The Relationship Between Frailty and Schizophrenia: A Genetic Association and Mendelian Randomization Study

Ming-Gang Deng (✉ deng.ganggang@outlook.com)

  Department of Psychiatry, Wuhan Mental Health Center

Kai Wang

  Department of Public Health, Wuhan Fourth Hospital

Fang Liu

  School of Public Health, Wuhan University

Xiuxiu Zhou

  Department of Psychiatry, Wuhan Mental Health Center

Jiewei Liu (✉ liujiewei@hust.edu.cn)

  Department of Psychiatry, Wuhan Mental Health Center

Research Article

Abstract

Importance

Frailty was associated with elevated risks of various diseases and could induce many adverse outcomes in schizophrenia patients. However, the association and causality between frailty and schizophrenia are still unclear.

Objective

To investigate the genetic association and causality between frailty and schizophrenia.

Design, Setting, and Participants

We obtained the summary genetic data related to frailty and schizophrenia from the large-scale genome-wide association studies in the European population. Genetic association analyses were investigated from 5 aspects: global genetic correlation, local genetic correlation, shared genomic loci, overlapped tissue enrichments, and shared functional genes. The causality was inferred via the bidirectional Mendelian Randomization (MR) analyses.

Main Outcomes and Measures

The genetic association and causality between frailty and schizophrenia.

Results

The global genetic correlation analyses presented they were positively associated, and the local genetic correlation analyses demonstrated they were locally correlated in three genomes. Furthermore, 111 genomic loci were found to be jointly associated with frailty and schizophrenia. Additionally, the tissue enrichment and summary-data-based MR analyses demonstrated the genetic variants related to frailty and schizophrenia have overlapped tissue enrichments and functional genes in the brain. Lastly, the MR results implied there was a bidirectional causal relationship between frailty and schizophrenia.

Conclusions and Relevance

Our study indicated that frailty and schizophrenia had plenty of shared genetic basis and supported their bidirectional causality. Further studies are warranted to validate these findings in non-European populations.

Key Points

Question

Is there a genetic association or causality between frailty and schizophrenia?

Findings

The genetic association analyses indicated they had significant positive genetic correlation and shared genetic basis. The Mendelian Randomization analyses demonstrated that frailty was bidirectionally causal associated with schizophrenia.

Meaning

Our findings not only provided genetic evidence on the close relationship between frailty and schizophrenia but also highlighted the important implications for intervention and treatment targets of these two simultaneously.

1. Introduction

Frailty is defined as a clinical state of deficit accumulation in which individuals are more vulnerable to developing adverse health outcomes when exposed to endogenous or exogenous stressors[1]. According to current knowledge, frailty is associated with an elevated risk of developing various physical and mental diseases, which include but are not limited to coronary artery disease[2], type 2 diabetes[2], stroke[3], osteoarthritis[4], anxiety[5], bipolar disorder[6], and depression[7]. These findings indicate that understanding the potential correlation between frailty and frailty-related outcomes would be important and beneficial for disease prevention and control.

Schizophrenia is a serious mental disorder characterized by positive, negative, or cognitive symptoms, which affects up to 1% of the population[8] and could significantly reduce patients' life expectancy[9]. Epidemiology studies have identified a series of factors related to schizophrenia risks, such as physical activity[10], cannabis use[11], circulating selenium level[12], and C-reactive protein[13], which greatly contribute to implementing effective primary prevention measures.

Nevertheless, regarding the relationship between frailty and schizophrenia, research is relatively limited and mainly focuses on the adverse effects of frailty in patients diagnosed with schizophrenia. For instance, the previous retrospective cohort study analyzed the frailty status of 78 adults with treatment-resistant schizophrenia and found that frailty was at a very high prevalence and positively correlated to disease severity[14]. In addition, another two observational studies discovered that schizophrenia and fragile individuals were more likely to reduce employment duration and income[15], and had a lower life quality[16]. However, whether frailty plays a role in schizophrenia pathology and whether people are more likely to be fragile after developing schizophrenia remain unclear.

Based on the aforementioned background, we intend to investigate the relationship between frailty and schizophrenia from the genetic perspective by utilizing the data from the genome-wide association studies (GWAS)[17,18]. Our results indicated non-negligible shared genetic components between frailty and schizophrenia, and a significant bidirectional causal relationship was discovered.

2. Materials and methods

2.1. Data sources

Data related to frailty was obtained from the recent GWAS of fried frailty scores (FFS) in 386,565 European descent participants enrolled in the UK Biobank, whose average age was 57 years old and females occupied a percentage of 54%[17]. FFS consists of five criteria including weight loss, exhaustion, physical activity, walking speed, and grip strength, and ranges from 0 to 5 scores according to the number of criteria met[19]. Although FFS was commonly modeled as a binary variable (scores $\geq$ 3 being frailty), Ye Y et al. analyzed it as an ordinal variable in the original GWAS in order to reduce information loss and enhance statistical power[17]. Compared to the other commonly employed frailty measures called frailty index[20], FFS is more concise and maneuverable in practice[21]. In addition, the ability of FFS to detect frailty has been validated in various epidemiological studies[22–24].

Schizophrenia associated data was retrieved from the recent multi-ancestry GWAS of up to 76,755 individuals with schizophrenia and 243,649 controls[18], which include a total of 67,390 cases and 94,015 controls from a core Psychiatric Genomics Consortium (PGC) dataset of 90 cohorts of European and East Asian ancestry, 7,386 cases and 7,008 controls from 9 African American and Latino ancestry cohorts, 1,979 cases and 142,626 controls from deCODE. In our study, we extracted the summary-level genetic variants from a sub-sample of 52,017 individuals with schizophrenia and 75,889 controls with European ancestry.

2.2. Statistical analyses

An overview of statistical analysis procedures is presented in Fig. 1. We first examined the underlying genetic association between frailty and schizophrenia from five perspectives: global genetic correlation, local genetic correlation, identification of shared genetic loci, shared tissue enrichments, and shared functional genes. Then, the Mendelian Randomization (MR) design was utilized to estimate their bidirectional causality.

2.2.1. Global genetic correlation

The linkage disequilibrium score regression (LDSC), which could be applied to evaluate the cross traits genetic correlation from GWAS summary statistics[25], was performed to assess the global genetic correlation (r_g) between frailty and schizophrenia based on the GWAS summary statistics. The European samples from the 1,000 Genomes Project were used as reference panel[26].

