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RESEARCH ARTICLE

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# Mendelian randomization study on the causal effects of COVID-19 on childhood intelligence

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## Abstract

Although individuals with coronavirus disease 2019 (COVID-19) are known to be at increased risk for other conditions resulting from pathogenic changes (including metaplastic or anaplastic) in the lungs and other organs and organ systems, it is still unknown whether COVID-19 affects childhood intelligence. The present two-sample Mendelian randomization study aims to identify the genetic causal link between COVID-19 and childhood intelligence. Four COVID-19 genetic instrumental variants (IVs) were chosen from the largest genome-wide association studies (GWAS) for COVID-19 (hospitalized vs. population) (6406 cases and 902 088 controls of European ancestry). The largest childhood intelligence GWAS ($n$ = 12 441 individuals of European ancestry) was used to evaluate the effect of the identified COVID-19-associated genetic IVs on childhood intelligence. We found that as the genetic susceptibility to COVID-19 increased, childhood intelligence followed a decreasing trend, according to mr_egger ($\beta$ = −0.156; $p$ = 0.601; odds ratio [OR] = 0.856; 95% confidence interval [CI]: 0.522–1.405), simple mode ($\beta$ = −0.126; $p$ = 0.240; OR = 0.882; 95% CI: 0.745–1.044), and weighted mode ($\beta$ = −0.121; $p$ = 0.226; OR = 0.886; 95% CI: 0.758–1.036) analyses. This trend was further demonstrated by the weighted median ($\beta$ = −0.134; $p$ = 0.031; OR = 0.875; 95% CI: 0.774–0.988) and the inverse variance weighted ($\beta$ = −0.152; $p$ = 0.004; OR = 0.859; 95% CI: 0.776–0.952). Our analysis suggests a causal link between genetically increased COVID-19 and decreased childhood intelligence. Thus, COVID-19 may be a risk factor for declines in childhood intelligence.

**KEYWORDS**

childhood intelligence, COVID-19 pandemic, genetic variants, genome-wide association study, Mendelian randomization

## 1 | INTRODUCTION

In late 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-induced respiratory distress syndrome named coronavirus disease 2019 (COVID-19) was identified in humans.[1] The ongoing COVID-19 pandemic has affected millions worldwide and continues to present a serious public health threat.[2] Researchers have estimated that 30% of COVID-19 survivors may be affected by the long-term consequences of the illness, known as post-COVID-19 condition after they recover from acute illness.[3]

Gaizhi Zhu and Shan Zhou contributed equally to this study as the first authors.

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COVID-19 and cancer demonstrate some clinical and molecular similarities in the four major signaling pathways: immune checkpoint signaling, type I interferon, cytokine, and androgen receptor.[4] Histopathological analyses revealed diffuse alveolar damage including viral cytopathic changes, metaplastic epithelial changes, intra-alveolar hemorrhaging, and pulmonary edema. These studies suggest that COVID-19 infection may result in an increased risk of other diseases such as lung cancer.

COVID-19 can infect people of ages, including children.[5] Children comprise a small percentage of the total number of COVID-19 cases and usually present with milder symptoms than adults.[5] Only 6% of pediatric cases have been classified as severe and critical.[6] The symptoms of severe and critical COVID-19 are acute respiratory distress syndrome, hypoxia (defined as blood oxygen saturation of less than 92%), shock, and the failure of organs such as the heart and kidneys.[5,6] Children with both mild and severe COVID-19 have experienced long-term symptoms including tiredness, fatigue, headache, trouble sleeping, trouble concentrating, muscle and joint pain, and cough. In addition, the levels of cardiac troponin, a marker of myocardial (heart muscle) injury, are elevated in an unexpected number of patients hospitalized with COVID-19.[7] One underexplored area of long COVID is how COVID-19 may affect children's intelligence.

Using genetic variants independent of many factors that bias observational studies, Mendelian randomization (MR) studies have many advantages in assessing the causal association between an exposure and an outcome.[8–13] Thus, we used a two-sample MR study to identify the causal genetic link between COVID-19 and childhood intelligence.

