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ORIGINAL RESEARCH

Causal Relationship Between Intelligence, Noncognitive Education, Cognition and Urinary Tract or Kidney Infection: A Mendelian Randomization Study

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Background: The occurrence of urinary tract or kidney infection is correlated with intelligence, noncognitive education and cognition, but the causal relationship between them remains uncertain, and which risk factors mediate this causal relationship remains unknown.

Methods: The intelligence (n=269,867), noncognitive education (n=510,795) and cognition data (n=257,700) were obtained from genome-wide association studies (GWAS) conducted in individuals of European ethnicities. The genetic associations between these factors and urinary tract or kidney infection (UK Biobank, n=397,867) were analyzed using linkage disequilibrium score regression. We employed a two-sample univariate and multivariate Mendelian randomization to evaluate the causal relationship, and utilized a two-step Mendelian randomization to examine the involvement of 28 potential mediators and their respective mediating proportions.

Results: The genetic correlation coefficients of intelligence, noncognitive education, cognition, and urinary tract or kidney infection were −0.338, −0.218, and −0.330. The Mendelian randomization using the inverse variance weighted method revealed each 1-SD increase in intelligence, the risk of infection decreased by 15.9%, while after adjusting for noncognitive education, the risk decreased by 20%. For each 1-SD increase in noncognitive education, the risk of infection decreased by 8%, which further reduced to 7.1% after adjusting for intelligence and to 6.7% after adjusting for cognition. For each 1-SD increase in cognition, the risk of infection decreased by 10.8%, increasing to 11.9% after adjusting for noncognitive education. The effects of intelligence and cognition are interdependent. 2 out of 28 potential mediating factors exhibited significant mediation effects in the causal relationship between noncognitive education and urinary tract or kidney infection, with body mass index accounting for 12.1% of the mediation effect and smoking initiation accounting for 14.7%.

Conclusion: Enhancing intelligence, noncognitive education, and cognition can mitigate the susceptibility to urinary tract or kidney infection. Noncognitive education exhibited independent effect, while body mass index and smoking initiation assuming a mediating role.

Keywords: cognition, intelligence, kidney infection, mediation analyses, Mendelian randomization, noncognitive education, urinary tract infection

Introduction

Urinary tract infections (UTIs) pose a significant threat to global public health, affecting over 150 million individuals annually across various demographics.[1] These infections can manifest in both genders and all age groups, presenting treatment challenges such as recurrent episodes, pathogen diversity, and the emergence of antibiotic resistance.[2] Severe

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UTIs may ultimately result in kidney failure.[3] Intelligence, education, and cognition exert a pervasive influence on all facets of life and serve as significant prognosticators for socioeconomic attainment, health outcomes, and longevity.[4,5] Prospective cohort study has demonstrated a significant association between childhood intelligence quotient (IQ) and the levels of infectious inflammatory markers, including interleukin-6 and C-reactive protein.[6] Cross-sectional study has demonstrated that pregnant women with lower educational attainment are at a higher risk of developing UTIs.[7] Case-control study has demonstrated that elderly patients with cognitive dysfunction exhibit more pronounced pro-inflammatory responses during acute bacterial infections including UTIs, which is evidenced by decreased expression of miR-145 in circulating exosomes and increased expression of CR1 in circulating CD14 monocytes.[8] However, the causal relationship between these factors and UTIs remains uncertain. Recent studies have established correlations between genetic variation and intelligence, education, and cognition levels.[9,10] Analyzing genetic factors and lifestyle data indicated that intelligence, education, and cognition collectively influence various life outcomes, while also exhibiting relatively independent effects.[11] The objective of this study is to investigate the causal effects of intelligence, noncognitive education, and cognition on urinary tract or kidney infection from genetic variation perspective in order to enhance our understanding of the pathogenesis of UTIs and provide guidance for prevention and management measures.

Mendelian randomization (MR) utilizes the random assignment of individual genotypes from ancestral genotypes to explore causal inference in etiological epidemiology.[12] The utilization of genetic variation as instrumental variables facilitates the examination of the causal relationship between exposure and outcome, while minimizing the bias of confounding factors. Comparable to randomized assignment trials, this approach is extensively employed and offers cost-effective benefits. We employed univariate Mendelian randomization (UVMR) to examine the total causal association between each exposure and outcome, conducted multivariate Mendelian randomization (MVMR) to assess the independent effects of each exposure while accounting for mutual correction in the same instrumental variable model,[13] and utilized 2-step UVMR to investigate the mediating factors in the causal relationship.[14] The subject of MR in relation to our topic has not been previously explored, and as far as our knowledge goes, we are the pioneers in utilizing this methodology to investigate the causality within this subject.

Methods

Study Design

The MR framework is based on three fundamental assumptions: (1) The association hypothesis posits a robust correlation between genetic variables and at least one exposure; (2) The independence hypothesis assumes that genetic variables remain unaffected by all confounding factors associated with the exposure and outcome, such as environmental influences; (3) The pleiotropy hypothesis suggests that genetic variables can solely influence outcomes through one or more exposures, without any horizontal pleiotropic effects. This study encompasses 3 stages of analysis (study design shown in Figure 1). In stage 1, we employed UVMR to examine the total causal effects of intelligence, noncognitive education, and cognition on urinary tract or kidney infection. In stage 2, we utilized MVMR to investigate the independent causal effects of intelligence, noncognitive education, and cognition in the same model that accounted for mutual adjustment for urinary tract or kidney infection. In stage 3, we adopted a two-step UVMR to analyze the mediating factors and quantify the proportion of mediation in the causal relationship between noncognitive education and urinary tract or kidney infection. This present study adhered to the guideline for Strengthening the Reporting of Observational Studies in Epidemiology Using Mendelian Randomization (STROBE-MR).[15]

GWAS Data Sources

The GWAS data sources for exposure, outcome, and mediating factors in this study have been summarized in Table 1. All data can be obtained from the IEU OpenGWAS project (https://gwas.mrcieu.ac.uk/) and GWAS Catalog (https://www.ebi.ac.uk/gwas/home) databases, with the corresponding GWAS ID provided in Table S1. The GWASs included in this study have all received ethical approval from the relevant institutional review board, obtained informed consent from the participants, and implemented strict quality control measures. This study received approval from the Medical Ethics Committee of Wuhan No.1 hospital (Approval No. [2024] 128). The potential for sample overlap in GWASs has been

