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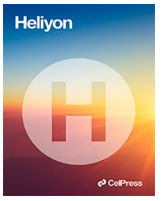

Research article

Causal effect of COVID-19 on longitudinal volumetric changes in subcortical structures: A mendelian randomization study

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ABSTRACT

A few observational neuroimaging investigations have reported subcortical structural changes in the individuals who recovered from the coronavirus disease-2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), but the causal relationships between COVID-19 and longitudinal changes of subcortical structures remain unclear. We performed two-sample Mendelian randomization (MR) analyses to estimate putative causal relationships between three COVID-19 phenotypes (susceptibility, hospitalization, and severity) and longitudinal volumetric changes of seven subcortical structures derived from MRI. Our findings demonstrated that genetic liability to SARS-CoV-2 infection had a great long-term impact on the volumetric reduction of subcortical structures, especially caudate. Our investigation may contribute in part to the understanding of the neural mechanisms underlying COVID-19-related neurological and neuropsychiatric sequelae.

1. Introduction

Over the past few years, the rapid spread of coronavirus disease-2019 (COVID-19) around the world has caused more than 6.9 million deaths and posed a serious threat to the global economy [1–3]. The pathogen that causes COVID-19 is named severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2). Mounting evidence suggests that the respiratory tract is not the only organ affected by SARS-CoV-2, and it has been reported that approximately one-third of patients with COVID-19 develop a variety of neurological and neuropsychiatric symptoms in the acute stage [4–7]. Neuroimaging studies to date have primarily focused on acute cases in hospitalized COVID-19 patients, and radiological findings based on CT, MRI, and PET have revealed a wide range of abnormalities, including signs of ischaemic or haemorrhagic strokes, white matter hyper-intensity or hypo-perfusion throughout the whole brain, but in an inconsistent pattern [8–10].

Although substantial progress has been made in addressing the acute neurological and neuropsychiatric effects of COVID-19, the long-term consequences for recovered patients remain largely unclear. An increasing number of patients, including those without specific nervous system manifestations in the acute phase, have reported post-acute neurological and neuropsychiatric sequelae; this is

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known as long-COVID, which can last weeks, months, or even years after infection [11–14]. Patients with long-COVID can have a wide range of neurological and neuropsychiatric symptoms, such as headache, fatigue, difficulty thinking (sometimes referred to as "brain fog"), sleep problems, changes in smell or taste, depression or anxiety, etc [15,16]. Further investigation into the pathophysiology of long-COVID is necessary, as it is a prerequisite for early diagnosis and timely, appropriate treatment of discharged patients, especially elderly patients who are associated with higher comorbidity, hospitalization rates, and poorer prognoses [17,18]. In addition, it is equally beneficial to patients without acute and clear neurological manifestations, as their increased risk of developing long-COVID has been easily overlooked, even though they represent a large proportion of this pandemic [19,20]. As the population of recovered COVID-19 patients continues to grow, the scientific and medical community should pay more attention to post-infection care and the long-term effects of mild-to-moderate COVID-19 [21]. Therefore, a deeper investigation into the sequelae of COVID-19 is essential for creating individualized medical care for recovered patients. An open question remains to be addressed in the urgent efforts to elucidate the neural mechanisms underlying long-COVID-associated cognitive impairment.

In-depth neuropathological examination have revealed an inflammatory response and hypoxic-ischemic damage in the brain of COVID-19 death cases, and these neuropathological changes may be related to the neurological and neuropsychiatric sequelae seen in COVID-19 long haulers [22,23]. The long-term presence of neurological and neuropsychiatric symptoms suggests that the neuronal damage may also be long-term, but the exact duration is uncertain. Pathological research on a large sample size is inaccessible due to the difficulty of obtaining postmortem brain tissue. As a non-invasive method, MRI is an essential tool to evaluate the structure and function of the brain, and changes in brain structure and function might be related to cognitive impairment [24]. Therefore, it is of utmost importance to gain a better understanding of the neural mechanisms underlying long-COVID and identify the long-term effect of COVID-19 on the brain by using MRI. Whilst the acute effects of COVID-19 on the brain have been widely documented, studies

