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CLINICAL RESEARCH

Genetically Predicted Body Selenium Concentration and estimated GFR: A Mendelian Randomization Study

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Introduction: Selenium is a trace mineral that is commonly included in micronutrient supplements. The effect of selenium on kidney function remains unclear. A genetically predicted micronutrient and its association with estimated glomerular filtration rate (eGFR) can be used to assess the causal estimates by Mendelian randomization (MR).

Methods: In this MR study, we instrumented 11 genetic variants associated with blood or total selenium levels from a previous genome-wide association study (GWAS). The association between genetically predicted selenium concentration and eGFR was first assessed by summary-level MR in the chronic kidney disease(CKDGen) GWAS meta-analysis summary statistics, including 567,460 European samples. Inverse-variance weighted and pleiotropy-robust MR analyses were performed, in addition to multivariable MR adjusted for the effects of type 2 diabetes mellitus. Replication analysis was performed with individual-level UK Biobank data, including 337,318 White individuals of British ancestry.

Results: Summary-level MR analysis indicated that a genetically predicted 1 SD increase in selenium concentration was significantly associated with lower eGFR (−1.05 [−1.28, −0.82] %). The results were similarly reproduced by pleiotropy-robust MR analysis, including MR-Egger and weighted-median methods, and consistent even in the multivariable MR adjusted for diabetes. In the UK Biobank data, genetically predicted higher selenium concentration was also significantly associated with lower eGFR (− 0.36 [−0.52, −0.20] %), and the results were similar when body mass index, waist circumference, hypertension, and diabetes mellitus covariates were adjusted (−0.33 [−0.50, −0.17] %).

Conclusion: This MR study supports the hypothesis that higher genetically predicted body selenium is causally associated with lower eGFR.

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The kidney is a vital organ associated with various health parameters. Impairment of kidney function increases the risk of mortality and cardiovascular diseases.[1] Diverse factors may affect kidney function, including metabolic or nutritional components.

Selenium is an essential trace element that has several biologic functions. Humans primarily take up selenium from food, including yeast, nuts, meat, and fish, and recently, there have been various commercial oral supplements with selenium components.[2] These results suggest that selenium supplements have certain antioxidative effects by increasing the activity of glutathione peroxidase and glutathione reductase, which may be helpful for immunity.[3] However, excess selenium levels are associated with side effects, including gastrointestinal discomfort, and an extremely high dose of selenium may cause organ failure. In

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addition, previous studies suggested that selenium supplementation may cause a higher risk of glucose intolerance.[4]

The effects of selenium on kidney function have yet to be determined. A deficient level of selenium is common in chronic kidney disease patients,[5] and there have been reports that selenium may ameliorate kidney injury through its antioxidative effects.[3,6] On the other hand, selenium toxicity may adversely affect the kidney, and the kidney may suffer from excessive selenium, considering that selenium is primarily excreted via urine. Because the biologic effect of selenium is not fully understood, additional research is necessary to investigate the causal effect of body selenium concentration on kidney function parameters. MR is an analytical tool to investigate causal estimates from modifiable complex exposure to outcomes under specific assumptions.[7] MR is an instrumental variable analysis using one's genotype to predict exposure phenotype, and because genotype is fixed before birth, the causal estimates are minimally affected by confounding effects or reverse causation. MR has been widely performed in the medical literature, including in the nephrology field, to reveal various causal pathways.[8–11] In this study, we performed MR analysis utilizing a large-scale genetic database to investigate the causal estimates of body selenium concentrations on the eGFR. We hypothesized that genetically predicted body selenium concentrations would be causally related to changes in eGFR.

METHODS

Ethical Considerations

The study was approved by the institutional review boards of Seoul National University Hospital (No. E-2203-053-1303) and the UK Biobank consortium (application No. 53799). The institutional review boards waived the requirement for informed consent, because we studied anonymous databases that are available in the public. The study was performed in accordance with the Declaration of Helsinki. The current study was performed following the current guideline and the STROBE-MR checklist has been attached as supplemental material.[12]

