

Supplementary Information

Causal effects of specific gut microbiota on CKD and renal function —— A two-sample mendelian randomization study

Ning Li¹; Ping Wei¹; Yu Min²; Manshu Yu¹; Guowei Zhou¹; Gui Yuan³; Jinyi Sun¹;
Huibo Dai¹; Enchao Zhou^{1*}; Weiming He¹; Meixiao Sheng¹; Kun Gao¹; Min Zheng¹;
Wei Sun¹; Dong Zhou^{3*}; Lu ZHANG^{1*}

Group	Exposure	Outcome	Cochran's Q-derived P value	MR-PRESSO-Global-test-derived P value	MR-Egger intercept-derived P value
Class	Bacteroidia	CKD	0.48	0.49	0.14
	Deltaproteobacteria	CKD	0.98	0.99	0.828
	Gammaproteobacteria	CKDi25	0.76	0.79	0.56
	Bacteroidia	CKDi25	0.64	0.64	0.32
	Deltaproteobacteria	CKDi25	0.22	0.27	0.58
	Bacteroidia	eGFR	0.67	0.69	0.33
	Deltaproteobacteria	eGFR	0.11	0.18	0.95
	Lentisphaeria	UACR	0.22	0.31	0.59
	FamilyXIII	CKD	0.58	0.60	0.347
	Lachnospiraceae	CKD	0.48	0.52	0.731
Family	Defluviitaleaceae	CKDi25	0.45	0.5	0.35
	Pasteurellaceae	eGFR	0.83	0.80	0.30
	Coprococcus	CKD	0.81	0.83	0.613
	LachnospiraceaeUCG010	CKD	0.54	0.6	0.47
	Ruminococcus	CKD	0.53	0.53	0.81
Genus	Streptococcus	CKD	0.77	0.78	0.59
	Actinomyces	CKDi25	0.76	0.77	0.90
	Butyricimonas	CKDi25	0.73	0.76	0.93
	DefluviitaleaceaeUCG011	CKDi25	0.51	0.56	0.35
	Streptococcus	CKDi25	0.44	0.47	0.59
	Anaerofilum	Dialysis	0.90	0.91	0.82
	Christensenellaceae	Rapid3	0.72	0.77	0.94
	Terrisporobacter	Rapid3	0.86	0.88	0.73
	Anaerofilum	eGFR	0.51	0.55	0.83

	Lachnospirace aeUCG001	eGFR	0.51	0.52	0.48
Order	Parasutterella	UACR	0.37	0.41	0.41
	Bacteroidales	CKD	0.35	0.4	0.26
	Desulfovibrion ales	CKDi25	0.52	0.56	0.69
	Bacteroidales	eGFR	0.72	0.72	0.39
	Clostridiales	eGFR	0.27	0.30	0.95
	Pasteurellales	eGFR	0.37	0.34	0.66
	Pasteurellales	UACR	0.36	0.41	0.09
Phylum	Rhodospirillal es	UACR	0.26	0.29	0.85
	Lactobacillales	UACR	0.09	0.13	0.96
	Actinobacteria	Dialysis	0.98	0.99	0.57
	Bacteroidetes	eGFR	0.29	0.29	0.13

Supplement Table S1. Mendelian randomized outliers and level pleiotropy test of exposure and outcome

Abbreviation: MR:Mendelian randomized, CKD: Chronic kidney disease, eGFR: estimated glomerular filtration rate, CKDi25: defined as the decrease of eGFR \geq 25% of baseline accompanied by the progression from no CKD to CKD, Rapid3: eGFR decreases by more than 3 mL/min/1.73m² per year, UACR: urine albumin to creatinine ratio.

Consortium	Author	Composition	Number	Research object
MiBioGen Consortium	Author Kurilshikov	24 cohorts	n=18340	211 gut microbiota
CKDGen Consortium	Wuttke M	23 cohort	41,395 patients and 439,303 controls	CKD
CKDGen Consortium	Stanzick KJ	GWAS summary statistics for CKDGen and UKB	n = 765,348 (CKDGen) and 436561 (UKB)	eGFR
CKDGen Consortium	Teumer A	54 GWAS summary statistics files	n=564,257	UACR
CKDGen Consortium	Mathias Gorski	42 genome-wide association studies	34,874 cases and 107,090 controls	Rapid3
CKDGen Consortium	Mathias Gorski	42 genome-wide association studies	19,901 cases, 175,244 controls	CKDi25

Supplement Table S2. Summary presentation of included studies

Exposure	nSNP	Odd ratio	95%lower	95%upper	P value
Class					
Bacteroidia	11	1.13	1.02	1.25	0.02
Deltaproteobacteria	6	0.87	0.77	0.98	0.04
Family					
FamilyXIII	8	1.19	1.01	1.39	0.038
Lachnospiraceae	6	0.84	0.72	0.98	0.026
Genus					
Coprooccus	9	1.17	1.03	1.32	0.01
LachnospiraceaeUCG010	10	1.12	1.01	1.23	0.02
Ruminococcus	9	1.14	1.02	1.26	0.04
Streptococcus	15	0.93	0.86	0.99	0.03
Order					
Bacteroidiales	9	1.17	1.04	1.31	0.01

Supplement Table S3. Sensitivity analysis for CKD (fix effect model)

Exposure	Outcome	β (95%CI)	p value
Class			
CKD	Bacteroidia	0.0003(0.0001, 0.0005)	0.03
	Deltaproteobacteria		
Family			
CKD	FamilyXIII	0.0003(-0.0008, 0.0013)	0.56
	Lachnospiraceae	0.0008 (-0.0003,0.0012)	0.74
Genus			
CKD	Coprooccus	-0.0005(-0.0026, 0.0024)	0.83
CKD	LachnospiraceaeUCG010	-0.0002(-0.0004, 0.001)	0.73
CKD	Ruminococcus	0.0002(-0.0004, 0.0015)	0.61

CKD	Streptococcus	-0.0004(-0.002, 0.002)	0.45
Order			
CKD	Bacteroidales	-0.001(-0.008, 0.001)	0.62

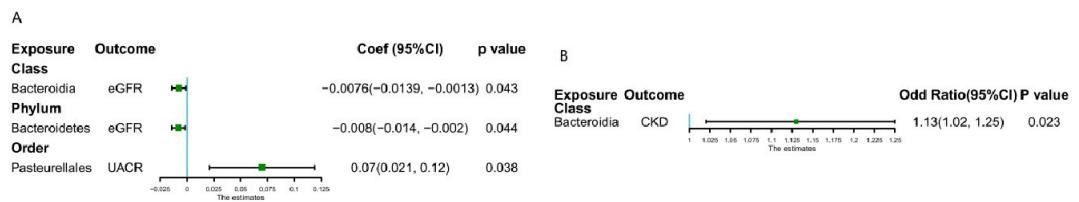
Supplement Table S4. Reverse causal analysis of CKD on gut microbiota

Supplement Figure S1

MR-Rgger analysis of causal effect between exposure microbiotas and various outcomes.

A) Categorical variable outcomes; B) Continuous variable outcomes

Abbreviation: MR:Mendelian randomized, CKD: Chronic kidney disease, eGFR: estimated glomerular filtration rate, CKDi25: defined as the decrease of eGFR \geq 25% of baseline accompanied by the progression from no CKD to CKD, Rapid3: eGFR decreases by more than 3 mL/min/1.73m² per year, UACR: urine albumin to creatinine ratio.



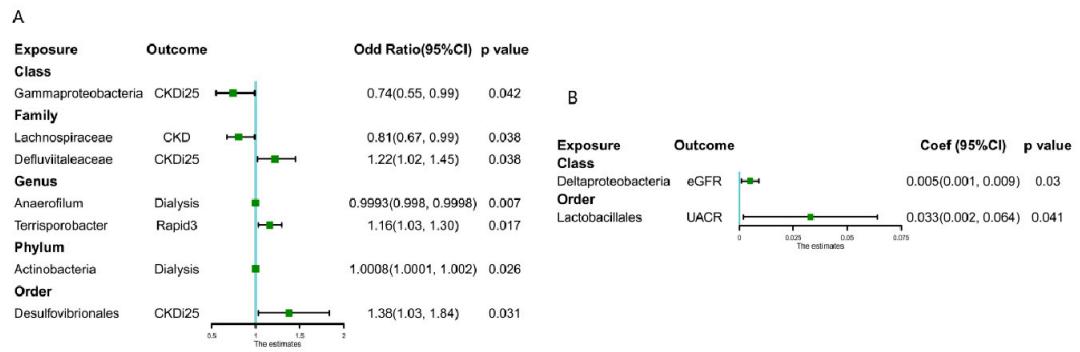
Supplement Figure S2

Weight mean analysis of causal effect between exposure microbiotas and various outcomes.

