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Effect of Hematuria Markers and Antibody Immunity on both Hypertension and Chronic Kidney Disease—Based on Mendelian Randomization Study

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Abstract: Purpose: Hypertension(HTN) and chronic kidney disease(CKD) represent a major global public health burden. Prior research has illuminated the influence of hematuria markers and antibody immunity on both conditions, yet the underlying mechanisms remain incompletely understood. Design: Genetic associations of 35 hematuria markers on HTN and CKD were investigated, particularly the mediating role of antibody immune response. Participants: The data for HTN and CKD are both from Finland R11. HTN includes 137,312 cases and 316,345 controls, while CKD includes 11,265 cases and 436,208 controls. Method: In a mendelian randomization approach, we used the inverse variance weighted (IVW) method as the primary analytical tool in univariate MR analysis to evaluate the causal relationship between exposure and outcome, supplementary methods such as weighted median and MR Egger regression are used to ensure robust causal estimates even in the presence of invalid instrumental variables or horizontal pleiotropy to some extent. And the MR-PRESSO method was applied to detect and correct outliers caused by horizontal pleiotropy. In addition, Cochran's Q statistic is used to evaluate heterogeneity among SNPs. To further ensure the reliability of the results, we conducted a Leave one out analysis, excluding each SNP one by one and recalculating the overall causal effects to evaluate the impact of individual SNPs on the research results. Result: We observed causal positive associations between 17 hematuria markers and 8 antibody immunizations with HTN, and between 11 hematuria markers and 12 antibody immunities with CKD. We uncover a pathway mediated by non-albumin protein exposure and human herpesvirus 6 (HHV-6) IE1B antibody levels. This pathway exhibited a mediation effect of 0.0097. Conclusion: We evaluate the effects of 35 hematuria markers on both HTN and CKD, elucidating the mediatory role of antibody immune responses, supporting clinical trials to test their effectiveness in HTN and CKD prevention and treatment.

Keywords: Hematuria; hypertension; chronic kidney disease (CKD)

1. Introduction

HTN, characterized by elevated systemic arterial blood pressure (both systolic and diastolic), stands as a major risk factor for cardiovascular disease (CVD) and mortality[1]. It is a pervasive global health issue, impacting a substantial portion of the population annually and projected to affect nearly 29.2% of the world's population by 2025[2-3]. According to the World Health Organization (WHO), in 2019, the age-standardized prevalence of HTN among individuals aged 30-79 was estimated to be 33%, with an increasing incidence observed across age groups[3]. HTN manifests with symptoms such as headaches, fatigue, arrhythmia, palpitations, and tinnitus, among others, and is believed to be the culmination of genetic and environmental interactions, alongside contributions from the nervous, endocrine, humoral, and hemodynamic systems, albeit with an incompletely understood mechanism[4-7].

CKD poses another significant and escalating threat to global health, marked by rising prevalence and mortality rates[8]. In particular, lower-middle-income countries bear a disproportionate economic burden, where the costs associated with end-stage renal disease (ESRD) frequently exceed available healthcare resources. Consequently, over half of ESRD patients in these regions face the risk of discontinuing vital dialysis treatments due to financial constraints, highlighting the urgent need for sustainable healthcare solutions[9]. Despite the burgeoning impact of CKD on public health and economies worldwide, effective treatments to slow renal function decline and prevent ESRD remain notably absent.

Hematuric metabolites, substances that traverse the glomerulus and undergo reabsorption or excretion in the renal tubules, have garnered attention for their potential associations with HTN and renal diseases[10-16]. Furthermore, several autoantibodies have been implicated in HTN and renal diseases, albeit without a firmly established causal relationship[17].

Previous studies have shed light on the critical role of metabolic dysregulation and immune responses in the pathogenesis of HTN and CKD, though several limitations should be noted. He et al. (2020) identified 24 blood pressure-associated metabolites across multiple biochemical classes[18]. However, this cross-sectional study could not establish temporal relationships, and the unknown metabolites warrant further structural characterization. The inflammatory marker CRP was investigated by Davey Smith et al. (2005) using MR methodology[17]. While their study suggested CRP elevation may be a consequence rather than cause of HTN, the analysis was constrained by the limited number of CRP-associated genetic variants available at the time, potentially reducing the strength of causal inference. Similarly, Hou et al. (2022) conducted an MR analysis of 1,400 metabolites across eight CKD phenotypes[19]. Although they identified 48 significant metabolite associations, the study's reliance on European ancestry datasets may limit generalizability to other populations, and the lack of metabolite measurements in kidney tissue restricts direct mechanistic interpretations.

Collectively, these studies underscore the complex interplay between metabolism, inflammation and cardiorenal diseases while highlighting important methodological constraints. Despite these advancements, the mechanisms underlying the effects of hematuria metabolites and antibody immunity on HTN and CKD remain largely unexplored. Therefore, this study aims to further investigate these associations and contribute to the understanding of the complex interplay between HTN, CKD, and their associated biomarkers.

2. Methods

2.1. Ethics Statement

Specific ethical approval was not required for this study as all data were obtained from publicly available sources. The research adhered strictly to the principles outlined in the Declaration of Helsinki, and individual patient-level consent was not necessary.

2.2. Study Samples

Genome-Wide Association Study Dataset for metabolic factors. 35 types of blood and urine data identified 1,857 loci associated with at least one feature from a genetic basis measured in the laboratory (sample size=363,228 people), including 3,374 finely mapped associations and another set of large effect (>0.1 standard deviation) protein alterations, human leukocyte antigen (HLA), and copy number variation (CNV) associations[20].

Genome-Wide Association Study Dataset for antibody immune factors. Antibody immune response data can be used for serological measurements and whole genome genotyping of up to 10000 infectious diseases. It used data from 13 pathogens and defined 46 phenotypes: 15 serum positive case-control phenotypes and 31 quantitative antibody measurement phenotypes. For each phenotype, we conducted genome-wide association studies (GWAS) using the fastGWA linear mixed model package and used Lasso regression for variable selection to analyze the association between human leukocyte antigen (HLA) classical alleles and amino acid residues. A total of 8,735 individuals were included for case-control phenotype analysis, with an average sample size (range) of 4,286 (276-8555) for each quantitative analysis[21].

