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Assessing the Causality Between Frailty and Epilepsy: Bidirectional 2-Sample Mendelian Randomization

Yan Wang[1], Ling Chen[2]

[1]*Department of Basic Medicine, Cangzhou Medical College, Cangzhou, China*

[2]*Department of Gynecology, Cangzhou People's Hospital, Affiliated to Cangzhou Medical Vocational School, Cangzhou, China*

Background: Whereas a potential connection between epilepsy and frailty has been proposed in past research, the causal nature of this relationship requires additional study.

Objective: This research was designed to evaluate the bidirectional causality between epilepsy and frailty index (FI) through 2-sample Mendelian randomization (MR).

Methods: In this study, we applied genome-wide association studies to perform forward and reverse MR within a 2-sample context to explore the potential bidirectional causality between FI and epilepsy. The main analysis approach was the inverse variance weighted (IVW) used to assess the potential influence of causal relationships and to carry out sensitivity checks.

Results: MR analysis revealed a positive correlation between FI and the heightened risk of epilepsy [$OR_{IVW} = 1.2126$, 95% confidence interval (CI): 1.0143–1.4497, $P = 0.0343$]. This correlation persists in MR analysis that excluded aberrant single nucleotide polymorphisms ($OR_{IVW} = 1.1862$, 95% CI: 1.0236–1.3746, $P = 0.0232$). Reverse MR analysis corroborated a significant positive relationship between epilepsy and FI ($OR_{IVW} = 1.0896$, 95% CI: 1.0242–1.1592, $P = 0.0066$), which was confirmed in subsequent replication analysis ($OR_{IVW} = 1.0975$, 95% CI: 1.0532–1.1436, $P = 9.69e\text{-}06$). Sensitivity analysis further supported the hypothesis of a causal link between FI and epilepsy.

Conclusion: There is an evident bidirectional causal relationship between FI and epilepsy.

Key words: Causality – Epilepsy – Frailty index – Mendelian randomization – Single nucleotide polymorphism

Epilepsy, a complex chronic neurologic condition, is marked by the sporadic interruption of cerebral function due to the abnormal synchronization of neuronal discharges, which severely impacts an individual's

Corresponding author: Ling Chen, Department of Obstetrics and Gynecology, Cangzhou People's Hospital, Affiliated to Cangzhou Medical Vocational School, No. 39 West Jiuhe Road, Cangzhou, 061001, China.
Tel.: 18131797810; E-mail: wdb19771219@163.com

overall well-being and daily functioning.[1] Recognized as one of the prevalent severe neurologic afflictions, it is estimated that, annually, nearly 5 million individuals receive an epilepsy diagnosis with a current global prevalence affecting approximately 50 million people, representing 0.5% of the global disease burden. This condition exerts considerable demands on health care systems, contributes to premature deaths, and handicaps work productivity.[2] The intricate pathophysiologic mechanisms underlying epilepsy remain elusive with a spectrum of diseases and habits, including cerebral infections, neoplasms, stress, alcohol abuse, and smoking, identified as potential risk factors for the onset of epilepsy.[3–5]

Frailty also stands as a public health challenge. It is identified by heightened vulnerability to stress and undermined system functionality.[6] Frailty leads to a host of negative outcomes, such as lower life quality and increased morbidity and mortality, a widespread condition that naturally comes with aging.[7] Evidence from epidemiologic studies suggests that frailty is a precursor to chronic ailments and precipitates a cascade of adverse health ramifications, encompassing cardiovascular disorders, delirium, hospital admissions, and fatalities.[8–11] Research on the nexus between frailty and epilepsy has pointed to a pronounced relationship between the frailty status of geriatric epilepsy sufferers and their antiepileptic drug responsiveness.[12] Another study utilizing a United Kingdom primary care database has correlated the exacerbation of dementia and frailty to an elevated mortality rate among patients with late-onset epilepsy.[13] Nonetheless, the intrinsic causality between frailty and epilepsy has yet to be explored on a broad population scale. Pinpointing this link is vital. Early identification of risk factors for epilepsy can better prevent the development of the disease, guide intervention strategies, and mitigate the escalating health crisis.

