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Causal association between aspirin use and risk of endometrioid carcinoma: a Mendelian randomization study

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Abstract. – OBJECTIVE: The aim of the study was to investigate the causal relationship between aspirin use and the risk of endometrial endometrioid cancer (EEC) using two-sample Mendelian randomization (TSMR) and multivariable Mendelian randomization (MVMR) study.

MATERIALS AND METHODS: A TSMR analysis was conducted to estimate the potential causal relationship between aspirin use and the risk of EEC using genome-wide data from Genome-wide association study (GWAS). The causal association between aspirin use and EEC was further analyzed by MVMR analysis after adjusting for various factors such as obesity, hypertension, diabetes, and infertility. The single nucleotide polymorphism (SNP) data associated with aspirin use and EEC was obtained from the GWAS catalog database.

RESULTS: A total of six SNPs were included as instrumental variables in TSMR, which showed that taking aspirin reduced the risk of EEC [OR = 0.02, 95% CI = 0-0.28, $p = 0.005$, inverse variance weighted (IVW) method]. Besides, the results of the weighted median (WME) method, weighted mode, and simple mode were consistent with the results shown by the IVW method. After further using the MVMR method, the causal association of aspirin use and prevention of EEC onset remained significant after adjusting for the effects of obesity, hypertension, and diabetes (OR = 0.076, 95% CI = 0.007-0.793, $p = 0.031$). Sensitivity analyses, including heterogeneity, horizontal multiplicity, and leave-one-out tests, showed the reliability of the instrumental variables, proving that the results were reliable and not significantly biased.

CONCLUSIONS: Taking aspirin can reduce the risk of EEC morbidity, and it is expected to be of great significance for the early prevention and treatment of endometrial cancer by exploring the biological mechanism of aspirin on endometrioid cancer at a deeper level.

Key Words:
Aspirin, Endometrioid cancer, Mendelian randomization, Causal inference.

Introduction

Endometrial cancer (EC) is one of the three most common gynecologic cancers in women, with an incidence of 4% in recent years[1]. In the last two decades, the incidence of endometrial cancer has been increasing due to increased obesity rate, decreased physical activity, and longer life expectancy in women[2-4]. Among them, endometrial endometrioid cancer (EEC) is the most common type, the morbidity age of which is gradually becoming younger. Many women are diagnosed at childbearing age, which seriously affects their quality of life[5].

It has been shown that the onset of EEC is associated with chronic inflammation, and that noncombative estrogen, obesity, diabetes, the use of tamoxifen, and polycystic ovary syndrome are associated with the increase of proinflammatory response in the endometrium, resulting in the elevation of inflammatory factors, such as tumor necrosis factor-α (TNF-α), which mediates estrogen or roles as an independent mechanism in the occurrence and development of EEC[6]. Aspirin, also known as acetylsalicylic acid, is a nonsteroidal anti-inflammatory drug that exerts its anti-inflammatory effects mainly by inhibiting cyclooxygenase (COX)[7]. Several studies[8,9] at home and abroad have shown that aspirin consumption is associated with a reduction in the incidence of endometrial cancer. Arango et al[8] found that aspirin exerted a dose-dependent inhibitory effect on endometrial adenocarcinoma cells in an in *vitro* study. A meta-analysis[9] of 13 observational studies with a total of 11,323 cases showed that regular aspirin use was associated with a possible reduction in the risk of EEC. In addition, Matsuzaki et al[10] found that aspirin also significantly improved survival in EEC patients under 60 years

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of age. However, Sperling et al[11] found that aspirin consumption did not reduce the incidence of EEC. Rather, heavy, and long-term aspirin consumption may be associated with the increase in EEC mortality (HR = 1.15, 95% CI = 0.97-1.36). Studies above[8-11] are interfered with by many confounding factors, resulting in inconsistencies in the effect of aspirin on preventing the onset of EEC.

