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Research Article

Father with Alzheimer's Disease Increases the Risk of Cervical Adenocarcinoma: Two-Sample Mendelian Randomization Study

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A B S T R A C T

Objective: Based on the two-sample Mendelian randomization method, this study explores the causal relationship between Alzheimer 's family history and cervical malignant tumors.

Methods: We extracted data from the IEU Open GWAS database and Finnish R9 database from the Alzheimer family history, cervical malignant tumors (such as cervical squamous cell carcinoma, cervical adenocarcinoma and other cervical malignant tumors). By setting the correlation strength and eliminating the linkage disequilibrium, the instrumental variables are screened out. Inverse variance weighting (IVW) was used as the main analysis method, supplemented by weighted median, MR-Egger and weighted pattern as supplementary analysis methods to evaluate causal effects. In addition, the Cochran Q test of IVW and MR-Egger was used for heterogeneity analysis and the MR-Egger intercept and MR-PRESSO analysis method were used for pleiotropic test. At the same time, the stability of the results was evaluated using the leave-one-out method. Finally, meta-analysis was used to further clarify the causal relationship between the two.

Results: The results of MR analysis between father's disease history and cervical adenocarcinoma suggested that father 's Alzheimer 's disease increased the risk of cervical adenocarcinoma (OR=1.99; 95 % CI:1.04-3.80, P =0.037) and no association was found in the MR analysis between the other two samples. Heterogeneity test suggested that there was no heterogeneity in the study. The results of the leave-one-out method and the multi-effect test showed stability.

Conclusion: The study confirmed that the father with Alzheimer 's disease will increase the risk of cervical adenocarcinoma, but has no significant effect on cervical squamous cell carcinoma. In addition, the mother with Alzheimer 's disease or other family history of Alzheimer 's disease has no significant effect on the occurrence of cervical malignant tumors. In the future clinical work, we should appropriately strengthen the monitoring and follow-up of women with Alzheimer 's disease in their fathers to prevent or detect cervical malignant lesions early.

Keywords: Cervical cancer, Alzheimer's disease, Mendelian randomization

1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that is the most common cause of dementia among older adults. The "World Alzheimer Report 2023" indicates that in 2019, there were 55 million people globally living with dementia and this number is projected to increase to 139 million by 2050[1]. Genetically, AD can be classified into sporadic AD (SAD) and familial AD (FAD) based on its heritability[2], The familial form of AD, which accounts for about 5-10% of all cases, typically has an earlier onset and follows a Mendelian pattern of inheritance[3]. On the other hand, cervical cancer is the fourth most common cancer in women, with an estimated 570,000 new cases in 2018 globally. Despite the introduction of human papillomavirus vaccines and improved screening methods, there were over 311,000 deaths due to cervical cancer in the same year[4]. Both diseases pose significant challenges in terms of early detection and intervention, highlighting the need for a deeper understanding of their etiologies.

Mendelian Randomization (MR) has emerged as a robust method for investigating the causal relationships between genetic variants and complex diseases. By using genetic variants as instrumental variables, MR leverages the random assortment of alleles at conception to infer causality from observational data while minimizing confounding and reverse causation[5]. For instance, MR studies have provided insights into risk factors for coronary artery disease and type 2 diabetes that have been validated through randomized controlled trials[6].To be an effective tool for causal inference in MR studies, genetic variation must satisfy three core assumptions: (1) genetic variation as an instrumental variable must be truly related to exposure (Alzheimer 's family history or cervical malignancy) , (2) Genetic variation was not associated with exposure-outcome confounding factors.,(3) Genetic variation only affects the outcome through exposure and has nothing to do with other pathways. In this study, we aimed to explore the causal relationships between genetic variants and both familial AD and cervical cancer using MR analysis. Our findings suggest potential causal relationships between specific genetic variants and both familial AD and cervical cancer. our study contributes to a better understanding of the genetic underpinnings of familial AD and cervical cancer. The application of MR provides a powerful approach to unraveling complex disease mechanisms that could pave the way for novel therapeutic targets.

2. Method

2.1. Data source

In this study, the IEU Open GWAS database and the Finnish R9 database data were used for two-sample MR analysis to explore the causal relationship between the family history of Alzheimer 's disease and cervical malignant tumors. The data are summarized in **(Table 1)**.

Table 1: Data information on exposure and outcome.

