Advances in Clinical Medicine 临床医学进展, 2023, 13(6), 10487-10495
Published Online June 2023 in Hans. https://www.hanspub.org/journal/acm
https://doi.org/10.12677/acm.2023.1361468

Hans汉斯

肠道菌群与痤疮之间的因果关系：两样本孟德尔随机化

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收稿日期：2023年5月28日；录用日期：2023年6月23日；发布日期：2023年6月30日

摘 要

背景：越来越多的研究表明肠道菌群与痤疮之间存在一定联系。但由于混杂因素的影响，肠道菌群与痤疮之间是否存在因果关系还未可知。肠道菌群可能通过肠道－皮肤轴增加感染痤疮的风险。方法：我们采用两样本孟德尔随机化(MR)研究来探讨肠道菌群与痤疮之间的关系，使用已发表的全基因组关联研究中的遗传变异作为工具变量。采用逆方差加权法(IVW)、MR Egger回归、加权中位数法和最大似然值法评估两者间因果关系，并进行多重敏感性分析以确保结果的准确。结果：我们确定了*Bacteroidaceae*与痤疮的因果关系[优势比(OR)：2.25; 95%置信区间(CI)：1.48~3.42；P_{ivw} = 0.0001；错误发现率(FDR) = 0.05]，*Bacteroides* (OR, 2.25; 95% CI: 1.48~3.42; P_{ivw} = 0.0001; FDR = 0.01)，*Allisonella* (OR: 1.42; 95% CI: 1.18~1.70; P_{ivw} = 0.0002; FDR = 0.01)。敏感性分析验证了这些因果关系的可靠性。结论：这是第一个确定肠道菌群和痤疮之间因果关系的MR研究。我们的研究揭示了一些肠道菌群是痤疮的危险因素，为痤疮的潜在治疗靶点提供了新的信息，但痤疮与肠道菌群因果关系的内在机制还有待深入研究。

关键词

孟德尔随机化，肠道菌群，痤疮，因果关系

The Causal Relationship between Gut Microbiota and Acne: A Two-Sample Mendelian Randomization Study

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Received: May 28th, 2023; accepted: Jun. 23rd, 2023; published: Jun. 30th, 2023

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文章引用: 顾昀帆, 叶星兰. 肠道菌群与痤疮之间的因果关系: 两样本孟德尔随机化[J]. 临床医学进展, 2023, 13(6): 10487-10495. DOI: 10.12677/acm.2023.1361468

Abstract

Background: Acne is linked to the gut microbiota according to several studies. The association between gut microbiota and acne has yielded conflicting results due to confounding factors, and the causal relationship between them remains undetermined. Intestinal flora may increase the risk of acne infection through the gut-skin axis. Methods: We used a two-sample Mendelian randomization (MR) study to explore the relationship between gut flora and acne, using genetic variation from published genome-wide association studies as an instrumental variable. Inverse variance weighted (IVW), weighted median, MR Egger, and maximum likelihood methods were applied to access causal relationships. Several sensitivity analyses were also performed to ensure the accuracy of the results. Results: We found causal associations of *Bacteroidaceae* [odds ratio (OR), 2.25; 95% confidence interval (CI), 1.48~3.42; P_{ivw} = 0.0001; false discovery rate (FDR) = 0.05], *Allisonella* (OR, 1.42; 95% CI, 1.18~1.70; P_{ivw} = 0.0002; FDR = 0.01), and *Bacteroides* (OR, 2.25; 95% CI, 1.48~3.42; P_{ivw} = 0.0001; FDR = 0.01) with acne. These results are corrected for false discovery rate. Sensitivity analyses validated the associations' robustness, and reverse MR confirmed that the results were not influenced by the reverse effect. Conclusion: This is the first MR study to determine a causal relationship between intestinal flora and acne. Our study revealed some gut microbiotas are risk factors for acne, providing new information on the potential therapeutic targets for acne. The possible connection of the gut skin axis was again confirmed. Further research is needed on the mechanisms behind these relationships.

Keywords

Mendelian Randomization, Gut Microbiota, Acne, Causal Relationship

1. 介绍

皮肤是人体最大的器官，皮肤屏障保护人体免受外界侵害，并调节各种免疫反应[1]。肠道内定植的大量菌群与机体相互作用，从而在肠道、肝脏、皮肤和大脑等器官间形成复杂的通讯网络，涉及多种代谢途径、信号通路、免疫和炎症反应[2]。这个网络可以双向调节肠道和皮肤组织的生理病理状态。银屑病、荨麻疹、痤疮和特应性皮炎等皮肤病有不同的病因，越来越多的研究表明，这些疾病不仅发生在皮肤表面，与其他疾病[3] [4] [5]，包括肠道菌群失调密切相关。一项包括 16 名银屑病关节炎患者、15 名银屑病患者和 17 名健康对照的临床研究表明，银屑病患者肠道内 *Akkermansia*，*Ruminococcus* 等重要菌群明显减少，影响内环境的稳定[6]。而特应性皮炎患者体内含有更多的 *Faecalibacterium prausnitzii*，使丙酸盐、丁酸盐等抗炎物质含量下降，促使患者发生免疫紊乱[7]。

