

Mediating function of heart failure in the causal relationship between diastolic blood pressure and hypertensive renal disease with renal failure: a mediated Mendelian randomization study[†]



Original article

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Abstract: Objective: To study the causality relationship between diastolic blood pressure (DBP) and hypertensive renal disease with renal failure (HRDRF) and the mediating role of heart failure (HF) in the causality relationship by network Mendelian randomization (MR).

Methods: Genome-wide analysis of DBP, HRDRF, and HF was downloaded from the public database (Genome-Wide Analysis Study [GWAS]) and was used to analyze the results and to conduct mediated MR analysis.

Results: Analysis showed that DBP was positively correlated with HRDRF (OR = 1.0002, 95% CI: 1.0001–1.0003, $P = 1.8076e-05$) and DBP was positively correlated with HF (OR = 1.0295, 95% CI: 1.0221–1.0370, $P = 2.5292e-15$). HF and HRDRF had a positive causal effect (OR = 1.0001, 95% CI: 1.0000–1.0001, $P = 0.0152$). Mediation analysis showed that the contribution ratio of HF to the combined effect of DBP and HRDRF was 24.69%.

Conclusions: DBP can increase the risk of renal disease with renal failure, and HF may play an important role in mediating this causal relationship.

Keywords: atherosclerotic heart disease • diastolic blood pressure • heart arrhythmia • heart failure • hypertensive renal disease with renal failure • Mendelian randomization

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1. Introduction

Hypertensive renal disease is one of the common chronic kidney diseases (CKDs) and an important cause of end-stage renal disease (ESRD) all over the world.¹

At present, the pathogenesis of renal failure caused by hypertensive renal disease has not been fully elucidated in the academic community, which may be related to

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blood pressure, metabolic excretion disorder, acid–base balance disorder, electrolyte disorder, and so on.² Later studies have shown that there is a correlation between diastolic blood pressure (DBP) and hypertensive renal disease with renal failure (HRDRF).³ Previous studies have found that hypertensive patients with elevated DBP are more likely to develop HRDRF and have a higher severity of the disease.⁴ However, most of these results are from observational studies and may be affected by confounding factors, so the causal relationship between DBP and HRDRF is not clear. In addition, cardiac function (e.g., heart failure [HF], heart arrhythmia [HA], and atherosclerotic heart disease [AHD]) is decreased in patients with DBP. HF is a complex syndrome with impaired ventricular filling or ejection capacity, which is the end-stage state of cardiovascular disease in most patients.⁵ HF is often used as a risk factor to predict the morbidity and mortality of renal disease with renal failure.⁶

It was found that HF was associated with the increased risk of HRDRF.⁷ This suggests that HF may be a mediating factor affecting the causality relationship between DBP and HRDRF. Therefore, this study uses the network Mendelian randomization (MR) method, and the causality relationship between DBP and HRDRF was analyzed. It was also tested whether HF as a mediating factor mediates the relationship between DBP and HRDRF.

MR analysis is often used to study the causal effect between exposure factors and outcome factors.⁸ This method was proposed by Katan⁹ in 1986. The core idea is to use genetic variation as instrument variables (IVs) to study the causal relationship between exposure factors and outcome factors. This method avoids the interference of reverse causality and potential confounders encountered in traditional randomized controlled trials.⁹ We investigated the role of mediating factors using mediated MR, a causal inference method developed from traditional MR methods.¹⁰ Assuming that part of the causal relationship between exposure factors and outcome factors is mediated by mediating factors, the causal effect between mediating factors and outcome

variables is attributed to the indirect effect of exposure factors on outcome factors.

2. Methods

2.1. Study design

The data used in this study were publicly available from the Genome-Wide Association Study (GWAS) statistical results. DBP was taken as the exposure factor and HRDRF was taken as the outcome factor. HF, HA, and AHD were included in the mediation analysis. Firstly, the overall causal effect of DBP and HRDRF was analyzed. Then the causality relationship between DBP and mediating factors was analyzed. The mediating factors significantly associated with DBP and HRDRF were selected for causal inference. Finally, we analyzed the proportion of mediating factors in the causality relationship between DBP and HRDRF. Summary statistics of genetic associations were obtained from the latest GWAS for different phenotypes. Table 1 summarizes the GWAS data used in this study and Figure 1 shows the study design.

