Genetic Associations Between Gastrointestinal Diseases and Chronic Kidney Disease: An Integrated Mendelian Randomization and Bioinformatics Analysis

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Keywords. Mendelian Randomization; Gastrointestinal diseases; Celiac disease; Inflammatory bowel disease; Chronic Kidney Disease

Introduction. Chronic kidney disease (CKD) is a progressive condition with complex genetic and environmental influences. This study aims to investigate the genetic causal relationships between gastrointestinal diseases and CKD using the Mendelian Randomization (MR) approach and bioinformatics analysis.
Methods. We analyzed genetic associations between nineteen gastrointestinal diseases including celiac disease (CeD), inflammatory bowel disease (IBD), intestinal malabsorption, and CKD. A two-sample MR analysis was performed using publicly available Genome-Wide Association Studies (GWAS) data with Single Nucleotide Polymorphisms (SNPs) as instrumental variables (IVs). The primary analysis employed the inverse variance weighted (IVW) method, with MR-Egger and weighted median as supplements. To explore potential biological mechanisms, Functional Mapping and Annotation (FUMA) analysis was used to map genes corresponding to IVs, followed by Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses.
Results. Significant genetic causal effects were observed for CeD (OR = 1.021, 95% CI = 1.002–1.041, *P* = .032), IBD (OR = 1.051, 95% CI = 1.014–1.089, *P* = .006), and intestinal malabsorption (OR = 1.031, 95% CI = 1.006–1.056, *P* = .013) on the risk of developing CKD. Other gastrointestinal diseases did not demonstrate significant causal effects on CKD. Reverse MR analyses did not reveal significant causal effects of CKD on CeD, IBD, or intestinal malabsorption, respectively. FUMA analysis identified 93 genes associated with CeD, 143 genes with IBD, and 26 genes with intestinal malabsorption. GO and KEGG enrichment analyses highlighted key pathways, including T-cell receptor signaling, cytokine-cytokine receptor interaction, chromatin regulation, and immune-related pathways.
Conclusions. This study provides genetic and bioinformatics evidence linking CeD, IBD, and intestinal malabsorption to an increased risk of CKD, highlighting the systemic impact of immune dysregulation and inflammation on kidney health.

IJKD 2026;20:25-45
www.ijkd.org

INTRODUCTION

Chronic kidney disease (CKD) is a progressive disorder characterized by a gradual loss of renal function,[1] ultimately resuling in end-stage kidney disease (ESKD) and increased mortality risk. Affecting approximately 10% of the global population, CKD

poses a major public health issue due to its high prevalence, economic burden, and lack of curative treatments. The pathogenesis of CKD remains incompletely understood, with multiple contributing factors including hypertension, diabetes mellitus, and genetic predisposition. In recent years, increasing attention has been given to the potential role of gastrointestinal (GI) disorders in the development of CKD, as emerging evidence suggests a bidirectional relationship between gut health and kidney function.

Inflammatory bowel diseases (IBD),[2] encompassing Crohn's disease (CD) and ulcerative colitis (UC),[3,4] are chronic, immune-mediated conditions that, despite primarily affecting the gastrointestinal tract, exerting systemic effects. Beyond intestinal inflammation, IBD has been associated with extraintestinal manifestations, including IgA nephropathy and an increased risk of CKD.[5] Similarly, celiac disease (CeD),[6] an autoimmune disorder triggered by gluten ingestion, has been associated with kidney dysfunction. Other intestinal disorders, including intestinal malabsorption syndromes,[7] chronic gastroenteritis, and vascular diseases of the intestine, have also been implicated in CKD pathophysiology, highlighting the complex interplay between gut and kidney health.[8,9]

Despite growing epidemiological evidence linking GI diseases with CKD, the underlying causal mechanisms remain unclear. Observational studies are often limited by confounding factors and reverse causation, making it challenging to establish direct causal relationships. To address these limitations, this study employs Mendelian randomization (MR),[10] a genetic epidemiology approach that utilizes single nucleotide polymorphisms (SNPs) as instrumental variables to infer causality. By leveraging genome-wide association study (GWAS) data, we aim to systematically investigate the causal effects of various intestinal disorders—including IBD, CeD, and other GI conditions—on CKD risk.[11] Additionally, we integrate bioinformatics analysis to identify key genes and biological pathways mediating these associations. By combining genetic epidemiology with bioinformatics, this study provides novel insights into the gut-kidney axis, offering potential implications for therapeutic and preventive strategies.

MATERIALS AND METHODS

MR Study design

A two-sample MR analysis was performed to explore the causal relationships between CKD and GI diseases which included IBD, celiac disease, intestinal malabsorption, irritable bowel syndrome, gastroenteritis, colitis, noninfective enteritis and colitis, mucosal proctocolitis, intestinal infectious diseases, gastrointestinal hemorrhage, paralytic ileus, intestinal stricture, intestinal adhesions without obstruction, other functional intestinal disorders, benign neoplasm of small intestine, malignant neoplasm of small intestine, and vascular diseases of the intestine. An overview of the study design is shown in Figure 1. These GI diseases were identified through a systematic search of the Integrative Epidemiology Unit (IEU), FinnGen, and GWAS databases, using the keywords "gastrointestinal" or "bowel" to retrieve all relevant traits.

The MR analysis was based on three core assumptions: (1) selected single nucleotide polymorphisms (SNPs) must be strongly associated with the exposure, (2) SNPs should not be linked to confounding factors that could bias the results, and (3) SNPs should influence the outcome only through the exposure and not via alternative pathways.[12] This study adhered to the STROBE-MR guidelines for the design and reporting of Mendelian randomization research (Supplementary STROBE-MR Checklist).[13]

Data sources description

The datasets employed in this study were obtained from genome-wide association studies (GWAS; https://gwas.mrcieu.ac.uk/) are openly accessible as listed in Table 1. We selected studies that only included individuals of European ancestry to avoid population bias. Since all identified data sets involved in this study are publicly available, no additional ethical approval or informed consent was required.

Selection of genetic instrumental variables

The SNPs were employed as instrumental variables (IVs) at the genome-wide significance threshold ($P < 5\times10^{-8}$). To achieve independent loci, these SNPs were clumped with a linkage disequilibrium (LD) threshold $r^2 = 0.001$ and 10000kb as the clumping window. To include more SNPs that contributed to other intestinal diseases, a more relaxed threshold ($P < 5 \times 10^{-6}$, $r^2 = 0.01$ and 1000kb) was applied. Then we harmonized

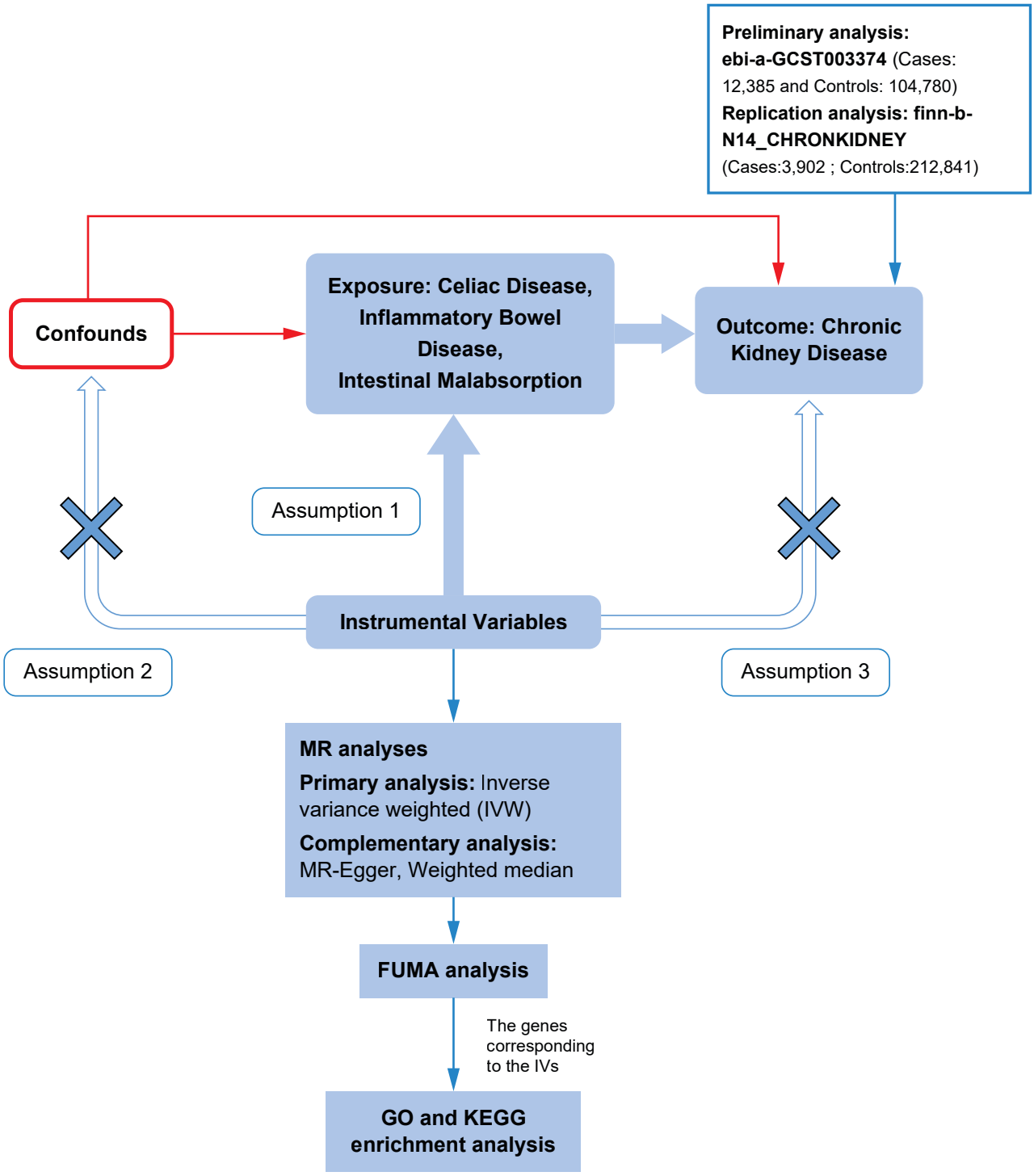


Figure 1. Flow chart of Mendelian randomization (MR) analysis.

the exposure and outcome SNPs and removed the potential palindromic SNPs. The SNPs were selected from the outcome data to eliminate the effect of confounding factors of CKD. The F-statistics and R^2-value were calculated to estimate the strength of IVs. These values can identify whether IVs are strong enough to lessen the weak-tool bias. After all, we carried out MR-Egger intercepts and MR-PRESSO (MR pleiotropy residual sum and outlier),[14] to identify and exclude potential outliers.

