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Association between gynecologic cancer and Alzheimer's disease: a bidirectional mendelian randomization study

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Abstract

Background Alzheimer's disease (AD) manifests with a higher rate of occurrence in women. Previous epidemiological studies have suggested a potential association between AD and gynecological cancers, but the causal relationship between them remains unclear. This study aims to explore the causal link between 12 types of gynecological cancers and AD using a bidirectional Mendelian randomization (MR) approach.

Methods We obtained genetic correlation tools for AD using data from the most extensive genome-wide association study. Genetic correlation data for 12 types of gynecological cancers were also sourced from the Finnish Biobank. These cancers include breast cancer (BC), cervical adenocarcinoma (CA), cervical squamous cell carcinoma (CSCC), cervical cancer (CC), endometrial cancer (EC), ovarian endometrioid carcinoma (OEC), ovarian cancer (OC), ovarian serous carcinoma (OSC), breast carcinoma in situ (BCIS), cervical carcinoma in situ (CCIS), endometrial carcinoma in situ (ECIS), and vulvar carcinoma in situ (VCIS). We used the inverse-variance weighted (IVW) model for causal analysis and conducted horizontal pleiotropy tests, heterogeneity tests, MR-PRESSO tests, and leave-one-out analyses to ensure the robustness of our results. We also applied replication analysis and meta-analysis to further validate our experimental results.

Results The study found that EC (P_{IVW} =0.037, OR [95% CI] = 1.032 [1.002, 1.064]) and CCIS (P_{IVW} = 0.046, OR [95% CI] = 1.032 [1.011, 1.064]) increase the risk of AD, whereas OC was negatively correlated with AD (P_{IVW} = 0.016, OR [95% CI] = 0.974[0.954, 0.995]). In reverse MR analysis, AD increased the risk of CC (P_{IVW} = 0.039, OR [95% CI] = 1.395 [1.017, 1.914]) and VCIS (P_{IVW} = 0.041, OR [95% CI] = 1.761 [1.027, 2.021]), but was negatively correlated with OEC (P_{IVW} = 0.034, OR [95% CI] = 0.634 [0.417, 0.966]). Sensitivity analysis results demonstrated robustness. These findings were further substantiated through replication and meta-analyses.

Conclusions Our MR study supports a causal relationship between AD and gynecological cancers. This encourages further research into the incidence of gynecological cancers in female Alzheimer's patients and the active prevention of AD.

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Background

Gynecological cancer refers to cancers that originate in the female reproductive system [1]. Since the incidence of breast cancer in women is higher than in men, this article classifies breast cancer as a form of gynecological cancer, a perspective shared by some research studies [2, 3]. Breast cancer, cervical cancer, ovarian cancer, and endometrial cancer, as common malignancies among women, have seen a gradual increase in incidence rates in recent years, with the age of onset trending towards younger populations [4]. According to the latest global cancer statistics from 2020, the incidence rate of breast cancer in women has surpassed that of lung cancer, making it the most common cancer worldwide [5]. In 2020, there were 2.3 million new cases of breast cancer globally, accounting for 11.7% of all cancer cases, with breast cancer deaths comprising 6.9% of all cancer-related deaths. New cases of cervical cancer were 0.60 million, representing 3.1% of all cancer cases; endometrial cancer had 0.42 million new issues, accounting for 2.2%; and ovarian cancer had nearly 0.31 million new cases, making up 1.6% of all topics [6]. These figures indicate a substantial economic burden on society [7]. For gynecological cancers, particularly recurrent and advanced stages, traditional standard treatments often leave much to be desired [8]. While developing new treatment strategies is crucial, preventing these diseases is also important and is increasingly recognized as a priority by the public.

Alzheimer's Disease [AD] is a common neurodegenerative condition in the geriatric population [9], with studies finding a higher prevalence in women [10–12]. Epidemiological evidence supports an inverse relationship between the incidence of cancer and AD [13, 14] – a diagnosis of cancer reduces the risk of developing AD, and vice versa [15]. However, does this apply to all cancers? Research indicates that women with breast cancer have a significantly increased risk of early-onset Alzheimer's and related dementias [ADRD] [16]. Additionally, older breast cancer survivors exhibiting age-related phenotypes and genotypes may face increased risks of cognitive decline [17]. Studies have also found that breast cancer patients carrying the APOE4 allele experience declines in memory, attention, and learning abilities for an extended period post-treatment [18]. In a study involving over six million women, 36,131 breast cancer patients and 3019 cervical cancer patients were found to have early-onset ADRD [19]. Moreover, AD patients tend to be diagnosed with gynecological cancers at a later stage, when the disease is more severe, often missing the optimal treatment window [20]. Due to the

limitations of clinical cancer research and the communication challenges posed by cognitive impairments in AD patients, establishing a causal relationship between the two conditions is challenging.

Like randomized controlled trials, Mendelian randomization [MR] studies involve the random allocation of genes during embryonic development, similar to the random assignment of interventions at the start of a trial [21]. This method reduces the impact of confounding factors. It overcomes common causality issues in observational epidemiological studies, avoiding the high costs, ethical concerns, feasibility, and experimental environment issues associated with the randomized controlled trial [22, 23]. Hence, this study designed a bidirectional MR study using single nucleotide polymorphisms [SNPs] as instrumental variables [IVs] to explore the bidirectional causal effects between gynecological tumors and AD, offering new insights into preventing and treating AD and cancer.

Methods

Study design

To explore the causal relationship between gynecologic cancer and AD, the present study conducted a bidirectional MR analysis. Figure 1 illustrates our study's methodology and process. The selected genetic IVs need to satisfy three assumptions of MR analysis [24]. First, genetic variations are assumed to be closely related to the exposure event. Second, there is no relation between gynecologic cancer, AD, and confounding factors. Finally, genetic variations are assumed to directly influence disease outcomes through exposure factors, excluding other pathways. We derived our genetic instruments for exposure and outcome from publicly available genome-wide association study [GWAS] summary statistics. As all ethical aspects have been addressed in the original research, our study requires no additional ethical approval. This study follows the STROBE-MR writing guidelines.