Genetic Instruments for Body Selenium Concentration

We used the genetic variants associated with toenail and blood selenium concentrations as the genetic instrument for body selenium concentrations from a previous GWAS (Supplementary Table S1).[13] The GWAS meta-analysis for toenail selenium was performed on 4162 European samples, and that for blood selenium was performed on 5477 European individuals. Toenail and blood selenium levels are both valid markers for body selenium concentration, and the toenail concentration is considered to reflect an average level for a longer period. As in a previous MR study, we included a total of 11 independent genetic variants that showed a genome-wide significant association ($< 5E-8$) with toenail or blood selenium concentrations, pruned for linkage disequilibrium ($r2 < 0.3$).[14,15] The genetic variants all had F-statistics >10 and explained >4% of the variance in body selenium concentration in total in the original GWAS meta-analysis. Second, we performed sensitivity analysis manually excluding genetic variants associated with a potential confounding phenotype with genome-wide significance ($P < 5E-8$) identified from Phenoscanner. Because 2 of the genetic variants were also associated with blood homocysteine levels, which are adversely linked to the antioxidative pathway,[16] we performed MR analysis after removing the 2 genetic variants to robustly test the assumption of independence. Third, for more robust independence, we additionally trimmed the genetic instruments by disregarding 5 more genetic variants in the weak linkage disequilibrium state ($r2 > 0.01$). In the sensitivity analysis, the remaining 4 genetic variants not associated with blood homocysteine levels and in a robust independent ($r2 < 0.01$) state in the 1000 Genome data were instrumented.

MR Assumptions

MR requires 3 assumptions to be made to demonstrate causal effects.[7] First, the relevance assumption is that the genetic instrument should be closely related to the exposure. Because we included genome-wide significant genetic variants to genetically predict body selenium concentration, this assumption was considered to be met. Second, the independence assumption is that the genetic instrument should not be associated with other confounders. Although directly identifying all potential confounders is difficult, we performed sensitivity analysis after disregarding the genetic variants showing a strong association with blood homocysteine levels, because blood homocysteine was also reported to affect kidney function.[16] In addition, we performed pleiotropy-robust MR sensitivity analyses, which relaxes the independence assumption, to calculate pleiotropy-robust causal estimates. Third, the exclusion-restriction assumption is that the causal effect should occur through the exposure of interest. Although a direct test for this assumption is difficult, we performed median-based MR analysis, which relaxes this assumption for up to half of the genetic instruments, serving as a sensitivity analysis toward the third assumption.

Summary-Level Outcome Data–CKDGen

We used the CKDGen phase 4 GWAS meta-analysis for log-eGFR (based on serum creatinine levels) as the outcome data for summary-level MR analysis (Figure 1).[17] We used the results from 567,460 European ancestry samples to match the ethnic distribution with the exposure data. The data have been used in various MR studies because this provides one of the largest GWAS summary-level results regarding the eGFR trait.[9,10]

Summary-Level MR Analysis

The multiplicative random-effect inverse-variance weighted method was the main method for summary-level MR analysis following the current guidelines[18] The method allows balanced pleiotropic effects and is considered the valid method to assess the association between genetically predicted exposure by multiple genetic variants and outcome. We also performed pleiotropy-robust MR sensitivity analyses. MR-Egger regression with bootstrapped standard error was performed, as MR-Egger regression provides pleiotropy-robust causal estimates under the attainment of the InSIDE (Instrument Strength Independent of Direct Effect) assumption.[19] In addition, the MR-Egger intercept *P* value is a statistical measure to test the presence of directional pleiotropy, and a significantly different MR-Egger intercept from the other causal estimates indicates that a directional pleiotropic effect may be present. Next, we performed the weighted-median method, which can demonstrate valid causal estimates even though up to half of the instrumented genetic weights are invalid.[20] The method has a particular strength, because it relaxes the independence and exclusion-restriction assumption for up to half of the instruments.

When the main and pleiotropy-robust causal estimates all indicated significant (2-sided P value < 0.05) findings, the result was considered to reflect the presence of a causal effect. Single-instrument and leave-one-out analyses were performed to inspect whether there was a disproportionate effect from a single genetic variant.