Genome-Wide Association Study Dataset for HTN and CKD. The data for HTN and CKD are both from Finland R11. HTN includes 137,312 cases and 316,345 controls, while CKD includes 11,265 cases and 436,208 controls.

2.3. Medelian Randomization Analyses

Mendelian randomization (MR) is a genetic variant-based approach for causal inference, with its core concept being the use of genetic variants as instrumental variables (IVs). By analyzing the associations between genetic variants, exposures, and outcome variables, MR enables the assessment of causal effects of exposures on outcomes. This method effectively addresses the confounding factors that are difficult to avoid in conventional observational studies, thereby enhancing the reliability of causal inference. The approach relies on three fundamental assumptions[22]: the genetic variants must be strongly associated with the exposure, independent of confounding factors, and influence the outcome only through the exposure. we applied five complementary MR methods: (1) random-effects inverse-variance weighted (IVW)[23], which is most effective when instrumental variables are free of measurement errors and satisfy the balanced pleiotropy assumption, while remaining stable even with partially invalid instruments; (2) MR-Egger regression[24], which evaluates pleiotropic effects by testing the significance of regression intercepts; (3) weighted median[25], whose particular advantage lies in tolerating nearly half of the instruments violating assumptions; (4) weighted mode[26], which obtains reliable estimates by detecting clustering characteristics of instrumental variable effect sizes; (4) MR pleiotropy residual sum and outlier (MR-PRESSO)[27], which systematically identifies and excludes genetic variants exhibiting abnormal pleiotropic effects. These complementary methods collectively ensure the reliability of research conclusions. To better interpret the results, we converted the obtained Beta values into odds ratios (OR) and calculated 95% confidence intervals (CI).

Our analytical protocol incorporated complementary approaches: the inverse-variance weighted (IVW) estimator, which delivers optimal efficiency under balanced pleiotropy conditions, and MR-Egger regression, which introduces an intercept parameter to accommodate and quantify directional pleiotropy. While MR-Egger sacrifices some precision, it provides more conservative estimates when instrument validity cannot be assured. This dual-method implementation substantially bolsters result credibility, with all statistical tests maintaining a Bonferroni-corrected significance level of 0.05.

The aim of this study is to evaluate the effects of 35 hematuria markers on HTN and CKD, particularly the mediating role of antibody immune response. Through a two-step and multivariate Mendelian randomization approach, we utilized single nucleotide polymorphisms (SNPs) as instrumental variables to reveal the causal relationship and potential mediating mechanisms of hematuria markers in HTN and CKD. Mendelian randomization can effectively reduce the influence of common confounding factors in traditional observational studies, and mediating Mendelian randomization can also help reveal the size of its role in the mediating mechanism by evaluating the mediating variables (Figure 1).

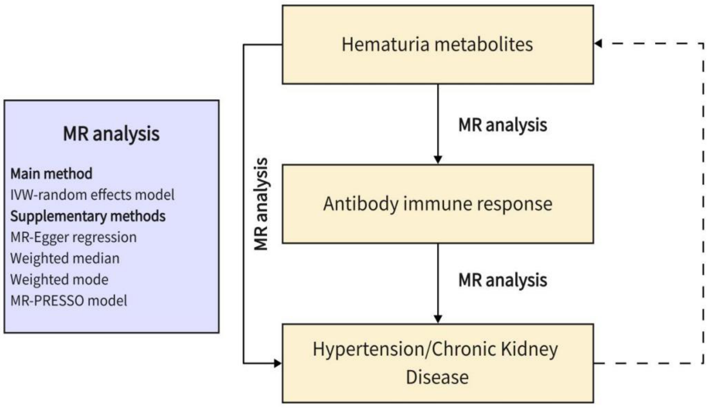


Figure 1. Research design framework

In order to ensure that all data can be screened for SNPs, we used the 5e-8 condition to screen for 35 blood and urine metabolite data. For antibody immune response data, we used the 1e-5 condition to screen for SNPs. To reduce multicollinearity and potential linkage disequilibrium effects, the linkage disequilibrium (LD) between selected SNPs was limited to $r^2<0.001$. To further ensure independence, the aggregation distance between SNPs needs to be greater than 10000KB. To ensure that all SNPs are closely related to exposure factors, we ensured that the F-values of all selected SNPs were greater than 10. For reverse Mendelian randomization and reverse MR, both diseases were screened using a P-value of 5e-8, with linkage disequilibrium (LD) and aggregation distance consistent with the positive screening conditions.

