

COVID-19与月经不规则及异常子宫出血之间的关系：一项两样本孟德尔随机分析

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收稿日期: 2025年2月25日; 录用日期: 2025年3月18日; 发布日期: 2025年3月25日

摘要

观察性研究发现, 在2019冠状病毒大流行期间, 女性月经不调、异常子宫出血的发病率较前增加, 但没有研究证明两者之间存在因果关系。孟德尔随机化分析可以使用独立于混杂因素的遗传变异来获得因果关系的估计。我们旨在通过MR分析探讨COVID-19感染与异常子宫出血及月经不规则之间的因果关系。采用逆方差加权法(IVW)进行主要分析, 并进行敏感性分析和多变量MR分析。结果发现, 不同疾病程度的COVID-19患者与子宫内膜息肉存在因果关系, 感染、患有严重的呼吸道疾病、住院患者的p值分别为0.0376、0.0298、0.00281, 当COVID-19病毒感染进展到严重呼吸道疾病和住院阶段时, 月经大出血的风险增大, p值分别为0.0432和0.0338。当接受MR-Egger回归法作为结果时, 感染新冠肺炎病毒与宫颈息肉之间存在因果关系($p = 0.0490$), 因新冠肺炎住院的患者得子宫内膜恶性肿瘤的风险增大($p = 0.0310$)。我们进一步研究了COVID-19与可能导致月经不规则的激素之间的关系, 发现COVID-19可以影响宿主雌二醇和前列腺素E2的表达(COVID-19感染与前列腺素E2 $p = 0.011$; COVID-19感染患有严重呼吸道疾病病例与雌二醇 $p = 0.005$; COVID-19感染住院病例与雌二醇 $p = 0.027$)。综上所述, 不同程度的新冠肺炎感染增加了女性月经大出血、子宫息肉甚至子宫内膜恶性肿瘤的风险, 新冠肺炎感染同样会导致女性雌二醇及前列腺素E2水平降低, 这可能进一步影响女性月经。

关键词

COVID-19, 月经不规则, 异常的子宫出血, 孟德尔随机化, 雌激素, 前列腺素E2

Association between COVID-19 and Irregular Menstruation and Abnormal Uterine Bleeding: A Two-Sample Mendelian Randomized Analysis

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文章引用: 崔紫程, 陈爱平. COVID-19 与月经不规则及异常子宫出血之间的关系: 一项两样本孟德尔随机分析[J]. 临床医学进展, 2025, 15(3): 2357-2368. DOI: 10.12677/acm.2025.153871

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Received: Feb. 25th, 2025; accepted: Mar. 18th, 2025; published: Mar. 25th, 2025

Abstract

Observational studies have identified a rise in the incidence of irregular menstruation and abnormal uterine bleeding among women during the COVID-19 pandemic. However, no studies have established a causal link between the two. Mendelian randomization analysis leverages genetic variation, which is independent of confounding factors, to estimate causality. Our aim was to explore the causal relationship between COVID-19 infection and abnormal uterine bleeding as well as irregular menstruation using MR analysis. The main analysis employed the variance inverse weighting method (IVW). Sensitivity analysis and multivariate MR analysis were also conducted. The results indicated a causal relationship between patients with varying disease severity and endometrial polyps, with p-values for patients with infection, severe respiratory disease, and hospitalization being 0.0376, 0.0298, and 0.00281, respectively. As COVID-19 virus infection progressed to severe respiratory disease and hospitalization stages, the risk of heavy menstrual bleeding increased, with p-values of 0.0432 and 0.0338, respectively. When the MR-Egger regression method was considered, there was a causal relationship between COVID-19 virus infection and cervical polyps ($p = 0.0490$), and the risk of endometrial malignancies in hospitalized patients due to COVID-19 also increased ($p = 0.0310$). We further investigated the relationship between COVID-19 and hormones that may cause menstrual irregularities. We found that COVID-19 can affect the expression of estradiol and prostaglandin E2 in the host ($p = 0.011$ for COVID-19 infection and prostaglandin E2; $p = 0.005$ for patients with severe respiratory disease and estradiol p ; $p = 0.027$ for inpatients with COVID-19 infection and estradiol). In summary, varying degrees of COVID-19 infection elevates the risk of heavy menstrual bleeding, uterine polyps, and even endometrial malignancies in women. COVID-19 infection also leads to lower levels of estradiol and prostaglandin E2 in women, which may further impact their menstruation.