Causal estimates were scaled to the standard deviation change in body selenium concentration toward the percentage change in eGFR. The summary-level MR analysis was performed by the TwoSampleMR package in R (version 4.2.0).[21]

Summary-Level Multivariable MR Analysis

We additionally performed multivariable MR analysis because body selenium concentration was reported to be causally linked to the risk of type 2 diabetes, which is also a well-known etiology for kidney function impairment.[14,22] The summary statistics for type 2 diabetes mellitus were extracted from a previous GWAS meta-analysis including 62,892 type 2 diabetes cases and 596,424 controls of European ancestry.[23] Multivariable MR analysis directly adjusted the genetic variant effects on a potential confounder.[24] The instruments of 11, 9, and 4 genetic variants were all tested for the causal estimates adjusted for the effects on diabetes. One genetic variant did not have available information and thus was disregarded from the instruments. The multivariable MR analysis was performed by the MVMR package.[24]

Individual-Level Outcome Data–UK Biobank

We included the UK Biobank data as a replication cohort, because the data are independent of the CKDGen samples (Figure 1). In addition, individual-level MR analysis was possible in the data, directly adjusting for clinical covariates. UK Biobank data are

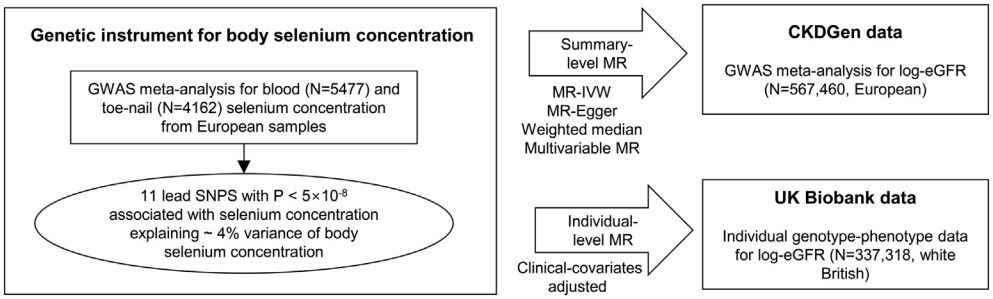

Figure 1. Study flow diagram. Genetic instrument for body selenium concentration was developed from a GWAS meta-analysis for blood and toenail selenium concentration. The genetic instrument was applied to summary statistics toward log-transformed eGFR values from the CKDGen GWAS meta-analysis including 567,460 European ancestry samples. Multiplicative random-effect inverse-variance weighted model and various pleiotropy-robust sensitivity analyses were performed. For replication, the genetic instrument was applied to UK Biobank data including 337,318 White British samples, and individual-level analysis based on polygenic score was performed. CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; GWAS, genome-wide association study; MR, Mendelian randomization; MR-IVW, multiplicative random-effect inverse-variance weighted.

one of the largest phenotype-genotype databases, including >500,000 individuals from the UK aged 40 years to 69 years. By providing deep genotyping data, the UK Biobank database has been widely used for various genetic analyses, including MR. The other details of the UK Biobank project have been published previously.[25,26]

As in our previous studies,[8–11,27] we screened 337,318 individuals of White British ancestry by passing a sample quality control filter. Those with sex chromosomal aneuploidy, excess kinship, or poor quality genotype data were excluded. Among them, 321,260 individuals had available serum creatinine-based eGFR values. We log-transformed the eGFR values as the UK Biobank data.

Individual-Level MR Analysis

We performed allele score analysis as the individual-level MR. Utilizing individual-level data has strength in that direct adjustment for clinical covariates and additional investigation toward other phenotypes were possible.

We calculated the allele score for body selenium concentration by multiplying the gene dosage matrix with the effect size betas of the genetic instruments by using PLINK 2.0 (version alpha 2.3).[28] The associations between genetically predicted body selenium concentrations by allele score and other traits were tested by linear regression analysis adjusted for age, sex, and 10 first genetic principal components.

We first assessed the association between allele score for selenium levels and log-transformed clinical covariates, including body mass index, systolic blood pressure, and diabetes mellitus, as the binary outcome because body selenium concentration was reported to be causally linked to metabolic disturbance, particularly to glucose intolerance.[14,22]

Next, we performed the main individual-level MR analysis of log-eGFR values. For sensitivity analysis, we additionally performed an analysis by clinical covariate adjustments, adjusted for body mass index, hypertension medication histories, systolic blood pressure and diabetes mellitus, self-reported days per week of moderate physical activity, days per week of alcohol consumption, and current smoking history. For missing values, complete-case analysis was performed. In addition, we performed sensitivity analysis as summary-level MR using genetic instruments after additional trimming.