2.2. Data sources

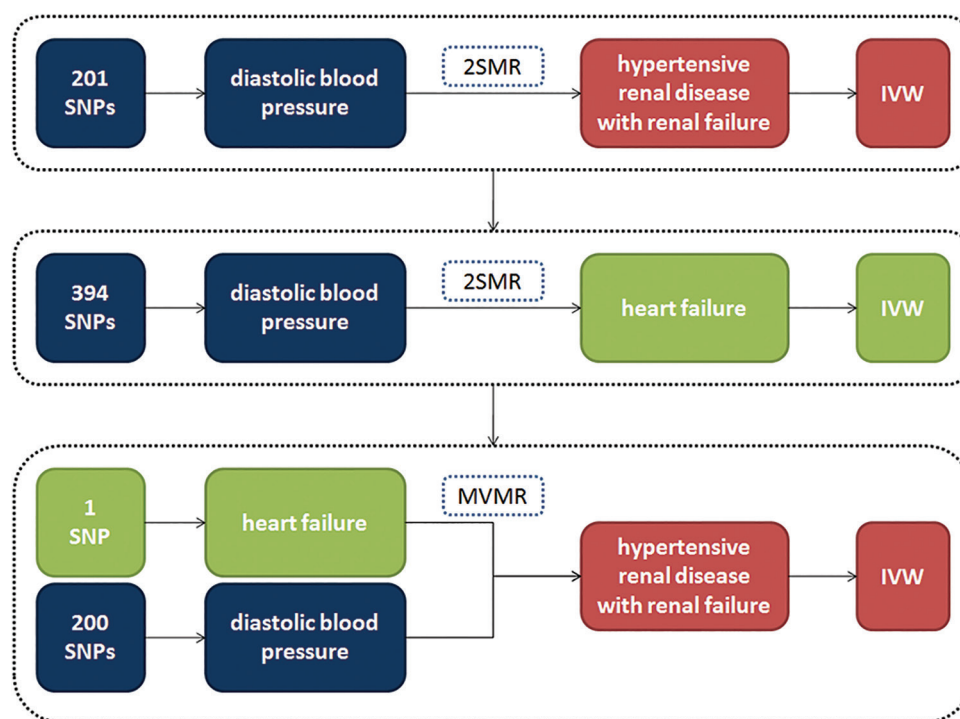
All the above data were from the website (<https://gwas.mrcieu.ac.uk/datasets>). The above GWAS data are from the European origin population, and their brief information is shown in Tables 2 and 3. In this study, effective SNPs for DBP and HF were selected as IVs. DBP had a total of 201 SNPs as IVs, and HF had 394 SNPs as IVs. Tables 2 and 3 show some IVs-related information of these 2 exposure factors, including effect allele, other allele, beta, eaf, chromosome number, chromosome physical position, standard error, and *P*-value. All selected SNPs and their associations with DBP, mediators, and HRDRF were extracted from the GWAS studies in Table 1. Independent ($r^2 < 0.1$) genome-wide significant ($P < 5 \times 10^{-8}$) SNPs were used as major genetic tools.

For each mediator, genetic tools were selected from recent large-scale GWAS data.¹¹ We then

GWAS ID	Year	Trait	Consortium	Sample size	Number of SNPs
ieu-b-39	2018	DBP	International Consortium of Blood Pressure	757,601	7,160,619
ebi-a-GCST009541	2020	HF	NA	977,323	7,773,021
ukb-b-3703	2018	HA	MRC-IEU	462,933	9,851,867
ukb-b-1668	2018	AHD	MRC-IEU	463,010	9,851,867
ukb-b-19955	2018	HRDRF	MRC-IEU	463,010	9,851,867

Note: AHD, atherosclerotic heart disease; DBP, diastolic blood pressure; HA, heart arrhythmia; HF, heart failure; HRDRF, hypertensive renal disease with renal failure.

Table 1. Brief description for the GWAS data used in this study.



Note: IVW, inverse variance weighted; MR, Mendelian randomization.

Figure 1. Study design.