Keywords

COVID-19, Irregular Menstruation, Abnormal Uterine Bleeding, Mendelian Randomization, Estrogen, Prostaglandin E2

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1. 背景

由严重急性呼吸系统综合征冠状病毒 2 型(SARS-CoV-2)引起的 2019 冠状病毒病(COVID-19)是一场全球性的流行病,已导致严重的健康危机。COVID-19 的主要症状是呼吸系统症状,如感冒、发烧和咳嗽,并可能导致一些不良结局,如肺炎、支气管炎和严重急性呼吸综合征[1]。在随后的研究中发现, SARS-CoV-2 感染能够引起多系统病变,包括心血管系统[2]、肾脏疾病[3]和神经系统病变等[4]。

随着新冠肺炎防控措施的开放, 临床观察到许多女性感染新冠肺炎后出现月经周期不规律、异常子宫出血或绝经后阴道出血等症状。在美国亚利桑那州开展的一项关于 COVID-19 长期后果的队列研究中, 在一组由 127 名年龄在 18~45 岁的非怀孕女性 SARS-CoV-2 阳性参与者组成的子样本中, 16% 的人报告了月经周期的变化, 包括月经不规律(60%)和月经周期延长(35%) [5]。2021 年 3 月, 英国开展了一项名为“COVID-19 大流行与妇女生殖健康”的在线调查[6], 其中指出有 COVID-19 疾病史的育龄期女性出现了月经周期缩短、月经量增大、月经持续时间延长等月经周期改变。相比之下, SARS-CoV-2 与在护士健康研究[7]中, 未观察到感染和月经周期变化相关性。在该样本中, 与疫苗接种($n = 3527, 91\%$)相比, SARS-CoV-2 感染的患病率较低($n = 421, 11\%$), 超过一半的 COVID-19 阳性个体($n = 223$)在感染前接种了疫苗, 这可能限制了研究检测小到中度影响的能力。虽然 COVID-19 感染已不再被视为重大国际公共卫生问题, 但仍有暴发流行的可能, 因此对 COVID-19 感染潜在后果的研究不能停止。

月经是女性生殖系统的一种周期性生理现象, 其正常与否与多种激素的协同作用密切相关, 其中包括雌激素(Estrogen)、孕激素(Progesterone)、卵泡刺激素(Follicle Stimulating Hormone, FSH)、黄体生成素(Luteinizing Hormone, LH)、前列腺素(Prostaglandin)和泌乳素(Prolactin)。异常子宫出血(Abnormal Uterine Bleeding, AUB)可以根据有无结构性改变分为两类: 有结构改变引起的包括子宫内膜息肉(Polyp)所致 AUB (AUB-P)、子宫腺肌病(Adenomyosis)所致 AUB (AUB-A)、子宫平滑肌瘤(Leiomyoma)所致 AUB (AUB-L)、子宫内膜恶变和不典型增生所致 AUB (AUB-M); 没有结构改变的异常子宫出血包括全身凝血相关疾病(Coagulopathy)所致 AUB (AUB-C)、排卵障碍(Ovulatory Dysfunction)相关的 AUB (AUB-O)、子宫内膜局部异常(Endometrial)所致 AUB (AUB-E)、医源性(Iatrogenic) AUB (AUB-J)、未分类(Not Yet Classified)的 AUB (AUB-N)。

孟德尔随机化(Mendelian Randomization, MR)是一种流行病学方法, 已被广泛应用于评估暴露与结果之间的潜在因果关系[8]。根据孟德尔定律, 基因变异在减数分裂时是随机分配的[9]。MR 分析使用遗传变异作为工具变量(IVs), 可以最大限度地减少混杂因素或反向因果关系的影响。鉴于目前研究方法的局限性, 我们试图使用 MR 方法评估月经紊乱、异常子宫出血及相关因素与 COVID-19 结局的潜在影响和因果关系。

2. 材料和方法

我们首先基于 COVID-19 宿主遗传学倡议的 GWAS 水平汇总数据进行两样本孟德尔随机化(Two Sample Mendelian Randomization, TSMR)分析, 探讨异常子宫出血、月经频繁和月经不规则、绝经后阴道流血与 COVID-19 感染之间的因果关系。然后我们进行了 COVID-19 感染与月经紊乱相关因素如雌激素、黄体生成素、卵泡刺激素、睾酮、前列腺素 E2 等的因果分析。本研究的设计如图 1 所示。

2.1. 数据来源: COVID-19 宿主遗传学倡议

采用全基因组关联研究(GWAS)数据库进行双样本孟德尔随机化研究。COVID-19 的 GWASs 数据来自 COVID-19 宿主遗传学倡议[10] [11], 这是一项旨在阐明宿主遗传因素在 SARS-CoV-2 病毒大流行易感性和严重程度中作用的全球倡议。新冠肺炎汇总数据可根据对照分组分为新冠肺炎感染病例与正常人群(ebi-a-GCST011071, ebi-a-GCST011072, ebi-a-GCST011073, ebi-a-GCST011074), 新冠肺炎确诊为严重呼吸道疾病病例与正常人群(ebi-a-GCST011075, ebi-a-GCST011076, ebi-a-GCST011077, ebi-a-GCST011078), 新冠肺炎住院病例与非住院病例(ebi-a-GCST011079, ebi-a-GCST011080)及因新冠肺炎住院病例与正常人群(ebi-a-GCST011081, ebi-a-GCST011082, ebi-a-GCST011083, ebi-a-GCST011084), 具体内容可见表 1。此数据根据患者的年龄、性别等进行调整, 所有病例均通过了明确的临床诊断。