肠道－皮肤轴通过大量的免疫细胞相互交流，当它被免疫成分激活后[8]，为阻止炎症蔓延和微生物扩散，限制微生物与肠道上皮膜的接触变得至关重要，以保持宿主内稳态平衡[9]。有证据表明，一旦肠道屏障受损，肠道内定植的微生物渗入血液，积聚在皮肤组织中，皮肤的内环境出现失衡[10]。由于肠道菌群对于炎症性疾病有显著影响，使用益生菌可以防治多种皮肤病[11]，包括痤疮[12]，银屑病[13]，荨麻疹和特应性皮炎[14]。然而，一些研究结果表明 *bifidobacteria* 对痤疮有负面影响[15] [16]。已发表的研究结果之间存在相互矛盾的情况。例如，与其他研究结果不同[17] [18]，Deng 等人发现痤疮患者体内的

Firmicutes 丰度低于健康人[19]。在这些研究中，肠道菌群的作用被人群、疾病的轻重和持续时间等混淆因素的影响，可能导致结果不一致。更重要的是，大多数调查都是病例对照研究，其中暴露时间和结果都难以验证。此外，观察性研究可能受到反向因果关系和年龄、体重、生活方式等混杂因素的影响[20]。

由于这些限制，Walter 等人提出使用创新的统计方法，如孟德尔随机化(MR)，来检验肠道菌群与人类疾病间的因果关系[21]。在流行病学中使用 MR 可以评估多次暴露与结果间可能的因果关系，同时消除某些假设下的潜在混杂。MR 通过分析暴露的遗传变异作为工具变量，被广泛用于评估因果关系[22]。一般认为遗传变异是在出生时随机分布的，其很大程度上不受环境影响，在发病之前就已经存在，所以 MR 能够避免如残差和反向因果关系[23]等困扰传统观察性研究的问题。通过使用全基因组关联分析(GWASs)的数据，能够提高 MR 分析的效能，从而确定因果关系。因此，我们使用来自 MiBioGen [24]和 FinnGen [25]的 GWAS 汇总数据进行了两样本双向 MR 分析，以评估肠道菌群与痤疮间的因果关系。

2. 材料与方法

2.1. 数据来源

2.1.1. 肠道菌群数据及分析

从 MiBioGen 数据库中提取肠道微生物分类的汇总统计数据。这项多种族研究涵盖了来自 24 个队列的 18,000 多人，其中主要是欧洲血统(n = 13,266)。在控制年龄、性别、技术因素和主要遗传因素的前提下，采用 Spearman 相关分析验证了影响菌群变异、菌群分类和菌群丰度的相关位点。

2.1.2. 痤疮数据及分析

从 FinnGen 数据库 R8 发布的 GWAS 数据中提取出痤疮的汇总数据，痤疮患者 2313 例，健康对照 328,747 例。所有研究对象都是欧洲血统。分析数据时，年龄、性别和其他主要变量都被考虑在内。

2.2. 工具变量的选择

为保证研究结果的可靠性，我们使用多种质控措施来选择工具变量：

- 从与肠道菌群相关的 GWAS 数据的单核苷酸多态性(SNP)中选择工具变量，根据 Sanna 等人的研究，$P < 1 \times 10^{-5}$ 是与肠道菌群相关的 SNPs 的最佳阈值。
- 将连锁不平衡(LD)阈值设为 $R^2 < 0.001$，窗口范围设置为 10,000 kb。以欧洲的 1000 基因组计划作为参考计算 LD 值，去除不符合要求的 SNP 以满足 MR 假设。
- 为防止等位基因影响因果关联的结果，MR 分析中排除了回文 SNP。
- 通过使用 PhenoScanner 数据库验证所选的 SNP，并在全基因组水平上去除与任何潜在混杂因素显著相关的 SNP。
- 采用公式 $F = \frac{R^2 \times (N-k-1)}{(1-R^2) \times K}$ [31]计算工具变量强度，其中 R^2 表示由工具变量解释的暴露方差比例，n 为样本量，k 为工具变量数量。$F < 10$ 被认为是弱工具变量被排除。

2.3. 统计分析

所有统计分析均在 R 语言(版本 4.2.1)中进行，使用 TwoSampleMR (版本 0.5.6)和 MR-PRESSO 包(版本 1.0)。运用 Circlize (版本 0.4.15)和 tidyverse (版本 1.3.2)包使图形可视化。为控制错误发现率(FDR) [26]，采用 Benjamini-Hochberg (BH)对多个评价结果进行修正，显著性水平定义为校正 FDR 后 $P < 0.05$。此外，我们应用 mRnd 工具(http://cnsgenomics.com/shiny/mRnd/)计算了 MR 的统计效率[27]。