Variable	ID	Sample size	Multitude	Sex	The year of publication
Father has Alzheimer's disease	ebi-a-GCST005920	260,279	Europe	Mixed	2018
Mother has Alzheimer's disease.	ebi-a-GCST005923	288,676	Europe	Mixed	2018
Family history of Alzheimer's	ebi-a-GCST005921	314,278	Europe	Mixed	2018
Cervical adenocarcinoma	FinlandR9	167301	Europe	F	2023
cervical squamous cell carcinoma	FinlandR9	167353	Europe	F	2023
Cervical malignancy	FinlandR9	167558	Europe	F	2023

2.2. Selection of instrumental variables

In order to obtain SNPs significantly associated with exposure, we set the P value to 5 × 10-8 as the genome-wide significance threshold. At the same time, because the existence of linkage disequilibrium (LD) will lead to the deviation of the final analysis results, we set that the LD of SNPs significantly related to exposure should meet r 2 10 000. Our MR analysis excluded palindromic SNPs with a moderate allele frequency. In addition, we performed F-statistic to quantify the strength of the genetic tool for all SNPs. The calculation formula is (β2 / se2) and SNPs with F-statistic values<10 are excluded. The remaining SNPs are considered to be strong variable tools for further analysis.

2.3. MR analysis

Statistical analysis was performed using the R programming language (version 4.3.0). MR analysis was performed using the 'TwoSampleMR' software package (version 0.5.6) and the 'MRPRESSO' software package (version 1.0) was used to apply MRPRESSO analysis to identify outliers and detect pleiotropic effects. For the causal analysis between exposure and outcome, we used the random effect inverse variance weighting method (IVW) as the main analysis method and MR-Egger, weighted median and weighted mode as supplementary analysis methods. Since the outcome indicators are all dichotomous variables, we obtained the corresponding odds ratio (OR) and 95% confidence interval (95% CI) by converting the ratio estimates. OR>1 indicates that the exposure factor is a risk factor for the outcome variable or< 1 indicates that the exposure factor is a protective factor for the outcome variable and P< 0.05 indicates statistical significance. The IVW method assumes that all the SNPs included in the analysis can be used as effective IV, which can provide great help for the analysis. The pleiotropic nature of genetic variation may lead to the failure of the three hypotheses of IV. The weighted median gives an accurate estimate based on the assumption that the effective number of IV is 50 % and the causal effect can still be accurately calculated. MR-Egger regression assumes that all IVs are invalid IV and the estimation accuracy of this method is relatively low. The weighted model was used to evaluate the robustness of MR results.

2.4. Sensitivity analysis

In addition, we will conduct a series of sensitivity analyses, including heterogeneity and pleiotropy. IVW and MR-Egger regression were used to test heterogeneity and Cochran Q statistics were calculated to quantify heterogeneity. When P<0.05, it represents heterogeneity. If there is heterogeneity, we deal with IVW with random effects for analysis. Horizontal pleiotropic for our study is very important because the influence of horizontal pleiotropy may lead to the instability of effect estimation. The test of pleiotropic level mainly includes

MR-Egger intercept and MR-PRESSO analysis. When $P < 0.05$, it represents horizontal pleiotropic. The MR-Egger intercept method estimates the possibility of horizontal pleiotropy by calculating the intercept term obtained after linear regression analysis. MR-PRESSO analysis can evaluate the overall pleiotropicity of the study and screen out abnormal SNPs that may have horizontal pleiotropicity. We used the software package to set the distribution number in MR-PRESSO analysis to 5 000. Global test was used to observe whether there was pleiotropic effect and the robustness of MR analysis results was evaluated by eliminating SNPs one by one and judging the influence of each SNP on MR analysis results **(Figure 1)**.