SNP	EA	OA	beta	eaf	chr	pos	se	p
rs10048404	T	C	-0.1096	0.3694	18	54578482	0.0183	2.00e-09
rs10054208	T	C	0.1187	0.3617	5	55688992	0.0185	1.49e-10
rs10279432	A	C	0.1178	0.6234	7	7279010	0.018	5.73e-11
rs1035673	C	T	-0.1625	0.6032	2	2.19e+08	0.0176	3.00e-20
rs1039897	A	G	-0.1085	0.6503	2	2.2e+08	0.0183	3.26e-09
rs1049212	G	A	0.1788	0.5694	16	4932929	0.0175	1.30e-24
rs10759697	A	G	0.1308	0.4906	9	1.17e+08	0.0173	3.93e-14
rs10804330	C	T	-0.1331	0.4329	2	2.27e+08	0.0176	4.60e-14
rs10838702	T	G	0.2375	0.3875	11	47410888	0.0178	1.27e-40
rs10873612	T	C	-0.1096	0.5961	15	26105602	0.0179	9.51e-10
rs9368	A	C	0.1121	0.3871	12	56988342	0.0178	3.24e-10
rs9406076	T	C	0.101	0.3278	6	8023804	0.0185	4.65e-08
rs9419374	G	A	-0.1164	0.646	10	1.34e+08	0.0185	3.44e-10
rs9526707	A	G	-0.1217	0.3222	13	51489186	0.0186	6.59e-11
rs964941	A	G	0.1726	0.5183	1	2.28e+08	0.0174	3.31e-23
rs9791312	C	A	0.1225	0.3452	6	1.43e+08	0.0184	2.89e-11
rs9841978	A	G	0.1766	0.3251	3	53730735	0.0185	1.12e-21
rs9889262	A	T	0.2283	0.3666	17	47398070	0.018	7.11e-37
rs9900637	A	C	0.0992	0.4961	17	3951975	0.0176	1.73e-08
rs990619	G	C	0.1592	0.5234	4	1.57e+08	0.0173	2.90e-20
rs9937801	C	T	-0.1554	0.4308	16	21088130	0.0174	4.81e-19

Note: DBP, diastolic blood pressure.

Table 2. Information on instrumental variables of DBP (201 SNPs).

SNP	EA	OA	beta	eaf	chr	pos	se	p
rs10048404	T	C	-0.1096	0.3694	18	54578482	0.0183	2.00e-09
rs10054208	T	C	0.1187	0.3617	5	55688992	0.0185	1.49e-10
rs10062049	T	C	0.2208	0.1359	5	61553881	0.0255	4.50e-18
rs1006545	T	G	0.3633	0.8875	10	1.03e+08	0.0275	7.96e-40
rs10069690	T	C	0.1615	0.2581	5	1279790	0.021	1.42e-14
rs10087280	G	A	-0.1381	0.1683	8	49391836	0.0232	2.54e-09
rs10164193	G	T	0.2196	0.0777	18	31161426	0.0327	1.87e-11
rs10279432	A	C	0.1178	0.6234	7	7279010	0.018	5.73e-11
rs1035673	C	T	-0.1625	0.6032	2	2.19e+08	0.0176	3.00e-20
rs1039897	A	G	-0.1085	0.6503	2	2.2e+08	0.0183	3.26e-09
rs9508495	T	C	-0.1944	0.7569	13	30146201	0.0204	1.34e-21
rs9526707	A	G	-0.1217	0.3222	13	51489186	0.0186	6.59e-11
rs962369	C	T	-0.1684	0.3013	11	27734420	0.0189	6.02e-19
rs964941	A	G	0.1726	0.5183	1	2.28e+08	0.0174	3.31e-23
rs9791312	C	A	0.1225	0.3452	6	1.43e+08	0.0184	2.89e-11
rs9841978	A	G	0.1766	0.3251	3	53730735	0.0185	1.12e-21
rs9900637	A	C	0.0992	0.4961	17	3951975	0.0176	1.73e-08
rs9918907	G	A	0.1188	0.2162	8	1.25e+08	0.021	1.59e-08
rs9932220	A	G	-0.1591	0.2177	16	51758116	0.021	3.76e-14
rs9937801	C	T	-0.1554	0.4308	16	21088130	0.0174	4.81e-19

Note: HF, heart failure.

