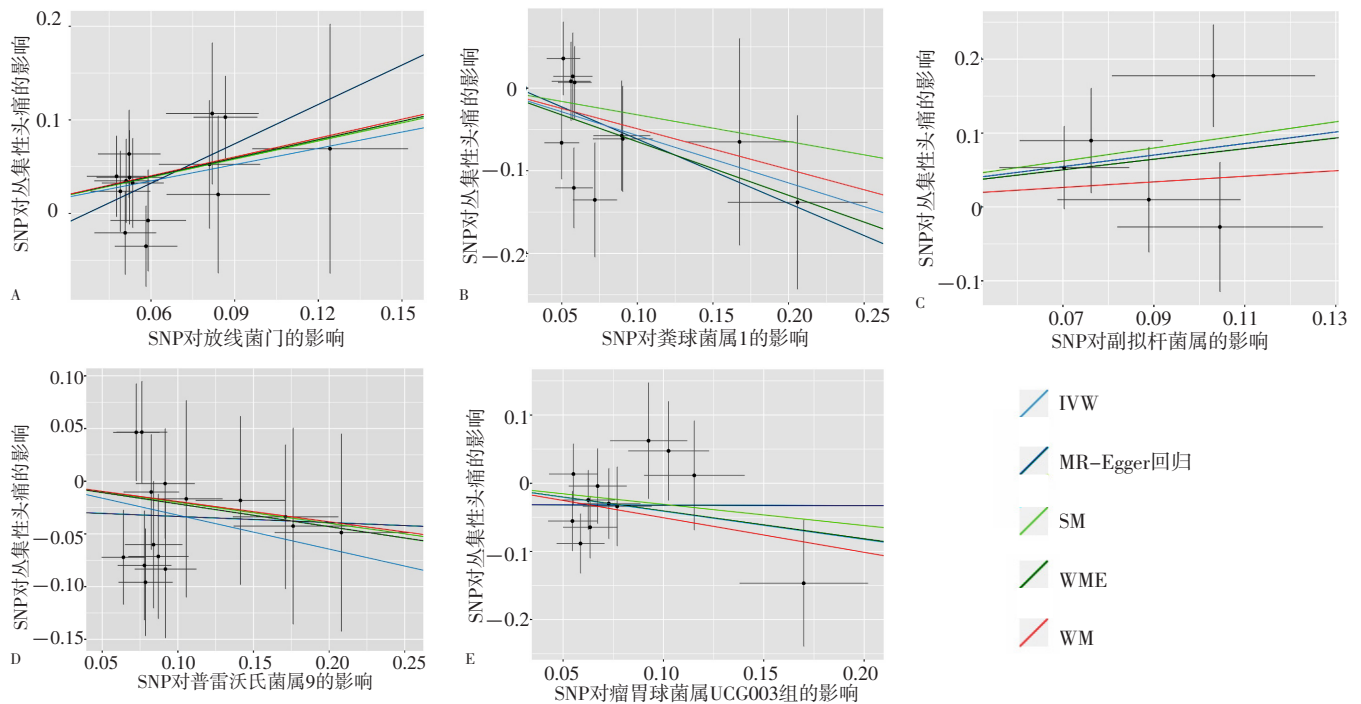
Table 2 Results of Cochran Q test, MR-Egger regression and MR-PRESSO method analysis of SNP highly correlated with intestinal flora

暴露	Cochran Q检验			MR-Egger回归		MR-PRESSO法	
	方法	Q值	P值	截距项	P值	β 值	P值
放线菌门	IVW	7.249	0.889	-0.052	0.378	0.580	0.869
粪球菌属1	IVW	10.549	0.394	0.016	0.722	-0.574	0.472
副拟杆菌属	IVW	4.418	0.352	<0.001	0.999	0.780	0.391
普雷沃氏菌属9	IVW	11.057	0.682	-0.028	0.541	-0.322	0.724
瘤胃球菌属UCG003组	IVW	8.500	0.668	-0.031	0.548	-0.413	0.707