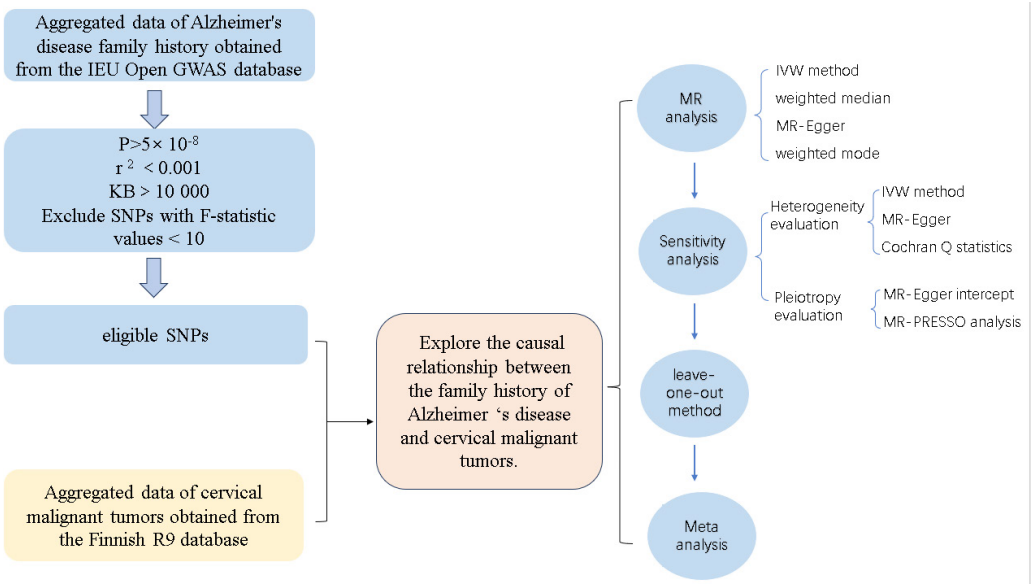

Figure 1: Technical route.

The summary data of family history of Alzheimer's disease were obtained from the IEU Open GWAS database and the summary data of cervical malignant tumors were obtained from the Finnish R9 database. The instrumental variables that met the requirements were selected. The causal relationship between family history of Alzheimer 's disease and cervical malignant tumors was determined by MR analysis, sensitivity analysis, leave-one-out method and Meta analysis.

3. Results

3.1. Selection of instrumental variables

First, we used the R language to extract instrumental variables from the IEU Open GWAS database that meet the appeal criteria for family history of Alzheimer 's disease (including father history, mother history and family history). Instrumental variables were extracted from the Finnish R9 database data for cervical malignancies (including cervical adenocarcinoma, cervical squamous cell carcinoma and cervical cancer) that met the appeal criteria. Because of the large volume of data, the results of follow-up studies suggest that fathers with Alzheimer 's disease increase the risk of cervical adenocarcinoma in their offspring. Therefore, the process of MR analysis is shown below with fathers with Alzheimer 's disease as the exposure factor and offspring with cervical adenocarcinoma as the outcome variable. For the choice of instrumental variables, we included 18 independent SNPs (r 2 10,000) that were significantly associated with father 's Alzheimer 's disease. When these SNPs were associated with the summary data of the outcome, we harmonized the exposure and outcome data (removing unmatchable and palindromic data), which resulted in the deletion of three SNPs (rs72563085, rs883178, rs11595013). Finally, the SNP of IVs analyzed as a father with Alzheimer 's disease and cervical adenocarcinoma is shown in **(Table 2)**. For the instrumental variables used for the final analysis, all F statistics are greater than 10. It is shown that these are robust IVs and satisfy the strong correlation hypothesis of MR analysis and the same method is used to select the instrumental variables of other exposure and outcome factors.

Table 2: Instrumental variables for MR studies on the relationship between father's AD and cervical adenocarcinoma.

SNP	Chr	EA	0A	Beta	Eaf	F	P值
rs10753570	1	G	A	-0.0536797	0.565006	22.36424831	2.26E-06
rs114373075	1	A	C	1.13221	0.00739156	22.24894507	2.39E-06
rs13082929	3	A	G	-0.232869	0.227641	21.76172568	3.09E-06
rs146652660	10	T	C	0.836881	0.00782675	21.8733233	2.91E-06
rs184336441	7	T	C	-0.0103829	0.021446	21.38922554	3.75E-06
rs188423362	8	C	T	-0.0479785	0.0776668	23.4974	1.25E-06
rs2972558	19	T	C	0.189375	0.766033	55.46667642	9.51E-14
rs35765215	18	G	A	-0.23809	0.137722	20.91159245	4.81E-06
rs429358	19	C	T	0.380142	0.182736	1127.185568	1.00E-200
rs56141511	11	G	A	-1.02904	0.0236884	21.6872662	3.21E-06
rs58124010	17	T	C	0.333966	0.169088	20.99074949	4.62E-06

rs6733839	2	T	C	0.127465	0.373747	31.11999985	2.43E-08
rs673751	11	C	A	-0.176672	0.645357	29.29215115	6.22E-08
rs72940158	2	G	A	0.11539	0.052581	21.51055077	3.52E-06
rs878190	11	G	A	0.0220269	0.499013	21.21379929	4.11E-06

