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Research Article

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# Mendelian Randomization Study on Causal Association of Il-6 With Intelligence

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## Abstract

***Objective***

*Previous observational studies have shown the association of IL-6 levels and intelligence. The present two-sample MR study aims to identify the genetic causal link between IL-6 and intelligence.*

***Methods***

*IL-6 signaling and its negative regulator soluble IL-6 receptor (sIL-6R) genetic instrumental variants were chosen from IL-6-signaling-associated genome-wide association studies (GWAS) (204,402 European individuals) and sIL-6R-associated GWAS (1650 European individuals), respectively. Intelligence GWAS (149,051 European participants) were used to evaluate the causal link between IL-6 and intelligence by performing a two-sample MR study.*

***Results***

*We found that as IL-6-signaling genetically increased, intelligence significantly decreased using IVW (odds ratio [OR] = 0.828, 95% confidence interval [CI]: 0.702–0.975, p = 0.024) and weighted mode (OR = 0.865, 95% CI: 0.749–0.999, p = 0.049). Conversely, as genetic changes of sIL-6R increased, intelligence significantly increased using Wald ratio (OR = 1.052, 95% CI: 1.000–1.107, p = 0.049).*

***Conclusions***

*Our analysis suggests that genetically increased IL-6-signaling reduces intelligence, whereas genetically increased sIL-6R upregulates intelligence. Thus, IL-6 may be a risk factor for intelligence.*

**Keywords:** IL-6, SIL-6R, Intelligence, Genome-Wide Association Study, Mendelian Randomization

## 1. Introduction

Intelligence is a kind of the ability to select, adapt to, and shape environments and to learn from previous experiences [1]. Human intelligence is broadly sorted into fluid intelligence and crystallized intelligence [2]. Fluid intelligence refers to the flexible ability to adaptively respond to novel situations, whereas crystallized intelligence refers to learning knowledge from past experiences [3].

Previous study has shown that the heritability coefficient is between 0.4 and 0.8 on intelligence [1]. Further understanding of the causative genetic association and pathological genetic defects has led to some potential improvements of intelligence [4].

Higher intelligence quotient (IQ) has been correlated with the lower systemic inflammation, whereas lower IQ is associated with disease risk [5]. The anti-inflammatory cytokines (e.g., IL-10) demonstrated beneficial effects, whereas the pro-inflammatory cytokines such as Interleukin (IL)-6 showed negative effects, on multiple dimensions of intelligence [6]. It is reported that higher IQ was associated with lower IL-6 ($\gamma$ = -0.225, SE = 0.111, p = .045) [5]. These observational studies have showed the association of IL-6 levels and intelligence.

Many factors including reverse causation and confounding bias observational studies and result in the absence of high-quality randomized controlled trials (RCT). Based on the principle that genetic variants are randomly allocated at meiosis, MR study is independent of many factors that bias observational studies [7-16]. To identify the causal link between IL-6 and intelligence, we used a two-sample Mendelian randomization (MR) study to explore the effect of IL-6 signaling and its negative regulator soluble IL-6 receptor (sIL-6R) genetic instrumental variables (IVs) on intelligence.

## 2. Material and Methods

### 2.1 IL-6-Signaling and SIL-6R Genetic IVs

Six IL-6 signaling genetic IVs were generated from a meta-analysis of a large-scale chronic inflammation GWAS of 204,402 European individuals [17]. They have been used to identify the causal link between IL-6 and autoimmune arthritis ischemic stroke and other cardiovascular outcomes depressive symptoms cardiovascular diseases, immune-related disorders and longevity [18-21]. The Linkage disequilibrium (LD) matrix Tool was used to determine LD levels of SNPs (https://ldlink.nci.nih.gov/?tab=ldmatrix, CEU; r2 < 0.1). "IL6 signaling" referred to IL-6R genetic instruments and weighted by the level of CRP and plasma sIL-6R with sgp130 forms an inhibitory receptor to suppress IL-6 signaling [20,22]. One sIL-6R genetic IV (rs2228145 variant) was significantly associated with sIL-6R level in 1650 individuals identified by IL-6R Genetics Consortium Emerging Risk Factors Collaboration in 2012 [23]. It has been used to identify causal link between IL-6 and neurodegenerative diseases [24]. The summary information about six IL-6-signaling and one sIL-6R genetic IVs are shown in Table 1.