## 2 | METHODS

### 2.1 | COVID-19 genetic instrumental variants (IVs)

The largest GWAS for COVID-19 (hospitalized vs. population) RELEASE 4 was described by the COVID-19 Host Genetics Initiative in 2020.[14] This GWAS data set is based on 6406 cases and 902 088 controls with European ancestry. The summary data set is available in https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST010779. Four independent COVID-19 genetic IVs were obtained based on the following three criteria: (1) genome-wide significance threshold $p < 5 \times 10^{-8}$; (2) $r^2 < 0.001$, indicating no linkage disequilibrium between single-nucleotide polymorphisms (SNPs); (3) no effects on other potential risk factors including body mass index, smoking, and blood pressure. Detailed information about these IVs is shown in Table 1.

### 2.2 | Childhood intelligence GWAS

Benyamin et al.[15] described the largest GWAS for childhood. This GWAS consists of 12 441 individuals of European ancestry. The profile of this GWAS is provided in Table 2. The summary data set is available at https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST001837.

**TABLE 1** COVID-19 genetic IVs.

| SNP | EA | NEA | EAF | β | SE | p Value |
|---|---|---|---|---|---|---|
| rs2166172 | C | A | 0.410 | 0.124 | 0.022 | 2.74E−08 |
| rs143334143 | A | G | 0.088 | 0.229 | 0.036 | 1.28E−10 |
| rs2269899 | T | C | 0.685 | 0.124 | 0.022 | 3.24E−08 |
| rs13050728 | C | T | 0.649 | −0.153 | 0.023 | 1.91E−11 |

Abbreviations: β, the regression coefficient based on the COVID-19 effect allele; COVID-19, coronavirus disease 2019; EA, effect allele; EAF, effect allele frequency; IVs, instrumental variants; NEA, non-effect allele; SE, standard error; SNP, single-nucleotide polymorphism.

### 2.3 | Association of COVID-19 genetic IVs with childhood intelligence GWAS

Potential proxy SNPs were identified by the LD proxy tool ($r^2 > 0.8$) when COVID-19 genetic IVs could not be found in childhood intelligence summary statistics. However, we were able to successfully extract four independent COVID-19 genetic IVs from the childhood intelligence GWAS summary data set. The association of four independent COVID-19 genetic IVs with childhood intelligence GWAS is shown in Table 3.

### 2.4 | Pleiotropy test

Both mr_egger_intercept and PRESSO methods[16,17] were used to test the pleiotropy of four independent COVID-19 genetic IVs in the childhood intelligence GWAS data set. The results of the pleiotropy test are shown in Table 4. A $p$ value > 0.05 represents no significant pleiotropy of the four independent COVID-19 genetic IVs in childhood intelligence GWAS.

### 2.5 | Heterogeneity test

Both mr_egger and inverse variance weighted (IVW) in Cochran's $Q$ statistic[18,19] were used to test the heterogeneity of four independent COVID-19 genetic IVs in the childhood intelligence GWAS data set. The results of the heterogeneity test are shown in Table 4. A $p$ value > 0.05 represents no significant heterogeneity in the four independent COVID-19 genetic IVs in the childhood intelligence GWAS.

### 2.6 | MR analysis

mr_egger, weighted median, IVW, simple mode, and weighted mode methods[16,20,21] were used to analyze the causal association of COVID-19 with childhood intelligence. The results of the MR analysis are shown in Table 5. A $p$ value < 0.05 represents a causal association of COVID-19 with childhood intelligence.

**TABLE 2** GWAS for childhood intelligence.

| GWAS ID | Year | Trait | Sample size | nsnp | Population | PMID |
|---|---|---|---|---|---|---|
| ebi-a-GCST001837 | 2013 | Intelligence (childhood) | 12 441 | 1 374 543 | European | 23358156 |

Abbreviations: GWAS, genome-wide association study; GWAS ID, GWAS identity; nsnp, the number of single-nucleotide polymorphism; PMID, PubMed unique identifier.