3.2. Two-sample MR analysis

We used the statistical power calculation website to calculate the statistical power of two sample MR studies (https://shiny.cnsgenomics.com/mRnd/) and the statistical power of MR analysis was 99 %. The data were detected by IVW method, MR-Egger method, WME method, Simple Mode method and Weighted Mode method. The results showed that the results of IVW method, MR-Egger method, WME method, Simple Mode method and Weighted Mode method were consistent. IVW as the main analysis method, suggesting that fathers with Alzheimer ‘s disease increased the risk of cervical adenocarcinoma by 99 % (OR=1.99; 95 % CI: 1.04-3.80, P = 0.037). Secondary analysis methods included MR-Egger (OR = 2.19; 95 % CI: 0.84-5.73, P = 0.132), weighted median (OR = 2.07; 95 % CI: 1. 12-3. 84, P = 0. 021), weighted model (OR = 2. 09; 95 % CI: 1. 13-3. 88, P = 0. 035), the OR values were greater than 1 **(Figures 2 and 3)**. IVW suggested that fathers with Alzheimer ‘s disease were not associated with uterine squamous cell carcinoma and other cervical malignant tumors and mothers with Alzheimer ‘s disease or a family history of Alzheimer ‘s disease did not increase the risk of cervical malignant tumors **(Figure 2)**.

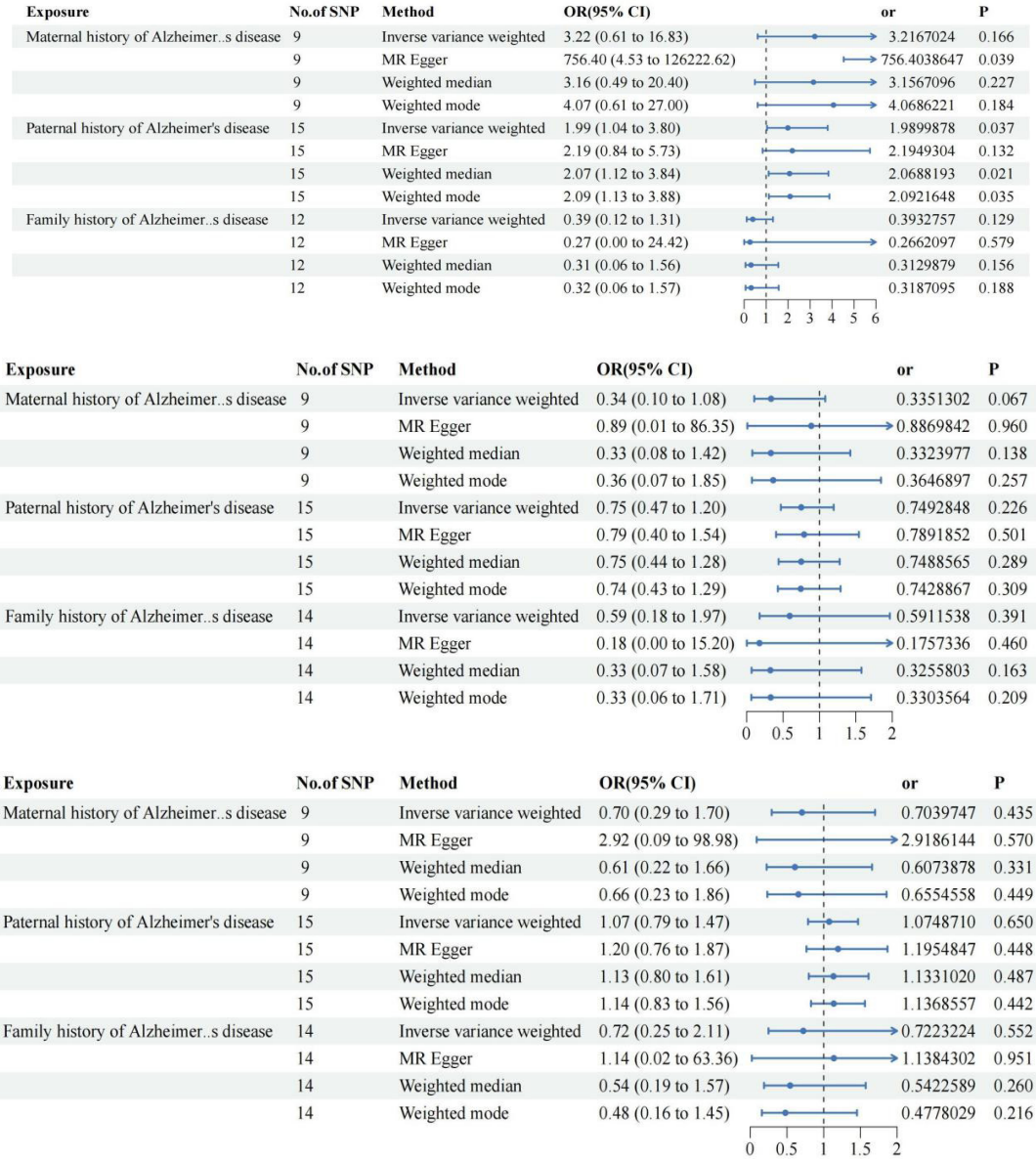

Figure 2: Alzheimer ‘s family history of cervical cancer risk.