A) Categorical variable outcomes; B) Continuous variable outcomes

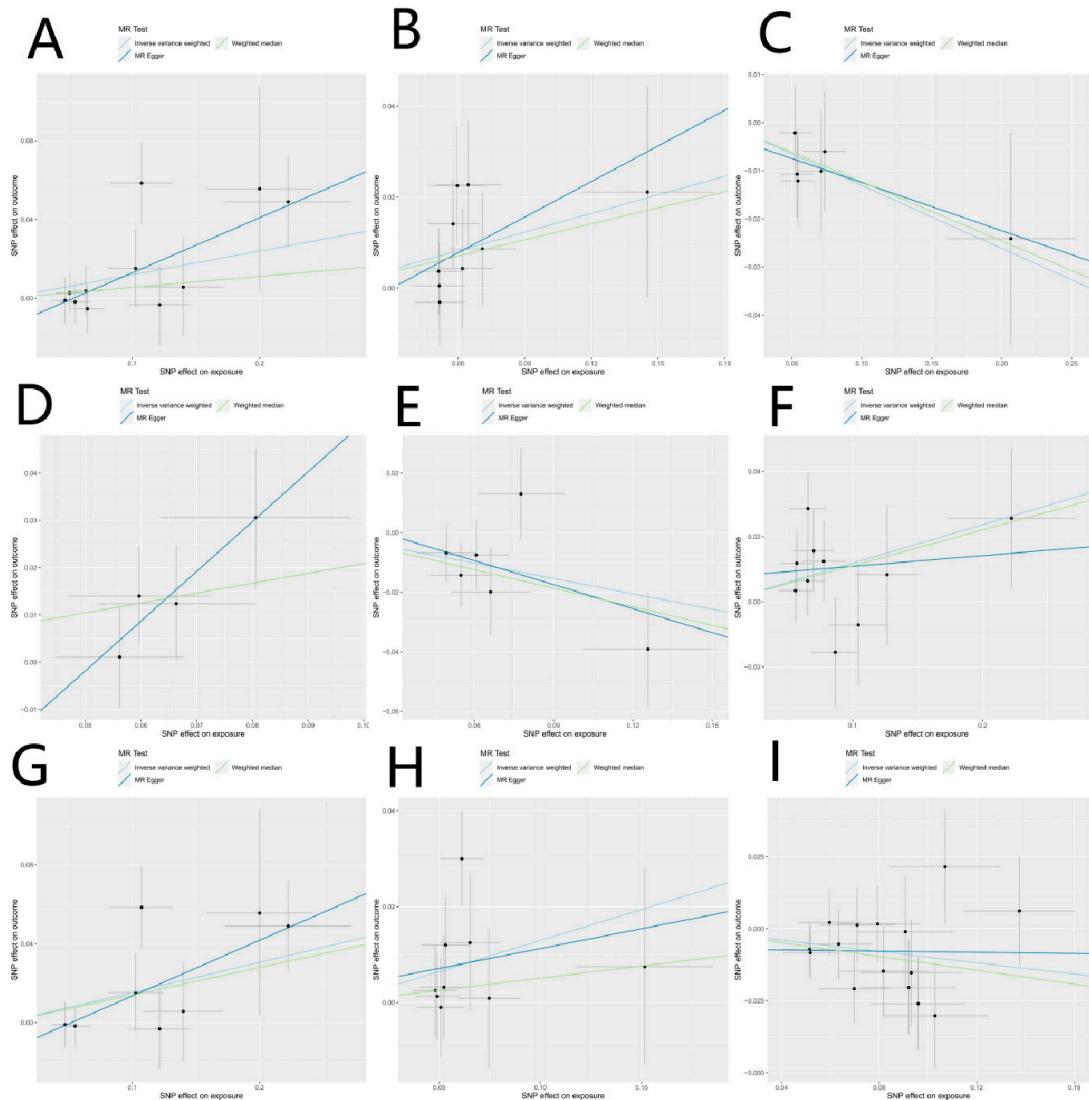
Abbreviation: MR:Mendelian randomized, CKD: Chronic kidney disease, eGFR: estimated glomerular filtration rate, CKD_{i25}: defined as the decrease of eGFR \geq 25% of baseline accompanied by the progression from no CKD to CKD, Rapid3: eGFR decreases by more than 3 mL/min/1.73m² per year, UACR: urine albumin to

creatinine ratio.



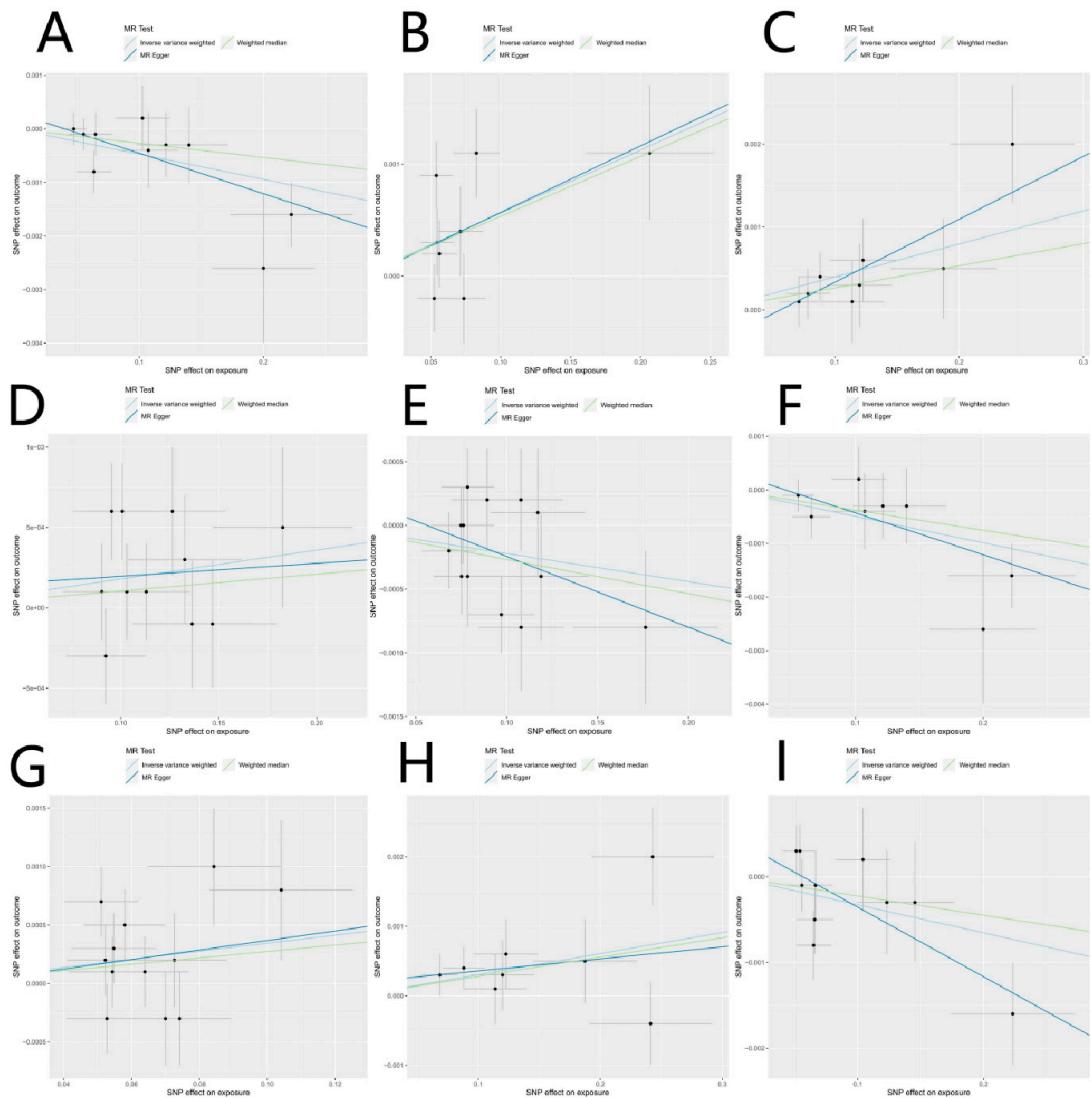
Supplement Figure S3

Scatter plots of significant and nominal significant estimates from genetically predicted microbiotas { (A) Class.Bacteroidia; (B) Genus.Coprococcus; (C) Class.Deltaproteobacteria; (D) Family.Lachnospiraceae; (E) Family.FamilyXIII ; (F) Genus.LachnospiraceaeUCG010; (G) Order.Bacteroidales; (H) Genus.Ruminococcus; (I) Genus.Streptococcus} on CKD