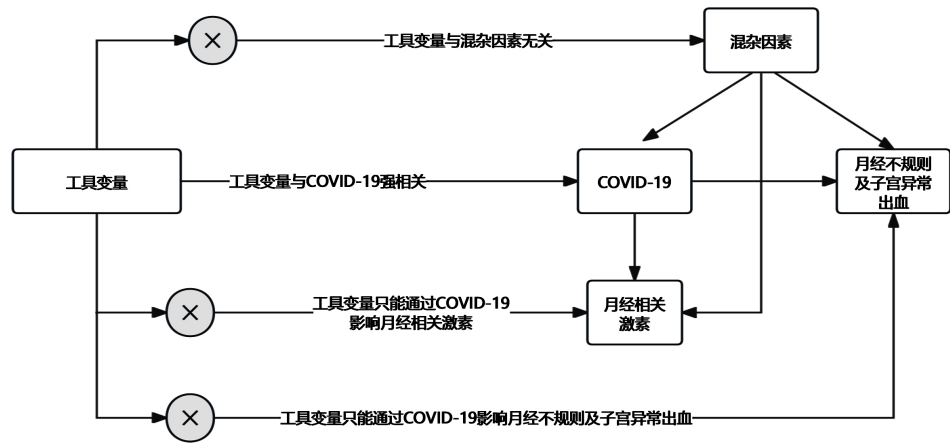


Figure 1. A two-sample Mendelian randomization study design of COVID-19 infection associated with irregular menstruation, abnormal uterine bleeding, and hormones associated with menstruation
图 1. COVID-19 感染与月经不规则及子宫异常出血、月经相关激素有关的两样本孟德尔随机化研究设计

Table 1. The details of IVWs of COVID-19
表 1. COVID-19 工具变量详情

暴露因素	GWAS ID	发表年份	样本量	SNPs 数目	来源
感染病例	ebi-a-GCST011071	2020	1,588,783	8,103,014	https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST011071/
	ebi-a-GCST011072	2020	1,058,410	7,750,967	https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST011072/
	ebi-a-GCST011073	2020	1,683,768	8,660,177	https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST011073/
	ebi-a-GCST011074	2020	1,348,071	8,666,451	https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST011074/
严重呼吸道疾病病例	ebi-a-GCST011075	2020	1,388,342	9,739,225	https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST011075/
	ebi-a-GCST011076	2020	707,407	7,475,770	https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST011076/
	ebi-a-GCST011077	2020	1,059,456	7,496,658	https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST011077/
	ebi-a-GCST011078	2020	1,059,456	9,817,241	https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST011078/
新冠肺炎住院病例与非住院病例	ebi-a-GCST011079	2020	10,365	4,971,116	https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST011079/
	ebi-a-GCST011080	2020	16,645	8,360,206	https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST011080/
新冠肺炎住院病例	ebi-a-GCST011081	2020	1,887,658	8,107,040	https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST011081/
	ebi-a-GCST011082	2020	1,557,411	6,814,406	https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST011082/
	ebi-a-GCST011083	2020	1,557,411	8,110,403	https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST011083/
	ebi-a-GCST011084	2020	1,206,629	7,534,178	https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST011084/

2.2. 月经紊乱、异常子宫出血的遗传工具

英国生物银行(UKB)是英国最大的关于导致或预防疾病遗传和环境因素的信息库。该项目收集了 50 万名年龄在 40 岁至 69 岁之间的英国志愿者的基因信息、血液样本、生活方式和环境暴露数据，并在之后的几十年里追踪他们的健康记录[12]。根据 ICD-10 的诊断标准，我们的研究获得了 UKBB 的子宫和阴道异常出血、月经过度频繁和不规则、月经大出血、绝经后阴道流血、子宫肌瘤、子宫腺肌病、子宫息肉及宫颈息肉的 GWAS 数据。子宫内膜恶性肿瘤的 GWAS 数据来源于一项关于 220 种人类深层表型全基