IVW suggested that fathers with Alzheimer ‘s disease were not associated with uterine squamous cell carcinoma and other cervical malignant tumors and mothers with Alzheimer ‘s disease or a family history of Alzheimer ‘s disease did not increase the risk of cervical malignant tumors.

Scatter plot to visualize the casual relationship between Alzheimer ‘s family history and cervical malignant tumors. Figures A to I respectively showed the effect of ebi-a-GCST005920, ebi-a-GCST005923 and ebi-a-GCST005921 on cervical squamous cell carcinoma, cervical adenocarcinoma and

other cervical malignant tumors. Figures A,B and C suggested that Alzheimer ‘s family history was a protective factor for cervical squamous cell carcinoma. Other figures suggested it was a risk factor for cervical adenocarcinoma and other cervical malignant tumors.

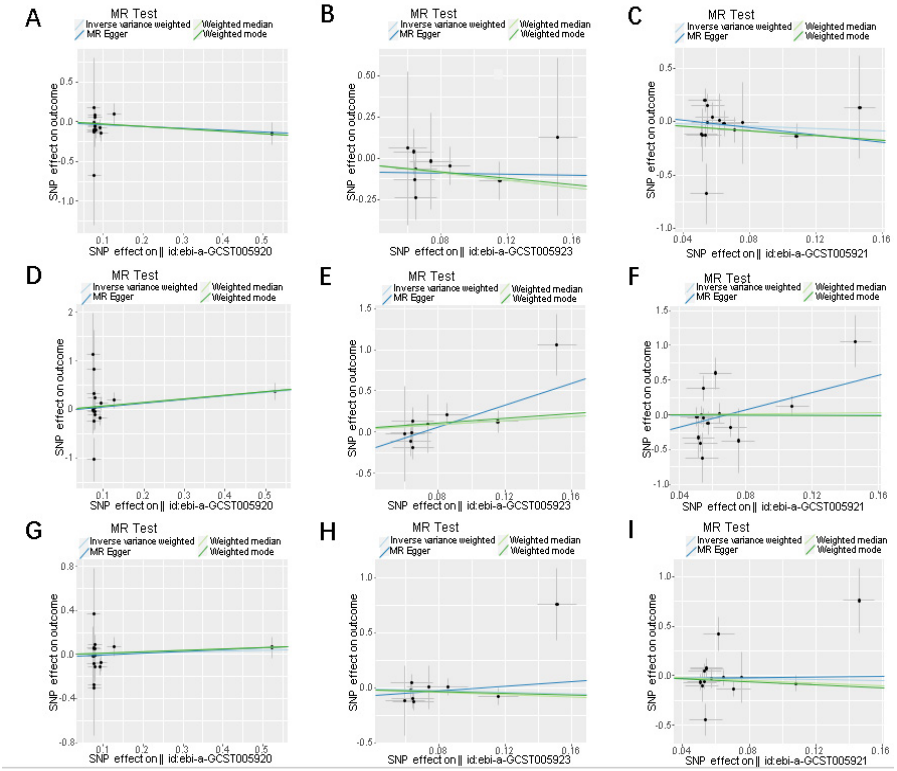

Figure 3: Scatter plot of Alzheimer ‘s family history and risk of cervical cancer.

3.3. Sensitivity analysis and visualization

MR-Egger regression (Cochran Q = 18.47, P = 0.14) and IVW (Cochran Q = 18.58, P = 0.18) of fathers with Alzheimer ‘s disease and cervical adenocarcinoma indicated that there was no heterogeneity in the study, as shown in Table 3. The funnel plot was a visualization of heterogeneity **(Figure 4)**. MR-Egger intercept did not show horizontal pleiotropic (irritability: Egger intercept: −0.02, P = 0.78). See **(Figure 5)**. No abnormal values were found by MR-PRESSO test and the Global test was 0.36, indicating that there was no pleiotropic effect, as shown in Table 3. We used the leave-one-out method to remove SNPs one by one to determine whether the causal association was caused by a single IV. The final results showed that the results of the two-sample MR analysis were robust, as shown in **(Figure 6)**.

