Correspondence on '*Prevotella copri* in individuals at risk for rheumatoid arthritis'

We read with great interest the articles by Alpizar-Rodriguez *et al*[1] with regard to the impact of dysbiosis on the risk of rheumatoid arthritis (RA). Meanwhile, we noticed the opposite conclusions of Mendelian randomisation (MR) research works from Inamo[2] and Lee.[3] For obtaining a reliable result, we thought some issues were supposed to pay attention to and illustrate clearly in the MR study. To begin with, single nucleotide polymorphisms (SNPs) associated with gut microbiome at the genome-wide significance level ($p<5\times10^{-8}$) should be derived from a genome-wide association study (GWAS) with the largest sample size or a meta-analysis of GWASs, rather than combining SNPs from different GWASs to analyse directly.[4 5] Initially, we obtained a total of 41 genetic instrumental variables (IVs) from the results of the gut microbiome GWAS carried out with up to 1812 individuals of European ancestry.[6] To avoid the ethnic heterogeneity of genetic associations, the effect size and standard errors for the associations of IVs with RA were extracted from a large RA GWAS, including 14 361 cases and 43 923 controls of European population.[7] Of these IVs, one variant (rs11724031) was absent in the RA GWAS dataset. We replaced it by a suitable proxy (rs11722967), which was in high linkage disequilibrium (LD) with rs11724031 ($r^2=0.88$ in European populations). Moreover, four SNPs (rs12149695, rs17421787, rs34613612 and rs3925158) were excluded for being palindromic with intermediate allele frequencies. LD of all significant SNPs associated with gut microbiome met the condition: $r^2<0.001$. Thus, 37 SNPs were finally incorporated in the MR analysis (online supplemental table 1).

As shown in table 1, in terms of the inverse variance weighted (IVW) method, the OR of gut microbiome on RA was estimated to be 0.98 (95% CI=0.97–1.00, p=0.024). While MR-Egger, weighted median and weighted mode methods represented non-casual associations between gut microbiome and RA (p=0.919, p=0.186, p=0.542, respectively). Horizontal pleiotropy between IVs and outcome was evaluated by MR-Egger regression, and the results indicated no evidence for a significant intercept (intercept=−0.012, p=0.152). Furthermore, no significant heterogeneity was assessed by Cochrane Q statistics across estimates of included SNPs. The leave-one-out analysis showed that two IVs (rs11722967 and rs986417) can influence the estimated causal effect (online supplemental figure 1). Association of p value derived from IVW, MR-Egger, weighted median and weighted mode methods all turned out to be not significant after removing the two IVs. What is more, as mentioned in the GWAS study of gut microbiome, the included SNPs were virtually associated with specific individual bacterial traits.[6] Then, we classified these SNPs into 19 categories and conducted MR analysis in each category separately (online supplemental table 2). Similarly, we did not find that any genetically predicted abundance of bacterial taxon was relevant with RA risk (online supplemental table 3). As demonstrated by Alpizar-Rodriguez *et al*,[1] individuals at risk for RA tend to have an enrichment of *Prevotella spp* compared with first-degree relatives' controls. Even though the genome-wide significant SNPs of genus *Prevotella* were unable to acquire, MR analysis can be performed at the phylum level for genus *Prevotella* belonged to *Bacteroidetes* phylum (online supplemental table 4). A decrease in genetically predicted bacterial traits of *Bacteroidetes* phylum was not significantly associated with RA by IVW method (95% CI: 0.97–1.01, p=0.098). The OR estimates obtained from other methods were also not significant (online supplemental table 5). The above statistical analyses were performed using 'TwoSampleMR' package in R V.3.5.3.

In summary, our results supported that there was no causal link between gut microbiome and RA. Certainly, the lack of genetic power of the limited SNPs may contribute to the potential failure to explore the association between gut microbiome and RA, as the proportion of gut microbiome variation explained by genetic variation among individuals is not estimated,[6] whereas we still need to note that which variable is appropriate to represent intestinal dysbiosis and whether β diversity is a better choice. Further study with updated SNPs of individual bacterial traits or β diversity from GWASs can help to elucidate the potential role of intestinal bacterial traits on RA.

Tianyue Sun,[1] **Jing Ni** [2]

[1]The First School of Clinical Medicine, Nanjing Medical University, Nanjing, China
[2]Department of Epidemiology and Biostatistics, School of Public Health, Anhui Medical University, Hefei, China

Correspondence to Dr Jing Ni, Department of Epidemiology and Biostatistics, Anhui Medical University School of Public Health, Hefei, China; nijing@ahmu.edu.cn

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Table 1 Two-sample MR results for causality for gut microbiome influencing RA