Additionally, we utilized the high-definition likelihood (HDL) method to estimate the global genetic correlation between frailty and schizophrenia, which can reduce the variance of genetic correlation estimates and improve estimation accuracy than LDSC[27]. The HDL was performed with 1,029,876 QCed UK Biobank imputed HapMap3 SNPs as the reference panel[27].

2.2.2. Local genetic correlation

In addition to global correlation analysis, we also attempted to explore whether frailty and schizophrenia were locally correlated at a special region across the entire genome. We utilized the ρ-HESS (Heritability Estimation from Summary Statistics)[28,29], which was software for estimating and visualizing local SNP-heritability and genetic correlation based on GWAS summary data. ρ-HESS partitioning the entire genome into 1,703 LD independent regions of 1.6 MB window size on average based on the European population LD reference panel. Then, the local

genetic correlation between frailty and schizophrenia was quantified in each region, and the Bonferroni corrected p-value of $p < 0.05/1,703$ was set as the significance threshold.

2.2.3. Identification of shared genomic loci

We used the pleiotropy-informed false discovery rate (pleioFDR)[30] to determine if any shared genetic variants contribute to both frailty and schizophrenia. This software helps to increase the discovery of genetic loci in low-powered GWAS by leveraging pleiotropic enrichment with a larger GWAS on a related phenotype and identifying genetic loci jointly associated with the two phenotypes.

We first employed the conditional false discovery rate (condFDR) as a means to improve the identification of genetic variations associated with frailty and schizophrenia. The condFDR methodology relies on an empirical Bayesian statistical framework and leverages summary statistics from both a primary (schizophrenia) and a conditional (frailty) trait. This enables the estimation of the posterior probability that a SNP is not related to the primary trait. By reranking the test statistics of schizophrenia conditional on the strength of the correlation with frailty, this technique enhances the detection of genetic variants linked to schizophrenia. Similarly, the reverse condFDR statistics that frailty conditional on schizophrenia were calculated when the primary and conditional traits were inverted. The significance level for the condFDR was set as condFDR < 0.01[30].

Next, we calculated conjunctional FDR (conjFDR) statistics to identify any genetic loci that might be shared by frailty and schizophrenia, which is an extension of the condFDR and it represents the maximum of the two condFDR statistics for a specific SNP. This value estimates the posterior probability that an SNP is null for either trait or both, given that the p values for both phenotypes are as small as or smaller than the p values for each trait individually. The significance level for the condFDR was set as conjFDR < 0.05[30].

2.2.4. Tissue enrichment

To explore whether the GWAS SNP heritability related to frailty and schizophrenia were enriched in some shared tissues, we utilized the MAGMA (Multi-marker Analysis of GenoMic Annotation)[31] that was implemented in FUMA[32] to perform the tissue enrichment analyses based on the expression profiles from GTEx v8 tissues[33]. The major parameters we used in FUMA including the maximum p-value of lead SNPs were set as $p < 5\times10^{-8}$, and the upstream and downstream windows size of genes to assign SNPs were limited to 35 and 10 kb[34], respectively. The other parameters and settings were used default. Bonferroni correction was applied to adjust for multiple testing and a p-value less than $0.05/54$ was set as the significance threshold.

2.2.5. Summary-data-based Mendelian Randomization (SMR) analysis

We conducted SMR analysis to identify potential shared causal risk genes for frailty and schizophrenia[35]. This was done by integrating GWAS summary statistics for each phenotype with human brain expression quantitative trait loci (eQTL) data. The brain cis-eQTL data, which included 2,865 brain cortex transcriptomic data from 7 cohorts[36], were retrieved from the SMR website (https://yanglab.westlake.edu.cn/software/smr). The heterogeneity in dependent instrument (HEIDI)-outlier filtering method was preliminarily performed to distinguish causality or pleiotropy from linkage, and those with p-values for HEIDI < 0.05 and $N_{SNPs\_HEIDI} < 10$ were considered likely caused by pleiotropy and removed. The SMR analyses were performed using the SMR software (version 1.3.1) with the default parameters, and a false discovery rate of 0.05 was considered as the significant threshold.

2.2.6. Mendelian Randomization

Using the genetic variants as the instruments, MR is a useful method to obtain plausible causal inference and the instruments should satisfy the relevance, independence, and exclusion restriction assumptions to make the causal estimates valid[37]. The diagram of MR design in this study is illustrated in **Supplementary Fig S1**. We performed MR within two directions: 1) genetic variants related to frailty as exposure to assess whether fragile people are more likely to develop schizophrenia and, 2) genetic variants associated with frailty as outcome to evaluate whether the schizophrenia patients are more fragile.

Instruments robustly related to exposure were initially screened at genome-wide significance ($p < 5\times10^{-8}$). Then, the identified variants were clumped for linkage disequilibrium (LD) using the European samples from the 1,000 Genomes Project[26] as the reference panel, with the cutoff of clumping R^2 set as 0.001 in the window of 10,000 KB. To avoid the bias from weak instruments, the F statistic for each was calculated and only those with F statistics greater than 10 were reserved[38]. In addition, the modified Cochran's Q test was performed to identify outlier pleiotropic SNP as the Q statistic much larger than N_{SNP}-1 suggests the violation of the independence assumption or exclusion restriction[39]. After harmonization of exposure and outcome data with no palindromic SNPs, the remaining genetic variants were used to perform MR analysis.

The inverse variance weighted (IVW) method was utilized as the primary method for causal inference, and the IVW method under fixed-effect was adopted when no obvious heterogeneity was found, otherwise, under the random-effect. Several other methods including MR-Egger, weighted-median, MR-PRESSO (Pleiotropy RESidual Sum and Outlier), and MR-cML (Constrained maximum likelihood) were supplemented to assess the stability of the results. Two additional sensitivity analyses were performed including the MR-Egger regression intercept to check the horizontal pleiotropy and the leave-one-out analysis to assess whether the causality was driven by a single variant.

The effect size was reported in beta values with the 95% confidence interval (CI) when the outcome was frailty and converted to odds ratio (OR) when the outcome was schizophrenia. Statistical analyses were performed in R software (version 4.3.1, R Foundation for Statistical Computing) with TwoSampleMR (version 0.5.7), MendelianRandomization (version 0.8.0), and RadialMR (version 1.1) packages.

3. Results

3.1. Genetic association between frailty and schizophrenia

3.1.1. Global genetic correlation

The result of LDSC presented that genetic variants related to frailty and schizophrenia were positively correlated (r_g = 0.117, SE = 0.024, p = 6.686×10^{-7}), and a similar positive correlation between frailty and schizophrenia (r_g = 0.101, SE = 0.014, p = 5.63×10^{-13}) was obtained by the HDL method.