Mendelian randomization (MR) is a method of applying genetic instrumental variables to analyze genetic data, which can provide estimates of causal effects, avoid the influence of confounders in observational studies, and better reflect the long-term effects of exposure on outcomes, and has become an important evaluation method for establishing causal associations between diseases and risk factors[12]. Multivariable Mendelian randomization (MVMR) is a complement to TSMR, which takes into account the pleiotropy of the same SNP, namely the same SNP may be associated with more than one phenotype. The MVMR allows the inclusion of multiple potentially highly correlated exposures in the MR estimation and evaluates the direct causal effect of a particular exposure of interest on the outcome by adjusting the effects of other exposures. As mentioned above, our study explored the association between aspirin use and the risk of developing EEC using GWAS genome-wide data and utilizing the TSMR and MVMR methods.

Materials and Methods

All analyses used publicly available Genome-wide association study (GWAS) summarized data, and therefore, ethical approval from institutional review boards was not necessary. Figure 1 illustrates the study design based on the three core hypotheses of the TSMR: (1) Association hypothesis: There is a strong correlation between the instrumental variables (IVs) and the exposure (taking aspirin). (2) Independence hypothesis: IVs are not relevant with any confounders of the association between taking aspirin and EEC. (3) Exclusivity hypothesis: There was no direct causal relationship between IVs and outcome, and they can only influence outcome through exposure. Previous studies[13,14] have provided evidence of genetic associations between a variety of characteristics and aspirin use and endometrioid cancer, including factors such as body mass index (BMI)[13], hypertension (HBP)[14], and type II diabetes mellitus (T2DM)[15]. Thus, these three variables were included in the MVMR study.

In the TSMR, single nucleotide polymorphisms (SNPs) associated with aspirin use (instrumental variable) and EEC (outcome variable) were obtained from the GWAS catalog, and instrumental variables (IVs) were selected to determine the causality between aspirin use and ECC with the help of various statistical methods, such as inverse variance weighted (IVW), weighted median, MR Egger, simple mode, weighted mode, and so on. We further analyzed the causal association between aspirin use and EEC after correcting for factors such as body mass index (BMI), high blood pressure (HBP), and diabetes mellitus type 2 (T2DM) by MVMR using the multivariate IVW method as the main analytical method.

GWAS Data Sources

The data related to aspirin use and EEC were obtained from the GWAS catalog database. The database summarizes 42,347 datasets from the Genome-wide association study (GWAS) database, with a total of 245,542,320,999 genetic associations. Among them, the data related to aspirin use came from a study by UK Biobank, which included 337,159 European populations, containing 45,012 sample sizes and 10,894,596 SNPs (https://gwas.mrcieu.ac.uk/datasets, GWAS ID:ukb-b-8755). In this study, aspirin use in the case group was less than 75 mg (tablets) per day. However, there was no mention of a time frame for aspirin use. In contrast, the GWAS data on EEC came from a study by O'Mara et al[16] regarding the EC susceptibility loci in European populations, containing 54,884 cases of EEC, with 9,464,330 SNPs (see Table I). The GWAS data related to BMI, HBP, and T2DM were obtained from the IEU open GWAS project (https://gwas.mrcieu.ac.uk/).

Statistical Analysis

Five methods including IVW, weighted median, MR Egger, simple mode, and weighted mode were performed to assess the causal association between aspirin use and EEC. The primary MR analyses were conducted by utilizing the IVW method. For exposures with more than 3 SNPs, the estimates for variants were then pooled using the random multiplicative effects IVW method. For exposures instrumented by only 2 SNPs, the fixed-effects IVW method was employed[17]. The weighted median estimator can generate resilient causal estimates, maintaining robustness even when up to 50% of instrumental variables may be invalid[18]. Besides, the MR Egger method intro-

