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ORIGINAL ARTICLE

Causal effects of education on chronic kidney disease: a Mendelian randomization study

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ABSTRACT

Background. Poor socio-economic status, including low education attainment, has been reported in chronic kidney disease (CKD) patients. We aimed to investigate the causal effects of education attainment on the risk of CKD.

Methods. The study was an observational cohort study including Mendelian randomization (MR) analysis. First, the clinical association between education attainment years as the exposure and prevalent CKD Stages 3–5 as the outcome was investigated by multivariable logistic regression in 308 741 individuals 40–69 years of age from the UK Biobank. MR analysis was performed with a previously reported genetic instrument from a genome-wide association meta-analysis of education attainment. Two-sample MR was performed with summary statistics for CKD in 567 460 individuals with European ancestry in the CKDGen genome-wide association meta-analysis. The findings were replicated by allele score–based MR in 321 260 individuals of white British ancestry in the UK Biobank with quality-controlled genetic data.

Results. Higher education attainment was significantly associated with lower adjusted odds for CKD in the clinical analysis {>17 years versus <16 years, adjusted odds ratio [OR] 0.910 [95% confidence interval (CI) 0.849–0.975]}. The causal estimates obtained by the inverse variance method in the two-sample MR indicated that higher genetically predicted education attainment causally reduced the risk of CKD [OR 0.934 (95% CI 0.873–0.999)]. Allele score–based MR also supported that higher education attainment was causally linked to a decreased risk of CKD [adjusted OR 0.944 (95% CI 0.922–0.966)].

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Conclusion. The study suggests that higher education attainment causally reduces the risk of CKD development in the general population.

Keywords: chronic kidney disease, education, Mendelian randomization, socioeconomic status

INTRODUCTION

Chronic kidney disease (CKD) is a globally emerging morbidity with a large socio-economic burden [1]. CKD patients suffer from impaired quality of life and an increased risk of cardiovascular disease or even death. As the prevalence of CKD is increasing with global trends of aging and obesity, identifying modifiable risk factors to reduce CKD is an important public health issue.

The development of CKD is commonly associated with poor metabolic health, including obesity, hypertension, diabetes mellitus and dyslipidemia [2]. As metabolic disorders are closely linked to lifestyle and socio-economic factors, studies investigating the effect of socio-economic status on the risk of metabolic diseases or CKD have been performed [3, 4]. Among the related socio-economic factors, education attainment plays an important role in the development of various morbidities, including cardiovascular diseases [5]. Although a previous observational finding indicated that education attainment was also associated with the risk of incident CKD [3], direct evaluations of the causal effects of education attainment on CKD have rarely been performed. This is because education attainment is a socio-economic exposure factor that would be inappropriate for clinical trials and because the association between CKD and education attainment would likely be affected by numerous confounders.

Mendelian randomization (MR) is a useful tool to investigate the causal effects of a modifiable environmental factor on a complex disease [6]. As MR utilizes a genetic instrument, which is determined inborn and minimally affected by clinical confounding or reverse causation, the method can reveal causal estimates based on several assumptions. MR has been a popular method in recent epidemiologic studies along with the availability of large-scale genetic databases. MR also revealed the causal effects of education attainment on the development of cardiovascular diseases [5].

In this study we hypothesized that a higher education attainment level would have a causal effect on a decreased risk of CKD. We performed a cross-sectional clinical analysis, a summary-level data-based two-sample MR and an allele score–based MR with individual-level data from the UK Biobank to demonstrate the causal linkage between education attainment and the risk of CKD.

MATERIALS AND METHODS

Ethical considerations

The study was performed in accordance with the Declaration of Helsinki. The study was approved by the institutional review boards of Seoul National University Hospital (E-2007-049-1140) and the UK Biobank Consortium (53799). The summary statistics analysed in this study are available in the public domain and are distributed by the Social Science Genetic Association Consortium (SSGAC) and the CKDGen Consortium.