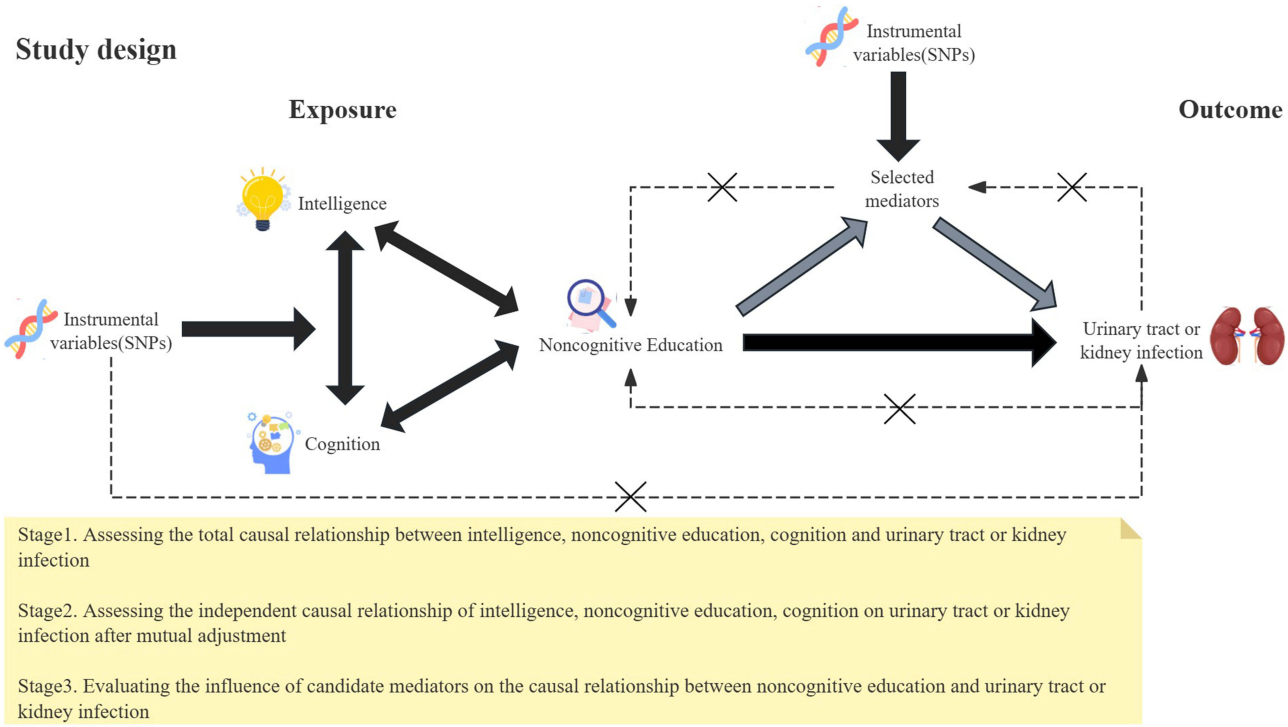

Figure 1 The study design.

minimized to the greatest extent possible. Previous research indicates that when the instrumental variable intensity F-statistic exceeds 10, partial sample overlap has minimal impact on the analysis results.[16] The linkage disequilibrium score regression (LDSC) was employed to analyze GWAS data on exposures and outcome, enabling the assessment of their heritability and genetic correlation without being influenced by sample overlap.[17,18]

Table 1 Summary of the GWAS Data Used in the MR Analyses

Phenotype	Unit	No of Participants	Ancestry	Consortium/ cohort	Author	Year of Publication	PubMed ID
Exposure							
Intelligence[9]	SD	269867	European	Meta	Savage et al	2018	29942086
Noncognitive education[11]	SD	510795	European	SSGAC	Demange et al	2021	33414549
Cognition[11]	SD	257700	European	COGENT	Demange et al	2021	33414549
Outcome							
Urinary tract or kidney infection[19]	Event	397867	European	UK Biobank	Mbatchou et al	2021	34171740
28 candidate mediators							
Selected mediator							
BMI[20]	SD	681275	European	GIANT	Yengo et al	2018	30124842
Smoking initiation[21]	Event	607291	European	GSCAN	Liu et al	2019	30643251
Excluded mediator							

(*Continued*)

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Table 1 (Continued).

Phenotype	Unit	No of Participants	Ancestry	Consortium/ cohort	Author	Year of Publication	PubMed ID
WHR[22]	SD	212244	European	GIANT	Shungin et al	2015	25673412
Waist circumference[22]	SD	231353	European	GIANT	Shungin et al	2015	25673412
BF%[23]	SD	65831	European	Meta	Lu et al	2016	26833246
Childhood obesity[24]	Event	13848	European	EGG	Bradfield et al	2012	22484627
Age of smoking initiation[21]	SD	341427	European	GSCAN	Liu et al	2019	30643251
Smoking heaviness[21]	SD	337334	European	GSCAN	Liu et al	2019	30643251
Alcohol drinking[21]	SD	335394	European	GSCAN	Liu et al	2019	30643251
Coffee intake	SD	428860	European	UK Biobank	Ben et al	2018	NA
Neuroticism[25]	SD	170911	European	SSGAC	Okbay et al	2016	27089181
Depressive symptoms[25]	SD	161460	European	SSGAC	Okbay et al	2016	27089181
Major depression[26]	Event	500199	European	PGC	Howard et al	2019	30718901
Bipolar disorder[27]	Event	413466	European	PGC	Niamh et al	2021	34002096
Schizophrenia[28]	Event	127906	European	PGC	Trubetskoy et al	2022	35396580
Anxiety	Event	187576	European	FinnGen	Kurki et al	2021	NA
Sleeping disorders	Event	168798	European	FinnGen	Kurki et al	2021	NA
SBP[29]	Mmhg	757601	European	ICBP	Evangelou el al	2018	30224653
DBP[29]	Mmhg	757601	European	ICBP	Evangelou et al	2018	30224653
Fasting insulin[30]	SD	151013	European	MAGIC	Chen et al	2021	34059833
Fasting glucose[30]	SD	200622	European	MAGIC	Chen et al	2021	34059833
Two-hour glucose[30]	SD	63396	European	MAGIC	Chen et al	2021	34059833
Triglycerides[31]	SD	177861	Mixed*	GLGC	Willer et al	2013	24097068
Total cholesterol[31]	SD	187365	Mixed*	GLGC	Willer et al	2013	24097068
LDL-C[31]	SD	173082	Mixed*	GLGC	Willer et al	2013	24097068
HDL-C[31]	SD	187167	Mixed*	GLGC	Willer et al	2013	24097068
C-reactive protein[32]	SD	204402	European	CIWG	Ligthart et al	2018	30388399
Procalcitonin[33]	SD	3301	European	NHSBT	Sun et al	2018	29,875,488