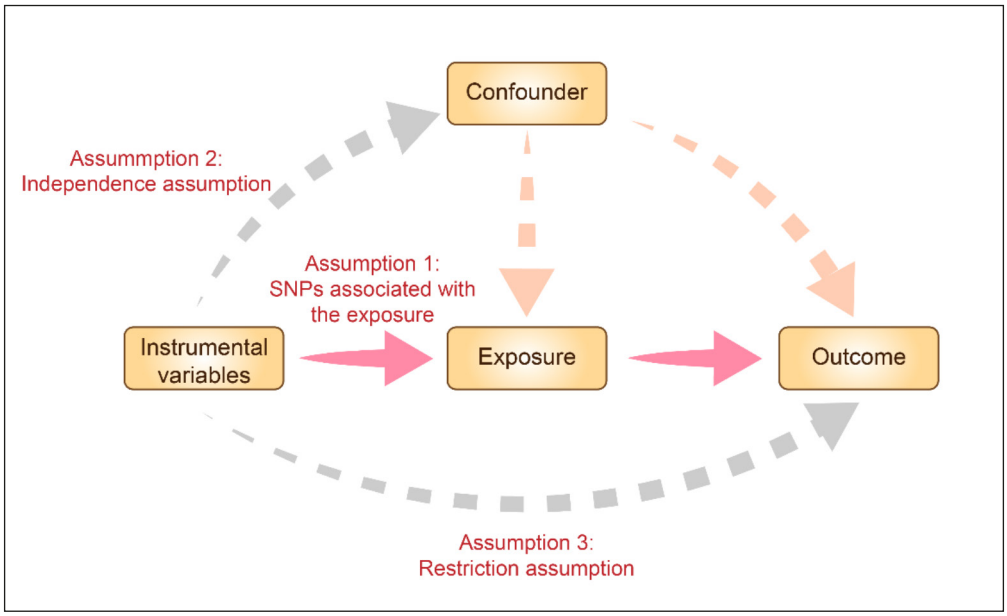

Figure 1. The three core hypotheses of the two-sample Mendelian randomization.

duces an intercept term in the regression model to assess the directional pleiotropy[19]. Further, simple mode provides robustness for pleiotropy[20], and weighted mode is sensitive to the difficult bandwidth selection for mode estimation[21].

We employed Cochran's Q test to evaluate the heterogeneity among IVs. In case notable heterogeneity was detected ($p < 0.05$), the random-effects model was employed; conversely, if heterogeneity was not significant ($p > 0.05$), the fixed-effects model was utilized. A leave-one-out analysis was conducted to pinpoint influential SNPs in the causal estimations. The MR-PRESSO method can detect outliers and provide a causal estimate after the removal of corresponding outliers[22]. A threshold of statistical significance was set at $p < 0.05$ (two-sided). All analyses were performed using "TwoSampleMR" (version 0.5.7, Stephen Burgess, Chicago, IL, USA) in R software (version 3.6.3, R Foundation for Statistical Computing, Vienna, Austria)

Results

Two-Sample Mendelian Randomization

SNP loci of genetic variation whose association with aspirin use was genome-wide significant ($p < 5\times10^{-8}$). A threshold of 0.01 was set for the linkage disequilibrium parameter (r^2), and the genetic distance Kb was 5,000. A total of eight SNPs that were strongly associated with aspirin use were screened. We excluded SNPs whose corresponding phenotypes had correlation significance with EEC (N = 0), and removed 2 palindromic sequences after pooling the 8 SNPs above with the ending database. Finally, 6 SNPs were retained after the screening with F values > 10[23], which were

Table I. Summary information on exposure and outcome GWAS data.

Exposure/Outcome	Data sources	Population	Sample size	nSNPs	Year
Aspirin use	UK Biobank	European	337,154	10,894,596	2017
EEC	O'Mara TA	European	54,884	9,464,330	2018
BMI	IEU	European	99,998	7,191,606	2022
T2DM	IEU	European	20,480	23,808,617	2019
HBP	IEU	European	337,199	10,894,596	2017

EEC: Endometrial endometrioid cancer; BMI: body mass index; T2DM: type II diabetes mellitus; HBP: hypertension; nSNPs: Single nucleotide polymorphisms number.