Data sources

The 12 selected common cancers in women for this study, including breast cancer (BC), cervical adenocarcinoma (CA), cervical squamous cell carcinoma (CSCC), cervical cancer (CC), endometrial cancer (EC), ovarian endometrioid carcinoma (OEC), ovarian cancer (OC), ovarian serous carcinoma (OSC), breast carcinoma in situ (BCIS), cervical carcinoma in situ (CCIS), endometrial carcinoma in situ (ECIS), and vulvar carcinoma in situ (VCIS), were analyzed using IVs from the Finnish Cancer Registry (R9) in the Finnish Biobank. The Finnish
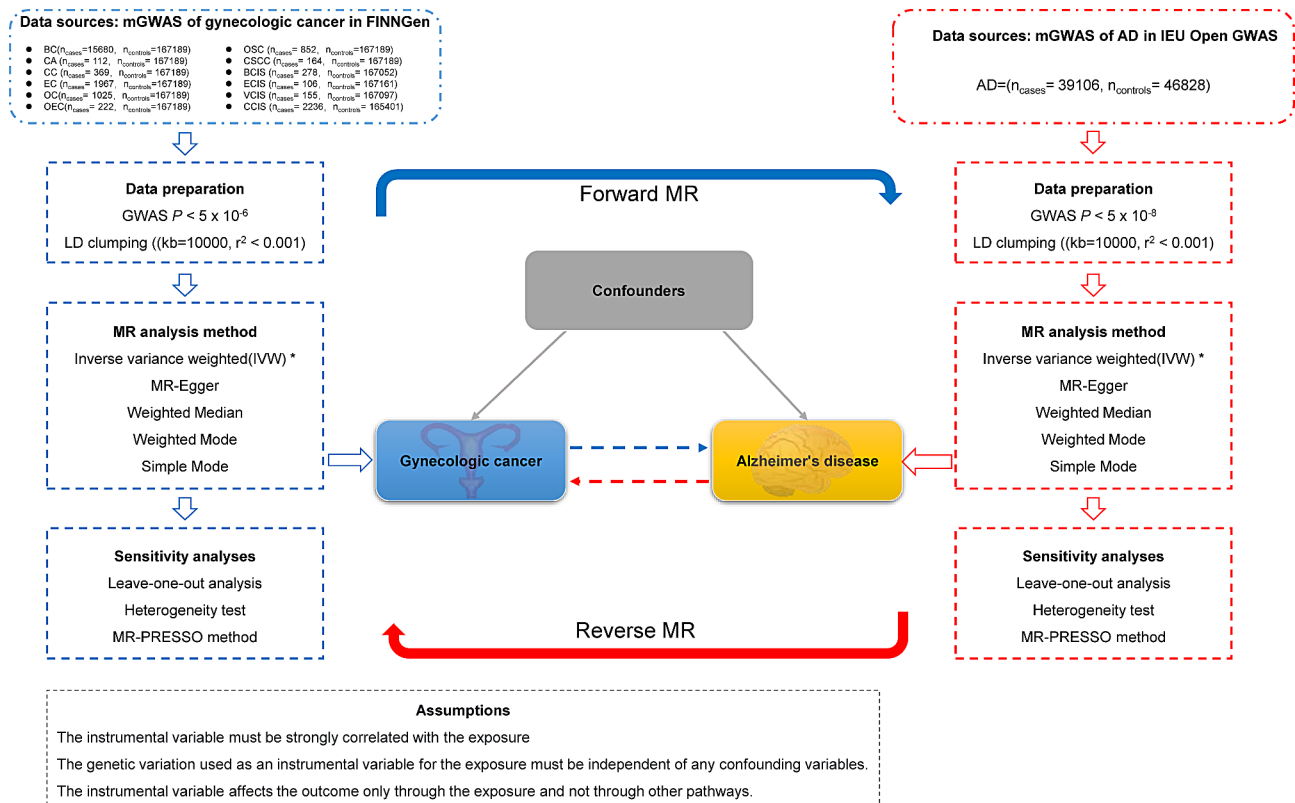
Fig. 1 Flowchart of the bidirectional Mendelian randomization study. *Abbreviations* MR, Mendelian randomization; SNP, Single nucleotide polymorphism; GWAS, genome-wide association study; LD, linkage disequilibrium

Table 1 Details of studies included in mendelian randomization analyses

Traits	Data source	Author and year	Sample size(cases/controls)	Ancestry	GWAS ID
Exposure					
BC	FinnGen	NA. (2021)	182,869 (15,680 / 167,189)	European	finn-b-C3_BREAST_EXALLC
CA	FinnGen	NA. (2021)	167,301 (112 / 167,189)	European	finn-b-C3_CERVIX_ADENO_EXALLC
CSCC	FinnGen	NA. (2021)	167,353 (164 / 167,189)	European	finn-b-C3_CERVIX_SQUAM_EXALLC
CC	FinnGen	NA. (2021)	17,558 (369 / 167,189)	European	finn-b-C3_CERVIX_UTERI_EXALLC
EC	FinnGen	NA. (2021)	169,156 (1,967 / 167,189)	European	finn-b-C3_CORPUS_UTERI_EXALLC
OEC	FinnGen	NA. (2021)	167,411 (222 / 167,189)	European	finn-b-C3_OVARY_ENDOMETROID_EXALLC
OC	FinnGen	NA. (2021)	168,214 (1,025 / 167,189)	European	finn-b-C3_OVARY_EXALLC
OSC	FinnGen	NA. (2021)	168,041 (852 / 167,189)	European	finn-b-C3_OVARY_SEROUS_EXALLC
BCIS	FinnGen	NA. (2021)	167,330 (278 / 167,052)	European	finn-b-CD2_INSITU_BREAST_EXALLC
CCIS	FinnGen	NA. (2021)	167,277 (2,236 / 165,041)	European	finn-b-CD2_INSITU_CERVIX_UTERI_EXALLC
ECIS	FinnGen	NA. (2021)	165,147 (106 / 167,161)	European	finn-b-CD2_INSITU_ENDOMETRIUM_EXALLC
VCIS	FinnGen	NA. (2021)	167,252 (155 / 167,097)	European	finn-b-CD2_INSITU_VULVA_EXALLC
Outcome					
AD$_1$	IEU Open GWAS	Bellenguez C (2022)	487,511 (39,106 / 46,828)	European	ebi-a-GCST90027158
AD$_2$	GWAS Catalog	Jansen IE (2019)	455,258 (71,880 / 383,378)	European	GCST007320