Table 3. Information on instrumental variables of HF (394 SNPs).

selected genome-wide significant SNPs ($P < 1 \times 10^{-8}$ BMI = 8) for each trait.¹² We performed pairwise linkage disequilibrium (LD) thresholds for each mediated trait based on the original GWAS, and the LD thresholds for each trait were $r^2 < 0.1$ within a 1 MB window.¹³ Then, for all SNPs, we reconciled coding and non-coding alleles in summary statistics for each GWAS. For palindromic SNPs, we inferred chains based on allele frequencies.¹⁴ Palindromic SNPs with ambiguous allele frequencies (frequencies 0.3–0.7) were removed.¹⁵

2.3. MR analysis

2.3.1. Effect of DBP on HRDRF

We used 2-sample MR to estimate the overall effect of DBP on HRDRF. We used inverse variance weighted (IVW) analysis as our main method.¹⁶ The IVW method is widely used in MR. The principle is to take the inverse of each IV variance as the weight for weighting calculation.¹⁷ The results are close to the maximum likelihood estimation MR method. It is consistent with the estimate of the second-order least square method of the traditional single-sample MR

analysis.¹⁸ The final result is a weighted average of all IV effect values.¹⁹ Its advantage is that the variance of effect estimate is the smallest among the common methods.

2.3.2. Mediation analysis

We used IVW as our primary method to estimate the effect of DBP on each mediator.²⁰ We used regression-based MVMR to assess the effect of each mediator on the risk of HRDRF, while adjusting for genetic effects of instrumental DBP variables.²¹ For the individual mediating effect of each risk factor (HF, arrhythmia, atherosclerosis), we mainly used the coefficient product method to estimate the mediating effect of DBP on HRDRF.²² This involved first assessing the effect of DBP on each mediator individually and then multiplying the effect of DBP on the mediator with the effect of the mediator on the DBP adjustment of the outcome.²³ The mediating effect was divided by the total effect to estimate the proportion of the total effect mediated by DBP on the risk factors of HRDRF. Standard errors were estimated by the delta method²⁴ and the effects obtained by 2-sample MR analysis.

To estimate the combined proportional mediators, we used the differential MVMR method of regression coefficients to simultaneously adjust for the genetic effects of several mediators to obtain a direct effect of DBP on HRDRF.²⁵ Then, the combined indirect effect of the mediators considered is the residual of the total effect. We explored all possible meaningful combinations of intermediaries to find the one with the highest proportion of intermediaries and to assess potential overlap between intermediaries.²⁶

2.4. MR sensitivity analyses

To assess the robustness of the MR results, sensitivity analyses were performed.

- (1) In addition to the main analysis IVW, we also used the 2-sample MR method and found that it was robust to the violation assumption of SNP level pleiotropy.²⁷
- (2) In order to verify the estimation results of coefficient multiplication, we use the multivariate MR method, and use the product method to calculate the individual mediation effect of each mediator.²⁸
- (3) The MVMR–Egger method and leave-One-out method were used to evaluate the obtained model. The hypothesis of the MR–Egger²⁹ method is that IV intensity is independent of IV effect size. The intercept term of this method is the estimate of pleiotropy. The *P*-value of the intercept term was not significant ($P > 0.05$), indicating no pleiotropy. Leave-one-out method is also a common

MR reliability-evaluation method, which can test the effect value of each IV in turn to determine whether the obtained MR results are driven by a single IV.

MR analysis was performed using R (version 4.1.2)³⁰ and TwoSampleMR R Package version 0.5.6.

3. Results

3.1. MR analysis Results

In this study, 3 times of MR were conducted: (1) respectively DBP on HRDRF, (2) DBP on mediating factors, such as HF, HA, and AHD, and (3) significant mediating factors on HRDRF.

The main analysis methods are IVW method and weighted median method, and the results are shown in Table 4.

In Table 4, the overall effect direction of the IVW method and the weighted median method is consistent and significant. It indicated that DBP was a risk factor for HRDRF, OR = 1.0002 (95% CI: 1.0001–1.0003, $P = 1.8076e-05$). HF was causally related to DBP (OR = 1.0295, 95% CI: 1.0221–1.0370, $P = 2.5292e-15$).