3.1.2. Local genetic correlation

The results of ρ-HESS to investigate the local genetic correlation across 1,703 genomic regions between frailty and schizophrenia were presented in Fig. 2 and **Supplementary Table S1**. Frailty and schizophrenia were initially discovered to be locally correlated in a total of 202 genomes at $p < 0.05$, after correction for multiple tests, there were three regions [chr9: 94167203−96671698 (p = 2.21×10^{-6}), chr11: 112459488−114257728 (p = 1.01×10^{-5}), and chr18: 77149991−78017158 (p = 9.57×10^{-6})] remaining significant.

3.1.3. Leveraging condFDR and conjFDR to identify shared genomic loci

We first checked the quantile-quantile (Q-Q) plots of frailty when conditioned on the p-value of schizophrenia and vice versa. We observed sharp leftward deflection from the theoretical black dashed line (no association) to an increasing association with schizophrenia when condition on frailty (Fig. 3A) and vice versa (Fig. 3B). At condFDR < 0.01, we identified 289 loci that showed significant association with schizophrenia when conditional on frailty, and reversely 79 loci that showed significant association with frailty when conditional on schizophrenia (**Supplementary Table S2-S3**).

To identify the shared genomic association between frailty and schizophrenia, we calculated the conjFDR for these two phenotypes, and the results are presented in Fig. 4 and **Supplementary Table S4**. We identified 111 genomic loci in total which are jointly associated with both frailty and schizophrenia, and the most significant locus is located in chromosome 4 (Lead SNP: rs13107325, p = 2.90×10^{-21}). When assessing their effects on each trait, we discovered that there were 80 SNPs yielded consistent (both positive or negative) effects on frailty and schizophrenia, while the rest 41 SNPs did not.

3.1.4. Tissue enrichment

To identify which tissues the frailty and schizophrenia GWAS SNPs enriched in, we performed MAGMA tissue enrichment analysis based on frailty and schizophrenia GWAS summary statistics respectively by using GTEx tissue expression profiles. The results indicated that genetic variants related to frailty were significantly enriched in 11 brain tissues after correction p values, which were all overlapped by the tissues in which schizophrenia associated genetic variants enriched (Fig. 5 and **Supplementary Table S5**). In addition, Brain Frontal Cortex BA9 (beta$_{schizophrenia}$ = 0.098, p = 9.21×10^{-27}; beta$_{frailty}$ = 0.042, p = 9.57×10^{-8}) and Brain Cortex (beta$_{schizophrenia}$ = 0.097, p = 1.20×10^{-24}; beta$_{frailty}$ = 0.041, p = 3.36×10^{-7}) were the top 2 significant enriched tissues for both frailty and schizophrenia.

3.1.5. Shared genes identified by SMR

Since the tissue enrichment analyses demonstrated that genetic variants related to frailty and schizophrenia were both significantly enriched in brain tissues, we further conducted the SMR analyses using the brain cis-QTL to investigate the shared genes between frailty and schizophrenia. The results of SMR presented that there were 101 genes associated with frailty, and the top 3 genes were *SULT1A1* (p_{HEIDI} = 0.269, N$_{SNPs\_HEIDI}$ = 20, p_{SMR}=1.56×10^{-9}), *AFF3* (p_{HEIDI} = 0.098, N$_{SNPs\_HEIDI}$ = 20, p_{SMR}=6.02×10^{-9}), *ADCY3* (p_{HEIDI} = 0.240, N$_{SNPs\_HEIDI}$ = 20,

p_{SMR}=1.18×10^{-8}), respectively (**Supplementary Table S6**). Similarly, a total of 425 genes were found to be related to schizophrenia, and the top 3 genes were *GATAD2A* (p_{HEIDI} = 0.729, N$_{SNPs\_HEIDI}$ = 20, p_{SMR}=3.08×10^{-14}), *INO80E* (p_{HEIDI} = 0.208, N$_{SNPs\_HEIDI}$ = 20, p_{SMR}=1.31×10^{-11}), *ZSCAN26* (p_{HEIDI} = 0.120, N$_{SNPs\_HEIDI}$ = 20, p_{SMR}=4.02×10^{-11}), respectively (**Supplementary Table S7**).

After combining the two SMR results, we found that 11 risk genes were shared between frailty and schizophrenia, and the results are presented in Table 1. Among them, *AP000662.1, ZDHHC5, ZFYVE21*, and *CGREFI* were both associated with lower risks of frailty and schizophrenia, while *UBE2Z, SNF8, DCC, NEGRI, AC096570.1, SLC35F6* were both correlated to higher risk of frailty and schizophrenia. However, the gene *ATP5MC1* has the opposite effect on frailty and schizophrenia.

Table 1
Shared genes between frailty and schizophrenia identified by the SMR analyses

Gene	probeID	topSNP	A1	A2	Freq	SMR for Frailty			SMR for Schizophrenia		
						beta	se	pval	beta	se	pval
AP000662.1	ENSG00000254602.2	rs36036499	C	T	0.436	-0.042	0.009	4.960E-06	-0.199	0.044	5.150E-06
ZDHHC5	ENSG00000156599.11	rs2847308	C	T	0.313	-0.069	0.015	7.170E-06	-0.297	0.069	1.840E-05
ZFYVE21	ENSG00000100711.14	rs2273175	C	T	0.302	-0.039	0.010	1.260E-04	-0.265	0.055	1.190E-06
ATP5MC1	ENSG00000159199.14	rs1962412	T	C	0.280	-0.039	0.004	4.250E-05	0.062	0.017	3.430E-04
UBE2Z	ENSG00000159202.18	rs957557	G	T	0.437	0.014	0.004	3.440E-04	0.063	0.019	7.470E-04
SNF8	ENSG00000159210.10	rs999475	A	G	0.266	0.012	0.003	4.020E-05	0.051	0.014	2.970E-04
DCC	ENSG00000187323.12	rs1504746	C	T	0.401	0.028	0.006	6.080E-06	0.114	0.028	6.180E-05
NEGR1	ENSG00000172260.15	rs2815749	A	G	0.182	0.025	0.007	2.470E-04	0.106	0.033	1.370E-03
AC096570.1	ENSG00000228999.4	rs4665495	G	T	0.491	0.043	0.010	1.050E-05	0.158	0.043	2.140E-04
SLC35F6	ENSG00000213699.9	rs4665904	T	C	0.402	0.024	0.005	5.910E-06	0.101	0.024	2.830E-05
CGREF1	ENSG00000138028.16	rs11681562	A	G	0.368	-0.025	0.006	4.410E-05	-0.112	0.029	9.480E-05

3.2. Causality inferred by Mendelian Randomization

Based on the aforementioned criteria, a total of 21 and 111 SNPs related to frailty and schizophrenia are respectively utilized to perform the bidirectional MR analyses, and the proportions of variance explained by their corresponding data sets are 0.129 and 18.340% (**Supplementary Table S8**).

