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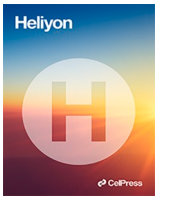

Research article

Study on the causal relationship between educational attainment and delirium: A two-sample Mendelian randomization study

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ABSTRACT

This study aimed to investigate whether there is a causal relationship between educational attainment and delirium at the genetic level using the Mendelian randomization method, and provide new evidence for studies in this field. We found a causal relationship between educational attainment and delirium at the genetic level after excluding confounders using Mendelian randomization. The inverse variance weighting method of random effects was the main analysis method. The weighted median and Mendelian Randomization-Egger methods, as well as simple, and weighted modes were used as supplementary analysis methods. Additionally, horizontal pleiotropy tests were conducted, including the Mendelian Randomization-Egger intercept test and Mendelian Randomization Pleiotropy RESidual Sum and Outlier. Cochran's Q statistic was used to assess the size of heterogeneity. We retrieved all second single nucleotide polymorphism features and performed multivariate Mendelian randomization to adjust for the effect of potential confounders on our results. The inverse variance weighting suggested a negative correlation between genetically predicted educational attainment and delirium (0.67[0.49–0.92], $p = 0.013$); Mendelian Randomization Pleiotropy RESidual Sum and Outlier (0.67[0.49–0.92], $p = 0.013$) and multivariate Mendelian randomization (0.52[0.33–0.82], $p = 0.005$) results were generally consistent with the inverse variance weighting method. The Mendelian Randomization-Egger, simple, and weighted mode results were consistent with the inverse variance weighting results. Our results were not affected by pleiotropy or heterogeneity ($p > 0.05$, for both pleiotropy and heterogeneity). In addition, the "leave-one-out" analysis showed that the results of our Mendelian randomization analysis were not influenced by individual single nucleotide polymorphisms. Studies have found a causal relationship between educational attainment and delirium at the genetic level; higher educational attainment may be a protective factor against delirium. Clinically, more attention should be paid to patients at a high risk of delirium with low educational attainment.

1. Introduction

Delirium is a group of clinical syndromes characterized by impaired consciousness and altered cognitive function [1,2]. The

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incidence of delirium is estimated to be approximately 20%–50%, and the incidence of delirium in critically ill patients receiving mechanical ventilation is as high as 60%–80% [1]. The pathogenesis of delirium is mainly associated with genetic and risk factors, and it is currently believed to be associated with the apolipoprotein E4 (ApoE4) allele [3], dopamine [4]and N-methyl-D-aspartate (NMDA) receptor genes [5]. On the other hand, delirium-related risk factors have a non-negligible influence on the development of delirium, and common risk factors include age, smoking, surgery, infection, and history of previous use of certain drugs [6]. Given that the presence of risk factors can greatly increase the possibility of delirium occurrence, high vigilance should be exercised [7]. Although delirium is a common clinical disorder, its treatment is still mainly controlled and treated by drugs, and its efficacy remains unsatisfactory [8,9]. Delirium is a common clinical complication in orthopedic patients [10,11]. It can lead to increased morbidity and mortality, prolonged duration of mechanical ventilation and hospitalization, increased risk of hospitalization and readmission, a significant decrease in the ability to perform daily activities, and long-term cognitive dysfunction in more severe cases, which seriously affects patient prognosis and increases medical costs, thereby requiring adequate attention [12].

Educational attainment (EA) is widely recognized as a socioeconomic and heritable health determinant [13]. EA can be used as a tool to assess brain and neurodevelopment, biological aging, health behaviors, and health knowledge. Studies have found an extremely strong association between lower levels of education and higher rates of dementia, and education may be one of the most important protective factors against dementia [14–16]. Additionally, EA has been associated with various disorders [17,18]. Some studies have pointed to a possible relationship between EA and delirium [19]. However, the relationship between EA and delirium has been less studied, and there is no clear definitive conclusion regarding this relationship [20].

The Mendelian randomization (MR) approach makes causal inferences about exposure and outcome by building a model with genetic variation as an instrumental variable (IV), in which alleles are randomly assigned to offspring, and genes are unidirectionally inherited. Therefore, using genetic variation as an IV can effectively avoid the confounding factors and reverse causality that often occur in previous epidemiological and observational studies, greatly improving the accuracy and credibility of the results. Currently, the MR method has been widely used to assess the relationship between exposure factors and diseases. For example, one study used the MR method to determine that low education is a causal risk factor for the development of lung cancer [21]. Studies have also pointed to the potential causal protective effects of EA on type 2 diabetes [22]. In addition, a study using MR methods found that vitamin D is causally related to delirium at the genetic level and that delirium can be effectively prevented by correcting hypovitaminosis D [23]. Additional studies have found a causal relationship between EA and multiple psychiatric symptoms at a genetic level [24–26]. Previous studies have found that MR methods have a good ability to infer genetic-level causality between EA and multiple psychiatric symptoms. In this study, we attempted to infer a causal relationship between EA and delirium at the genetic level using MR, which can help in the prevention, treatment, and prognosis of delirium.