Table 1. A detailed description of the GWAS data involved in this study.

Disease	Population	Cases	Controls	Number of SNPs	GWAS ID	Website
Chronic kidney disease	European	12385	104780	2179497	ebi-a-GCST003374	https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST003374/
Celiac disease	European	11812	229	97422	ebi-a-GCST005523	https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST005523/
Inflammatory bowel disease	Mixed	25042	34915	9619016	ebi-a-GCST004131	https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST004131/
Intestinal malabsorption	European	582	210964	16380436	finn-b-K11_MALABSORB	https://gwas.mrcieu.ac.uk/datasets/finn-b-K11_MALABSORB/
Irritable bowel syndrome	European	4605	182423	16380376	finn-b-K11_IBS	https://gwas.mrcieu.ac.uk/datasets/finn-b-K11_IBS/
Diarrhoea and gastroenteritis of presumed infectious origin	European	15255	197298	16380447	finn-b-AB1_GASTROENTERITIS_NOS	https://gwas.mrcieu.ac.uk/datasets/finn-b-AB1_GASTROENTERITIS_NOS/
Colitis, primary sclerosing	European	197	195144	16380405	finn-b-K11_PSC_COLITIS	https://gwas.mrcieu.ac.uk/datasets/finn-b-K11_PSC_COLITIS/
Noninfective enteritis and colitis	European	8492	210300	16380466	finn-b-K11_ENERCOLNONINF	https://gwas.mrcieu.ac.uk/datasets/finn-b-K11_ENERCOLNONINF/
Other noninfective gastroenteritis and colitis	European	3804	210300	16380455	finn-b-K11_OTHENTERCOL	https://gwas.mrcieu.ac.uk/datasets/finn-b-K11_OTHENTERCOL/
Mucosal proctocolitis	European	1973	210300	16380454	finn-b-MUCOPROCT	https://gwas.mrcieu.ac.uk/datasets/finn-b-MUCOPROCT/
Gastrointestinal diseases	European	107110	111682	16380466	finn-b-K11_GIDISEASES	https://gwas.mrcieu.ac.uk/datasets/finn-b-K11_GIDISEASES/
Gastrointestinal hemorrhage	African American or Afro-Caribbean	429	6127	15525857	ukb-e-578_AFR	https://gwas.mrcieu.ac.uk/datasets/ukb-e-578_AFR/
Intestinal infectious diseases	European	21494	197298	16380466	finn-b-AB1_INTESTINAL_INFECTIONS	https://gwas.mrcieu.ac.uk/datasets/finn-b-AB1_INTESTINAL_INFECTIONS/
Paralytic ileus	European	517	182423	16380364	finn-b-K11_PARALIL	https://gwas.mrcieu.ac.uk/datasets/finn-b-K11_PARALIL/
Other functional intestinal disorders	African American or Afro-Caribbean	303	6333	15480139	ukb-e-K59_AFR	https://gwas.mrcieu.ac.uk/datasets/ukb-e-K59_AFR/
Intestinal stricture	European	4461	214331	16380466	finn-b-K11_STRICTURE	https://gwas.mrcieu.ac.uk/datasets/finn-b-K11_STRICTURE/
Intestinal adhesions without obstruction	European	1121	182423	16380373	finn-b-K11_ADHE	https://gwas.mrcieu.ac.uk/datasets/finn-b-K11_ADHE/
Benign neoplasm: Small intestine	European	549	218243	16380466	finn-b-CD2_BENIGN_SMALL_INTESTINE	https://gwas.mrcieu.ac.uk/datasets/finn-b-CD2_BENIGN_SMALL_INTESTINE/

Table 1. Continued

Disease	Population	Cases	Controls	Number of SNPs	GWAS ID	Website
Malignant neoplasm of small intestine	European	252	218540	16380466	finn-b-C3_SMALL_INTESTINE	https://gwas.mrcieu.ac.uk/datasets/finn-b-C3_SMALL_INTESTINE/
Vascular diseases of the intestine	European	415	206541	16380410	finn-b-I9_VASCINT	https://gwas.mrcieu.ac.uk/datasets/finn-b-I9_VASCINT/
Crohn's disease	European	5956	14927	12276506	ieu-a-30	https://gwas.mrcieu.ac.uk/datasets/ieu-a-30/
Ulcerative colitis	South Asian	1239	990	156116	ieu-a-971	https://gwas.mrcieu.ac.uk/datasets/ieu-a-971/

GWAS: whole-genome association studies.

MR Analysis

The causal relationship between exposures and outcomes was investigated using several MR approaches, namely the inverse variance weighted (IVW) method, MR-Egger, weighted median, simple mode, and weighted mode. IVW was chosen as the primary analytical method for its strong detection power of causal relationships.[15] Furthermore, the causal effects of CD and UC on CKD were estimated separately by subgroup analysis. All statistical analyses were performed using R packages, including Two-Sample MR (version 0.6.6) and MR-PRESSO (version 1.0) on the R platform (version 4.2.2). $P < .05$ was considered to be statistically significant.

Sensitivity analyses

We implied the Cochran'Q test to estimate the heterogeneity. The MR-Egger intercepts and MR-PRESSO were utilized to determine whether directional or horizontal pleiotropy existed.[16] A leave-one-out analysis was performed to evaluate whether the MR estimate was biased by a single SNP. To minimize the bias inherent in the genetic data, we chose another CKD GWAS data from the FinnGen database (r9) for sensitivity analysis (GWAS ID: finn-b-N14_CHRONKIDNEYDIS).

FUMA Analysis

Using GWAS summary statistics as input, the SNP2GENE function in FUMA was applied to functionally annotate SNPs based on their biological significance.[17] This approach enabled the identification of potential causal genes by mapping significant SNPs to associated genes through positional, eQTL, and chromatin interaction mapping.

Enrichment Analyses

The candidate genes identified through functional mapping and annotation (FUMA) analysis were further examined using Gene Ontology (GO) analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis to explore their biological roles.[17,18] GO analysis categorized genes into biological processes, cellular components, and molecular functions, while KEGG analysis highlighted key signaling pathways associated with CKD development. Both analyses were conducted in R (v4.3.2),[19] with a statistical significance

threshold of $P < .05$. The top five GO terms, ranked by *P*-values, were selected for interpretation. To enhance visualization, results were presented through bar charts and bubble plots, providing a clear overview of the most enriched functional terms and pathways.

RESULTS

Causal effects between GI diseases on CKD

Genetic instruments for MR analysis comprised 68 SNPs associated with IBD, 32 SNPs specific to CeD, and 13 SNPs related to intestinal malabsorption were employed as IVs. Details of SNPs for all GI diseases were listed in Supplementary Table S1. These selected SNPs had an F-statistic > 10, indicating a low risk of weak instrument bias.[20] The IVW method indicated a statistically significant positive association between CeD and increased risk of CKD (Odds Ratio [OR] = 1.021; 95% Confidence Interval [CI] = 1.002-1.041; $P = .032$; Figure 3A; Table 2).

Supplementary Table S1. Final SNPs used as genetic instruments

Outcome	Exposure	SNP	Effect allele	Other allele	β	SE	*P*
Chronic kidney disease	Celiac disease	rs1018326	C	T	0.152	0.019	3.06E-16
		rs1050976	T	C	-0.111	0.018	1.84E-09
		rs10790269	T	C	0.157	0.024	5.44E-11
		rs10947460	A	G	-0.125	0.023	3.61E-08
		rs11801183	T	C	-0.138	0.025	1.69E-08
		rs11851414	C	T	0.12	0.022	4.71E-08
		rs11875687	C	T	0.16	0.025	1.92E-10
		rs1250552	G	A	-0.155	0.019	7.97E-17
		rs13003464	G	A	0.154	0.019	4.34E-16
		rs13195040	G	A	1.12	0.029	1E-200
		rs1323292	A	G	0.262	0.025	4.23E-25
		rs1378938	C	T	-0.118	0.02	7.79E-09
		rs1431403	C	T	0.648	0.02	1E-200
		rs17264332	G	A	0.251	0.022	4.98E-30
		rs182429	G	A	-0.15	0.019	8.49E-16
		rs1893592	C	A	-0.124	0.021	2.96E-09
		rs1980422	T	C	-0.172	0.022	1.43E-15
		rs2030519	A	G	0.278	0.019	3E-49
		rs2269423	C	A	0.925	0.024	1E-200
		rs2499714	T	C	0.189	0.031	6.08E-10
		rs3184504	C	T	-0.176	0.019	5.42E-21
		rs4445406	C	T	-0.136	0.02	5.42E-12
		rs4821124	C	T	0.151	0.023	5.72E-11
		rs6498114	T	G	-0.131	0.021	5.83E-10
		rs6715106	G	A	-0.237	0.041	8.38E-09
		rs7104791	C	T	-0.148	0.022	1.89E-11
		rs744254	A	G	0.116	0.021	3.04E-08
		rs76830965	A	C	0.307	0.028	2.57E-27
		rs79758729	G	A	0.163	0.029	2.12E-08
		rs9258302	C	T	-0.358	0.039	2.61E-20
		rs9268303	A	G	-0.639	0.027	1.54E-121
		rs990171	C	A	-0.178	0.022	1.22E-16
	Inflammatory bowel disease	rs10041497	C	T	0.082	0.013	1.95E-10
		rs10114470	C	T	0.148	0.014	4.1E-27
		rs10761659	G	A	0.159	0.013	2.3E-36
		rs10800309	G	A	-0.123	0.013	1.94E-20
		rs10826797	T	G	-0.099	0.014	3.99E-13
		rs10953551	G	A	-0.103	0.013	4.94E-16
		rs11066188	A	G	0.087	0.013	1.76E-11
		rs11152949	G	A	0.102	0.013	1.56E-14
		rs11195128	T	C	0.079	0.013	2.74E-09