**TABLE 3** Association of COVID-19 genetic IVs with childhood intelligence GWAS.

| | Exposure (COVID-19) GWAS | | | Outcome (childhood intelligence) GWAS | | |
|---|---|---|---|---|---|---|
| SNP | *β* | SE | *p* Value | *β* | SE | *p* Value |
| rs13050728 | −0.153 | 0.023 | 1.91E−11 | 0.017 | 0.014 | 0.227 |
| rs143334143 | 0.229 | 0.036 | 1.28E−10 | −0.041 | 0.026 | 0.113 |
| rs2166172 | 0.124 | 0.022 | 2.74E−08 | −0.015 | 0.013 | 0.262 |
| rs2269899 | 0.124 | 0.022 | 3.24E−08 | −0.027 | 0.014 | 0.048 |

Abbreviations: *β*, the regression coefficient based on COVID-19 raising effect allele; COVID-19, coronavirus disease 2019; GWAS, genome-wide association study; IVs, instrumental variants; SE, standard error; SNP, single-nucleotide polymorphism.

**TABLE 4** Pleiotropy and heterogeneity test of COVID-19 genetic IVs in childhood intelligence GWAS.

| Pleiotropy test | | | | Heterogeneity test | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| mr_egger | | | PRESSO | mr_egger | | | IVW | | |
| Intercept | SE | *p* Value | *p* Value | Q | Q_df | *p* Value | Q | Q_df | *p* Value |
| 0.001 | 0.037 | 0.989 | 0.896 | 0.676 | 2 | 0.713 | 0.677 | 3 | 0.879 |

*Note*: *p* value > 0.05 represent no significant pleiotropy. Q_*p* value > 0.05 represents no significant heterogeneity.

Abbreviations: COVID-19, coronavirus disease 2019; GWAS, genome-wide association study; IVs, instrumental variants; IVW, inverse variance weighted; MR, Mendelian randomization; SE, standard error.

**TABLE 5** The causal association of COVID-19 with childhood intelligence.

| Method | nsnp | *β* | SE | *p* Value | OR | OR_lci95 | OR_uci95 |
|---|---|---|---|---|---|---|---|
| mr_egger | 4 | −0.156 | 0.253 | 0.601 | 0.856 | 0.522 | 1.405 |
| Weighted median | 4 | −0.134 | 0.062 | **0.031** | 0.875 | 0.774 | 0.988 |
| IVW | 4 | −0.152 | 0.052 | **0.004** | 0.859 | 0.776 | 0.952 |
| Simple mode | 4 | −0.126 | 0.086 | 0.240 | 0.882 | 0.745 | 1.044 |
| Weighted mode | 4 | −0.121 | 0.080 | 0.226 | 0.886 | 0.758 | 1.036 |

*Note*: *p* < 0.05 represents the causal association of the increased COVID-19 with childhood intelligence.

Abbreviations: *β*, the regression coefficient based on COVID-19 raising effect allele; COVID-19, coronavirus disease 2019; IVW, inverse variance weighted; MR, Mendelian randomization; nsnp, number of single-nucleotide polymorphism; OR, odds ratio; OR_lci95, lower limit of 95% confidence interval for OR; OR_uci95, upper limit of 95% confidence interval for OR; SE, standard error.

### 2.7 | Single SNP effect analysis

"mr" and "mr_scatter_plot" were used to test the individual putative causal effects of COVID-19 on childhood intelligence (Figure 1). "mr_singlesnp" and "mr_forest_plot" were used to determine single SNP effect size for COVID-19 on childhood intelligence (Figure 2). "mr_singlesnp" and "mr_leaveoneout_plot" were used to analyze the effect of leave-one-out of the four independent COVID-19 genetic IVs of childhood intelligence (Figure 3).