The results of MR estimations on the directional relationship between frailty and schizophrenia are displayed in Table 2. The Cochran's Q tests indicate there is no obvious heterogeneity among the SNPs associated with frailty or schizophrenia. Therefore, the effect sizes were evaluated by the fixed-effect IVW method. The IVW method presents higher FFS is positively correlated with the risk of schizophrenia (OR: 1.763, 95% CI: 1.259, 2.468, p = 0.001), and this association is supported by the weighted median (OR: 1.697, 95% CI: 1.057, 2.729, p = 0.029), MR-PRESSO (OR: 1.763, 95% CI: 1.316, 3.021, p = 0.001), and MR-cML (OR: 1.749, 95% CI: 1.209, 2.529, p = 0.003) methods. Reversely, the IVW method indicates that schizophrenia patients are more likely to have a higher FFS (β: 0.012, 95% CI: 0.006, 0.018, p < 0.001), and the supplemented methods including weighted median, MR-PRESSO, and MR-cML also provide similar estimations. The scatter plots of SNP potential effects on exposure versus come are demonstrated in **Supplementary Fig S2**, with the slope of each representing the evaluated effect size per method.

Table 2
The Mendelian Randomization estimations on the relationship between frailty and schizophrenia.

Exposure	Outcome	Methods	OR/β (95% CI)	p-value	p for heterogeneity* or pleiotropy†	
FFS	SCZ	IVW	1.763 (1.259, 2.468)	0.001	15.048	0.774
		MR-Egger	2.467 (0.595, 10.237)	0.213		0.639
		Weighted Median	1.697 (1.057, 2.729)	0.029		
		MR-PRESSO	1.763 (1.316, 3.021)	0.001		
		MR-cML	1.749 (1.209, 2.529)	0.003		
SCZ	FFS	IVW	0.012 (0.006, 0.018)	< 0.001	126.545	0.164
		MR-Egger	0.002 (-0.023, 0.026)	0.902		0.375
		Weighted Median	0.010 (0.001, 0.019)	0.037		
		MR-PRESSO	0.012 (0.006, 0.018)	< 0.001		
		MR-cML	0.012 (0.006, 0.018)	0.001		

*p-value for heterogeneity based on Cochran's Q statistic.

†p value or pleiotropy based on MR-Egger regression intercept.

Abbreviation: CI, confidence interval; cML, constrained maximum likelihood; FFS, fried frailty scores; IVW, inverse variance weighted; MR, Mendelian Randomization; OR, odds ratio; PRESSO, Pleiotropy RESidual Sum and Outlier; SCZ, schizophrenia.

Sensitivity analyses present that there are no significant horizontal pleiotropies among the two instrumental data sets ($p = 0.639$ for frailty as exposure and $p = 0.375$ for schizophrenia as exposure, Table 2). The significant and bidirectional causal relationship between frailty and schizophrenia is not driven by single genetic variants (**Supplementary Fig S3** and **Table S9**).

4. Discussion

Our study investigated the genetic association and causality between frailty and schizophrenia from the genetic perspective based on the large-scale GWASs summary data. First of all, the global genetic correlation analyses presented they were positively associated, and the local genetic correlation demonstrated they were locally correlated in three genomes. Furthermore, the condFDR/conjFDR method indicated there were 111 genomic loci in total which are jointly associated with both frailty and schizophrenia. In addition, the tissue enrichment and SMR analyses demonstrated the genetic variants related to frailty and schizophrenia have overlapped tissue enrichments and functional genes in the brain. Lastly, the MR results implied there was a bidirectional causal relationship between frailty and schizophrenia.

Consistent with the previous study that reported a moderate genetic correlation between frailty and depression[7], our LDSC and HDL analyses indicated that genetically predicted frailty was meanwhile positively related to schizophrenia. This genetic positive correlation was observed in several epidemiology studies demonstrating the prevalence of frailty in patients with schizophrenia was significantly higher than in the controls[16,40]. Additionally, we examined their local genetic correlation and discovered they were correlated in 202 genomic regions, while only three of these remained significant after correction for multiple tests. The gene NFIL3[41] in the first region (chr9: 94167203−96671698) and five genes in the second region (chr11: 112459488−114257728) including NCAM1[42], DRD2[43], HTR3A[44], HTR3B[44], and ZBTB16[45], were involved in the pathobiology of schizophrenia. While the relevant studies on frailty were relatively limited, we did not find any risk genes that had been studied for frailty in these three regions.

We further identified 111 genomic loci that were shared by frailty and schizophrenia via the pleioFDR software, among which the most significant locus is located in chromosome 4 (Lead SNP: rs13107325 in the SLC39A8 gene). Currently, multiple studies have not only validated the association between rs13107325 and schizophrenia in Europeans[46] but also in Chinese[47]. Besides, among the 228 independent SNPs in the shared genomic loci, an appropriate 10% were located in the three local genomic regions identified by the local genetic correlation analyses: 5 SNPs (rs1351117, rs10992733, rs10821168, rs10761245, rs10761247) in chr9: 94167203−96671698, 13 SNPs (rs17529477, rs10891564, rs7107293, rs78169211, rs12420205, rs10891570, rs12222458, rs10891571, rs4373974, rs6589386, rs75059851, rs733856, rs12277680) in chr11: 112459488−114257728, and 6 SNPs (rs55905661, rs12457876, rs586275, rs71367544, rs516890, rs62103240) in chr18: 77149991−78017158. These results further emphasized the 3 locally correlated loci play an important role for both traits.

The results of tissue enrichments indicated the tissues in which genetic variants related to frailty enriched were all brain tissues and completely overlapped by schizophrenia associated genetic variants. In addition, their top 2 significant enriched tissues were the Brain Frontal Cortex BA9 and Brain Cortex. These findings were consistent with the existing results that frailty was associated with reduced cortex volume[48], and increased cortical brain infarcts[49]. Meanwhile, schizophrenia patients also have widespread cortical thinning and smaller cortical surface area, especially in frontal and temporal lobe regions[50].