Supplementary Table S1. Continued

Outcome	Exposure	SNP	Effect allele	Other allele	β	SE	*P*
Chronic kidney disease	Inflammatory bowel disease	rs11221335	C	T	0.083	0.015	2.44E-08
		rs1131095	C	T	0.164	0.013	1.22E-35
		rs11669299	T	C	-0.111	0.016	1.84E-12
		rs11677002	C	T	-0.093	0.013	1.37E-13
		rs11768365	G	A	-0.084	0.015	3.88E-08
		rs12136659	C	T	0.087	0.014	1.02E-09
		rs1250573	A	G	-0.098	0.014	1.11E-12
		rs12825700	A	G	0.132	0.013	1.27E-25
		rs12936409	T	C	0.141	0.012	7.73E-30
		rs1297264	G	A	-0.146	0.013	3.98E-31
		rs1317209	A	G	0.116	0.016	3.79E-13
		rs1336900	A	G	-0.085	0.013	2.98E-11
		rs13422838	C	T	-0.114	0.021	2.56E-08
		rs1445004	T	C	0.169	0.013	3.48E-40
		rs1456896	T	C	0.088	0.013	4.5E-11
		rs154873	A	G	-0.081	0.013	7.38E-10
		rs1558619	T	G	-0.084	0.012	8.9E-12
		rs16940202	C	T	0.113	0.017	2.5E-11
		rs17656349	T	C	0.073	0.013	5.17E-09
		rs194746	T	C	0.083	0.012	1.84E-11
		rs212402	A	G	-0.074	0.013	1.06E-08
		rs2384352	G	A	0.095	0.013	3.12E-13
		rs2413583	T	C	-0.173	0.017	4.6E-24
		rs243505	G	A	-0.081	0.013	3.04E-10
		rs2836881	T	G	-0.164	0.015	1.96E-29
		rs2838517	C	T	-0.128	0.013	1.83E-24
		rs3024493	A	C	0.191	0.017	4.04E-31
		rs341295	T	C	0.07	0.012	1.45E-08
		rs34140409	T	C	-0.158	0.024	2.28E-11
		rs35171809	G	A	0.109	0.012	1.16E-18
		rs3792111	T	C	0.139	0.012	5.12E-29
		rs3820330	A	C	-0.089	0.014	1.72E-10
		rs3829110	G	A	0.157	0.013	3.52E-36
		rs3850378	C	T	0.154	0.021	1.1E-13
		rs3897234	C	T	0.097	0.015	1.9E-11
		rs4256018	G	T	0.079	0.014	1.23E-08
		rs4380956	A	G	0.091	0.013	1.12E-12
		rs4807569	C	A	0.128	0.015	4.24E-17
		rs503734	G	A	-0.069	0.012	2.67E-08
		rs5754100	C	T	0.129	0.016	7.14E-16
		rs5763793	T	G	0.073	0.013	1.47E-08
		rs6017342	C	A	0.116	0.014	1.07E-17
		rs62126610	G	A	0.141	0.017	2.6E-17
		rs62408218	T	C	-0.082	0.013	2.4E-10
		rs6579807	T	C	0.125	0.019	4.01E-11
		rs6584282	G	A	-0.152	0.012	1.19E-34
		rs6740847	G	A	-0.092	0.013	1.22E-13
		rs6873866	C	T	-0.092	0.013	6.15E-13
		rs6933404	C	T	0.086	0.015	6.64E-09
		rs714910	C	A	-0.096	0.014	6.23E-12
		rs7190426	C	A	-0.087	0.016	2.06E-08
		rs744166	G	A	-0.111	0.013	1.34E-18
		rs7532133	G	A	0.079	0.013	3.83E-09

Supplementary Table S1. Continued

Outcome	Exposure	SNP	Effect allele	Other allele	β	SE	*P*
Chronic kidney disease	Inflammatory bowel disease	rs755374	T	C	0.177	0.013	1.59E-39
		rs7608697	C	A	0.14	0.013	1.67E-28
		rs76286777	C	T	0.1	0.015	4.65E-11
		rs7918084	T	C	0.071	0.013	1.38E-08
		rs938650	A	G	-0.107	0.019	1.41E-08
		rs9934775	T	C	-0.112	0.017	8.77E-11
	Intestinal malabsorbtion	rs10520168	C	T	-0.3171	0.0647	9.46E-07
		rs10878359	C	T	0.3001	0.0622	1.39E-06
		rs12047433	A	C	0.5314	0.1144	3.41E-06
		rs2071466	T	C	0.3731	0.0724	2.55E-07
		rs3117439	A	G	0.731	0.1336	4.42E-08
		rs3130923	A	G	0.9179	0.109	3.65E-17
		rs3132625	G	A	0.7364	0.1111	3.46E-11
		rs408036	C	T	-0.2818	0.0593	2.05E-06
		rs419009	C	T	-0.4553	0.0988	4.03E-06
		rs56862318	A	G	0.5465	0.1127	1.23E-06
		rs72854513	T	A	0.6171	0.1336	3.82E-06
		rs7932933	G	A	0.5602	0.1152	1.15E-06
		rs9277476	A	T	0.9821	0.1532	1.46E-10

Table 2. Mendelian randomization (MR) analysis of the causality of Bowel Diseases on CKD

Outcome	Exposure	ID	Method	nSNPs	β	*P*	OR	95%CI
Chronic kidney disease || id:ebi-a-GCST003374	Celiac disease	ebi-a-GCST005523	IVW	32	0.021	.032	1.021	1.002 - 1.041
	Inflammatory bowel disease	ebi-a-GCST004131	IVW	68	0.050	.006	1.051	1.014 - 1.089
	Intestinal malabsorption	finn-b-K11_MALABSORB	IVW	13	0.030	.013	1.031	1.006 - 1.056
	Irritable bowel syndrome	finn-b-K11_IBS	IVW	6	-0.055	.483	0.946	0.812 - 1.104
	Diarrhoea and gastroenteritis of presumed infectious origin	finn-b-AB1_ GASTROENTERITIS_NOS	IVW	8	0.079	.389	1.082	0.904 - 1.295
	Colitis, primary sclerosing	finn-b-K11_PSC_COLITIS	IVW	8	0.008	.428	1.008	0.989 - 1.027
	Noninfective enteritis and colitis	finn-b-K11_ENERCOLNONINF	IVW	4	-0.060	.439	0.942	0.810 - 1.096
	Other noninfective gastroenteritis and colitis	finn-b-K11_OTHENTERCOL	IVW	4	0.070	.420	1.072	0.905 - 1.271
	Mucosal proctocolitis	finn-b-MUCOPROCT	IVW	16	-0.008	.753	0.992	0.943 - 1.043
	Gastrointestinal diseases	finn-b-K11_GIDISEASES	IVW	21	0.099	.291	1.104	0.919 - 1.326
	Gastrointestinal hemorrhage	ukb-e-578_AFR	IVW	6	0.012	.495	1.012	0.977 - 1.049
	Intestinal infectious diseases	finn-b-AB1_INTESTINAL_ INFECTIONS	IVW	10	0.125	.168	1.133	0.949 - 1.353
	Paralytic ileus	finn-b-K11_PARALIL	IVW	5	0.023	.332	1.023	0.977 - 1.071
	Other functional intestinal disorders	ukb-e-K59_AFR	IVW	6	0.014	.304	1.014	0.988 - 1.041
	Intestinal stricture	finn-b-K11_STRICTURE	IVW	6	0.033	.698	1.034	0.874 - 1.224
	Intestinal adhesions without obstruction	finn-b-K11_ADHE	IVW	3	0.044	.294	1.045	0.962 - 1.134
	Benign neoplasm: Small intestine	finn-b-CD2_BENIGN_SMALL_ INTESTINE	IVW	3	0.025	.367	1.025	0.971 - 1.082
	Malignant neoplasm of small intestine	finn-b-C3_SMALL_INTESTINE	IVW	3	0.008	.717	1.008	0.967 - 1.050
	Vascular diseases of the intestine	finn-b-I9_VASCINT	IVW	4	0.008	.779	1.008	0.953 - 1.066

nSNPS: number of SNPs used in MR; OR: odds radio; CI: confidence interval; IVW: inverse variance weighted.

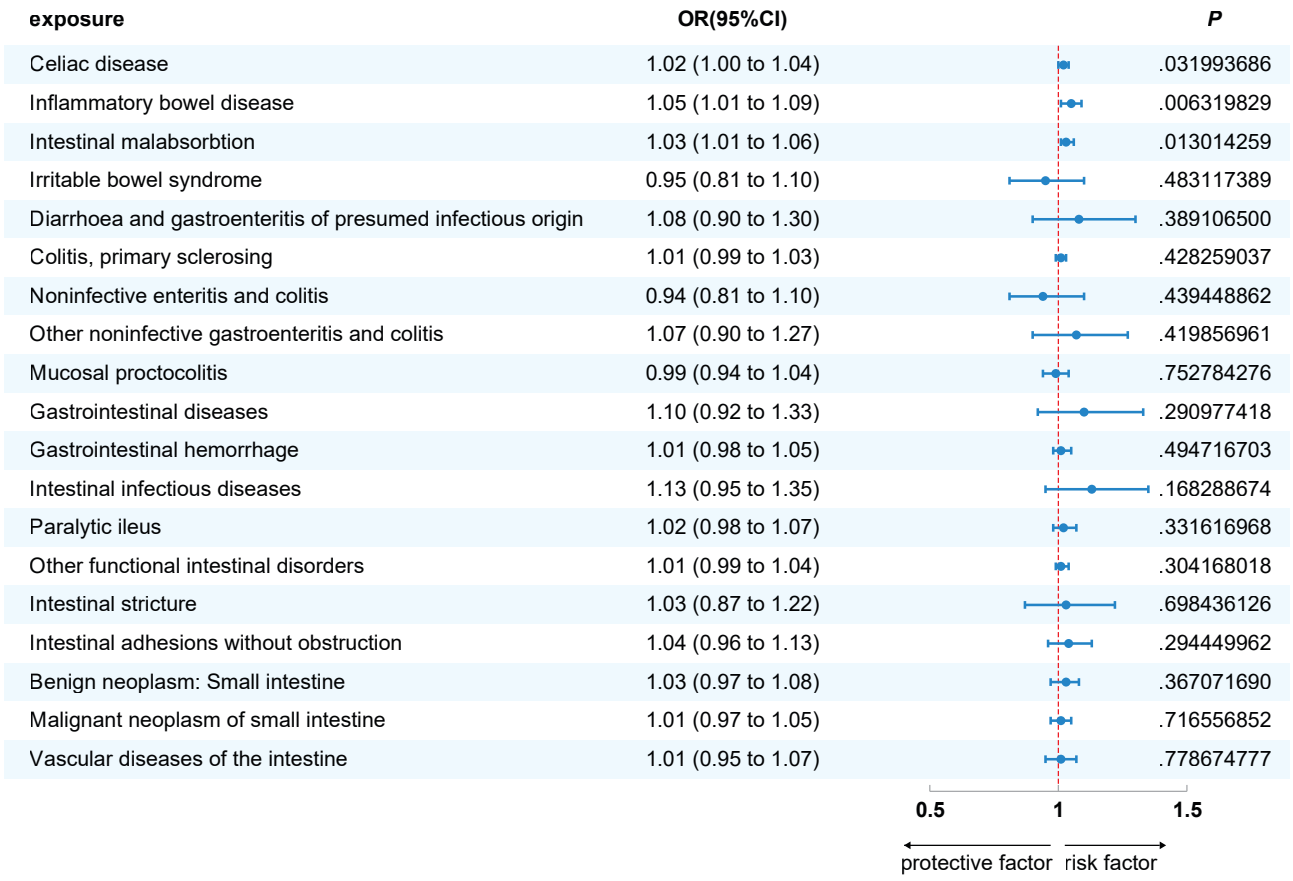


Figure 2. MR estimates of the causal effect of Gastrointestinal Diseases on Chronic kidney disease (CKD).