## 3 | RESULTS

### 3.1 | No significant pleiotropy or heterogeneity was observed among the four COVID-19 genetic IVs

Four COVID-19 genetic IVs (Table 1) were successfully extracted from the childhood intelligence GWAS data set (Table 2). The association of the four COVID-19 genetic IVs with childhood intelligence GWAS is shown (Table 3).

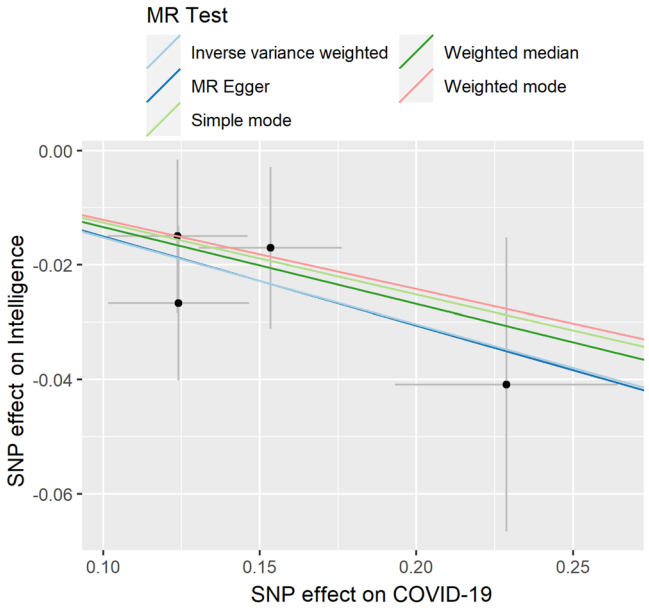


**FIGURE 1** Individual estimates about the putative causal effect of COVID-19 on childhood intelligence. The *x*-axis shows the SNP effect and SE on each of COVID-19 IVs. The *y*-axis shows the SNP effect and SE on childhood intelligence. The regression line for mr_egger, weighted median, IVW, simple mode, and weighted mode is shown. COVID-19, coronavirus disease 2019; IV, instrumental variant; IVW, inverse variance weighted; MR, Mendelian randomization; SE, standard error; SNP, single-nucleotide polymorphism.

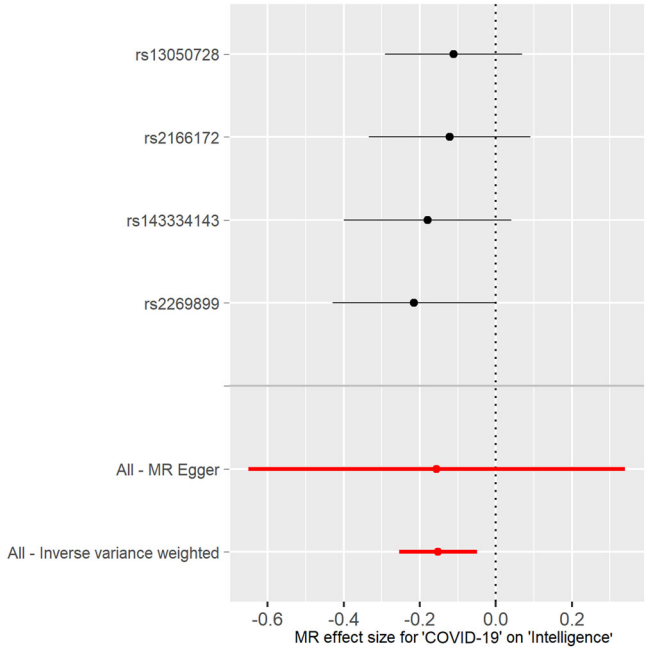


**FIGURE 2** Forest plot of COVID-19 associated with childhood intelligence. The *x*-axis shows MR effect size for COVID-19 on childhood intelligence. The *y*-axis shows the analysis for each of SNPs. COVID-19, coronavirus disease 2019; MR, Mendelian randomization; SNP, single-nucleotide polymorphism.