表3 CH与肠道菌群因果关系的IVW、MR-Egger回归分析结果

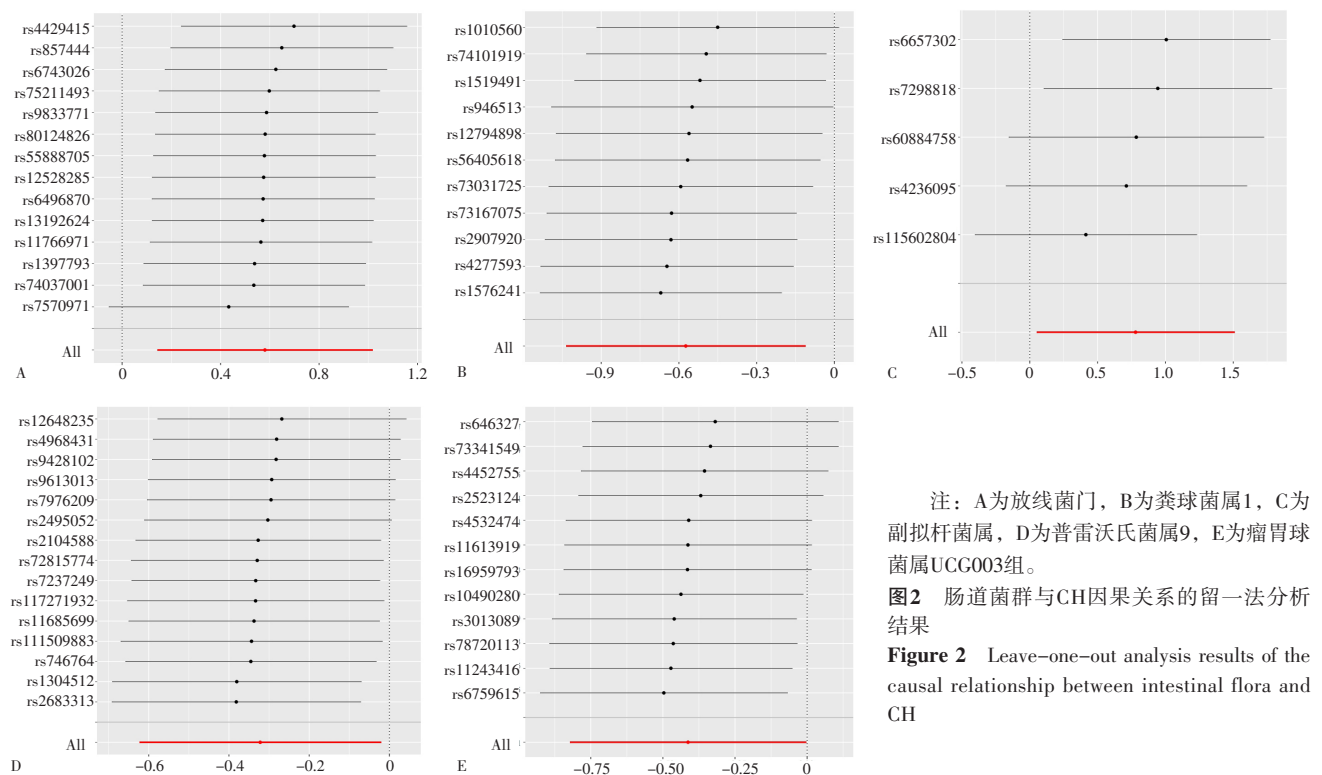
Table 3 IVW and MR-Egger regression analysis results of the causal relationship between CH and intestinal flora

