The Causal Relationship between Plasma Protein-to-Protein Ratios and Chronic Kidney Disease: A Proteomic Mendelian Randomization Study

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Introduction. Chronic Kidney Disease (CKD) is a major global health burden, with rising prevalence and high mortality in patients with end-stage kidney disease (ESKD). While hypertension and diabetes are known risk factors, confounding limits the ability of observational studies to establish causality. This study aims to identify plasma protein ratios genetically associated with overall CKD susceptibility using Mendelian randomization (MR).
Methods. We performed a two-sample MR analysis using genetic variants as instrumental variables to assess causal relationships between 2,821 plasma protein ratios and CKD. Protein ratio data were derived from large-scale proteomics studies, and CKD outcome data were obtained from genome-wide association studies (GWAS).
Results. The MR analysis observed inverse genetically predicted associations between CD74-related protein ratios and CKD risk, including CD74/NPDC1 (OR = 0.8449, P = .0026) and CD74/TNFRSF21 (OR = 0.8644, P = .0007), although these findings did not remain significant after Bonferroni correction and should be considered exploratory.
Conclusion. Our findings provide novel evidence that CD74 and related protein ratios may represent exploratory genetic signals associated with CKD susceptibility. These results highlight their potential for CKD management, although further biological validation is warranted.

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INTRODUCTION

Chronic Kidney Disease (CKD) is a significant public health concern worldwide, with its prevalence continuously rising. End-stage kidney disease (ESKD) is the final stage of CKD. Patients with ESKD have nearly a sixfold higher risk of mortality compared to those with an estimated glomerular filtration rate (eGFR) of 60 mL/min/1.73 m².[1] CKD is also a major cause of cardiovascular disease (CVD).[2] Although numerous studies have established associations between various known risk factors (such as hypertension, diabetes mellitus, and obesity) and CKD,[3-5] traditional observational studies often struggle to demonstrate a direct causal relationship. This limitation arises from their inability to adequately control for confounding factors. Therefore, a more in-depth investigation into the etiology of CKD and its potential biomarkers is a significant challenge in current research.

In recent years, proteins have gained attention as potential biomarkers for early diagnosis of disease, monitoring progression.[6-8] Protein levels reflect an individual's physiological state and play crucial roles in various pathological processes. Notably, protein ratios serve as comprehensive biomarkers that can more accurately represent

protein interactions and their synergistic roles in physiological and pathological contexts. The potential of protein ratios as disease markers has garnered increasing interest, particularly in cancer.[9,10] However, the causal relationship between plasma protein ratios and CKD remains unclear, and traditional observational studies face challenges in inferring causal effects, highlighting the urgent need for more robust causal inference methods.

Mendelian randomization (MR), a causal inference method utilizing genetic variants as instrumental variables, has become extensively employed in recent years to study the causal mechanisms underlying complex diseases.[11] This method leverages genetic variation as a natural experiment to infer causal relationships between exposure factors and diseases by examining the relationship between genotype and phenotype.[12] Given that genetic variants are randomly distributed among individuals, MR effectively reduces confounding bias, thus providing more reliable causal evidence. In proteomics, the MR approach has emerged as a crucial tool for assessing the causal relationships between proteins or protein ratios and diseases, particularly in exploring associations between proteomes and complex diseases such as type 2 diabetes mellitus, cardiovascular diseases, and related metabolic disorders.[13-15]

In this study, we integrated data from 2,821 plasma protein ratios derived from large-scale proteomics studies and applied MR to systematically evaluate the causal relationship between these protein ratios and CKD. We identified CD74 and its associated protein ratios, CD74/NPDC1 and CD74/TNFRSF21, which may be closely linked to the onset and progression of CKD. This study provides new scientific evidence supporting CD74 and its associated protein ratios as potential biomarkers or therapeutic targets for CKD.

MATERIALS AND METHODS

Study design

MR analysis involves using genetic variations that are strongly associated with the exposure factor as instrumental variables (IVs) to assess the causal relationship between the exposure factor and the outcome. By using genetic variations as IVs, the influence of confounding factors on the results can be reduced, thereby improving the reliability of causal inference. Therefore, we conducted MR analysis utilizing summary statistics data from genome-wide association studies (GWAS) to identify single nucleotide polymorphisms (SNPs) strongly associated with plasma protein ratios as IVs. We studied the causal relationship between plasma protein ratios and chronic kidney disease.

Data source

The research data were based on published GWAS summary data. The exposure data consists of GWAS summary data on plasma protein ratios from the literature, including 2810 plasma protein ratios from Europeans.[16] Considering that population confounding may lead to biased estimates, we restricted the genetic background of the population in the MR study to individuals of European descent. The outcome data: CKD: the GWAS summary data from the FinnGen dataset R11.0 included 11265 CKD patients and 436208 healthy controls with a total of 1010464 SNPs.

SNP in exposure and outcome selection

All SNPs will be aggregated to minimize linkage disequilibrium within a strict window ($r^2 = 0.001$, kb = 10,000). The threshold is set at $P < 5 \times 10^{-8}$ to select significant SNPs. F-statistic > 10 to ensure sufficient strength of the IVs related to the exposure traits. Finally, we identified a total of 94926 SNPs associated with 2,821 protein ratios that satisfied the above criteria.

For the reverse MR analysis, in order to ensure an adequate number of SNPs for CKD as the exposure, a less stringent threshold of $P < 1 \times 10^{-5}$ was applied. This approach allowed the inclusion of sufficient IVs for robust evaluation of potential causal effects of CKD on protein ratios.

During harmonization, effect alleles were aligned between the exposure and outcome datasets based on SNP identifiers and allele information. Palindromic SNPs were systematically evaluated using allele frequency information, and only variants with ambiguous strand orientation were excluded to avoid potential strand misclassification. SNPs with inferable strand orientation were retained after allele alignment. Full SNP-level summary statistics before harmonization are provided in Table S1, whereas the harmonized exposure–outcome datasets used for Mendelian randomization analyses are presented in Table S2.