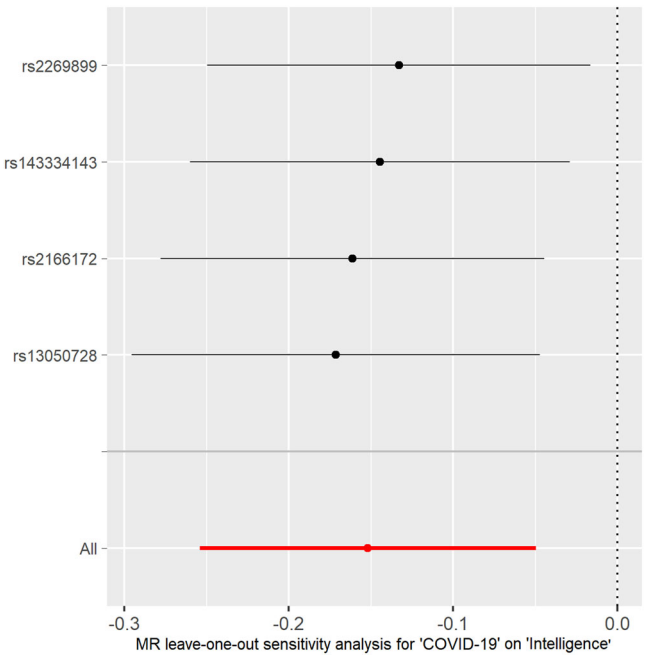


**FIGURE 3** MR leave-one-out sensitivity analysis for the effect of COVID-19 SNPs on childhood intelligence. The *x*-axis shows MR leave-one-out sensitivity analysis for COVID-19 on childhood intelligence. The *y*-axis shows the analysis for the effect of leave-one-out of SNPs on childhood intelligence. COVID-19, coronavirus disease 2019; MR, Mendelian randomization; SNP, single-nucleotide polymorphism.

Both mr_egger_intercept and PRESSO methods suggested no significant pleiotropy in the four independent COVID-19 genetic IVs in the childhood intelligence GWAS (Table 4). Both mr_egger and IVW in Cochran's Q statistic showed no significant heterogeneity in the four independent COVID-19 genetic IVs in the childhood intelligence GWAS (Table 4). Therefore, all selected COVID-19-associated genetic variants can be taken as the effective IVs in this MR study.

## 3.2 | COVID-19 genetically reduces childhood intelligence

We found that as COVID-19 genetically increased, childhood intelligence had an decreased trend using mr_egger ($\beta = -0.156$; $p = 0.601$; odds ratio [OR] = 0.856; 95% confidene interval [CI]: 0.522–1.405), simple mode ($\beta = -0.126$; $p = 0.240$; OR = 0.882; 95% CI: 0.745–1.044), and weighted mode ($\beta = -0.121$; $p = 0.226$; OR = 0.886; 95% CI: 0.758–1.036) (Table 5). This trend was further demonstrated by weighted median ($\beta = -0.134$; $p = 0.031$; OR = 0.875; 95% CI: 0.774–0.988) and IVW ($\beta = -0.152$; $p = 0.004$; OR = 0.859; 95% CI: 0.776–0.952) (Table 5). Altogether, our analysis suggests a causal link between genetically increased COVID-19 and reduced childhood intelligence.

### 3.3 | Single COVID-19 SNP effect is robust without obvious bias

The individual MR estimates (mr_egger, weighted median, IVW, simple mode, and weighted mode) demonstrate that as the effect of a single SNP on COVID-19 increased, the suppressive effect of a single SNP on childhood intelligence increased (Figure 1). All effect size analyses suggest that each effect of COVID-19 SNPs on childhood intelligence was robust (Figure 2). MR leave-one-out sensitivity analysis suggested that removing a specific SNP of the four COVID-19 SNPs did not change the results (Figure 3). Altogether, these results indicate that our data were robust without obvious bias.

## 4 | DISCUSSION

The present MR study showed that genetic predisposition to a higher COVID-19 was genetically associated with reduced childhood intelligence. Thus, to protect childhood intelligence, COVID-19 prevention in children is essential.