2.3.1. MR 分析

我们使用系数比率法(Wald ratio)评估单个菌群 SNP 对痤疮的因果效应。对于含有一个以上 SNP 的肠道菌群，我们使用逆方差加权法(IVW)、MR-Egger 回归、加权中位数法(WM)和最大似然值法(ML)来综合评估其对痤疮的因果效应。对于没有水平基因多效性的 SNP，采用 IVW 作为评估因果效应的主要手段，以产生无偏估计[28]。在工具变量多效性效应独立于工具变量与暴露因素之间的关联(InSIDE)假设下，MR-Egger 回归可以得出因果效应的一致估计，但其统计能力低于 IVW，且 1 型错误率高于预期[29]。WM 可以大幅度提高准确识别因果效应的能力，如果 InSIDE 假设被证明错误，那么它比 MR-Egger 回归更能避免 I 型错误的发生[30]。ML 可以通过最大化似然函数，有效估计概率分布的参数，从而产生较小的标准误差。在不存在异质性和水平多效性的情况下，该方法结果准确，标准误差小于 IVW [31]。我们综合评估了上述四种方法所得的结果，以使因果关联的证据更加有力。

2.3.2. 敏感性分析

尽管 IVW 在确定因果关系方面有很强的效力，但当工具变量存在缺陷和多效性时，很难满足其基本要求。我们进行了敏感性分析以评估结果的可靠性。首先使用 Cochrane Q 检验判断各肠道菌群与痤疮是否存在异质性，$P < 0.05$ 认为存在异质性[32]。接下来，使用 MR-Egger 回归和 MR-PRESSO 分析排除潜在多效性。MR-Egger 回归的非零截距用于检验是否存在未知的垂直多效性[33]。MR-PRESSO 用于检测水平多效性并剔除异常工具变量[34]，如果存在多效性，剔除异常工具变量后再次重复 MR 分析重新评估因果效应。我们使用留一法，每次剔除一个 SNP，重复 MR 分析，检验多效性对因果效应的潜在影响。最后，使用 MR Steiger 方向性检验来保证反向因果关系不干扰结果。

3. 结果

3.1. 工具变量

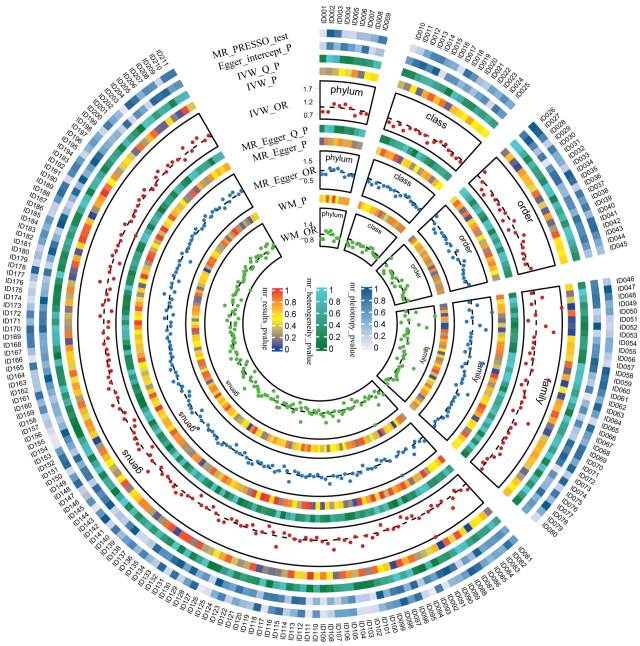

Figure 1. All results of MR analyses and sensitivity analyses between gut microbiota and acne
图 1. 所有肠道菌群与痤疮的 MR 分析及敏感性分析

如图 1 所示包括 9 门 16 类 20 目 35 科 131 属的 211 种肠道菌群 GWAS 汇总数据被用来筛选工具变量，根据上述工具变量的筛选流程，共有 2247 个 SNP 被筛选为肠道菌群的显著工具变量，剔除多效性后保留 2241 个 SNP。工具变量的 F 值介于 14.6 到 88.4，均大于 10，可以排除弱工具变量。

3.2. MR 分析

如图 2 所示，FDR 校正后，*Bacteroidaceae*、*Clostridiaceae1*、*Allisonella* 和 *Bacteroides* 与痤疮存在因果关系，其中 *Bacteroidaceae* 与痤疮的因果关系[优势比(OR)：2.25；95%置信区间(CI)：1.48~3.42；P_{ivw} = 0.0001；错误发现率(FDR) = 0.05]，*Allisonella* (OR: 1.42; 95% CI: 1.18~1.70; P_{ivw} = 0.0002; FDR = 0.01)，*Bacteroides* (OR, 2.25; 95% CI, 1.48~3.42; P_{ivw} = 0.0001; FDR = 0.01)，而 *Clostridiaceae1* (OR, 1.69; 95% CI, 1.20~2.39; P_{ML} = 0.002; FDR = 0.05)，主要方法 IVW 未通过 FDR 校正。