基因组关联研究[13], 详见表 2。

Table 2. The details of IVWs of menstrual disorder and AUB

表 2. 月经不规则、异常子宫出血工具变量的详情

结局因素	GWAS ID	发表年份	样本量	SNPs 数目	来源
异常的子宫和阴道不明原因的出血	ukb-b-10849	2018	463,010	9,851,867	ukbiobank
月经频繁和月经不规则	ukb-a-578	2017	337,199	10,894,596	ukbiobank
绝经后阴道流血	ukb-b-5712	2018	463,010	9,851,867	ukbiobank
月经大出血	ukb-b-19719	2018	462,933	9,851,867	ukbiobank
子宫息肉	ukb-b-15136	2018	462,933	9,851,867	ukbiobank
宫颈息肉	ukb-b-19110	2018	463,010	9,851,867	ukbiobank
子宫肌瘤	ukb-a-522	2018	337,199	9,851,867	ukbiobank
子宫腺肌症	ukb-b-9668	2018	463,010	9,851,867	ukbiobank
子宫内膜恶性肿瘤	ebi-a-GCST90018838	2021	240,027	24,135,295	https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST90018838/

2.3. 月经相关激素的遗传工具

与月经相关的激素包括雌激素、LH、FSH、泌乳素、睾酮、前列腺素 E2 的 GWAS 汇总数据来自欧盟开放 GWAS 数据项目, 仅包括欧洲人群[14]-[19]。其中, 我们用雌二醇来代表雌激素在人体内的水平[16], 详见表 3。

Table 3. The details of IVWs of hormones associated with menstruation

表 3. 与月经相关激素工具变量详情

结局因素	GWAS ID	发表年份	样本量	SNPs 数目	来源
雌二醇	ebi-a-GCST90020092	2020	163,985	7,488,193	PubMed ID: 32042192
FSH	prot-a-528	2021	3301	10,534,735	PubMed ID: 29875488
LH	prot-a-529	2021	3301	10,534,735	PubMed ID: 29875488
泌乳素	ebi-a-GCST90012030	2020	21,758	20,208,673	PubMed ID: 33067605
睾酮	ebi-a-GCST90012104	2020	382,988	16,137,327	PubMed ID: 32042192
前列腺素 E2	ebi-a-GCST90019410	2020	10,708	15,566,910	PubMed ID: 33328453

2.4. 工具变量的选择

选择作为工具变量的 SNP 需要满足孟德尔随机化的三个假设: 1) 与暴露相关; 2) 独立, 不受其他混杂影响; 3) 只有暴露因素会对结局变量产生影响。我们设置了一个 $P < 5 \times 10^{-6}$ 的 SNP 选择阈值, 同时计算 F 值来检验工具变量的强度, 并选择与 $F > 10$ 作为强相关的工具变量。连锁不平衡系数设为 $r^2 < 0.001$, 连锁不平衡距离的 r^2 值为 10000 kb。

2.5. 数据分析

所有统计分析均使用 R 软件 4.3.3 版中的 TwoSampleMR R 包进行。在这项 MR 研究中, 逆方差加权 (Inverse Variance Weighting, IVW) 被用作估计总体效应大小的主要方法[20]。补充方法包括 MR-Egger 回归法和加权中位数 (Weight Median, WM), 用于验证 MR 结果的稳健性。MR-PRESSO 显示原始 Global Test p 值 < 0.05 , 去除异常值后 MR 结果 ($p < 0.05$) 与原始结果有显著差异。Cochrane 的 Q 值用于评估遗传工具估计值之间的异质性, 如果未观察到异质性, 则采用固定效应模型 ($p < 0.05$); 否则, 采用随机效应模型。MR-Egger 中截取的 p 值用于检测水平多效性。此外, 我们使用“留一法”验证来确定单个 SNP 是否对 MR 估计具有显著的独立影响。