Causal estimates were also scaled to the SD change in body selenium concentration toward the percentage change in outcome.

Post hoc Power Analysis

Post hoc power analysis for the main MR investigation was performed by online "mRnd" software (URL: https://shiny.cnsgenomics.com/mRnd/, last accessed 2022-09-01), and the power under 5% type 1 error rate was calculated. We used the causal estimates by the main MR method as the sizes of the causal and observational association between exposure and outcome. Because the variance of the eGFR values in phase 4 CKDGen data was unavailable, we used the information from the UK Biobank.

MR Analysis Toward Relevant Kidney Function-Related Characteristics

We validated our findings regarding the eGFR outcome in the meta-analysis of the CKDGen and the UK Biobank data by the summary-level MR analysis.[29] We additionally investigated CKD (eGFR <60 ml/min per 1.73 m^2 or relevant diagnostic codes) and urine albumin-to-creatinine ratio traits in the CKDGen and the UK Biobank data.[30] To test the causal estimates toward critical eGFR decrement, we performed summary-level MR toward the summary statistics provided by a recent GWAS meta-analysis[31] which investigated the rapidly decreasing eGFR outcome (>3 ml/min per 1.73 m^2 per year) and performed individual-level MR analysis toward the stage 4 or higher CKD (eGFR <30 ml/min per 1.73 m^2, end-stage kidney disease, or relevant ICD-10 diagnostic codes) in the UK Biobank data.

RESULTS

Characteristics of the Study Population

The samples from the CKDGen data for summary-level MR had a median age of 54 years; 50% of the samples were obtained from males; the median eGFR was 91.4 ml/min per 1.73 m^2; and the prevalence of CKD was 9%.

The samples of the UK Biobank data for individual-level MR analysis had a median age of 58 years old; 49% of the samples were obtained from males; and the median eGFR was 92.5 ml/min per 1.73 m^2. The prevalence of eGFR <60 ml/min per 1.73 m^2 or kidney replacement therapy was 2%. The median body mass index was 26.7 kg/m^2, with a 5% prevalence of diabetes. There were 22% of individuals taking antihypertensive medications, and the median systolic blood pressure of the population was 137 mmHg.

Summary-Level MR Analysis

In the CKDGen data, a 1 standard deviation increase in genetically predicted selenium concentration by a total of 11 genetic variants was significantly associated with lower eGFR (Table 1 and Figure 2). The results were

Table 1. Summary-level Mendelian randomization results in CKDGen data

Genetic instruments	Cochrans' heterogeneity Q value	MR-Egger intercept P	Mendelian randomization methods	eGFR change beta (%)	95% confidence interval (%)	*P* value
11 genetic variants	0.85	0.60	MR-IVW	−1.05	−1.28, −0.82	2E-32
			Weighted median	−1.06	−1.38, −0.74	2E-10
			MR-Egger	−0.99	−1.38, −0.61	< 0.001
			Multivariable Mendelian randomization [a]	−0.96	−1.23, −0.68	1E-4
9 genetic variants after disregarding homocysteine-associated variants	0.90	0.92	MR-IVW	−1.08	−1.24, −0.92	2E-39
			Weighted median	−1.09	−1.44, −0.75	4E-10
			MR-Egger	−1.03	−1.42, −0.64	< 0.001
			Multivariable Mendelian randomization[a]	−0.93	−1.24, −0.62	0.001
4 genetic variants after additional LD pruning (r2 < 0.01)	0.71	0.66	MR-IVW	−1.24	−1.52, −0.97	2E-18
			Weighted median	−1.29	−1.74, −0.83	4E-8
			MR-Egger	−1.31	−1.90, −0.72	< 0.001
			Multivariable Mendelian randomization[a]	−1.99	−2.76, −1.22	0.04

eGFR, estimated glomerular filtration rate; LD, linkage disequilibrium; MR, Mendelian randomization; MR-IVW, multiplicative random-effect inverse-variance weighted.
[a]Multivariable Mendelian randomization analysis was adjusted for the genetic effects toward type 2 diabetes mellitus. One genetic variant was not included in the analysis because the summary statistics were unavailable in the GWAS results for type 2 diabetes.
All effect sizes were aligned and scaled toward genetically predicted standard deviation increase in body selenium concentration for % change in eGFR.

consistent with the MR-Egger regression and weighted-median methods. The MR-Egger regression intercept *P* value ($P = 0.60$) did not indicate a suspected pleiotropic effect. Furthermore, the results of the single genetic variant analysis and leave-one-out analysis demonstrated that there was no suspected disproportionate effect of a genetic variant on the causal estimates (Figure 2).