The frailty index (FI), a composite metric for gauging the impact of aging on health, compares health deficits to a comprehensive set of measured variables.[13] It operates independently of any particular variables, amalgamating a multitude of health indicators into a singular index via a basic mathematic model. This index bespeaks unpredictability of environmental factors as well as the ability to recuperate from illnesses, thereby emerging as an acutely sensitive gauge of frailty.[14] Mendelian randomization (MR), recognized for its strength in epidemiologic research, serves as a potent instrument to determine the causal links between exposures and health outcomes. MR minimizes the confounding effects of environmental factors by relying on the random distribution of genetic variations at the moment of conception, and it precludes the issue of reverse causation because an individual's genotype is not dictated by diseases.[15] The purpose of our study was to use MR analysis to probe into the causality between FI and epilepsy and to investigate, through reverse causation analysis, the potential influence of epilepsy on the incidence and development of frailty. Although our findings may not bring any groundbreaking changes to the existing knowledge of epilepsy's etiology, they pave the way for future inquiries in this domain.

Methods

Research design

A 2-sample MR analysis was performed to assess the causality between FI and epilepsy with the schematic flow of the study design outlined in Fig. 1. FI was set as the exposure and epilepsy as the outcome. In a reverse scenario, epilepsy was chosen as the exposure and FI as the outcome. Utilizing independent genetic variants as instrumental variables (IVs), the MR analyses were grounded in 3 basic postulates: (1) a tight

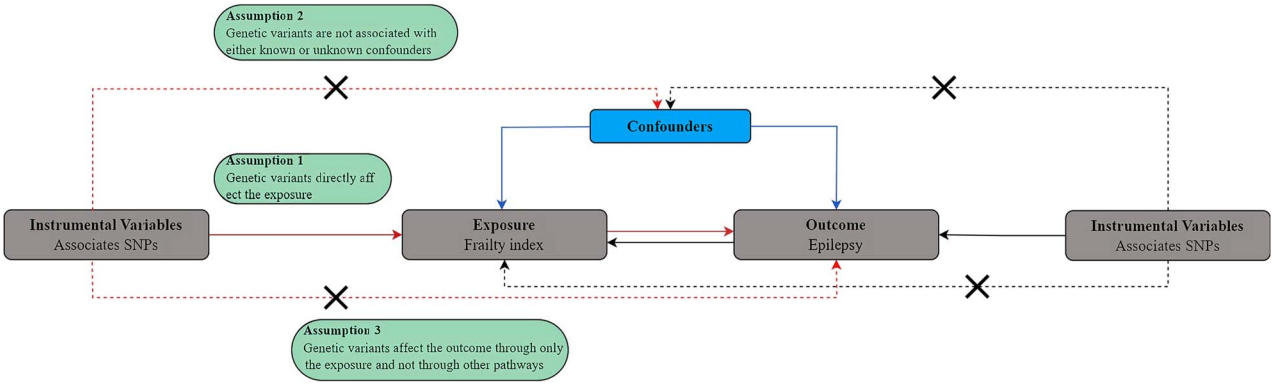

Fig. 1 Flow chart of the MR study design.

correlation between IVs and the exposure is necessary, (2) IVs must remain uncorrelated with confounders, (3) the influence of IVs on the outcome should be mediated exclusively through the exposure.[16] To avoid bias due to population heterogeneity, the main body of the genome-wide association studies (GWAS) data we selected comes from individuals of European descent with a minor representation from other ancestries. These populations exhibit a high degree of independence.

The data for this study were all derived from research that has been published or from GWAS summary statistics. These summary statistics, open to the public, have been ethically approved and are recorded in the initial GWAS publications. Approval from the institutional review boards was secured for each study we analyzed, and all participants have supplied written informed consent.

Data source

FI data

FI is widely accepted as a standard for frailty assessment. Our MR analysis included GWAS data related to FI from the United Kingdom Biobank and Twin Gene.[17] All data for this study are publicly accessible and can be retrieved from the website http://ftp.ebi.ac.uk/pub/databases/gwas/summary_statistics/GCST90020053/. A total of 175,226 subjects with European ancestry were included with 164,610 from the United Kingdom Biobank and 10,616 from Twin Gene.

Epilepsy data

The International League Against Epilepsy provided the GWAS summary data for epilepsy, covering various epilepsy phenotypes, including all epilepsy, generalized seizures, focal seizures, childhood absence epilepsy, juvenile absence epilepsy, juvenile myoclonic epilepsy, tonic-clonic seizures in generalized epilepsy, hippocampal sclerosis in focal epilepsy, and lesional negative focal epilepsy.[18] The data set comprises 15,212 epilepsy cases and 29,677 healthy controls with the majority being of European descent and a smaller number of African and Asian individuals (Caucasian: 38,752, Asian: 3,406, African: 2,731). Additional information is detailed in Table 1.