Notes: *Thirty-seven out of forty-five studies primarily involved participants of European descent.

Abbreviations: BF% was body fat percentage; BMI, body mass index; CIWG, Cohorts for Heart and Aging Research in Genomic Epidemiology Consortium (CHARGE) Inflammation Working Group; COGENT, Cognitive Genomics Consortium; DBP, diastolic blood pressure; EGG, Early Growth Genetics Consortium; GIANT, Genetic Investigation of Anthropometric Traits; GLGC, Global Lipids Genetics Consortium; GSCAN, GWAS & Sequencing Consortium of Alcohol and Nicotine use; GWAS, genome-wide association study; HDL-C, high-density lipoprotein cholesterol; ICBP, International Consortium of Blood Pressure; LDL-C, low-density lipoprotein cholesterol; MAGIC, Meta-Analyses of Glucose and Insulin-related traits Consortium; MR, Mendelian randomization; NA, not available; NHSBT, National Health Service Blood and Transplant; PGC, Psychiatric Genomic Consortium; SBP, systolic blood pressure; SSGAC, Social Science Genetic Association Consortium; Two-hour glucose was measured after an oral glucose challenge; WHR, waist-to-hip ratio.

The genetic instrumental variables associated with intelligence were derived from a meta-analysis of 14 independent epidemiological cohorts comprising individuals of European ethnicities. Intelligence was primarily assessed using various neurocognitive tests. The intelligence GWAS had a sample size of 269,867 individuals and analyzed 7,276,181 single nucleotide polymorphisms (SNPs).[9] The education-related raw genetic instrumental variables were derived from a study on the years of schooling of 1,131,381 Europeans conducted by the Social Science Genetics Association. Similarly, the cognition-related raw genetic instrumental variables were obtained from a meta-analysis on cognitive performance scores of 257,841 Europeans conducted by the Cognitive Genomics Consortium and the UK Biobank.[10] However, for this study, the genetic instrumental variables associated with noncognitive education and cognition were derived from a re-analysis of these studies using genomic structural equation modeling, participants from 23andMe were excluded as well. This is because previous research has shown that success in school and life depends not only on cognitive skills but also on noncognitive skills which have different genetic variations influencing educational attainment. The GWAS for noncognitive education included a sample size of 510,795 individuals and analyzed 7,305,956 SNPs, while the GWAS for cognition had a sample size of 257,700 individuals and analyzed an identical number of SNPs.[11]

The raw genetic instrumental variables for the outcome of urinary tract or kidney infection were derived from data obtained from the UK Biobank (https://www.ukbiobank.ac.uk/), a study that enrolled over half a million individuals aged 40 to 69 in the United Kingdom between 2006 and 2010. This comprehensive research initiative collected physical measurements, lifestyle information, medical history records, as well as conducted extensive analysis on blood, urine, and saliva samples. Additionally, long-term health follow-up was performed. However, the genetic instrumental variables utilized in this study were the data that underwent Firth logistic regression test for correction by a novel machine-learning method called REGENIE, based on UK Biobank data. This methodology is highly compatible with distributed computing frameworks and offers excellent accuracy and computational advantages. The GWAS for urinary tract or kidney infection included a sample size of 397,867 individuals and analyzed 11,037,343 SNPs.[19]

In this study, we examined 28 potential variables that may mediate the causal relationship between noncognitive education and urinary tract or kidney infection. These variables encompassed physical traits (body mass index [BMI],[20] waist-to-hip ratio [WHR],[22] waist circumference,[22] body fat percentage [BF%],[23] childhood obesity[24]), smoking and drinking habit (smoking initiation, age of smoking initiation, smoking heaviness, alcohol drinking, coffee intake),[21] psycho-related traits (neuroticism,[25] depressive symptoms,[25] major depression,[26] bipolar disorder,[27] schizophrenia,[28] anxiety, sleeping disorders), blood pressure (systolic blood pressure [SBP], diastolic blood pressure [DBP]),[29] glucose related traits (fasting insulin, fasting glucose, two-hour glucose),[30] lipid traits (triglycerides, total cholesterol, low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein cholesterol [HDL-C]),[31] and infective biomarkers (C-reactive protein,[32] procalcitonin[33]). All biochemical parameters have been standardized in the initial GWAS study. The process of mediating factor analysis comprises three sequential steps, as shown in Figure 2. In the first step, we assessed the unidirectional causal effects of noncognitive education on candidate mediating variables; subsequently, we examined the unidirectional causal effects between candidate mediating variables and urinary tract or kidney infection; finally, we scrutinized the significant mediating influence of mediating variables in the causal relationship between noncognitive education and urinary tract or kidney infection.