HF was selected as a mediating factor for further MR, and the results in Table 5 show that it was a risk factor for HRDRF, OR = 1.0000 (95% CI: 1.0000–1.0001, $P = 0.0152$). This mediated effect accounted for 24.69% of the total causal effect, indicating that this causal pathway could not be ignored. DBP will increase the risk of HRDRF by increasing HF. The causality relationship of DBP, HF, and HRDRF is shown in Figure 2 and the Forest plot is show in Figure 3.

Exposure	Outcome	IVW			WME		
		OR	95% CI	<i>P</i> -value	OR	95% CI	<i>P</i> -value
DBP	HRDRF	1.0002	1.0001–1.0003	1.8076e–05	1.0002	1.0001–1.0004	1.1617e–03
DBP	HF	1.0295	1.0221–1.0370	2.5292e–15	1.0394	1.0300–1.0488	4.9222e–17
DBP	HA	1.0001	1.0000–1.00022	0.0932	1.0000	0.9999–1.00024	0.7875
DBP	AHD	1.0017	1.0014–1.0020	1.4957e–29	1.0017	1.0013–1.0020	1.1820e–20

Note: AHD, atherosclerotic heart disease; DBP, diastolic blood pressure; HA, heart arrhythmia; HF, heart failure; HRDRF, hypertensive renal disease with renal failure; IVW, inverse variance weighted.

Table 4. Results of DBP on HRDRF and related indicators.

Exposure	Outcome	OR	95% CI	<i>P</i> -value
HF	HRDRF	1.0017	1.0004–1.0030	0.0108

Note: HF, heart failure; HRDRF, hypertensive renal disease with renal failure.

Table 5. Mediation analysis results.

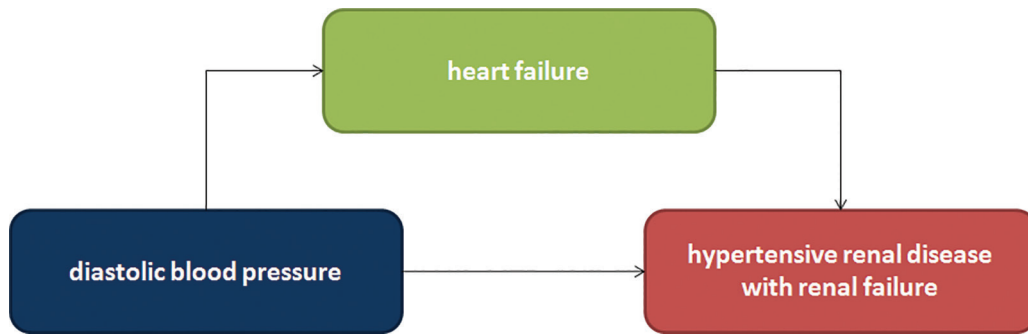
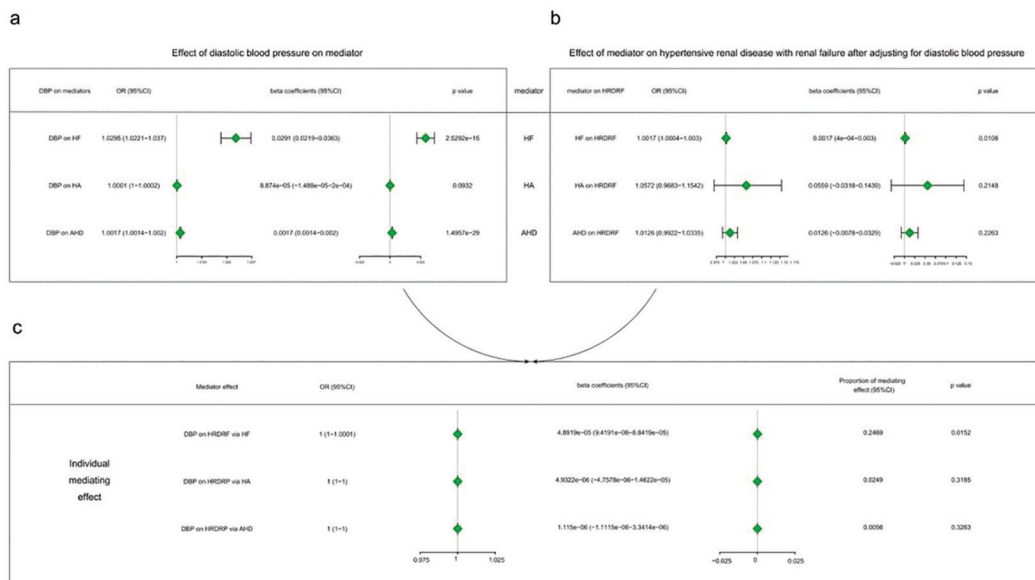