Table S1. Exposure GWAS summary statistics prior to harmonization

Exposure	Chr	Pos	Effect_ allele	Other_ allele	Beta	Se	Eaf	Neg_ log_10_*P*_ value	SNP	Sample size	Beta_ numerator	Standard_ error_ numerator	log_10_*P*_ value_ numerator	Beta_ denomintor	Error_ denomintor	Neg_ log_10_p_ value_denom	Log_10_p_ gain	*P*	R^2	F	Mranf
CD74.NPDC1	2	103,070,568	T	C	0.048	0.008	0.228	8.175	rs917997	42,004	0.030	0.008	3.871	-0.018	0.008	1.732	4.304	6.68E-9	0.001	33.639	104.035
CD74.NPDC1	2	111,790,804	G	C	-0.042	0.009	0.835	5.232	rs3789088	41,946	-0.026	0.009	2.580	0.010	0.009	0.617	2.652	5.86E-6	0.000	20.536	104.035
CD74.NPDC1	2	211,349,092	A	G	-0.036	0.008	0.756	5.207	rs72932418	41,970	-0.030	0.008	4.261	0.004	0.008	0.216	0.946	6.21E-6	0.000	20.427	104.035
CD74.NPDC1	5	131,824,486	A	C	-0.044	0.007	0.657	8.632	rs2070722	41,954	-0.049	0.007	12.158	-0.013	0.007	1.180	-3.526	2.33E-9	0.001	35.687	104.035
CD74.NPDC1	5	149,793,650	G	A	-0.081	0.011	0.891	12.784	rs79078220	41,927	-0.078	0.010	13.352	-0.003	0.010	0.129	-0.569	1.65E-13	0.001	54.422	104.035
CD74.NPDC1	6	32,385,119	C	T	-0.143	0.009	0.840	54.129	rs28732208	42,029	-0.127	0.009	48.267	0.005	0.009	0.240	5.861	7.43E-55	0.006	244.015	104.035
CD74.NPDC1	6	32,723,715	C	A	0.091	0.014	0.939	9.735	rs116212553	42,006	0.059	0.014	4.892	-0.027	0.014	1.331	4.844	1.84E-10	0.001	40.648	104.035
CD74.NPDC1	6	33,048,467	G	T	-0.087	0.008	0.781	24.663	rs1126513	42,022	-0.072	0.008	19.258	0.012	0.008	0.864	5.405	2.17E-25	0.003	108.556	104.035
CD74.NPDC1	6	147,701,133	T	G	0.042	0.007	0.409	8.841	rs9373523	41,764	-0.005	0.007	0.307	-0.051	0.007	13.836	-4.995	1.44E-9	0.001	36.625	104.035
CD74.NPDC1	8	57,286,474	A	C	-0.082	0.018	0.963	5.132	rs77489913	41,919	-0.056	0.017	2.970	0.017	0.017	0.472	2.163	7.37E-6	0.000	20.098	104.035
CD74.NPDC1	9	139,883,221	C	T	0.114	0.014	0.940	14.517	rs77740311	41,876	0.017	0.014	0.677	-0.107	0.014	14.193	0.324	3.04E-15	0.001	62.286	104.035
CD74.NPDC1	9	139,945,051	A	G	0.145	0.012	0.098	34.665	rs7869520	42,003	-0.010	0.011	0.450	-0.169	0.011	51.209	-16.544	2.16E-35	0.004	154.413	104.035
CD74.NPDC1	10	62,590,031	C	A	0.116	0.024	0.980	5.689	rs17246768	41,978	0.076	0.023	3.064	-0.014	0.023	0.267	2.625	2.05E-6	0.001	22.557	104.035
CD74.NPDC1	11	128,096,708	T	C	-0.043	0.008	0.713	7.648	rs1793328	41,978	-0.036	0.007	6.280	0.002	0.007	0.103	1.368	2.25E-8	0.001	31.276	104.035
CD74.NPDC1	12	68,571,378	C	T	0.037	0.007	0.386	6.599	rs7137814	41,866	0.037	0.007	7.455	0.007	0.007	0.511	-0.856	2.52E-7	0.001	26.594	104.035
CD74.NPDC1	12	111,800,258	G	A	-0.081	0.008	0.700	26.287	rs3809272	41,727	-0.072	0.007	23.764	0.003	0.007	0.184	2.523	5.16E-27	0.003	115.993	104.035
CD74.NPDC1	12	113,235,279	C	T	-0.037	0.007	0.565	6.936	rs7132088	41,833	-0.035	0.007	7.003	-0.001	0.007	0.033	-0.067	1.16E-7	0.001	28.099	104.035
CD74.NPDC1	14	92,309,325	A	G	-0.050	0.007	0.420	12.331	rs1884840	41,994	0.002	0.007	0.092	0.059	0.007	18.251	-5.920	4.67E-13	0.001	52.371	104.035
CD74.NPDC1	16	10,965,126	G	A	0.149	0.008	0.763	73.012	rs12922863	41,459	0.128	0.008	60.993	-0.011	0.008	0.766	12.019	9.73E-74	0.008	331.281	104.035
CD74.NPDC1	16	10,997,243	C	G	-0.104	0.012	0.917	16.728	rs78372326	41,958	-0.084	0.012	12.417	0.013	0.012	0.560	4.311	1.87E-17	0.002	72.337	104.035
CD74.NPDC1	17	7,091,650	T	C	0.047	0.007	0.652	10.302	rs314253	41,959	0.035	0.007	6.706	-0.009	0.007	0.769	3.596	4.99E-11	0.001	43.201	104.035
CD74.TNFRSF21	1	109,817,192	A	G	0.066	0.008	0.778	15.862	rs7528419	42,593	0.000	0.008	0.012	-0.076	0.008	20.518	-4.655	1.37E-16	0.002	68.397	75.242
CD74.TNFRSF21	1	150,739,035	C	T	-0.047	0.010	0.866	6.092	rs34711732	42,778	-0.002	0.009	0.080	0.049	0.010	6.290	-0.197	8.09E-7	0.001	24.343	75.242
CD74.TNFRSF21	1	179,526,214	C	T	-0.078	0.017	0.963	5.196	rs61747728	42,867	0.066	0.017	4.043	0.175	0.017	22.971	-17.775	6.36E-6	0.000	20.380	75.242
CD74.TNFRSF21	2	27,742,603	T	C	0.036	0.007	0.377	6.875	rs780093	42,839	-0.016	0.007	1.705	-0.062	0.007	18.423	-11.548	1.33E-7	0.001	27.824	75.242
CD74.TNFRSF21	2	103,054,449	G	A	0.037	0.008	0.229	5.667	rs2058660	42,820	0.030	0.008	3.974	-0.003	0.008	0.177	1.693	2.15E-6	0.001	22.459	75.242
CD74.TNFRSF21	3	12,851,170	G	T	0.102	0.022	0.978	5.243	rs142983871	42,897	0.074	0.022	3.138	-0.017	0.023	0.352	2.105	5.72E-6	0.000	20.585	75.242
CD74.TNFRSF21	3	58,397,102	G	A	0.045	0.007	0.636	9.948	rs62258127	42,789	0.038	0.007	7.795	-0.002	0.007	0.122	2.153	1.13E-10	0.001	41.605	75.242
CD74.TNFRSF21	3	156,798,775	T	C	0.030	0.007	0.606	5.012	rs900400	42,467	0.006	0.007	0.386	-0.028	0.007	4.219	0.793	9.73E-6	0.000	19.568	75.242