Selection of IVs

Criteria for the selection of IVs are as follows: (1) Single nucleotide polymorphisms (SNPs) significantly related to FI were selected as potential suitable IVs with $p < 1e{-}6$ to pinpoint SNPs with substantial relevance to frailty; (2) clumping of SNPs was conducted to eliminate the impact of linkage disequilibrium ($r^2 = 0.001$, region length = 10,000 kb); (3) the *F*-statistic, which signifies the strength of the instrument, was used to screen out weak IVs with only those SNPs exceeding an *F*-statistic of 10 being included. After the exclusion of palindromic sequences and weak IVs from the exposure and outcome data sets, the remaining SNPs were employed in MR analysis. Outliers, if any, should be removed, with the analysis reiterated.

Table 1 Detailed information of the genome-wide association studies in our analysis

Disease	Year	ID	Sample size	Control	Case
Frailty index	2021	GCST90020053	175,226	NA	NA
Epilepsy	2018	ieu-b-8	44,889	29,677	15,212

Bidirectional MR analysis

To mitigate the risk of pleiotropic influences, we applied 5 distinct MR methods to examine the 2-way causality between FI and epilepsy, including inverse variance weighted (IVW), MR Egger, weighted median, simple mode, and weighted mode. When employing IVW, favored as the main analytic technique for its consistency, it is crucial to make sure that the SNPs do not exhibit pleiotropy to avert substantial bias in the outcomes. The MR Egger method, which considers the existence of an intercept, can complement IVW but may lead to bias and amplify the likelihood of a type I error.[19] The weighted median, simple mode, and weighted mode were also utilized to gather additional evidence.

The causal link between FI as the exposure and epilepsy as the outcome was investigated initially. Then, we examined whether epilepsy, as an exposure, would affect FI (outcome) with the same workflow for MR analysis. Due to the paucity of loci significant for epilepsy, a more lenient threshold for significance was implemented ($P < 1e{-}06$).

Sensitivity analysis was performed to evaluate the dependability of our findings and to detect any potential heterogeneity and horizontal pleiotropy. MR Egger regression and MR-PRESSO were utilized to assess horizontal pleiotropy of the IVs with significance set at $P < 0.05$.[19,20] The Cochran Q test was then used to gauge the stability of the findings, in which $P < 0.05$ indicated heterogeneity. A random effects IVW model was employed in cases of heterogeneity; otherwise, a fixed effects IVW model was the default.[21] Furthermore, a leave-one-out analysis was conducted to determine if the observed

Table 2 Results of causal association of 5 methods MR regression

Outcome	Exposure	Method	SNPs	Beta	Se	*P*	OR (95% CI)
Epilepsy	Frailty	MR Egger	35	1.1335	0.6515	0.0912	3.1065 (0.8663–11.1395)
Epilepsy	Frailty	Weighted median	35	0.2326	0.0993	0.0192	1.2619 (1.0387–1.5330)
Epilepsy	Frailty	Inverse variance weighted	35	0.1928	0.0911	0.0343	1.2126 (1.0143–1.4497)
Epilepsy	Frailty	Simple mode	35	0.3037	0.2360	0.2069	1.3549 (0.8531–2.1518)
Epilepsy	Frailty	Weighted mode	35	0.2959	0.2340	0.2147	1.3443 (0.8497–2.1268)

causality was contingent upon or unduly swayed by an individual SNP.

Statistical analysis

Two-sample MR analysis was performed using R (version 4.3.1) software and the *Two Sample MR* R package. The random effects IVW method was our primary approach to ascertain the causal relationship between exposure and outcome. Supportive analyses included MR Egger regression, weighted median, weighted mode, and simple mode. In MR analyses, the presence of a significant causal relationship was denoted by $P < 0.05$.

Results

Selection of IVs

After the exclusion of linkage disequilibrium and palindromes, we were left with 35 SNPs as a final set of IVs, all markedly related to the exposure, with all *F*-statistics above the threshold of 10. Supplemental Table S1 provides further information.

Causal effect of FI on the risk of epilepsy

In Table 2, the data show a pronounced link between the FI and epilepsy. IVW analysis indicates a positive correlation between genetically forecasted FI and epilepsy (OR = 1.2126, 95%CI: 1.0143-1.4497, $P = 0.0343$), and the Weighted Median method detected a congruent causal effect [odds ratio (OR) = 1.2619, 95% confidence interval (CI): 1.0387–1.5330, $P = 0.0192$]. The detailed MR forest plot is provided in Appendix 1.