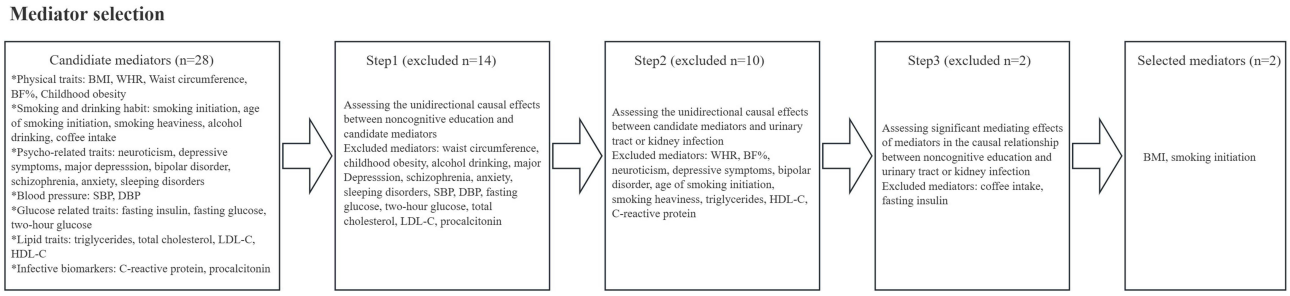

Figure 2 Process of mediator selection.

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MR Analysis Statistical Method

All MR analyses in this study were performed in R software (version 4.4.1; the R Foundation for Statistical Computing, Vienna, Austria). The R packages utilized include "TwoSampleMR", "ieugwasr", "MRPRESSO", "MendelianRandomization", "MVMR", "RMediation", "ldscr" and "forestploter". These packages can be obtained from GitHub or Comprehensive R Archive Network (CRAN).

The Selection of Instrumental Variables

The SNPs utilized in this study exhibited a robust association with exposure (P<5e-8) and successfully passed the linkage disequilibrium (LD) assessment ($r^2 < 0.001$; distance threshold > 10,000kb). The use of a strongly linked SNP (LD > 0.8) as a proxy SNP is recommended when no corresponding SNP is identified in the outcome GWAS data. The exposure and outcome data were harmonized to eliminate the palindrome structure, while the allele frequency of the palindrome was used for infer the positive chain alleles. Subsequently, the harmonized data underwent Steiger directivity test, which ensuring unidirectional causality between exposure and outcome by analyzing the strength of association between genetic instrumental variables and both exposure and outcome. Simultaneously, we computed the F-statistic to assess the validity of instrumental variables. Generally, an F-statistic value below 10 indicates weak instrumental variables.[34] The presence of weak instrumental variables may result in false positive test outcomes. To obtain a more reliable estimate of the causal effect, we employed a random phenotypic covariance matrix and minimized heterogeneity using the Q statistic for correction testing in MVMR.[35]

UVMR and MVMR Analyses

The random effect model is analyzed in UVMR and MVMR using three methods: inverse variance weighted (IVW), weighted median, and MR-Egger. Among these methods, the IVW method is the primary calculation approach, requiring all SNPs to adhere to the three fundamental assumptions of MR and exhibiting the lowest tolerance for horizontal pleiotropy. The weighted median method can yield unbiased results when the MR assumptions is satisfied by more than 50% of valid SNPs.[36] However, the MR-Egger method allows for 100% of SNPs to not satisfy the three assumptions of MR while demonstrating the highest tolerance for horizontal pleiotropy.[37] We computed the Q statistic value to assess heterogeneity among the instrumental variables, although the random effects model can tolerate some degree of heterogeneity. We employed the intercept of MR-egger to evaluate horizontal pleiotropy in MR, and MR-PRESSO test was utilized to examine whether any outliers influence horizontal pleiotropy. Scatter plots and funnel plots were plotted for visualizing sensitivity analyses. P<0.05 indicates statistical significance. When the direction of the statistically significant results is consistent and the sensitivity analysis reveals no statistically significant horizontal pleiotropy in the absence of outliers, we consider the IVW method results as primary causal evidence. The odds ratio (OR), association coefficient β, proportion, and their 95% confidence intervals (CI) demonstrate the causal effect.

Two-Step Mediation MR Analyses

We employed two-step unidirectional UVMR to evaluate the mediating factors, thereby mitigating the bias associated with weak instrumental variables.[38] By conducting UVMR on the causal relationship between noncognitive education and the mediating variables, we obtained the association coefficient β1. Subsequently, through further UVMR on the unidirectional causal relationship between the mediating variables and urinary tract or kidney infection, we derived the association coefficient β2, which represents the strength of mediation effect as β1 xβ2. The standard errors (SEs) of this mediation effect were estimated using the Delta method.[39] Finally, we quantified the proportion of mediating effect as β1 xβ2 divided by total β from UVMR of noncognitive education on urinary tract or kidney infection.

Table 2 Genetic Correlation Between Intelligence, Noncognitive Education, Cognition and Urinary Tract or Kidney Infection

Trait	Mean Chi-square	Lambda GC	Intercept	Ratio	H2_Observed	Rg	P value
Intelligence	2.06	1.74	1.08	7.79e-02	0.178	−0.338	1.58e-14
Noncognitive Education	1.58	1.46	1.02	4.29e-02	5.35e-02	−0.218	2.45e-06
Cognition	2.04	1.72	1.05	4.80e-02	0.189	−0.330	2.78e-12
Urinary tract or kidney Infection	1.09	1.08	1.01	0.144	9.42e-03	NA	NA

Notes: H2_observed was genetic contribution of single nucleotide polymorphisms; Rg was correlation coefficient between the corresponding exposure and urinary tract or kidney infection as outcome; NA, not available.

Results

Total Causal Relationship Between Intelligence, Noncognitive Education, Cognition and Urinary Tract or Kidney Infection