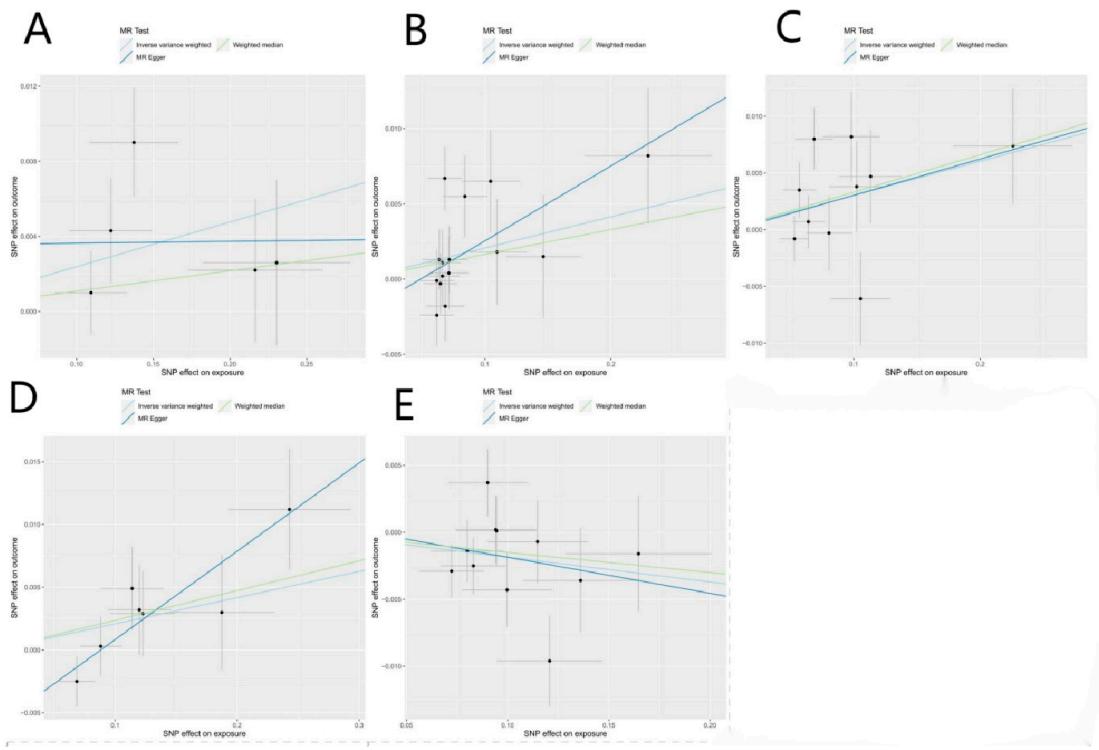
Supplement Figure S4

Scatter plots of significant and nominal significant estimates from genetically predicted microbiotas { (A) Class.Bacteroidia; (B) Class.Deltaproteobacteria; (C) Family.Pasteurellaceae; (D) Genus.Anaerofilum; (E) Genus.LachnospiraceaeUCG001 ; (F) Order.Bacteroidales; (G) Order.Clostridiales; (H) Order.Pasteurellales; (I) Phylum.Bacteroidetes} on eGFR



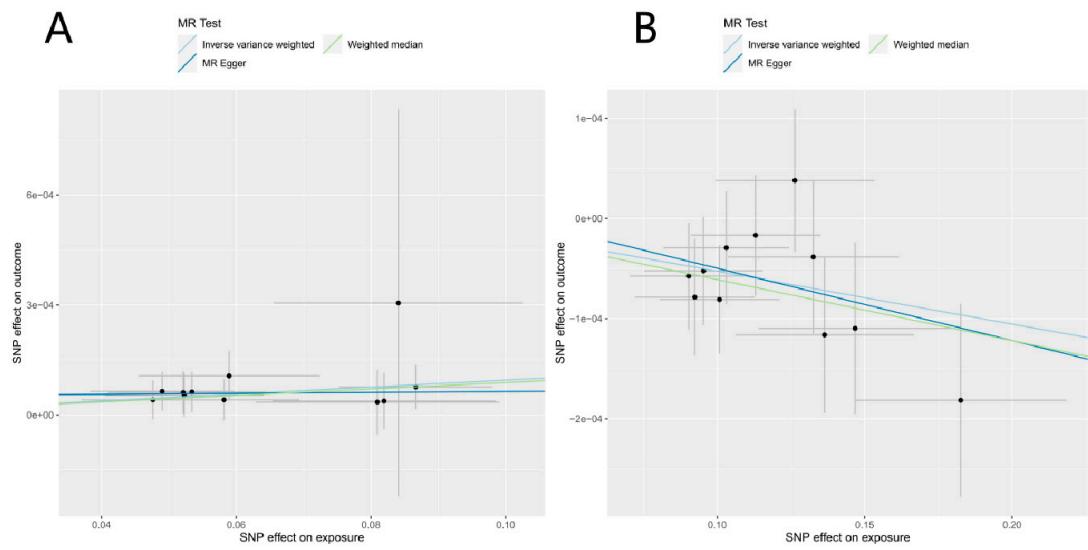
Supplement Figure S5

Scatter plots of significant and nominal significant estimates from genetically predicted microbiotas { (A) Class.Lentisphaeria; (B) Genus.Parasutterella; (C) Order.Lactobacillales; (D) Order.Pasteurellales; (E) Order.Rhodospirillales } on UACR