Clinical analysis

We first performed an observational cross-sectional cohort study with the UK Biobank data. The UK Biobank cohort is a population-scale cohort including >500 000 participants ages 40–69 years; data were obtained from 2006 to 2010 in the UK and include wide ranges of phenotypic and genetic data. Along with the collection of various demographic data and laboratory test results, the participants answered a touchscreen-based questionnaire asking about diverse environmental factors. Additional details about UK Biobank data collection have been described previously [7, 8].

In total, 502 505 individuals were available for enrollment in this study; we included those with available information for the baseline estimated glomerular filtration rate (eGFR) and identifiable education attainment, resulting in the inclusion of 308 741 individuals in the clinical analysis dataset (Figure 1). Those with unidentifiable education attainment were additionally inspected for clinical characteristics to report possible selection bias, and among those with available eGFR values, those who did not report education attainment status were likely to have lower median age, lower prevalence of metabolic disorders or related comorbidities and better income status (Supplementary data, Table S1).

Information about the exposure factor, education attainment years, was collected by asking the following question: 'At what age did you complete continuous full-time education?'. The participants could also choose 'never went to school', 'do not know' or 'prefer not to answer' and, as stated, those who did not provide an education attainment age were excluded from the study. As 16 and 17 years of age were the first and second tertile values for the exposure, respectively, we stratified the included individuals into education attainment groups: <16, 16–17 and >17 years. The divided subgroups also reflect the typical education levels in the UK, as the <16 years category includes those who could not complete the compulsory schooling and >17 years includes those who received tertiary education.

The study outcome was prevalent CKD Stages 3–5, determined by a baseline eGFR <60 mL/min/1.73 m^2 or a prevalent history of end-stage kidney disease. The baseline eGFR was calculated by serum creatinine levels measured by enzymatic methods using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [9]. A prevalent history of end-stage kidney disease was identified by self-reports or hospital admission data.

The observational association between education attainment and the prevalence of CKD Stages 3–5 was investigated by logistic regression analysis. Univariable and multivariable models were constructed and, as there was missing information in the collected covariates, results from a multiple imputed dataset obtained by both the chained equation method and a complete-case method are presented [10]. The other details of the collected covariates and statistical analysis in the observational analysis are described in the Supplementary data.

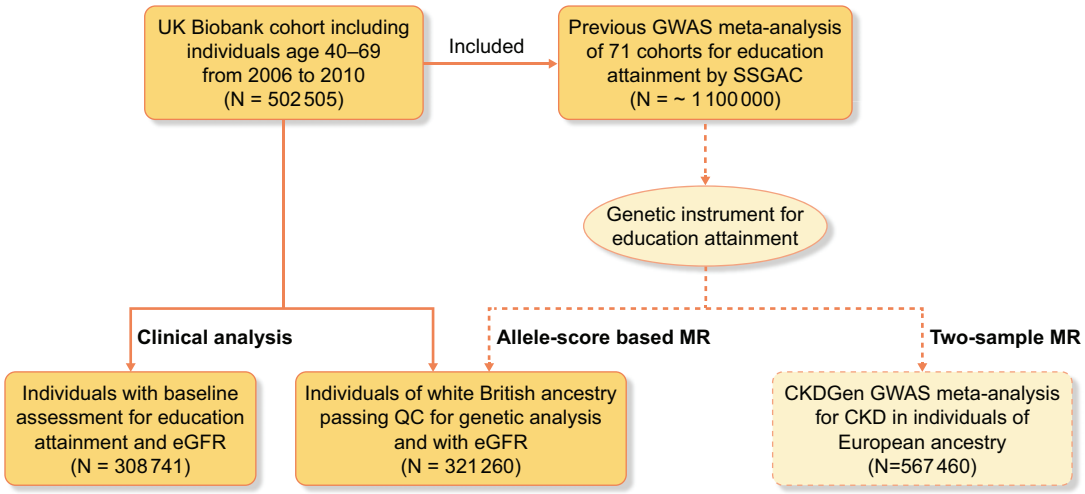

FIGURE 1: Study flow diagram. QC: quality control.