The LDSC analysis revealed that the SNPs accounted for a genetic contribution of 0.178, 5.35e-02, 0.189, and 9.42e-03 to intelligence, noncognitive education, cognition, and urinary tract or kidney infection. Furthermore, the genetic correlation coefficients between intelligence, noncognitive education, cognition and urinary tract or kidney infection were found to be −0.338 (P=1.58e-14), −0.218 (P=2.45e-06), and −0.330 (P=2.78e-12) respectively. The results of LDSC analysis are presented in Table 2. After conducting LD assessment, removing palindrome structure through exposure and outcome harmonization, and performing the Steiger directionality test, a total of 114 SNPs showing significant correlation with intelligence, 44 SNPs associated with noncognitive education, and 114 SNPs related to cognition were identified. The intensity F-statistic for the genetic instrumental variables of intelligence was 40.942, while that for the genetic instrumental variables of noncognitive education was 38.317, and for the cognition genetic instrumental variables it was 44.115. All F-statistics exceeding 10 indicated a strong correlation between the selected SNPs and exposure. The results of the three exposures in UVMR analysis using IVW method were statistically significant and consistent with other statistically significant methods, indicating that for 1-SD unit increase in intelligence, the OR of urinary tract or kidney infection decreased to 0.841 (95% CI: 0.743 to 0.952). Additionally, each 1-SD higher of noncognitive education years was associated with a decrease in the OR to 0.920 (95% CI: 0.858 to 0.986), while each 1-SD increase of cognition was associated with a decrease to 0.892 (95% CI: 0.850 to 0.935). In the sensitivity analysis, significant heterogeneity was observed in the genetic instrumental variables of intelligence (Q:152.451, P=0.008) and noncognitive education (Q:60.538, P=0.040) for the outcome of urinary tract or kidney infection, while no significant heterogeneity was found in cognition (Q:128.083, P=0.157). There were no statistically significant differences in the intercepts of the MR-egger models, indicating an absence of significant horizontal pleiotropy in all exposures. The MR-PRESSO test did not identify any outliers among the genetic instrumental variables for the three exposure factors. The UVMR results are presented in Figure 3 and Table S2. Figure 4 displays scatter plots of three statistical analysis methods for each exposure, as well as funnel plots of heterogeneity analysis for each exposure.

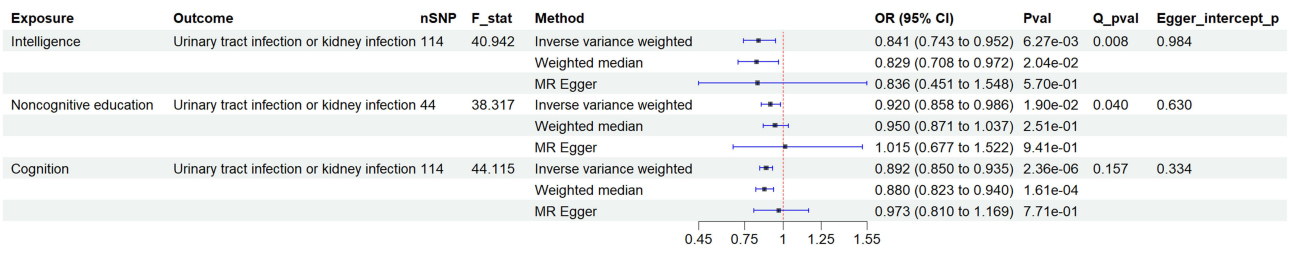

Figure 3 Summary of results of UVMR and forest plot.

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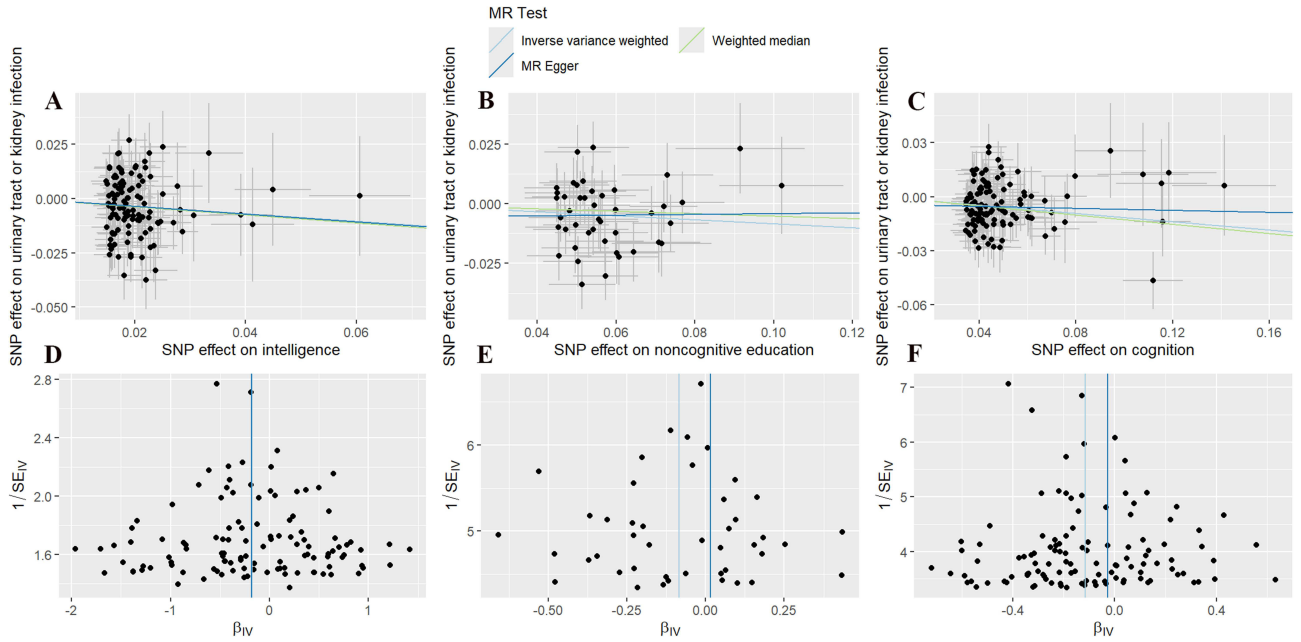

Figure 4 (**A**), (**B**), and (**C**) represent the scatterplots of intelligence, noncognitive education, and cognition on urinary tract or kidney infection in UVMR framework. (**D**), (**E**), and (**F**) represent the funnel plots for SNPs of intelligence, noncognitive education, and cognition. Each plot includes regression lines generated using three different statistical methods.