Based on the findings from shared enrichment of tissue types, we further utilized the brain cis-QTL and SMR method to explore their shared risk genes in brain, and we identified 425 candidate causal risk genes for schizophrenia and 101 for frailty. Interestingly, 11 were found to be shared between these two traits. Many of shared genes are reported to play important roles in central nervous systems. For instance, Deleted in Colorectal Cancer (*DCC*) has shown a significant association with various psychiatric diseases, including schizophrenia, bipolar disorder, and depression, according to the PGC cross-trait GWAS studies[51]. Functional studies have suggested that *DCC* may participate in axonal guidance[52] and regulate synaptic function and plasticity[53], indicating its potential contribution to these diseases by affecting synapse functions. Another gene, Neuronal growth regulator 1 (*NEGR1*), has been reported to be significantly associated with depression and schizophrenia[46,54]. Dysregulation of *NEGR1* protein and gene transcript has been observed in the prefrontal cortex (PFC) region of individuals with schizophrenia[55,56]. *NEGR1* is known to participate in cell adhesion and belongs to the IgLON superfamily[57], which is associated with various central nervous functions such as intelligence[58], learning, and behavior[59,60]. Additionally, *NEGR1* has been reported to regulate synapse formation in hippocampal neurons[61] and hippocampal neurogenesis[60]. Both *DCC* and *NEGR1* have functions in synapses, suggesting that they may play a role in mediating the connection between schizophrenia and frailty.

We used the bidirectional MR to assess the causality between frailty and schizophrenia, and significant causality was discovered and supported by the series of sensitivity analyses. Although current studies on frailty and schizophrenia were very limited, our findings were consistent with some results of research targeting the relationship between schizophrenia and frailty components. Firstly, for physical activity, the meta-analysis of randomized trials found that physical activity interventions could obviously reduce the symptoms of schizophrenia[62], and reversely the schizophrenia patients were found to engage in significantly less moderate and vigorous physical activity versus controls[63]. For the walking speed and grip strength, a reduced walking capacity and significant lower handgrip strength were discovered in schizophrenia patients due to impaired muscular fitness[64,65], thus strength and endurance training were recommended for schizophrenia[66]. In addition, patients with schizophrenia spectrum disorders reported significantly higher fatigue scores than the general population[67]. However, opposite to weight loss, the prevalence of obesity and schizophrenia was positively correlated[68,69], and plenty of genetic overlap between body mass index and schizophrenia was discovered by the recent study[70].

Our study has several strengths worth pointing out. Firstly, to the best of our knowledge, this is the first study to investigate the relationship including the genetic association and causality between frailty and schizophrenia. Secondly, multiple statistical methods were performed to explore their genetic association, which improved the stability and reliability of our findings. Thirdly, our study implemented the two-sample MR analyses based on the genetic data from the large-scale GWASs, making the causality inference robust and unlikely to suffer from the bias from conventional observational studies, such as reverse causality, confounding factors, etc.

Despite these strengths, our findings should be interpreted in the context of some limitations. Firstly, the current study lacked ethnic diversity as the GWAS summary statistics were largely derived from individuals of European ancestry. Therefore, it is necessary to validate the findings in other ethnicities and conduct trans-ethnic GWAS to obtain more comprehensive results[71]. Secondly, it is important to note that GWAS only captures the association between common genetic variations and phenotypes. However, a complete understanding of the genetic components underlying disease risk requires consideration of other types of genetic variants, such as structural variations[72]. Therefore, further studies should be conducted if data on these variants are available for both schizophrenia and frailty. Thirdly, the frailty index was another useful scale to assess the frailty status based on 44 or 49 self-reported items on symptoms, disabilities, and diagnosed diseases. We adopted the fried frailty score as the measurement of frailty in our study as it was more concise and maneuverable than the frailty index. This discrepancy may induce different findings and need further investigation.

5. Conclusions

Based on the summary genetic data from the large-scale GWASs, our study uncovered the shared genetic components between frailty and schizophrenia and illustrated their bidirectional causal relationship, which provided new evidence for their close relationship and would further be helpful for the prevention and intervention of frailty and schizophrenia.

Declarations

Author contributions

Data availability

The datasets generated and/or analyzed in this study are publicly available. GWAS summary datasets for frailty are from figshare (https://figshare.com/s/6683396c68807fe4e729). GWAS summary datasets for schizophrenia are from the Psychiatric Genomics Consortium (https://pgc.unc.edu/for-researchers/download-results/). All data are available in the main text or the supporting information.