结局	与CH高度相关的SNP数量(个)	方法	β	SE	OR (95%CI)	P值
放线菌门	7	IVW	-0.004	0.024	0.996 (0.950 ~ 1.044)	0.863
		MR-Egger回归	0.110	0.064	1.116 (0.985 ~ 1.265)	0.147
粪球菌属1	7	IVW	0.023	0.021	1.023 (0.982 ~ 1.067)	0.275
		MR-Egger回归	0.012	0.068	1.012 (0.886 ~ 1.156)	0.869
副拟杆菌属	7	IVW	-0.020	0.034	0.980 (0.916 ~ 1.048)	0.553
		MR-Egger回归	-0.101	0.112	0.904 (0.726 ~ 1.125)	0.407
普雷沃氏菌属9	7	IVW	0.013	0.028	1.013 (0.960 ~ 1.069)	0.639
		MR-Egger回归	-0.072	0.089	0.930 (0.781 ~ 1.108)	0.456
瘤胃球菌属UCG003组	7	IVW	0.005	0.035	1.005 (0.939 ~ 1.076)	0.884
		MR-Egger回归	0.119	0.108	1.126 (0.912 ~ 1.392)	0.320



注: A为放线菌门, B为粪球菌属1, C为副拟杆菌属, D为普雷沃氏菌属9, E为瘤胃球菌属UCG003组; SNP=单核苷酸多态性, IVW=逆方差加权法, WME=加权中位数法, WM=加权众数法, SM=简单众数法。

Figure 1 Scatter plots of the results of five MR analysis methods for the causal relationship between intestinal flora and CH



注: A为放线菌门, B为粪球菌属1, C为副拟杆菌属, D为普雷沃氏菌属9, E为瘤胃球菌属UCG003组。

图2 肠道菌群与CH因果关系的留一法分析结果

Figure 2 Leave-one-out analysis results of the causal relationship between intestinal flora and CH

歧杆菌、短双歧杆菌、丁酸梭菌、嗜热链球菌、粪肠杆菌等可以产生5-羟色胺酸和5-羟色胺。CH与偏头痛在发病机制及临床症状方面具有相似性^[2]。近年学者发现,肠道菌群可通过脑肠轴与偏头痛产生关联^[33],

此外,很多神经系统疾病如多发性硬化症、精神分裂症、阿尔茨海默病、帕金森病等都与脑肠轴功能障碍有关^[34-36],CH同为神经疾病,故可能与肠道菌群相关。

本研究采用两样本MR分析探讨肠道菌群与CH的因

果关系,结果显示,放线菌门是CH的危险因素,粪球菌属1是CH的保护因素,副拟杆菌属、普雷沃氏菌属9、瘤胃球菌属UCG003组与CH具有潜在关联。分析原因:与降钙素基因相关肽和5-羟色胺呈正相关的双歧杆菌属于放线菌门,其衍生的神经递质、炎症因子等物质可能通过脑肠轴或通透性增加的肠壁而直接或间接地影响颅神经,从而诱发CH;普雷沃氏菌是一种可产生丰富丁酸和丙酸的肠道菌群,而丁酸和丙酸能有效抑制炎症反应,从而延缓CH的发生^[37];但目前,粪球菌属1、副拟杆菌属、瘤胃球菌属UCG003组与CH相关的具体机制尚未见报道,仍有待进一步研究探索。

本研究的优势:(1)本研究样本量较大,可有效避免混杂因素的干扰;(2)IVW结果稳定可靠。本研究的局限性:(1)由于肠道菌群的最低分类水平是属,故无法在物种水平上分析肠道菌群与CH的因果关系;(2)本研究数据来源于欧洲人群,该结果是否在亚洲人群中成立尚有待进一步研究证实;(3)既往关于肠道菌群与CH关系的研究报道较少,无法深入阐释上述肠道菌群与CH相关的机制。

4 结论

综上所述,放线菌门是CH的危险因素,粪球菌属是CH的保护因素,副拟杆菌属、普雷沃氏菌属9、瘤胃球菌属UCG003组与CH具有潜在关联。后期仍有待大样本量RCT进一步阐明放线菌门、粪球菌属与CH的因果关系及具体作用机制。

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