### 2.2 Intelligence GWAS Dataset

In 2018, Ben Ellsworth extracted intelligence GWAS dataset using Pheasant derived variables from UK Biobank. This summary dataset is available in MRC-IEU (UK Medical Research Council-Integrative Epidemiology Unit) Consortium and https://gwas.mrcieu.ac.uk/datasets/ukb-b-5238/. The trait of this GWAS is based on fluid intelligence score using 149,051 participants of European ancestry. The summary information about intelligence GWAS dataset is shown in Table 2.

### 2.3 Extraction of IL-6-Signaling and SIL-6R Genetic IVs in Intelligence GWAS Dataset

The LD proxy Tool was used to identify potential proxy SNPs (r2>0.8) when IL-6-signaling and sIL-6R IVs could not be found in intelligence summary statistics. All six independent IL-6-signaling and one sIL-6R genetic IVs were successively extracted. The association of IL-6-signaling and sIL-6R genetic IVs within intelligence GWAS dataset is shown in Table 3.

### 2.4 Pleiotropy and Heterogeneity Test

Both MR-egger intercept and MR-PRESSO methods were used to test the pleiotropy of independent IL-6-signaling and sIL-6R genetic IVs in intelligence GWAS datasets. Both MR Egger and Inverse variance weighted (IVW) in Cochran's Q statistic were used to test the heterogeneity of independent IL-6-signaling and sIL-6R genetic IVs in intelligence GWAS dataset. The summary results about pleiotropy and heterogeneity tests are shown in Table 4. A P>0.05 represents no significant pleiotropy and heterogeneity of independent IL-6-signaling and sIL-6R genetic IVs in intelligence GWAS dataset.

### 2.5 MR Analysis

MR analysis methods including IVW (inverse variance weighted) as the primary MR analysis and weighted median as a supplement were used to analyze the causal association of IL-6-signaling with intelligence. Wald ratio was used to analyze the causal association of sIL-6R levels with intelligence. The summary results about MR analysis are shown in Table 5. A P<0.05 represents a causal association of IL-6-signaling or sIL-6R levels with intelligence.

### 2.6 Analysis of Single SNP Effect

Individual causal effect, single SNP effect size, and leave-one-out effect were used to analyze the single SNP effect of IL-6-signaling-associated IVs on intelligence.