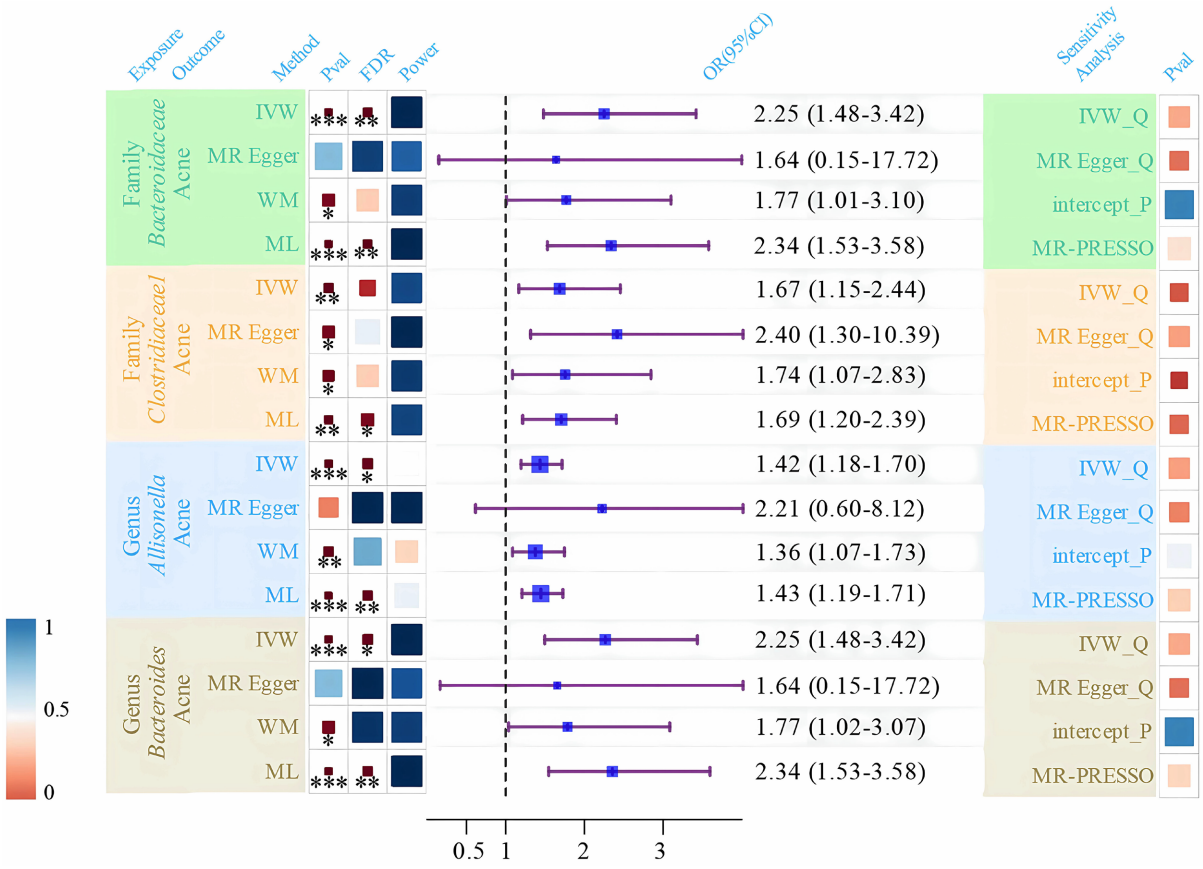

Figure 2. The results of MR analyses and sensitivity analyses for the causal association between gut microbiota and acne
图 2. 肠道菌群与痤疮因果关系的 MR 分析和敏感性分析的结果

3.3. 敏感性分析

Cochran Q 检验未发现肠道菌群与痤疮因果关系的异质性。MR-Egger 回归的 P 值均大于 0.05，全局 MR-PRESSO 分析没有发现显著的异常值，综合两者的结果提示肠道菌群与痤疮的因果关系没有多效性，这些结果证实了 IVW 与 ML 的可靠性。留一法的结果如图 3 所示，提示单个 SNP 不会使因果关系产生偏差。此外 MR Steiger 方向性测试中的 P 值范围在 10^{-13} 到 10^{-84} 之间，提示肠道菌群与痤疮间不存在反向因果关系。我们通过 mRnd 计算的统计效率都大于 80%，也进一步证实了结果的可靠性。