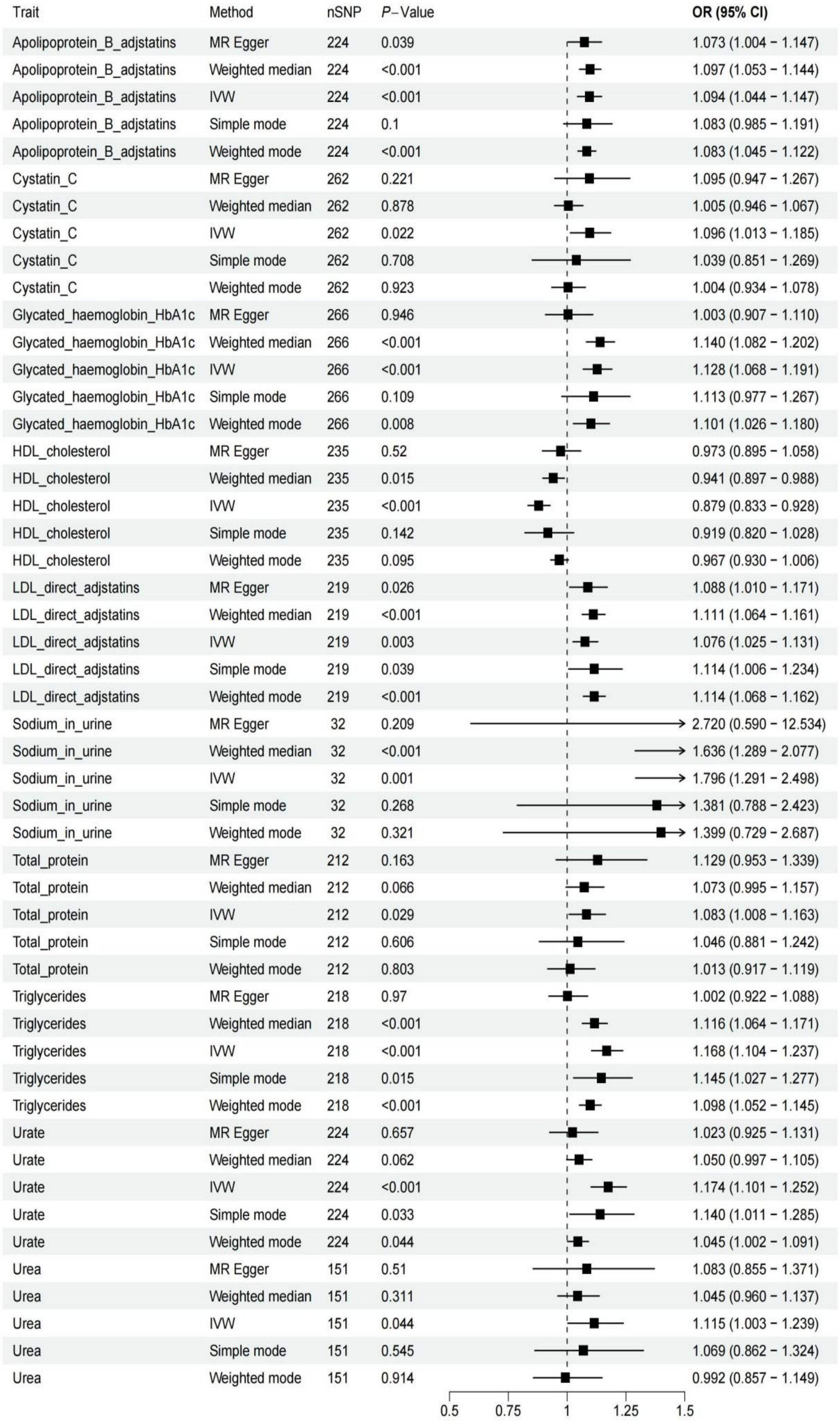
The statistical analysis of this study mainly used R software version 4.3.1 (https://www.r-project.org) Go ahead. We used R software packages such as “TwoSampleMR” (v0.5.8), “MR-PRESSO” (v1.0), and “MVMR” (v0.4) to perform mediation Mendelian randomization (MR) analysis. Firstly, to evaluate the causal relationship between exposure and outcome, we used the inverse variance weighted (IVW) method as the primary analytical tool in univariate MR analysis, as this method has high robustness in integrating multiple SNP effects and provides reliable causal estimates in the absence of horizontal pleiotropy. In addition, we also employed supplementary methods such as weighted median and MR Egger regression to ensure robust causal estimates even in the presence of invalid instrumental variables or horizontal pleiotropy to some extent. And the MR-PRESSO method was applied to detect and correct outliers caused by horizontal pleiotropy. In addition, Cochran’s Q statistic is used to evaluate heterogeneity among SNPs. If the p-value of Cochran’s Q test is greater than 0.05, it indicates that heterogeneity is not significant, thus supporting the consistency of the research results. To further ensure the reliability of the results, we conducted a Leave one out analysis, excluding each SNP one by one and recalculating the overall causal effects to evaluate the impact of individual SNPs on the research results.

3. Results

3.1. The Causal Relationship between Hematuria Markers and Two Diseases

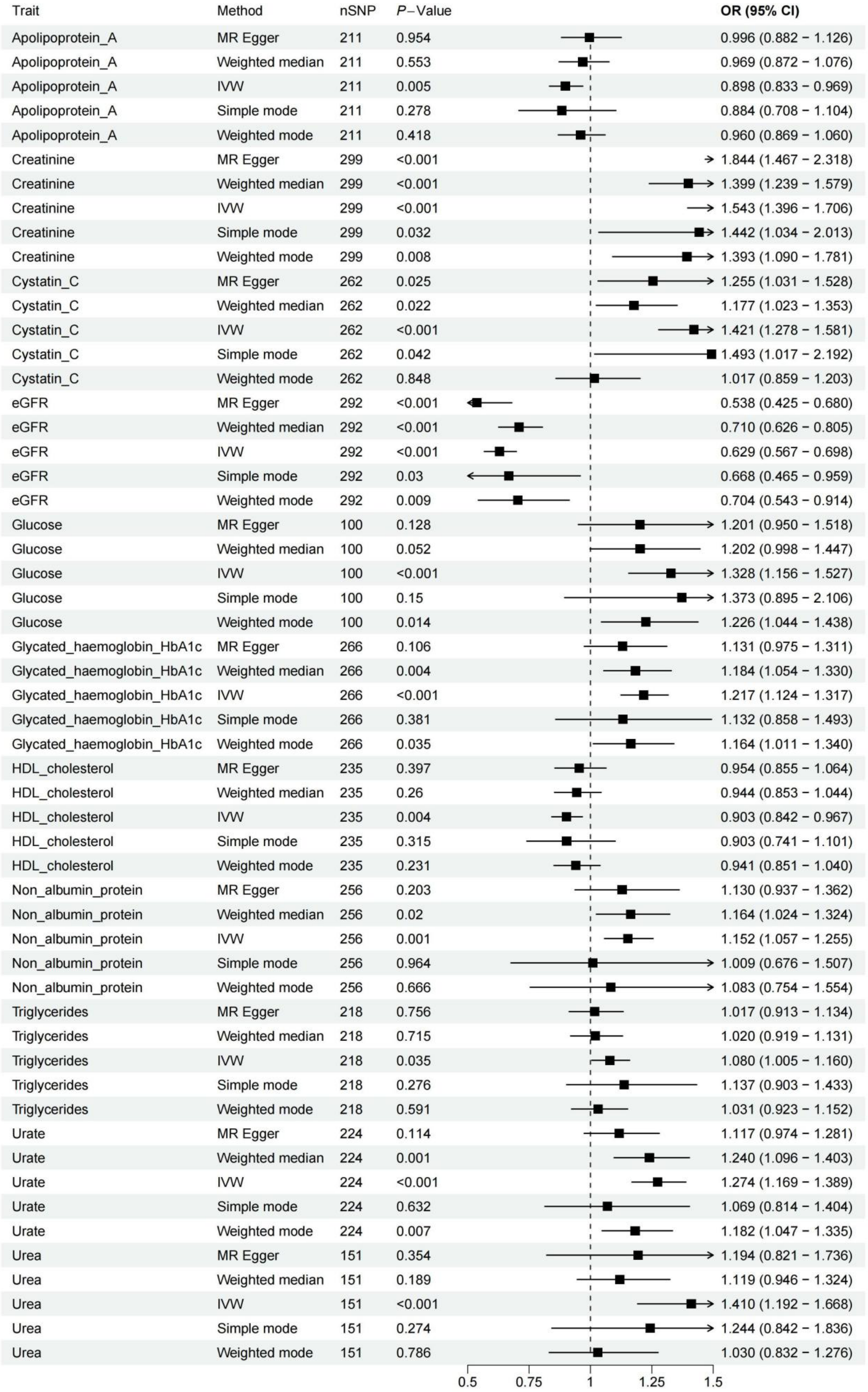
Using the IVW method, a positive causal relationship was found between 17 hematuria markers and HTN (Supplementary Material 1). The causal relationship between 7 hematuria markers and HTN was excluded, as their MR Egger, Weighted median, and IVW directions were not consistent (Figure 2), and therefore were not used for subsequent analysis. Among the remaining 10 positive results, there is a reverse causal relationship (Supplementary Material 2) between Cystatin-C, HDL_cholesterol, LDL_direct-adjstatins, and Urate, while the positive results of Glycated_haemoglobin-HbA1c and Triglycorides have pleiotropy (Supplementary Material 3) and are not used for subsequent analysis.