3. 结果

3.1. COVID-19 与月经不规则及子宫异常出血的孟德尔随机分析

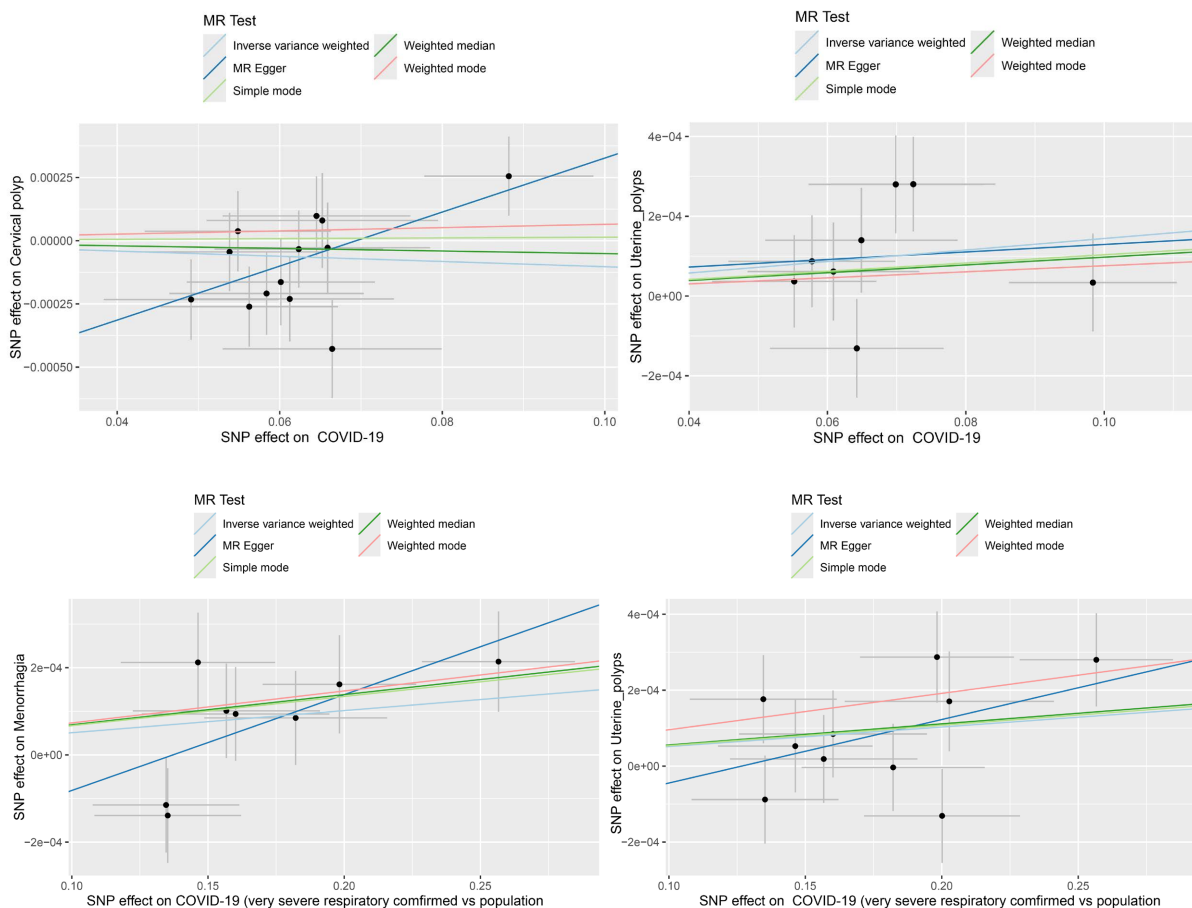
在我们的孟德尔随机研究中, 根据 MR 中的 IVW 方法, 不同疾病程度的 COVID-19 患者与子宫内膜息肉存在因果关系, 感染、患有严重的呼吸道疾病、住院患者的 p 值分别为 0.0376、0.0298、0.00281。当 COVID-19 病毒感染进展到严重呼吸道疾病和住院阶段时, 月经大出血的风险增大, p 值分别为 0.0432 和 0.0338。SNPs 对暴露和结果的估计效应大小显示在散点图中 (图 1)。研究结果与另外 4 种 MR 方法的敏感性分析一致。此外, Cochran's Q 检验和 MR-Egger 回归在子宫息肉中未发现 SNP 异质性和定向多效性之间的证据。当接受 MR-Egger 回归法作为结果时, 感染新冠肺炎病毒与宫颈息肉之间存在因果关系 ($p = 0.0490$), 因新冠肺炎住院的患者得子宫内膜恶性肿瘤的风险增大 ($p = 0.0310$)。IVW 及其他两种方法的 β 、 se 、 p 值如表 4 所示。图 2 展示了描述主要结果的散点图。

Table 4. Mendelian randomized analysis of COVID-19 and irregular menstruation and abnormal uterine bleeding
表 4. COVID-19 与月经不规则及子宫异常出血的孟德尔随机分析

暴露	结局	方法	SNP	Beta	Se	P-value
COVID-19 感染病例	宫颈息肉	MR-Egger	8	0.000944152	0.00405596	0.823668623
		Weighted Median	8	0.000974486	0.000896264	0.276915003
		Inverse Variance Weighted	8	0.00144232	0.000694028	0.037692257
	子宫息肉	MR-Egger	13	0.010681509	0.004830143	0.049095925
		Weighted Median	13	-0.000509744	0.001105771	0.644809355
		Inverse variance weighted	13	-0.001028386	0.000833324	0.217174223
	子宫息肉	MR-Egger	10	0.001672449	0.001182189	0.194876327
		Weighted Median	10	0.000556754	0.000304477	0.067465912
		Inverse Variance Weighted	10	0.000514765	0.000236979	0.029840981
严重呼吸道疾病病例	月经大出血	MR-Egger	8	0.00219742	0.001049969	0.08127823
		Weighted Median	8	0.000691156	0.00028732	0.016149135
		Inverse Variance Weighted	8	0.000507868	0.000251205	0.043204201