Code availability

LDSC: https://github.com/bulik/ldsc

HDL: https://github.com/zhenin/HDL

ρ-hess: https://huwenboshi.github.io/hess/

pleioFDR: https://github.com/precimed/pleiofdr

FUMA: https://fuma.ctglab.nl/

SMR: https://yanglab.westlake.edu.cn/software/smr/

TwoSampleMR: https://mrcieu.github.io/TwoSampleMR/index.html

MendelianRandomization: https://github.com/cran/MendelianRandomization

RadialMR: https://github.com/WSpiller/RadialMR/

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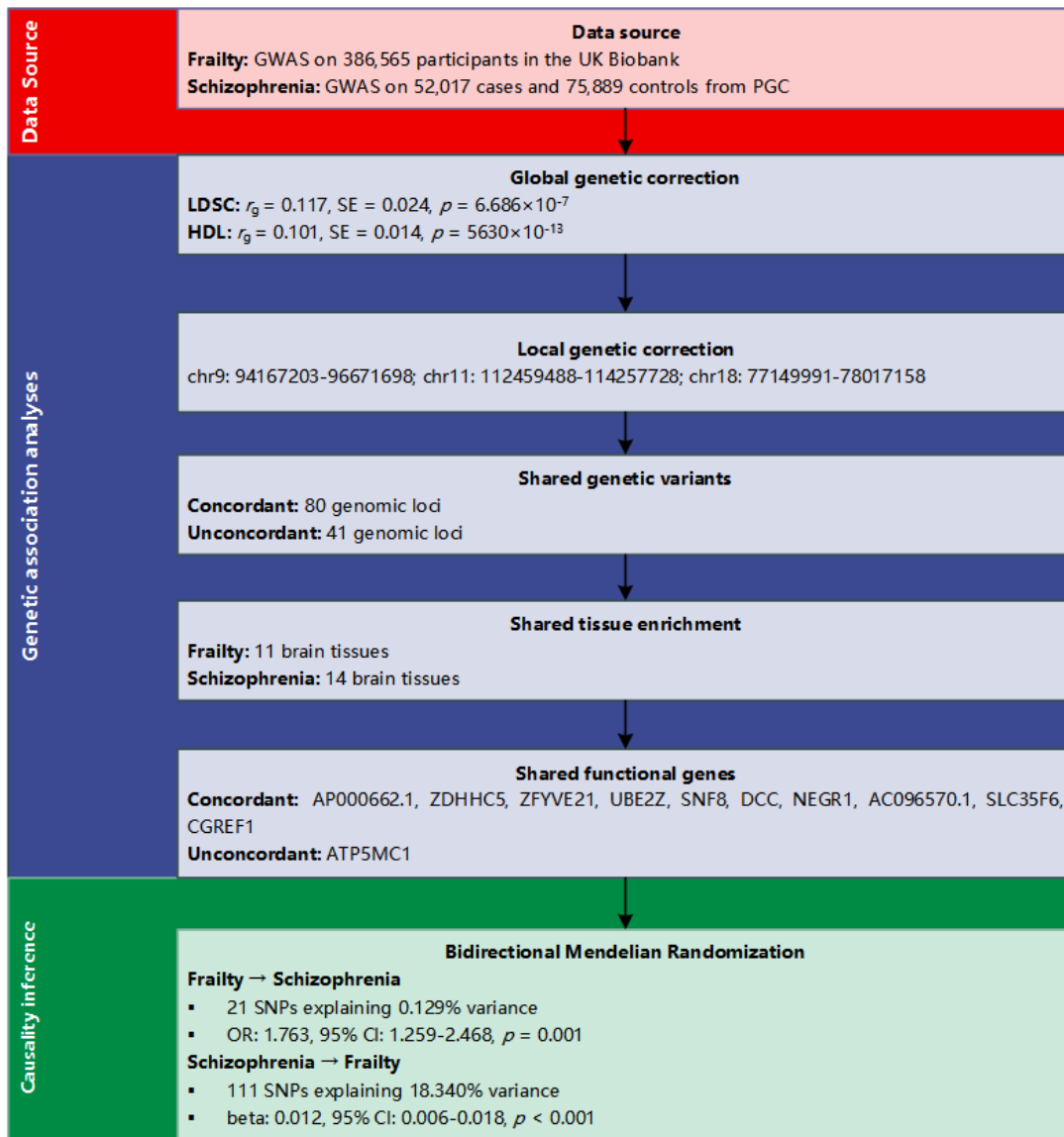
Figures

Data Source

Data source
Frailty: GWAS on 386,565 participants in the UK Biobank
Schizophrenia: GWAS on 52,017 cases and 75,889 controls from PGC

Genetic association analyses

Global genetic correction
LDSC: r_g = 0.117, SE = 0.024, p = 6.686×10^{-7}
HDL: r_g = 0.101, SE = 0.014, p = 5630×10^{-13}

Local genetic correction
chr9: 94167203-96671698; chr11: 112459488-114257728; chr18: 77149991-78017158

Shared genetic variants
Concordant: 80 genomic loci
Unconcordant: 41 genomic loci

Shared tissue enrichment
Frailty: 11 brain tissues
Schizophrenia: 14 brain tissues

Shared functional genes
Concordant: AP000662.1, ZDHHC5, ZFYVE21, UBE2Z, SNF8, DCC, NEGR1, AC096570.1, SLC35F6, CGREF1
Unconcordant: ATP5MC1

Causality inference

Bidirectional Mendelian Randomization
Frailty → Schizophrenia
- 21 SNPs explaining 0.129% variance
- OR: 1.763, 95% CI: 1.259-2.468, p = 0.001

Schizophrenia → Frailty
- 111 SNPs explaining 18.340% variance
- beta: 0.012, 95% CI: 0.006-0.018, p < 0.001

Figure 1
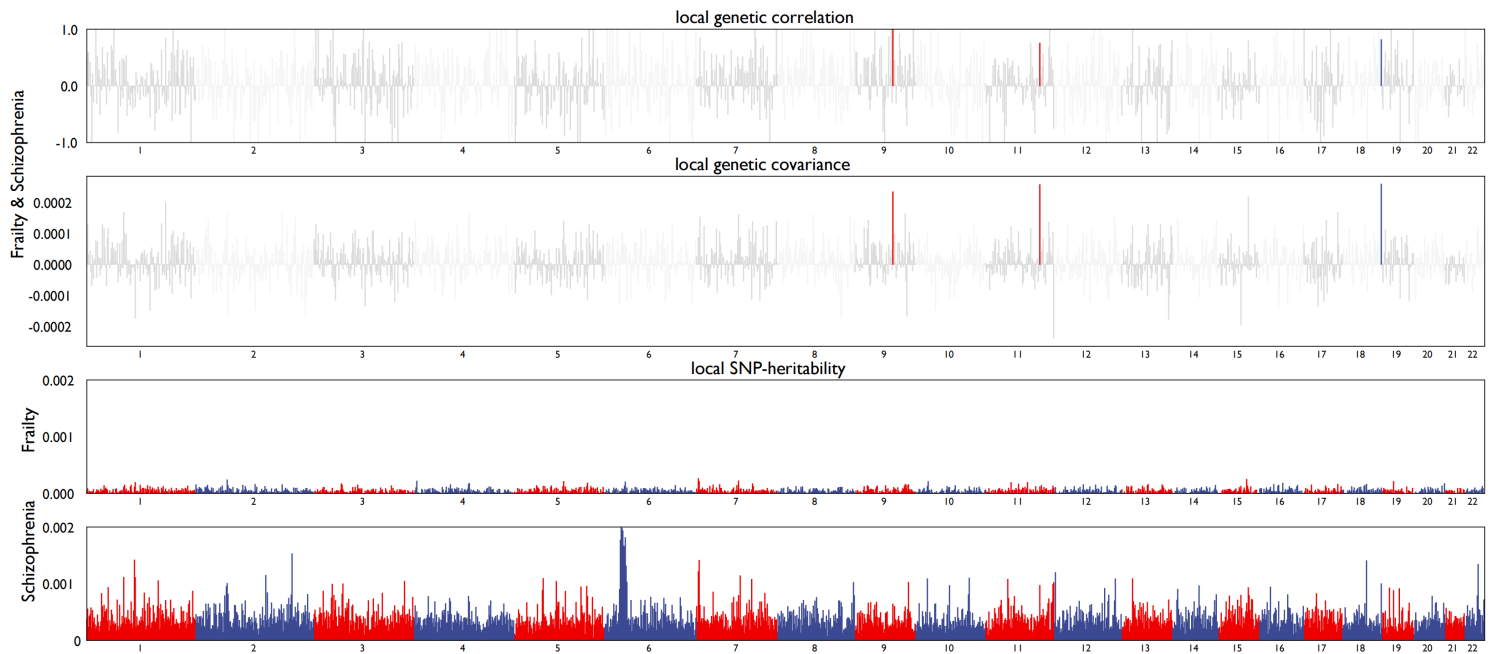
An overview of study design.