BC, breast Cancer; CA, Cervical adenocarcinoma; CSCC, cervical squamous cell carcinoma; CC, cervical cancer; EC, endometrial cancer; OEC, ovarian endometrioid carcinoma; OC, ovarian cancer, OSC, ovarian serous carcinoma; BCIS, breast carcinoma in situ; CCIS, cervical carcinoma in situ; ECIS, endometrial carcinoma in situ; VCIS, vulvar carcinoma in situ; AD$_1$, initial analysis data for Alzheimer's Disease; AD$_2$, validation analysis data for Alzheimer's Disease

Biobank was established in the early 20th century and contains data related to healthcare, genetics, familial inheritance, demographics, education, employment, and other aspects, offering high research value and practicality [25]. The AD whole-genome dataset is derived from the European Alzheimer's Disease Biobank (EADB) Alliance, which consists of 39,106 samples and 46,828 controls, with a sample size of 487,511 and 20,921,626 SNPs [26]. All participants are of European ancestry. More details can be found in Table 1.

Selection and evaluation of IVs

In the forward MR analysis, gynecologic cancer is considered the exposure factor, and AD is the outcome event. The IVs associated with gynecologic cancer should demonstrate genome-wide significance ($P<5e-06$). Initially, we selected genetic variations adhering to the criterion of $P<5e-08$. However, under these stringent conditions, no available SNPs were available for cancers such as CA and CSCC. In the reverse MR analysis, AD is treated as the exposure and gynecologic cancer as the outcome, with AD-related IVs meeting the $P<5e-08$ threshold. In the bidirectional MR analysis, to obtain independent SNPs, the linkage disequilibrium (LD) parameters (R^2) should be <0.001 and kb=10,000. The F-statistic represents the strength of the MR analysis, with a value greater than 10 indicating statistical robustness [27]. The formula for calculating the F-statistic is $R^2(N-2)/(1-R^2)$ [28]. It is essential to exclude SNPs associated with confounding factors. We utilized Phenoscanner (version 2, accessed on October 30, 2023) to eliminate SNPs linked to potential confounders. The filtered SNPs will serve as the IVs for our study.

MR analysis

MR studies investigating the relationship between exposure and outcome primarily use the inverse-variance weighted (IVW) method because it can obtain a robust result without pleiotropy [29]. MR-Egger, Simple Mode, weighted median (WM), and Weighted Mode methods are used as supplementary methods to assess the robustness of the primary analysis.

We conducted various sensitivity analyses to ensure the robustness of the outcomes obtained from the bidirectional MR. Sensitivity analysis includes horizontal pleiotropy test, heterogeneity test, MR-PRESSO test, and leave-one-out analysis. The horizontal pleiotropy test is performed by MR-Egger regression. If a significant intercept term is found in MR-Egger analysis, it indicates the presence of horizontal pleiotropy [30, 31]. Cochran's Q test is used to assess the heterogeneity of SNPs. If Cochran's Q statistic is statistically significant ($P\leq0.05$), it suggests considerable heterogeneity in the analysis results. MR-PRESSO test using MR pleiotropy residual sum and outlier test is used to detect outliers [32]. If outliers are detected, they will be removed, and the remaining IVs will be reanalyzed. Leave-one-out analysis is used to evaluate whether a single SNP determines significant results [33]. The risk association between gynecologic cancer and AD is expressed as an odds ratio [OR] and 95% confidence interval (CI). If $P\leq0.05$, it provides evidence for a possible causal relationship. We used the Steiger test to perform directionality testing to avoid biases caused by reverse causation. Analysis was conducted using R 4.3.1, utilizing several packages, including TwoSampleMR, ggplot2, and MRPRESSO.

Confirmatory analysis and meta-analysis

To ensure the reliability of our study results, we conducted a replication validation using an additional AD GWAS dataset from the GWAS Catalog, with accession number GCST007320 [34]. This dataset includes 71,880 cases and 383,378 controls, all of European ancestry. We applied this AD dataset to conduct a bidirectional MR analysis with 12 types of gynecological cancers. The selection process of IVs, the MR analysis standards, and sensitivity testing methods were consistent with the initial analysis. We performed a meta-analysis to combine the IVW results from the replication and initial analyses that showed causal associations. The choice of effect model was based on the heterogeneity of the results. When heterogeneity was not significant, a fixed-effect model was used; otherwise, a random-effect model was applied [35]. The meta-analysis was performed using the meta package and Review Manager 5.3.

Results

Causal effect of gynecologic cancer on AD

In the forward MR analysis, we included a total of 78 independent SNPs associated with BC, 2 independent SNPs associated with CA, 4 independent SNPs associated with CSCC, 6 independent SNPs associated with CC, 11 independent SNPs associated with EC, 5 independent SNPs associated with OEC, 6 independent SNPs associated with OC, 11 independent SNPs associated with OSC, seven independent SNPs associated with BCIS, 12 independent SNPs associated with CCIS, one independent SNP associated with ECIS, and 3 independent SNPs associated with VCIS (Supplementary Table 1). Importantly, all IVs exhibited F-statistics well above 10, ranging from 256.345 to 34274.379, which indicates a low risk of bias and supports fulfilling the strong instrumental assumptions required for MR (Supplementary Table 3).