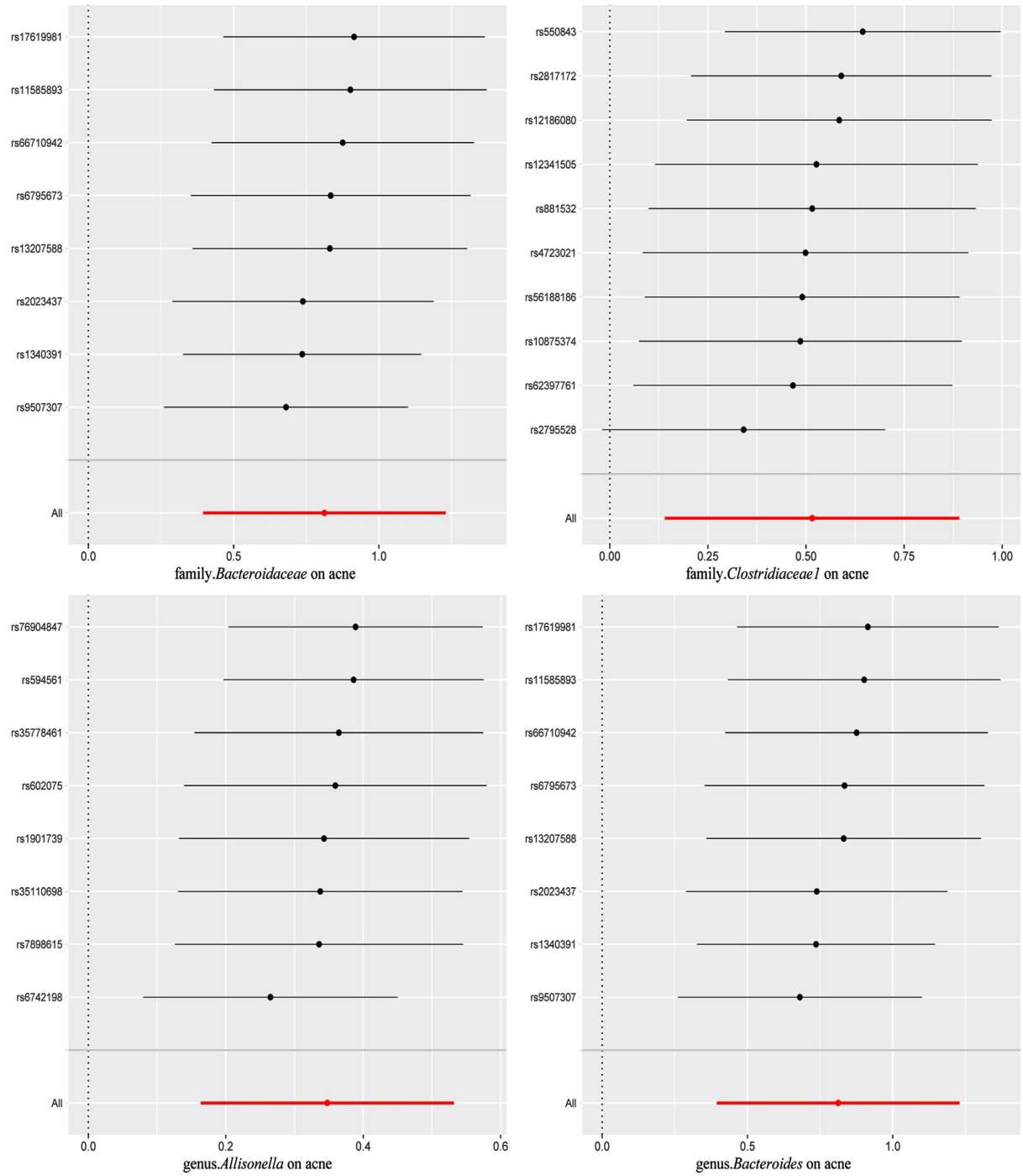

Figure 3. Leave-one-out plots for the causal association between gut microbiota and acne
图 3. 留一法检测肠道菌群与痤疮因果关系

4. 讨论

在这一 MR 分析中，我们使用肠道菌群与痤疮的 GWAS 数据，分析了 211 种肠道菌群与痤疮的因果关系，经过 FDR 校正，发现 *Bacteroidaceae*、*Bacteroides* 和 *Allisonella* 与痤疮存在因果关系，增加了痤疮的患病风险。*Bacteroides* (*Bacteroidaceae* 科)是一种常见的肠道微生物，被认为是痤疮的潜在病因[19]

[35] [36]，*Bacteroides* 是脂多糖(LPS)的主要生产者[37]，LPS 可通过损害结肠上皮的完整性，降低其保护能力并刺激促炎细胞因子释放引起全身炎症[38] [39]。*Bacteroides* 丰度增加与脂肪摄入过多、纤维摄入不足有关，对 10 名受试者进行低脂/高纤维或高脂/低纤维饮食 24 h 对照喂养，肠道内 *Bacteroides* 的变化与脂肪摄入呈正相关与纤维摄入呈负相关[40]，而纤维的缺乏会引发该菌基因表达和酶的变化[41]，高脂肪、低纤维饮食的代表西方饮食，会促进 *Bacteroides* 突变[42]，从而促进宿主聚糖的消耗，降低粘液层厚度，增加疾病易感性[43]。长期西方饮食导致菌群代谢失衡，破坏肠道屏障，使 *Bacteroides* 通过肠黏膜进入无菌区域[44]。Gil-Cruz 等人发现一种 *Bacteroides* 编码的肽，可以在肠道中募集肌球蛋白特异性 T 细胞，从而产生免疫球蛋白(Ig)A 和 IgG 抗体[45]。此外，*Bacteroides* 可以将毒力基因传递给周围的菌群，为它们提供毒力因子，促进肠外疾病[46]。这些因素导致全身慢性低度炎症[47]，导致痤疮的发病和发展。本次结果中 *Allisonella* 与痤疮的关系在文献中报道较少，但有研究表明 *Allisonella* 的丰度增加与西方饮食和炎症有关，它是基于肠道菌群预测肥胖相关炎症水平模型的关键组成部分[48]。考虑所检测菌群数量过多采用了 FDR 校正，可能过于严苛而过滤了部分阳性结果，但可以保证筛选后结果的可靠性，*Bacteroidaceae*、*Bacteroides* 和 *Allisonella* 丰度的增加都可能促进痤疮的发生发展。本次 MR 使用了现今最全面的肠道菌群 GWAS 数据库，但其研究的主要人种集中于欧洲，亚洲人种肠道菌群与痤疮的因果关系仍待进一步挖掘。