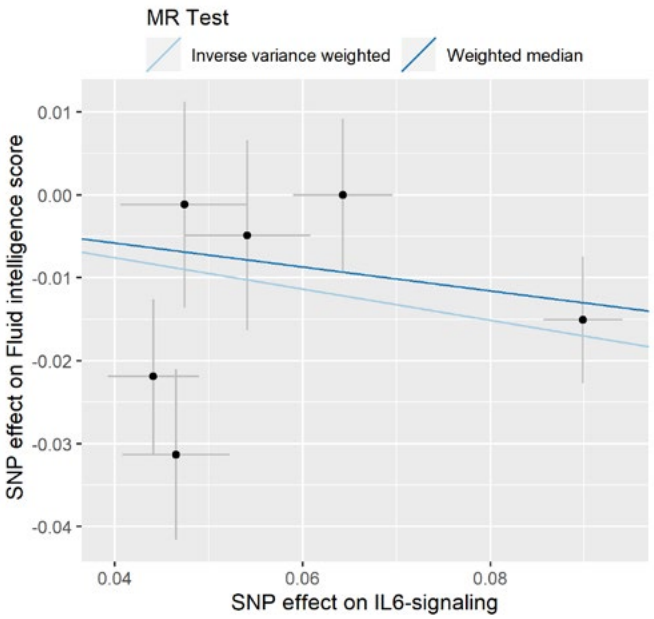


**Figure 1:** Individual Estimates about the Causal Effect of IL-6-Signaling on Intelligence.
The X-Axis shows the SNP (Single Nucleotide Polymorphism) Effect and SE (Standard Error) on IL-6-Signaling. The Y-Axis Shows the SNP Effect and SE on Intelligence. The Regression Line for IVW (Inverse Variance weighted) and Weighted Median is Shown

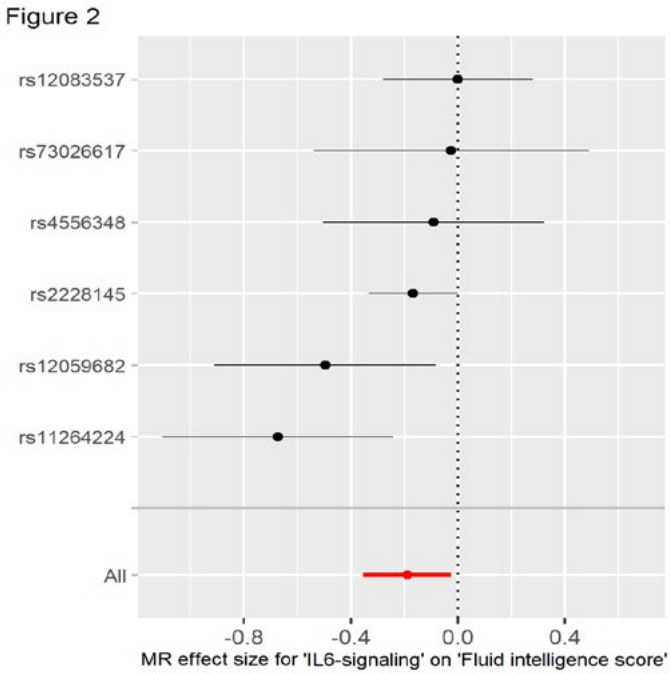


**Figure 2:** Forest Plot of IL-6-Signaling Associated with Intelligence.
The X-Axis Shows MR Effect Size for IL-6-Signaling on Intelligence. The Y-Axis Shows the Analysis for Each or the Total of SNPs on Intelligence using IVW Methods.

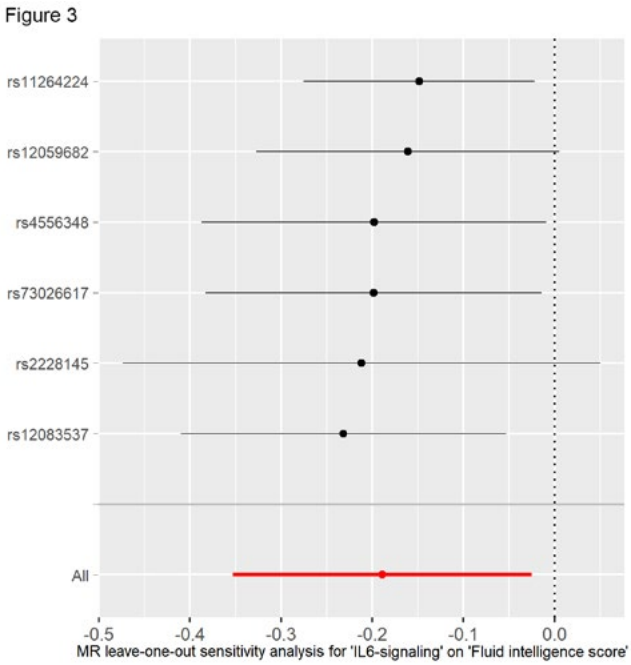


**Figure 3:** MR Leave-One-Out Sensitivity Analysis for the Effect of IL-6-Signaling on Intelligence.
The X-Axis Shows MR Leave-Oneout Sensitivity Analysis for IL-6-Signaling on Intelligence. The Y-Axis Shows the Analysis for the Effect of Leave-One-Out Effect of Each or the Total of SNPs on Intelligence using IVW Methods.