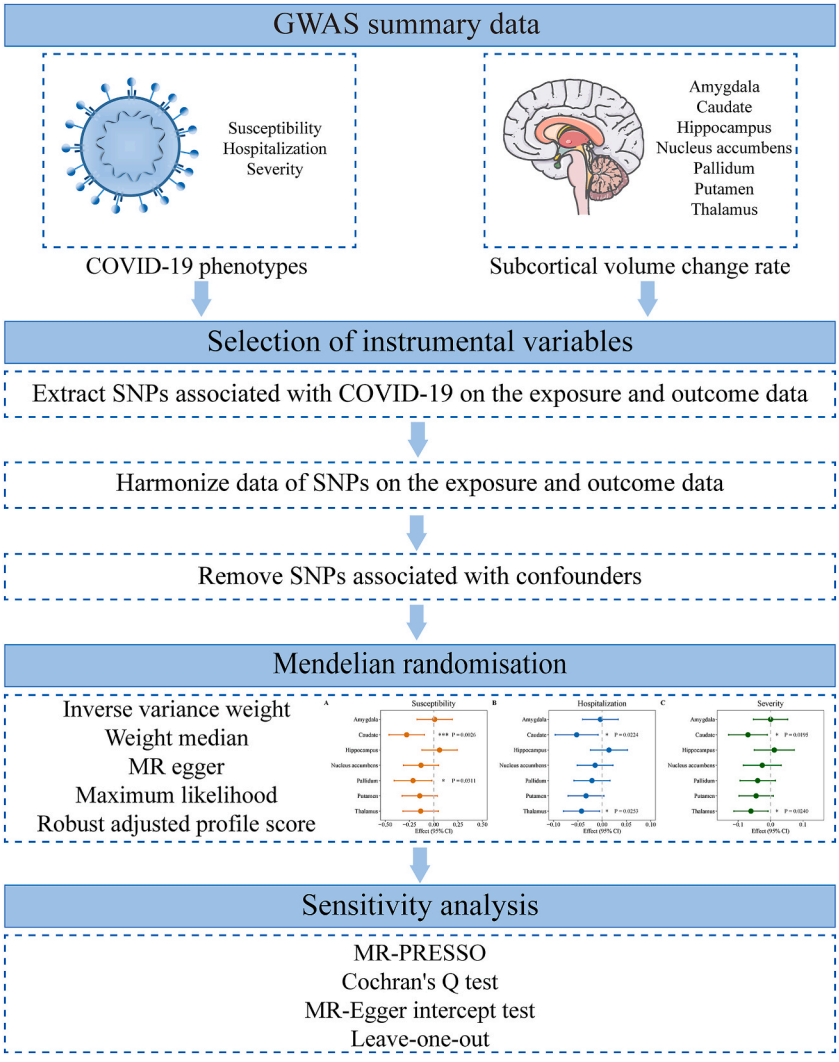

Fig. 1. Mendelian Randomization Analysis Overview. Study flow chart of the causal inference between COVID-19 phenotypes (susceptibility, hospitalization, and severity) and longitudinal volume changes in subcortical brain structures.

investigating the long-term effects remain scarce [8,25]. To date, only a few observational neuroimaging investigations with relatively small sample sizes have reported longitudinal changes in brain structure and function in COVID-19 recovered individuals [26–29]. In addition, observational studies can only yield correlations rather than true causality because the effects of confounding factors and reverse causality cannot be eliminated [30]. Taking observational neuroimaging studies specifically, although these studies found COVID-19 to be associated with some specific brain abnormalities, the abnormalities may have existed prior to SARS-CoV-2 infection [26]. The causal effect of long-term COVID-19 on brain structures remains unknown.

Mendelian randomization (MR) is a causal analysis method that can eliminate the interference of some common biases (e.g., confounding factors and reverse causation) in classical observational studies [31]. By using genetic variants (e.g., single nucleotide polymorphisms [SNPs]) that are specifically associated with a putative exposure as instrumental variables (IVs), MR can be used to make inferences about the causal effect of an exposure on an outcome [32]. Due to the random assortment of alleles at conception, the distribution of genetic variants that are associated with a particular exposure is largely independent of factors that confound exposure-outcome associations in conventional observational analyses. Therefore, estimates from MR are less affected by environmental confounders and can provide more reliable insights into causal relationships between risk factors and traits or diseases than classical observational studies. In addition, given that the genotype of an individual is determined at conception and cannot be modified by subsequent outcomes, the direction of causation is always from the genetic variants to the traits or diseases of interest, and therefore, it eliminates the potential of the variables being reverse causation [33–35]. Genome-wide association studies (GWAS) are the primary method for studying the association of SNPs with phenotypes, providing an adequate and reliable source of information for the identification of appropriate IVs. The rapid development of GWAS and increased summary-level data availability have led to a proliferation of MR studies.