5. 总结

这一两样本 MR 揭示了肠道菌群与痤疮间的因果关系，肠道菌群能够充当肠道和皮肤间交流的媒介，肠道菌群影响肠道的免疫功能，从而引起皮肤炎症，促进痤疮的发生。我们发现的这些菌群作为痤疮的风险因素，为痤疮的治疗提供新的靶点，值得更多深入的研究探寻其内在机制。

致　谢

我们感谢每位参与 MiBioGen 和 FinnGen 数据库构建的工作人员。

参考文献

[1] Yi, R. and Fuchs, E. (2010) MicroRNA-Mediated Control in the Skin. *Cell Death & Differentiation*, **17**, 229-235. https://doi.org/10.1038/cdd.2009.92

[2] Nicholson, J.K., Holmes, E., Kinross, J., Burcelin, R., Gibson, G., Jia, W. and Pettersson, S. (2012) Host-Gut Microbiota Metabolic Interactions. *Science*, **336**, 1262-1267. https://doi.org/10.1126/science.1223813

[3] Kunz, M., Simon, J.C. and Saalbach, A. (2019) Psoriasis: Obesity and Fatty Acids. *Frontiers in Immunology*, **10**, Article No. 1807. https://doi.org/10.3389/fimmu.2019.01807

[4] Burton, J.L. (1989) Dietary Fatty Acids and Inflammatory Skin Disease. *The Lancet* (*London*, *England*), **1**, 27-31. https://doi.org/10.1016/S0140-6736(89)91682-6

[5] Papadimitriou, N., Dimou, N., Tsilidis, K.K., *et al.* (2020) Physical Activity and Risks of Breast and Colorectal Cancer: A Mendelian Randomisation Analysis. *Nature Communications*, **11**, Article No. 597. https://doi.org/10.1038/s41467-020-14389-8

[6] Scher, J.U., Ubeda, C., Artacho, A., *et al.* (2015) Decreased Bacterial Diversity Characterizes the Altered Gut Microbiota in Patients with Psoriatic Arthritis, Resembling Dysbiosis in Inflammatory Bowel Disease. *Arthritis & Rheumatology* (*Hoboken NJ*), **67**, 128-139. https://doi.org/10.1002/art.38892

[7] Song, H., Yoo, Y., Hwang, J., Na, Y.C. and Kim, H.S. (2016) *Faecalibacterium prausnitzii* Subspecies-Level Dysbiosis in the Human Gut Microbiome Underlying Atopic Dermatitis. *Journal of Allergy and Clinical Immunology*, **137**, 852-860. https://doi.org/10.1016/j.jaci.2015.08.021

[8] Merana, G.R., Dwyer, L.R., Dhariwala, M.O., *et al.* (2022) Intestinal Inflammation Alters the Antigen-Specific Immune Response to a Skin Commensal. *Cell Reports*, **39**, Article ID: 110891. https://doi.org/10.1016/j.celrep.2022.110891

[9] Macpherson, A.J., Slack, E., Geuking, M.B. and McCoy, K.D. (2009) The Mucosal Firewalls against Commensal Intestinal Microbes. *Seminars in Immunopathology*, **31**, 145-149. https://doi.org/10.1007/s00281-009-0174-3

[10] Ramírez-Boscá, A., Navarro-López, V., Martínez-Andrés, A., *et al*. (2015) Identification of Bacterial DNA in the Peripheral Blood of Patients with Active Psoriasis. *JAMA Dermatology*, **151**, 670-671. https://doi.org/10.1001/jamadermatol.2014.5585

[11] Jeong, J.H., Lee, C.Y. and Chung, D.K. (2016) Probiotic Lactic Acid Bacteria and Skin Health. *Critical Reviews in Food Science and Nutrition*, **56**, 2331-2337. https://doi.org/10.1080/10408398.2013.834874

[12] Baldwin, H. and Tan, J. (2021) Effects of Diet on Acne and Its Response to Treatment. *American Journal of Clinical Dermatology*, **22**, 55-65. https://doi.org/10.1007/s40257-020-00542-y

[13] Groeger, D., O'Mahony, L., Murphy, E.F., Bourke, J.F., Dinan, T.G., Kiely, B., Shanahan, F. and Quigley, E.M. (2013) Bifidobacterium Infantis 35624 Modulates Host Inflammatory Processes beyond the Gut. *Gut Microbes*, **4**, 325-339. https://doi.org/10.4161/gmic.25487

[14] Lee, J., Seto, D. and Bielory, L. (2008) Meta-Analysis of Clinical Trials of Probiotics for Prevention and Treatment of Pediatric Atopic Dermatitis. *Journal of Allergy and Clinical Immunology*, **121**, 116-121.e11. https://doi.org/10.1016/j.jaci.2007.10.043

[15] Taylor, A.L., Dunstan, J.A. and Prescott, S.L. (2007) Probiotic Supplementation for the First 6 Months of Life Fails to Reduce the Risk of Atopic Dermatitis and Increases the Risk of Allergen Sensitization in High-Risk Children: A Randomized Controlled Trial. *Journal of Allergy and Clinical Immunology*, **119**, 184-191. https://doi.org/10.1016/j.jaci.2006.08.036