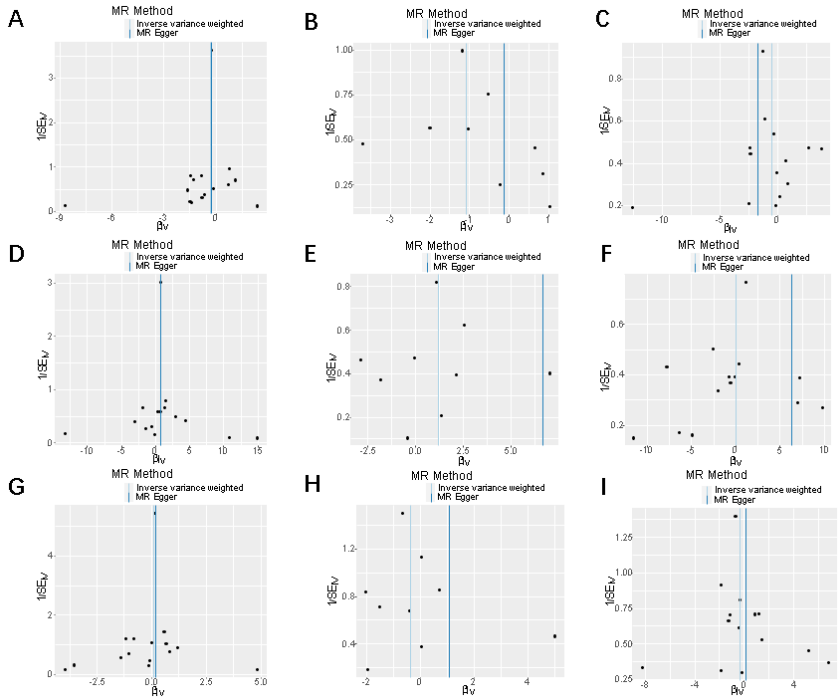

Figure 4: Funnel plot of Alzheimer ‘s family history and risk of cervical cancer.

Funnel plot: Visualization of overall heterogeneity testing between Alzheimer ‘s family history and cervical malignant tumors. If there is symmetry in the funnel plot, it means there is no heterogeneity.

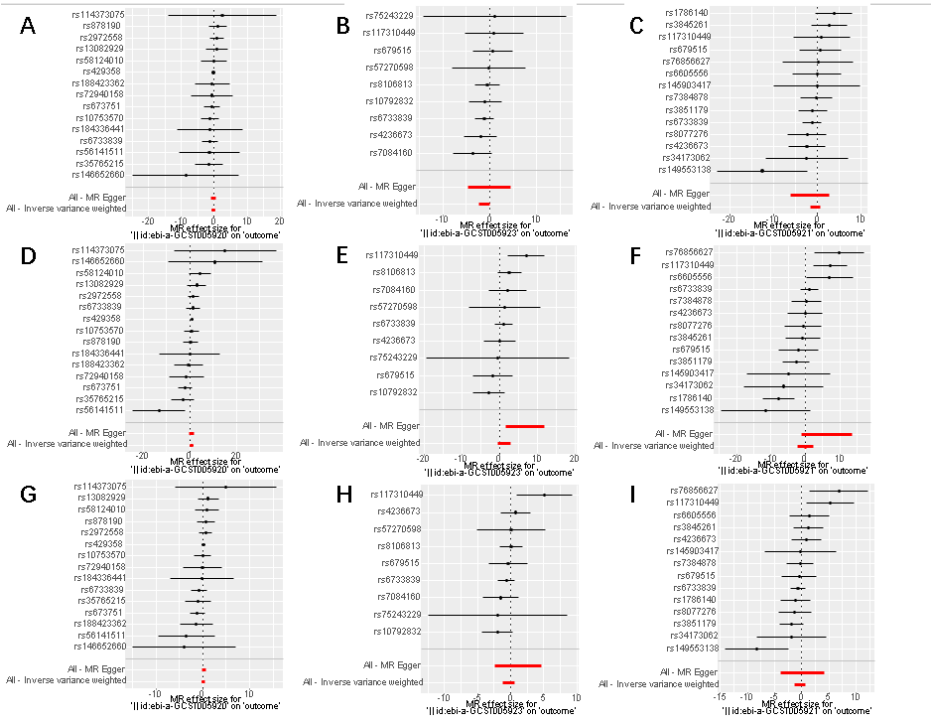

Figure 5: A forest map of the risk of Alzheimer ‘s family history and cervical cancer.

Forest plot representing the casual effects of Alzheimer ‘s family history and cervical malignant tumors. Figures A to I respectively showed the effect of ebi-a-GCST005920, ebi-a-GCST005923 and ebi-a-GCST005921 on cervical squamous cell carcinoma, cervical adenocarcinoma and other cervical malignant tumors. Figures D and G reflected that the father with Alzheimer ‘s disease will increase the risk of cervical adenocarcinoma and other cervical malignant tumors. Figures A and B showed that the father with Alzheimer ‘s disease and the mother with Alzheimer ‘s disease will increase the risk of cervical squamous cell carcinoma.