COVID-19 Host Genetics Initiative (COVID-19 HGI) conducted a GWAS on COVID-19 susceptibility, hospitalization, and severity, shedding light on the role of host genetic factors in the pandemic in a large sample size of 219,692 cases and >3 million controls [36]. A recent GWAS conducted by Enhancing NeuroImaging Genetics through Meta-Analysis (ENIGMA) consortium has identified common genetic variants that affected longitudinal volumetric changes in seven subcortical structures (amygdala, caudate, hippocampus, nucleus accumbens, pallidum, putamen, and thalamus) in 15,640 individuals of European descent throughout their lifespan, which were associated with aging, psychiatric, developmental, and neurodegenerative diseases [37]. These two GWASs have provided publicly available summary-level data which can be used to determine the causal relationships between COVID-19 phenotypes and longitudinal volumetric changes in subcortical structures. With the aim of understanding the genetic links between COVID-19 and longitudinal volumetric changes in subcortical structures, we performed a two-sample MR analysis to explore the causal effects of three COVID-19 phenotypes (susceptibility, hospitalization, and severity) on long-term volumetric changes in seven subcortical structures. Our study may help to reveal the long-term effects of SARS-CoV-2 infection on the subcortical structures and thereby explain, to some extent, the neurological sequelae in COVID-19 recovered patients. The frame chart of our MR analysis is presented in Fig. 1.

2. Material and methods

2.1. Two GWAS summary datasets

The GWAS summary-level data of COVID-19 phenotypes were acquired from the COVID-19 HGI (RELEASE 7, April 2022) (https://www.covid19hg.org/). COVID-19 HGI is the largest GWAS of COVID-19, which combines data from over 3 million individuals across 82 large cohorts. Three COVID-19 related phenotypes are included: (1) susceptibility, which is defined as individuals who reported positive (self-reports, laboratory diagnosis, or physician diagnosis) for SARS-CoV-2 infection (up to 159,840 cases and 2,782,977 controls, with 88.3% of participants being of European origin), (2) hospitalization, which is defined as individuals who were hospitalized for related infection symptoms with laboratory-confirmed SARS-CoV-2 infection (up to 44,986 cases and 2,356,386 controls, with 87.3% participants being of European origin), and (3) severity, which is defined as COVID-19-confirmed individuals with very severe respiratory symptoms or those who died from this disease (up to 18,152 cases and 1,145,546 controls, with 93.3% participants being of European origin).

Recently, the ENIGMA consortium has released the GWAS summary-level data of the common genetic variants associated with annual volumetric change rates in seven subcortical structures (amygdala, caudate, hippocampus, nucleus accumbens, pallidum, putamen, and thalamus) across the lifespan in 15,640 individuals of European descent across 40 cohorts [37]. For each subcortical structure, only the average volume of both sides can be obtained, which is equal to the left and right volumes divided by two. The annual rate of change was calculated using follow-up volume minus baseline volume and divided by the year(s) of follow-up duration. The mean follow-up durations were from 0.3 to 7.5 years across 40 cohorts and the minimum and maximum were 0.2 and 16.7 years, respectively. All the two datasets in our study are publicly available GWAS summary statistics (Supplementary Table S1), and so no additional ethical approval was required. Detailed ethical approval and participants' consent can be found in the original GWAS publications [36,37].

2.2. The estimated standardized effect size of SNPs

The estimated standardized effect size (β) and standard error (se) were obtained using minor allele frequency (MAF), sample size, original effect size, and standard error. The following equation is described previously [38].

$$\beta = \frac{z}{\sqrt{2f(1-f)(n+z^2)}} \tag{1}$$

$$se = \frac{1}{\sqrt{2f(1-f)(n+z^2)}} \tag{2}$$

where z can be calculated as β/se from the original summary data, n is total sample size, and f is MAF.