Figure 2

Local genetic correlation and genetic covariance between frailty and schizophrenia, and local SNP heritability estimation for frailty and schizophrenia respectively.
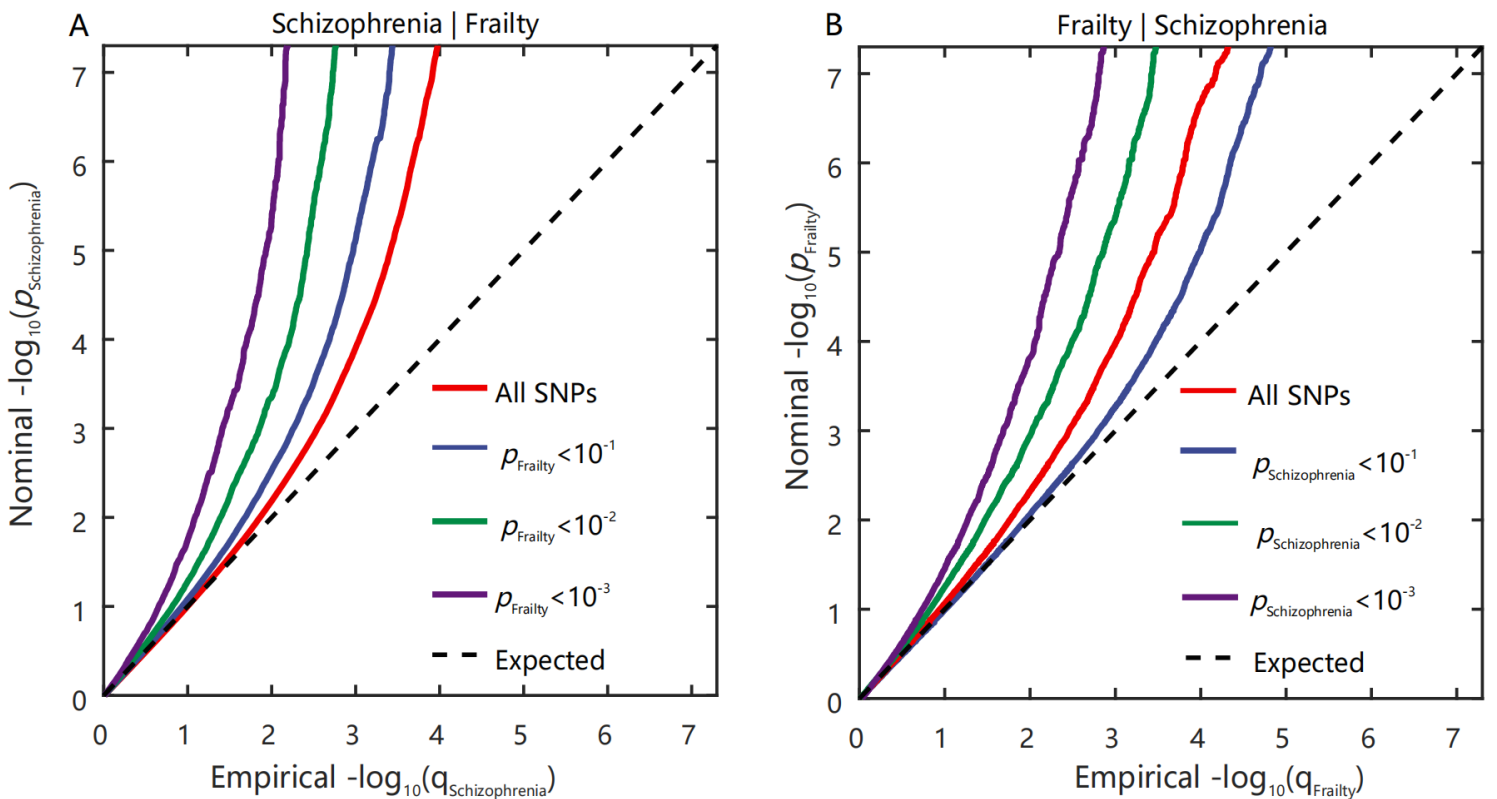