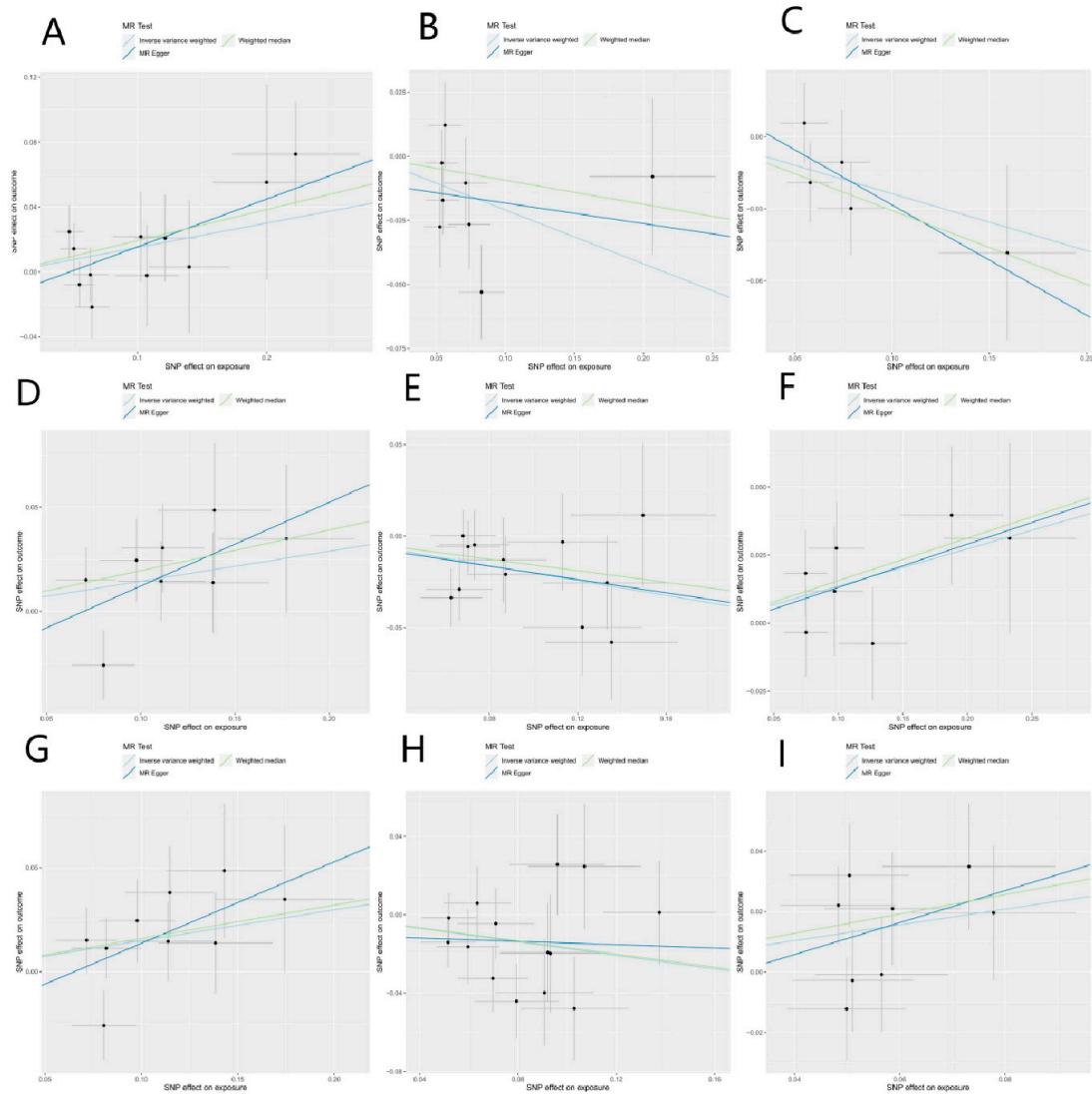
Supplement Figure S6

Scatter plots of significant and nominal significant estimates from genetically predicted microbiotas { (A) Phylum.Actinobacteria; (B) Genus.Anaoerofilum } on Dialysis



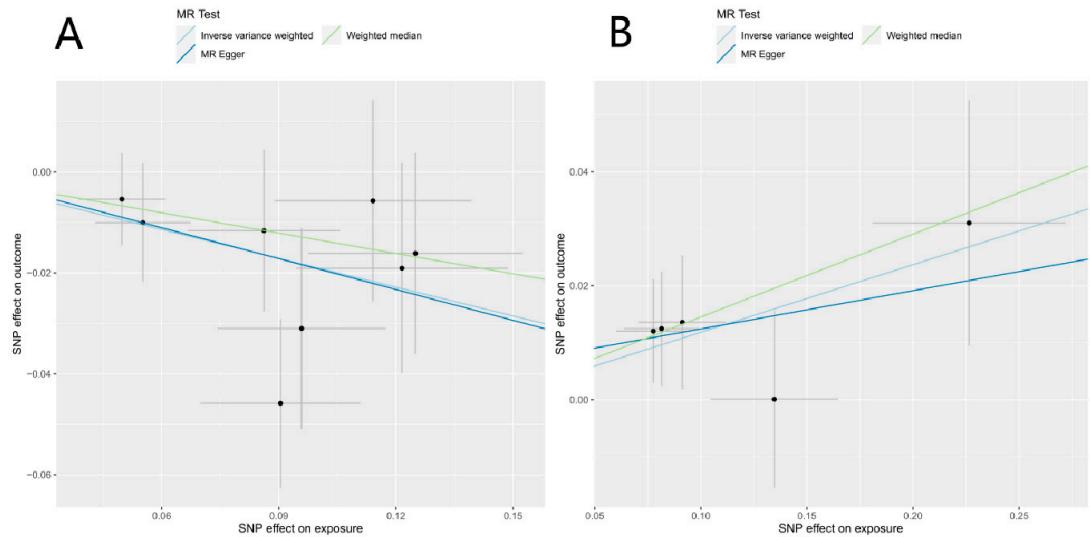
Supplement Figure S7

Scatter plots of significant and nominal significant estimates from genetically predicted microbiotas { (A) Class.Bacteroidia; (B) Class.Deltaproteobacteria; (C) Class.Gammaproteobacteria; (D) Family.Defluviitaleaceae; (E) Genus.Butyrimonas ; (F) Genus.Actinomyces; (G) Genus.DefluviitaleaceaeUCG011; (H) Genus.Streptococcus; (I) Order.Desulfovibrionales} on CKDi25



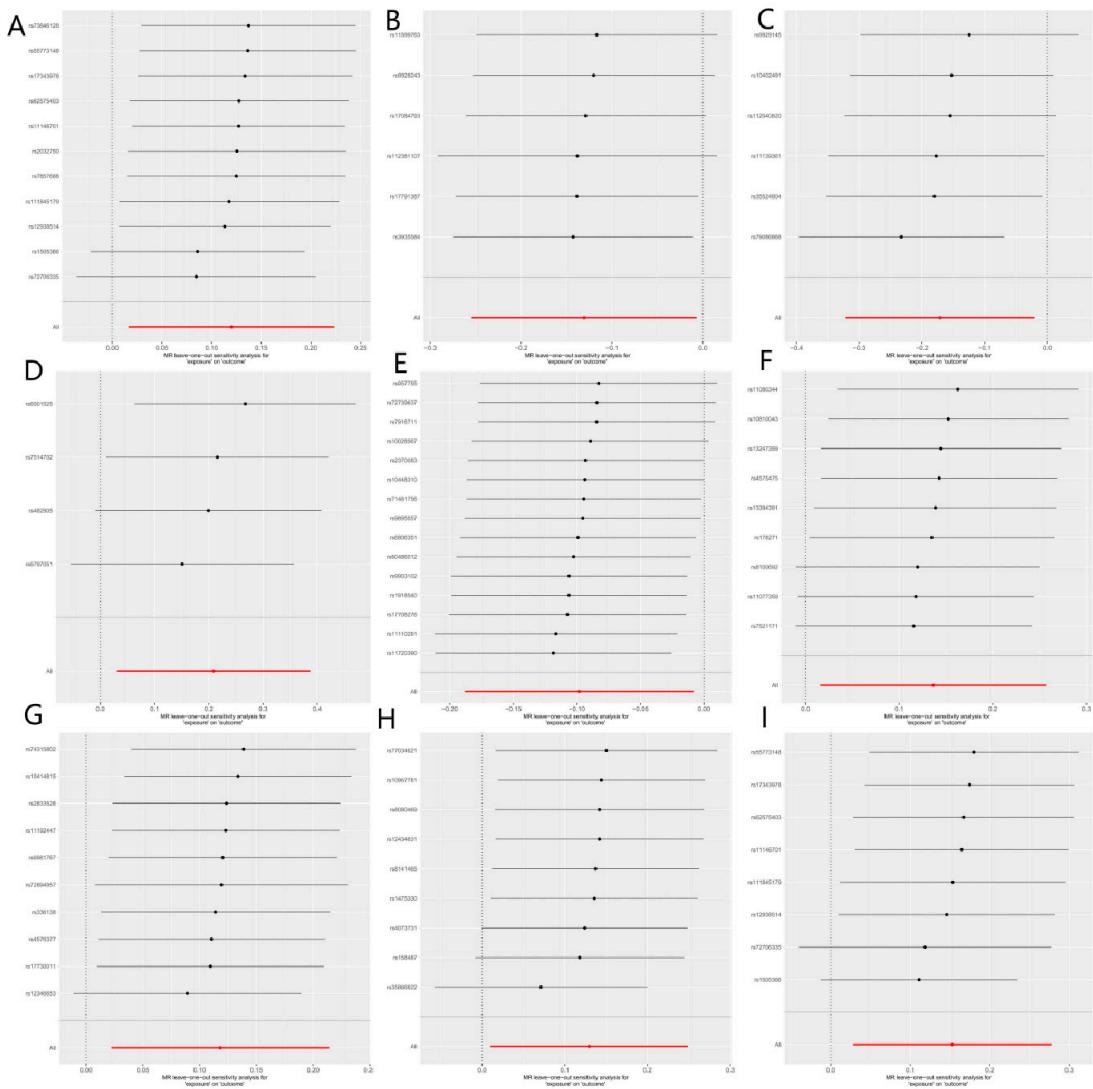
Supplement Figure S8

Scatter plots of significant and nominal significant estimates from genetically predicted microbiotas { (A) Genus.Christensenellaceae; (B) Genus.Terrisporobacter } on Rapid3