续表

COVID-19 住院病例	子宫息肉	MR-Egger	13	0.000392972	0.001698672	0.821297219
		Weighted Median	13	0.000984895	0.000357831	0.005915966
		Inverse Variance Weighted	13	0.000772135	0.000258488	0.002816139
	月经大出血	MR-Egger	12	0.003788508	0.001697342	0.049671771
		Weighted Median	12	0.000676394	0.000320905	0.035051214
		Inverse Variance Weighted	12	0.000501559	0.000236397	0.033864763
	子宫内膜恶性肿瘤	MR-Egger	33	-0.220156583	0.097443657	0.031040062
		Weighted Median	33	-0.025761848	0.058692278	0.660711686
		Inverse Variance Weighted	33	-0.013838251	0.041359809	0.737940354



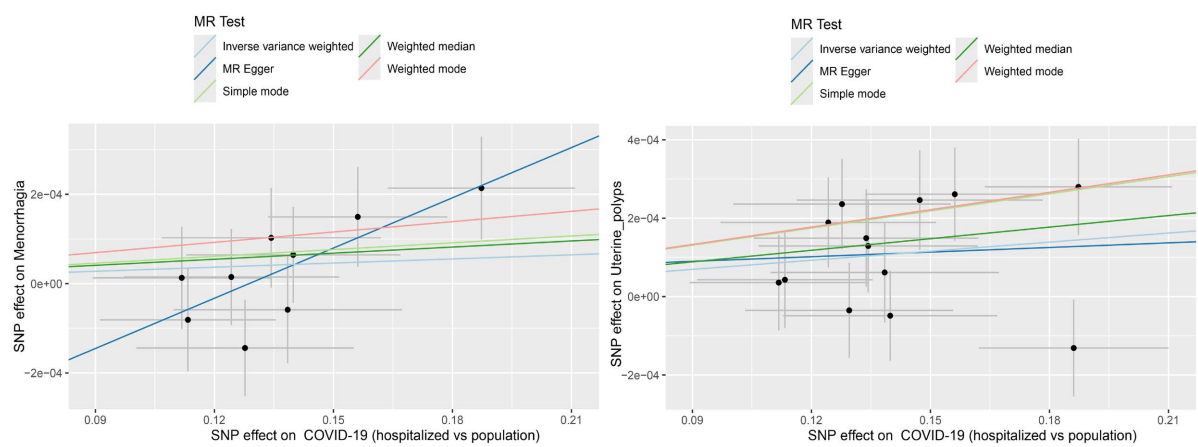


Figure 2. Scatter plot of Mendelian randomized analysis of COVID-19 and irregular menstruation and abnormal uterine bleeding
图 2. COVID-19 与月经不规则及子宫异常出血的孟德尔随机分析散点图

3.2. COVID-19 与月经相关激素的孟德尔随机化分析

我们进一步通过 TSMR 分析了 COVID-19 与雌二醇、FSH、LH、IGF-1、催乳素、DHEA-S 睾酮、前列腺素 E2 之间的关系。其中,我们发现 COVID-19 与雌二醇、前列腺素 E2 之间存在显著性结果。Cochran's Q 检验和 MR-Egger 回归发现了 SNP 异质性和定向多效性之间的证据。IVW 及其他两种方法的 beta、se、p 值如表 5 所示。图 3 展示了描述主要结果的散点图。

Table 5. Mendelian randomization analysis of COVID-19 and menstrual-related hormones
表 5. COVID-19 与月经相关激素的孟德尔随机化分析

暴露	结局	Method	SNP	Beta	Se	P-value
COVID-19 疾病病例	前列腺素 E2	MR-Egger	20	-0.131827476	0.204147488	0.526590898
		Weighted Median	20	-0.126405422	0.081671163	0.121685802
		Inverse Variance Weighted	20	-0.154712009	0.061157811	0.011415427
严重呼吸道 疾病病例	雌二醇	MR-Egger	31	0.05541441	0.03691021	0.144081012
		Weighted Median	31	0.048291752	0.019287424	0.012286929
		Inverse Variance Weighted	31	0.038311368	0.013714806	0.00521521
COVID-19 住院病例	雌二醇	MR-Egger	29	0.042900724	0.050472655	0.402810987
		Weighted Median	29	0.077346316	0.03210824	0.015999623
		Inverse Variance Weighted	29	0.050720295	0.022889121	0.026697476