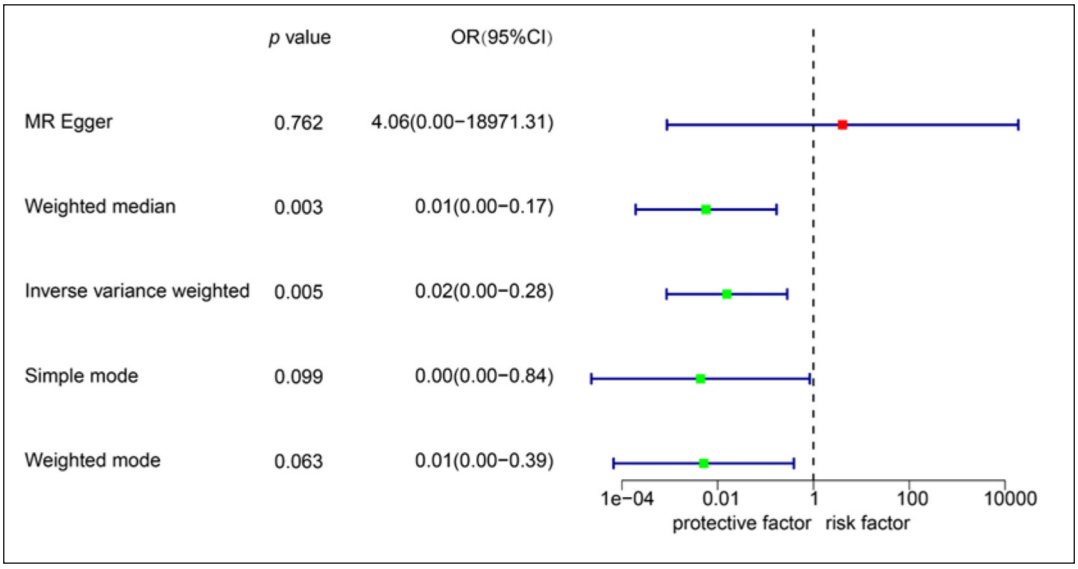

Figure 2. TSMR analysis of aspirin use and risk of EEC.

rs10455872, rs117733303, rs1831733, rs583104, rs73015016, and rs7412, respectively. The chromosome where each SNP locus was located, related genes, effector alleles, Minimum Alternate Allele Frequency (MAF), β coefficients, and *p*-value and F-value of association with aspirin use and EEC were extracted (see Table II).

TSMR analysis was done with the IVW random effects model, MR Egger, weighted median, simple mode, and weighted mode. The results showed that there was a significant causal association between aspirin use and the risk of EEC, and taking aspirin could make the risk of developing EEC lower (OR = 0.02, 95% CI = 0.00-0.28, $p = 0.005^{**}$, IVW method). Additionally, the results of the weighted median method were similar to those of the IVW method: Taking aspirin reduced the risk of developing EEC (OR = 0.01, 95% CI = 0.00-0.17, $p = 0.003^{**}$, weighted median method) (Figure 2).

The Cochran's Q test was used to test for heterogeneity in the study results and did not reveal significant heterogeneity among IVs (Q: 4.58, $p = 0.24$). MR-Egger regression analysis was chosen to test the results of randomization analyses for multivariate validity, indicating that multivariate validity does not significantly bias the results (MR Egger intercept = -0.05, $p = 0.25$), and the MR-PRESSO test results showed no outlying SNPs and no significant horizontal multivariate validity ($p = 0.34$). In addition, this study used the Leave-one-out method to analyze the effect of individual SNPs on the overall results, and no matter which SNP was removed, it did not fundamentally affect the results, which revealed that the results of this MR were robust.

Although the results of MR Egger, simple mode, and weighted mode were not statistically significant, they were considered to be reliable

Table II. Instrumental variable information summary.

SNP	Chr	Gene	EA	MAF	Aspirin use		EEC		F-value
					beta	*p*	beta	*p*	
rs10455872	6	LPA	G	0.081	0.013	7.31 × 10-19	-0.110	0.21	78.68
rs117733303	6	LPAL2	G	0.019	0.020	9.25 × 10-11	0.046	0.79	41.98
rs1831733	9	CDKN2B-AS1	C	0.476	0.007	2.15 × 10-18	0.035	0.42	76.56
rs583104	1	CELSR2	T	0.227	0.006	2.27 × 10-10	-0.033	0.53	40.22
rs73015016	19	LDLR	A	0.119	-0.007	1.03 × 10-8	0.068	0.32	32.78
rs7412	19	APOE	T	0.081	-0.009	5.45 × 10-10	0.216	0.01	38.51

SNP: Single nucleotide polymorphisms number; Chr: Chromosome; EA: Effect allele; MAF: minor allele frequency; EEC: Endometrial endometrioid cancer.