2. Materials and methods

2.1. Study design

We used EA as exposure and conducted a two-sample MR on the Finnish database delirium population, which is subject to three assumptions: (i) IV must be strongly associated with exposure factors, (ii) IV is not associated with other confounding factors, and (iii) IV can affect the outcome through only one pathway, exposure factors [27].

2.2. Data resources

Table 1 showcases the data sources. Genetic data for EA were obtained from the genome-wide association study (GWAS) summary data of the Social Science Genetic Association Consortium (SSGAC) consortium, which involved more than 3 million individuals [28]. The cohort involved in this study investigated the education level of the study population using a questionnaire (e.g., What is the highest level of education you have completed? Which of the following qualifications do you have?). To date, this is the largest GWAS meta-analysis on education, yielding more than 3952 near-independent genome-wide significant single nucleotide polymorphisms (SNPs) that explain approximately 14% of the variance in EA [28]. Genetic data for delirium were obtained from the most recent sample data from FinnGen Biobank in June 2022, a prospective cohort study designed to collect genetic and health data on 500,000

Table 1
This is the basic information of the exposure and outcome samples.

Variables	Delirium	EA
N	294,500(cases = 2090)	3,037,499
Fraction women	37%	55%
Mean age	67	62
Measurements	ICD-10(F05) ICD-9(2930)	highest level of education
ancestry	European	European
Database	FinnGen	SSGAC
Year	2022	2022

(Note: EA = educational attainment; N = sample size; SSGAC=Social Science Genetic Association Consortium; ICD=International Classification of Diseases).

Finns [29]. A total of 2090 patients with delirium were screened by the International Classification of Diseases (ICD:ICD-10(F05); ICD-9(2930)) diagnosis codes for multiple factors such as dementia combined with delirium, postoperative d elirium, and other types of unspecified delirium but not alcohol and other psychoactive drug-induced delirium (detailed information on above is available at https://r7.risteys.finngen.fi/). The GWAS-pooled data from EA-elicited delirium are from different databases of populations of European ancestry, with little possibility of sample overlap. The original studies on these data were approved by relevant ethical review boards [28,29]. Therefore, no additional ethical review was required for this study.

2.3. Instrumental variable (IV) selection

The number of genome-wide significant SNPs associated with EA was as high as 3952; therefore, we set the threshold for correlation of these instrumental variables (IVs) with exposure at $p < 5 \times e{-}20$. Specific screening steps were performed. First, we extracted the relevant SNPs from the GWAS summary data of EA using the TwoSampleMR package in the R language. Second, to avoid the effect of linkage disequilibrium, we clumped these SNPs (parameters were set to r2 = 0.001 and kb = 10000 kb) to filter independent SNPs. Third, we eliminated the echo sequences that indicated the presence of the above SNPs and queried them in the ending GWAS data with related information. Fourth, to maximize control for the influence of confounding factors (MR Hypothesis 2), we searched all the above SNPs using PhenoScanner for potential confounding factors [30]. Finally, we evaluated the strength of IVs using the F-test. The F-test {calculated as $F = [(n\text{-}k\text{-}1)/k] \times [R2/(1\text{-}R2)]$, $R2 = 2 \times EAF \times (1\text{-}EAF) \times beta2$, EAF = effect of allele frequency, sample size = n, and number of IVs = k} indicates the strength of the relationship between IVs and exposure [31].