Similarly, a positive genetic causal effect was reported for total IBD and intestinal malabsorption regarding CKD risk. For IBD, the OR was 1.051 with a CI of 1.014-1.089 (P = .006; Figure 4A; Table 2), and for intestinal malabsorption, the OR was 1.031, with a CI of 1.006-1.056 (P = .013; Figure 5A; Table 2). However, MR analysis did not support a causal effect of other GI disease with CKD accordingly, as detailed in Table 2.

Sensitivity analysis

To validate these findings, we replicated the analysis using another independent CKD GWAS dataset (GWAS ID: finn-b-N14_CHRONKIDNEYDIS). Positive causal effects were also corroborated for CeD and overall IBD. Thirty-eight CeD-specific SNPs and 214 SNPs related to IBD were identified as IVs. Furthermore, there were also 52 SNPs linked to CD and three SNPs associated with UC in subgroup analysis. The detailed MR results are listed in Supplementary Table S2. The scatter plots illustrating these MR findings are displayed in Supplementary Figure S1. Alternative MR methods, including MR-Egger and WM, corroborated the direction of the IVW findings across all diseases.

Reverse two-sample MR results did not observe the casual relationship of CKD on CeD (P = .435; OR = 0.939). The reverse MR result of CKD on IBD and intestinal malabsorption was also negative (For IBD, P = .166; OR = 1.120; for intestinal malabsorption, P = .695; OR = 0.944). The scatter plots of reverse MR results are shown in Figures 3D, 4D, and 5D.

Assessment of potential pleiotropy and heterogeneity

The MR-Egger intercepts revealed no significant horizontal pleiotropy across the studied conditions (For CeD, intercept = 0.003, P = .557; For IBD, intercept = -0.0003, P = .969; For intestinal malabsorption, intercept = 0.016, P = .340) (Table 3). The MR-PRESSO test further supported the absence of pleiotropic bias affecting the causality estimates

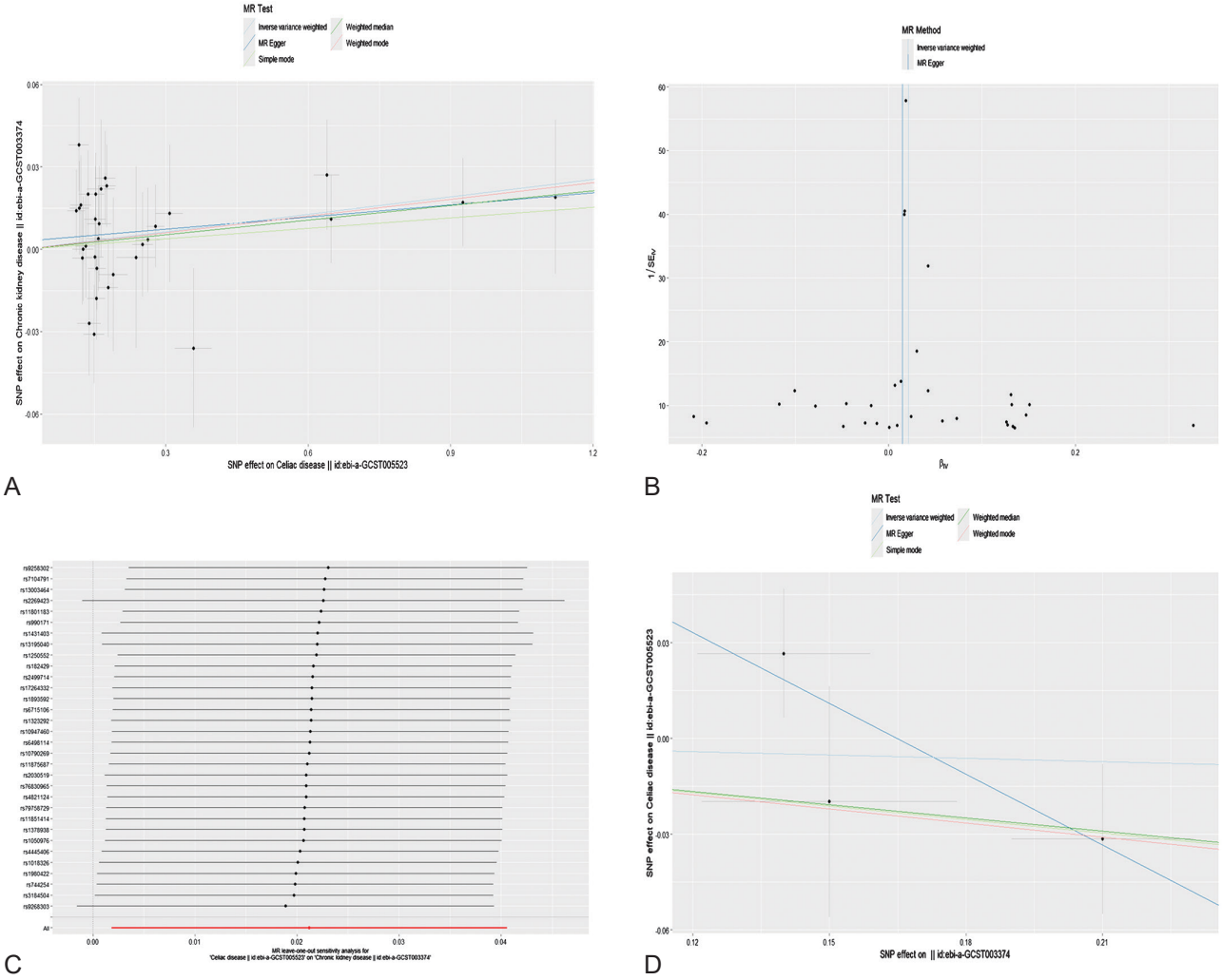


Figure 3. MR analysis of the causal effect of celiac disease (CeD) on CKD. (A) The scatter plot of CeD on CKD. (B) Funnel plot of the effect of CeD on CKD. (C) The leave-one-out plot of the effect of CeD on CKD. (D) The scatter plot of CKD on CeD.

($P > .05$) (Table 3). Additionally, Cochran's Q test indicated no significant heterogeneity among the instrumental variables ($P > .05$) (Table 3), and the funnel plots confirmed this finding (Figure 3B, 4B, and 5B). Lastly, the leave-one-out analysis did not identify any individual SNP that significantly influenced the overall outcomes (Figures 3C, 4C, and 5C).

FUMA analyses

To identify candidate genes based on the GWAS summary statistics in forward MR analyses, FUMA analyses identified 93 corresponding genes associated with CeD, 143 genes related to IBD, and 26 genes related to intestinal malabsorption (Supplementary Table 3). The Manhattan plots generated using MAGMA based on the input GWAS association results were presented in Figure 6-8.

Bioinformatics Analysis

To explore the biological relevance of the identified genes, GO and KEGG enrichment analyses were performed. The top five enriched biological processes (BP), cellular components (CC), and molecular functions (MF) are visualized in Figures 6-8 using bubble charts.

For CeD, key biological processes involved nucleosome assembly, antigen receptor-mediated signaling, and T-cell receptor signaling, suggesting immune system involvement in CKD risk. The enriched molecular functions included structural chromatin components and NAD+ nucleosidase activity, indicating potential roles in DNA regulation and metabolic pathways.