CD74.TNFRSF21	3	159,653,368	A	C	0.031	0.007	0.439	5.435	rs13084736	42,798	0.020	0.007	2.713	-0.008	0.007	0.586	2.723	3.67E-6	0.001	21.434	75.242
CD74.TNFRSF21	5	96,124,330	T	C	-0.033	0.007	0.343	5.714	rs30187	42,827	-0.009	0.007	0.716	0.025	0.007	3.471	2.244	1.93E-6	0.001	22.667	75.242
CD74.TNFRSF21	5	131,864,152	C	T	0.038	0.008	0.748	6.226	rs11739623	42,685	0.036	0.007	5.778	0.004	0.008	0.241	0.448	5.95E-7	0.001	24.936	75.242
CD74.TNFRSF21	5	149,793,650	G	A	-0.098	0.011	0.891	19.718	rs79078220	42,788	-0.078	0.010	13.352	0.010	0.011	0.444	6.365	1.92E-20	0.002	85.959	75.242
CD74.TNFRSF21	5	176,630,984	T	C	0.037	0.008	0.222	5.393	rs7721671	42,814	0.045	0.008	7.977	0.016	0.008	1.305	-2.584	4.05E-6	0.000	21.247	75.242
CD74.TNFRSF21	6	32,341,398	A	G	-0.145	0.009	0.842	58.900	rs9391858	42,809	-0.129	0.009	48.480	-0.003	0.009	0.135	10.419	1.26E-59	0.006	266.018	75.242
CD74.TNFRSF21	6	32,723,715	C	A	0.089	0.014	0.939	10.043	rs116212553	42,869	0.059	0.014	4.892	-0.026	0.014	1.212	5.151	9.06E-11	0.001	42.034	75.242
CD74.TNFRSF21	6	33,086,448	G	A	-0.043	0.007	0.689	8.606	rs1883414	42,831	-0.041	0.007	8.360	-0.007	0.007	0.478	0.247	2.47E-9	0.001	35.572	75.242
CD74.TNFRSF21	6	47,104,856	T	C	-0.039	0.007	0.447	8.152	rs1630504	42,816	0.000	0.007	0.021	0.043	0.007	9.764	-1.612	7.05E-9	0.001	33.534	75.242
CD74.TNFRSF21	6	47,193,893	C	T	-0.061	0.011	0.886	7.940	rs78448796	41,206	0.008	0.011	0.331	0.080	0.011	12.799	-4.859	1.15E-8	0.001	32.585	75.242
CD74.TNFRSF21	6	47,303,011	T	G	-0.080	0.007	0.629	31.075	rs6458558	42,699	0.007	0.007	0.503	0.100	0.007	46.489	-15.414	8.42E-32	0.003	137.931	75.242
CD74.TNFRSF21	6	137,179,387	G	A	0.033	0.007	0.372	5.769	rs2012700	42,759	0.013	0.007	1.318	-0.020	0.007	2.424	3.345	1.70E-6	0.001	22.910	75.242
CD74.TNFRSF21	8	11,702,375	G	A	0.038	0.008	0.743	6.456	rs3947	42,863	0.030	0.007	4.285	-0.004	0.008	0.255	2.171	3.50E-7	0.001	25.959	75.242
CD74.TNFRSF21	9	136,149,399	G	A	-0.163	0.009	0.819	80.157	rs507666	42,809	-0.133	0.008	55.683	0.012	0.009	0.810	24.474	6.96E-81	0.008	364.317	75.242
CD74.TNFRSF21	9	136,356,448	G	A	0.139	0.027	0.984	6.533	rs76643124	42,802	0.144	0.027	7.166	0.031	0.027	0.595	-0.633	2.93E-7	0.001	26.303	75.242
CD74.TNFRSF21	10	1,011,958	T	C	-0.041	0.008	0.814	5.913	rs11253540	42,559	-0.024	0.008	2.459	0.015	0.008	1.091	3.455	1.22E-6	0.001	23.550	75.242
CD74.TNFRSF21	11	126,226,775	G	C	-0.080	0.013	0.923	9.515	rs73632737	42,860	-0.001	0.013	0.015	0.090	0.013	11.566	-2.051	3.05E-10	0.001	39.658	75.242
CD74.TNFRSF21	11	128,096,708	T	C	-0.033	0.007	0.713	5.094	rs1793328	42,839	-0.036	0.007	6.280	-0.013	0.007	1.062	-1.186	8.05E-6	0.000	19.930	75.242
CD74.TNFRSF21	12	68,534,520	A	G	0.055	0.007	0.290	13.348	rs2193045	42,813	0.043	0.007	8.942	-0.005	0.007	0.293	4.406	4.48E-14	0.001	56.980	75.242
CD74.TNFRSF21	12	111,800,258	G	A	-0.089	0.007	0.700	34.450	rs3809272	42,584	-0.072	0.007	23.764	0.008	0.007	0.533	10.686	3.55E-35	0.004	153.424	75.242
CD74.TNFRSF21	12	112,471,090	G	T	-0.055	0.012	0.918	5.188	rs12298022	42,861	-0.033	0.012	2.187	0.019	0.012	0.904	3.002	6.48E-6	0.000	20.345	75.242
CD74.TNFRSF21	12	113,235,279	C	T	-0.038	0.007	0.565	7.860	rs7132088	42,693	-0.035	0.007	7.003	-0.002	0.007	0.124	0.856	1.38E-8	0.001	32.224	75.242
CD74.TNFRSF21	15	24,923,283	G	A	-0.079	0.017	0.963	5.341	rs36032407	42,892	-0.050	0.017	2.486	0.027	0.017	0.939	2.855	4.56E-6	0.000	21.018	75.242
CD74.TNFRSF21	16	10,965,126	G	A	0.160	0.008	0.763	90.801	rs12922863	42,310	0.128	0.008	60.997	-0.014	0.008	1.142	29.804	1.58E-91	0.010	413.673	75.242
CD74.TNFRSF21	16	10,997,243	C	G	-0.110	0.012	0.917	20.243	rs78372326	42,822	-0.084	0.012	12.418	0.016	0.012	0.733	7.825	5.72E-21	0.002	88.355	75.242
CD74.TNFRSF21	16	61,918,243	G	A	0.132	0.029	0.987	5.119	rs79027597	42,903	0.074	0.029	1.987	-0.054	0.030	1.151	3.132	7.60E-6	0.000	20.039	75.242
CD74.TNFRSF21	16	81,534,790	T	C	0.040	0.007	0.300	7.579	rs2925979	42,871	0.015	0.007	1.433	-0.028	0.007	3.959	3.620	2.64E-8	0.001	30.967	75.242
CD74.TNFRSF21	17	76,404,893	C	T	0.038	0.008	0.755	6.222	rs11658146	42,742	0.043	0.008	7.796	0.011	0.008	0.783	-1.574	6.00E-7	0.001	24.919	75.242
CD74.TNFRSF21	20	44,576,502	T	C	0.048	0.009	0.818	7.740	rs7679	42,699	0.045	0.008	7.171	0.004	0.009	0.210	0.569	1.82E-8	0.001	31.689	75.242
CD74.TNFRSF21	21	42,648,821	T	G	0.036	0.007	0.498	7.077	rs12482242	42,736	0.023	0.007	3.283	-0.009	0.007	0.799	3.794	8.38E-8	0.001	28.726	75.242
CD74.TNFRSF21	22	30,038,152	A	C	0.039	0.009	0.823	5.133	rs2530664	42,870	0.027	0.008	2.779	-0.007	0.009	0.400	2.353	7.37E-6	0.000	20.099	75.242
CD74.TNFRSF21	22	46,915,621	G	T	0.038	0.008	0.783	5.455	rs9615375	42,889	0.019	0.008	1.716	-0.018	0.008	1.581	3.739	3.51E-6	0.001	21.523	75.242