For CKD, we found a positive causal relationship between 11 hematuria markers and CKD (Supplementary Material 4), and the directions of MR Egger, Weighted median, and IVW were consistent among these eleven results (Figure 3). Cystatin-C and Urea have a reverse causal relationship (Supplementary Material 5) and are not used for subsequent analysis. All available positive data do not have multiple effects (Supplementary Material 6).



Trait	Method	nSNP	*P*−Value	OR (95% CI)
Apolipoprotein_B_adjstatins	MR Egger	224	0.039	1.073 (1.004 − 1.147)
Apolipoprotein_B_adjstatins	Weighted median	224	<0.001	1.097 (1.053 − 1.144)
Apolipoprotein_B_adjstatins	IVW	224	<0.001	1.094 (1.044 − 1.147)
Apolipoprotein_B_adjstatins	Simple mode	224	0.1	1.083 (0.985 − 1.191)
Apolipoprotein_B_adjstatins	Weighted mode	224	<0.001	1.083 (1.045 − 1.122)
Cystatin_C	MR Egger	262	0.221	1.095 (0.947 − 1.267)
Cystatin_C	Weighted median	262	0.878	1.005 (0.946 − 1.067)
Cystatin_C	IVW	262	0.022	1.096 (1.013 − 1.185)
Cystatin_C	Simple mode	262	0.708	1.039 (0.851 − 1.269)
Cystatin_C	Weighted mode	262	0.923	1.004 (0.934 − 1.078)
Glycated_haemoglobin_HbA1c	MR Egger	266	0.946	1.003 (0.907 − 1.110)
Glycated_haemoglobin_HbA1c	Weighted median	266	<0.001	1.140 (1.082 − 1.202)
Glycated_haemoglobin_HbA1c	IVW	266	<0.001	1.128 (1.068 − 1.191)
Glycated_haemoglobin_HbA1c	Simple mode	266	0.109	1.113 (0.977 − 1.267)
Glycated_haemoglobin_HbA1c	Weighted mode	266	0.008	1.101 (1.026 − 1.180)
HDL_cholesterol	MR Egger	235	0.52	0.973 (0.895 − 1.058)
HDL_cholesterol	Weighted median	235	0.015	0.941 (0.897 − 0.988)
HDL_cholesterol	IVW	235	<0.001	0.879 (0.833 − 0.928)
HDL_cholesterol	Simple mode	235	0.142	0.919 (0.820 − 1.028)
HDL_cholesterol	Weighted mode	235	0.095	0.967 (0.930 − 1.006)
LDL_direct_adjstatins	MR Egger	219	0.026	1.088 (1.010 − 1.171)
LDL_direct_adjstatins	Weighted median	219	<0.001	1.111 (1.064 − 1.161)
LDL_direct_adjstatins	IVW	219	0.003	1.076 (1.025 − 1.131)
LDL_direct_adjstatins	Simple mode	219	0.039	1.114 (1.006 − 1.234)
LDL_direct_adjstatins	Weighted mode	219	<0.001	1.114 (1.068 − 1.162)
Sodium_in_urine	MR Egger	32	0.209	2.720 (0.590 − 12.534)
Sodium_in_urine	Weighted median	32	<0.001	1.636 (1.289 − 2.077)
Sodium_in_urine	IVW	32	0.001	1.796 (1.291 − 2.498)
Sodium_in_urine	Simple mode	32	0.268	1.381 (0.788 − 2.423)
Sodium_in_urine	Weighted mode	32	0.321	1.399 (0.729 − 2.687)
Total_protein	MR Egger	212	0.163	1.129 (0.953 − 1.339)
Total_protein	Weighted median	212	0.066	1.073 (0.995 − 1.157)
Total_protein	IVW	212	0.029	1.083 (1.008 − 1.163)
Total_protein	Simple mode	212	0.606	1.046 (0.881 − 1.242)
Total_protein	Weighted mode	212	0.803	1.013 (0.917 − 1.119)
Triglycerides	MR Egger	218	0.97	1.002 (0.922 − 1.088)
Triglycerides	Weighted median	218	<0.001	1.116 (1.064 − 1.171)
Triglycerides	IVW	218	<0.001	1.168 (1.104 − 1.237)
Triglycerides	Simple mode	218	0.015	1.145 (1.027 − 1.277)
Triglycerides	Weighted mode	218	<0.001	1.098 (1.052 − 1.145)
Urate	MR Egger	224	0.657	1.023 (0.925 − 1.131)
Urate	Weighted median	224	0.062	1.050 (0.997 − 1.105)
Urate	IVW	224	<0.001	1.174 (1.101 − 1.252)
Urate	Simple mode	224	0.033	1.140 (1.011 − 1.285)
Urate	Weighted mode	224	0.044	1.045 (1.002 − 1.091)
Urea	MR Egger	151	0.51	1.083 (0.855 − 1.371)
Urea	Weighted median	151	0.311	1.045 (0.960 − 1.137)
Urea	IVW	151	0.044	1.115 (1.003 − 1.239)
Urea	Simple mode	151	0.545	1.069 (0.862 − 1.324)
Urea	Weighted mode	151	0.914	0.992 (0.857 − 1.149)