2.3. Selection of IVs

The COVID-19 HGI has recently released summary statistics of a second updated GWAS which reported 21, 40, and 30 independent SNPs associated with COVID-19 susceptibility, hospitalization, and severity at a genome-wide significance ($P < 5 \times 10^{-8}$) [36]. To minimize the bias due to population stratification, our MR analyses were performed only in the participants of European ancestry (COVID-19 susceptibility: 122,616 cases and 2,475,240 controls; hospitalization: 32,519 cases and 2,062,805 controls; severity: 13,769 cases and 1,072,442 controls). Statistical information about the SNPs were obtained. Data harmonization was performed in the exposure and outcome data to ensure the effect alleles were aligned in different GWAS summary data, and palindromic SNPs were removed with intermediate allele frequencies. The outcomes, longitudinal volumetric changes in seven subcortical structures-related SNPs were removed in our MR analysis. The potential confounders including drinking behavior, smoking behavior, body mass index (BMI), and education have been reported to affect brain structures in previous studies [39–42]. We also removed the SNPs associated with the above-mentioned potential confounders. The phenoScanner V2 database [43] (http://www.phenoscanner.medschl.cam.ac.uk/) was used to check the information on the association of SNPs and phenotypes. The *F*-statistics were calculated for instrument strength [44]. The R^2 of IVs is the sum of R^2 of each IV. R^2 was calculated using the reported effect estimate, standard error, MAF of the SNPs, and the sample size of exposures to represent the proportion of variance explained by the SNPs in the exposure variable, and the formula is as follows.

$$F = \frac{R^2 \times (n-2)}{(1-R^2)} \tag{3}$$

$$R^2 = 2 \times \beta^2 \times f \times (1-f) \tag{4}$$

where R^2 is the explained variance of IVs on the exposure, β is the genetic effect size from the exposure GWAS, n is the sample size from the exposure GWAS, and f is MAF.

2.4. Two-sample MR analysis

The casual analyses were performed using several MR analysis methods: i) IVW, ii) weighted median (WM), iii) MR-Egger, and iv) maximum likelihood (ML) in "TwoSampleMR" [45] package, and v) and Robust Adjusted Profile (RAPS) in "mr.raps" package [46]. In our study, the IVW random-effects model was used as the primary MR analysis method to estimate causal effects [47] and four other complementary MR methods were used to further verify our MR findings. The IVW method is the most efficient and robust analysis and has been widely used in MR analysis, especially in the absence of pleiotropy [48,49]. It combines the Wald ratio estimates of different SNPs to obtain the estimate of the causal effect. The WM method is more resistant to pleiotropy. The median IV estimate of all the variants is used and therefore is applied to eliminate the influence of outliers [50]. The MR-Egger method considers a non-zero intercept term in the presence of pleiotropic effects when it applies a weighted linear regression [51]. The intercept term is used to assess the magnitude of pleiotropy and the slope represents a causal estimate. The RAPS method contributes to assessing the measurement error (due to a weak instrument). The combination of different MR analysis methods was performed to strengthen the causal inference. Bonferroni correction was performed for multiple comparisons at a significant level of $P < 0.007$ (0.05/7, seven subcortical structures). The Bonferroni correction is too stringent, as a result, causal association with $P < 0.05$ was regarded as nominally significant.

2.5. MR sensitivity analyses

Sensitivity analyses on different assumptions were performed including heterogeneity and pleiotropy tests after MR analysis to strengthen causal inference. The MR-Egger intercept test was applied to assess possible pleiotropy and the statistical significance was $P < 0.05$. MR Pleiotropy RESidual Sum and Outlier (MR-PRESSO) approach was performed to identify potentially pleiotropic outliers that affecting the overall results and to evaluate the causal estimate after removing outliers [52]. Cochran's Q statistic was calculated to assess the heterogeneity among IVs and the statistical significance was $P < 0.05$. In addition, leave-one-out sensitivity analysis was carried out to pinpoint potential outliers and validate robustness of the results. In the leave-one-out sensitivity test, IVs were eliminated one by one, and then a two-sample MR analysis was conducted based on the remaining IVs. The sensitivity analyses were conducted using the "TwoSampleMR" [45] and "MRPRESSO" packages [52].

2.6. Power calculation

The statistical power for all the MR analysis results was calculated via an online web tool (https://sb452.shinyapps.io/power/) [53] and the alpha level was set at 0.05. Briefly, the power calculation was based on the causal effect of MR analysis results, explained variance of IVs on the exposure, and GWAS sample size on the outcome.

3. Results

3.1. Genetic IVs selection and instrument strength

Among the 21, 40, and 30 independent SNPs associated with COVID-19 susceptibility, hospitalization, and severity, one SNP associated with education and two SNPs associated with BMI were removed. None of the SNPs associated with longitudinal volumetric changes in subcortical structures overlapped with the SNPs of COVID-19 phenotypes. The *F*-statistics for these genetic instruments included in the MR model were all greater than 10, indicating no significant weak instrumental bias [54]. Finally, a total of 20, 38, and 29 independent SNPs associated with susceptibility, hospitalization, and severity of COVID-19, respectively, were selected as the genetic IVs of the exposure. Details of the SNPs used in the MR analysis and those associated with potential confounders are provided in Supplementary Tables S2–3.