Full SNP-level summary statistics of the exposure protein ratios (CD74/NPDC1 and CD74/TNFRSF21) before harmonization with the outcome GWAS.

Table S2. Harmonized exposure–outcome dataset used for Mendelian randomization analysis

exposure	outcome	SNP	effect_ allele. exposure	other_ allele. exposure	effect_ allele. outcome	other_ allele. outcome	beta. exposure	beta. outcome	eaf. exposure	eaf. outcome	chr. outcome	pos. outcome	pval. outcome	se.outcome	samplesize. outcome	chr. exposure	pos. exposure	se.exposure	samplesize. exposure	pval. exposure	R2	f	meanf
CD74.NPDC1	CKD	rs1126513	G	T	G	T	-0.087	-0.021	0.781	0.836	6	33,080,690	2.52E-1	0.019	447,473	6	33,048,467	0.008	42,022	2.17E-25	0.003	108.556	74.050
CD74.NPDC1	CKD	rs116212553	C	A	C	A	0.091	-0.022	0.939	0.891	6	32,755,938	3.09E-1	0.022	447,473	6	32,723,715	0.014	42,006	1.84E-10	0.001	40.648	74.050
CD74.NPDC1	CKD	rs12922863	G	A	G	A	0.149	-0.023	0.763	0.724	16	10,871,269	1.34E-1	0.015	447,473	16	10,965,126	0.008	41,459	9.73E-74	0.008	331.281	74.050
CD74.NPDC1	CKD	rs17246768	C	A	C	A	0.116	0.011	0.980	0.988	10	60,830,273	8.62E-1	0.063	447,473	10	62,590,031	0.024	41,978	2.05E-6	0.001	22.557	74.050
CD74.NPDC1	CKD	rs1793328	T	C	T	C	-0.043	0.035	0.713	0.665	11	128,226,813	1.60E-2	0.015	447,473	11	128,096,708	0.008	41,978	2.25E-8	0.001	31.276	74.050
CD74.NPDC1	CKD	rs1884840	A	G	A	G	-0.050	0.012	0.420	0.445	14	91,842,981	3.88E-1	0.014	447,473	14	92,309,325	0.007	41,994	4.67E-13	0.001	52.371	74.050
CD74.NPDC1	CKD	rs2070722	A	C	A	C	-0.044	-0.007	0.657	0.669	5	132,488,794	6.14E-1	0.015	447,473	5	131,824,486	0.007	41,954	2.33E-9	0.001	35.687	74.050
CD74.NPDC1	CKD	rs28732208	C	T	C	T	-0.143	0.055	0.840	0.797	6	32,417,342	1.00E-3	0.017	447,473	6	32,385,119	0.009	42,029	7.43E-55	0.006	244.015	74.050
CD74.NPDC1	CKD	rs314253	T	C	T	C	0.047	-0.023	0.652	0.584	17	7,188,331	9.40E-2	0.014	447,473	17	7,091,650	0.007	41,959	4.99E-11	0.001	43.201	74.050
CD74.NPDC1	CKD	rs3789088	G	C	G	C	-0.042	0.025	0.835	0.860	2	111,033,227	2.12E-1	0.020	447,473	2	111,790,804	0.009	41,946	5.86E-6	0.000	20.536	74.050
CD74.NPDC1	CKD	rs3809272	G	A	G	A	-0.081	0.021	0.700	0.645	12	111,362,454	1.41E-1	0.015	447,473	12	111,800,258	0.008	41,727	5.16E-27	0.003	115.993	74.050
CD74.NPDC1	CKD	rs7132088	C	T	C	T	-0.037	0.011	0.565	0.535	12	112,797,474	4.06E-1	0.014	447,473	12	113,235,279	0.007	41,833	1.16E-7	0.001	28.099	74.050
CD74.NPDC1	CKD	rs7137814	C	T	C	T	0.037	-0.015	0.386	0.520	12	68,177,598	2.83E-1	0.014	447,473	12	68,571,378	0.007	41,866	2.52E-7	0.001	26.594	74.050
CD74.NPDC1	CKD	rs72932418	A	G	A	G	-0.036	0.015	0.756	0.732	2	210,484,368	3.38E-1	0.016	447,473	2	211,349,092	0.008	41,970	6.21E-6	0.000	20.427	74.050
CD74.NPDC1	CKD	rs77489913	A	C	A	C	-0.082	-0.007	0.963	0.941	8	56,373,915	8.24E-1	0.029	447,473	8	57,286,474	0.018	41,919	7.37E-6	0.000	20.098	74.050
CD74.NPDC1	CKD	rs77740311	C	T	C	T	0.114	0.080	0.940	0.978	9	136,988,769	9.30E-2	0.047	447,473	9	139,883,221	0.014	41,876	3.04E-15	0.001	62.286	74.050
CD74.NPDC1	CKD	rs78372326	C	G	C	G	-0.104	0.022	0.917	0.931	16	10,903,386	4.14E-1	0.027	447,473	16	10,997,243	0.012	41,958	1.87E-17	0.002	72.337	74.050
CD74.NPDC1	CKD	rs7869520	A	G	A	G	0.145	0.012	0.098	0.089	9	137,050,599	6.21E-1	0.024	447,473	9	139,945,051	0.012	42,003	2.16E-35	0.004	154.413	74.050
CD74.NPDC1	CKD	rs79078220	G	A	G	A	-0.081	-0.001	0.891	0.935	5	150,414,087	9.85E-1	0.028	447,473	5	149,793,650	0.011	41,927	1.65E-13	0.001	54.422	74.050
CD74.NPDC1	CKD	rs917997	T	C	T	C	0.048	-0.006	0.228	0.191	2	102,454,108	7.34E-1	0.017	447,473	2	103,070,568	0.008	42,004	6.68E-9	0.001	33.639	74.050
CD74.NPDC1	CKD	rs9373523	T	G	T	G	0.042	0.011	0.409	0.477	6	147,379,997	4.22E-1	0.014	447,473	6	147,701,133	0.007	41,764	1.44E-9	0.001	36.625	74.050
CD74.TNFRSF21	CKD	rs11253540	T	C	T	C	-0.041	-0.007	0.814	0.835	10	966,018	7.15E-1	0.018	447,473	10	1,011,958	0.008	42,559	1.22E-6	0.001	23.550	53.625
CD74.TNFRSF21	CKD	rs116212553	C	A	C	A	0.089	-0.022	0.939	0.891	6	32,755,938	3.09E-1	0.022	447,473	6	32,723,715	0.014	42,869	9.06E-11	0.001	42.034	53.625
CD74.TNFRSF21	CKD	rs11658146	C	T	C	T	0.038	0.001	0.755	0.801	17	78,408,812	9.31E-1	0.017	447,473	17	76,404,893	0.008	42,742	6.00E-7	0.001	24.919	53.625
CD74.TNFRSF21	CKD	rs11739623	C	T	C	T	0.038	0.004	0.748	0.747	5	132,528,460	8.16E-1	0.016	447,473	5	131,864,152	0.008	42,685	5.95E-7	0.001	24.936	53.625
CD74.TNFRSF21	CKD	rs12298022	G	T	G	T	-0.055	-0.002	0.918	0.961	12	112,033,286	9.58E-1	0.035	447,473	12	112,471,090	0.012	42,861	6.48E-6	0.000	20.345	53.625
CD74.TNFRSF21	CKD	rs12482242	T	G	T	G	0.036	-0.016	0.498	0.554	21	41,276,894	2.34E-1	0.014	447,473	21	42,648,821	0.007	42,736	8.38E-8	0.001	28.726	53.625
CD74.TNFRSF21	CKD	rs12922863	G	A	G	A	0.160	-0.023	0.763	0.724	16	10,871,269	1.34E-1	0.015	447,473	16	10,965,126	0.008	42,310	1.58E-91	0.010	413.673	53.625