Figure 2. Univariable Mendelian randomisation of hematuria markers on HTN



Trait	Method	nSNP	P−Value	OR (95% CI)
Apolipoprotein_A	MR Egger	211	0.954	0.996 (0.882 − 1.126)
Apolipoprotein_A	Weighted median	211	0.553	0.969 (0.872 − 1.076)
Apolipoprotein_A	IVW	211	0.005	0.898 (0.833 − 0.969)
Apolipoprotein_A	Simple mode	211	0.278	0.884 (0.708 − 1.104)
Apolipoprotein_A	Weighted mode	211	0.418	0.960 (0.869 − 1.060)
Creatinine	MR Egger	299	<0.001	1.844 (1.467 − 2.318)
Creatinine	Weighted median	299	<0.001	1.399 (1.239 − 1.579)
Creatinine	IVW	299	<0.001	1.543 (1.396 − 1.706)
Creatinine	Simple mode	299	0.032	1.442 (1.034 − 2.013)
Creatinine	Weighted mode	299	0.008	1.393 (1.090 − 1.781)
Cystatin_C	MR Egger	262	0.025	1.255 (1.031 − 1.528)
Cystatin_C	Weighted median	262	0.022	1.177 (1.023 − 1.353)
Cystatin_C	IVW	262	<0.001	1.421 (1.278 − 1.581)
Cystatin_C	Simple mode	262	0.042	1.493 (1.017 − 2.192)
Cystatin_C	Weighted mode	262	0.848	1.017 (0.859 − 1.203)
eGFR	MR Egger	292	<0.001	0.538 (0.425 − 0.680)
eGFR	Weighted median	292	<0.001	0.710 (0.626 − 0.805)
eGFR	IVW	292	<0.001	0.629 (0.567 − 0.698)
eGFR	Simple mode	292	0.03	0.668 (0.465 − 0.959)
eGFR	Weighted mode	292	0.009	0.704 (0.543 − 0.914)
Glucose	MR Egger	100	0.128	1.201 (0.950 − 1.518)
Glucose	Weighted median	100	0.052	1.202 (0.998 − 1.447)
Glucose	IVW	100	<0.001	1.328 (1.156 − 1.527)
Glucose	Simple mode	100	0.15	1.373 (0.895 − 2.106)
Glucose	Weighted mode	100	0.014	1.226 (1.044 − 1.438)
Glycated_haemoglobin_HbA1c	MR Egger	266	0.106	1.131 (0.975 − 1.311)
Glycated_haemoglobin_HbA1c	Weighted median	266	0.004	1.184 (1.054 − 1.330)
Glycated_haemoglobin_HbA1c	IVW	266	<0.001	1.217 (1.124 − 1.317)
Glycated_haemoglobin_HbA1c	Simple mode	266	0.381	1.132 (0.858 − 1.493)
Glycated_haemoglobin_HbA1c	Weighted mode	266	0.035	1.164 (1.011 − 1.340)
HDL_cholesterol	MR Egger	235	0.397	0.954 (0.855 − 1.064)
HDL_cholesterol	Weighted median	235	0.26	0.944 (0.853 − 1.044)
HDL_cholesterol	IVW	235	0.004	0.903 (0.842 − 0.967)
HDL_cholesterol	Simple mode	235	0.315	0.903 (0.741 − 1.101)
HDL_cholesterol	Weighted mode	235	0.231	0.941 (0.851 − 1.040)
Non_albumin_protein	MR Egger	256	0.203	1.130 (0.937 − 1.362)
Non_albumin_protein	Weighted median	256	0.02	1.164 (1.024 − 1.324)
Non_albumin_protein	IVW	256	0.001	1.152 (1.057 − 1.255)
Non_albumin_protein	Simple mode	256	0.964	1.009 (0.676 − 1.507)
Non_albumin_protein	Weighted mode	256	0.666	1.083 (0.754 − 1.554)
Triglycerides	MR Egger	218	0.756	1.017 (0.913 − 1.134)
Triglycerides	Weighted median	218	0.715	1.020 (0.919 − 1.131)
Triglycerides	IVW	218	0.035	1.080 (1.005 − 1.160)
Triglycerides	Simple mode	218	0.276	1.137 (0.903 − 1.433)
Triglycerides	Weighted mode	218	0.591	1.031 (0.923 − 1.152)
Urate	MR Egger	224	0.114	1.117 (0.974 − 1.281)
Urate	Weighted median	224	0.001	1.240 (1.096 − 1.403)
Urate	IVW	224	<0.001	1.274 (1.169 − 1.389)
Urate	Simple mode	224	0.632	1.069 (0.814 − 1.404)
Urate	Weighted mode	224	0.007	1.182 (1.047 − 1.335)
Urea	MR Egger	151	0.354	1.194 (0.821 − 1.736)
Urea	Weighted median	151	0.189	1.119 (0.946 − 1.324)
Urea	IVW	151	<0.001	1.410 (1.192 − 1.668)
Urea	Simple mode	151	0.274	1.244 (0.842 − 1.836)
Urea	Weighted mode	151	0.786	1.030 (0.832 − 1.276)