Figure 2. Schematic diagram of causality.



Note: AHD, atherosclerotic heart disease; DBP, diastolic blood pressure; HA, heart arrhythmia; HF, heart failure; HRDRF, hypertensive renal disease with renal failure; MR, Mendelian randomization.

Figure 3. (a) MR-estimated effects of DBP on each mediator separately, presented as β /OR with 95% CI. (b) MR-estimated effects of each mediator separately on HRDRF after MVMR adjustment for DBP, presented as β /OR with 95% CI. (c) MR estimated effects of indirect effects of each mediator separately, by product of coefficients method with delta method-estimated 95% CIs. MR estimated proportions mediated (%) are presented with 95% CIs.

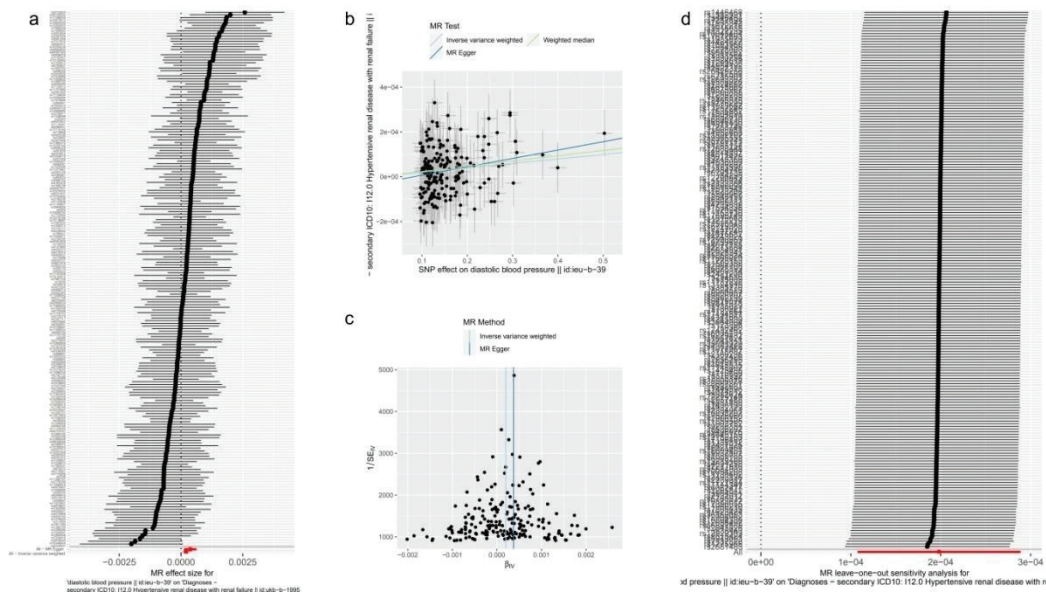
3.2. MR sensitivity analysis

MR-Egger results showed that the OR values of the intercept terms were all close to 1, and the P -value results were not significant, which proved that pleiotropy did not exist, indicating that our analysis results were not interfered by multiple effects.

The leave-one-out method showed that the analysis results for each of the IVs highlighted that all the IVs were calculated to make these causal relationships significant. There are no leading IVs in HF and HRDRF, and the previous MR results are effective (Figure 4).

4. Discussion

Hypertension is one of the common complications of CKD, and the two cause and effect each other, forming a vicious cycle. Clinical studies have shown that if blood pressure is not well controlled, glomerular arteriolar sclerosis, renal parenchymal ischemia, glomerular fibrosis, and other pathological changes can often be caused, and then accelerate renal artery atherosclerosis, resulting in the decline of renal function.³¹ In severe cases, CKD can accelerate the progression to ESRD, and hypertension is also a risk factor for cardiovascular events.³²



Note: DBP, diastolic blood pressure; HRDRF, hypertensive renal disease with renal failure; MR, Mendelian randomization.