CD74.TNFRSF21	CKD	rs13084736	A	C	A	C	0.031	-0.022	0.439	0.488	3	159,935,580	1.02E-1	0.014	447,473	3	159,653,368	0.007	42,798	3.67E-6	0.001	21.434	53.625
CD74.TNFRSF21	CKD	rs142983871	G	T	G	T	0.102	0.019	0.978	0.968	3	12,809,671	6.22E-1	0.039	447,473	3	12,851,170	0.022	42,897	5.72E-6	0.000	20.585	53.625
CD74.TNFRSF21	CKD	rs1630504	T	C	T	C	-0.039	-0.022	0.447	0.273	6	47,137,120	1.51E-1	0.015	447,473	6	47,104,856	0.007	42,816	7.05E-9	0.001	33.534	53.625
CD74.TNFRSF21	CKD	rs1793328	T	C	T	C	-0.033	0.035	0.713	0.665	11	128,226,813	1.60E-2	0.015	447,473	11	128,096,708	0.007	42,839	8.05E-6	0.000	19.930	53.625
CD74.TNFRSF21	CKD	rs1883414	G	A	G	A	-0.043	0.008	0.689	0.748	6	33,118,671	6.30E-1	0.016	447,473	6	33,086,448	0.007	42,831	2.47E-9	0.001	35.572	53.625
CD74.TNFRSF21	CKD	rs2012700	G	A	G	A	0.033	-0.005	0.372	0.404	6	136,858,249	7.03E-1	0.014	447,473	6	137,179,387	0.007	42,759	1.70E-6	0.001	22.910	53.625
CD74.TNFRSF21	CKD	rs2058660	G	A	G	A	0.037	-0.005	0.229	0.191	2	102,437,989	7.59E-1	0.017	447,473	2	103,054,449	0.008	42,820	2.15E-6	0.001	22.459	53.625
CD74.TNFRSF21	CKD	rs2193045	A	G	A	G	0.055	-0.033	0.290	0.385	12	68,140,740	1.90E-2	0.014	447,473	12	68,534,520	0.007	42,813	4.48E-14	0.001	56.980	53.625
CD74.TNFRSF21	CKD	rs2530664	A	C	A	C	0.039	-0.029	0.823	0.854	22	29,642,163	1.34E-1	0.019	447,473	22	30,038,152	0.009	42,870	7.37E-6	0.000	20.099	53.625
CD74.TNFRSF21	CKD	rs2925979	T	C	T	C	0.040	0.020	0.300	0.323	16	81,501,185	1.66E-1	0.015	447,473	16	81,534,790	0.007	42,871	2.64E-8	0.001	30.967	53.625
CD74.TNFRSF21	CKD	rs30187	T	C	T	C	-0.033	-0.018	0.343	0.352	5	96,788,627	2.11E-1	0.014	447,473	5	96,124,330	0.007	42,827	1.93E-6	0.001	22.667	53.625
CD74.TNFRSF21	CKD	rs34711732	C	T	C	T	-0.047	0.009	0.866	0.876	1	150,766,559	6.78E-1	0.021	447,473	1	150,739,035	0.010	42,778	8.09E-7	0.001	24.343	53.625
CD74.TNFRSF21	CKD	rs36032407	G	A	G	A	-0.079	0.026	0.963	0.976	15	24,678,136	5.74E-1	0.045	447,473	15	24,923,283	0.017	42,892	4.56E-6	0.000	21.018	53.625
CD74.TNFRSF21	CKD	rs3809272	G	A	G	A	-0.089	0.021	0.700	0.645	12	111,362,454	1.41E-1	0.015	447,473	12	111,800,258	0.007	42,584	3.55E-35	0.004	153.424	53.625
CD74.TNFRSF21	CKD	rs3947	G	A	G	A	0.038	0.004	0.743	0.804	8	11,844,866	8.30E-1	0.017	447,473	8	11,702,375	0.008	42,863	3.50E-7	0.001	25.959	53.625
CD74.TNFRSF21	CKD	rs61747728	C	T	C	T	-0.078	0.021	0.963	0.937	1	179,557,079	4.71E-1	0.029	447,473	1	179,526,214	0.017	42,867	6.36E-6	0.000	20.380	53.625
CD74.TNFRSF21	CKD	rs62258127	G	A	G	A	0.045	0.006	0.636	0.752	3	58,411,375	7.09E-1	0.016	447,473	3	58,397,102	0.007	42,789	1.13E-10	0.001	41.605	53.625
CD74.TNFRSF21	CKD	rs6458558	T	G	T	G	-0.080	-0.012	0.629	0.676	6	47,335,275	4.19E-1	0.015	447,473	6	47,303,011	0.007	42,699	8.42E-32	0.003	137.931	53.625
CD74.TNFRSF21	CKD	rs7132088	C	T	C	T	-0.038	0.011	0.565	0.535	12	112,797,474	4.06E-1	0.014	447,473	12	113,235,279	0.007	42,693	1.38E-8	0.001	32.224	53.625
CD74.TNFRSF21	CKD	rs73632737	G	C	G	C	-0.080	-0.003	0.923	0.918	11	126,356,880	9.03E-1	0.025	447,473	11	126,226,775	0.013	42,860	3.05E-10	0.001	39.658	53.625
CD74.TNFRSF21	CKD	rs7528419	A	G	A	G	0.066	-0.013	0.778	0.785	1	109,274,570	4.34E-1	0.017	447,473	1	109,817,192	0.008	42,593	1.37E-16	0.002	68.397	53.625
CD74.TNFRSF21	CKD	rs76643124	G	A	G	A	0.139	0.003	0.984	0.896	9	133,491,326	8.81E-1	0.023	447,473	9	136,356,448	0.027	42,802	2.93E-7	0.001	26.303	53.625
CD74.TNFRSF21	CKD	rs7679	T	C	T	C	0.048	-0.011	0.818	0.851	20	45,947,863	5.67E-1	0.019	447,473	20	44,576,502	0.009	42,699	1.82E-8	0.001	31.689	53.625
CD74.TNFRSF21	CKD	rs7721671	T	C	T	C	0.037	0.021	0.222	0.251	5	177,203,983	1.89E-1	0.016	447,473	5	176,630,984	0.008	42,814	4.05E-6	0.000	21.247	53.625
CD74.TNFRSF21	CKD	rs780093	T	C	T	C	0.036	-0.006	0.377	0.352	2	27,519,736	6.76E-1	0.014	447,473	2	27,742,603	0.007	42,839	1.33E-7	0.001	27.824	53.625
CD74.TNFRSF21	CKD	rs78372326	C	G	C	G	-0.110	0.022	0.917	0.931	16	10,903,386	4.14E-1	0.027	447,473	16	10,997,243	0.012	42,822	5.72E-21	0.002	88.355	53.625
CD74.TNFRSF21	CKD	rs78448796	C	T	C	T	-0.061	0.021	0.886	0.839	6	47,226,157	2.71E-1	0.019	447,473	6	47,193,893	0.011	41,206	1.15E-8	0.001	32.585	53.625
CD74.TNFRSF21	CKD	rs79027597	G	A	G	A	0.132	-0.047	0.987	0.978	16	61,884,339	3.33E-1	0.048	447,473	16	61,918,243	0.029	42,903	7.60E-6	0.000	20.039	53.625
CD74.TNFRSF21	CKD	rs79078220	G	A	G	A	-0.098	-0.001	0.891	0.935	5	150,414,087	9.85E-1	0.028	447,473	5	149,793,650	0.011	42,788	1.92E-20	0.002	85.959	53.625
CD74.TNFRSF21	CKD	rs900400	T	C	T	C	0.030	-0.004	0.606	0.684	3	157,080,986	7.79E-1	0.015	447,473	3	156,798,775	0.007	42,467	9.73E-6	0.000	19.568	53.625
CD74.TNFRSF21	CKD	rs9391858	A	G	A	G	-0.145	0.052	0.842	0.774	6	32,373,621	2.00E-3	0.017	447,473	6	32,341,398	0.009	42,809	1.26E-59	0.006	266.018	53.625
CD74.TNFRSF21	CKD	rs9615375	G	T	G	T	0.038	0.024	0.783	0.841	22	46,519,724	1.98E-1	0.019	447,473	22	46,915,621	0.008	42,889	3.51E-6	0.001	21.523	53.625