Independent Causal Relationship Between Intelligence, Noncognitive Education, Cognition and Urinary Tract or Kidney Infection

The exposures were subjected to mutual adjustment analysis using IVW method primarily within the framework of MVMR. In the adjustment model for intelligence and noncognitive education, intelligence was significantly associated with 131 SNPs (F-statistic=27.174), while noncognitive education showed significant association with 31 SNPs (F-statistic=10.074)., these genetic instrumental variables exhibited a robust correlation with exposure. Each 1-SD increase in intelligence reduced the OR of urinary tract or kidney infection to 0.800 (95% CI: 0.716 to 0.895), while 1-SD higher in noncognitive education years reduced the OR to 0.929 (95% CI: 0.867 to 0.996). In the adjustment model for cognition and noncognitive education, cognition was found to be associated with 110 SNPs (F-statistic = 21.554), whereas noncognitive education showed association with 34 SNPs (F-statistic =10.644), genetic instrumental variables also demonstrated a strong relationship with exposure. Increasing cognition by 1-SD decreased the OR of urinary tract or kidney infection to 0.881 (95% CI: 0.838 to 0.925), while increasing 1-SD unit in noncognitive education years reduced it to 0.933 (95% CI: 0.874 to 0.995). These findings suggested that noncognitive education has an independent causal effect on urinary tract or kidney infection regardless of intelligence and cognition. However, in the adjustment model of intelligence and cognition, the genetic instrumental variables associated with them exhibited a weak correlation, and the IVW method results of MVMR analysis did not reach statistical significance. In the combined adjustment model encompassing intelligence, noncognitive education, and cognition, the genetic instrumental variables also displayed a weak correlation, and the results of MVMR analysis were not statistically significant. These findings suggest that intelligence or cognition represented non-independent causal effect on urinary tract or kidney infection. The genetic instrumental variables exhibited heterogeneity in the adjustment model for intelligence and noncognitive education (Q:209.989, P=0.003), but not in those adjustment for cognition and noncognitive education (Q:150.858, P=0.198). The intercept of the MR-Egger did not show significant statistic difference in these two models, indicating no apparent horizontal pleiotropy. Additionally, no outliers were detected by the MR-PRESSO test. The MVMR results are presented in Figure 5 and Table S3.

Exposure	Outcome	nSNP	F_stat	OR (95% CI)	Pval	Q_pval	Egger_intercept_p
Intelligence, unadjusted	Urinary tract infection or kidney infection	114	40.942	0.841 (0.743 to 0.952)	6.27e-03	0.008	0.984
Intelligence, adjusted for noncognitive education		131	27.174	0.800 (0.716 to 0.895)	9.29e-05	0.003	0.651
Intelligence, adjusted for cognition		122	0.531	1.347 (0.744 to 2.438)	3.25e-01	0.049	0.285
Intelligence, adjusted for noncognitive education and cognition		114	0.433	1.076 (0.595 to 1.945)	8.10e-01	0.058	0.219
Noncognitive education, unadjusted	Urinary tract infection or kidney infection	44	38.317	0.920 (0.858 to 0.986)	1.90e-02	0.040	0.630
Noncognitive education, adjusted for intelligence		31	10.074	0.929 (0.867 to 0.996)	3.70e-02	0.003	0.651
Noncognitive education, adjusted for cognition		34	10.644	0.933 (0.874 to 0.995)	3.46e-02	0.198	0.636
Noncognitive education, adjusted for intelligence and cognition		30	4.135	0.944 (0.881 to 1.013)	1.08e-01	0.058	0.219
Cognition, unadjusted	Urinary tract infection or kidney infection	114	44.115	0.892 (0.850 to 0.935)	2.36e-06	0.157	0.334
Cognition, adjusted for intelligence		109	0.508	0.785 (0.602 to 1.023)	7.30e-02	0.049	0.285
Cognition, adjusted for noncognitive education		110	21.554	0.881 (0.838 to 0.925)	4.78e-07	0.198	0.636
Cognition, adjusted for intelligence and noncognitive education		106	0.414	0.852 (0.653 to 1.112)	2.39e-01	0.058	0.219

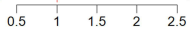

Figure 5 Summary of IVW method results of MVMR and forest plot.

The Effect of Mediators in the Causal Relationship Between Noncognitive Education and Urinary Tract or Kidney Infection

In the analysis of 28 candidate mediators, we initially performed a series of UVMR analyses with noncognitive education as exposure and the candidate mediators as outcomes. We excluded 14 mediators that did not show statistical significance, including waist circumference, childhood obesity, alcohol drinking, major depression, schizophrenia, anxiety, sleeping disorders, SBP, DBP, fasting glucose, two-hour glucose, total cholesterol, LDL-C and procalcitonin. Subsequent UVMR analyses was conducted with candidate mediators as exposures and urinary tract or kidney infection as outcome. We excluded 10 mediating factors that were not statistically significant, including WHR, BF%, neuroticism, depressive symptoms, bipolar disorder, age of smoking initiation, smoking heaviness, triglycerides, HDL-C and C-reactive protein. The remaining four mediators were analyzed for their mediating effects using the Delta method. However, coffee intake and fasting insulin did not reach statistical significance and were therefore excluded from further analysis. Finally, BMI and smoking initiation were selected as significant mediating factors in our study, their two-step UVMR results are presented in Tables 3 and 4. The two-step UVMR results for all potential mediators are summarized in Table S4 and Table S5. The final analysis revealed that BMI accounted for 12.1% (β: −0.010; 95% CI: −0.019 to −0.001; P=0.022) of the mediation effect in the causal relationship between noncognitive education and urinary tract or kidney infection, while smoking initiation accounted for 14.7% (β: −0.012; 95% CI: −0.023 to −0.001; P=0.030), The relevant results are presented in Table 5 and Table S6.

Table 3 UVMR Assessing the Causal Association Between Noncognitive Education and Selected Mediator

Mediator	Method	No of SNPs	β	0R (95% CI)	P value
BMI	IVW	37	−0.042	0.958 (0.927 to 0.992)	1.42e-02
	Weighted Median	37	−0.049	0.953 (0.930 to 0.976)	8.31e-05
	MR Egger	37	0.148	1.159 (0.931 to 1.443)	0.19
Smoking initiation	IVW	45	−0.062	0.940 (0.904 to 0.977)	1.78e-03
	Weighted Median	45	−0.041	0.960 (0.928 to 0.991)	1.32e-02
	MR Egger	45	0.175	1.191 (0.957 to 1.482)	0.12

Abbreviations: BMI was body mass index; IVW, inverse variance weighted; MR, Mendelian randomization; OR, odds ratio; SNPs single-nucleotide polymorphisms; UVMR, univariable Mendelian randomization.