## 3. Results

### 3.1 Genetic Variant of SIL-6R is Positively Associated with Intelligence

We successfully extracted one sIL-6R genetic IV (Table 1) from intelligence GWAS dataset (Table 2). The association of sIL-6R genetic IV in intelligence GWAS dataset is shown (Table 3). We found that as sIL-6R genetic changes increased, intelligence significantly increased using Wald ratio (Beta = 0.051, p = 0.049; OR = 1.052, 95% CI: 1.000–1.107) (Table 5). Thus, our data suggest a causal association of increased sIL-6R from greater genetic variation with increased intelligence.

### 3.2 No Significant Pleiotropy or Heterogeneity Among IL-6-Signaling Genetic IVs

We successfully extracted all selected IL-6-signaling genetic IVs (Table 1) from intelligence GWAS dataset (Table 2). The association of IL-6-signaling genetic IVs in intelligence GWAS dataset is shown (Table 3). We found no significant pleiotropy or heterogeneity of IL-6-signaling genetic IVs in intelligence GWAS dataset (Table 4). Thus, all selected IL-6-signaling genetic variants can be taken as the effective IVs in this MR study.

### 3.3 Genetic Variant of IL-6-Signaling is Negatively Associated with Intelligence

We found that as IL-6-signaling genetically increased, intelligence significantly decreased using IVW (Beta = -0.189, p = 0.024; OR = 0.828, 95% CI: 0.702–0.975) and weighted mode (Beta = -0.145, p = 0.049; OR = 0.865, 95% CI: 0.749–0.999) (Table 5). Collectively, our data suggested the causal association of genetically increased IL-6-signaling levels with reduced intelligence.

### 3.4 Single SNP Effect of IL-6-Signaling on Intelligence were Robust without Obvious Bias

The individual MR estimates demonstrated that as the effect of a single SNP on IL-6-signaling increased, the suppressive effect of a single SNP on intelligence increased, as determined using IVW and weighted median (Fig. 1). Each effect size analysis suggested that each effect of IL-6-signaling SNPs on intelligence were robust (Fig. 2). MR leave-one-out sensitivity analysis showed that removing a specific SNP of six IL-6-signaling SNPs did not change the results (Fig. 3). Altogether, these results indicate that our data were robust without obvious bias.

| Exposure | SNP | Beta | SE | EA | NEA | EAF | p val | Gene |
|---|---|---|---|---|---|---|---|---|
| IL-6-signaling | rs73026617 | 0.047 | 0.007 | T | C | 0.29 | 3.16E-12 | IL6R |
| | rs12083537 | 0.064 | 0.005 | A | G | 0.29 | 7.14E-34 | IL6R |
| | rs4556348 | 0.054 | 0.007 | T | C | 0.29 | 6.77E-16 | IL6R |
| | rs2228145 | 0.090 | 0.004 | A | C | 0.29 | 1.21E-101 | IL6R |
| | rs11264224 | 0.047 | 0.006 | A | C | 0.29 | 3.41E-16 | ADAR |
| | rs12059682 | -0.044 | 0.005 | T | C | 0.29 | 2.26E-19 | ADAR |
| sIL-6R | rs2228145 | 0.295 | 0.015 | C | A | 0.39 | 2.44E-88 | IL6R |

**Table 1: IL-6-Signaling and sIL-6R Genetic Instrumental Variants (IVs).**

IL-6: interleukin-6; sIL-6R: soluble IL-6 receptor; IVs: instrumental variants; SNP: single-nucleotide polymorphism; Beta: the regression coefficient based on the IL-6-signaling or sIL-6R raising effect allele; SE: standard error; EA: effect allele; NEA: non-effect allele; EAF: effect allele frequency.