SNP-level harmonized exposure and outcome summary statistics for the protein ratios CD74/NPDC1 and CD74/TNFRSF21 used in the Mendelian randomization analyses.

Colocalization analyses

Colocalization analyses were performed to evaluate whether the same causal variants underlie both the exposure and outcome associations. Summary statistics for NPDC1 and TNFRSF21 were obtained from the eQTLGen database. Bayesian colocalization analysis was conducted using standard default priors to estimate the posterior probability of a shared causal variant (PP4). CD74 could not be successfully extracted from the eQTLGen dataset and was therefore not included in the colocalization analysis. A colocalization signal was considered significant when PP4 exceeded the conventional threshold.

Statistical analysis

MR analysis was performed using R software, with the TwoSample package and the MR-PRESSO package. The classical inverse variance weighting model (IVW) was used for the primary MR analysis. Additionally, the MR Egger, weighted median, and weighted mode were employed to estimate causal effects. Heterogeneity among IVs was assessed using Cochran's Q statistic. Sensitivity analysis was conducted using leave-one-out testing to evaluate the stability of MR results by sequentially excluding IVs. The MR-Egger and MR-PRESSO methods were used to assess whether the instrumental variables (IVs) were influenced by confounding factors. Causal estimates are reported as odds ratios (ORs) with 95% confidence intervals.

Statistical power was calculated using a standard MR framework based on the total variance explained by the instrumental variables (R^2), the sample size of the outcome GWAS, and the observed causal effect estimates (β = logOR), under a significance level of 0.05 using a non-central chi-square distribution approximation.

RESULTS

Both the CD74/NPDC1 ratio and the CD74/TNFRSF21 ratio were negatively associated with the risk of CKD.

To evaluate the association between 2,821 protein level ratios and CKD risk, we employed the inverse variance weighted (IVW) method, the primary approach in Mendelian randomization analyses. The IVW results indicated that a one-standard-deviation increase in the CD74/NPDC1 ratio was associated with a 16% lower odds of CKD (odds ratio, OR = 0.84; 95% confidence interval, CI: 0.76–0.94; *P* = .0026; FDR = 0.0025) (Figure 1). However, given the large number of tests performed (n = 2,821), this association did not survive Bonferroni correction (P threshold = 1.77 × 10^{-5}) and should therefore be interpreted as an exploratory finding.

In addition to CD74/NPDC1, the IVW analysis identified an inverse association between the CD74/TNFRSF21 ratio and CKD risk (OR = 0.86; 95% CI: 0.79–0.94; *P* = .0007; FDR = 0.0014) (Figure 1). A one-standard-deviation increase in this ratio corresponded to approximately 14% lower odds of CKD. Similarly, this association did not survive Bonferroni correction and should also be considered exploratory.

Statistical power analysis indicated that the MR analyses were well-powered to detect the observed

exposure	method	nsnp	pval	OR(95%CI)	FDR
CD74/NPDC1	MR Egger	21	0.4249	0.9100 (0.7254−1.1416)	
	Weighted median	21	0.0116	0.8239 (0.7088−0.9577)	
	Inverse variance weighted	21	0.0026	0.8449 (0.7573−0.9427)	0.0025
	Simple mode	21	0.0757	0.7665 (0.5804−1.0124)	
	Weighted mode	21	0.0142	0.7969 (0.6752−0.9405)	
CD74/TNFRSF21	MR Egger	39	0.0192	0.8147 (0.6915−0.9600)	
	Weighted median	39	0.0221	0.8529 (0.7443−0.9775)	
	Inverse variance weighted	39	<0.001	0.8644 (0.7944−0.9405)	0.0014
	Simple mode	39	0.1341	0.8170 (0.6308−1.0583)	
	Weighted mode	39	0.0150	0.8170 (0.6995−0.9544)	

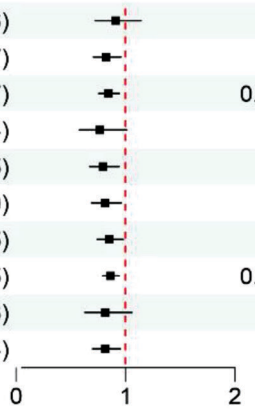


Figure 1. Forest plot. Mendelian randomization showed that the CD74-related protein ratio was negatively associated with chronic kidney disease. CI, confidence interval; OR, odds ratio; FDR, false discovery rate.

associations, with estimated power exceeding 90% (Table S3). Furthermore, we applied several additional MR methods (MR Egger, weighted median, and weighted mode) to test for potential bias or violations of assumptions, ensuring the robustness of our results. The findings from both the weighted median and weighted mode analyses were consistent with the IVW method, indicating negative causality (Figure 1). The Cochran Q-test demonstrated no heterogeneity in the MR results (Q_*P* > .05) (Table S4). Both MR-Egger regression (*P* > .05) and MR-PRESSO analysis (*P* > .05) indicated no significant overall level of pleiotropy (Tables S5, S6). These results were further illustrated through scatter plots (Figures 2A-2C, 3A-3C). Additionally, a leave-one-out analysis confirmed that the overall estimates were not influenced by any single SNP (Figures 2D, 3D).

Notably, reverse MR analyses showed no significant causal effect of CKD on the CD74-related protein ratios (Supplementary Figure 1). Consistent with the forward analyses, these reverse analyses also showed no heterogeneity or horizontal pleiotropy (Q_*P* > .05; MR-Egger intercept *P* > .05; MR-PRESSO global test *P* > .05), indicating that the lack of causal effect is robust (Table S4, S5, S6).

Table S6. MR-PRESSO evaluation of instrumental variables revealing no outliers

Exposure	Outcome	*P*
CD74/NPDC1	Chronic kidney disease	.209
CD74/TNFRSF21	Chronic kidney disease	.486
Chronic kidney disease	CD74/NPDC1	.142
Chronic kidney disease	CD74/TNFRSF21	.182

Colocalization analysis was additionally performed for NPDC1 and TNFRSF21 using the eQTLGen database to explore whether shared genetic signals exist between gene expression and CKD-associated loci. As shown in Supplementary Figure 2, no strong evidence of colocalization was observed.

DISCUSSION

These findings suggest that genetically predicted higher CD74/NPDC1 and CD74/TNFRSF21 ratios are associated with lower susceptibility to overall CKD in a European two-sample Mendelian randomization dataset. However, these results should be interpreted as exploratory genetic associations rather than evidence of causality or biological mechanisms. Our MR analysis identified inverse associations between these ratios and

Table S3. MR Statistical power analysis

Exposure	SNPs	Total R^2	Mean F-statistic	CKD	Control	Total	β	Statistical Power
CD74/NPDC1	21	0.0378	74.05	11265	436208	447473	-0.1685	> 90%
CD74/TNFRSF21	39	0.039	53.62	11265	436208	447473	-0.1457	> 90%

Table S4. Results of IVW and MR-Egger analysis demonstrating no heterogeneity among instrumental variables

Exposure	Outcome	Method	Q	Q_df	Q_*P*
CD74/NPDC1	Chronic kidney disease	Inverse variance weighted	24.46	20	.22
CD74/NPDC1	Chronic kidney disease	MR Egger	23.69	19	.2
CD74/TNFRSF21	Chronic kidney disease	Inverse variance weighted	37.72	38	.48
CD74/TNFRSF21	Chronic kidney disease	MR Egger	37.04	37	.47
Chronic kidney disease	CD74/NPDC1	MR Egger	8.45	3	.08
Chronic kidney disease	CD74/NPDC1	Inverse variance weighted	9.65	4	.07
Chronic kidney disease	CD74/TNFRSF21	MR Egger	6.31	3	.09
Chronic kidney disease	CD74/TNFRSF21	Inverse variance weighted	8.89	4	.06

Table S5. MR-Egger analysis indicated that the causal relationship between CD74-related protein ratios and chronic kidney disease was not influenced by horizontal pleiotropy

Exposure	Outcome	Egger intercept	se	*P*
CD74/NPDC1	Chronic kidney disease	-0.006	0.009	.472
CD74/TNFRSF21	Chronic kidney disease	0.004	0.005	.415
Chronic kidney disease	CD74/NPDC1	0.026	0.04	.56
Chronic kidney disease	CD74/TNFRSF21	0.036	0.033	.349