The IVW method showed that when AD was the outcome factor, EC could increase the risk of AD (P_{IVW} = 0.037, OR [95% CI]=1.032 [1.002, 1.064]), while OC could suppress the risk of AD (P_{IVW} = 0.016, OR [95% CI]=0.974 [0.954, 0.995]), and CCIS could promote the risk of AD (P_{IVW} = 0.046, OR [95% CI]=1.032 [1.011, 1.064]) (Fig. 2[A]). The calculation results of MR Egger, WM, Simple mode, and Weighted mode were consistent with the direction of the IVW results, indicating the robustness and reliability of the primary analysis methods. There was no causal relationship between other common tumors in women and AD.
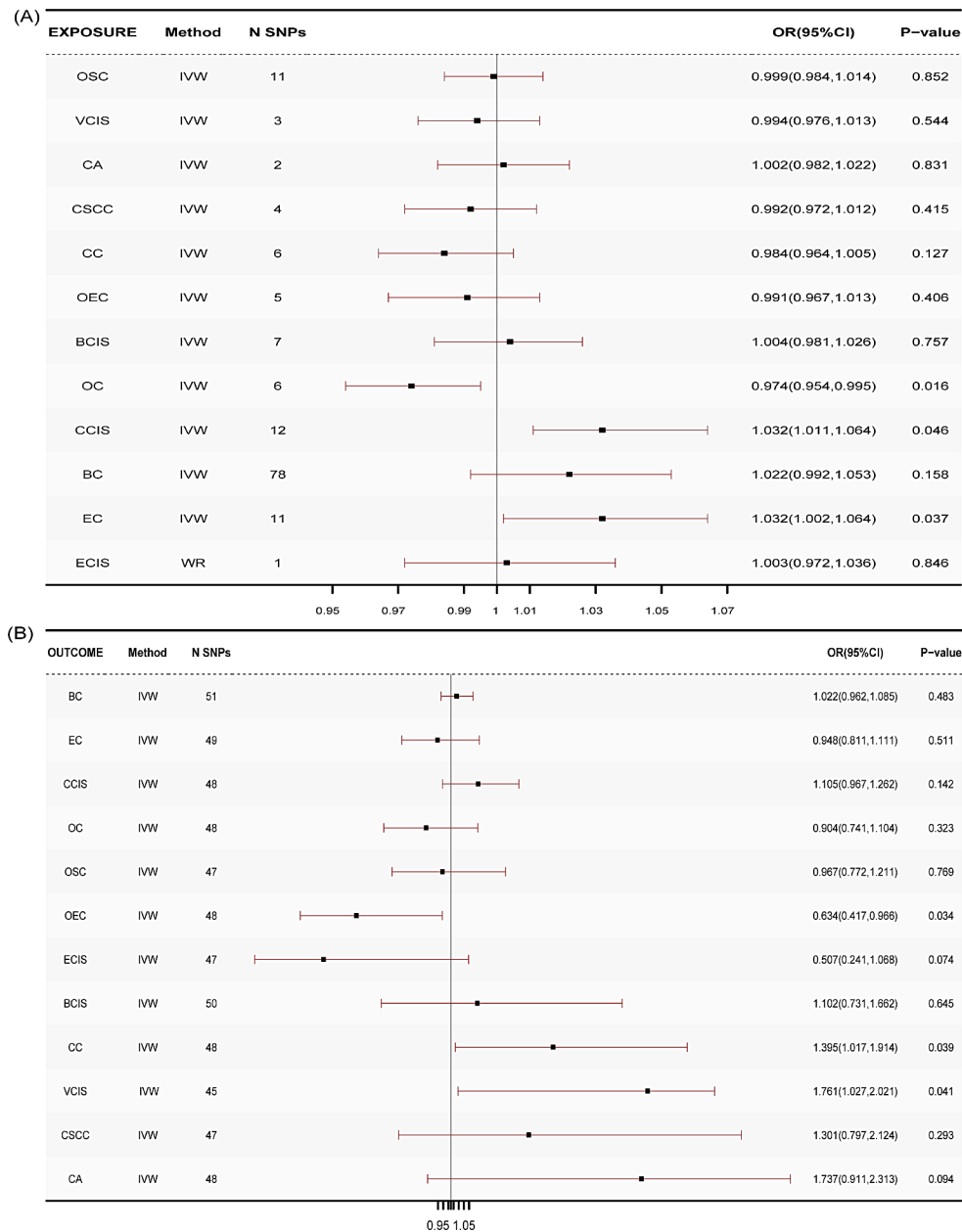
Fig. 2 Forest plots depicting the causal estimates between gynecological cancer and AD. (**A**) Forward MR analysis forest plot, with gynecological cancer as the exposure event and AD as the outcome event. (**B**) Reverse MR analysis forest plot, with AD as the exposure event and gynecological cancer as the outcome event. *Abbreviations* N SNPs, number of SNPs; OR, odds ratio; CI, confidence interval; AD, Alzheimer's disease; BC, breast cancer; CA, cervical adenocarcinoma; CSCC, cervical squamous cell carcinoma; CC, cervical cancer; EC, endometrial cancer; OEC, ovarian endometrioid carcinoma; OC, ovarian cancer, OSC, ovarian serous carcinoma; BCIS, breast carcinoma in situ; CCIS, cervical carcinoma in situ; ECIS, endometrial carcinoma in situ; VCIS, vulvar carcinoma in situ; IVW, Inverse-variance weighted

Causal effect of AD on gynecologic cancer

In the reverse MR analysis, focusing on gynecologic cancer as the outcome, we observed a definitive causal link between AD and conditions such as CC, VCIS, and OEC. Specifically, AD appears to elevate the risk for CC (P_{IVW} = 0.039, OR [95% CI] = 1.395 [1.017, 1.914]) and VCIS (P_{IVW} = 0.041, OR [95% CI] = 1.761 [1.027, 2.021]). At the same time, it conversely reduces the risk for OEC (P_{IVW} = 0.034, OR [95% CI] = 0.634 [0.417, 0.966]), as illustrated in (Fig. 2[B]) and detailed in Supplementary Table 2. Notably, no causal links were found between AD and other common tumors in females. The consistency of these findings across various analytical methods, aligning with the direction of the IVW results, underscores their reliability. Furthermore, all IVs exhibit an F-statistic significantly above 10 (Supplementary Tables 4 to 15),

suggesting a minimal influence of weak instrument bias on the MR analysis.

Sensitivity analyses results

In addition, sensitivity analysis using the leave-one-out method in both forward and reverse MR analyses showed no evidence of directional pleiotropy (Fig. 3). The funnel plot revealed no evidence of asymmetry, indicating a lower risk of directional pleiotropy. MR-Egger regression testing with all *P*-values>0.05 showed no directional pleiotropy between gynecologic cancer and AD. Cochran's Q statistic showed no significant heterogeneity among instrumental SNP effects (*P*>0.05). Furthermore, MR-PRESSO results demonstrated no statistically substantial outliers or influential points (*P*>0.05), suggesting no significant interference or bias was found when evaluating the relationship between exposure and outcome (Table 2). The Supplementary Figs. 1–23 present scatter

plots, funnel plots, leave-one-out sensitivity analyses and forest plots.