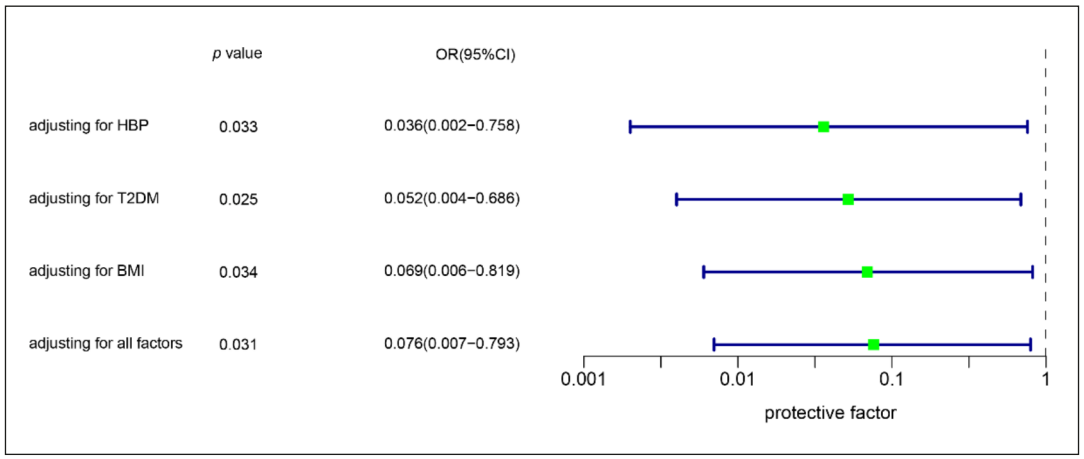

Figure 3. MVMR analysis of oral aspirin and risk of EEC.

positive results, allowing for the β values of all five methods to be > 0 and no multiplicity or heterogeneity was observed[24].

Multivariable Mendelian Randomization

To better assess the genetically predicted causal relationship between aspirin use and EEC, we performed MVMR analysis by adjusting for BMI, HBP, and T2DM. The multivariate IVW MR method was used to estimate causality.

When we adjusted only for BMI, there was a direct causal effect between taking aspirin and a reduced risk of EEC (adjusted for BMI: OR = 0.069, 95% CI = 0.006-0.819, $p = 0.034^{*}$). Similarly, the same conclusion was obtained after adjusting for hypertension, and type II diabetes (adjusted for hypertension: OR = 0.036, 95% CI = 0.002-0.758, $p = 0.033^{*}$; adjusting for T2DM: OR = 0.005, 95% CI = 0.004-0.686, $p = 0.025^{*}$); and when we adjusted for all three factors, strong evidence which was genetically predicted showed that taking aspirin prevented the onset of EEC (OR = 0.076, 95% CI = 0.007-0.793, $p = 0.031^{*}$) (Figure 3).

Discussion

In this study, we used large-scale GWAS pooled data and two-sample MR analysis to explore the causal relationship between aspirin use and the risk of developing EEC. The results of our study showed that taking aspirin can significantly reduce the risk of developing EEC. In addition, MVMR analysis showed that the effect of aspirin on EEC was not influenced by BMI, HBP, or T2DM.

The preventive effect of aspirin administration in EEC has been found in several previous studies[25,26]. Matsuo et al[25], in a multicenter retrospective study on EEC, found there was a 10% improvement in 5-year disease-free survival of patients who took aspirin (90.6% *vs.* 80.9%, adjusted HR = 0.46, 95% CI = 0.25-0.86), and the effect was even more pronounced in patients younger than 60 with a BMI > 30. Webb et al[26] conducted a pooled analysis of more than 7,000 women with EC, and showed that a nearly 20% reduction in the risk of developing EEC was observed in obese women who took aspirin 2-6 times per week (OR = 0.81, 95% CI = 0.68-0.96).