[16] Hidalgo-Cantabrana, C., Gómez, J., Delgado, S., Requena-López, S., Queiro-Silva, R., Margolles, A., Coto, E., Sánchez, B. and Coto-Segura, P. (2019) Gut Microbiota Dysbiosis in a Cohort of Patients with Psoriasis. *British Journal of Dermatology*, **181**, 1287-1295. https://doi.org/10.1111/bjd.17931

[17] Somboonna, N., Wilantho, A., Srisuttiyakorn, C., Assawamakin, A. and Tongsima, S. (2017) Bacterial Communities on Facial Skin of Teenage and Elderly Thai Females. *Archives of Microbiology*, **199**, 1035-1042. https://doi.org/10.1007/s00203-017-1375-0

[18] Dreno, B., Martin, R., Moyal, D., Henley, J.B., Khammari, A. and Seité, S. (2017) Skin Microbiome and Acne Vulgaris: Staphylococcus, a New Actor in Acne. *Experimental Dermatology*, **26**, 798-803. https://doi.org/10.1111/exd.13296

[19] Deng, Y., Wang, H., Zhou, J., Mou, Y., Wang, G. and Xiong, X. (2018) Patients with Acne Vulgaris Have a Distinct Gut Microbiota in Comparison with Healthy Controls. *Acta Dermato-Venereologica*, **98**, 783-790. https://doi.org/10.2340/00015555-2968

[20] Vujkovic-Cvijin, I., Sklar, J., Jiang, L., Natarajan, L., Knight, R. and Belkaid, Y. (2020) Host Variables Confound Gut Microbiota Studies of Human Disease. *Nature*, **587**, 448-454. https://doi.org/10.1038/s41586-020-2881-9

[21] Walter, J., Armet, A.M., Finlay, B.B. and Shanahan, F. (2020) Establishing or Exaggerating Causality for the Gut Microbiome: Lessons from Human Microbiota-Associated Rodents. *Cell*, **180**, 221-232. https://doi.org/10.1016/j.cell.2019.12.025

[22] Lawlor, D.A., Harbord, R.M., Sterne, J.A., Timpson, N. and Davey, S.G. (2008) Mendelian Randomization: Using Genes as Instruments for Making Causal Inferences in Epidemiology. *Statistics in Medicine*, **27**, 1133-1163. https://doi.org/10.1002/sim.3034

[23] Smith, G.D. and Ebrahim, S. (2003) "Mendelian Randomization": Can Genetic Epidemiology Contribute to Understanding Environmental Determinants of Disease? *International Journal of Epidemiology*, **32**, 1-22. https://doi.org/10.1093/ije/dyg070

[24] Kurilshikov, A., Medina-Gomez, C., Bacigalupe, R., *et al*. (2021) Large-Scale Association Analyses Identify Host Factors Influencing Human Gut Microbiome Composition. *Nature Genetics*, **53**, 156-165.

[25] Kurki, M.I., Karjalainen, J., Palta, P., *et al*. (2022) FinnGen: Unique Genetic Insights from Combining Isolated Population and National Health Register Data.

[26] Benjamini, Y. and Hochberg, Y. (1995) Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. *Journal of the Royal Statistical Society*, *Series B* (*Methodology*), **57**, 289-300. https://doi.org/10.1111/j.2517-6161.1995.tb02031.x

[27] Brion, M.J., Shakhbazov, K. and Visscher, P.M. (2013) Calculating Statistical Power in Mendelian Randomization Studies. *International Journal of Epidemiology*, **42**, 1497-1501. https://doi.org/10.1093/ije/dyt179

[28] Burgess, S., Butterworth, A. and Thompson, S.G. (2013) Mendelian Randomization Analysis with Multiple Genetic Variants Using Summarized Data. *Genetic Epidemiology*, **37**, 658-665. https://doi.org/10.1002/gepi.21758

[29] Burgess, S. and Thompson, S.G. (2017) Interpreting Findings from Mendelian Randomization Using the MR-Egger Method. *European Journal of Epidemiology*, **32**, 377-389. https://doi.org/10.1007/s10654-017-0255-x

[30] Bowden, J., Davey, S.G., Haycock, P.C. and Burgess, S. (2016) Consistent Estimation in Mendelian Randomization with Some Invalid Instruments Using a Weighted Median Estimator. *Genetic Epidemiology*, **40**, 304-314. https://doi.org/10.1002/gepi.21965

[31] Milligan, B.G. (2003) Maximum-Likelihood Estimation of Relatedness. *Genetics*, **163**, 1153-1167. https://doi.org/10.1093/genetics/163.3.1153

[32] Hemani, G., Bowden, J. and Davey, S.G. (2018) Evaluating the Potential Role of Pleiotropy in Mendelian Randomization Studies. *Human Molecular Genetics*, **27**, R195-R208. https://doi.org/10.1093/hmg/ddy163

[33] Bowden, J., Davey, S.G. and Burgess, S. (2015) Mendelian Randomization with Invalid Instruments: Effect Estimation and Bias Detection through Egger Regression. *International Journal of Epidemiology*, **44**, 512-525. https://doi.org/10.1093/ije/dyv080