Validation analysis and meta-analysis

After applying another GWAS data for AD (accession number GCST007320) and conducting bidirectional MR analysis, we observed trends similar to those found in the preliminary analysis. Specifically, EC (P_{IVW} = 0.030, OR [95% CI]=1.013 [1.011,1.016]) and CCIS (P_{IVW} = 0.001, OR [95% CI]=1.007 [1.006,1.008]) were found to possibly increase the risk of AD, while OC (P_{IVW} = 0.045, OR [95% CI]=0.997 [0.995,0.999]) could reduce the risk of AD. Reverse MR analysis indicated that AD might increase the disease risk for CC (P_{IVW} = 0.038, OR [95% CI]=2.257 [1.592,3.199]) and VCIS (P_{IVW} = 0.008, OR [95% CI]=2.210 [2.047,2.386]), and decrease the onset risk for OEC (P_{IVW} = 0.015, OR [95% CI]=0.798 [0.735,0.866]). Sensitivity analysis showed no irregularities. Additionally, meta-analysis of the OR results from
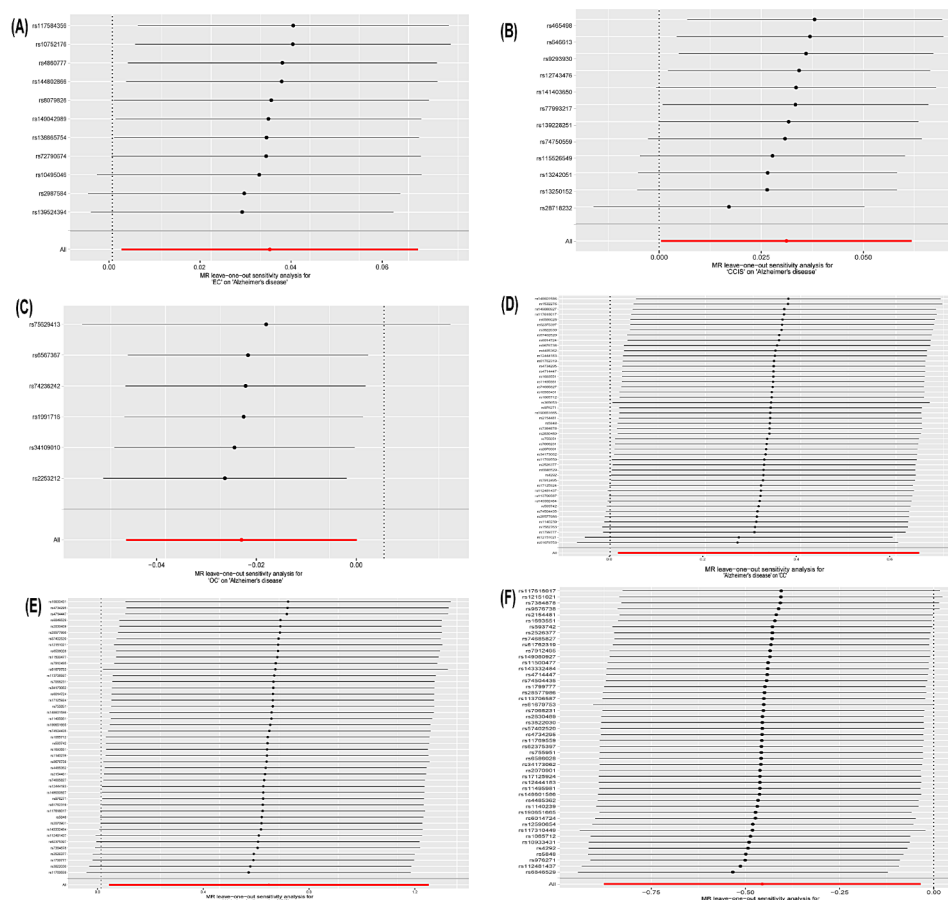
Fig. 3 The leave-one-out plot of SNPs associated with gynecological cancer and AD. (**A**) Forward MR leave-one-out sensitivity analysis for the 'EC' on 'Alzheimer's disease'. (**B**) Forward MR leave-one-out sensitivity analysis for the 'CCIS' on 'Alzheimer's disease'. (**C**) Forward MR leave-one-out sensitivity analysis for the 'OC' on 'Alzheimer's disease'. (**D**) Reverse MR leave-one-out sensitivity analysis for the 'Alzheimer's disease' on 'CC'. (**E**) Reverse MR leave-one-out sensitivity analysis for the 'Alzheimer's disease' on 'VCIS'. (**F**) Reverse MR leave-one-out sensitivity analysis for the 'Alzheimer's disease' on 'OEC'. *Abbreviations* CC, cervical cancer; EC, endometrial cancer; OEC, ovarian endometrioid carcinoma; OC, ovarian cancer, CCIS, cervical carcinoma in situ; VCIS, vulvar carcinoma in situ

Table 2 Results of sensitivity analysis on gynecologic cancer and Alzheimer's diseases