2.4. Statistical analysis

The inverse variance weighting (IVW) method of random effects was the main analysis method. The weighted median, Mendelian Randomization-Egger (MR-Egger), simple, and weighted modes were used as supplementary analysis methods, as well as horizontal pleiotropy tests, including the MR-Egger intercept test and the Mendelian Randomization Pleiotropy RESidual Sum and Outlier (MR-PRESSO). Cochran's Q test was used to assess the magnitude of heterogeneity. First, IVW assumes that all SNPs are valid instruments, the Wald ratios for all SNPs are combined as an estimate of the causal effect of exposure on the outcome. This method requires strict control over the effect of horizontal multiplicity [32]. Second, the weighted median method adjusts for the effect of invalid IVs and yields a robust assessment, even in the presence of 50% invalid IVs [33]. Third, the MR-Egger relaxes the requirement for the SNP pleiotropy, and its intercept can be used to assess horizontal pleiotropy. The MR-Egger intercept test compares the MR-Egger intercept term with 0. A large difference indicates the presence of large horizontal pleiotropy [34]. Fourth, MR-PRESSO can provide the results of the main analysis method IVW after adjusting for horizontal pleiotropy, where the MR-PRESSO global test can assess the size of the overall horizontal pleiotropy of IVs, and MR-PRESSO outlier test can assess the abnormal SNPs that contribute to the overall horizontal pleiotropy [35]. Fifth, Cochran's Q test was used to assess the magnitude of heterogeneity in the IVW and MR-Egger analyses (Supplementary Table 1). Finally, simple and weighted mode methods have weaker statistical efficacy than IVW and are mainly used to verify the robustness of IVW (Table 2).

Meanwhile, we used the leave-one-out method for sensitivity analysis. This method calculates the results of the remaining SNPs by eliminating them one by one. If the result obtained after eliminating an single nucleotide polymorphism (SNP) is significantly different from that of the previous result, it indicates that the MR results are not robust. Visual funnel plot symmetry can indicate the presence or absence of significant heterogeneity. On the other hand, density plots reflect the frequency of the distribution of SNPs with different effect. All statistical analyses were performed using RStudio version 4.2.1, and the R packages used were TwoSampleMR version 0.5.6 and MR-PRESSO version 1.0, with an implementation date of November 2022 (Supplementary Table 2).

3. Results

Finally, we selected 284 SNPs that were strongly associated with EA ($p < 5 \times e{-}20$), and the PhenoScanner queries suggested a partial association between these SNPs and body mass index (BMI) (Supplementary Table 3). To exclude the potential effects of BMI on the results, we performed a multivariate MR using data from independent evaluation unit (IEU) sources (BMI = ieu-a-835, delirium = finn-b-F5_DELIRIUM, EA = ieu-a-1239, https://gwas.mrcieu.ac.uk/). This approach includes the effect of BMI in the EA model on delirium, which can be adjusted for the effect of BMI [36].

As shown in Fig. 1, the main IVW analysis method suggested a negative correlation between EA and delirium for genetic prediction

Table 2
Horizontal pleiotropy and heterogeneity assay results.

Method	Cochran's Q		MRPRESSO		MR-Egger
	MR-IVW	MR-Egger	MRPRESSO Global Test	Outlier-corrected	Egger intercept Test
Statistic	299.07	299.19	301.45	NA	−0.003
P	0.232	0.243	0.235	NA	0.737

Result of recalculation after removing outliers
(Note: MR = Mendelian randomization; MR-PRESSO = Mendelian Randomization Pleiotropy RESidual Sum and Outlier; IVW = inverse variance weighting; MR-Egger = Mendelian Randomization-Egger).

[0.67(0.49–0.92), p = 0.013]; MR-PRESSO [0.67(0.49–0.92], p = 0.013) and multivariate MR [0.52(0.33–0.82], p = 0.005) results were generally consistent with that of the IVW method. The estimate of the weighted median method is at a critical value [0.63 (0.40–1.01), p = 0.053], which is ultimately weakly effective considering that it assumes that half of the IVs are invalid. Although the MR-Egger method, simple mode, and weighted mode confidence intervals touched the null line and were significantly insignificant, they exhibited the same nature of causal effects as that of the IVW, both being negatively correlated (Fig. 2A). Additionally, the wider confidence intervals of the three methods included the confidence range of the IVW. The leave-one-out method did not suggest outliers (Fig. 2C). A funnel plot showed that all SNPs exhibited a symmetric distribution (Fig. 2B). Density plots suggested that the frequencies of the individual SNP effect estimates were mainly distributed around the IVW (Fig. 2D). Both pleiotropy and heterogeneity were detected ($p > 0.05$), as shown in Table 2. Therefore, the robustness of our IVW results from the main analysis was not affected by any potential level of pleiotropy or heterogeneity.

The statistical efficacy of our results was assessed using an online tool (https://shiny.cnsgenomics.com/mRnd/). On the basis of the original article, IVs explain approximately 14% of the genetic explanation for exposure [28]. The statistical efficacy of our main analysis method, IVW, was close to 100% when the type-I error rate was 0.05%.

4. Discussion

We investigated the causal relationship between EA and delirium at the genetic level using the MR method and found that EA showed a negative causal relationship with delirium, that is, higher EA was a protective factor for delirium.