Similarly, aspirin reduced the incidence of endometrial cancer in a susceptible population. Lynch syndrome is an autosomal dominant disorder caused by germline mutations in the DNA mismatch repair (MMR) gene. As one of the high-risk factors for the morbidity of endometrial cancer, the incidence of colorectal cancer and EC in this group of patients is about 75% and 50%, respectively, during their lifetime[27]. Burn et al[28] showed that taking aspirin for 2 years or more significantly reduced the incidence of colorectal cancer (HR = 0.41, 95% CI = 0.19-0.86). The results of a prospective study indicated that the incidence of all non-colorectal Lynch syndrome-related cancers, including EC (38 cases in total), reduced by 37% when aspirin was taken by patients with Lynch syndrome (HR = 0.63, 95% CI = 0.34-1.19)[29].

Over the past 40 years, an increasing number of studies[30-33] have supported the therapeutic role of aspirin in the secondary prevention of malignant tumors (general population and high-risk

groups) and in the tertiary prevention of malignant tumors (adjuvant therapy). Factors such as obesity, HBP, and T2DM mellitus are common features of patients with EEC. Some studies[30,31] have shown that chronic inflammation in the body driven by obesity may be an important pathogenesis of EC. On the one hand, the aromatase present in obese patients can convert androstenedione, etc., into estrogen to promote endometrial hyperplasia, and on the other hand, the estrogen produced can promote interleukin-6 (IL-6) and induce the production of aromatase, thus creating positive feedback. Chronic inflammation also causes elevated levels of TNF-α, IL-6, and C-reactive protein in the body and induces insulin resistance, promoting the pathogenesis of EC. While aspirin, as a steroidal anti-inflammatory drug, can inhibit the activation of the Wnt/β-catenin pathway, as well as NF-κB, thereby inhibiting tumor cell signaling and promoting their apoptosis[32,33]. In our MVMR study, after adjusting for the effects of BMI, hypertension, and diabetes mellitus, there was still a significant causal association between aspirin use and the development of EEC, suggesting that the prevention of endometrial cancer by aspirin may be achieved through other pathways. Evidence from various basic and clinical studies has illustrated that aspirin prevents the development of EEC[34,35]. Aspirin plays a great role in tumor control.

Our study has the characteristics of stability and data quantification by using the MR method, in which genetic variants in the population associated with aspirin use were used as exposure factors. Compared with observational studies, MR studies can simulate randomized controlled trials in an observational setting, which reduces the interference of confounding factors such as social environment and lifestyle in observational studies, avoiding the interference of reverse causality and ethical issues. In this study, the TSMR and MVMR study of aspirin use, and EEC was conducted with the help of the GWAS database platform, which provided evidence for elucidating the role of aspirin use in lowering the risk of EEC from a genetic point of view and provided basis for subsequent related molecular studies, which is of great significance for the prevention of EEC patients. As a first-line anticoagulant, aspirin may become an important adjunctive drug for the prevention and treatment of EEC in the future, providing a new option for anti-EEC therapy.

Limitations

However, this study also has some limitations in exploring the causal relationship between the two. First, the study used pooled data from the GWAS catalogue database, which only assessed the linear relationship between aspirin use and EEC, and the nonlinear relationship was unclear. Besides, the GWAS data for aspirin used in this study did not specifically describe age, gender, or duration of drug use, so we were unable to conduct further research at this time. Finally, the study data was derived from populations of European ancestry. Thus, the results may have changed in other ethnic populations.

Conclusions

This study showed that taking aspirin reduces the risk of developing EEC, and by exploring the biological mechanisms of aspirin on EEC at a deeper level, it is expected to be of great importance for the early prevention and treatment of EC.

Conflict of Interest

The authors declare that they have no conflict of interests.

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Authors' Contributions

X. Chang and L. Han contributed to the conception, study design, and data interpretation. L. Han and S.-J. Liu contributed to writing the manuscript. S.-J. LIU contributed to performing statistical analysis. All authors contributed to the article and approved the submitted version.

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Data Availability

The datasets generated during and/or analyzed during the current study are available in the GWAS Catalog (https://www.ebi.ac.uk/gwas/).

Ethics Approval and Informed Consent

The relevant review boards approved all GWAS data in this present Mendelian randomized study, and all participants provided consent and did not involve any direct interaction with human subjects or animals. Therefore, no ethical clearance or additional informed consent was required.

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