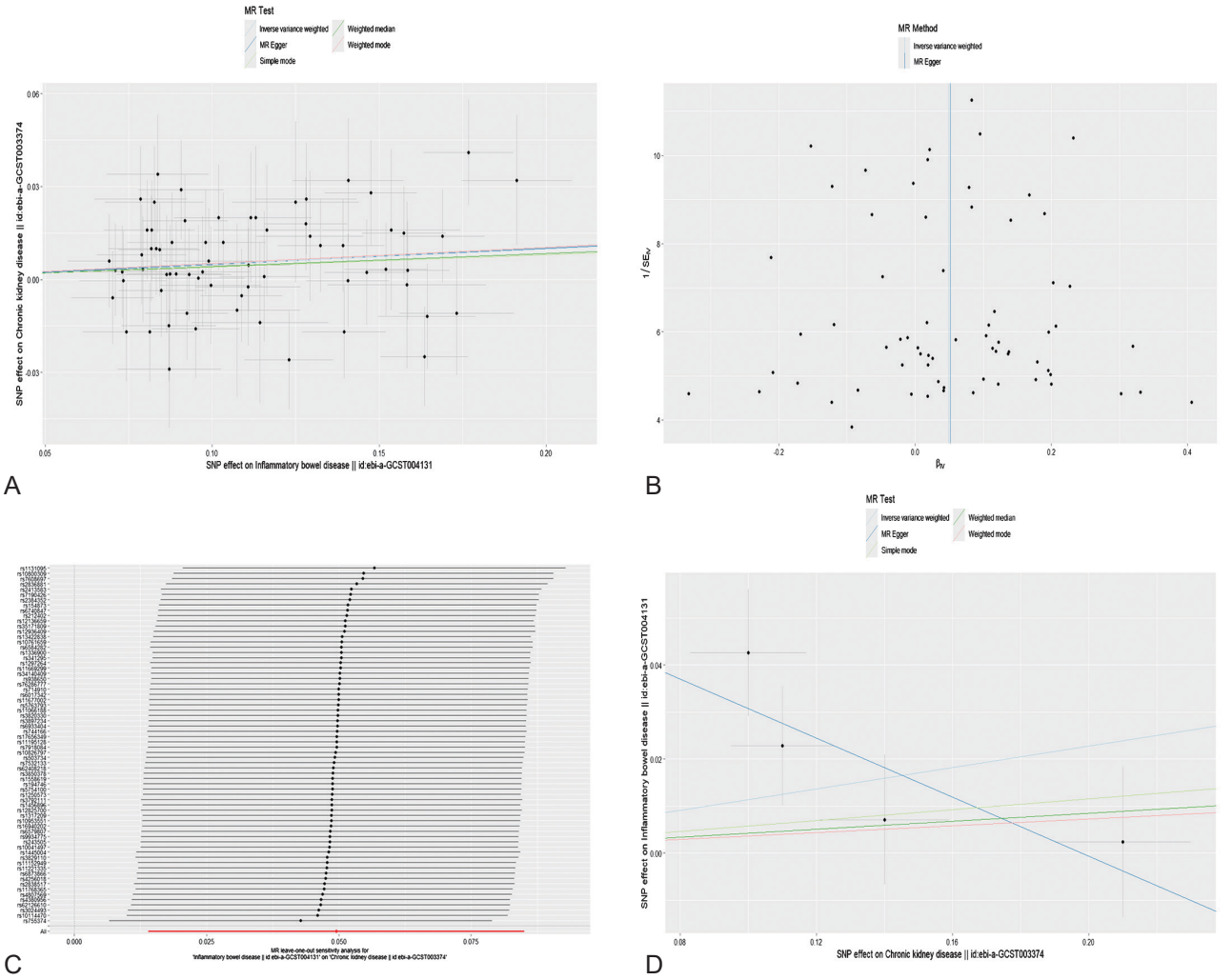


Figure 4. MR analysis of the causal effect of Inflammatory bowel disease (IBD) on CKD. (A) The scatter plot of IBD on CKD. (B) Funnel plot of the effect of IBD on CKD. (C) Leave-one-out plot of the effect of IBD on CKD. (D) The scatter plot of CKD on IBD.

For IBD, significant biological processes included mononuclear cell differentiation, B-cell activation, and regulation of cell adhesion, while molecular functions were enriched in miRNA binding and fibronectin binding, highlighting immune response and extracellular matrix interactions as potential contributing factors to CKD development.

For intestinal malabsorption, biological processes were mainly associated with sensory perception and chemical stimulus detection, while molecular functions were enriched in olfactory receptor activity and odorant binding, indicating possible metabolic or systemic interactions between the gut and kidney function.

KEGG pathway analysis revealed that CeD was significantly associated with pathways such as systemic lupus erythematosus, neutrophil extracellular trap formation, and viral protein interaction with cytokines and cytokine receptors. For IBD, enriched pathways included cytokine-cytokine receptor interactions, chemokine signaling, and viral protein interactions, suggesting immune-mediated mechanisms linking IBD and CKD. In contrast, intestinal malabsorption was predominantly associated with olfactory transduction pathways.

DISCUSSION

This integrated MR and bioinformatics study provided compelling evidence supporting a genetic causal link between specific gastrointestinal diseases—including IBD, CeD, intestinal malabsorption,—and CKD. Our findings emphasize the importance of genetic predispositions in

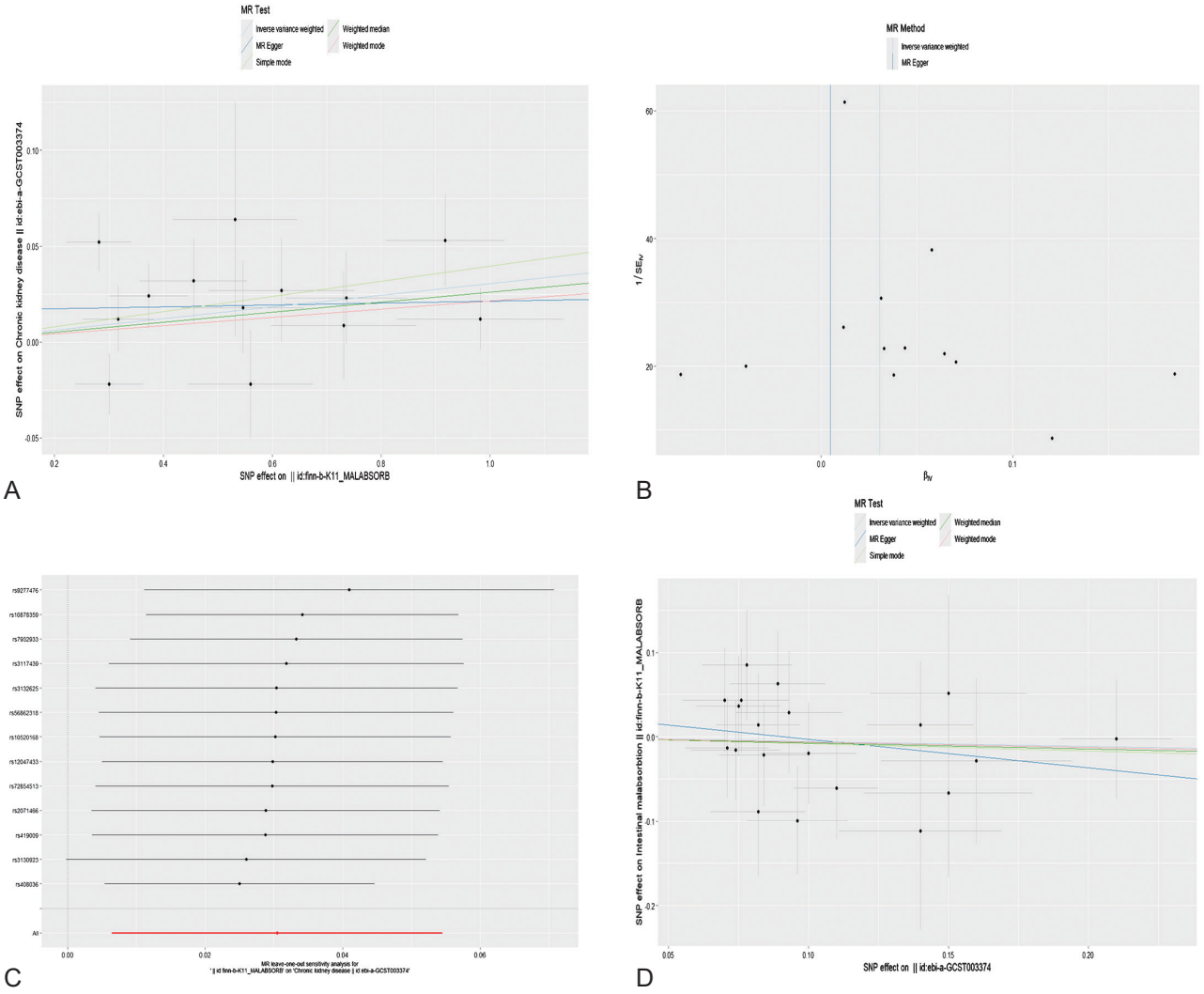


Figure 5. MR analysis of the causal effect of Intestinal malabsorption on CKD. (A) The scatter plot of Intestinal malabsorption on CKD. (B) Funnel plot of the effect of Intestinal malabsorption on CKD. (C) Leave-one-out plot of the effect of Intestinal malabsorption on CKD. (D) The scatter plot of CKD on Intestinal malabsorption.

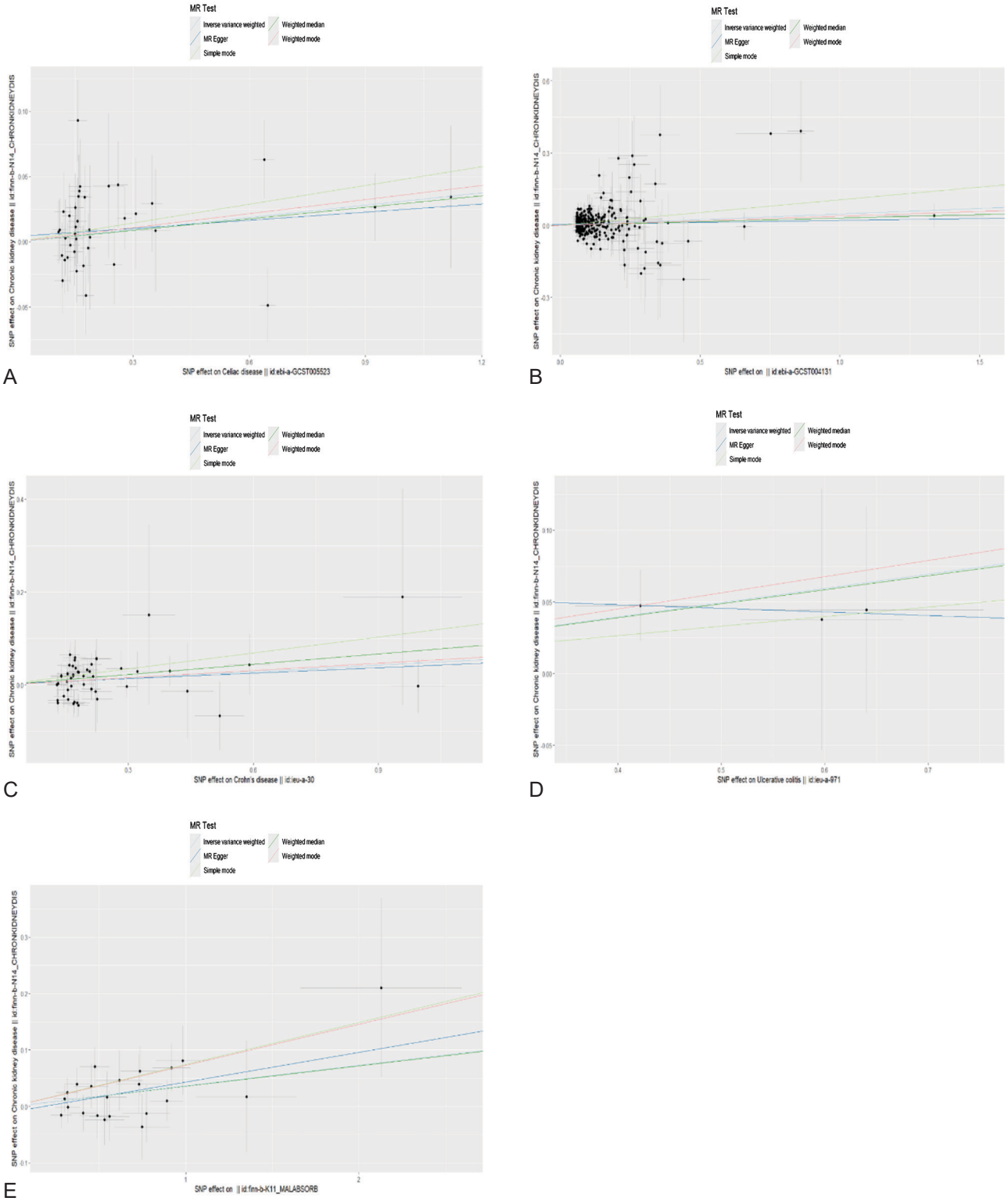
influencing kidney health across a spectrum of gastrointestinal conditions. By leveraging genetic variants as instrumental variables, the study demonstrates strong associations between CeD, IBD, intestinal malabsorption, and risk of CKD development, supported by multiple MR approaches, including IVW, MR-Egger, and weighted median analyses. These results remain consistent in sensitivity analyses, underscoring their reliability and robustness.