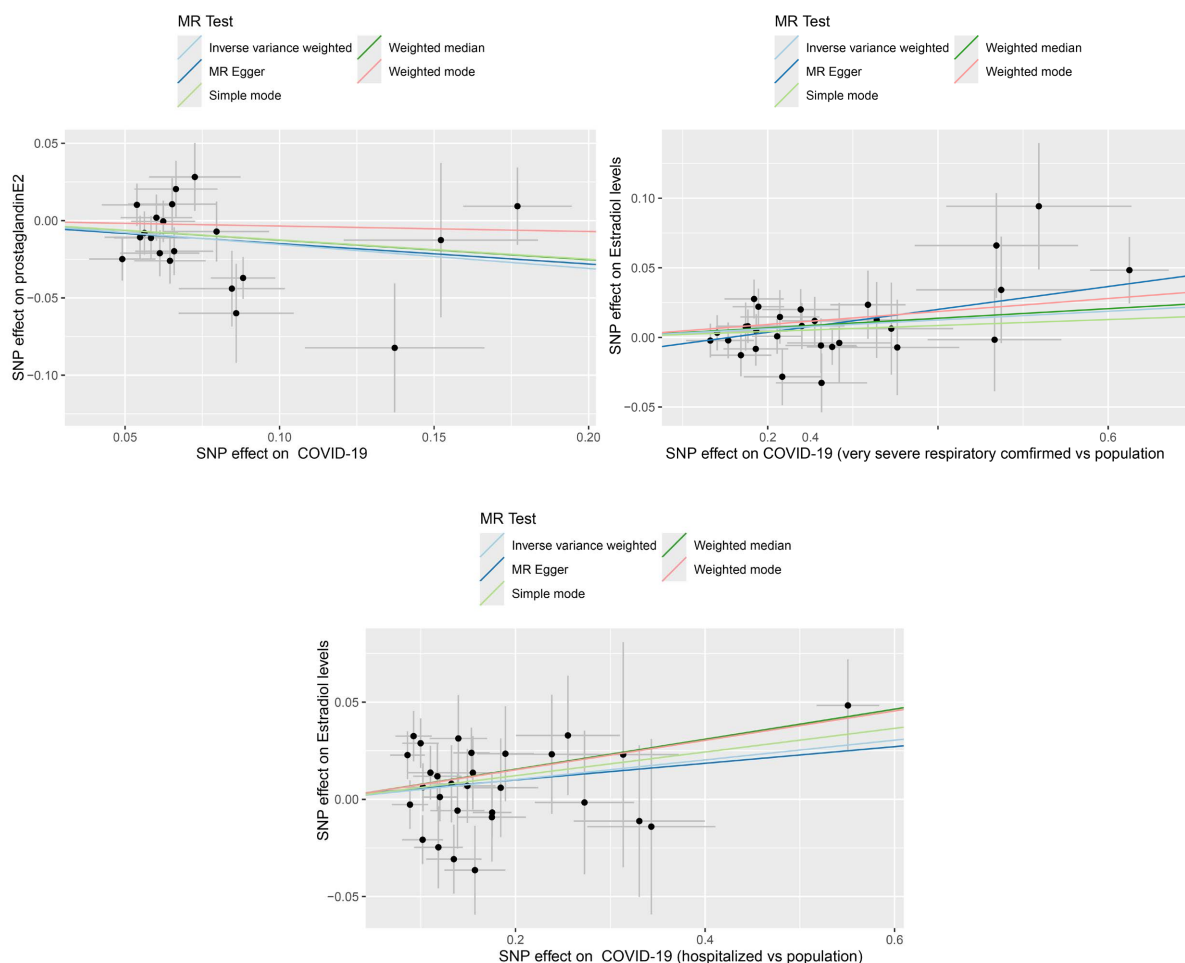


Figure 3. Scatter plot of Mendelian randomization analysis of COVID-19 and menstrual-related hormones

图 3. COVID-19 与月经相关激素的孟德尔随机化分析散点图

4. 讨论

新型冠状病毒的传播极大地改变了人们的生活方式，给人们的健康造成了不可估量的危害。这种危害不仅反映在呼吸道症状上，还包括其他系统的许多其他潜在变化[21]。一些研究报告称，COVID-19 病毒对女性和男性的影响不同，英国的一项前瞻性多中心队列研究发现，50 岁以下的女性比同龄男性更容易感染 COVID-19，尤其是年轻女性[22]。

COVID-19 对女性生殖系统健康的影响引起了众多学者的关注[21]。中国武汉的一项回顾性横断面研究调查了 COVID-19 对育龄妇女卵巢储备功能、性激素和月经周期的影响[23]，在参与研究的 177 名患者中，28% 的人月经周期发生了变化，25% 的人月经量发生了变化。另一项针对育龄女性保健工作者的横断面研究也报告，新冠肺炎病毒大流行期间月经紊乱的程度明显高于之前，且伴有月经量和经期时间减少[24]。据我们所知，这是第一个研究 COVID-19 与月经不规则、异常子宫出血之间关系的因果研究。