Sensitivity analyses

A suite of sensitivity analyses was executed, including the MR Egger intercept, funnel plot examination, MR-PRESSO detection, Cochran Q test, and exclusion analyses, to verify the precision of the positive outcomes. The results (Table 3) showed $P < 0.05$ for both the IVW and the MR Egger intercept, suggesting heterogeneity between the SNPs. Nevertheless, the combined results of the MR Egger intercept and the MR-PRESSO global tests indicated that the MR analysis was unaffected by any potential horizontal pleiotropy ($P > 0.05$) (Appendix 1). Considering the presence of outliers and pleiotropy in the MR-PRESSO test (Table 3), we iterated these analyses after the removal of the outlier SNPs identified by the MR-PRESSO test (rs11245450 and rs755249). More information can be found in Appendix 1. The leave-one-out test revealed SNPs that potentially affected the causal association (Supplemental Figure S1). Yet, as no other statistical methods showed any abnormalities, the impact of the outlier SNPs on the results was not significant. These analyses affirmed the robustness and reliability of our MR findings.

Results for iterated MR

After the elimination of outlier SNPs, the aforementioned analyses were reiterated. The IVW method was utilized for causal analysis, which supported a positive correlation between FI and epilepsy, identifying that the epilepsy risk in frail populations is 1.1862 times greater than in those who are not frail (95% CI: 1.0236–1.3746, $P = 0.0232$) (Table 4). The closeness of the IVW estimate to that of the weighted median (OR = 1.2622, 95% CI: 1.0309–1.5455, $P = 0.0242$) demonstrates the

Table 3 Tests for heterogeneity and pleiotropy

		Heterogeneity				Pleiotropy			
		MR Egger		IVW					
Exposure	Outcome	Statistics Q	*P*	Statistics Q	*P*	Egger intercept	SE	*P*	Global PRESSO *P*
Frailty	Epilepsy	53.2570	0.0142	56.6863	0.0086	−0.0189	0.0130	0.1544	0.0080

Table 4 Outlier SNPs were removed to replicate Mendelian randomization results

Outcome	Exposure	Method	SNPs	Beta	Se	*P*	OR (95% CI)
Epilepsy	Frailty	MR Egger	33	0.8711	0.5348	0.1135	2.3895 (0.8377–6.8156)
Epilepsy	Frailty	Weighted median	33	0.2329	0.1033	0.0242	1.2622 (1.0309–1.5455)
Epilepsy	Frailty	Inverse variance weighted	33	0.1707	0.0752	0.0232	1.1862 (1.0236–1.3746)
Epilepsy	Frailty	Simple mode	33	0.3123	0.2333	0.1902	1.3665 (0.8650–2.1589)
Epilepsy	Frailty	Weighted mode	33	0.3011	0.2343	0.2081	1.3513 (0.8537–2.1392)

reliability of the FI-epilepsy effect estimation. The MR forest plot is presented in Appendix 2.

The Cochran Q test showed no significant heterogeneity ($P > 0.05$), and both the MR Egger regression intercept test and the MR-PRESSO test did not suggest horizontal pleiotropy ($P > 0.05$) (Table 5). Scatterplots and funnel plots illustrate a symmetric distribution of all the SNPs included, implying that the causal association is not likely to be biased (Appendix 2). Sensitivity analysis confirmed the reliability of the MR results in this study (Figure S2).

Results for reverse MR

IVs

Eighteen SNPs were ascertained as the ultimate set of IVs, all demonstrating remarkable relevance to the exposure. With epilepsy as the exposure and FI as the outcome, all *F*-statistics surpassed 10. Further details are provided in Supplemental Table S2.

Causal effect of epilepsy on the risk of FI

Table 6 demonstrates evidence of a reverse causality. The IVW model indicates that epilepsy raised the risk of FI (OR = 1.0896, 95% CI: 1.0242–1.1592, $P = 0.0066$), a finding that was supported by the weighted median model (OR = 1.0955, 95% CI: 1.0326–1.1621, $P = 0.0025$). The Cochran Q test pointed to heterogeneity among the included SNPs in the outcomes ($P < 0.05$) (Appendix 3). The MR Egger intercept test confirmed that the MR analysis is not biased by any potential horizontal pleiotropy ($P > 0.05$), notwithstanding the presence of outliers and pleiotropy in the MR-PRESSO test for MR (Appendix 3). The leave-one-out test found no evident impact of SNPs on the causal estimate, suggesting robustness in the MR outcomes (Supplemental Figure S3).