In MR analysis, selected IVs (SNPs) should satisfy the following three assumptions: (1) be strongly associated with exposure (Relevance); (2) be independent of confounding factors of exposure-outcome association (Independence); and (3) cannot affect outcome directly except through indirect effect on the exposure (Exclusion restriction). In our study, the IVs (independent SNPs) were selected from a recently second updated meta-analysis GWAS of COVID-19 at a genome-wide significance ($P < 5 \times 10^{-8}$) in a large sample size of 219,692 cases and >3 million controls [36]. The calculation of *F*-statistics and the removal of SNPs associated with potential confounders and outcomes ensured that the selected IVs in our MR analyses met all the three assumptions.

Causal associations of three COVID-19 phenotypes on longitudinal volumetric change rate in subcortical structures.

We identified that genetically predicted COVID-19 susceptibility was significantly negatively associated with the longitudinal volumetric change rate of caudate (IVW beta = −0.2791, 95 % CI: 0.4610 to −0.0972, $P = 0.0026 < 0.007$, surpassing Bonferroni correction) and nominally negatively associated with the longitudinal volumetric change rate of pallidum (IVW beta = −0.2136, 95 % CI: 0.4078 to −0.0194, $P = 0.0311$) (Fig. 2). An increase of 1 SD in genetically predicted COVID-19 susceptibility was associated with a decrease of 0.2791 SD in longitudinal volumetric change rate of caudate, which suggested that host genetic susceptibility to SARS-CoV-2 infection causally led to faster shrinkage of caudate volume, in the long-term effect. The causal estimates of COVID-19 susceptibility on the longitudinal volumetric change of caudate were significant by all the four other MR analysis methods (WM, MR-egger, ML, and RAPS) and the estimated statistical power was 88.4 % when the alpha was set at 5 %, which indicated the reliability of our result. The directions of the causal estimates of COVID-19 susceptibility on the longitudinal volumetric change of pallidum by all the four other MR analysis methods were the same as those of the IVW method, but were only significant by ML and RAPS methods. Furthermore, COVID-19 hospitalization and severity were nominally negatively associated with the longitudinal volumetric change rate of caudate (IVW beta = −0.0695, 95 % CI: 0.1292 to −0.0098, $P = 0.0304$; IVW beta = −0.0525, 95 % CI: 0.0966 to −0.0084, $P = 0.0195$) and thalamus (IVW beta = −0.0604, 95 % CI: 0.1133 to −0.007, $P = 0.0253$; IVW beta = −0.0425, 95 % CI: 0.0794 to −0.0056, $P = 0.0240$). The causal estimates of COVID-19 hospitalization and severity on the longitudinal volumetric change rate of caudate were significant by all the four other MR analysis methods. The directions of the causal estimates of COVID-19 hospitalization and severity on the longitudinal volumetric change rate of the thalamus by all the four other MR analysis methods were the same as those of the IVW method, but were only significant by ML and RAPS methods. However, we did not find any causal association ($P > 0.05$) between the

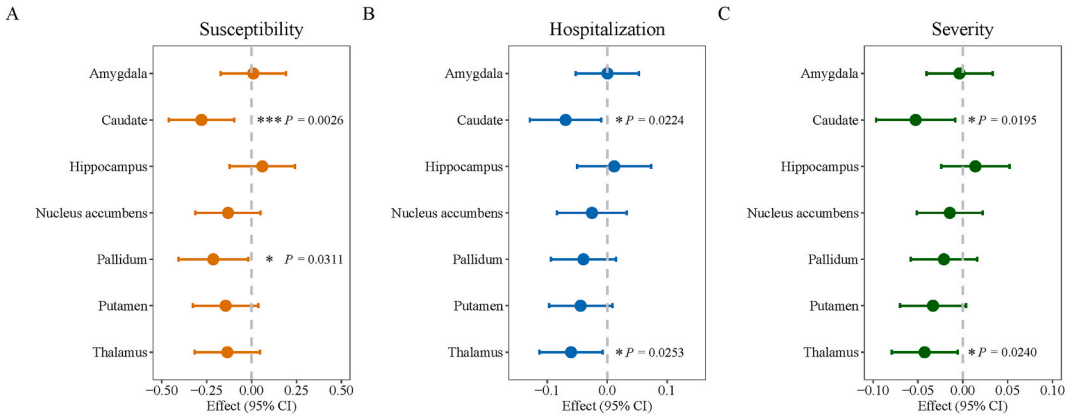

Fig. 2. IVW estimates from COVID-19 phenotypes on longitudinal volume changes in seven subcortical brain structures. **(A)** COVID-19 susceptibility, **(B)** COVID-19 hospitalization, **(C)** COVID-19 severity. ***P value < 0.007 (0.05/7, seven subcortical structures) is defined as significant after Bonferroni correction for multiple testing, and *P value < 0.05 is defined as nominal significant. IVW: inverse variance weighted.