Genetic instrument

The genetic instrument for this study was a set of single-nucleotide polymorphisms (SNPs) associated with education attainment years identified by the SSGAC (https://www.thessgac.org/data) [11]. The genetic instrument included SNPs in linkage equilibrium ($R^2 < 0.1$) with a significant genome-wide ($P < 5 \times 10^{-8}$) association with education attainment years identified by a genome-wide association study (GWAS) of 1.1 million individuals of European ancestry. The study was a meta-analysis of 71 quality-controlled GWASs. The study reported 1271 independent SNPs in autosomal chromosomes, explaining 11–13% of the variance in education attainment and 7–10% of the variance in cognitive performance. The SNPs included variants related to neural communications and brain functions, further suggesting the phenotypic validity of the results. Additional details are available in the What previously published material?[11].

Two-sample MR with summary-level data

Two-sample MR was performed by using the independent summary statistics from the CKDGen Consortium [12]. The CKDGen Consortium performed the largest currently available genome-wide association meta-analysis of kidney function outcomes. We utilized the summary statistics for CKD from >500 000 individuals of European ancestry, which are provided by the CKDGen Consortium on a public website (https://ckdgen.imbi.uni-freiburg.de/). We identified the SNPs that overlapped with the SNPs included in the CKDGen data and disregarded the palindromic SNPs with intermediate allele frequencies [13], leaving 1211 SNPs in the implemented genetic instrument.

The main method for two-sample MR was the conventional fixed effects inverse variance–weighted method. As a sensitivity analysis, we implemented the penalized weighted median approach, which provides valid causal estimates even in the presence of invalid instruments [14]. Another sensitivity analysis was performed by MR-Egger regression with bootstrapped standard errors, providing a direct test for possible pleiotropy and pleiotropy-robust causal estimates [15]. Furthermore, we implemented MR-PRESSO [16], which identifies and corrects the effects of heterogeneous outliers among the instrument. The standard effect sizes from a standard deviation (SD) increase in genetically predicted education attainment years were presented. The above analysis was performed with the R package TwoSampleMR (R Foundation for Statistical Computing, Vienna, Austria) [17].

Allele score–based MR with individual-level data

To perform individual-level data-based MR with the UK Biobank data, we constructed a genetic analysis dataset including 337 138 white individuals of British ancestry who passed basic quality controls, who were not outliers regarding missing data or heterogeneity, without excess kinship and without sex chromosome aneuploidy (Figure 1). Additionally, those without baseline eGFR values were excluded, as that information was necessary to determine the CKD Stages 3–5 outcome, defined as in the clinical analysis, resulting in 321 260 individuals in the genetic analysis dataset.

We performed allele score–based MR and the allele scores for education attainment were calculated by multiplying the β effect sizes of the genetic instrument and the gene dosage matrix in PLINK 2.0 [18, 19]. The associations of the calculated polygenic allele scores and outcomes were assessed by logistic regression and adjusted for age, sex, genotype measurement batch and the first 10 principal components of the genetic information. An additional sensitivity analysis was performed by the two-stage residual inclusion method, also known as the control function estimator, to incorporate the effects from measured/unmeasured confounders [20]. As the residuals reflect the effects of measured/unmeasured confounders, the method was implemented to decrease bias due to possible horizontal pleiotropy and has also been used in previous MR studies [21, 22]. The sensitivity analysis included 216 151 individuals with available

information about phenotypic education attainment years from the genetic analysis dataset. We further tested the association between genetically predicted education attainment years and possible risk factors for CKD, including hypertension, diabetes mellitus, obesity and current smoking, by performing regression analysis.