Supplement Figure S9

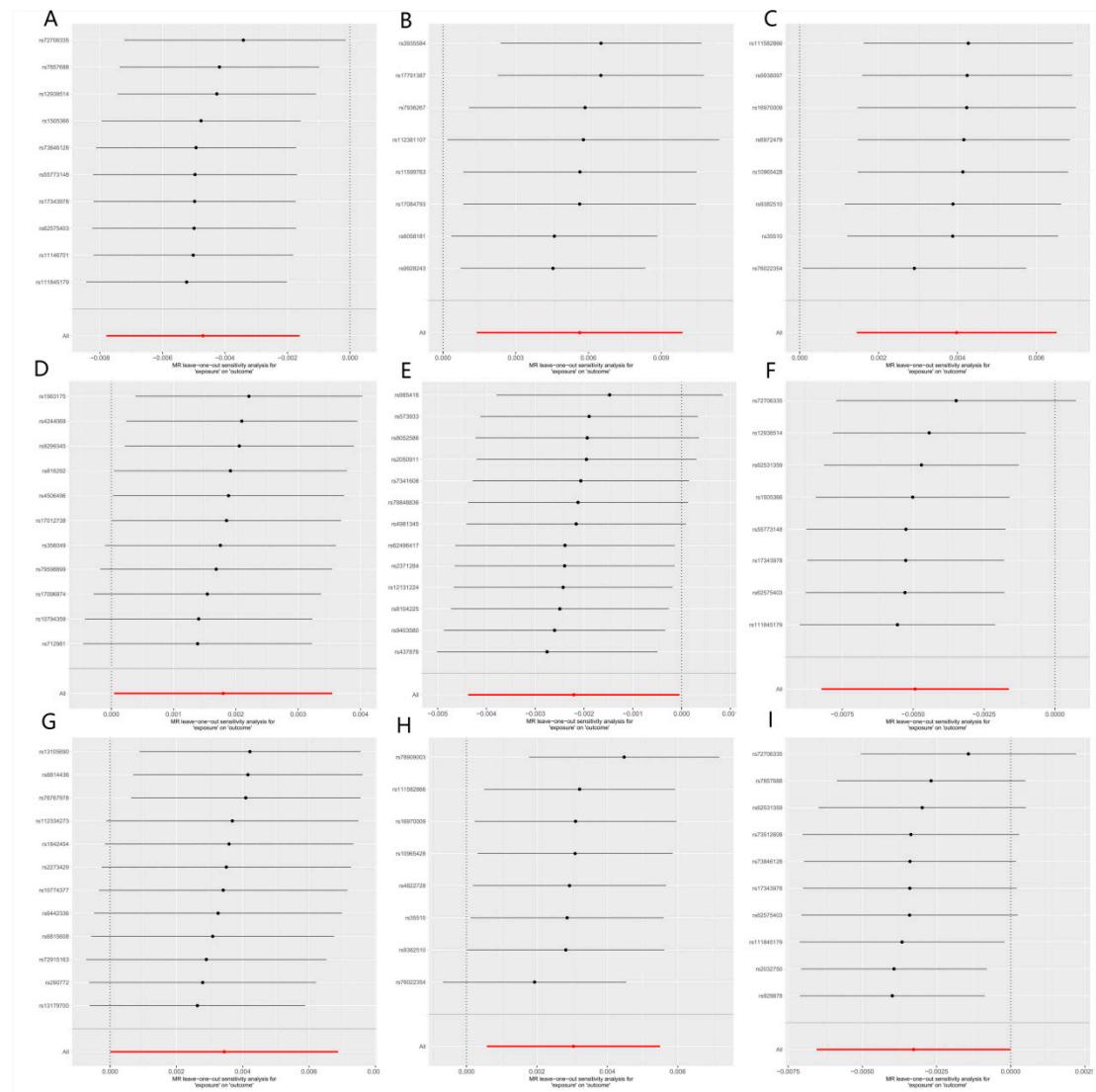
Leave-one-out plots of significant and nominal significant estimates from genetically predicted microbiotas { (A) Class.Bacteroidia; (B) Class.Deltaproteobacteria; (C) Family.Lachnospiraceae; (D) Family.FamilyXIII; (E) Genus.Streptococcus; (F) Genus.Coprococcus; (G) Genus.LachnospiraceaeUCG010; (H) Genus.Ruminococcus; (I) Order.Bacteroidales;} on CKD



Supplement Figure S10

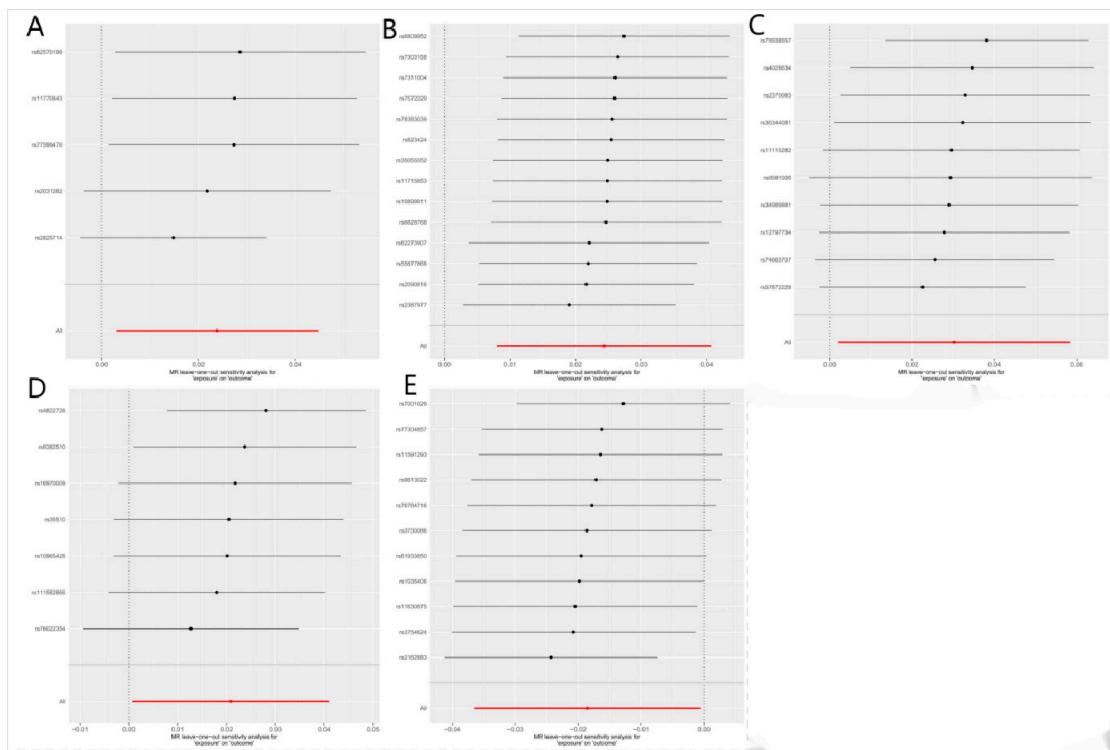
Leave-one-out plots of significant and nominal significant estimates from genetically predicted microbiotas { (A) Class.Bacteroidia; (B) Class.Deltaproteobacteria; (C) Family.Pasteurellaceae; (D) Genus.Anaerofilum; (E) Genus.LachnospiraceaeUCG001 ; (F) Order.Bacteroidales; (G)

Order.Clostridiales; (H) Order.Pasteurellales; (I) Phylum.Bacteroidetes} on eGFR



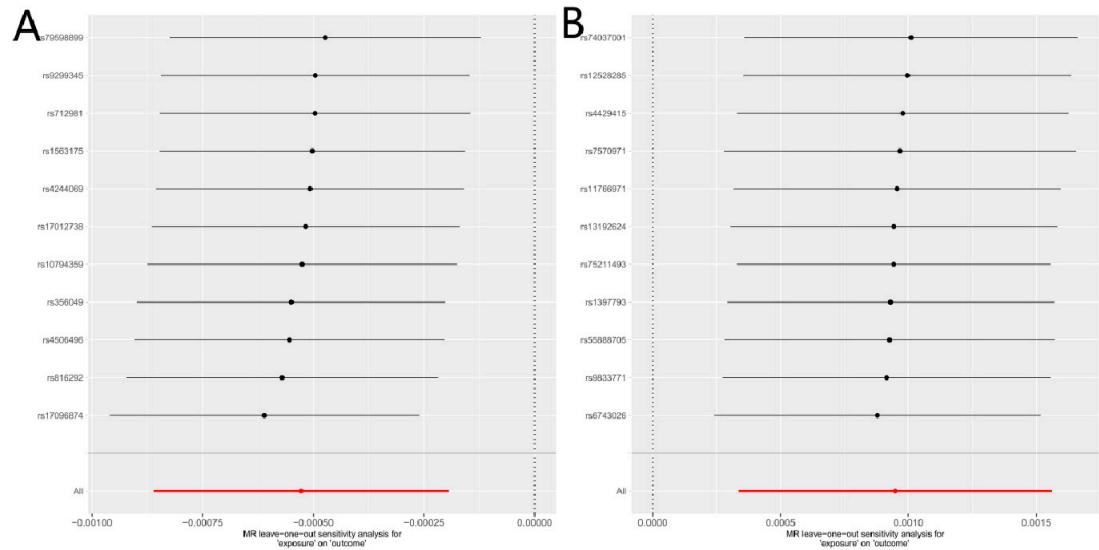
Supplement Figure S11

Leave-one-out plots of significant and nominal significant estimates from genetically predicted microbiotas { (A) Class.Lentisphaeria; (B) Genus.Parasutterella; (C) Order.Lactobacillales; (D) Order.Pasteurellales; (E) Order.Rhodospirillales } on UACR