COVID-19 phenotypes and other subcortical structures (amygdala, hippocampus, nucleus accumbens, putamen). The causal effects of genetically predicted three COVID-19 phenotypes on the longitudinal volumetric change rates in subcortical structures by using IVW methods are displayed in Table 1 and as a forest map in Fig. 2. The result of all MR methods performed in our study are presented in Supplementary Table S4.

Sensitivity analyses were applied to confirm the MR results. The MR-Egger intercept and MR-PRESSO tests indicated that there was no notably possible pleiotropy. No heterogeneity across the selected IVs was detected using Cochran's Q statistic (Supplementary Table S5). Additionally, the leave-one-out analysis indicated that there was no single SNP driving the MR estimates, which are displayed in Supplementary Figs. S1–S3.

4. Discussion

So far as we know, this is the first MR study to assess the causal relationship between three COVID-19 phenotypes (susceptibility, hospitalization, and severity) and longitudinal volume changes in seven subcortical structures. Our MR analyses indicated that genetic liability to COVID-19 susceptibility was negatively associated with longitudinal volumetric change of caudate (surpassing Bonferroni correction) and pallidum. Furthermore, COVID-19 hospitalization and severity were negatively associated with longitudinal volumetric changes of caudate and thalamus. Our finding demonstrated that COVID-19 had a long-term impact on the subcortical structures and led to the reduction of their volumes, especially caudate. Since no heterogeneity or pleiotropy in sensitivity analyses was detected, the inferred causalities between three COVID-19 phenotypes and longitudinal volumetric changes in the subcortical structures described above were reliable. Additionally, the estimated causal effect of COVID-19 susceptibility on the longitudinal volumetric change of caudate was significant by all the five MR analysis methods (IVW, WM, MR-egger, ML, and RAPS), and the estimated statistical power was 88.4% when the alpha was set at 5%, which indicated the robustness of our result.

The large difference in the sample size of the cases among three COVID-19 phenotypes (susceptibility: 122,616 cases; hospitalization: 32,519 cases; and severity: 13,769 cases) may influence the MR results. Due to the lack of clinical information on the patients with COVID-19, we are unable to perform MR analysis only in mild cases of COVID-19 by excluding the hospitalized and severe cases. Nonetheless, most of the patients with COVID-19 susceptibility were mild cases according to the sample size of the three phenotypes (susceptibility: 122,616 cases; hospitalization: 32,519 cases; and severity: 13,769 cases; the hospitalized and severe cases are included in the susceptible cases, accounting for only 26.50% and 11.29% of the susceptible cases, respectively). For this reason, we roughly considered that the causal effect of COVID-19 susceptibility on longitudinal volumetric reduction of the caudate was mainly caused by mild SARS-CoV-2 infection.

The subcortical regions join with cortical areas to form circuits that coordinate movement, learning, memory, and motivation, and alterations in the circuits can lead to abnormal behaviors and diseases [55–60]. The caudate is part of the cortico-striatal-thalamic loop engaging in normal emotional modulation [61–63]. It also functions in planning, execution, learning, memory, and other related functions [64–67]. The primary function of the globus pallidus is to control conscious and proprioceptive movements, and it also connects to cortical areas that support motivation and cognition [68–70]. The thalamus is part of the brain that relays sensory and motor signals from various locations to the cerebral cortex [71–73]. Additionally, it plays a role in alertness, sleep, and consciousness

Table 1
The IVW estimates of three COVID-19 phenotypes (susceptibility, hospitalization, and severity) on the longitudinal volumetric changes of seven subcortical structures.