In early 1994, a study pointed out that low educational level and living alone were important risk factors for delirium and that a longer duration of education was a protective factor for delirium [37]. A risk factor for acute psychosis after hip surgery in older patients with low educational levels was found [38]. In addition, in a retrospective study, the risk of delirium was found to be higher in hospitalized older adults with low educational levels than in those with higher educational levels [39]. In addition, some studies have also concluded a negative association between education and delirium, that is, individuals with low educational level are at higher risk of delirium than those with high educational level [19,40]. However, this conclusion tends to be controversial. In a study on the relationship between brain and cognitive reserve markers (including education) and the risk of postoperative delirium in older patients, education was not found to be associated with delirium [20]. Several other studies have reached similar conclusions [41–43]. Previous studies have not reached consistent conclusions regarding the relationship between EA and delirium, and some controversy remains. We consider that these controversies may be due to the fact that previous studies are mostly observational in nature, and their conclusions are mostly influenced by confounding factors, which did not directly reflect the direct relationship between EA and delirium but only the correlation between them. Moreover, there were differences in the participants, research methods, and conditions, which led to different conclusions.

There is no conclusive evidence on the association between EA and delirium. Our study found a significant causal relationship between EA and delirium at a genetic level. We consider the possibility that the association between education and delirium may be multifactorial. Cognitive reserve has not been extensively studied at this stage in the development of delirium [44]. However, considering that EA is a way in which the brain's cognitive reserve is enhanced, education may increase the brain's reserve by promoting synaptic growth and/or generating new cognitive strategies [45–47]. Those with higher cognitive reserve can delay the onset of cognitive impairment or dementia symptoms caused by pathological changes in the brain through compensatory mechanisms [44];

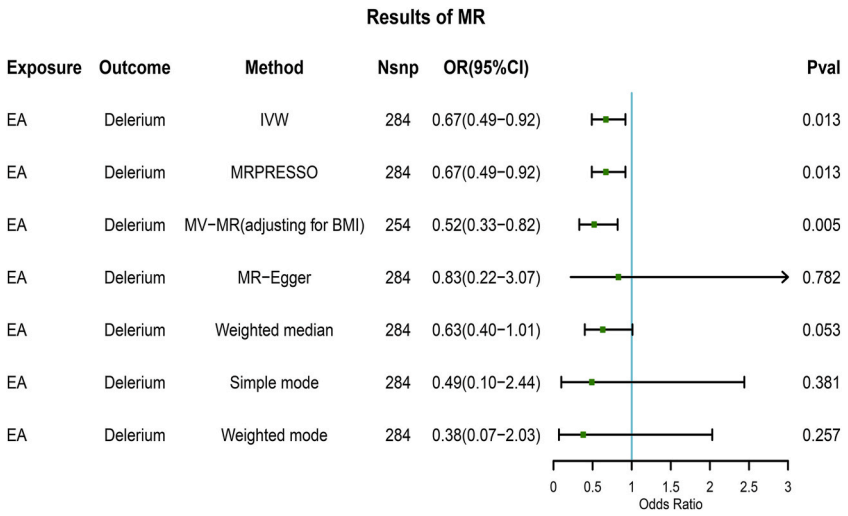

Fig. 1. Forest plot of MR analysis results. IVW is the main analysis method, MRPRSEEO provides IVW results after adjusting for horizontal pleiotropy, MV-MR provides IVW results after adjusting for BMI, and other methods represent different MR models.
(Note: MR = Mendelian randomization; EA = educational attainment; OR= Odds ratio; MR-PRESSO = Mendelian Randomization Pleiotropy RESidual Sum and Outlier; IVW = inverse variance weighting; MR-Egger = Mendelian Randomization-Egger; BMI = body mass index).