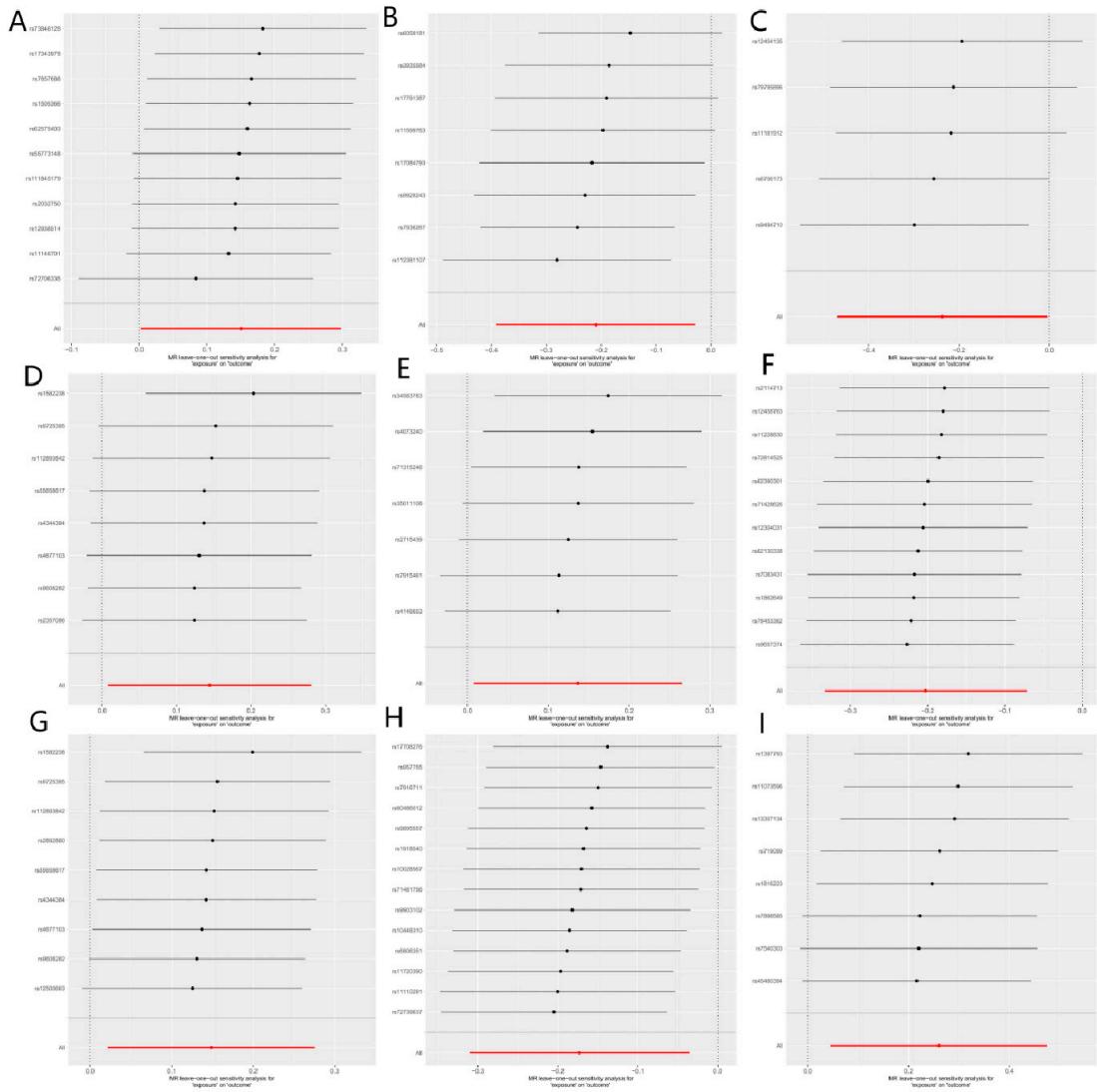
Supplement Figure S12

Leave-one-out plots of significant and nominal significant estimates from genetically predicted microbiotas { (A) Genus.Anaerofilum; (B) Phylum.Actinobacteria; } on Dialysis



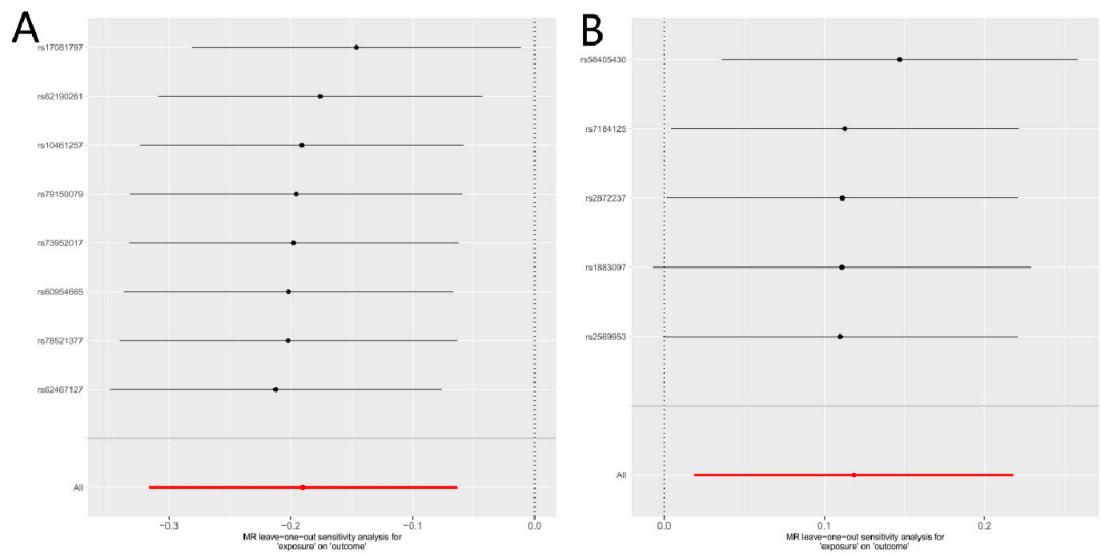
Supplement Figure S13

Leave-one-out plots of significant and nominal significant estimates from genetically predicted microbiotas { (A) Class.Bacteroidia; (B) Class.Deltaproteobacteria; (C) Class.Gammaproteobacteria; (D) Family.Defluvitaleaceae; (E) Genus.Actinomyces; ; (F) Genus.Butyrimonas (G) Genus.DefluvitaleaceaeUCG011; (H) Genus.Streptococcus; (I) Order.Desulfovibrionales} on CKDi25