COVID-19 phenotypes	Subcortical structures	Beta	P-value	SE	CI lower	CI upper
Susceptibility	Amygdala	0.010	0.918	0.093	−0.172	0.191
Susceptibility	Caudate	−0.279	0.003***	0.093	−0.461	−0.097
Susceptibility	Hippocampus	0.060	0.520	0.093	−0.122	0.242
Susceptibility	Nucleus accumbens	−0.131	0.156	0.092	−0.313	0.050
Susceptibility	Pallidum	−0.214	0.031*	0.099	−0.408	−0.019
Susceptibility	Putamen	−0.145	0.120	0.093	−0.327	0.038
Susceptibility	Thalamus	−0.135	0.146	0.093	−0.317	0.047
Hospitalization	Amygdala	0.000	0.989	0.027	−0.052	0.053
Hospitalization	Caudate	−0.070	0.022*	0.030	−0.129	−0.010
Hospitalization	Hippocampus	0.012	0.711	0.031	−0.050	0.073
Hospitalization	Nucleus accumbens	−0.025	0.391	0.030	−0.084	0.033
Hospitalization	Pallidum	−0.040	0.154	0.028	−0.094	0.015
Hospitalization	Putamen	−0.044	0.100	0.027	−0.097	0.008
Hospitalization	Thalamus	−0.060	0.025*	0.027	−0.113	−0.007
Severity	Amygdala	−0.004	0.848	0.019	−0.040	0.033
Severity	Caudate	−0.053	0.020*	0.023	−0.097	−0.008
Severity	Hippocampus	0.014	0.471	0.019	−0.024	0.052
Severity	Nucleus accumbens	−0.015	0.439	0.019	−0.051	0.022
Severity	Pallidum	−0.021	0.267	0.019	−0.058	0.016
Severity	Putamen	−0.033	0.078	0.019	−0.070	0.004
Severity	Thalamus	−0.042	0.024*	0.019	−0.079	−0.006

Notes: ***P value < 0.007 (0.05/7, seven subcortical structures) is defined as significant after Bonferroni correction for multiple testing, and *P value < 0.05 is defined as nominal significant. IVW: inverse variance weighted.

as well as learning and memory [74–77]. A few observational neuroimaging investigations disclosed the structural and functional impairment in these subcortical regions in post-COVID-19 patients [27,28,78–80]. Kas et al. explored the COVID-19-related longitudinal brain metabolic patterns using 18F-FDG-PET/CT, and they found a prominent hypometabolism in a widespread cerebral network including the caudate and this network remained mildly to severely impaired 6 months after disease onset [81]. A recent MRI study observed a decrease in left thalamus and pallidum volume in patients with post-COVID fatigue. Qin et al. reported microstructure changes in 3-month follow-up in patients who recovered from COVID-19 without neurological manifestations and they found that the severe group tended to have significantly reduced volumes of the bilateral thalami compared to the normal healthy group [27]. Our result further confirmed the causal links between genetically predicted COVID-19 and the longitudinal volumetric reduction of these subcortical regions.

Mounting evidence supports the strong association between COVID-19 and cognition impairment [82–84], neuropsychiatric [5,6,13,16,85] and neurodegenerative disorders [86–89]. A systematic review and meta-analysis selected 81 studies and found that a significant proportion of individuals after acute COVID-19 experienced persistent cognitive impairment [83]. Previous MR analyses indicated that genetic liabilities to SARS-CoV-2 infection and COVID-19 severity confer causal effects on intelligence [90]. A growing number of observational and MR studies revealed the link between COVID-19 and the increased risk of various neuropsychiatric and neurodegenerative disorders, such as anxiety [16,91], depression [16,92,93], schizophrenia [85,94], Alzheimer's disease [86,87], and Parkinson's disease [95]. Baranova et al. examined bidirectional causal associations between major depressive disorder (MDD) and COVID-19 to evaluate whether the MDD could aggravate the outcomes of COVID-19 or whether the genetic liability to COVID-19 could trigger MDD [96]. They found that genetic liability to MDD was associated with increased risk of SARS-CoV-2 infection, while genetic liability to the three COVID-19 outcomes did not confer any causal effects on MDD. Chen et al. also utilized bidirectional MR approach to investigate mutual influences between COVID-19 outcomes and childhood mental disorders including attention-deficit/hyperactivity disorder (ADHD), Tourette's syndrome (TS), and autism spectrum disorder (ASD) [97]. They revealed that ADHD confers a causal effect on hospitalized COVID-19 and TS confers a causal effect on critical COVID-19. However, genetic liability to the COVID-19 outcomes may not increase the risk for the childhood mental disorders. These two studies suggest that MDD, ADHD and TS may augment the susceptibility to COVID-19, which emphasizes the need to increase social support and improve mental health intervention for patients with neuropsychiatric disorders during the pandemic. Furthermore, the volumetric reductions of the caudate, pallidum, and thalamus have been reported in the above-mentioned neuropsychiatric [57,98–102] and neurodegenerative disorders [103–108]. Given the great impact of COVID-19 on the neuropsychiatric and neurodegenerative disorders and the pivotal role of these subcortical structures in pathological processes of these disorders, exploring the causal relationship between COVID-19 and longitudinal changes of subcortical structures is of great importance for understanding the underlying neural mechanism of the association between COVID-19 and these diseases. We speculate that triggered neuroinflammatory pathways [109,110] might be the potential molecular mechanisms of long-term brain impairment in patients with COVID-19. Our results might shed light on the long-term effects of COVID-19 on the alterations of subcortical structures, especially caudate, which might be one of the possible mechanisms contributing to COVID-19-related neurological and neuropsychiatric sequelae.