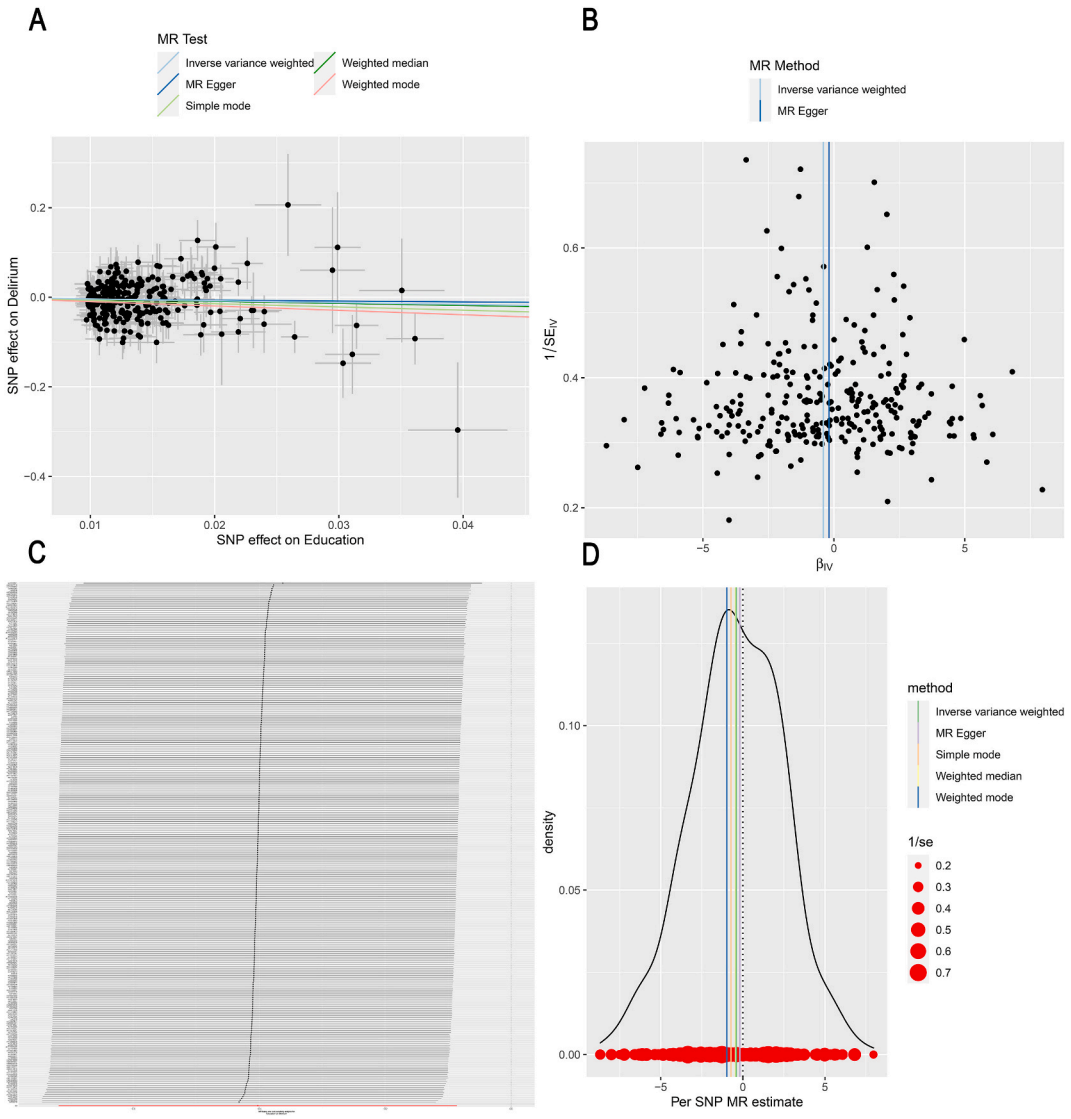

Fig. 2. A = scatter plot of MR results, B = funnel plot of MR results, C = leave-one-out method visualization results, D = density plot. (The trends of the scatter plots of the five MR methods remained consistent, the funnel and leave-one-out plots did not show significant outliers, and the density plots suggested that the different SNP effects were distributed around the IVW of the main analysis method.)
(Note: MR = Mendelian randomization; VW = inverse variance weighting; MR-Egger = Mendelian Randomization-Egger; SNP = single nucleotide polymorphism).

thus, higher education can be a protective factor for delirium. On the other hand, delirium is clinically influenced by several risk factors, such as poor lifestyles (smoking and alcohol consumption) and advanced age [1]. Studies have found that higher EA can correct the effect of occupational social class on health-related behaviors [48]. In a study conducted in Singapore, it was also found that individuals with lower educational levels were more likely to smoke daily, drink alcohol regularly, or not exercise regularly [49]. We are cautious to assume that the higher-educated population may have a reduced risk of delirium owing to the presence of fewer delirium risk factors through adverse lifestyle changes, which in turn reduces the risk of delirium. In our study, we investigated the causal relationship between EA and delirium at the genetic level, and found a causal relationship between EA and delirium from this new perspective at the genetic level and that higher EA may be a protective factor for delirium. Combined with previous studies, we consider that EA affects delirium in diverse and complex ways and may have an effect on delirium through multiple pathways.