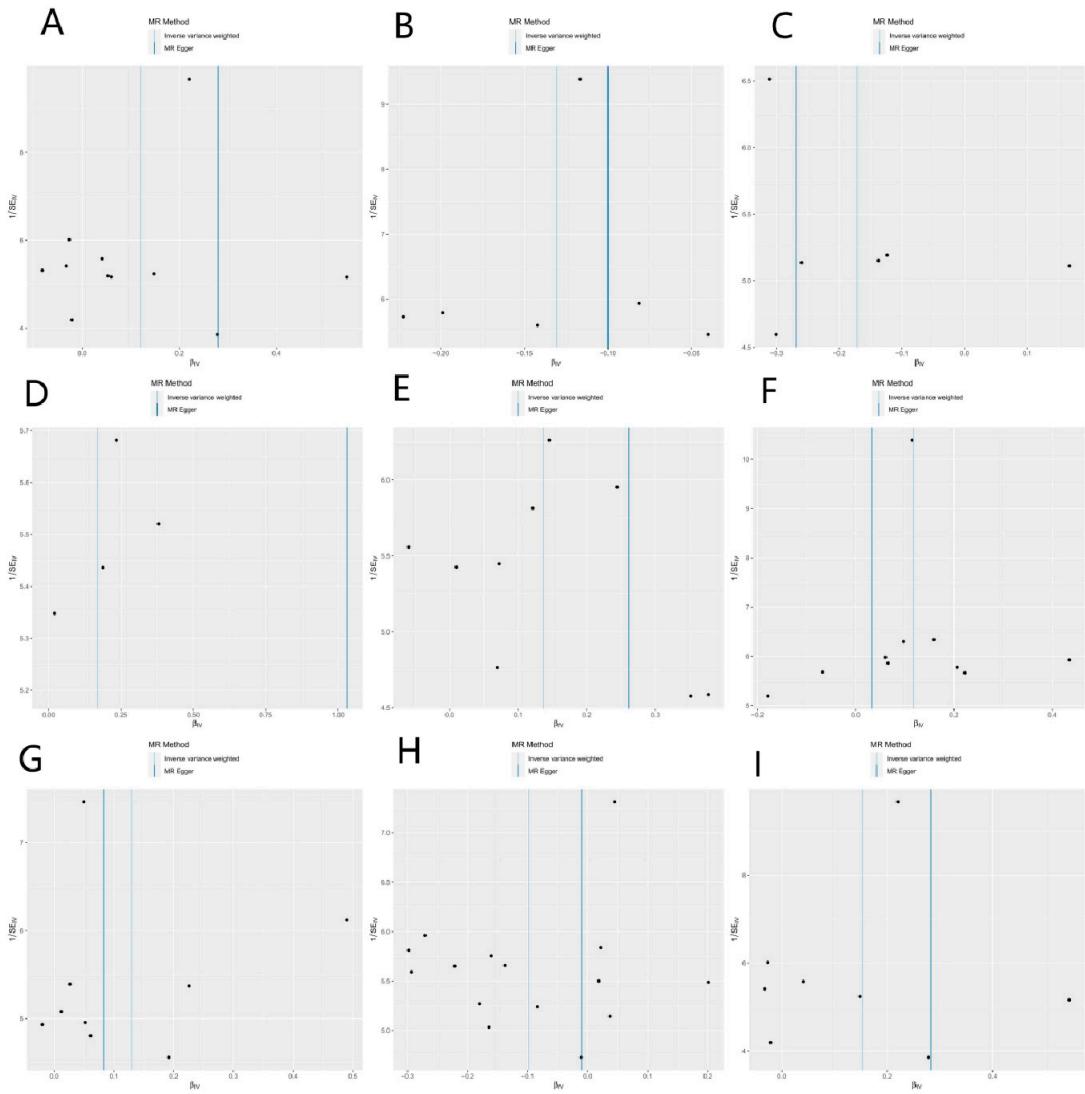
Supplement Figure S14

Leave-one-out plots of significant and nominal significant estimates from genetically predicted microbiotas { (A) Genus.Christensenellaceae; (B) Genus.Terrisporobacter } on Rapid3



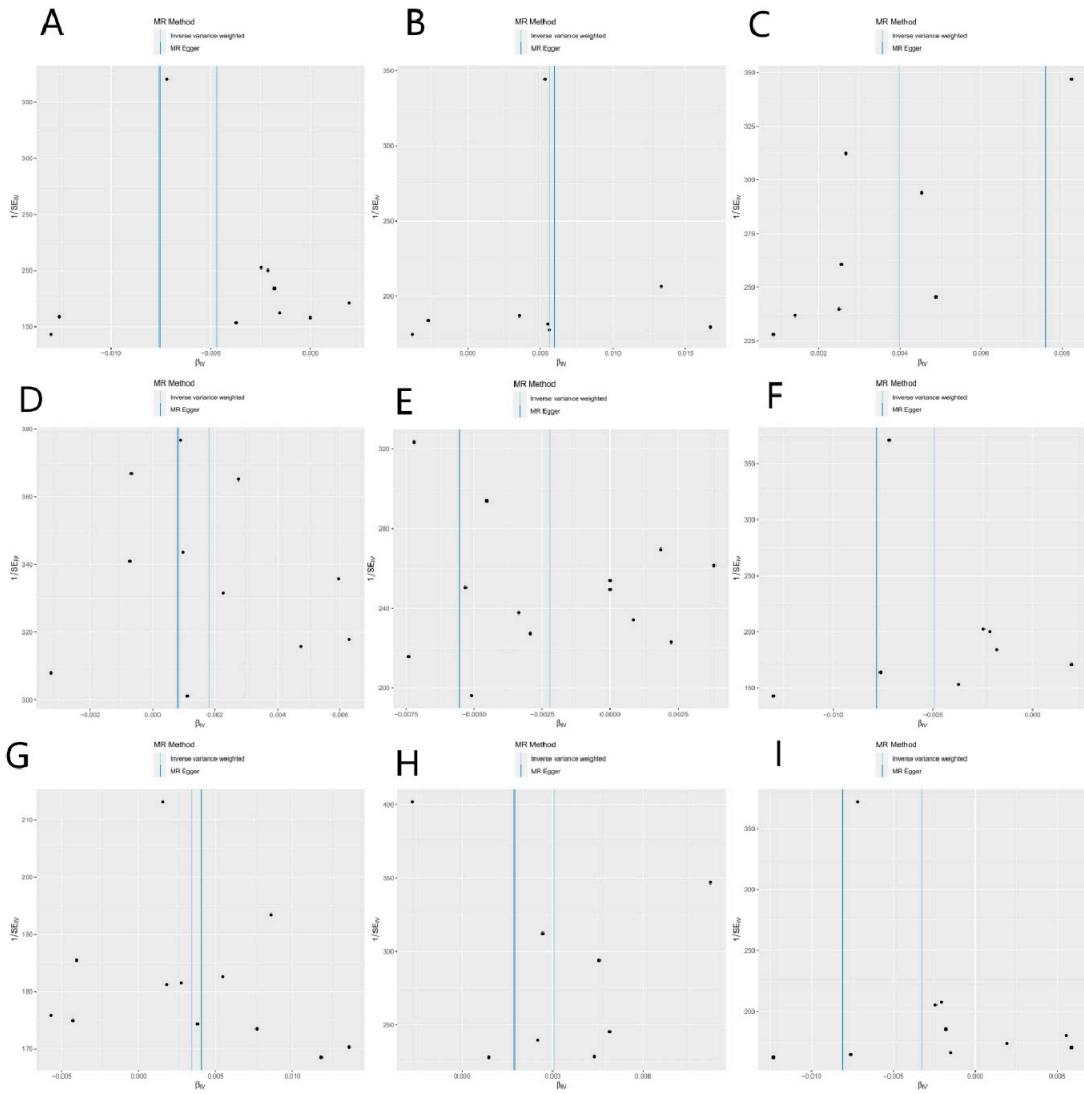
Supplement Figure S15

Funnel plots of significant and nominal significant estimates from genetically predicted microbiotas { (A) Class.Bacteroidia; (B) Class.Deltaproteobacteria; (C) Family.Lachnospiraceae; (D) Family.FamilyXIII; (E) Genus.Coprococcus; (F) Genus.LachnospiraceaeUCG010; (G) Genus.Ruminococcus; (H) Genus.Streptococcus; (I) Order.Bacteroidales;} on CKD