To ensure the veracity of the results, the analysis was repeated after excluding the outlier SNPs identified by the MR-PRESSO test (rs4638568 and rs61779328). Table 7 shows the causality between epilepsy and FI following the exclusion of the outlier SNPs. The IVW model pointed to a statistically significant difference (OR = 1.0975, 95% CI: 1.0532–1.1436, $P = 9.69e\text{-}06$), which was confirmed in the weighted median and MR Egger models (OR = 1.0970, 95% CI: 1.0363–1.1612, $P = 0.0014$; OR = 1.1670, 95% CI: 1.0153–1.3414, $P = 0.0473$). Epilepsy is recognized as a risk factor for frailty. Sensitivity analysis showed no evidence of heterogeneity or horizontal pleiotropy (Table 8), and no outlier SNPs were noted in other assessments (Appendix 4, Supplemental Figure S4), demonstrating the robustness of the MR results.

Discussion

For this study, we leveraged GWAS summary data to determine the causality between frailty and epilepsy. The bidirectional MR analysis provided preliminary evidence of a positive causal relationship between FI and epilepsy, suggesting that frailty could be a contributor to the risk of epilepsy. Inverse MR outcomes suggested that epilepsy patients suffer an elevated risk of FI, rendering epilepsy a risk factor for frailty. Our research is the first MR study to explore the bidirectional causality between epilepsy and frailty, aiding in the genetic contextualization of epilepsy risk and frailty.

Epilepsy, a common and formidable chronic neurologic disorder with heterogeneous causes, has become a focal point of public concern. Research has established that oxidative stress is a key characteristic of the pathophysiologic mechanisms behind epilepsy, integral to the harmful effects of epileptic activity

Table 5 Tests of MR heterogeneity and pleiotropy after removal of outlier SNPs

		Heterogeneity				Pleiotropy			
		MR Egger		IVW					
Exposure	Outcome	Statistics Q	*P*	Statistics Q	*P*	Egger intercept	SE	*P*	Global PRESSO *P*
Frailty	Epilepsy	32.5327	0.3913	34.3680	0.3550	−0.0141	0.0107	0.1957	0.3610

Table 6 Causal association results from 5 methods of reverse MR regression

Outcome	Exposure	Method	SNPs	Beta	Se	*P*	OR (95% CI)
Frailty	Epilepsy	MR Egger	18	0.0442	0.1088	0.6898	1.0452 (0.8445–1.2937)
Frailty	Epilepsy	Weighted median	18	0.0912	0.0301	0.0025	1.0955 (1.0326–1.1621)
Frailty	Epilepsy	Inverse variance weighted	18	0.0858	0.0316	0.0066	1.0896 (1.0242–1.1592)
Frailty	Epilepsy	Simple mode	18	0.0921	0.0519	0.0937	1.0965 (0.9905–1.2138)
Frailty	Epilepsy	Weighted mode	18	0.0939	0.0495	0.0747	1.0985 (0.9970–1.2103)

in the brain and associated with the advancement of neuronal damage.[22] In the epilepsy patient population, oxidative stress can inflict functional cellular damage, creating a surge of reactive oxygen species (ROS) that directly catalyze the transition of mitochondrial permeability, resulting in compromised mitochondrial membrane integrity, increased permeability, reduced membrane potential, mitochondrial dysfunction, and neuronal cell death.[23,24] Frailty, a dynamic clinical syndrome, is defined by a diminished capacity for physiologic reserve to sustain homeostasis.[7] Individuals identified as frail are facing greater risk of adverse health outcomes compared with the nonfrail population.[25] Frailty is marked by pronounced deficiencies in the innate immune function, T-cell activity, and antibody production in conjunction with an upregulation of oxidative stress biomarkers and a diminished antioxidant capacity.[26] This complex interplay culminates in the buildup of proinflammatory cytokines and the creation of byproducts associated with oxidative stress.[27–29] A study examining the effects of frailty and dementia on elderly epilepsy patients' mortality rates has shown that increased frailty is significantly linked to a higher risk of death.[13] A plethora of animal model studies on epilepsy now support the role of antioxidants in easing the condition by combating the adverse effects of an overabundance of ROS in mitochondria and preventing cell death.[30–32] Antioxidants, therefore, are emerging as a potential neuroprotective treatment for epilepsy.[33]