As far as our findings are concerned, as well as a large number of previous observational studies in clinical research, higher EA is a protective factor for delirium. Based on the results of this study, it is prudent to recommend asking and registering patients' educational level. Especially for patients who have a higher likelihood of delirium, such as those with advanced age, major trauma, or undergoing major surgery, knowing their education level before treatment can better prepare for the prevention of delirium, and for those with lower education level, we should be more vigilant about delirium when treating them in the clinic. Based on the results of

our study, we can conduct more in-depth research on how education level affects delirium in the future, so that we can have a clearer understanding of the relationship between the two, for example, we can use questionnaires to further understand whether education level affects delirium through lifestyle changes, and we can explore whether education level changes the quantity or quality of some neurotransmitters through neurotransmitter research. In addition, through neurotransmitter research, we can explore whether the level of education can change the amount or transmission rate of some neurotransmitters, which affects the stabilization of the nervous system, and then affects the occurrence of delirium, which may be one of the directions of research we can carry out in the future.

Our study inferred genetic-level causality between EA (exposure factor) and delirium (outcome) using MR methods, effectively avoiding confounding factors and reverse causation. Some studies have pointed out that a low BMI is a postoperative risk factor for hip fracture patients [50]. Another study has found that a higher BMI mediates protective effects on postoperative delirium (POD) through cerebrospinal fluid (CSF) biomarkers (t-tau and p-tau) [51]. Combining previous studies and considering the partial association between SNP and BMI, we performed multivariate MR on the data to reduce the effect of BMI on our results and make our conclusions more reliable. The final study found a causal relationship between EA and delirium at the genetic level and a protective effect of EA against delirium. This finding was not influenced by confounding factors. Our findings add a genetic dimension that has not been addressed by previous studies and provides new ideas for studies in this field.

However, there are some limitations to our study. First, our study database was drawn from European populations; and considering the possible differences in disease in different geographical populations, when using our findings in other populations, consideration should be given to the actual study population. Second, our data are not disaggregated by age and sex but rather aggregated data, which should be used with caution when discussing a particular age class or gender. Finally, the pathogenesis and clinical manifestations of the disease are diverse and complex, and our conclusions explain the causal relationship only at the genetic level, which needs to be analyzed and considered clinically in the context of multiple factors.

5. Conclusions

Our study found a negative causal relationship between EA and delirium using the MR method, that is, a higher educational level is a protective factor for delirium. The conclusion of this study provides new evidence for the prevention, treatment, and prognosis of delirium in clinical settings and helps researchers or clinicians gain new insights on delirium. However, in conjunction with previous studies, the specific clinical pathways through which the association between education and delirium occurs remain to be investigated in greater depth.

Institutional review board statement

All data used in this study were obtained from publicly available databases; further ethical approval was not required.

Informed consent statement

Not applicable.

Data availability statement

The datasets supporting this study are available from IEU OpenGWAS (GWAS ID: ieu-a-1239(EA) and ieu-a-835(BMI), https://gwas.mrcieu.ac.uk/) and the FinnGen consortium (https://www.finngen.fi/, finn-b-F5_DELIRIUM).

CRediT authorship contribution statement

Xianjie Wan: Writing – review & editing, Writing – original draft, Visualization, Methodology, Formal analysis, Conceptualization. **Hui Yu:** Writing – review & editing, Visualization, Methodology, Formal analysis. **Mingyi Yang:** Software, Formal analysis, Data curation. **Weikun Hou:** Software, Formal analysis, Data curation. **Jiale Xie:** Software, Data curation. **Ke Xu:** Software, Data curation. **Yujie Ma:** Software, Data curation. **Rui Ma:** Software, Data curation. **Fan Wang:** Software, Data curation. **Peng Xu:** Supervision, Funding acquisition, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Abbreviations

ApoE4	apolipoprotein E4
BMI	body mass index
CSF	cerebrospinal fluid
EA	educational attainment

GWAS Genome-wide association study
IVW inverse variance weighting
IV instrumental variable
IEU independent evaluation unit
ICD International Classification of Diseases
MR Mendelian randomization
MR-PRESSO Mendelian Randomization Pleiotropy RESidual Sum and Outlier
MR-Egger Mendelian Randomization-Egger
NMDA N-methyl-D-aspartate
OR Odds ratio
POD postoperative delirium
SSGAC Social Science Genetic Association Consortium
SNPs single nucleotide polymorphisms
SNP single nucleotide polymorphism

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e28697.