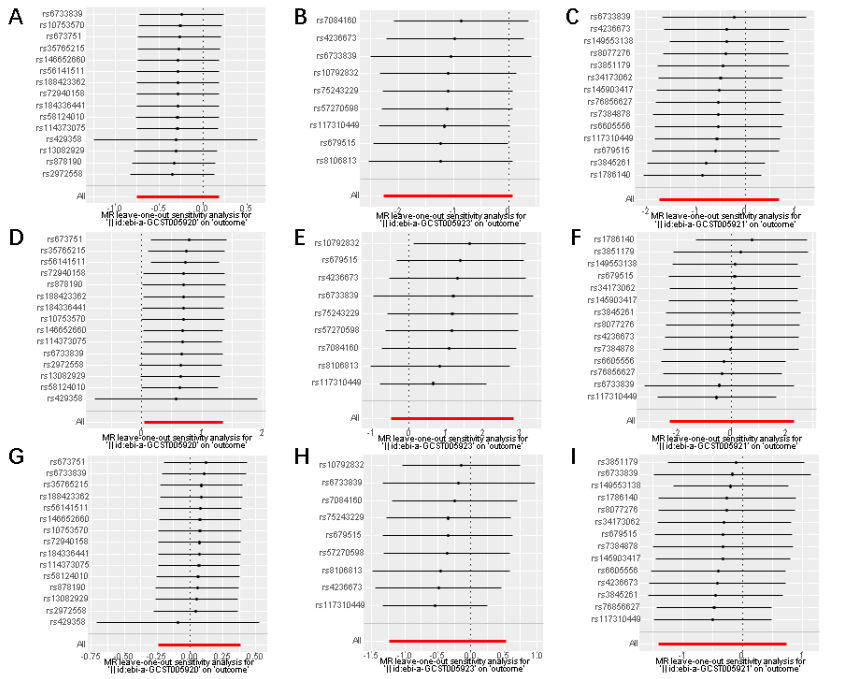

Figure 6: Leave-one-out analysis the risk of Alzheimer ‘s family history and cervical cancer.

Leave-one-out analysis: Eliminating SNPs one by one and judging the influence of each SNP on MR analysis results to affirming the robustness of the results. Only Figure D ‘s overall results of all SNPs do not cross/contain 0, indicating the stability of the results.

3.4. Heterogeneity and pleiotropic analysis of other MR studies

Heterogeneity and pleiotropic analysis results of other MR studies are shown in **(Table 3)**. The results suggest that there may be heterogeneity and pleiotropicity in the study of Alzheimer ‘s family history and cervical malignant tumors and there is no pleiotropicity and heterogeneity in other studies.

Table 3: Heterogeneity and multieffectiveness test.

Expose	Outcome	Heterogeneity test			Multipleiotropy test	
		Method	Q	P值	Method	P
Father has Alzheimer's disease	Cervical adenocarcinoma	MR-Egger	18.47	0.14	MR-Egger	0.78
		IVW	18.58	0.18	PRESSSO	0.36
Mother has Alzheimer's disease.		MR-Egger	6.75	0.46	MR-Egger	0.07
		IVW	11.47	0.18	PRESSSO	0.22
Family history of Alzheimer's		MR-Egger	9.73	0.46	MR-Egger	0.86
		IVW	9.76	0.55	PRESSSO	0.62
Father has Alzheimer's disease	cervical squamous cell carcinoma	MR-Egger	5.74	0.96	MR-Egger	0.84
		IVW	5.78	0.97	PRESSSO	0.98
Mother has Alzheimer's disease.		MR-Egger	2.93	0.89	MR-Egger	0.67
		IVW	3.12	0.93	PRESSSO	0.94
Family history of Alzheimer's		MR-Egger	14.09	0.30	MR-Egger	0.59
		IVW	14.45	0.34	PRESSSO	0.39
Father has Alzheimer's disease	Cervical malignancy	MR-Egger	9.30	0.75	MR-Egger	0.53
		IVW	9.72	0.78	PRESSSO	0.82
Mother has Alzheimer's disease.		MR-Egger	9.34	0.23	MR-Egger	0.44
		IVW	10.23	0.25	PRESSSO	0.33
Family history of Alzheimer's		MR-Egger	25.84	0.01	MR-Egger	0.82
		IVW	25.95	0.02	PRESSSO	0.03

4. Discussion

Our MR analysis has revealed a potential causal relationship between genetic variants associated with Alzheimer's disease in fathers and an increased risk of cervical cancer. The use of various MR methods, including IVW, MR-Egger, weighted median and mode-based estimates, has provided consistent evidence supporting this association[7].Furthermore, our sensitivity analyses strengthen the argument for a causal link by demonstrating robustness against heterogeneity and pleiotropy. The absence of significant heterogeneity or horizontal pleiotropy-as evidenced by Cochran Q tests and MR-Egger intercepts-suggests that the observed association is not confounded by these factors[8]. Additionally, MR-PRESSO did not detect outliers, indicating that our results are unlikely to be driven by individual SNPs with disproportionate effects.