Figure 4. (A) MR effect size for DBP on HRDRF. (B) SNP effect on DBP. (C) MR funnel plot of DBP on HRDRF. (D) MR leave-one-out sensitivity analysis of DBP on HRDRF.

This study used the statistical results of large-scale GWAS to analyze the causal relationship between DBP and hypertensive nephropathy complicated with renal failure and used network MR to analyze the mediating effect of HF.³³ The results showed that DBP increased the risk of hypertensive nephropathy complicated with renal failure and increased the risk of HF.³⁴ HF is considered as a risk factor for hypertensive nephropathy complicated with renal failure. Therefore, DBP is a risk factor for hypertensive nephropathy complicated with renal failure and can increase the condition by mediating the increase of HF.³⁵ The results of the MR-Egger and leave-one analyses showed that the results of MR analysis were not disturbed by pleiotropy.³⁶ Earlier studies exploring the causality relationship between DBP and HRDRF sought DBP from the genetic level. Therefore, it is closely related to the interpretation of genetic factors that are common to renal disease with renal failure.³⁷ Some patients have better vascular elasticity, when heart diastolic comes, the aortic elastic retraction is strong, coupled with the surrounding blood vessels in a state of contraction, then the pressure (that is, DBP) will be higher.³⁸ Long-term DBP at a high level will cause damage to the heart, brain, kidney, and other important organs. Studies have shown that when DBP was stratified by every 10 mmHg, the eGFR was significantly increased when DBP was 81–90 mmHg and 91–100 mmHg compared with DBP of 60–70 mmHg.³⁹ DBP is regulated by nerve–blood vessels, then nerve–endocrine dysfunction occurs, and target organ perfusion

imbalance, cardiac diastolic dysfunction and other factors, make the CKD patients with hypertension with renal function changes, especially in patients with stage 3 or 4 CKD, can be kidney damage due to long-term high blood pressure and blood pressure fluctuation is bigger, and its happening mechanism are made more complicated, Aggravating vascular sclerosis and causing renal function decline.⁴⁰ When the concentration of urine trace albumin in the urine increased, renal tubular resorption ability to drop, GFR will also rise, ACR levels, accelerate the destruction of the nephron, hardening and fibrosis, increase water sodium retention, increased vasoconstriction, increase peripheral resistance, and activate the renin–angiotensin, reduce prostaglandin, slow in renal antihypertensive material such as activated peptides. In turn, the blood pressure level increases, aggravating vascular sclerosis and promoting renal failure.⁴¹ This study makes it clear that there is a causal relationship between DBP and HRDRF. However, this study also has some limitations. Although the sample size of the data used was large, the conclusions were based on a population sample of European ancestry. Large-scale GWAS studies in global populations are lacking. Hypertension renal disease with renal failure data analysis results are not according to clinical classification will be divided into different classes, which makes us unable to study DBP through the mediation effect of hf concrete will affect hypertension nephropathy merger renal failure which the class of the disease, and evaluation of hypertension nephropathy merger related indicator of renal

failure. In addition, based on the experimental results, we have found a causal relationship between DBP and renal failure in patients with hypertensive nephropathy, and found that HF plays an important mediating role in this causal relationship. Therefore, in clinical nursing work, we need to closely monitor the DBP of patients with hypertensive nephropathy and reduce the possibility of HF in such patients.

In conclusion, this study confirmed the causal relationship between DBP and hypertensive nephropathy complicated with renal failure by mediating MR analysis and found that HF plays an important mediating role in this causal relationship.

Availability of data and materials

The datasets generated and/or analyzed during the current study are available in the GWAS summary data repository (<https://gwas.mrcieu.ac.uk/>).

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Authors' contributions

WS worked on the study design; HC, FL, and MW completed the data analysis, and LP and ZD completed the manuscript editing. All authors read and approved the final manuscript.

Ethical approval

Ethical issues are not involved in this paper.

Conflicts of interest

All contributing authors declare no conflicts of interest.

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