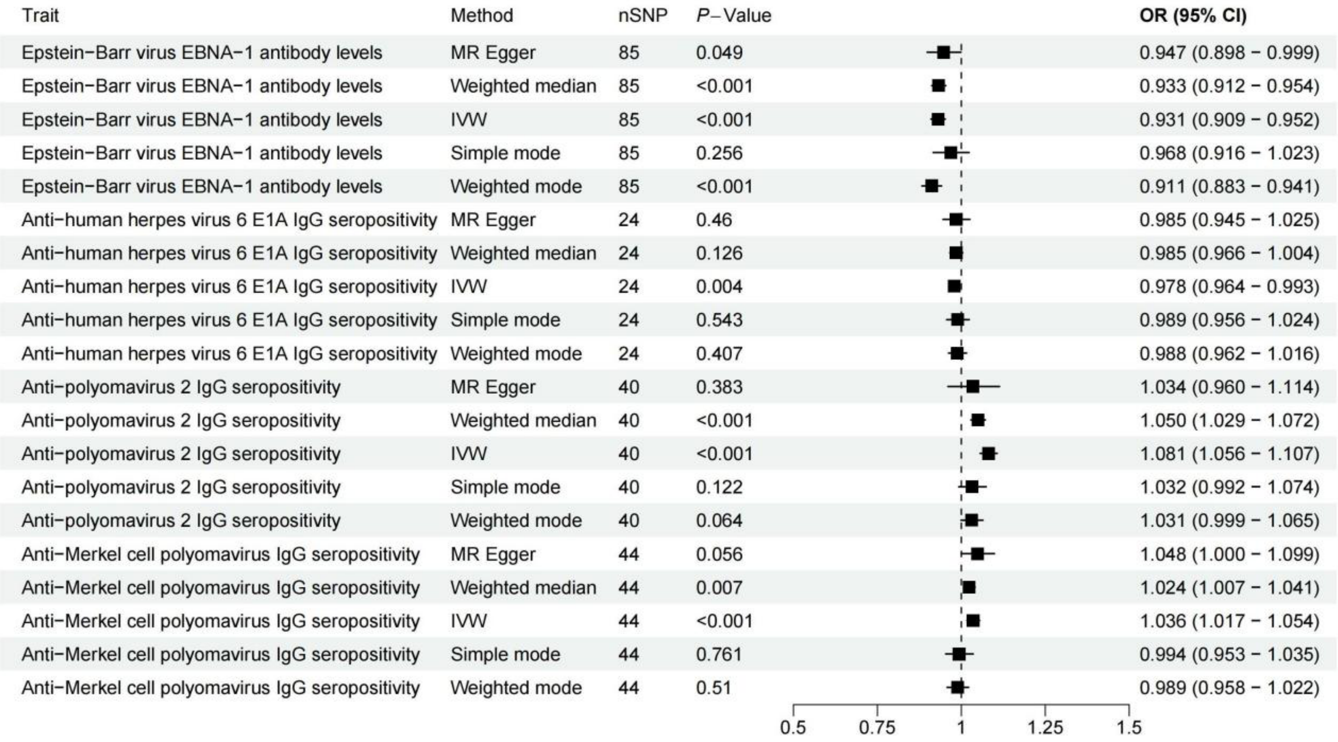
Figure 3. Univariable Mendelian randomisation of hematuria markers on CKD

3.3. The Causal Relationship between Antibody Immunity and Two Diseases

Similarly, using the IVW method, we analyzed the causal relationship between antibody immunity and HTN and CKD.

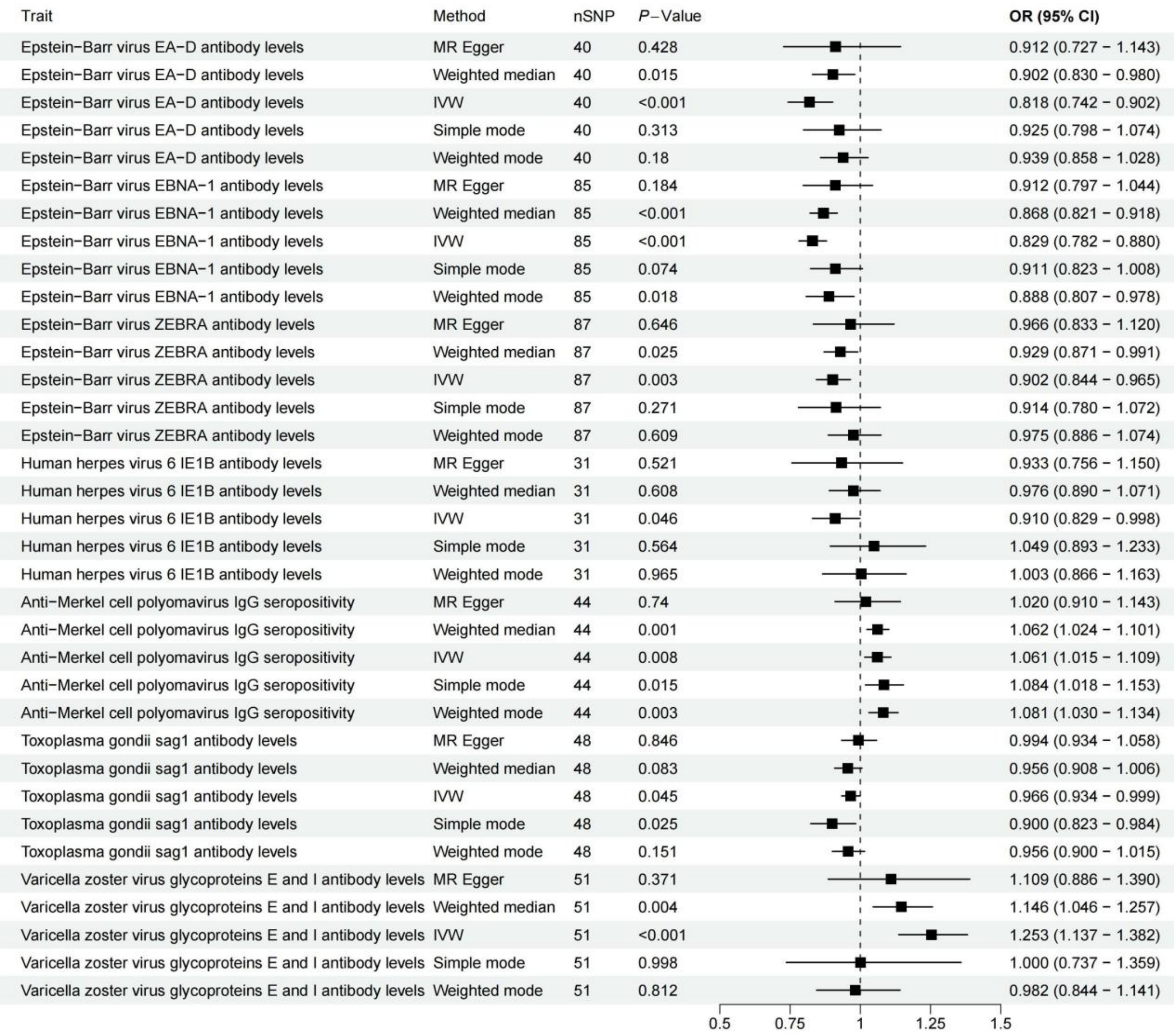
The results showed that there was a positive causal relationship between 8 types of antibody immunity and HTN (Supplementary Material 7), among which the directions of MR Egger, Weighted median, and IVW were inconsistent in the causal relationship of 4 types of antibody immunity (Figure 4), and were not used for subsequent analysis. There is no reverse causal relationship (Supplementary Material 8) or pleiotropy (Supplementary Material 8) among the remaining four antibody immunizations.