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Table 4 UVMR Assessing the Causal Association Between Selected Mediator and Urinary Tract or Kidney Infection

Mediator	Method	NO of SNPs	β	0R (95% CI)	P value
BMI	IVW	446	0.239	1.270 (1.183 to 1.363)	3.79e-11
	Weighted Median	446	0.152	1.164 (1.042 to 1.301)	7.16e-03
	MR Egger	446	0.055	1.056 (0.880 to 1.269)	0.56
Smoking initiation	IVW	72	0.197	1.218 (1.079 to 1.375)	1.44e-03
	Weighted Median	72	0.140	1.150 (0.982 to 1.347)	0.08
	MR Egger	72	0.520	1.682 (0.901 to 3.139)	0.11

Abbreviations: BMI was body mass index; IVW, inverse variance weighted; MR, Mendelian randomization; OR, odds ratio; SNPs single-nucleotide polymorphisms; UVMR, univariable Mendelian randomization.

Table 5 MR Estimates of Selected Mediator in the Causal Association Between Noncognitive Education and Urinary Tract or Kidney Infection

Mediator	β (95% CI)	Proportion Mediated (95% CI)	P value
BMI	−0.010 (−0.019 to −0.001)	12.1% (1.8% to 22.4%)	0.022
Smoking initiation	−0.012 (−0.023 to −0.001)	14.7% (1.4% to 28.0%)	0.030

Abbreviations: BMI was body mass index; MR, Mendelian randomization.

Discussion

Through this MR study, we have discovered that intelligence, noncognitive education and cognition exhibited negative causal effects on the occurrence of urinary tract or kidney infection. Furthermore, we have found that the causal effect of intelligence and cognition on urinary tract or kidney infection is not independent of each other, while the causal effect of noncognitive education on urinary tract or kidney infection is independent of intelligence and cognition. Specifically, for every 1-SD increase in noncognitive education years, there was an 8% decrease in the risk of urinary tract or kidney infection. Amongst 28 potential mediating factors examined in our study, both BMI and smoking initiation were identified as effective mediators with BMI accounting for a mediation role of 12.1% and smoking initiation accounting for a mediation role of 14.7%.

The previous GWAS have demonstrated bidirectional associations between intelligence, education, and cognition.[9] However, the current study suggests that noncognitive skills encompassing motivation, curiosity, persistence, and self-control exert distinct influences on educational attainment compared to cognitive abilities. These noncognitive skills play a significant role in shaping future socioeconomic achievements, mental behaviors, and health outcomes.[11] In a systematic review examining the relationship between noncognitive skills and academic achievement, it was found that higher levels of perceived stress are typically associated with lower academic performance, while greater conscientiousness, academic resilience, and perseverance tend to correlate with improved academic outcomes.[40] A two-sample MVMR study revealed that both intelligence and education exert potential influences on individuals' health and social well-being in later life, with education exhibiting a more pronounced direct impact on health compared to intelligence.[41] Another MVMR study demonstrated the causal effect of education on blood pressure, independent of intelligence and cognition.[42] Furthermore, our study also demonstrated the independent effects of noncognitive education on outcome related to urinary tract or kidney infection. Observational studies have demonstrated that enhancing educational attainment can significantly decrease the prevalence of UTIs,[43,44] while surveys have revealed notable disparities in disease awareness and access to health education between women afflicted with UTIs and those without.[45] Our study further expands upon these findings by elucidating the causal impact of noncognitive education on urinary tract or kidney infection through the lens of genetic variation. Previous research has demonstrated that cognitive dysfunction is linked to the dysregulation of multiple molecular signaling pathways in circulating exosomes and monocytes, which results in elevated serum levels of interleukin-6, TNF-alpha, and MCP-1/CCL2. This

suggests a heightened inflammatory response during acute infection.[8] Cross-sectional study has demonstrated a significant association between cognitive dysfunction and overactive bladder.[46] Symptoms such as nocturnal urination, urgency incontinence, and urinary incontinence may elevate the risk of UTIs. Meta-analysis of twin studies has demonstrated a substantial heritability of cognitive function.[47] While most cognitive tests, such as inductive and deductive reasoning abilities, along with the acquisition of declarative knowledge, contribute to the explanation of general intelligence, there exist specific assessments designed to evaluate distinct aspects of cognitive functioning. However, even polygenic scores fail to fully account for the complete heritability of intelligence.[48] This observation may elucidate why intelligence and cognition exhibit a correlated rather than independent influence within this study. Through biogenetic studies, it has been discovered that noncognitive functional genes influencing educational attainment are extensively enriched in brain neurons, and the composition of brain tissue is similar to that of cognitive functional genes. However, disparities exist in terms of gray matter volume within the brain,[11] which may elucidate the independent causal impact of noncognitive education observed in this study.

Additionally, we conducted an examination of the mediating role played by 28 potential factors in the causal relationship between noncognitive education and urinary tract or kidney infection. These factors encompassed physiological characteristics, lifestyle habits, mental state, basic vital signs, biochemical indicators, and other relevant aspects. Ultimately, the mediating effect of BMI and smoking initiation was found to be statistically significant in this study. In line with the findings of this study, another MR study involving 101,447 participants investigating the association between BMI and various infections revealed a consistent linear causal relationship specifically for UTIs.[49] An observational study has also indicated that obesity independently contributes to the risk of UTIs particularly in males.[50] This study extends the existing evidence by demonstrating that lower levels of noncognitive education are associated with an increased BMI, thereby elevating the risk of UTIs. However, no significant mediating effect was observed for other obesity-related traits such as waist circumference, WHR, BF%, and childhood obesity. Recent study has demonstrated male with similar BMI exhibit comparable urinary microbiome compositions. However, there are significant differences in the abundance of Corynebacterium, Staphylococcus, and Streptococcus among men classified as healthy weight, overweight, and obese.[51] We also discovered that while smoking initiation played a significant role as a mediating factor, the heaviness of smoking and age of smoking initiation did not exhibit substantial mediating effects. This suggests that lower levels of noncognitive education are associated with an increased susceptibility to smoking, and once initiated, smoking can potentially contribute to urinary tract or kidney infection. GWAS on susceptibility to upper UTIs further corroborated these findings by identifying smoking as a potential risk factor.[52] The combustion of cigarettes generates reactive oxygen species, and the resulting oxidative stress can trigger the activation of signaling cascades within epithelial cells. These signaling pathways encompass mitogen-activated protein kinase (MAPK), nuclear factor κB (NF-κB), signal transducer and activator of transcription (STAT), and activator protein-1 (AP-1), which play crucial roles in the regulation of inflammation, cell cycle progression, and the expression of various genes.[53] These mechanisms may account for the impact of smoking on UTIs. The mediating role of alcohol and coffee consumption was not found to be significant in our study, while the association between these factors and such infections still lacks convincing evidence from randomized controlled trials. In fact, the relationship between alcohol consumption and health outcomes remains subject to extensive debate.[54]