Exposure/Outcome	Method	Test of heterogeneity		Intercept term			Global Test	
		Q	*P*-value	Intercept	SE	*P*-value	RSSobs	*P*-value
Exposure								
BC	MR Egger	91.306	0.111	0.002	0.003	0.528	95.359	0.135
	IVW	91.789	0.120					
CA	MR Egger	NA	NA	NA	NA	NA	NA	NA
	IVW	0.014	0.906					
CSCC	MR Egger	2.207	0.332	0.002	0.024	0.926	2.412	0.721
	IVW	2.219	0.528					
CC	MR Egger	2.899	0.575	-0.007	0.016	0.698	4.725	0.705
	IVW	3.074	0.689					
EC	MR Egger	6.150	0.725	-0.001	0.009	0.946	7.140	0.822
	IVW	6.155	0.802					
OEC	MR Egger	4.487	0.213	0.009	0.068	0.899	6.120	0.453
	IVW	4.515	0.341					
OC	MR Egger	0.985	0.912	0.002	0.007	0.820	1.501	0.959
	IVW	1.044	0.959					
OSC	MR Egger	7.611	0.574	0.000	0.008	0.979	8.983	0.669
	IVW	7.612	0.667					
BCIS	MR Egger	4.381	0.496	0.028	0.011	0.057	16.581	0.085
	IVW	11.289	0.080					
CCIS	MR Egger	11.100	0.350	-0.006	0.010	0.525	20.898	0.153
	IVW	11.582	0.396					
VCIS	MR Egger	0.169	0.681	0.008	0.032	0.835	NA	NA
	IVW	0.239	0.887					
Outcome								
BC	MR Egger	60.978	0.117	-0.006	0.006	0.314	64.657	0.126
	IVW	62.268	0.114					
CA	MR Egger	57.139	0.126	0.389	0.054	0.474	59.791	0.135
	IVW	57.785	0.135					
CSCC	MR Egger	26.474	0.987	-0.033	0.040	0.401	28.810	0.988
	IVW	27.194	0.987					
CC	MR Egger	39.512	0.739	-0.014	0.027	0.609	41.607	0.744
	IVW	39.777	0.763					
EC	MR Egger	66.829	0.030	-0.009	0.012	0.461	69.456	0.045
	IVW	67.613	0.032					
OEC	MR Egger	49.780	0.325	-0.007	0.324	0.824	51.455	0.37
	IVW	49.834	0.361					
OC	MR Egger	38.127	0.789	-0.029	0.017	0.096	43.087	0.697
	IVW	41.010	0.718					
OSC	MR Egger	35.405	0.847	-0.036	0.019	0.065	41.234	0.735
	IVW	38.990	0.758					
BCIS	MR Egger	61.600	0.090	0.051	0.031	0.106	68.356	0.054
	IVW	65.078	0.062					
CCIS	MR Egger	48.062	0.389	0.008	0.011	0.484	50.364	0.405
	IVW	48.581	0.409					
ECIS	MR Egger	60.655	0.060	-0.078	0.064	0.227	64.989	0.053
	IVW	62.681	0.051					
VCIS	MR Egger	32.206	0.886	0.005	0.044	0.914	33.394	0.923
	IVW	32.218	0.906					

BC, breast cancer; CA, cervical adenocarcinoma; CSCC, cervical squamous cell carcinoma; CC, cervical cancer; EC, endometrial cancer; OEC, ovarian endometrioid carcinoma; OC, ovarian cancer; OSC, ovarian serous carcinoma; BCIS, breast carcinoma in situ; CCIS, cervical carcinoma in situ; ECIS, endometrial carcinoma in situ; VCIS, vulvar carcinoma in situ; IVW, Inverse variance weighted; SE, standard error

two IVW instances further reinforced this impression. Meta-analyzing the OR results from two IVW rounds further confirmed this impression. Details in Fig. 4 and Supplementary Tables 16 to 17. The scatter plots, funnel plots, leave-one-out sensitivity analysis, and forest plots for the replication MR analyses can be found in Supplementary Figs. 24–46.

Discussion

In today's society, as women's roles and importance in social life grow, so does the incidence of common tumors in women, influenced by their unique physiological makeup and hormone levels. In addition, epidemiological data shows that AD, with a tendency to affect women [36], presents significant challenges to society and families. Currently, there is a lack of solid scientific evidence linking AD with common cancers in women. We have initiated a bidirectional MR study, employing comprehensive GWAS summary statistics, to investigate potential causal links between common female cancers and AD.

Specifically, our research, utilizing forward MR analysis, suggests that individuals with EC and CCIS may be at a higher risk of developing AD. In comparison, those with OC may have a lower risk. Other common female cancers, like BC, seem not to impact the risk of developing AD. Although current research has shown that cancer

survivors have a reduced incidence of AD [37], there are also studies demonstrating a connection between EC and AD. One study found that the expression of SERPINA3 in EC is associated with disease progression, poor differentiation, high malignancy, and advanced stages of cancer [38], especially in cells expressing negative estrogen receptors (ER). Increased expression of SERPINA3 was observed in these ER-negative cells. Suppressing the presentation of the SERPINA3 gene can inhibit the proliferation of cancer cells. However, SERPINA3 also plays a crucial role in the development of AD [39], with elevated levels of SERPINA3 protein found in the blood, brain [including the hippocampus], and cerebrospinal fluid of AD patients [40]. Analysis has shown that one of the components of amyloid plaques in AD is the SERPINA3 protein and an increase in the levels of SERPINA3 protein in the cerebrospinal fluid may be indicative of mild cognitive impairment in the progression of AD [41]. Additionally, EC and AD are interconnected through multiple common pathways, such as the mTOR signaling network [42] and G-protein-coupled receptors (GPCRs) [43], which play significant roles in the pathology of both diseases. THOP1 (Thimet oligopeptidase), a neuropeptide processing enzyme, was observed to have significantly increased in AD brain tissue as a neuroprotective response to Aβ toxicity [44, 45]. However, in a comparative transcriptome analysis, researchers observed that the
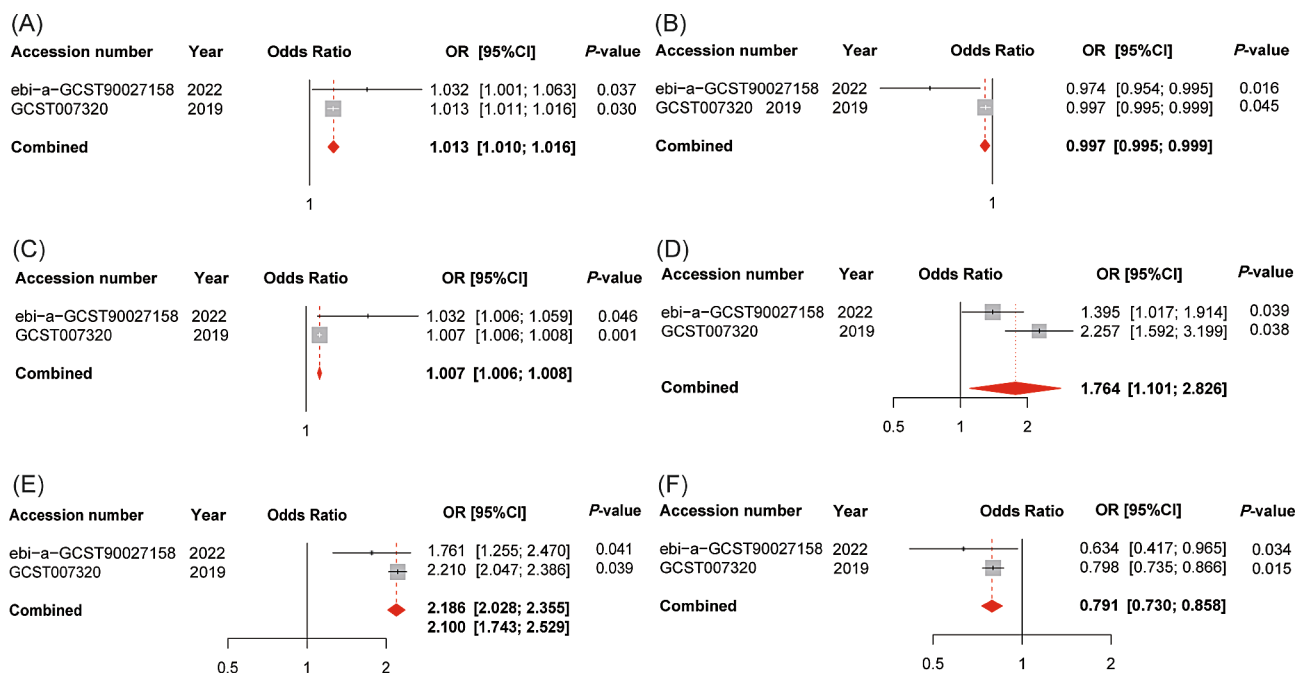
Fig. 4 Meta-analysis of causal associations ($P_{IVW} < 0.05$) between gynecological cancer and AD. (**A**) Meta-analysis of OR [95% CI] for EC with AD as the outcome. (**B**) Meta-analysis of OR [95% CI] for OC with AD as the outcome. (**C**) Meta-analysis of OR [95% CI] for CCIS with AD as the outcome. (**D**) Meta-analysis of OR [95% CI] for CC with AD as the exposure. (**E**) Meta-analysis of OR [95% CI] for VICS with AD as the exposure. (**F**) Meta-analysis of OR [95% CI] for OEC with AD as the exposure. *Abbreviations* CC, cervical cancer; EC, endometrial cancer; OEC, ovarian endometrioid carcinoma; OC, ovarian cancer, CCIS, cervical carcinoma in situ; VCIS, vulvar carcinoma in situ; 95% CI, 95% confidence interval; OR, odds ratio