Figure 3

Conditional Q-Q plots. Conditional Q-Q plots of nominal versus empirical -log10 transformed p-values in (A) schizophrenia as a function of significance of genetic association with frailty and (B) frailty as a function of significance of genetic association with schizophrenia at the level of p <0.1, p < 0.01, and p < 0.001. The red line represents all SNPs, and the black dotted line is the expected Q-Q plot under the hypothesis of no SNPs associated with the trait.
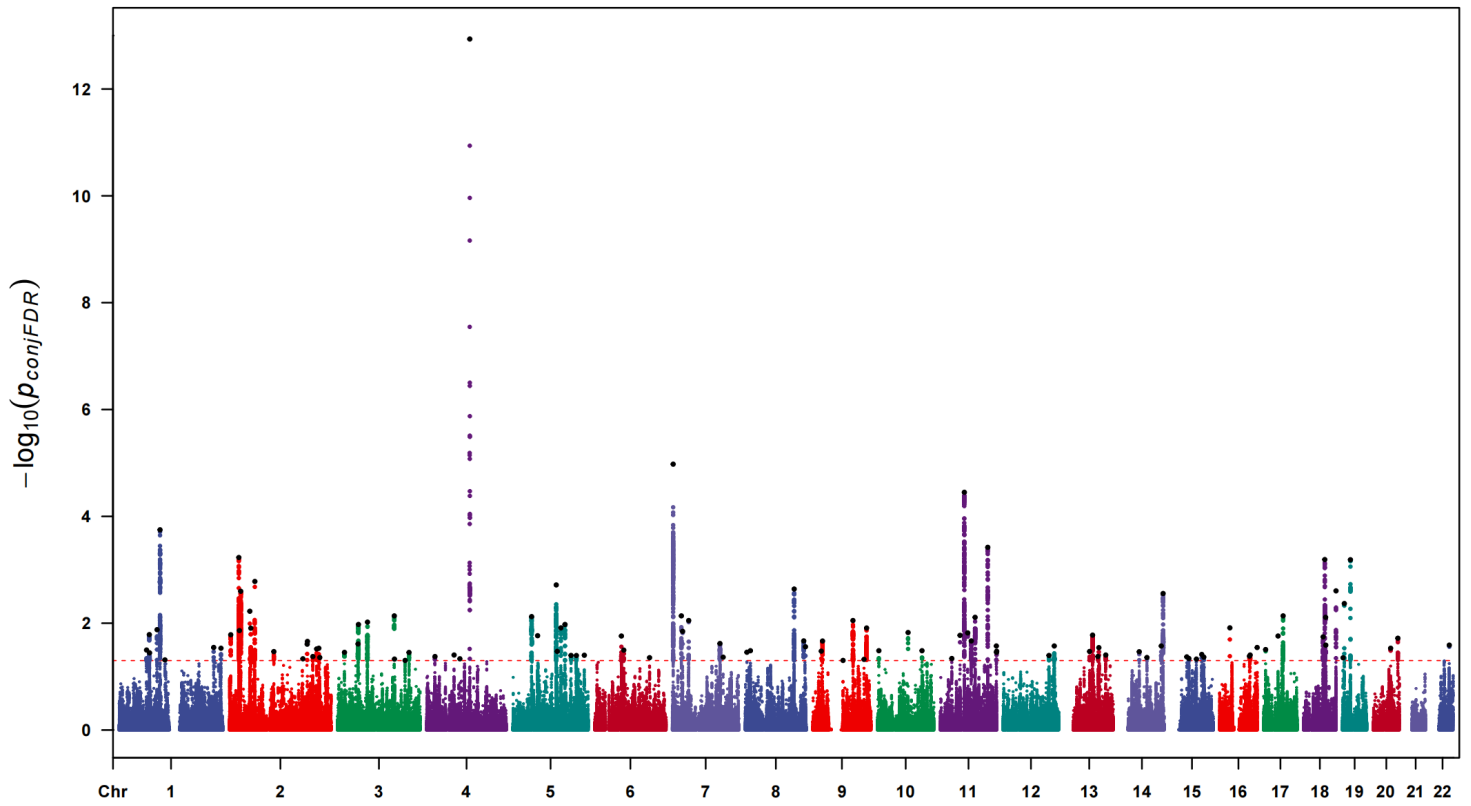
Figure 4

Manhattan plots for the conjFDR analysis. The red dashed line represents the threshold of p value for conjFDR < 0.05; The black points are the lead SNPs.
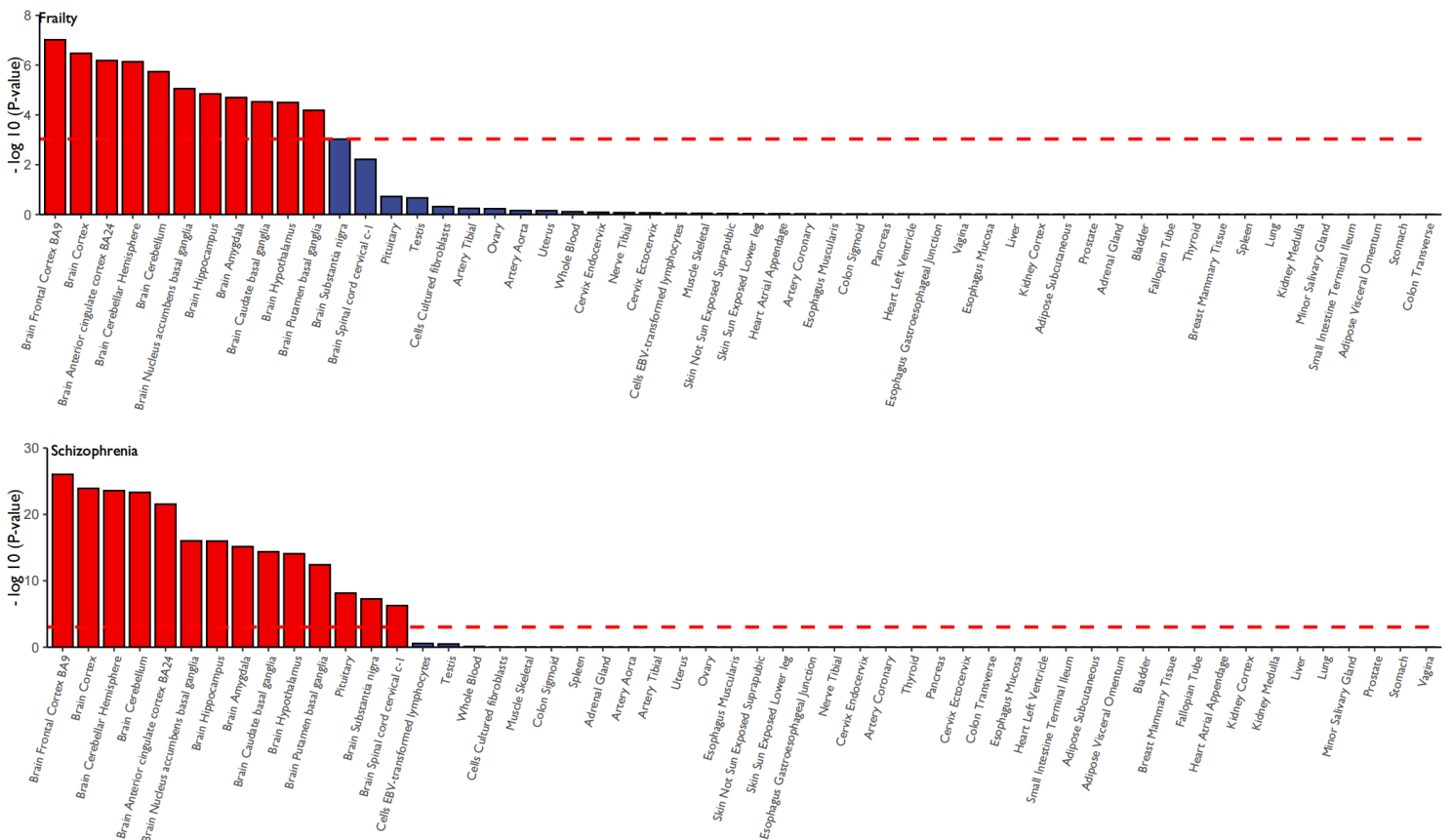
Figure 5

Tissue-type enrichments of frailty and schizophrenia GWAS associations. The red dashed line is the Bonferroni corrected significant level. Tissues that showed significant enrichment (corrected p value < 0.05) are shown in red.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryTables.xlsx