MR 利用受孕时基因变异的随机分配，独立于混杂因素，来识别混淆程度较低且不易发生反向因果关系的因果效应[8]。我们使用 SNP 作为工具变量来进行 MR 研究。三项分析提示 COVID-19 病毒感染对月经大出血、子宫息肉结局有因果影响。异质性分析和水平多效性分析也支持我们的结果。子宫内膜息肉是导致 AUB 的常见结构性因素，内源性雌激素增加、慢性炎症、肥胖等都可能致子宫内膜息肉。子

子宫内膜易受全身炎症和应激的影响, 子宫内膜月经生理异常可导致 AUB-E, 包括对局部炎症、血管功能、缺氧和组织修复的影响。月经期间的子宫内膜有许多典型的炎症标志物, 与正常对照组相比, 月经过多女性月经流出物中的促炎细胞因子肿瘤坏死因子 α (TNF- α) 和前列腺素含量更高[25]-[27]。Lucia 等对 COVID-19 感染的子宫内膜进行了 RNA 测序, 发现 COVID-19 改变了子宫内膜炎性环境, 也可能间接影响子宫内膜导致月经不调[28]。

鉴于多次临床回顾性观察, 发现 COVID-19 与月经周期改变存在相关性。我们进一步对 COVID-19 与月经相关激素的因果关系进行 TSMR 分析, 发现 COVID-19 与雌二醇和前列腺素 E2 之间存在负相关因果关系。这表明 COVID-19 可能会影响雌二醇和前列腺素 E2 的分泌, 进一步导致阴道不规则出血。但这只能部分解释 COVID-19 引起的阴道不规则出血。有证据表明, 新型冠状病毒可引起宿主免疫失调, 影响 HPO 轴, 导致下丘脑性腺功能减退, 引起暂时性闭经。更重要的是, COVID-19 还可能通过引起凝血功能障碍导致月经大量出血[29]。

除了 COVID-19 感染引起的宿主病理生理变化导致阴道不规则出血外, 医源性因素也是 AUB 的因素之一。一些用于治疗 COVID-19 早期症状的常见抗病毒药物含有细胞色素 P450 抑制剂(例如利托那韦)。因 COVID-19 住院的患者在治疗期间经常给予地塞米松, 内源性糖皮质激素已被证明可抑制子宫内膜血管生成[30]。COVID-19 疫苗引起的月经紊乱和绝经后阴道出血也引起了官方的关注[31]。

新冠肺炎病毒感染作为一个持续了 3 年的全球大流行感染, 社会环境的巨变同样可能引起月经周期的改变。月经周期正常通常被视为女性生殖健康的外在标志, COVID-19 病毒引起的月经紊乱和阴道不规则出血在大流行期间增加了女性的焦虑[32]。反过来, COVID-19 造成的压力和心理困扰会导致月经不规律。这种恶性循环将导致妇女在社会恢复期间不能充分参与工作[33]。对 COVID-19 与月经不规律之间关系的因果分析将有助于临床医生解释新冠肺炎流行期间的不规则阴道出血及月经紊乱相关问题, 并帮助患者缓解焦虑。Taha Takmaz 对土耳其女性医护人员进行在线问卷调查, 研究显示 COVID-19 大流行引起的焦虑、感知压力、抑郁症状与医疗保健提供者月经周期不规律患病率增加之间存在关联[34]。在此之前, 也有文献研究了大规模灾害和其他传染病影响男性患严重急性呼吸系统综合症的病死率是否高于女性[35]-[37]。沙特阿拉伯的一项关于中东呼吸综合征冠状病毒(MERS-CoV)的流行病学研究显示, 男性的发病率(62% vs 38%)与死亡率(52% vs 23%)均高于女性[35]。一项关于海湾战争退伍女兵的调查发现, 海湾战争导致的慢性疲劳影响了女性的性欲与性生活[36]。而卡特琳娜飓风自然灾害影响了年轻女性的生殖保健生活[37]。

虽然与观察性研究相比, 孟德尔随机化分析减少了混杂因素, 但仍有不足和缺陷。首先, 我们的结果是基于欧洲人群的遗传数据, 这限制了外推到其他人群的可能性。其次, 由于 SNPs 不足, 一些与月经有关的因素, 如孕激素和 GnRH, 未纳入 MR 分析。

5. 结论

不同程度的新冠肺炎感染增加了女性月经大出血、子宫息肉甚至子宫内膜恶性肿瘤的风险, 但与不明原因的异常子宫出血、月经不规则和月经频繁、绝经后阴道出血、宫颈息肉、子宫肌瘤及子宫腺肌病之间不存在因果关系。新冠肺炎感染同样会导致女性雌二醇及前列腺素 E2 水平降低, 但并不会对 LH、FSH、泌乳素、睾酮造成影响。

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