RESULTS

Clinical analysis results

There were 96 177, 134 934 and 77 630 individuals with education attainment <16, 16–17 and >17 years, respectively (Table 1). Those in the <16 years group were relatively older and more frequently obese or current smokers than those in the other groups. The individuals had a higher Townsend deprivation index, indicating greater deprivation, and the proportion of the individuals with education attainment <16 years with household income <£18 000 was approximately more than double that of the other subgroups. However, the deprivation index was lower and income levels were higher in those in the >17 years group. In addition, those who had fewer education attainment years had a higher prevalence of hypertension, diabetes, cerebrovascular diseases and CKD Stages 3–5 than those with more education attainment years. The prevalence of CKD Stages 3–5 ranged from 2 to 4% among the study groups.

In the univariable analysis (Table 2), those in the 16–17 and >17 years groups had approximately half the risk of developing prevalent CKD Stages 3–5 as those in the <16 years group. After multivariable adjustment for clinical confounders, those in the >17 years group had significantly lower adjusted odds (~9%) of developing CKD Stages 3–5 than those in the <16 years group. The results were similar between the multiple imputation and complete-case methods.

Two-sample MR results

The causal estimates from the two-sample MR with CKD as the outcome from the CKDGen Consortium showed significant inverse causal effects between genetically predicted education attainment and the risk of CKD (Figure 2 and Table 3), i.e. those who were genetically predisposed to higher education attainment had a lower risk of CKD development, with standardized odds ratios (ORs) ranging from 0.89 to 0.94 according to MR. Only the MR-Egger regression yielded marginal causal estimates {OR 0.890 [95% confidence interval (CI) 0.758–1.045], P = 0.079} of the association between education attainment and CKD. However, the MR-Egger test for directional pleiotropy suggested the absence of unbalanced pleiotropy (P = 0.660). Although Cochran's Q-test indicated significant heterogeneity among the implemented SNPs (P < 0.001), the MR-PRESSO analysis, which identified and corrected the effects from outlier SNPs, still resulted in significant causal estimates,

Table 1. Clinical characteristics of the studied participants according to education attainment years

Clinical characteristics	Education attainment <16 years	Education attainment 16–17 years	Education attainment >17 years
Subjects, *n*	96 177	134 934	77 630
Age (years), median (IQR)	62 (58–66)	56 (49–63)	56 (48–62)
Sex, *n* (%)			
Female	51 117 (53)	76 209 (56)	42 989 (55)
Male	45 060 (47)	58 725 (44)	34 641 (45)
Body mass index (kg/m^2), median (IQR)	27.7 (25.1–30.9)	27.0 (24.4–30.2)	26.6 (24.0–29.7)
Obesity, *n* (%)	29 762 (31)	35 505 (26)	17 981 (23)
Waist circumference (cm), median (IQR)	93 (83–102)	90 (81–99)	89 (80–98)
Central obesity, *n* (%)	40 552 (42)	47 712 (35)	24 994 (32)
Smoking, *n* (%)			
Non-smoker	41 399 (43)	71 345 (53)	46 128 (60)
Ex-smoker	41 026 (43)	46 591 (35)	24 173 (31)
Current smoker	13 029 (14)	16 579 (12)	7126 (9)
Number of household members, median (IQR)	2 (2–2)	2 (2–3)	2 (2–3)
Townsend deprivation index, median (IQR)	−1.59 (−3.26–1.47)	−2.23 (−3.65–0.32)	−2.46 (−3.82 to −0.06)
Income level (£), *n* (%)			
<18 000	36 273 (49)	27 465 (24)	11 198 (17)
18 000–30 999	22 277 (30)	34 359 (30)	17 628 (26)
31 000–51 999	11 651 (16)	32 393 (28)	20 268 (30)
52 000–100 000	3881 (5)	17 449 (15)	15 399 (23)
>100 000	492 (1)	2387 (2)	3142 (5)
Number receiving treatment, median (IQR)	3 (1–5)	2 (0–4)	2 (0–3)
Number of prevalent illnesses	2 (1–3)	1 (0–3)	1 (0–3)
Hypertension, *n* (%)	30 294 (32)	27 110 (20)	14 526 (19)
Systolic BP (mmHg), median (IQR)	141.5 (129.5–154.5)	136.0 (125.0–149.0)	135.0 (124.0–148.0)
Diastolic BP (mmHg), median (IQR)	82.5 (76.0–89.0)	82.0 (75.5–89.0)	82.0 (75.0–89.0)
Diabetes mellitus, *n* (%)	7279 (8)	6654 (5)	3930 (5)
Haemoglobin A1c (mmol/L), median (IQR)	36.2 (33.7–39.0)	35.2 (32.7–37.8)	35.1 (32.6–37.7)
Angina, heart attack or stroke history, *n* (%)	10 643 (11)	6966 (5)	3349 (4)
eGFR (mL/min/1.73 m^2), median (IQR)	89.7 (78.8–95.9)	93.3 (83.4–100.9)	93.73 (84.0–101.2)
CKD Stages 3–5, *n* (%)	3801 (4)	2951 (2)	1488 (2)