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expression of the THOP1 gene was significantly downregulated as EC progressed to its late stages, weakening its neuroprotective effect on AD [46].

CCIS, also known as grade 3 cervical intraepithelial neoplasia [47], had approximately 30–50% of cases potentially progressing to cancer [48]. CCIS is mainly associated with human papillomavirus (HPV) infection [49]. Our research findings indicated that CCIS might increase the risk of developing AD. A preliminary connection between the two diseases was identified through a detailed comparison of their pathology, etiology, and biological mechanisms. HPV may play a latent role in AD development, especially concerning inflammation and oxidative stress. Research using a systems biology approach has discovered that HPV interacts with several crucial genes linked to AD, like EGFR, APOE, APP, and CASP8 [50]. Research further indicated that HPV could disrupt the mucosal barrier and modify immune reactions, leading to the dissemination of invasive yeast into the brain, initiating inflammatory cytokines, and thus facilitating the generation of Aβ protein, indirectly leading to AD [51]. Additionally, machine learning studies have identified HPV-71 (OR=3.56, *P*=0.02) as a potential risk factor for AD [52]. This indicates the requirement for more comprehensive research to investigate the association between CCIS and AD and explain their underlying biological mechanisms.

Furthermore, this study found that OC may increase the risk of AD, a link that could be associated with the multifunctional protein BAG3. BAG3 is involved in the regulation of various cellular processes, such as apoptosis, development, and selective autophagy [53]. It has a significant impact on the development of both OC and AD. In OC, BAG3 enhances the invasive capabilities of tumor cells by interacting with matrix metalloproteinase-2, a calcium-dependent peptidase involved in extracellular matrix remodeling [54]. It also promotes cancer cell proliferation by interacting with the 3'-untranslated region of Skp2 mRNA, countering the suppressive effects of miR-21-5p on Skp2 expression, thereby bolstering the survival capacity of tumor cells [55]. Simultaneously, although miR-340 inhibits the survival and promotes the apoptosis of OC cells by downregulating BAG3, the overexpression of BAG3 effectively counteracts these effects and further accelerates tumor development by activating the PI3K/AKT signaling pathway [56]. However, in patients with AD, BAG3 plays a neuroprotective role. Research demonstrated that specifically removing BMAL1, a protein involved in circadian rhythms, from a mouse model activated astrocytes and stimulated BAG3 expression. The increased expression of BAG3 allowed astrocytes to more efficiently consume αSyn and tau, diminishing their activity in AD models, thereby assisting in managing the balance of neurotoxic proteins during AD progression [57]. Furthermore, research revealed that increasing BAG3 expression, under proteasome inhibition, promoted the degradation of tau in neurons and decreased phosphorylated tau levels [58]. In clinical research, a large cross-sectional study found that patients diagnosed with OC had a lower risk of developing AD upon discharge (multivariate OR [95% CI]=0.35 [0.30–0.41]) [59], indicating a strong negative correlation. OC treatment often involves oophorectomy, and a Danish prospective study found that dementia incidence increased by 18% following bilateral oophorectomy, while it decreased by 13% after unilateral oophorectomy [60]. This could be related to the everyday use of hormone replacement therapy (HRT) post-oophorectomy, and epidemiological studies have found that estrogen has a protective effect against AD [61–63]. This may be a reason why OC survivors are less likely to develop AD.