Furthermore, bioinformatics analyses provided additional insights into the underlying genetic

Supplementary Table S2. MR analysis for replication analysis.

Outcome	Exposure	ID	Method	nSNPs	β	*P*	OR	95%CI
Chronic kidney disease || id:finn-b-N14_ CHRONKIDNEYDIS	Celiac disease	ebi-a-GCST005523	IVW	38	0.031	0.049	1.032	1.000-1.064
	Inflammatory bowel disease	ebi-a-GCST004131	IVW	300	0.047	0.006	1.048	1.013-1.083
	Crohn's disease	ieu-a-30	IVW	51	0.047	0.020	1.048	1.008-1.090
	Ulcerative colitis	ieu-a-971	IVW	3	0.099	0.044	1.104	1.003-1.216
	Intestinal malabsorbtion	finn-b-K11_ MALABSORB	IVW	22	0.037	0.014	1.037	1.007-1.068

nSNPS: number of SNPs used in MR; OR: odds radio; CI: confidence interval; IVW: Inverse variance weighted.



Supplementary Figure S1. MR analysis of causal effect of replication analysis
(A) The scatter plot of CeD on CKD. (B) The scatter plot of IBD on CKD. (C) The scatter plot of Crohn's disease on CKD. (D) The scatter plot of ulcerative colitis on CKD. (E) The scatter plot of intestinal malabsorbtion on CKD.

mechanisms driving these associations. FUMA analysis identified 93 genes linked to CeD, 143 genes associated with IBD, and 26 genes relevant to intestinal malabsorption, highlighting a complex

Table 3. Sensitivity analysis of the MR analysis results

Outcome	Exposure	Heterogeneity test				Pleiotropy test			
		IVW		MR-Egger		MR-Egger regression		MR-PRESSO	
		Q	*P*	Q	*P*	Intercept	*P*	Outliers number	*P*
Chronic kidney disease	Celiac disease	25.696	.735	25.343	.708	0.003	.557	0	.787
	Inflammatory bowel disease	50.623	.932	50.621	.919	< 0.001	.969	0	.939
	Intestinal malabsorption	18.65731	.097	17.109	.105	0.016	.340	0	.144

IVW: inverse variance weighted; MR-PRESSO: MR pleiotropy residual sum and outlier

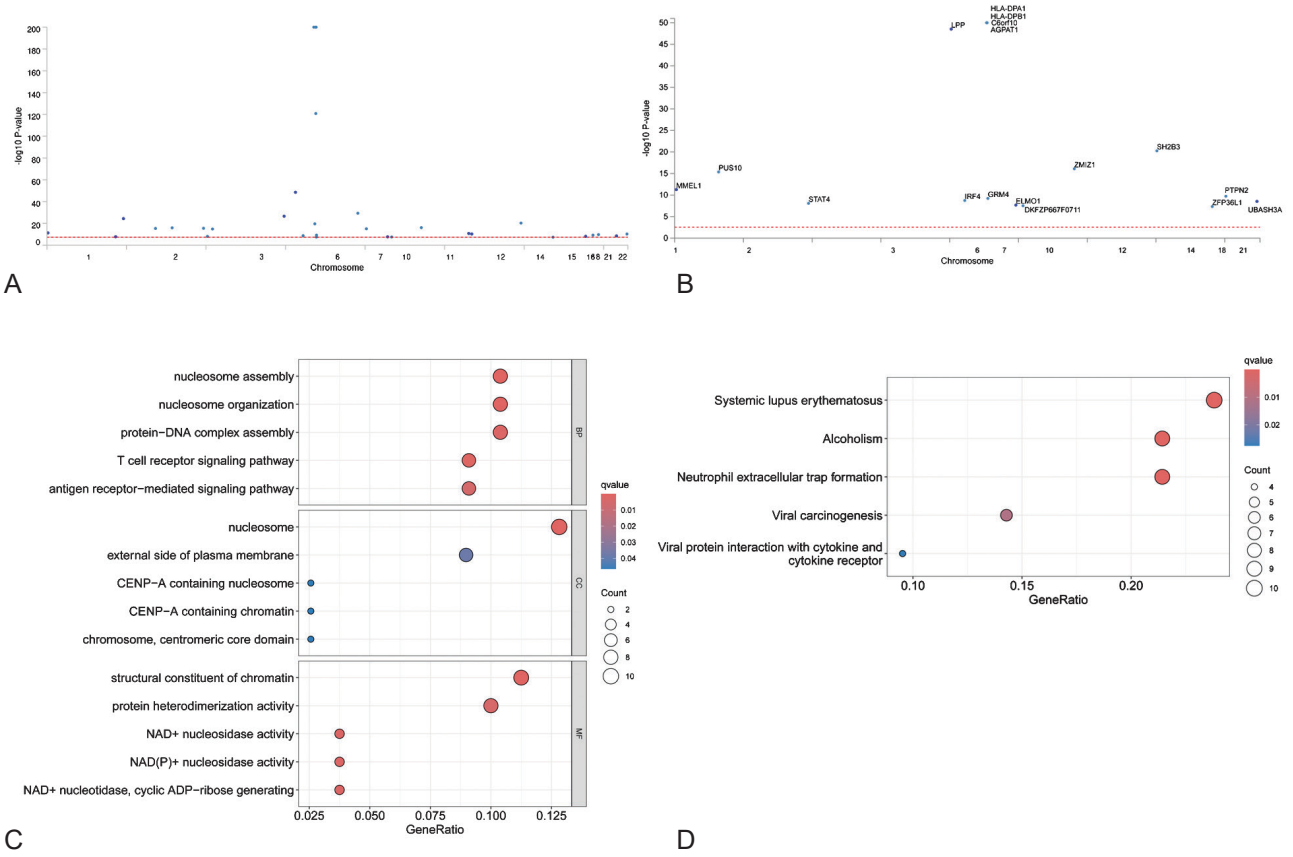


Figure 6. FUMA analysis and enrichment analysis of CeD on CKD.
(A) Manhattan Plot of GWAS summary statistics based on input GWAS summary statistics for CeD. (B) Manhattan Plot of Gene-based testing using MAGMA. (C) Bubble chart for GO analysis. (D) Bubble chart for KEGG analysis.

network of genetic interactions potentially contributing to CKD risk. GO and KEGG pathway enrichment analyses further revealed that key biological processes, such as T-cell receptor signaling, cytokine-cytokine receptor interaction, and immune-mediated pathways, may be involved in the systemic effects of these gastrointestinal diseases on kidney function. Notably, pathways related to chromatin regulation, antigen receptor signaling, and inflammatory cascades were significantly enriched in CeD and IBD, suggesting a possible involvement of epigenetic and immune dysregulation in renal impairment. The KEGG enrichment results also indicated neutrophil extracellular trap formation, chemokine signaling, and viral protein interactions with cytokine receptors as shared pathways between IBD and CKD, further reinforcing the hypothesis that chronic inflammation and immune dysregulation serve as major contributors to kidney disease progression. Additionally, intestinal malabsorption was associated with olfactory transduction pathways, indicating possible metabolic or neuroimmune interactions influencing CKD risk.

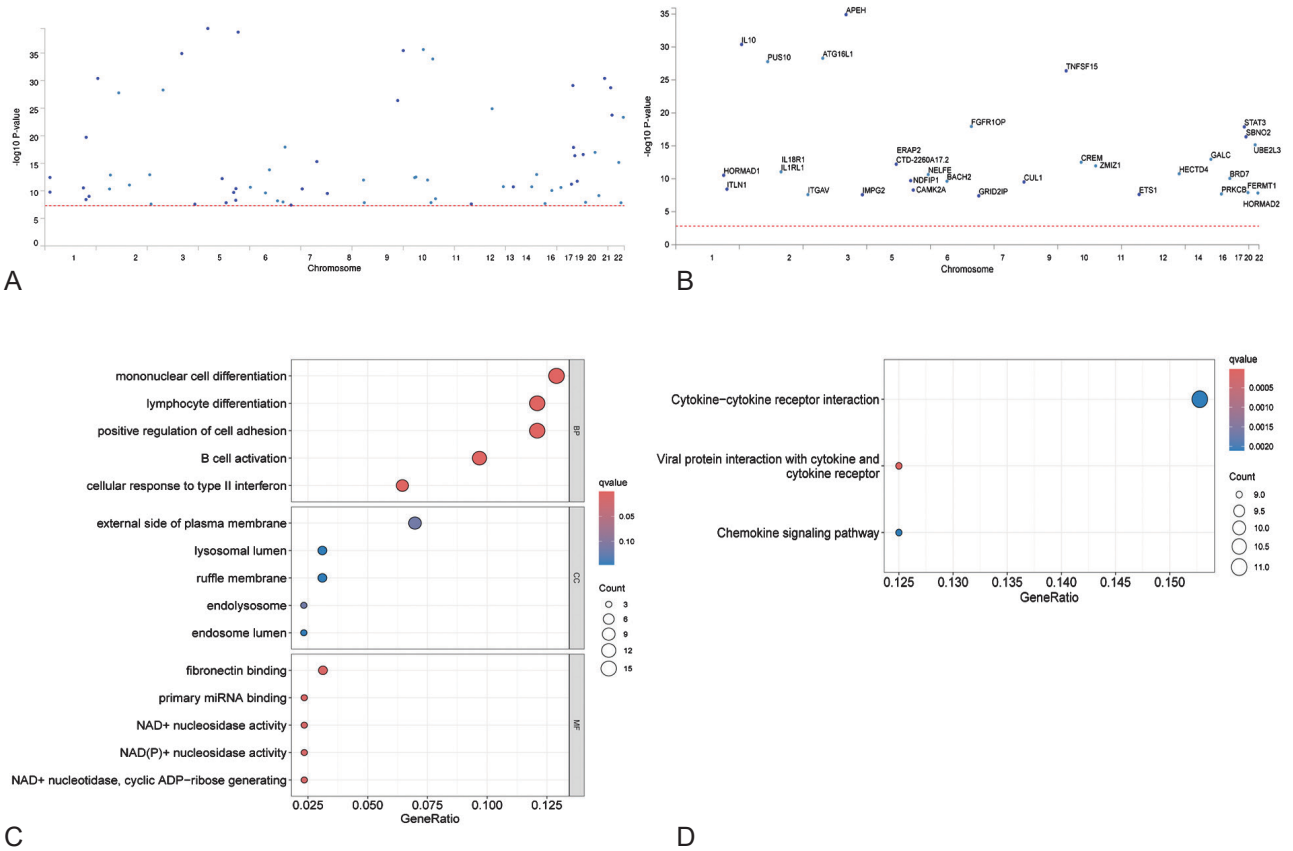


Figure 7. FUMA analysis and enrichment analysis of IBD on CKD. (A) Manhattan Plot of GWAS summary statistics based on input GWAS summary statistics for IBD. (B) Manhattan Plot of Gene-based testing using MAGMA. (C) Bubble chart for GO analysis. (D) Bubble chart for KEGG analysis.