In addition, when we excluded 2 genetic variants showing a certain association with blood homocysteine levels, the results were consistently similar by the inverse-variance weighted method, MR-Egger, and weighted-median methods. The results were also similar by 4 genetic variants with robust independence with all significant results by pleiotropy-robust methods. Again, the MR-Egger intercept *P* values indicated that a directional pleiotropic effect was unlikely (by 9 genetic variants: $P = 0.92$, by 4 genetic variants: $P = 0.66$).

Multivariable MR Analysis

When adjusting for the effects of type 2 diabetes mellitus, the causal estimates remained consistent, because genetically predicted higher selenium

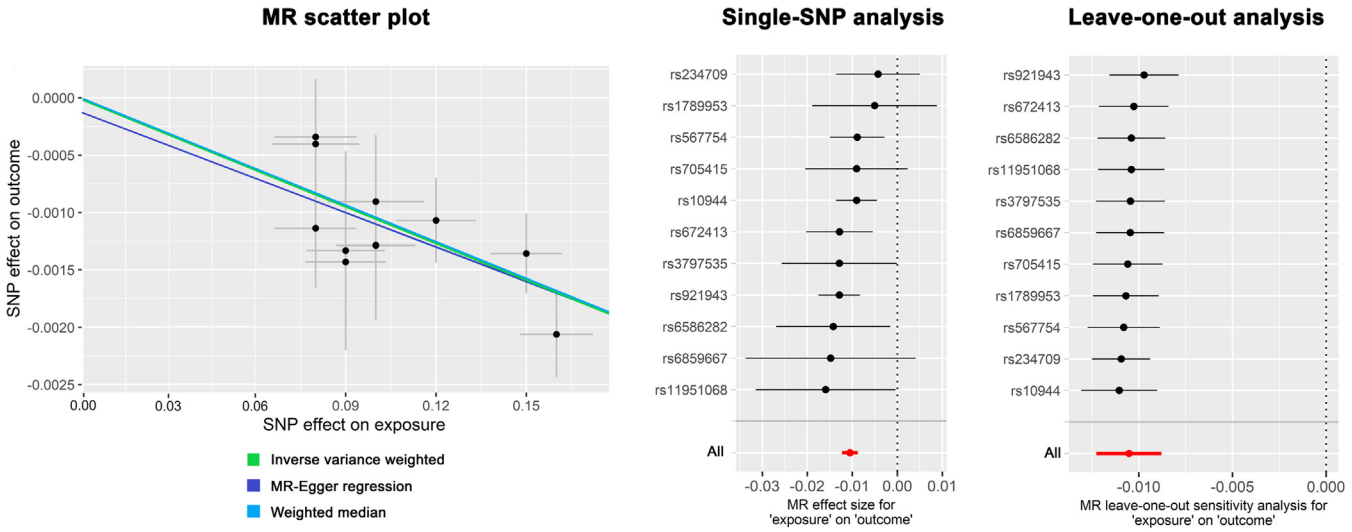

Figure 2. Mendelian randomization scatter plot, single-instrument analysis, and leave-one-out analysis. The scatter plot shows the genetic effects from single variant on exposure and outcome. Mendelian randomization analysis meta-analyze the wald ratio from each genetic variant, and the results by inverse-variance weighted (light blue), MR-Egger regression (dark blue), and weighted-median (green) are presented. The single genetic variant analysis tests the genetic variant effect on outcome (log-transformed eGFR) at a time, and the combined result by inverse-variance weighted method is presented as red dot and bars below. Leave-one-out analysis tests the causal estimates omitting a genetic variant at a time, and the causal estimates omitting the according genetic variant is presented in the figure. eGFR, estimated glomerular filtration rate; MR, Mendelian randomization.

concentration was significantly associated with lower eGFR (−0.96 [−1.23, −0.68]%) (Table 1). The results were similarly consistent even when we manually trimmed the genetic instruments.