| GWAS ID | Year | Trait | Sample size | nsnp | Population | Consortium | Author |
|---|---|---|---|---|---|---|---|
| ukb-b-5238 | 2018 | Fluid intelligence score | 149,051 | 9,851,867 | European | MRC-IEU | Ben Elsworth |

**Table 2: Intelligence Genome-wide Association Study (GWAS).**

GWAS: genome-wide association study; GWAS ID: GWAS identity; nsnp: the number of single-nucleotide polymorphism. MRC-IEU: UK Medical Research Council-integrative epidemiology unit.

| Exposure | SNP | Exposure (IL-6 or sIL-6R) GWAS | | | Outcome (Intelligence) GWAS | | |
|---|---|---|---|---|---|---|---|
| | | Beta | SE | *p* val | Beta | SE | *p* val |
| IL-6-signaling | rs11264224 | 0.047 | 0.006 | 3.41E-16 | -0.031 | 0.010 | 0.002 |
| | rs12059682 | -0.044 | 0.005 | 2.26E-19 | 0.022 | 0.009 | 0.019 |
| | rs12083537 | 0.064 | 0.005 | 7.14E-34 | 0.000 | 0.009 | 1.000 |
| | rs2228145 | 0.090 | 0.004 | 1.21E-101 | -0.015 | 0.008 | 0.049 |
| | rs4556348 | 0.054 | 0.007 | 6.77E-16 | -0.005 | 0.011 | 0.670 |
| | rs73026617 | 0.047 | 0.007 | 3.16E-12 | -0.001 | 0.012 | 0.930 |
| sIL-6R | rs2228145 | 0.295 | 0.015 | 2.44E-88 | 0.015 | 0.008 | 0.049 |

**Table 3: Association of IL-6-Signaling and sIL-6R Genetic Instrumental Variables (IVs) with Intelligence GWAS.**

IL-6: interleukin-6; sIL-6R: soluble IL-6 receptor; IVs: instrumental variants; GWAS: Genome wide association study; SNP: single-nucleotide polymorphism; Beta: the regression coefficient based on IL-6-signaling or sIL-6R raising effect allele; SE: standard error.

| Exposure | Pleiotropy test | | | | Heterogeneity test | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | MR_Egger | | PRESSO | | MR Egger | | | IVW | | |
| | Intercept | SE | *p* val | *p* val | Q | Q_df | Q_pval | Q | Q_df | Q_pval |
| IL-6-signaling | -0.020 | 0.019 | 0.351 | 0.216 | 7.323 | 4 | 0.120 | 9.355 | 5 | 0.096 |

**Table 4: Pleiotropy and Heterogeneity Test of IL-6-Signaling Genetic IVs in Intelligence GWAS.**

IL-6: interleukin-6; IVs: instrumental variants; GWAS: genome wide association study; IVW: inverse variance weighted; SE: standard error. A p val > 0.05 represents no significant pleiotropy. A Q_pval > 0.05 represents no significant heterogeneity.

| Exposure | Method | nsnp | Beta | SE | p val | OR | OR_lci95 | OR_uci95 |
|---|---|---|---|---|---|---|---|---|
| IL-6-signaling | Weighted median | 6 | -0.145 | 0.074 | 0.049 | 0.865 | 0.749 | 0.999 |
| | IVW | 6 | -0.189 | 0.084 | 0.024 | 0.828 | 0.702 | 0.975 |
| sIL-6R | Wald ratio | 1 | 0.051 | 0.026 | 0.049 | 1.052 | 1.000 | 1.107 |

**Table 5: The Causal Association of IL-6-Signaling and sIL-6R with Intelligence.**

IL-6: interleukin-6; sIL-6R: soluble IL-6 receptor; IVW: inverse variance weighted; nsnp: the number of single-nucleotide polymorphism; Beta: the regression coefficient based on IL-6-signaling or sIL-6R raising effect allele; SE: standard error; A $p < 0.05$ represents the causal association of the increased levels of IL-6-signaling or sIL-6R with intelligence; OR: odds ratio; OR_lci95: Lower limit of 95% confidence interval for OR; OR_uci95: Upper limit of 95% confidence interval for OR.