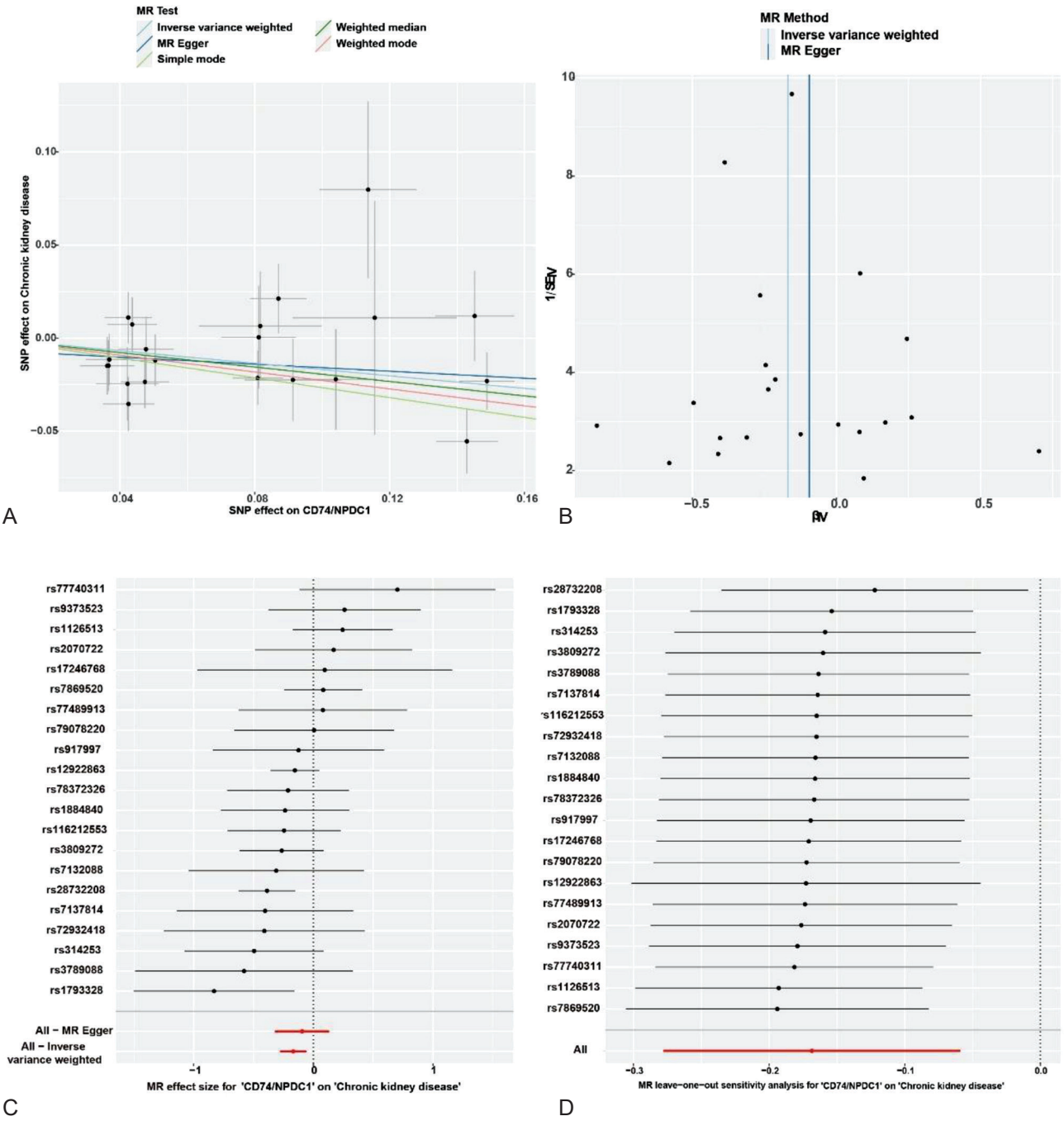


Figure 2. Mendelian randomization analysis for CD74/NPDC1 and CKD. (A) The MR analysis results for CD74/NPDC1 and CKD showed a negative slope, indicating that CD74/NPDC1 serves as a protective factor against CKD. (B) Funnel plots illustrated the absence of heterogeneity among the SNPs. (C) The forest plot of SNPs displayed the comprehensive findings, with the red line indicating that higher levels of CD74/NPDC1 correlate with a reduced risk of CKD. (D) Leave-one-out analysis examining the causal relationship of CD74/NPDC1.

CKD risk, with a one-standard-deviation increase associated with approximately 16% and 14% lower odds of CKD, respectively.

The pathological features of CKD encompass tubular interstitial fibrosis, glomerular lesions, and inflammatory responses.[17] Tubular cell damage and apoptosis, in conjunction with interstitial fibrosis, result in a gradual decline in renal function. Furthermore, as CKD progresses, there is an increased infiltration of inflammatory cells within the renal tissue, which exacerbates tissue damage and fibrosis.[18] CD74 is a critical receptor