Our reverse MR study results revealed that AD may heighten the risk for CC and VCIS while possibly lowering the risk for OEC. CC, as one of the common malignancies leading to female mortality [64], is generally preventable through early screening and treatment. However, the probability of dementia patients undergoing the Papanicolaou smear test (PST) for CC prevention is lower than that of the general population [65]. Simultaneously, epidemiological studies reveal a higher incidence of VCIS and OEC in middle-aged and elderly individuals, with a predominance of middle-aged women [66, 67]. Considering that a majority of older women may exhibit increased tolerance to diseases due to factors such as age, lifestyle convenience, and cognitive decline, there is a reduction in regular health check-ups and cancer screenings. Timely CC screenings can effectively prevent such diseases. The incidence of CC was highly associated with high-risk HPV infections, which also caused abnormal proliferation of vulvar cells, increasing the risk of carcinogenesis [68]. Vaccination against HPV effectively reduced the risk of VICS and CC [69]. Following a diagnosis of AD, the risk of misdiagnosis or delayed diagnosis when encountering other conditions such as CC, VCIS, and OEC is heightened due to the decline in cognitive function and expressive abilities.

In recent years, increasing research has identified AD as primarily an autoimmune disease occurring within the brain [70]. The immune system in AD patients has undergone various changes; a study based on the Healthy Aging in Neighborhoods of Diversity across the Life Span study found a significant correlation between the rate of decline in the immune system and the rate of cognitive decline, with poorer immune function associated with worse cognitive abilities [71]. The immune system is closely linked to the incidence of CC and VCIS, and immune suppression has been established as a risk factor for CC [72]. HPV infection is one of the primary

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causes of many gynecological cancers; it may evade host immune surveillance, leading to CC and VCIS [73, 74]. Consequently, the compromised immune system function facilitates persistent HPV infections, likely a critical factor in AD patients' higher risk of developing CC and VCIS. Female AD patients often experience reduced estrogen levels [75, 76], and excessive estrogen secretion is a common cause of OEC [77]; therefore, AD patients may reduce their risk of OEC through the estrogen pathway. Mutations in the PTEN gene are involved in the development of both AD and OEC [78]; PTEN, a tumor suppressor gene, regulates the proliferation and differentiation of neural stem cells in the nervous system, affecting neural regeneration [79]. In AD patients, PTEN often shows a decrease and distribution change [80]. PTEN deletion is also a common driving factor for OEC [81, 82], with patients carrying a PTEN expression deficit experiencing worse outcomes [83]. Therefore, further research is needed to verify whether AD provides a protective effect against OEC. Our findings suggest that future considerations could include enhanced screening and prevention of CC and VCIS among AD patients.

Our bidirectional MR study results have circumvented the issues of reverse causality and confounding biases encountered in traditional observational studies [84]. Simultaneously, it has also overcome the inconvenience associated with clinical observations of cancer and cognitive impairment patients. This study marks the first attempt to explore the causal relationship between AD patients and gynecological cancer, providing a novel research perspective on the prevention of both diseases. CC and CCIS represent two types of cancer occurring in the cervix at different stages, OC is a general term for malignant ovarian tumors, and OEC represents a subtype of these tumors. Due to the heterogeneity of cancer, which leads to diversity and variability at different stages and types, our study aimed to include as many current classifications of gynecological cancers as possible. Our results also showed that the causal relationship between AD and tumors of different natures and degrees, even those occurring in the same location, varies. However, our study does have certain limitations. In the reverse MR analysis, our conclusions indicate that AD patients are at risk of developing CC and VCIS, while there is a negative correlation between AD and OEC incidence. Nevertheless, there is a lack of direct clinical observation studies to confirm this standpoint. Additionally, the IVs for gynecological cancer were uniformly sourced from the Finnish database to ensure data consistency. Although the results from all methodologies exhibit a degree of robustness, the limitation lies in the relatively small sample size and the limited number of available IVs in our study. A replication MR analysis using an additional set of AD's GWAS data further validated the reliability of our study findings.

Furthermore, our analysis primarily focuses on the European population, necessitating caution when generalizing the research findings to other populations.

Conclusions

In conclusion, our study findings support the hypothesis of a causal relationship between AD and certain gynecological cancers. However, to validate this study's results, we recommend including a more extensive dataset from gynecological cancer GWAS and incorporating additional genetic IVs. We encourage more researchers to investigate the relationship between female AD patients and the incidence of gynecological cancer and to continue in-depth research in this field.

Abbreviations

AD	Alzheimer's disease
MR	Mendelian randomization
BC	Breast cancer
CA	Cervical adenocarcinoma
CSCC	Cervical squamous cell carcinoma
CC	Cervical cancer
EC	Endometrial cancer
OEC	Ovarian endometrioid carcinoma
OC	Ovarian cancer
OSC	Ovarian serous carcinoma
BCIS	Breast carcinoma in situ
CCIS	Cervical carcinoma in situ
ECIS	Endometrial carcinoma in situ
VCIS	Vulvar carcinoma in situ
IVW	Inverse-variance weighted
SNP	Single nucleotide polymorphism
IVs	Instrumental variables
GWAS	Genome-wide association study
EADB	European Alzheimer's Disease Biobank
LD	Linkage disequilibrium
WM	Weighted median
OR	Odds ratio
CI	Confidence interval
ER	Estrogen receptors
GPCRs	G-protein-coupled receptors
HPV	Human papillomavirus
HRT	Hormone replacement therapy
PST	Papanicolaou smear test

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Author contributions

DC and SZ conceived and designed the study. DC, YZ and MS performed the MR analyses. SZ and PW aided in data analyses. QY and PW assisted in interpreting results and writing the manuscript. All authors revised and approved the final manuscript.

Data availability
Data is provided within the manuscript or supplementary information files. The data for 12 gynecological cancers is sourced from the FinnGen database, and the dataset link is https://figshare.com/articles/dataset/Gynecological_ cancer_application_data/24980757. The GWAS data for Alzheimer's disease is sourced from IEU open GWAS and GWAS catalog, and the relevant dataset can be obtained from the following link: https://gwas.mrcieu.ac.uk/ datasets/ebi-a-GCST90027158/, https://ftp.ebi.ac.uk/pub/databases/gwas/ summary_statistics/GCST007001-GCST008000/GCST007320/.

Declarations

Ethical approval
The analyses were based on publicly available data approved by relevant review boards. All studies contributing data to these analyses had the appropriate institutional review board approval from each country under the Declaration of Helsinki, and all participants provided informed consent.

Competing interests
The authors declare no competing interests.

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