The identification of genetic variations through MR analysis has provided novel insights into the pathophysiology of familial Alzheimer's disease and cervical cancer, underscoring the importance of genetic predisposition in their etiology. APOE, which has been extensively documented as a major genetic risk factor for Alzheimer's disease[9]. The ε4 allele of APOE is associated with an increased risk of developing Alzheimer's disease, while the ε2 allele appears to have a protective effect[10]. Our findings suggest that individuals carrying certain APOE variants may also have an elevated risk of developing cervical adenocarcinoma, indicating a possible shared genetic pathway influencing both conditions. This observation could pave the way for further investigation into common molecular mechanisms underlying neurodegenerative and oncogenic processes.

The genetic predisposition to Alzheimer's disease may share common pathways with the development of certain cancers, which could be mediated by immune system dysregulation[11].The immune system plays a critical role in both neurodegeneration and tumor surveillance. Chronic inflammation, for instance, is a hallmark of Alzheimer's disease and has been implicated in the pathogenesis of various cancers, including cervical cancer[12]. The interplay between inflammatory processes and immune response modulation could provide insights into shared genetic susceptibilities that influence both conditions. Further research into the immunological aspects underlying this association could yield valuable information on the mechanisms at play. For example, exploring how specific alleles might influence immune cell function or cytokine production could illuminate pathways amenable to therapeutic intervention[13]. Ultimately, understanding these connections could pave the way for novel strategies in preventing or treating both Alzheimer's disease and cervical cancer through immune modulation.

Reflecting on this study's limitations, it is crucial to recognize that our conclusions rely on public database and statistical approaches without wet-lab validation. The sample sizes for some genetic variants might have been insufficient for detecting subtle associations or ensuring conclusion robustness. Moreover, we did not perform clinical validation analysis; thus, cautious interpretation is warranted before clinical application. Additionally, employing multiple datasets may introduce batch effects that could confound our findings.

In conclusion, this investigation applied MR methods to explore putative causal links between particular genetic variations and both Alzheimer's disease familial history as well as cervical malignancies. Our principal outcomes indicate a potential causative association with specific genes. Sensitivity analyses were performed addressing heterogeneity and pleiotropy concerns which bolstered result credibility despite limitations such as lack of experimental confirmation and possible dataset-related batch effects. These insights pave the way for future research endeavors which may ultimately lead towards enhanced diagnostics or treatments pending further clinical corroboration.

5. Declarations

5.1. Abbreviations

MR: Mendelian Randomization

IVW: Inverse variance weighting

AD: Alzheimer's disease

SAD: sporadic AD

FAD: familial AD

LD: Linkage disequilibrium

OR: odds ratio

5.2. Ethics approval and consent to participate

Ethical review was not required for this study as it involves the use of publicly available, anonymized data from a database. No new data were collected and no new ethical approval was required.

5.3. Consent for publication

All authors have agreed to the publication of this article.

5.4. Availability of data and materials

The datasets can be freely obtained from the IEU Open GWAS Database (https://gwas.mrcieu.ac.uk/) and the Finnish R9 Database (https://r9.finngen.fi/).

5.5. Competing interests

No, I declare that the authors have no competing interests as defined by BMC or other interests that might be perceived to influence the results and/or discussion reported in this paper.

5.6. Funding statement

This study was funded by Medical Key Strategic Project of Wuxi Health Commission.

5.7. Authors' contributions

Li was responsible for data collection and organization, as well as paper writing and revision. Xiong was in charge of data analysis and processing and paper writing. Gu took the lead in research design and planning and paper writing and supplementation. Zhao was responsible for research supervision and coordination and management of research resources. Yue was in charge of research technical support and paper writing and polishing. Jiang was responsible for fund support and paper improvement. Each author played their part while collaborating with each other in the research process, jointly completing this research project. Every author made significant contributions to the final outcome of the paper, ensuring the scientific nature and rigor of the research.

5.8. Acknowledgements

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