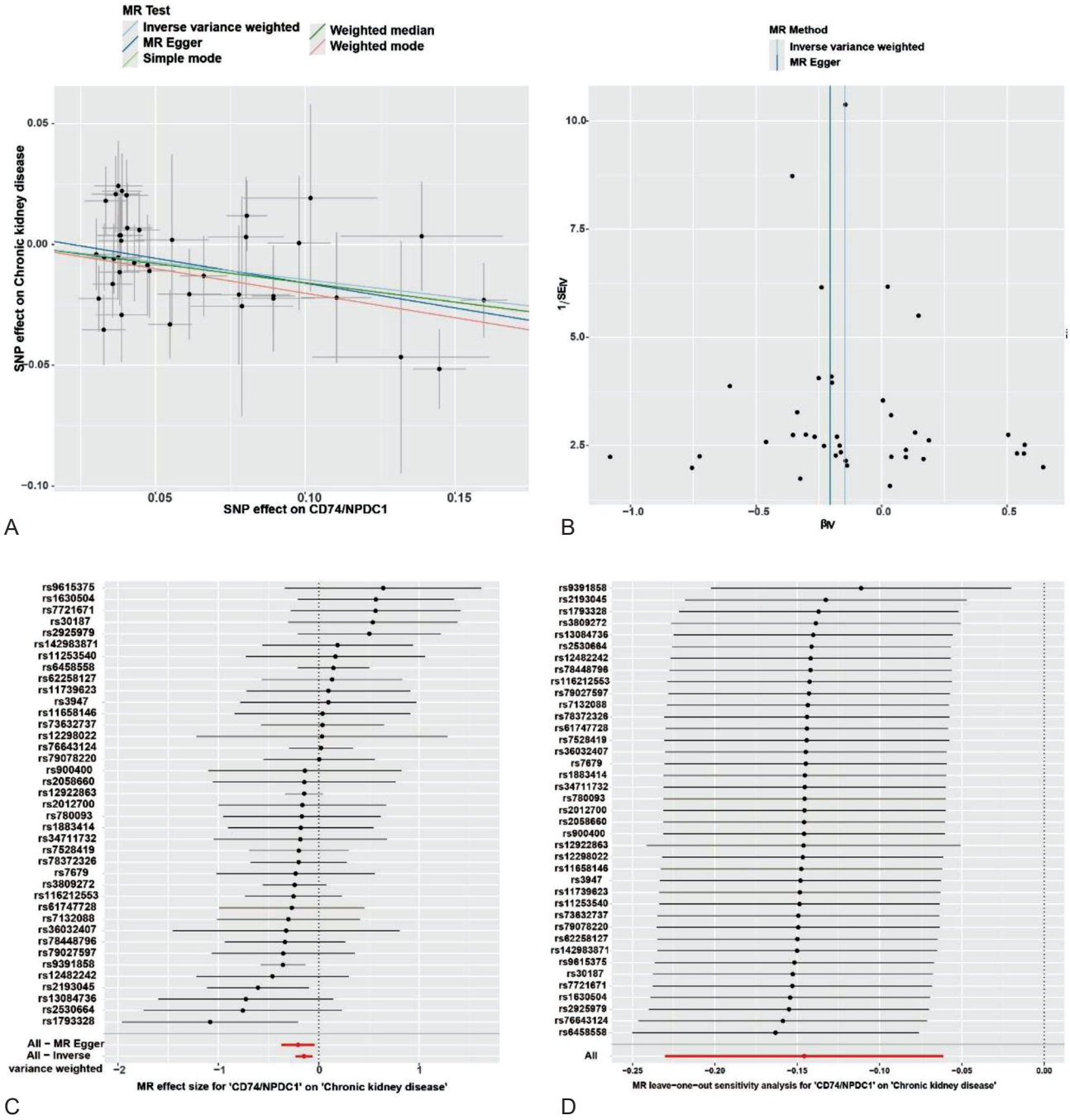
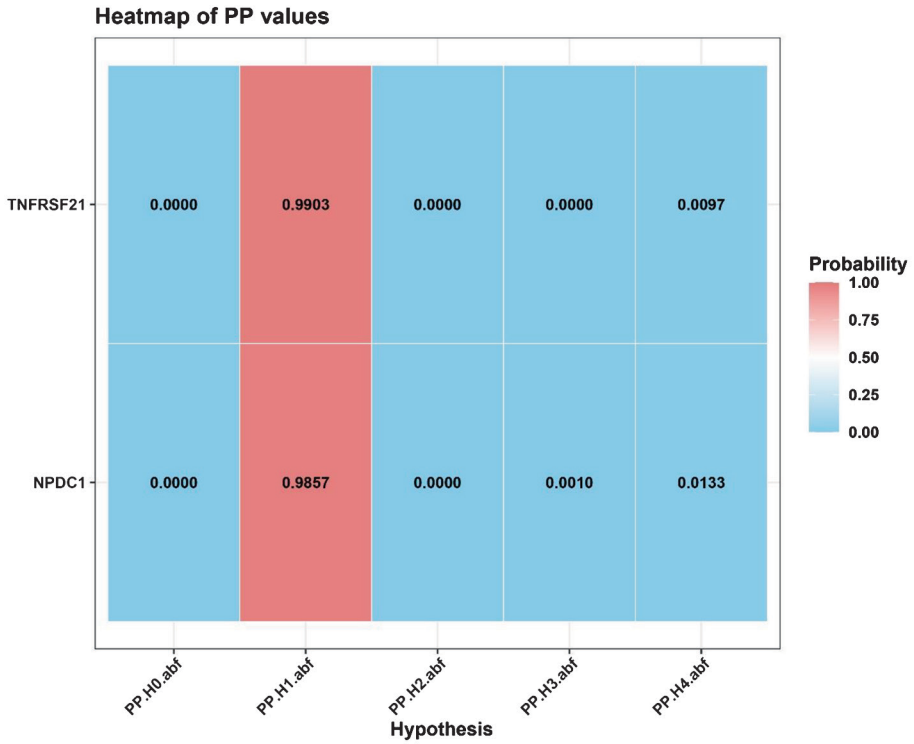


Figure 3. Mendelian Randomization Analysis for CD74/TNFRSF21 and CKD. (A) The MR analysis results for CD74/TNFRSF21 and CKD revealed a negative slope, suggesting that CD74/TNFRSF21 is a protective factor for CKD. (B) Funnel plots indicated no heterogeneity present among the SNPs. (C) In the forest plot of SNPs, the overall results are depicted, with the red line showing that increased CD74/TNFRSF21 levels were associated with a lower risk of CKD. (D) Leave-one-out analysis of the causal relationship involving CD74/TNFRSF21.

in the immune system, involved in immune responses and cytokine regulation.[19] TNFRSF21 belongs to the TNF/TNFR family and plays a key role in regulating inflammatory states and immune responses.[20] NPDC1 is a neuronal differentiation regulator that interacts with E2F-1 and inhibits cell cycle progression by affecting the function of E2F-1.[21,22] However, evidence regarding the expression and functional roles of NPDC1 and TNFRSF21 in kidney tissue is limited. Therefore, any biological interpretation of these ratios in CKD should be considered speculative.

outcome	method	nsnp	pval	OR(95%CI)
CD74/NPDC1	MR Egger	5	0.8706	0.9709 (0.7008−1.3453)
	Weighted median	5	0.1273	1.0960 (0.9742−1.2331)
	Inverse variance weighted	5	0.2610	1.0726 (0.9492−1.2119)
	Simple mode	5	0.2505	1.1390 (0.9419−1.3772)
	Weighted mode	5	0.1699	1.1193 (0.9808−1.2775)
CD74/TNFRSF21	MR Egger	5	0.5017	0.9000 (0.6863−1.1803)
	Weighted median	5	0.2786	1.0585 (0.9551−1.1731)
	Inverse variance weighted	5	0.5472	1.0353 (0.9248−1.1589)
	Simple mode	5	0.8157	0.9788 (0.8264−1.1591)
	Weighted mode	5	0.5378	1.0385 (0.9303−1.1592)

Supplementary Figure 1. Reverse Mendelian randomization indicated that CKD did not significantly affect the CD74-related protein ratio.



Supplementary Figure 2. Exploratory colocalization analysis of NPDC1 and TNFRSF21 with CKD using the eQTLGen database.

Previous studies demonstrated a positive correlation between CD74 and renal fibrosis and inflammation.[23,24] In contrast, we found that the ratios of CD74/NPDC1 and CD74/TNFRSF21 are reduced in CKD. MR analysis indicates a negative correlation between CD74/NPDC1 and CD74/TNFRSF21 with CKD. Lower ratios of CD74/NPDC1 and CD74/TNFRSF21 may reflect altered genetic regulation of immune-related pathways associated with CKD susceptibility, although the biological interpretation remains unclear. Whether these ratios represent causal drivers, downstream consequences, or shared genetic architecture cannot be determined from MR analysis. Any potential involvement in inflammatory or fibrotic signaling pathways is therefore speculative. Furthermore, the functional roles and interaction patterns of CD74, NPDC1, and TNFRSF21 in kidney disease

remain insufficiently characterized.

Although this study utilized publicly available summary-level genetic data, several important limitations should be acknowledged. The CKD cases included in the FinnGen R11 dataset represent a heterogeneous population with multiple underlying etiologies, and individual-level information on specific causes was not available. In addition, the publicly available summary statistics did not include information on comorbid conditions such as diabetes, multiple myeloma, or other malignancies, which therefore could not be excluded. Summary-data-based MR analyses, as well as tissue-specific validation, could not be performed due to the limited availability of sufficiently resolved kidney-specific pQTL ratio datasets for the proteins investigated. While this study included a relatively large sample size, further experimental validation in renal cell and animal models is required to clarify the biological relevance of these findings. However, such experimental validation was not performed in the present study and remains a future direction.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

CONTRIBUTIONS

All authors contributed to this article and approved the submitted version. Jiang Tan and Dawei Shen produced data and wrote the manuscript. Jiang Tan designed the study and revised the manuscript.

DATA AVAILABILITY

The datasets analysed during the current study are available in the FinnGen.

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None.

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