There is a positive causal relationship between 12 antibody immunizations and CKD (Figure 5), but the directions of MR Egger, Weighted median, and IVW are inconsistent in the causal relationships of 3 metabolites (Supplementary Material 9). There is a reverse causal relationship between the results of Anti Market Cell Polyomavirus IgG serosity and Toxoplasma gondii sag1 antibody levels (Supplementary Material 10), and there is pleiotropy between Epstein Barr virus VCA p18 antibody levels, Human heroes virus 7 U14 antibody levels, Anti Polyomavirus 2 IgG serosity, and Anti varicella zoster virus IgG serosity and outcomes (Supplementary Material 11), which are not used for subsequent analysis.



Trait	Method	nSNP	*P*−Value	**OR (95% CI)**
Epstein−Barr virus EBNA−1 antibody levels	MR Egger	85	0.049	0.947 (0.898 − 0.999)
Epstein−Barr virus EBNA−1 antibody levels	Weighted median	85	<0.001	0.933 (0.912 − 0.954)
Epstein−Barr virus EBNA−1 antibody levels	IVW	85	<0.001	0.931 (0.909 − 0.952)
Epstein−Barr virus EBNA−1 antibody levels	Simple mode	85	0.256	0.968 (0.916 − 1.023)
Epstein−Barr virus EBNA−1 antibody levels	Weighted mode	85	<0.001	0.911 (0.883 − 0.941)
Anti−human herpes virus 6 E1A IgG seropositivity	MR Egger	24	0.46	0.985 (0.945 − 1.025)
Anti−human herpes virus 6 E1A IgG seropositivity	Weighted median	24	0.126	0.985 (0.966 − 1.004)
Anti−human herpes virus 6 E1A IgG seropositivity	IVW	24	0.004	0.978 (0.964 − 0.993)
Anti−human herpes virus 6 E1A IgG seropositivity	Simple mode	24	0.543	0.989 (0.956 − 1.024)
Anti−human herpes virus 6 E1A IgG seropositivity	Weighted mode	24	0.407	0.988 (0.962 − 1.016)
Anti−polyomavirus 2 IgG seropositivity	MR Egger	40	0.383	1.034 (0.960 − 1.114)
Anti−polyomavirus 2 IgG seropositivity	Weighted median	40	<0.001	1.050 (1.029 − 1.072)
Anti−polyomavirus 2 IgG seropositivity	IVW	40	<0.001	1.081 (1.056 − 1.107)
Anti−polyomavirus 2 IgG seropositivity	Simple mode	40	0.122	1.032 (0.992 − 1.074)
Anti−polyomavirus 2 IgG seropositivity	Weighted mode	40	0.064	1.031 (0.999 − 1.065)
Anti−Merkel cell polyomavirus IgG seropositivity	MR Egger	44	0.056	1.048 (1.000 − 1.099)
Anti−Merkel cell polyomavirus IgG seropositivity	Weighted median	44	0.007	1.024 (1.007 − 1.041)
Anti−Merkel cell polyomavirus IgG seropositivity	IVW	44	<0.001	1.036 (1.017 − 1.054)
Anti−Merkel cell polyomavirus IgG seropositivity	Simple mode	44	0.761	0.994 (0.953 − 1.035)
Anti−Merkel cell polyomavirus IgG seropositivity	Weighted mode	44	0.51	0.989 (0.958 − 1.022)