Although COVID-19 primarily attacks the lungs, it can also affect many other organs such as the brain, heart, and kidneys. One previous study provided objective neuroimaging evidence for the coexistence of recoverable and long-term unrecovered changes in the brain at 10-month after acute COVID-19.[22] Moreover, COVID-19 has been found to lead to psychiatric illness.[23] Our study suggests that genetic predisposition to a higher COVID-19 reduced childhood intelligence.

The human brain develops over a prolonged period.[24–26] The infant's brain is relatively immature with simultaneous traits of competence and vulnerability.[26] It possesses an immense capacity to learn, remodel, and adapt, but is vulnerable and sensitive to environmental exposures.[26–30] Neurodevelopmental processes such as myelination and synaptogenesis and external cues such as maternal interaction and physical skin-to-skin "kangaroo" care play important roles in optimal brain development.[26,31–34] The brain's adaptive plasticity is promoted by positive and enriching environments[26,35–39] and impaired by neglect, insecurity, stress, and lack of stimulation.[26,40–42] Our results suggest that COVID-19 genetically reduces childhood intelligence. Thus, the brain development of infants and young children may be impaired by COVID-19 infection.

MR studies use genetic variants independent of many factors that bias observational studies in assessing the causal association of an exposure with an outcome.[8–12] Thus, the genetical effect of COVID-19 on childhood intelligence, identified by our present MR study, is not related to the lack of a stimulating environment during the pandemic but to COVID-19 infection. There is clear evidence that SARS-CoV-2 could infect neurons in the brain organoids, killing some and reducing the formation of synapses.[43,44] Animal studies have proposed that SARS-CoV-2 can infect cerebrovascular endothelium and brain parenchyma via the angiotensin-converting enzyme 2 receptor, resulting in COVID-19-related neuronal damage via apoptosis and necrosis.[45] In addition, SARS-CoV-2-induced immune-mediated demyelinating disease, cerebrovascular damage, neurodegeneration, and depression are among the neurological complications described.[46] Thus, COVID-19 infection may reduce childhood intelligence by SARS-CoV-2-induced neurological complications via direct damage and indirect immune responses.

One strength of our study is that because both COVID-19 genetic IVs and childhood intelligence GWAS were from populations with European ancestries, it removed the influence of population stratification. Second, four different analytical methods demonstrated no significant pleiotropy or heterogeneity in severe COVID-19 genetic IVs. Third, all five MR analyses (mr_egger, weighted median, IVW, simple mode, and weighted mode) showed the causal link between genetically increased COVID-19 and decreased childhood intelligence.

This study has several limitations. First, because four independent COVID-19 genetic IVs and childhood intelligence GWAS are from European ancestry, our conclusions cannot necessarily be extrapolated to populations of other ancestries. Second, randomized controlled trials are necessary to clarify whether COVID-19 can reduce childhood intelligence.

In conclusion, although our analysis suggests a causal link between genetically increased COVID-19 and reduced childhood intelligence, it is necessary for future studies to examine the mechanism underlying this link.

### AUTHOR CONTRIBUTIONS

Renxi Wang conceived, initiated, and supervised the project. Gaizhi Zhu, Shan Zhou, Yaqi Xu, Ran Gao, and Huan Li collected and analyzed the data. Wenting Su and Gencheng Han contributed to the interpretation of the results. Renxi Wang wrote a draft of the manuscript. All authors critically reviewed and revised the manuscript, and agreed to the published version of the manuscript.

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### DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in ieu open gwas project at https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST001837 for childhood intelligence GWAS and https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST010779 for COVID-19 GWAS. The MR analysis code can be found at https://mrcieu.github.io/TwoSampleMR/articles/index.html.

### CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

### ETHICS STATEMENT

This study was approved by the Ethics Committee of Beijing Institute of Brain Disorders in Capital Medical University and the ethical code number is AEEI-2021-077.

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