References

[1] M.L.P. Mattison, Delirium, Ann. Intern. Med. 173 (7) (2020) ITC49–ITC64.
[2] C.R. Keenan, S. Jain, Delirium, Med. Clin. 106 (3) (2022) 459–469.
[3] S.M. Vasunilashorn, et al., Apolipoprotein E genotype and the association between C-reactive protein and postoperative delirium: Importance of gene-protein interactions, Alzheimers Dement 16 (3) (2020) 572–580.
[4] B.C. van Munster, et al., The association of the dopamine transporter gene and the dopamine receptor 2 gene with delirium, a meta-analysis, Am J Med Genet B Neuropsychiatr Genet 153b (2) (2010) 648–655.
[5] K. Hirschfeldova, et al., Evidence for the association between the Intronic Haplotypes of Ionotropic glutamate receptors and first-episode schizophrenia, J. Personalized Med. 11 (12) (2021).
[6] J. Wu, et al., The risk factors for postoperative delirium in adult patients after hip fracture surgery: a systematic review and meta-analysis, Int. J. Geriatr. Psychiatr. 36 (1) (2021) 3–14.
[7] A. Burns, A. Gallagley, J. Byrne, Delirium, J. Neurol. Neurosurg. Psychiatry 75 (3) (2004) 362–367.
[8] J.A. Palakshappa, C.L. Hough, How we prevent and treat delirium in the ICU, Chest 160 (4) (2021) 1326–1334.
[9] D. Davis, S.D. Searle, A. Tsui, The Scottish Intercollegiate Guidelines Network: risk reduction and management of delirium, Age Ageing 48 (4) (2019) 485–488.
[10] C.A. Mosk, et al., Dementia and delirium, the outcomes in elderly hip fracture patients, Clin. Interv. Aging 12 (2017) 421–430.
[11] Y. Yang, et al., Incidence and associated factors of delirium after orthopedic surgery in elderly patients: a systematic review and meta-analysis, Aging Clin. Exp. Res. 33 (6) (2021) 1493–1506.
[12] B. Setters, L.M. Solberg, Delirium, Prim Care 44 (3) (2017) 541–559.
[13] A.C. Heath, et al., Education policy and the heritability of educational attainment, Nature 314 (6013) (1985) 734–736.
[14] S. Dekhtyar, et al., A life-course study of cognitive reserve in dementia–from childhood to old age, Am. J. Geriatr. Psychiatr. 23 (9) (2015) 885–896.
[15] X. Meng, C. D'Arcy, Education and dementia in the context of the cognitive reserve hypothesis: a systematic review with meta-analyses and qualitative analyses, PLoS One 7 (6) (2012) e38268.
[16] J. Hugo, M. Ganguli, Dementia and cognitive impairment: epidemiology, diagnosis, and treatment, Clin. Geriatr. Med. 30 (3) (2014) 421–442.
[17] A.K. Cohen, et al., Educational attainment and obesity: a systematic review, Obes. Rev. 14 (12) (2013) 989–1005.
[18] M. Tesli, et al., Educational attainment and mortality in schizophrenia, Acta Psychiatr. Scand. 145 (5) (2022) 481–493.
[19] S. Martins, et al., Delirium in elderly patients: association with educational attainment, Acta Neuropsychiatr. 29 (2) (2017) 95–101.
[20] J.S. Saczynski, et al., Cognitive and brain reserve and the risk of postoperative delirium in older patients: analysis of data from a prospective observational study, Lancet Psychiatr. 1 (6) (2014) 437–443.
[21] H. Zhou, et al., Education and lung cancer: a Mendelian randomization study, Int. J. Epidemiol. 48 (3) (2019) 743–750.
[22] J. Zhang, et al., Mediators of the association between educational attainment and type 2 diabetes mellitus: a two-step multivariable Mendelian randomisation study, Diabetologia 65 (8) (2022) 1364–1374.
[23] K. Bowman, et al., Vitamin D levels and risk of delirium: a mendelian randomization study in the UK Biobank, Neurology 92 (12) (2019) e1387–e1394.
[24] M.A. Nalls, et al., Identification of novel risk loci, causal insights, and heritable risk for Parkinson's disease: a meta-analysis of genome-wide association studies, Lancet Neurol. 18 (12) (2019) 1091–1102.
[25] M. Wang, et al., Educational attainment protects against epilepsy independent of cognitive function: a Mendelian randomization study, Epilepsia 62 (6) (2021) 1362–1368.
[26] A. Seyedsalehi, et al., Educational attainment, structural brain reserve and Alzheimer's disease: a Mendelian randomization analysis, Brain 146 (5) (2023) 2059–2074.
[27] J. Bowden, M.V. Holmes, Meta-analysis and Mendelian randomization: a review, Res. Synth. Methods 10 (4) (2019) 486–496.
[28] A. Okbay, et al., Polygenic prediction of educational attainment within and between families from genome-wide association analyses in 3 million individuals, Nat. Genet. 54 (4) (2022) 437–449.
[29] M.I. Kurki, et al., FinnGen: unique genetic insights from combining isolated population and national health register data, medRxiv (2022). https://doi.org/10.1101/2022.03.03.22271360.
[30] M.A. Kamat, et al., PhenoScanner V2: an expanded tool for searching human genotype-phenotype associations, Bioinformatics 35 (22) (2019) 4851–4853.
[31] S. Burgess, S.G. Thompson, Avoiding bias from weak instruments in Mendelian randomization studies, Int. J. Epidemiol. 40 (3) (2011) 755–764.
[32] S. Burgess, A. Butterworth, S.G. Thompson, Mendelian randomization analysis with multiple genetic variants using summarized data, Genet. Epidemiol. 37 (7) (2013) 658–665.
[33] J. Bowden, et al., Consistent estimation in mendelian randomization with some invalid instruments using a weighted median estimator, Genet. Epidemiol. 40 (4) (2016) 304–314.