BP: blood pressure; IQR: interquartile range.

Table 2. Clinical association between education attainment years and prevalent CKD Stages 3–5

Education attainment	Univariable model		Multivariable model, multiple imputation		Multivariable model, complete-case method	
	OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
SD increase (per 2.3 years)	0.804 (0.783–0.825)	<0.001	0.983 (0.960–1.006)	0.153	0.967 (0.939–0.996)	0.027
Categorized exposure						
<16 years	Reference		Reference		Reference	
16–17 years	0.543 (0.518–0.571)	<0.001	0.981 (0.931–1.033)	0.465	0.981 (0.925–1.040)	0.520
>17 years	0.475 (0.447–0.505)	<0.001	0.932 (0.874–0.994)	0.031	0.918 (0.852–0.990)	0.027

Multivariable model was adjusted for age, sex, hypertension history, systolic BP, diastolic BP, diabetes mellitus history, haemoglobin A1c level, history of cardiocerebrovascular disease (angina, heart attack or stroke), body mass index, waist circumference, smoking history (non-smoker, ex-smoker and current smoker), Townsend deprivation index and place of birth.

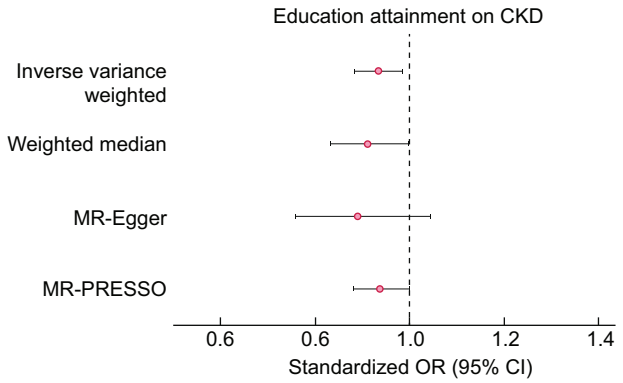

FIGURE 2: Two-sample MR results indicated higher education attainment causally reduces the risk of CKD development. Effect sizes were scaled to a 1 SD increase in the exposure.

Table 3. Causal estimates from the two-sample MR analysis

MR method	β	SE	P-value
Inverse variance weighted	−0.068	0.068	0.016
Weighted median method	−0.093	0.046	0.043
MR-Egger regression	−0.117	0.082	0.079
MR-PRESSO	−0.065	0.032	0.045

Causal estimates were scaled to an exposure of 1 SD unit. The Cochran's Q statistics indicated significant heterogeneity ($P < 0.001$) in the genetic instrument, so the MR-PRESSO analysis was performed correcting the effects from the outliers. The MR-Egger test for pleiotropy indicated an absence of significant unbalanced pleiotropy ($P = 0.860$).

indicating a protective effect of higher education attainment on the risk of CKD.