## 4. Discussion

Previous observational studies have shown the association of IL-6 levels and intelligence [5,6]. The present study used the two-sample MR study and identified a potential causal link between genetically increased IL-6-signaling and low intelligence or genetically decreased IL-6-signaling and high intelligence.

Inflammatory markers such as interleukin-6 (IL-6) has been used to predict mortality from multiple causes [25]. Better cognitive function is correlated with lower inflammatory markers including CRP and IL-6 among young, midlife, and older adults [26-29]. This relationship between inflammation and cognitive function is true for childhood [26]. These studies did not identify whether lower inflammation did not harm brain health and cognitive function or cognitive function blocked systemic inflammation. Our results suggest that genetically increased IL-6-signaling results in low intelligence, whereas genetically decreased IL-6-signaling causes high intelligence.

This study has several strengths. First, six independent IL-6-signaling and one independent sIL-6R genetic IVs were chosen from a previously reported large-scale IL-6-signaling-associated GWAS of 204,402 European individuals and sIL-6R-associated GWAS of 1650 European individuals respectively [17,23]. These IVs have broadly used in recent MR reports [18-21, 24]. Second, participants in all GWASs from European ancestry reduces the influence of population stratification. Third, we used four different MR analysis methods demonstrated no significant pleiotropy or heterogeneity of IL-6-signaling genetic IVs as the effective IVs. Fourth, both weighted median and IVW proved a causal link between genetically increased IL-6-signaling levels and low intelligence. Fifth, all three methods demonstrated that each effect of IL-6-signaling SNPs on intelligence was robust and no obvious bias. Sixth, we used IL-6-signaling levels and its negative regulator sIL-6R and critically, they showed the opposite result.

This study has several limitations. First, all GWAS datasets are from European ancestry. Therefore, our conclusion needs be proven in other ancestries. Second, randomized controlled trials are required to clarify whether IL-6 signaling could reduce intelligence. Third, the underlying mechanism by which IL-6-signaling levels genetically reduced intelligence is still unclear and worth to explore in the future.

## 5. Conclusions

Our results suggest that genetically increased IL-6-signaling may reduce intelligence, whereas genetically increased sIL-6R upregulates intelligence. This finding may highlight the potential of IL-6 blockade in the prevention of low intelligence resulted from IL-6.

## Abbreviations

IL-6: interleukin-6; sIL-6R: soluble IL-6 receptor; GWAS: Genome-wide association study; MR: Mendelian randomization; SNP: Single nucleotide polymorphism; IVW: Inverse variance weighted.


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## Authors' contributions

RW and WS conceived and initiated the project. JQ, BZ, MZ, QZ, GZ, RG, and HX analyzed the data. RW and WS wrote the manuscript. All authors contributed to the interpretation of the results, critical revision of the manuscript, and approved the final version of the manuscript. All authors read and approved the final manuscript.


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## Availability of Data and Materials

Intelligence GWAS datasets (GWAS ID: ukb-b-5238) can be found on ieu open gwas project at https://gwas.mrcieu.ac.uk/datasets/. The MR analysis code can be found at https://mrcieu.github.io/TwoSampleMR/articles/index.html.

## Ethics Approval and Consent to Participate

Our study was approved by the Ethics Committee of Beijing Institute of Brain Disorders in Capital Medical University. This article contains human participants collected by several previous studies. All participants gave informed consent in all the corresponding original studies, as described in the Methods.

## Competing Interests

The authors declare no competing interests.

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