Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letters to the Editor

Genetic variation associated with COVID-19 is also associated with endometrial cancer

Dear editor,

In this journal, Cai and colleagues described that uterine corpus endometrial carcinoma, esophageal carcinoma, kidney renal papillary cell carcinoma, lung adenocarcinoma, kidney chromophobe, and prostate adenocarcinoma were at the high risk of COVID-19 infection.[1] Recently, in this journal, Qiu and colleagues reported that the high expression of SARS-CoV-2 cell receptors might lead to higher COVID-19 infection rates in cancer patients.[2] However, it is still unclear whether COVID-19 infection is a risk factor for endometrial cancer.

Mendelian randomization (MR) study, based on the principle that genetic variants are randomly allocated at meiosis, is independent of many factors that bias observational studies.[3,4] MR study has been widely used to assess the causal link between an exposure and an outcome.[3–7] To assess the effect of COVID-19 on endometrial cancer, we performed the present two-sample MR study as followed.

First, we extracted genetic instrumental variants (IVs) from COVID-19 GWAS. To date, the largest COVID-19 GWAS was reported by the COVID-19 Host Genetics Initiative in 2020.[8] Primarily, this GWAS is to elucidate the role of host genetic factors in susceptibility and severity of the SARS-CoV-2 virus pandemic. The summary dataset of COVID-19 GWAS (14,134 cases and 1284,876 controls from European ancestry) is available in https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST010780. We selected three independent genome-wide significant variants as COVID-19 genetic IVs using the following criteria[1]: p value$(< 5 \times 10^{-8})$ on COVID-19;[2] linkage disequilibrium (LD) ($r^2 < 0.001$) between SNPs[3]; The F-statistics of all selected IVs (F-statistic > 10) were all above the threshold of weak instruments of F-statistic < 10.[9] The main characteristics of three selected COVID-19 genetic IVs are shown in **Suppl. Table 1**.

Second, we extracted three selected COVID-19 genetic IVs from endometrial cancer GWAS dataset. To date, the largest endometrial cancer GWAS, including 12,906 endometrial cancer cases and 108,979 controls of European ancestry from 17 studies via the Epidemiology of Endometrial Cancer Consortium (E2C2), the UK Biobank, and the Endometrial Cancer Association Consortium (ECAC), was described by O'Mara et al. in 2018.[10] The profiles of endometrial cancer GWAS are shown in **Suppl. Table 2**. The summary dataset of endometrial cancer GWAS is available in https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST006464. Three independent COVID-19 genetic IVs were successfully extracted from endometrial cancer GWAS. The association of three independent COVID-19 genetic IVs with endometrial cancer GWAS is shown in **Suppl. Table 3**.

Third, we tested whether there was significant pleiotropy or heterogeneity of three independent COVID-19 genetic IVs in endometrial cancer GWAS. MR-egger_intercept test and MR Egger test in Cochran's Q statistic suggested no significant pleiotropy or heterogeneity, respectively, of three independent COVID-19 genetic IVs in endometrial cancer GWAS (**Suppl. Table 4**). Therefore, all three selected COVID-19-associated genetic variants can be taken as the effective IVs in our MR study.

Finally, we performed MR analysis. We found that as COVID-19 genetically increased, the risk of endometrial cancer had an increased trend using IVW (Beta = 0.350, p = 0.098; OR = 1.418, 95% CI = [0.938∽2.145]), simple mode (Beta = 0.707, p = 0.116; OR = 2.028, 95% CI = [1.209∽3.404]), and weighted mode (Beta = 0.118, p = 0.412; OR = 1.125, 95% CI = [0.899∽1.408]) (**Table 1**). Importantly, this trend was further successfully proven using weighted median (Beta = 0.313, p = 0.004; OR = 1.368, 95% CI = [1.108∽1.689]) (**Table 1**). In addition, as the effect of single SNP on COVID-19 increased, the effect of single SNP on endometrial cancer risk increased using IVW, weighted median, simple mode, and weighted mode **(Suppl. Fig. 1)**. Critically, each effect size **(Suppl. Fig. 2)** and leave-one-out sensitivity **(Suppl. Fig. 3)** suggested that each effect of COVID-19-associated SNPs on endometrial cancer risk were robust.

This study has several limitations. First, because COVID-19 genetic IVs and endometrial cancer GWAS are from European ances-

Table 1
The causal association of COVID-19 with endometrial cancer.

Method	nsnp	Beta	SE	p val	OR	OR_lci95	OR_uci95
Weighted median	3	0.313	0.108	**0.004**	1.368	1.108	1.689
IVW	3	0.35	0.211	0.098	1.418	0.938	2.145
Simple mode	3	0.707	0.264	0.116	2.028	1.209	3.404
Weighted mode	3	0.118	0.114	0.412	1.125	0.899	1.408

COVID-19: Corona virus disease 2019; IVW: inverse variance weighted; NSNP: the number of single-nucleotide polymorphism; Beta: the regression coefficient based on COVID-19 raising effect allele; SE: standard error; $p < 0.05$ represents the causal association of the increased COVID-19 with endometrial cancer; OR: Odds ratio; OR_lci95: Lower limit of 95% confidence interval for OR; OR_uci95: Upper limit of 95% confidence interval for OR.

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try, our results need be proven in other ancestries. Second, it is necessary to prove our conclusion by randomized controlled trials. Third, the underlying mechanism by which COVID-19 genetically increased the risk of endometrial cancer is still unclear and worth to be explored in the future.

In summary, genetic variation associated with increased risk of COVID-19 is also associated with increased risk of endometrial cancer. Thus, COVID-19 may be a risk factor for endometrial cancer.

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Ethical approval

Our study was approved by the Ethics Committee of Beijing Institute of Brain Disorders in Capital Medical University. This article contains human participants collected by several studies performed by previous studies. All participants gave informed consent in all the corresponding original studies, as described in the Methods.

Availability of data and materials

The summary statistics for endometrial cancer GWAS (ID: ebi-a-GCST006464) and for COVID-19 GWAS (ID: ebi-a-GCST010780) are available in ieu open gwas project at https://gwas.mrcieu.ac.uk/datasets/. The MR analysis code can be found at https://mrcieu.github.io/TwoSampleMR/articles/index.html.

Declaration of Competing Interest

The authors have no potential conflicts of interest to disclose.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jinf.2022.01.026.

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