Our study has several limitations. First, we only included individuals of European ancestry to minimize the bias due to population stratification, and hence, our findings should be cautiously interpreted when generalizing to other ethnicities. Second, some participants from the UK Biobank were included both in the exposure and outcome GWAS datasets. The total number of overlapped participants was less than 2536. Even if all the 2536 overlapped participants in the outcome GWAS dataset were included in the COVID-19 GWAS data, the proportions were 0.098 %, 0.121 %, and 0.233 % for COVID-19 susceptibility, hospitalization, and severity, respectively. Based on Burgess's suggestion, a very small percentage of sample overlapping was not sufficient to bias the results of MR analysis [44]. Third, the sample size in the outcome GWAS data of the longitudinal change rate of brain structure phenotypes was relatively small (15,640 individuals). However, to our knowledge, this is so far the largest GWAS identifying the common genetic variants associated with longitudinal changes in brain structure across the lifespan. The power calculation results also indicated that our sample provided sufficient statistical power (Supplementary Table 5). Fourth, the GWAS data of the longitudinal change rate of regional brain structures only include seven subcortical structures, therefore, we cannot perform MR analysis of the effects of SARS-CoV-2 infection on the longitudinal changes of the other regional brain structures. Fifth, since the clinical information of the COVID-19 patients, such as patients' age, sex, vaccination status, the SARS-CoV-2 strains, and the use of drugs, was unavailable, we cannot perform stratified analysis. Sixth, the cognitive performance of the COVID-19 patients is also unavailable, we cannot perform the correlation between the volumetric change of subcortical structures and their cognitive function. Seventh, the follow-up durations of the longitudinal changes in subcortical structures vary from 0.2 to 16.7 years. Due to the unavailability of a detailed follow-up time in each individual, it's impossible to estimate the effects of SARS-CoV-2 infection on the longitudinal changes in subcortical structures during a relatively fixed period of time, since the longitudinal structure changes in patients with COVID-19 have been reported to be possibly dynamic [28]. Finally, the main strength of our study is that MR analysis is generally less affected by the confounding and reverse causation than the traditional observational studies [31], but we still cannot completely exclude the effects of potential confounding factors on our results even though we used the various MR analysis methods to validate our results and performed the sensitivity analyses to detect the heterogeneity and pleiotropy. Therefore, validation of our results in additional follow-up cohorts is warranted and the underlying neurological mechanisms of this causative association require further investigation.

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Data availability statement

The data associated with our study has been deposited into publicly available repositories. GWAS Summary statistics of three COVID-19 phenotypes can be downloaded from the COVID-19 HGI (RELEASE 7, April 2022) (https://www.covid19hg.org/). GWAS summary statistics of genetic variants associated with longitudinal changes in subcortical brain structures released by the ENIGMA consortium can be downloaded from the original publications [37]. The code in our study used to perform MR analyses and sensitivity analyses are available from the authors upon reasonable request.

Ethics approval and consent to participate

All the datasets in our study are publicly available GWAS summary statistics, and hence no additional ethical approval and participants' consent was required. Detailed ethical approval and participants' consent can be found in the original GWAS publications.

CRediT authorship contribution statement

Zirui Wang: Writing – original draft, Validation, Methodology, Data curation. **Siqi Wang:** Software, Data curation. **Haonan Li:** Validation, Methodology, Conceptualization. **Mengdong Wang:** Software, Data curation. **Xingyu Zhang:** Software, Methodology, Conceptualization. **Jiayuan Xu:** Supervision, Project administration, Methodology, Formal analysis. **Qiang Xu:** Supervision, Project administration, Methodology, Formal analysis, Conceptualization. **Junping Wang:** Writing – review & editing, Visualization, Supervision, Resources, Project administration, Investigation, Funding acquisition, Formal analysis.

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.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e37193.

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