[34] Verbanck, M., Chen, C.Y., Neale, B. and Do, R. (2018) Detection of Widespread Horizontal Pleiotropy in Causal Relationships Inferred from Mendelian Randomization between Complex Traits and Diseases. *Nature Genetics*, **50**, 693-698. https://doi.org/10.1038/s41588-018-0099-7

[35] Yan, H.M., Zhao, H.J., Guo, D.Y., Zhu, P.Q., Zhang, C.L. and Jiang, W. (2018) Gut Microbiota Alterations in Moderate to Severe Acne Vulgaris Patients. *The Journal of Dermatology*, **45**, 1166-1171. https://doi.org/10.1111/1346-8138.14586

[36] Huang, Y., Liu, L., Hao, Z., Chen, L., Yang, Q., Xiong, X. and Deng, Y. (2022) Potential Roles of Gut Microbial Tryptophan Metabolites in the Complex Pathogenesis of Acne Vulgaris. *Frontiers in Microbiology*, **13**, Article ID: 942027.

[37] Hevia, A., Milani, C., López, P., *et al*. (2014) Intestinal Dysbiosis Associated with Systemic Lupus Erythematosus. *mBio*, **5**, e01548-14. https://doi.org/10.1128/mBio.01548-14

[38] Martinez-Medina, M., Denizot, J., Dreux, N., Robin, F., Billard, E., Bonnet, R., Darfeuille-Michaud, A. and Barnich, N. (2014) Western Diet Induces Dysbiosis with Increased *E. coli* in CEABAC10 Mice, Alters Host Barrier Function Favouring AIEC Colonisation. *Gut*, **63**, 116-124. https://doi.org/10.1136/gutjnl-2012-304119

[39] Cani, P.D., Bibiloni, R., Knauf, C., Waget, A., Neyrinck, A.M., Delzenne, N.M. and Burcelin, R. (2008) Changes in Gut Microbiota Control Metabolic Endotoxemia-Induced Inflammation in High-Fat Diet-Induced Obesity and Diabetes in Mice. *Diabetes*, **57**, 1470-1481. https://doi.org/10.2337/db07-1403

[40] Thatikonda, S., Pooladanda, V., Sigalapalli, D.K. and Godugu, C. (2020) Piperlongumine Regulates Epigenetic Modulation and Alleviates Psoriasis-Like Skin Inflammation via Inhibition of Hyperproliferation and Inflammation. *Cell Death & Disease*, **11**, Article No. 21. https://doi.org/10.1038/s41419-019-2212-y

[41] Sonnenburg, J.L. and Bäckhed, F. (2016) Diet-Microbiota Interactions as Moderators of Human Metabolism. *Nature*, **535**, 56-64. https://doi.org/10.1038/nature18846

[42] Dapa, T., Ramiro, R.S., Pedro, M.F., Gordo, I. and Xavier, K.B. (2022) Diet Leaves a Genetic Signature in a Keystone Member of the Gut Microbiota. *Cell Host & Microbe*, **30**, 183-199.e10. https://doi.org/10.1016/j.chom.2022.01.002

[43] Kreuzer, M. and Hardt, W.-D. (2020) How Food Affects Colonization Resistance against Enteropathogenic Bacteria. *Annual Review of Microbiology*, **74**, 787-813. https://doi.org/10.1146/annurev-micro-020420-013457

[44] Archambaud, C., Derré-Bobillot, A., Lapaque, N., Rigottier-Gois, L. and Serror, P. (2019) Intestinal Translocation of Enterococci Requires a Threshold Level of Enterococcal Overgrowth in the Lumen. *Scientific Reports*, **9**, Article No. 8926. https://doi.org/10.1038/s41598-019-45441-3

[45] Gil-Cruz, C., Perez-Shibayama, C., De Martin, A., *et al*. (2019) Microbiota-Derived Peptide Mimics Drive Lethal Inflammatory Cardiomyopathy. *Science*, **366**, 881-886. https://doi.org/10.1126/science.aav3487

[46] Lobo, L.A., Jenkins, A.L., Jeffrey, S.C. and Rocha, E.R. (2013) Expression of *Bacteroides fragilis* Hemolysins *in Vivo* and Role of HlyBA in an Intra-Abdominal Infection Model. *Microbiology Open*, **2**, 326-337. https://doi.org/10.1002/mbo3.76

[47] Singh, D.P., Singh, J., Boparai, R.K., *et al*. (2017) Isomalto-Oligosaccharides, a Prebiotic, Functionally Augment Green Tea Effects against High Fat Diet-Induced Metabolic Alterations via Preventing Gut Dysbacteriosis in Mice. *Pharmacological Research*, **123**, 103-113. https://doi.org/10.1016/j.phrs.2017.06.015

[48] Aranaz, P., Ramos-Lopez, O., Cuevas-Sierra, A., Martinez, J.A., Milagro, F.I. and Riezu-Boj, J.I. (2021) A Predictive Regression Model of the Obesity-Related Inflammatory Status Based on Gut Microbiota Composition. *International Journal of Obesity*, **45**, 2261-2268. https://doi.org/10.1038/s41366-021-00904-4