Allele score-based MR results

Among the UK Biobank genetic analysis dataset, 7503/321 260 (2.3%) participants had prevalent CKD. In the allele score–based MR, genetically predicted higher education attainment was significantly associated with a decreased risk of CKD in the age-, sex- and genotype-adjusted model (Table 4). The causal estimates were again significant after applying the two-stage residual inclusion method, with additional adjustment for possible effects from measured/unmeasured confounders. A 1 SD increase in the allele scores for education attainment was associated with a 5–6% decreased risk of CKD. When we assessed the allele scores for their associations with the possible CKD-related covariates (Table 5), higher genetically predicted education attainment was significantly associated with a decreased risk of hypertension, diabetes mellitus, obesity and current smoking. Furthermore, higher allele scores were significantly related to a higher income grade and number of household members and a lower Townsend deprivation index.

DISCUSSION

In this study, causal effects of higher education attainment on lower risk of CKD were identified by MR analysis. The clinical analysis supported the finding, with cross-sectional results indicating that CKD is inversely associated with education attainment. The study supports that higher education attainment may causally reduce the risk of CKD development in the general population.

Associations between socio-economic factors and CKD have been reported previously. Demographic data of CKD patients suggested that poor socio-economic status is relatively common in CKD patients when compared with those with normal kidney function [4]. Thus evidence indicating whether the risk of CKD can be reduced through the modification of socio-economic status, including education attainment, is warranted, as such evidence would advise for a public policy measure targeting the emerging global burden of CKD. In addition, in the nephrology field, a poor education level has been suggested as a risk factor for a higher incident risk of CKD, suggesting a potential direct effect of education on CKD [3]. However, as CKD usually occurs later in life, years after the completion of education, it is difficult to eliminate the effects of various confounders in the association between CKD and education. In contrast, as education attainment is a genetically trackable phenotype, MR has been suggested to reveal the causal effects of education attainment on complex diseases [5]. In this study with MR analysis, the causal effects of higher education attainment on decreased risk of CKD were demonstrated. Therefore, when considering a public policy to decrease the burden of CKD, poor education attainment should be considered as a causative factor for the risk of CKD in the general population.

As the genetic instrument is determined inherently, preceding any clinical confounders or outcomes, it is minimally affected by confounding effects or reverse causation and can assess the association between risk and a prevalent outcome [6]. Thus, utilizing genetic instruments as a proxy of phenotypic information has been suggested to reveal causal estimates in MR analysis. MR requires three assumptions to be fulfilled to

Table 4. Allele score–based MR results

	Main analysis		Two-stage residual inclusion analysis	
Result	Adjusted OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
1 SD increase in allele score	0.944 (0.922–0.966)	< 0.001	0.968 (0.942–0.994)	0.018

The outcome was CKD Stages 3–5 including 7503 cases in the main analysis. Causal estimates were from the model adjusted for age, sex, genotype measurement batch and the first 10 principal components of the genetic information. The residuals (the difference between observed education attainment years and predicted education attainment years) in the linear regression model of allele score exposure and education attainment trait outcome were calculated in 216 151 individuals with available information of the observed education attainment trait. The second regression with allele score exposure and CKD outcome additionally included the residuals as a covariate.