The GWAS identified genetic variants in noncognitive education that were significantly associated with an increased susceptibility to multiple psychiatric disorders,[11] a finding which was further corroborated by this study. Utilizing a two-step MVMR mediation analysis, we observed a significant positive correlation between noncognitive education and bipolar disorder, while no statistically significant causal relationship was found between bipolar disorder and urinary tract or kidney infection. Similar to the findings of another MR study, we also observed a positive causal association between major depression and UTIs,[55] while no statistically significant evidence was found for a causal relationship between noncognitive education and major depression. Although UVMR revealed a negative causal relationship between noncognitive education and depressive symptoms, the limited availability of valid genetic instrumental variables for depressive symptoms prevents further statistical elucidation of the causality underlying urinary tract or kidney infection. In future studies, expanding the study population and exploring additional genetic loci through GWAS for depressive symptoms will facilitate the identification of more genetic instrumental variables related to UTIs. Moreover, there was no significant causal association detected between genetic variations in noncognitive education and blood pressure or blood glucose levels. Regarding lipids, despite a negative correlation with triglycerides and a positive correlation with HDL-C,

no significant causal relationship was observed between genetic variations in various lipid-related indicators and urinary tract or kidney infection. It is worth noting that C-reactive protein and procalcitonin are considered biomarkers of various infections, exhibiting high sensitivity to infection but low specificity to disease.[56,57] This study revealed a negative causal effect of genetic variation in noncognitive education on C-reactive protein levels, while no significant one-way causal effect of C-reactive protein on urinary tract or kidney infection was observed. These findings further suggest that infection biomarkers do not act as mediators between noncognitive education and urinary tract or kidney infection.

This study presents novel evidence supporting the development of preventive strategies for urinary tract or kidney infection. In addition to cognitive limitations observed in diverse populations, educational attainment is more likely to improve post-learning, and enhancing noncognitive abilities through education is particularly crucial in reducing the risk of UTIs. Given the unequal distribution of educational resources across different environments, maintaining a healthy weight and quitting smoking play pivotal roles in improving UTIs.

The present study represents the first attempt to investigate the causal impact of genetic variation in intelligence, education, and cognition on the occurrence of urinary tract or kidney infection. The study possesses several strengths. Firstly, by utilizing education attainment as an exposure variable, we have employed data that effectively eliminates the influence of cognitive function on education level while emphasizing the role of noncognitive abilities in education outcomes. Secondly, the outcome data used in this study were not simply derived from the original data of UK Biobank. Instead, they underwent processing using a novel machine learning method called REGENIE that enables more efficient handling of quantitative and binary phenotypic whole-genome regression models. And the Firth correction was applied to effectively control Class 1 errors associated with binary traits. Thirdly, we conducted genetic correlation analysis between exposure traits and outcome using LDSC, and employed the F-statistic to validate the robust association between SNPs and exposure. We further validated heterogeneity and horizontal pleiotropy through sensitivity analysis. Additionally, we utilized a random phenotypic covariance matrix with minimized Q statistic to mitigate bias arising from weak instrumental variables in MVMR, thereby ensuring the reliability of our test results. The unidirectional mediating effect of 28 potential factors was assessed using SNPs identified via Steiger test. There are still several limitations in this study. Firstly, the samples included in the study all originate from European ancestry, however, there may exist genetic phenotypic variations among different geographical populations. Future studies should further validate the conclusions of this study by utilizing GWAS data from diverse populations to enhance generalizability. Secondly, although efforts have been made to select GWAS data from diverse research groups as correlation studies, it is inevitable that some sample overlap among these GWAS cannot be completely ruled out. Thirdly, persistent heterogeneity among SNPs might introduce certain biases in the test results. Fourthly, despite investigating 28 potential mediating factors, further exploration is required to identify other factors that potentially mediate the relationship between noncognitive education and urinary tract or kidney infection.

The present MR study revealed that enhancing intelligence, educational attainment, and cognition can effectively mitigate the risk of urinary tract or kidney infection. Notably, noncognitive abilities in education exert an independent causal influence on this relationship, while BMI and smoking initiation act as mediators. These findings provide valuable guidance for preventing urinary tract or kidney infection.

Abbreviations

BF%, Body fat percentage; BMI, Body mass index; DBP, Diastolic blood pressure; GWAS, Genome-wide association study; HDL-C, High-density lipoprotein cholesterol; IVW, Inverse variance weighted; LDL-C, Low-density lipoprotein cholesterol; MR, Mendelian randomization; MVMR, Multivariable Mendelian randomization; PRESSO, Pleiotropy residual sum and outlier; SBP, Systolic blood pressure; SNP, Single-nucleotide polymorphism; UTIs, Urinary tract infections; UVMR, Univariable Mendelian randomization; WHR, Waist-to-hip ratio.

Data Sharing Statement

The GWAS datasets analyzed during the current study are available from the IEU OpenGWAS project and GWAS Catalog, the corresponding GWAS ID are provided in Table S1. The R code is available from the corresponding author on reasonable request, and the contact way can get through by Email to xiongf23@sina.com.

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Disclosure

All the authors declare that there is no conflict of interest in this work.

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