[34] J. Bowden, G. Davey Smith, S. Burgess, Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression, Int. J. Epidemiol. 44 (2) (2015) 512–525.
[35] M. Verbanck, et al., Detection of widespread horizontal pleiotropy in causal relationships inferred from Mendelian randomization between complex traits and diseases, Nat. Genet. 50 (5) (2018) 693–698.
[36] E. Sanderson, et al., An examination of multivariable Mendelian randomization in the single-sample and two-sample summary data settings, Int. J. Epidemiol. 48 (3) (2019) 713–727.
[37] P. Pompei, et al., Delirium in hospitalized older persons: outcomes and predictors, J. Am. Geriatr. Soc. 42 (8) (1994) 809–815.
[38] F.M. Yang, et al., Participation in activity and risk for incident delirium, J. Am. Geriatr. Soc. 56 (8) (2008) 1479–1484.
[39] R.N. Jones, et al., Does educational attainment contribute to risk for delirium? A potential role for cognitive reserve, J Gerontol A Biol Sci Med Sci 61 (12) (2006) 1307–1311.
[40] P. Galanakis, et al., Acute confusional state in the elderly following hip surgery: incidence, risk factors and complications, Int. J. Geriatr. Psychiatr. 16 (4) (2001) 349–355.
[41] B.W. Fisher, G. Flowerdew, A simple model for predicting postoperative delirium in older patients undergoing elective orthopedic surgery, J. Am. Geriatr. Soc. 43 (2) (1995) 175–178.
[42] J. McCusker, et al., Delirium in older medical inpatients and subsequent cognitive and functional status: a prospective study, CMAJ (Can. Med. Assoc. J.) 165 (5) (2001) 575–583.
[43] J.M. Leung, et al., Are preoperative depressive symptoms associated with postoperative delirium in geriatric surgical patients? J Gerontol A Biol Sci Med Sci 60 (12) (2005) 1563–1568.
[44] Y. Stern, What is cognitive reserve? Theory and research application of the reserve concept, J. Int. Neuropsychol. Soc. 8 (3) (2002) 448–460.
[45] J.A. Mortimer, et al., Very early detection of Alzheimer neuropathology and the role of brain reserve in modifying its clinical expression, J. Geriatr. Psychiatr. Neurol. 18 (4) (2005) 218–223.
[46] R. Katzman, Education and the prevalence of dementia and Alzheimer's disease, Neurology 43 (1) (1993) 13–20.
[47] C.M. Roe, et al., Education and Alzheimer disease without dementia: support for the cognitive reserve hypothesis, Neurology 68 (3) (2007) 223–228.
[48] J. García-Mayor, A. Moreno-Llamas, E. la Cruz-Sánchez, High educational attainment redresses the effect of occupational social class on health-related lifestyle: findings from four Spanish national health surveys, Ann. Epidemiol. 58 (2021) 29–37.
[49] C.W. Fong, et al., Educational inequalities associated with health-related behaviours in the adult population of Singapore, Singap. Med. J. 48 (12) (2007) 1091–1099.
[50] V. Juliebø, et al., Risk factors for preoperative and postoperative delirium in elderly patients with hip fracture, J. Am. Geriatr. Soc. 57 (8) (2009) 1354–1361.
[51] X. Deng, et al., The relationship between body mass index and postoperative delirium, Brain Behav 12 (4) (2022) e2534.