Individual-Level MR Analysis

In the UK Biobank data, allele score for higher body selenium concentrations was significantly associated with a higher risk for diabetes mellitus and higher waist circumference; however, it was nonsignificantly associated with systolic blood pressure or body mass index (Supplementary Table S2).

Next, in the main MR analysis of eGFR outcome, allele score for higher body selenium concentration predicted by 11 genetic variants was significantly associated with lower eGFR (Table 2). The results were consistent even after adjusting for important clinical covariates. When we further trimmed the allele score, a significant association between a higher genetically predicted body selenium concentration and lower eGFR was consistently identified by 9 or 4 genetic variants after disregarding homocysteine-associated variants and the weak variants in linkage disequilibrium state. Again, the results were consistent even after adjusting for important metabolic covariates (Table 2) or when stratified by age or sex (Supplementary Table S3).

Post hoc Power Calculation Results

The *post hoc* power calculation indicated that the analysis in the CKDGen data had 1.00 power for the investigated causal association and the analysis in the UK Biobank data had 0.89 power toward the eGFR phenotype.

MR Analysis Toward Relevant Kidney Function Traits

The causal estimates were similarly significant toward the eGFR outcome from the GWAS meta-analysis including both CKDGen and the UK Biobank data (Supplementary Table S4). When the CKD outcome was investigated, the inverse-variance weighted method provided significant causal estimates. Although the MR-Egger regression and weighted-median methods provided causal estimates in the same direction with similar effect sizes, the statistical significance was marginal. In addition, the allele score analysis indicated that genetically predicted higher body selenium concentration was significantly associated with higher odds of CKD in the UK Biobank data. Next, urine albumin-to-creatinine ratio was investigated (Supplementary Table S4), but the causal estimates were nonsignificant in the performed analyses. Similarly, the causal estimates were nonsignificant in the summary-level MR analysis toward rapid loss of eGFR outcome and in the individual-level MR analysis toward stage 4 or 5 CKDoutcome.

DISCUSSION

In this MR study, we identified a consistently significant association between genetically predicted higher body selenium concentrations and lower eGFR phenotypes in 2 large-scale, independent genetic databases. In addition, a higher selenium concentration was causally related to a higher risk of diabetes or higher waist circumference, again suggesting a link between selenium and metabolic disorders. The causal estimates also suggested that genetically predicted body selenium concentration is significantly associated with a higher risk of CKD, although the results were nonsignificant toward albuminuria, profound (stage 4/5) CKD, or rapid loss of eGFR.

Diverse biologic effects from selenium have been reported.[2] Various forms of selenoproteins have been revealed, and although most of their roles are still under investigation, deficiency in selenium was considered to cause decreased glutathione peroxidase activity, which has an important antioxidative role in the body. Therefore, high body selenium concentration was anticipated to have possible antioxidative effects and benefits regarding immune function. Previous reports addressed the benefits of high selenium concentration on ameliorating the risks of cancer or cardiovascular disease.[2,32,33] However, there are debates regarding the health effects of higher body selenium concentrations.[34] Not only regarding selenium

Table 2. Individual-level MR results in UK Biobank data

Genetic instruments	Regression model	eGFR change beta (%)	95% confidence interval	*P* value
11 genetic variants	Age, sex, 10 PCs	−0.36	−0.52, −0.20	1E-5
	Age, sex, 10 PCs, and clinical covariates	−0.33	−0.50, −0.16	1E-4
9 genetic variants	Age, sex, 10 PCs	−0.38	−0.55, −0.22	6E-6
	Age, sex, 10 PCs, and clinical covariates	−0.35	−0.52, −0.17	1E-4
4 genetic variants	Age, sex, 10 PCs	−0.52	−0.72, −0.32	5E-7
	Age, sex, 10 PCs, and clinical covariates	−0.52	−0.73, −0.30	2E-6

eGFR, estimated glomerular filtration rate; PC, principal component
Clinical covariates adjusted for the model included body mass index, waist circumference, systolic blood pressure, antihypertensive medication history, diabetes mellitus, self-reported days per week for moderate physical activity, days per week for alcohol consumption, and current smoking history.
All effect sizes were aligned and scaled toward genetically predicted standard deviation increase in body selenium concentration for % change in eGFR.