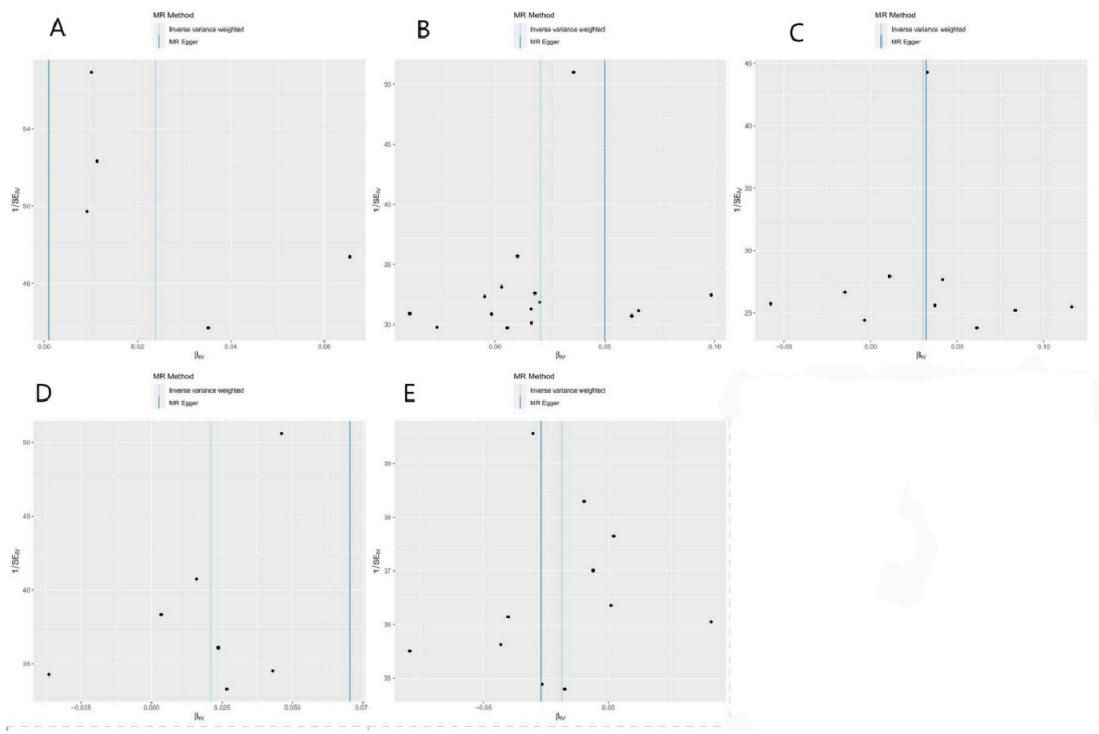
Supplement Figure S16

Funnel plots of significant and nominal significant estimates from genetically predicted microbiotas { (A) Class.Bacteroidia; (B) Class.Deltaproteobacteria; (C) Family.Pasteurellaceae; (D) Genus.Anaoerofilum; (E) Genus.LachnospiraceaeUCG001 ; (F) Order.Bacteroidales; (G) Order.Clostridiales; (H) Order.Pasteurellales; (I) Phylum.Bacteroidetes} on eGFR



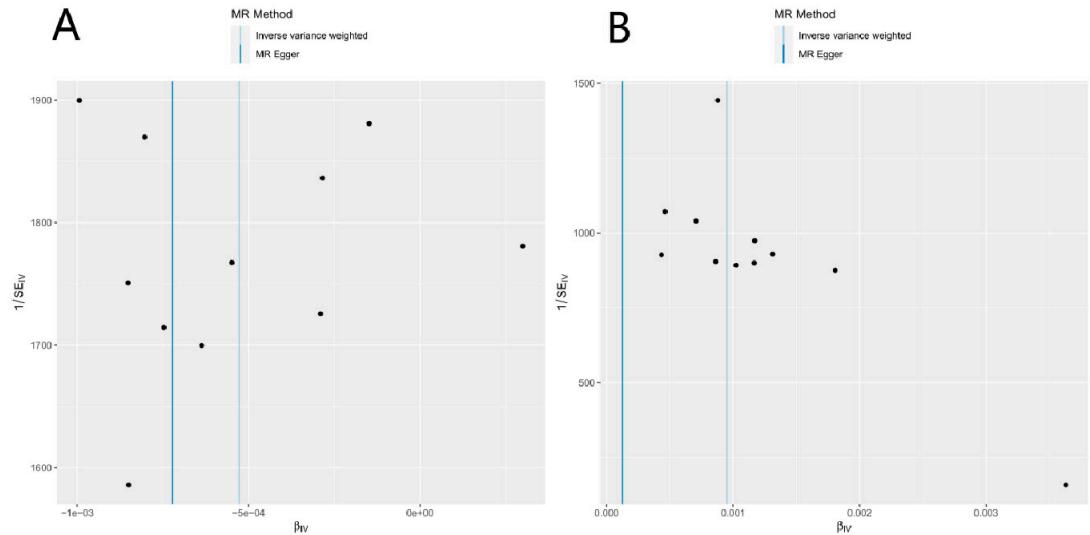
Supplement Figure S17

Funnel plots of significant and nominal significant estimates from genetically predicted microbiotas { (A) Class.Lentisphaeria; (B) Genus.Parasutterella; (C) Order.Lactobacillales; (D) Order.Pasteurellales; (E) Order.Rhodospirillales } on UACR



Supplement Figure S18

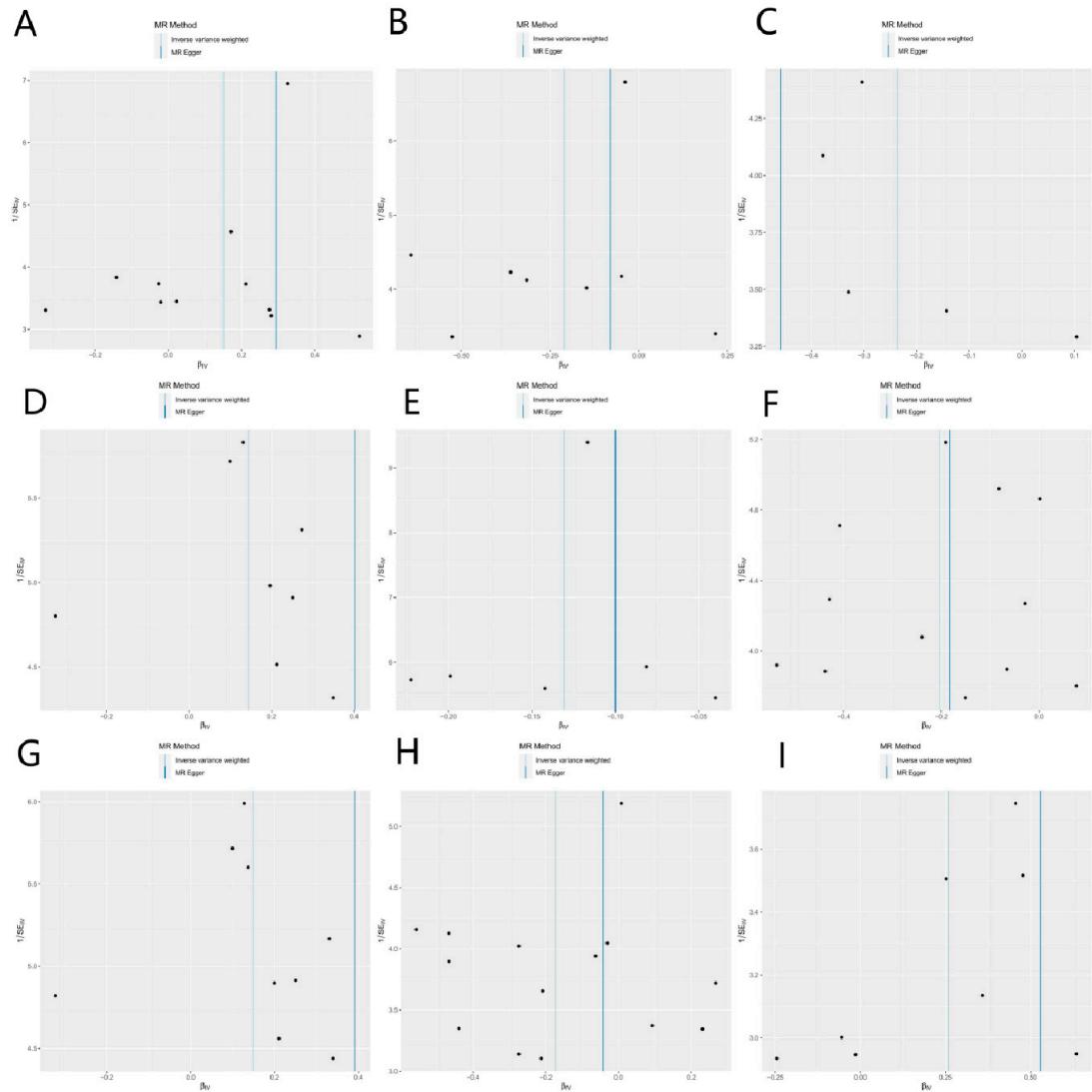
Funnel plots of significant and nominal significant estimates from genetically predicted microbiotas { (A) Genus.Anaerofilum; (B) Phylum.Actinobacteria; } on Dialysis



Supplement Figure S19

Funnel plots of significant and nominal significant estimates from genetically predicted microbiotas { (A) Class.Bacteroidia; (B) Class.Deltaproteobacteria; (C) Class.Gammaproteobacteria; (D) Family.Defluvitaleaceae; (E) Genus.Actinomyces; ; (F) Genus.Butyrimonas (G) Genus.DefluvitaleaceaeUCG011; (H) Genus.Streptococcus; (I)

Order.Desulfovibrionales} on CKD*i*25



Supplement Figure S20

Funnel plots of significant and nominal significant estimates from genetically predicted microbiotas { (A) Genus.Christensenellaceae; (B) Genus.Terrisporobacter } on Rapid3