Table 5. Allele score–based MR results for the covariates

Covariates	Adjusted OR or exp(β) (95% CI)	P-value
Hypertension	0.913 (0.905–0.921)	<0.001
Diabetes mellitus	0.871 (0.856–0.885)	<0.001
Obesity	0.859 (0.852–0.866)	<0.001
Current smoking	0.833 (0.823–0.843)	<0.001
Income grade (ordinal)	1.162 (1.157–1.166)	<0.001
Townsend deprivation index (continuous)	0.861 (0.853–0.870)	<0.001
Number of household member (continuous)	1.018 (1.013–1.022)	<0.001

Allele scores for education attainment were regressed to the covariates. Causal estimates were from the model adjusted for age, sex, genotype measurement batch and the first 10 principal components of the genetic information.

identify causal effects of a genetically predicted trait: the genetic instrument should be strongly associated with the exposure phenotype of interest (the relevance assumption), the genetic instrument should affect the disease of interest through the exposure trait (the exclusion restriction assumption) and possible effects from horizontal pleiotropy, which is present when the genetic instrument is related to a confounder, should not bias the results (the independence assumption). Because genetic instruments have been robustly developed from a previous meta-analysis, the first assumption would have been met. Although a direct test for the restriction exclusion assumption is impossible, considering the previous observational findings and our clinical analysis results, education attainment was a plausible exposure that was related to the risk of CKD. The MR-Egger pleiotropy test and the two-stage residual inclusion analysis indicated that the presence of unbalanced horizontal pleiotropy would not have caused bias in our findings, suggesting the fulfillment of the third assumption.

Our allele score–based MR for other factors was to suggest possible mediators and mechanisms for the causal effect of education attainment on CKD. Identifying such mediators is important, as they may be the practical targets to reduce CKD risks in those with poor education attainment, as clinicians commonly encounter individuals who have already completed their education. The results indicate that education attainment may act through various pathways to affect CKD, and the factors would be interpreted to have a vertical pleiotropic effect rather than being confounders considering reasonable biological sequences. The results indicate that higher education attainment would result in decreased risks of traditional risk factors, including hypertension, diabetes, obesity and harmful habitual behaviors such as smoking; moreover, it was associated with a higher socio-economic status, deprivation index, number of household members and income level. Such effects have also been identified in previous MR studies regarding the effects of education attainment on coronary artery disease [5]. The suggested factors that are possibly in the middle of the downstream effect from education attainment on the risk of CKD (e.g. vertical pleiotropy) should be actively assessed in those with poor education attainment and at risk of kidney function impairment.

Our study has several limitations. First, the MR-Egger regression, which provides robust causal estimates independent of pleiotropy, did not demonstrate significant results. However, the method has lower statistical power than the other MR methods [15], and this might have led to the causal estimates not achieving statistical significance. Second, education attainment information in the UK Biobank is self-reported, so the possibility of measurement bias cannot be excluded in the clinical analysis. In addition, those not reporting the education attainment information had different characteristics from those with the information, so potential selection bias might have been present in the observational findings. However, as the genetic instrument was developed from more than a million individuals from multiple cohorts, the effects of such bias might not be critical. Third, clinical and allele score–based MR analyses were performed with data from the UK Biobank cohort, which may result in healthy volunteer bias, leading to a lower prevalence of CKD than in the general population of the UK [23]. However, the bias would have acted toward a null finding, so the limitation would not effect the positive findings in this study. Fourth, the allele score–based MR overlapped between the exposure and outcome assessments, similar to that in the previous GWAS of the genetic instrument obtained from the UK Biobank [24]. A potential bias toward an observational finding is possible in this setting; however, the two-sample MR with independent CKDGen Consortium data also validated our findings. Last, the study was performed with individuals of European ancestry, so the generalizability of the results to other ethnic populations is not clear.

In conclusion, this study supports that education attainment causally affects CKD. The risk of CKD may be actively evaluated in those with poor education attainment status, along with the risks of related metabolic disorders and socio-economic impairment. A policy to reduce the growing burden of CKD may consider education attainment as a causal factor that may be targeted by public interventions.

SUPPLEMENTARY DATA

Supplementary data are available at ckj online.

DATA AVAILABILITY STATEMENT

The data utilized in the study will be made available via the UK Biobank. The summary statistics are available online from the SSGAC and CKDGen Consortium.

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CONFLICT OF INTEREST STATEMENT

None declared.

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