Figure 4. Univariable Mendelian randomisation of antibody immunity on HTN



Trait	Method	nSNP	*P*−Value	OR (95% CI)
Epstein−Barr virus EA−D antibody levels	MR Egger	40	0.428	0.912 (0.727 − 1.143)
Epstein−Barr virus EA−D antibody levels	Weighted median	40	0.015	0.902 (0.830 − 0.980)
Epstein−Barr virus EA−D antibody levels	IVW	40	<0.001	0.818 (0.742 − 0.902)
Epstein−Barr virus EA−D antibody levels	Simple mode	40	0.313	0.925 (0.798 − 1.074)
Epstein−Barr virus EA−D antibody levels	Weighted mode	40	0.18	0.939 (0.858 − 1.028)
Epstein−Barr virus EBNA−1 antibody levels	MR Egger	85	0.184	0.912 (0.797 − 1.044)
Epstein−Barr virus EBNA−1 antibody levels	Weighted median	85	<0.001	0.868 (0.821 − 0.918)
Epstein−Barr virus EBNA−1 antibody levels	IVW	85	<0.001	0.829 (0.782 − 0.880)
Epstein−Barr virus EBNA−1 antibody levels	Simple mode	85	0.074	0.911 (0.823 − 1.008)
Epstein−Barr virus EBNA−1 antibody levels	Weighted mode	85	0.018	0.888 (0.807 − 0.978)
Epstein−Barr virus ZEBRA antibody levels	MR Egger	87	0.646	0.966 (0.833 − 1.120)
Epstein−Barr virus ZEBRA antibody levels	Weighted median	87	0.025	0.929 (0.871 − 0.991)
Epstein−Barr virus ZEBRA antibody levels	IVW	87	0.003	0.902 (0.844 − 0.965)
Epstein−Barr virus ZEBRA antibody levels	Simple mode	87	0.271	0.914 (0.780 − 1.072)
Epstein−Barr virus ZEBRA antibody levels	Weighted mode	87	0.609	0.975 (0.886 − 1.074)
Human herpes virus 6 IE1B antibody levels	MR Egger	31	0.521	0.933 (0.756 − 1.150)
Human herpes virus 6 IE1B antibody levels	Weighted median	31	0.608	0.976 (0.890 − 1.071)
Human herpes virus 6 IE1B antibody levels	IVW	31	0.046	0.910 (0.829 − 0.998)
Human herpes virus 6 IE1B antibody levels	Simple mode	31	0.564	1.049 (0.893 − 1.233)
Human herpes virus 6 IE1B antibody levels	Weighted mode	31	0.965	1.003 (0.866 − 1.163)
Anti−Merkel cell polyomavirus IgG seropositivity	MR Egger	44	0.74	1.020 (0.910 − 1.143)
Anti−Merkel cell polyomavirus IgG seropositivity	Weighted median	44	0.001	1.062 (1.024 − 1.101)
Anti−Merkel cell polyomavirus IgG seropositivity	IVW	44	0.008	1.061 (1.015 − 1.109)
Anti−Merkel cell polyomavirus IgG seropositivity	Simple mode	44	0.015	1.084 (1.018 − 1.153)
Anti−Merkel cell polyomavirus IgG seropositivity	Weighted mode	44	0.003	1.081 (1.030 − 1.134)
Toxoplasma gondii sag1 antibody levels	MR Egger	48	0.846	0.994 (0.934 − 1.058)
Toxoplasma gondii sag1 antibody levels	Weighted median	48	0.083	0.956 (0.908 − 1.006)
Toxoplasma gondii sag1 antibody levels	IVW	48	0.045	0.966 (0.934 − 0.999)
Toxoplasma gondii sag1 antibody levels	Simple mode	48	0.025	0.900 (0.823 − 0.984)
Toxoplasma gondii sag1 antibody levels	Weighted mode	48	0.151	0.956 (0.900 − 1.015)
Varicella zoster virus glycoproteins E and I antibody levels	MR Egger	51	0.371	1.109 (0.886 − 1.390)
Varicella zoster virus glycoproteins E and I antibody levels	Weighted median	51	0.004	1.146 (1.046 − 1.257)
Varicella zoster virus glycoproteins E and I antibody levels	IVW	51	<0.001	1.253 (1.137 − 1.382)
Varicella zoster virus glycoproteins E and I antibody levels	Simple mode	51	0.998	1.000 (0.737 − 1.359)
Varicella zoster virus glycoproteins E and I antibody levels	Weighted mode	51	0.812	0.982 (0.844 − 1.141)

Figure 5. Univariable Mendelian randomisation of antibody immunity on CKD

3.4. Mediating MR Analysis between Hematuria Markers and Antibody Immunity and Two Diseases

Mediated MR analysis was performed on the positive hematuria markers and antibody immunity corresponding to two diseases. In the analysis of HTN, multivariate MR was used to analyze them, and no positive results were found in the end.

In the analysis of CKD, through the use of multivariate MR, we found a pathway mediated by Non-albumine-protein exposure and Human heroes virus 6 IE1B antibody levels, with a mediation effect of 0.0097.

4. Discussion

Our Mendelian randomization study provides robust evidence supporting causal relationships between hematuria markers and both HTN and CKD risk, while uncovering novel immune-mediated pathways. Hematuria markers play a crucial role in the development and progression of hypertension and CKD. Apolipoprotein B adjstatins and Cystatin C have been identified as independent risk factors for hypertension, where Apolipoprotein B adjstatins influences blood pressure through its involvement in lipid metabolism and atherosclerosis, while Cystatin C regulates blood pressure by reflecting renal impairment and mediating inflammatory responses. Additionally, Apolipoprotein A, creatinine, eGFR, glucose, Glycated haemoglobin HbA1c, HDL cholestero, Non albumin protein, Triglycerides, and Urate have been determined to be independent risk factors for CKD, indicating the critical role of metabolic abnormalities and renal impairment in the progression of CKD. Through Mendelian randomization analysis, the study also found that specific antibody levels of Epstein-Barr virus, human herpesvirus 6, polyomavirus, Toxoplasma gondii and herpes zoster virus were significantly associated with hypertension and CKD, suggesting that chronic viral infection may participate in disease occurrence through immune activation and inflammatory response.

The positive associations between urinary sodium, metabolic markers (apolipoprotein B, HbA1c, triglycerides, urate) and HTN, along with similar findings for CKD progression markers (creatinine, glucose, non-albumin protein), reinforce established pathophysiological mechanisms. Most remarkably, we identified a previously unreported protective association of Anti-Merkel Cell Polyomavirus IgG seropositivity against both conditions, suggesting complex virus-host interactions in chronic disease pathogenesis. These findings were robust across sensitivity analyses and align with existing literature while extending current knowledge through causal inference methodology.

The clinical implications of these results are multifaceted. First, they substantiate current therapeutic approaches targeting metabolic dysregulation in HTN and CKD management. Second, the sodium-HTN association reinforces public health strategies for dietary salt reduction. Most importantly, the novel immune findings open new avenues for research into immunomodulatory therapies and personalized prevention strategies. However, several limitations warrant consideration, including potential residual pleiotropy, European ancestry bias, and inability to assess non-linear relationships. These limitations highlight the need for mechanistic studies to elucidate the protective role of MCV antibodies, investigation of metabolic-immune interactions, and replication in diverse populations.

5. Conclusion

This study significantly advances our understanding of HTN and CKD pathogenesis by integrating metabolic and immunological perspectives through robust causal inference. The confirmation of established risk factors validates our approach, while the discovery of novel immune associations underscores the value of Mendelian randomization in uncovering unexpected disease mechanisms. Future research should focus on elucidating the biological basis of these findings and exploring their translational potential, potentially leading to more comprehensive strategies for prevention and treatment of these globally prevalent chronic conditions.

Disclosure statement

The author declares no conflict of interest.

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