The observed associations highlight several critical insights. First, the positive causal effect of CeD on CKD risk, though modest, suggests that systemic autoimmune responses in CeD may contribute to renal complications. This aligns with the systemic nature of autoimmune disorders where inflammatory processes potentially extend beyond the primary disease locus.[21] For IBD, including CD and UC, the stronger associations suggest more pronounced renal involvement, possibly attributable to chronic inflammation or immune dysregulation that commonly present in these conditions.[22] The underlying mechanisms might involve chronic systemic inflammation, immune complex deposition, or direct autoimmune attack, all of which are known to contribute to renal pathology.[23] The shared genetic pathways, indicated by HLA associations in CeD and similar immunological markers in IBD, could further elucidate the cross-talk between gastrointestinal and renal systems.[24]

Additionally, the significant association between intestinal malabsorption and CKD risk underscores the potential role of nutrient deficiencies and systemic inflammation in renal pathology. Intestinal malabsorption, characterized by impaired absorption of essential nutrients, may contribute to CKD progression through multiple mechanisms, including electrolyte imbalances, oxidative stress, and secondary hyperparathyroidism caused by vitamin D and calcium deficiencies.[7] These disruptions can exacerbate renal damage and further emphasize the need for nutritional assessment and management in patients with malabsorption syndromes.[25]

Our findings partly align with a previous MR study, which demonstrated a strong genetic link between IBD and IgA nephropathy, highlighting the complexity of gastrointestinal-renal interactions.[8] IgA nephropathy, a more specific renal disorder, may have a direct link to IBD, whereas CKD represents a broader spectrum of kidney dysfunction.[26] This distinction underscores the need to investigate specific kidney phenotypes when

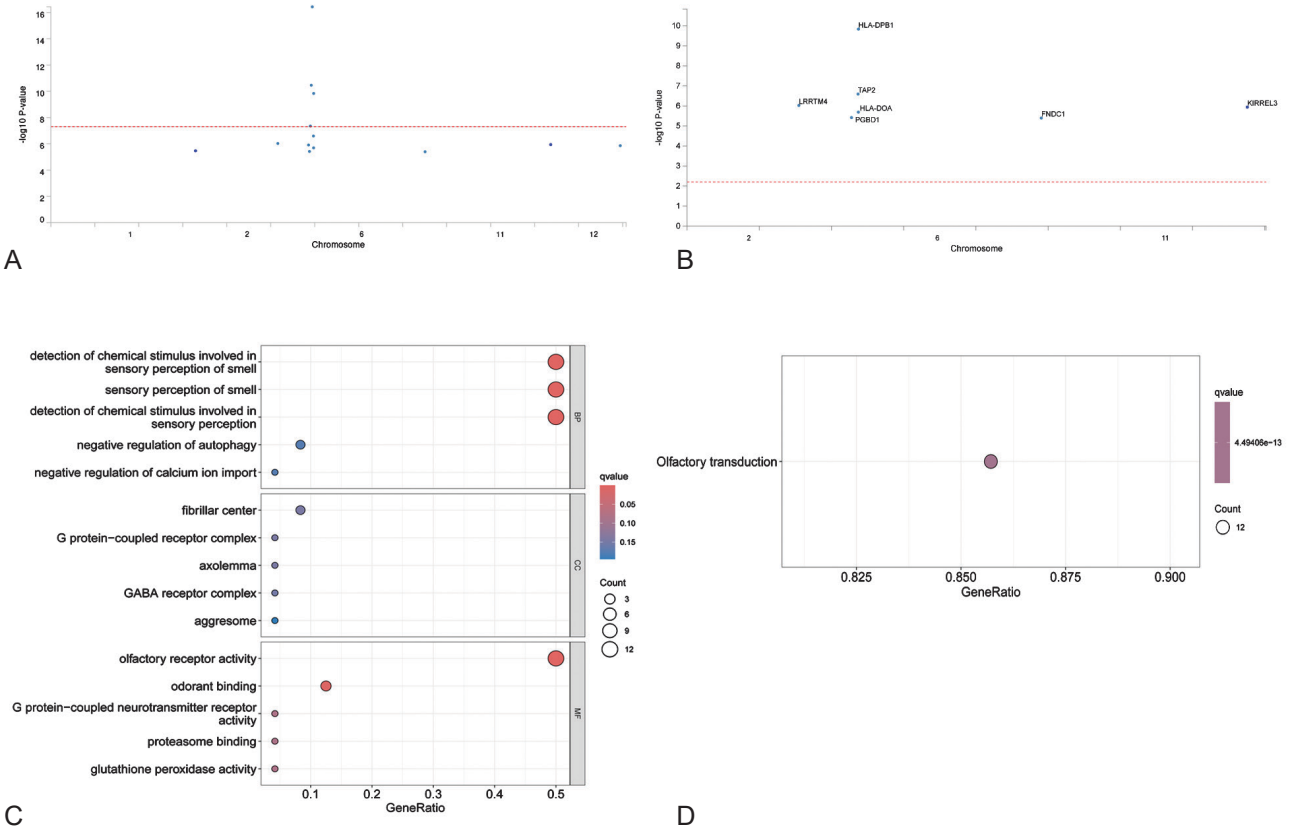


Figure 8. FUMA analysis and enrichment analysis of CeD on CKD.
(A) Manhattan Plot of GWAS summary statistics based on input GWAS summary statistics for Intestinal malabsorption. (B) Manhattan Plot of Gene-based testing using MAGMA. (C) Bubble chart for GO analysis. (D) Bubble chart for KEGG analysis.

examining the effects of gastrointestinal diseases. Moreover, our study did not find significant reverse causation, suggesting that CKD may not directly predispose individuals to IBD, CeD, or intestinal malabsorption. However, a recent study reported that a lower estimated glomerular filtration rate (eGFR), a marker of CKD, was associated with an increased risk of subsequent IBD, indicating a potential bidirectional relationship.[27] Future research incorporating reverse MR analyses could further clarify the causal directionality of these associations.

Limitations

One of the strengths of this study is the use of MR to overcome the limitations of observational studies, which are often plagued by confounding factors.[28] However, the study had several limitations. The genetic instruments used, while robustly associated with CeD, intestinal malabsorption, CD, UC, and IBD, may not capture all genetic factors influencing the disease pathways, and the possibility of unmeasured pleiotropy cannot be entirely excluded despite our analytical approaches. Sensitivity analyses were not conducted for the GI diseases that showed no genetic association with CKD, leaving the robustness of these null findings formally unevaluated. This limitation precludes us from fully excluding the potential influence of undetected biases or weak instrument effects. Additionally, integrating these genetic findings with environmental factors could provide a more comprehensive understanding of the disease mechanisms at play. The potential impact of important clinical factors, including pharmacological treatments and environmental variables, on CKD risk was not thoroughly discussed.[29] Medications commonly used in IBD, such as Sulfasalazine and immunosuppressants like Cyclosporine or Methotrexate,[30-32] can exert nephrotoxic effects, potentially confounding the observed associations. Similarly, environmental factors such as diet, lifestyle, and comorbidities may influence the risk of CKD among these patients.