toxicity because of excess selenium levels but also a high selenium concentration was previously reported regarding the risk of diabetes.[4,35,36] Furthermore, a recent MR study demonstrated that genetically predicted higher selenium concentrations were significantly associated with a higher risk of type 2 diabetes, whereas the benefit regarding the risk of coronary artery disease was uncertain.[14,22] Along with the growing evidence related to the uncertain benefits from high selenium levels,[4,34,35] additional investigations of the effects of selenium concentration on eGFR are warranted considering that kidney function impairment is a common and important comorbidity in the general population. Our study has strengths for investigating this issue as follows: (i) we performed MR analysis, which can demonstrate causal estimates less affected by confounding effects or reverse causation, (ii) we performed it along with multiple pleiotropy-robust MR sensitivity analysis, (iii) we performed sensitivity analysis with additional trimming for the variants, and (iv) we performed the replicative analysis in 2 large-scale genetic databases. Throughout the results, a higher genetically predicted body selenium concentration was consistently associated with a low eGFR, indicating that a high selenium concentration may adversely affect eGFR.

Based on our study results, as a high body selenium concentration is associated with a higher risk of diabetes or central obesity, such a metabolic pathway may also be related to the possible effect on eGFR. On the other hand, considering the significant causal estimates even after adjusting for major metabolic risk factors, a high body selenium concentration may have an independent effect on eGFR. Although the direct underlying mechanism cannot be revealed herein, the kidney is one of the major storage sites for excess selenium; thus, extraordinary production of selenoproteins may adversely affect kidney microstructure considering that the kidney is a major organ for handling excess nutrition and wastes. Overall, we believe the possibility that high selenium concentration may adversely affect eGFR should be carefully considered in clinical fields.

Caution is required to interpret our results because the causal estimates toward albuminuria, stage 4/5 CKD, or rapid loss of eGFR remained nonsignificant. Considering the null results toward profound or rapid loss of eGFR, our results are less likely to indicate that high body selenium concentration would acutely impair one's kidney function or cause severe kidney damage.

There are several limitations in this study. First, the current MR analysis cannot determine the range of body selenium that may be harmful to eGFR because of data availability.[37] Thus, the causal estimates from higher body selenium concentrations may be different in those with deficient states, although such deficiency is rare in modern societies. Second, MR studies cannot determine the mechanism of the identified causal estimates. Because our result is additional evidence that a high body selenium concentration may be adversely associated with the risk of metabolic disorders and eGFR, further study is warranted to reveal the biologic reason. Third, the effect sizes are from lifestyle exposure toward genetic predisposition; thus, the degree of clinical effect in the real world cannot be determined by our results.[38] Fourth, the UK Biobank data have health volunteer bias, reflected as a low prevalence of eGFR <60 ml/min per 1.73 m^2 and relatively small effect sizes.[39] Such bias might have led to difficulty in quantitative interpretation of the causal estimates and for performing analyses toward profound kidney function impairment, decreasing pattern of eGFR, or proteinuria. Fifth, the study, similar to many other MR studies, is mainly limited to individuals of European ancestry; thus, the generalizability should be further expanded. Lastly, MR analyses inevitably rely on some untestable assumption (e.g., random allocation of genotypes), thus, caution is required for the clinical application of our study results.

In conclusion, a high body selenium concentration may be causally linked to lower eGFR. Healthcare providers carefully consider kidney function and related risk factors such as glucose intolerance in regard to high body selenium concentration.

DISCLOSURE

All the authors declared no competing interests.

ACKNOWLEDGMENTS

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Data Sharing Statement

The data used for this study is available in the public database. The CKDGen data are openly available in the

consortium website (URL: https://ckdgen.imbi.uni-freiburg.de/) and the UK Biobank data is accessible after acquiring approval from the organization (application No. 53799).

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1. Summary statistics of the genetic instruments.

Table S2. Association between polygenic score for body selenium concentration and metabolic phenotypes.

Table S3. Age/sex stratified individual-level Mendelian randomization results in UK Biobank data.

Table S4. Additional Mendelian randomization analysis toward other outcome phenotypes in the CKDGen and UK Biobank data.

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