Individuals with epilepsy may undergo accelerated frailty when compared with their peers. A study focusing on the incidence of hospitalization for chronic conditions in young people has demonstrated that individuals with epilepsy are at an elevated risk of hospital admission relative to their peers (absolute risk reduction: 10.95, 95% CI: 9.98–12.02).[34] Our research has likewise identified a notable positive association between epilepsy and FI, marking epilepsy as a determinant of frailty. As previously stated, we conjectured that oxidative stress is pivotal in the pathophysiologic mechanisms linking frailty to epilepsy, prompting the emergence of great amounts of proinflammatory cytokines and ROS. It is documented that the continuous state of epilepsy, fueled by heightened ROS production, may lead to the accumulation of peroxidation products.[24] Epileptic seizures elicit an inflammatory response that activates inducible nitric oxide synthase and NADPH oxidase 2, leading to the production of reactive nitrogen species and ROS. These reactive molecules contribute to the severity of oxidative stress during seizures and, in conjunction with elevated levels of proinflammatory cytokines, facilitate the progression of the disease.[35,36] The rise in pro-inflammatory cytokines can affect the frail state either directly by enhancing protein breakdown or indirectly by influencing important metabolic pathways in the brain.[37–39] We speculate that this may be the reason for the increased frailty associated with epilepsy. Nonetheless, the esoteric mechanisms linking frailty and epilepsy necessitate further experimental confirmation.

This investigation is fortified by several key advantages. MR is adept at discerning the causality between FI and epilepsy while eliminating the impact of confounding factors. Furthermore, the use of nonoverlapping summary data for exposure and outcome in 2-sample MR effectively avoids bias. The study is enhanced by the deployment of large-scale GWAS summary data and sensitivity analyses, which

Table 7 Causal association results of reverse MR regression by 5 methods after removing outlier SNPs

Outcome	Exposure	Method	SNPs	Beta	Se	*P*	OR (95% CI)
Frailty	Epilepsy	MR Egger	16	0.1544	0.0710	0.0473	1.1670 (1.0153–1.3414)
Frailty	Epilepsy	Weighted median	16	0.0926	0.0290	0.0014	1.0970 (1.0363–1.1612)
Frailty	Epilepsy	Inverse variance weighted	16	0.0930	0.0210	9.69e-06	1.0975 (1.0532–1.1436)
Frailty	Epilepsy	Simple mode	16	0.0919	0.0512	0.0926	1.0963 (0.9916–1.2120)
Frailty	Epilepsy	Weighted mode	16	0.0961	0.0521	0.0850	1.1009 (0.9940–1.2193)

Table 8 Tests of reverse MR heterogeneity and pleiotropy after removal of abnormal SNPs

		Heterogeneity				Pleiotropy			
		MR Egger		IVW					
Exposure	Outcome	Statistics Q	*P*	Statistics Q	*P*	Egger intercept	SE	*P*	Global PRESSO *P*
Epilepsy	Frailty	13.7045	0.4720	14.5243	0.4862	−0.0034	0.0037	0.3806	0.5210

substantiate the robustness of our results. To sum up, the employment of genetic risk factors derived from GWAS, combined with the MR design and IVW statistical methodology, has reinforced the validity of our research findings, delivering valuable perspectives on the link between FI and epilepsy.

Despite its strengths, our study encounters some limitations. We could not perform subgroup analyses as we relied on summary data rather than the original data. The populations screened for SNPs associated with FI and epilepsy were primarily of European descent, indicating a need for further research in other ethnic groups to confirm the generalizability of our results. The impact of gender on epilepsy is notable with males showing a higher rate of prevalence.[40] Yet the 2-sample design of our study did not differentiate by gender; thus, the dissection of the relationship between FI and epilepsy in different genders is not achievable. Finally, whereas the positive bidirectional MR causal relationships between frailty and epilepsy suggest shared elements or mediators, a comorbidity analysis was beyond the scope of this study.

Conclusion

The MR analysis we conducted has brought to light a pronounced bidirectional causal relationship between frailty and epilepsy with both conditions influencing each other as risk factors. This revelation holds value for the early identification of risk, intervention, and therapeutic intervention for mental health issues, such as frailty and epilepsy. Future studies should investigate the underlying mechanisms of this causal relationship, aimed at crafting preventive and therapeutic strategies that may reshape the dynamic between frailty and epilepsy.

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