Supplementary Table S3. Gene list from FUMA analyses

Celiac disease		Inflammatory bowel disease			Intestinal malabsorbtion
TNFRSF14	PGBD1	RNF186	CAMK2A	GALC	PGBD1
FAM213B	ZSCAN31	ADAMTSL4	SMIM3	GPR65	ZSCAN31
MMEL1	ZKSCAN3	ADAMTSL4-AS1	AC010441.1	PRKCB	ZKSCAN3
TTC34	ZSCAN12	MCL1	IRGM	ADCY7	ZSCAN12
RGS1	ZSCAN23	ENSA	ZNF300	BRD7	ZSCAN23
PUS10	GRM4	GOLPH3L	BACH2	AC005549.3	GPX6
IL1RL1	RSPH3	HORMAD1	TAGAP	CCL2	SCAND3
IL18R1	TAGAP	CTSS	RP11-514O12.4	CCL7	TRIM27
IL18RAP	ELMO1	CTSK	RNASET2	CCL11	C6orf100
SLC9A4	DKFZP667F0711	ARNT	FGFR1OP	CCL8	ZNF311
STAT4	ZMIZ1	SETDB1	CCR6	GRB7	OR2W1
CD28	POU2AF1	CERS2	DAGLB	IKZF3	OR2B3
LPP	DDX6	ANXA9	KDELR2	ZPBP2	OR2J1
IRF4	CXCR5	CD244	FLJ20306	GSDMB	OR2J3
BTN3A3	SH2B3	ITLN1	GRID2IP	ORMDL3	OR2J2
BTN2A1	ATXN2	ITLN2	DLD	LRRC3C	OR14J1
BTN1A1	BRAP	FCGR2A	LAMB1	STAT3	OR5V1
HMGN4	ACAD10	IL10	CUL1	PTRF	OR12D3
ABT1	RP11-162P23.2	IL19	EZH2	GPX4	OR12D2
ZNF322	ALDH2	DNAJC27	TNFSF15	SBNO2	OR11A1
HIST1H2BJ	MAPKAPK5	EFR3B	GPSM1	ZGLP1	OR10C1
HIST1H2AG	NAA25	FOSL2	DNLZ	CTD-2369P2.10	OR2H1
PRSS16	TRAFD1	PUS10	CARD9	FDX1L	MAS1L
POM121L2	HECTD4	IL1RL1	SNAPC4	CTD-2369P2.12	UBD
ZNF391	RPL6	IL18R1	SDCCAG3	RAVER1	GABBR1
ZNF184	PTPN11	IL18RAP	PMPCA	ICAM3	OR2H2
HIST1H2BL	ZFP36L1	SLC9A4	INPP5E	TYK2	
HIST1H2AI	CYP1A2	ITGA4	MAP3K8	CDC37	
HIST1H3H	CSK	ITGAV	CUL2	PDE4A	
HIST1H2AJ	LMAN1L	FAM171B	CREM	KEAP1	
HIST1H2BM	CPLX3	ZSWIM2	CCNY	FERMT1	
HIST1H4J	ULK3	ATG16L1	ZMIZ1	HNF4A	
HIST1H4K	SCAMP2	SAG	IDE	ZNF831	
HIST1H2AK	MPI	USP4	KIF11	ICOSLG	
HIST1H2BN	FAM219B	GPX1	HHEX	RIMBP3C	
HIST1H2AL	COX5A	RHOA	NKX2-3	UBE2L3	
HIST1H1B	CIITA	TCTA	ETS1	YDJC	
HIST1H3I	PTPN2	AMT	SH2B3	CCDC116	
HIST1H4L	UBASH3A	NICN1	ATXN2	ASCC2	
HIST1H3J	RIMBP3C	DAG1	BRAP	MTMR3	
HIST1H2AM	UBE2L3	BSN	ACAD10	HORMAD2	
HIST1H2BO	YDJC	APEH	RP11-162P23.2	AL031590.1	
OR2B2	CCDC116	MST1	ALDH2	SYNGR1	
OR2B6		RNF123	MAPKAPK5		
ZNF165		IMPG2	NAA25		
ZSCAN16		CTD-2260A17.2	TRAFD1		
ZKSCAN8		ERAP2	HECTD4		
ZSCAN9		LNPEP	RPL6		
ZKSCAN4		NDFIP1	PTPN11		
NKAPL		SLC6A7	ZFP36L1		

Completed STROBE-MR Checklist. STROBE-MR checklist of recommended items to address in reports of Mendelian randomization studies[1,2]

Item No.	Section	Checklist item	Page No.
1	TITLE and ABSTRACT	Indicate Mendelian randomization (MR) as the study's design in the title and/or the abstract if that is a main purpose of the study	1, 2
	INTRODUCTION		
2	Background	Explain the scientific background and rationale for the reported study. What is the exposure? Is a potential causal relationship between exposure and outcome plausible? Justify why MR is a helpful method to address the study question	3
3	Objectives	State specific objectives clearly, including pre-specified causal hypotheses (if any). State that MR is a method that, under specific assumptions, intends to estimate causal effects	2
	METHODS		
4	Study design and data sources	Present key elements of the study design early in the article. Consider including a table listing sources of data for all phases of the study. For each data source contributing to the analysis, describe the following:	3
	a)	Setting: Describe the study design and the underlying population, if possible. Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection, when available.	3
	b)	Participants: Give the eligibility criteria, and the sources and methods of selection of participants. Report the sample size, and whether any power or sample size calculations were carried out prior to the main analysis	3
	c)	Describe measurement, quality control and selection of genetic variants	4
	d)	For each exposure, outcome, and other relevant variables, describe methods of assessment and diagnostic criteria for diseases	4
	e)	Provide details of ethics committee approval and participant informed consent, if relevant	4
5	Assumptions	Explicitly state the three core IV assumptions for the main analysis (relevance, independence and exclusion restriction) as well assumptions for any additional or sensitivity analysis	3
6	Statistical methods: main analysis	Describe statistical methods and statistics used	4
	a)	Describe how quantitative variables were handled in the analyses (i.e., scale, units, model)	4
	b)	Describe how genetic variants were handled in the analyses and, if applicable, how their weights were selected	4
	c)	Describe the MR estimator (e.g. two-stage least squares, Wald ratio) and related statistics. Detail the included covariates and, in case of two-sample MR, whether the same covariate set was used for adjustment in the two samples	4
	d)	Explain how missing data were addressed	4
	e)	If applicable, indicate how multiple testing was addressed	4
7	Assessment of assumptions	Describe any methods or prior knowledge used to assess the assumptions or justify their validity	4
8	Sensitivity analyses and additional analyses	Describe any sensitivity analyses or additional analyses performed (e.g. comparison of effect estimates from different approaches, independent replication, bias analytic techniques, validation of instruments, simulations)	4
9	Software and pre-registration		
	a)	Name statistical software and package(s), including version and settings used	4
	b)	State whether the study protocol and details were pre-registered (as well as when and where)	NA
	RESULTS		
10	Descriptive data		
	a)	Report the numbers of individuals at each stage of included studies and reasons for exclusion. Consider use of a flow diagram	4
	b)	Report summary statistics for phenotypic exposure(s), outcome(s), and other relevant variables (e.g. means, SDs, proportions)	4
	c)	If the data sources include meta-analyses of previous studies, provide the assessments of heterogeneity across these studies	NA
	d)	For two-sample MR: i. Provide justification of the similarity of the genetic variant-exposure associations between the exposure and outcome samples ii. Provide information on the number of individuals who overlap between the exposure and outcome studies	4

Completed STROBE-MR Checklist. Continued

Item No.	Section	Checklist item	Page No.
11	Main results		
	a)	Report the associations between genetic variant and exposure, and between genetic variant and outcome, preferably on an interpretable scale	4
	b)	Report MR estimates of the relationship between exposure and outcome, and the measures of uncertainty from the MR analysis, on an interpretable scale, such as odds ratio or relative risk per SD difference	4
	c)	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	4
	d)	Consider plots to visualize results (e.g. forest plot, scatterplot of associations between genetic variants and outcome versus between genetic variants and exposure)	S5-7
12	Assessment of assumptions		
	a)	Report the assessment of the validity of the assumptions	4
	b)	Report any additional statistics (e.g., assessments of heterogeneity across genetic variants, such as I2, Q statistic or E-value)	4
13	Sensitivity analyses and additional analyses		
	a)	Report any sensitivity analyses to assess the robustness of the main results to violations of the assumptions	5
	b)	Report results from other sensitivity analyses or additional analyses	5
	c)	Report any assessment of direction of causal relationship (e.g., bidirectional MR)	5
	d)	When relevant, report and compare with estimates from non-MR analyses	5
	e)	Consider additional plots to visualize results (e.g., leave-one-out analyses)	5
	DISCUSSION		
14	Key results	Summarize key results with reference to study objectives	5
15	Limitations	Discuss limitations of the study, taking into account the validity of the IV assumptions, other sources of potential bias, and imprecision. Discuss both direction and magnitude of any potential bias and any efforts to address them	5
16	Interpretation		
	a)	Meaning: Give a cautious overall interpretation of results in the context of their limitations and in comparison with other studies	5
	b)	Mechanism: Discuss underlying biological mechanisms that could drive a potential causal relationship between the investigated exposure and the outcome, and whether the gene-environment equivalence assumption is reasonable. Use causal language carefully, clarifying that IV estimates may provide causal effects only under certain assumptions	5
	c)	Clinical relevance: Discuss whether the results have clinical or public policy relevance, and to what extent they inform effect sizes of possible interventions	6
17	Generalizability	Discuss the generalizability of the study results (a) to other populations, (b) across other exposure periods/timings, and (c) across other levels of exposure	6
	OTHER INFORMATION		
18	Funding	Describe sources of funding and the role of funders in the present study and, if applicable, sources of funding for the databases and original study or studies on which the present study is based	6
19	Data and data sharing	Provide the data used to perform all analyses or report where and how the data can be accessed, and reference these sources in the article. Provide the statistical code needed to reproduce the results in the article, or report whether the code is publicly accessible and if so, where	6
20	Conflicts of Interest	All authors should declare all potential conflicts of interest	6

1. Skrivankova VW, Richmond RC, Woolf BAR, Yarmolinsky J, Davies NM, Swanson SA, et al. Strengthening the Reporting of Observational Studies in Epidemiology using Mendelian Randomization (STROBE-MR) Statement. JAMA. 2021;under review.
2. Skrivankova VW, Richmond RC, Woolf BAR, Davies NM, Swanson SA, VanderWeele TJ, et al. Strengthening the Reporting of Observational Studies in Epidemiology using Mendelian Randomisation (STROBE-MR): Explanation and Elaboration. BMJ. 2021;375:n2233.

CONCLUSION

In conclusion, this study provided genetic and bioinformatics evidence supporting an increased risk of GI diseases including IBD (CD and UC), CeD, and intestinal malabsorption associated with CKD risk. These findings underscored the systemic impact of chronic inflammation, immune dysregulation, and metabolic disturbances on CKD.

DECLARATIONS

Data Availability Statement

The analyses for this study were based on publicly available summary statistics. The datasets generated and analyzed during the current study are available in the IEU open GWAS project (https://gwas.mrcieu.ac.uk/).

Supplementary Material

Supplementary data are available at *IJE* online.

Supplementary Table S1. Final SNPs used as genetic instruments.

Supplementary Table S2. MR analysis for replication analysis.

Supplementary Table S3. Gene list from FUMA analyses.

Supplementary Figure S1. The scatter plots of MR analysis for replication analysis

Supplementary STROBE-MR Checklist

AUTHOR CONTRIBUTIONS

XC and MZ created the study concept and designed the studies. LX, CJ, HH, and YM conducted data analysis. LX, HK, LM, YB, ZC, ZL, XC, and MZ wrote and approved the final version of the manuscript.

FUNDING

This work was supported by grants from the National Natural Science Foundation of China (82200786, 82070705, 81770670, and 81873595). This work was supported by Oriental Talent Plan Outstanding Program 2023, Shanghai Municipal Key Clinical Specialty (shslczdzk02503), Shanghai Science and Technology Talent Program (19YF1450300), and Research Projects of Shanghai Science and Technology Committee (17411972100). Shanghai Shenkang Research Physician innovation and transformation ability training program SHDC2022CRD024. Shanghai Science and Technology Innovation Action Plan of Scientific Instruments and Chemical Reagents Project (24142201800). China Scholarship Council (202408310237).

CONFLICTS OF INTEREST

All the authors declared no competing interests.

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Received March 2025
Revised October 2025
Accepted December 2025