Method	nSNPs	OR (95% CI)	P value	Cochrane Q statistic	Heterogeneity p value	nSNPs*	OR (95% CI) *	P value*	Cochrane Q statistic*	Heterogeneity p value*
IVW	37	0.98 (0.97–1.00)	0.024	45.42	0.135	35	0.99 (0.97–1.01)	0.175	37.96	0.294
Weighted median	37	0.99 (0.96–1.01)	0.186	NA	NA	35	0.99 (0.97–1.01)	0.382	NA	NA
Weighted mode	37	0.99 (0.96–1.02)	0.542	NA	NA	35	0.99 (0.96–1.02)	0.604	NA	NA
MR-Egger	37	1.00 (0.97–1.03)	0.919	42.79	0.172	35	1.01 (0.99–1.04)	0.313	33.05	0.465

*Sensitivity analysis without rs1172296 and rs986417.
IVW, inverse variance weighted; MR, Mendelian randomisation; NA, not applicable; nSNPs, number of single nucleotide polymorphisms; RA, rheumatoid arthritis.

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ORCID iD
Jing Ni http://orcid.org/0000-0001-8284-4941

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Supplementary Table1. SNPs used as instrumental variables from gut microbiome and RA GWASs.

SNP	a1	a2	Exposure (gut microbiome)			Outcome (RA)		
			Beta	SE	p-value	Beta	SE	p-value
rs1009634	G	A	-1.31	0.23	7.12E-09	-0.02	0.05	7.40E-01
rs10928827*	G	A	-0.23	0.04	4.19E-09	-0.05	0.02	1.50E-02
rs11626933	G	A	-0.24	0.04	1.83E-08	0.02	0.02	4.10E-01
rs11722967*	G	A	-0.97	0.15	2.44E-10	-0.08	0.03	1.50E-02
rs11877825	G	T	-0.27	0.04	2.82E-11	-0.04	0.02	1.60E-01
rs11915634	T	C	-1.30	0.21	2.99E-10	0.02	0.04	5.20E-01
rs12442649	G	A	-1.49	0.27	3.72E-08	-0.06	0.06	2.60E-01
rs13096731	A	G	-0.43	0.08	2.55E-08	0.02	0.03	4.50E-01
rs13276516	A	G	-0.61	0.10	5.54E-09	0.00	0.02	8.70E-01
rs1362404	T	G	0.23	0.04	1.56E-08	-0.02	0.02	3.90E-01
rs148330122	C	T	-0.48	0.08	1.32E-09	0.05	0.04	2.00E-01
rs17085775	C	T	-1.03	0.18	2.06E-08	-0.03	0.03	3.80E-01
rs17661843	T	C	-1.40	0.18	3.72E-14	-0.05	0.04	1.60E-01
rs2071199	T	C	-0.32	0.06	1.24E-08	0.00	0.02	9.90E-01
rs2318350	T	C	-1.15	0.19	3.65E-09	0.01	0.04	8.50E-01
rs249733	T	C	-0.65	0.10	4.74E-10	0.01	0.02	5.30E-01
rs35275482	C	A	-0.54	0.08	3.72E-11	0.00	0.03	9.10E-01
rs4621152	C	T	-0.29	0.05	1.40E-08	0.00	0.02	8.60E-01
rs4669413	T	C	-0.18	0.03	1.20E-08	0.02	0.02	4.20E-01
rs479105	T	C	-0.22	0.04	1.21E-08	0.02	0.02	4.00E-01
rs56006724	A	G	-0.88	0.14	6.35E-10	0.00	0.03	9.20E-01
rs59042687	T	G	-0.23	0.04	6.22E-09	0.01	0.02	6.90E-01

rs597205	T	C	-0.62	0.11	7.68E-09	-0.02	0.03	6.20E-01
rs62295801	G	T	-0.27	0.04	5.32E-10	0.02	0.03	4.80E-01
rs7083345	T	C	0.25	0.04	3.38E-10	-0.05	0.02	1.80E-02
rs7113056	C	T	-0.50	0.07	1.72E-13	0.00	0.03	9.40E-01
rs75036654	C	T	-1.39	0.22	4.94E-10	0.05	0.04	2.50E-01
rs7646786	T	C	-0.22	0.04	2.29E-08	-0.03	0.03	1.20E-01
rs7656342	A	G	0.39	0.07	2.80E-09	-0.04	0.02	2.60E-02
rs79387448	C	T	-0.31	0.05	7.68E-11	-0.02	0.02	3.40E-01
rs9291879	C	T	-0.58	0.10	3.51E-09	0.03	0.03	4.00E-01
rs9300430	C	T	-0.61	0.10	1.30E-09	-0.03	0.04	4.80E-01
rs9323326	A	G	-0.21	0.03	8.76E-10	-0.02	0.02	2.20E-01
rs938295	C	T	-0.49	0.09	2.34E-08	-0.04	0.02	1.30E-01
rs9831278	C	T	-1.16	0.21	2.53E-08	0.00	0.05	9.70E-01
rs986417	C	T	-1.40	0.24	2.63E-09	-0.07	0.04	3.50E-02
rs9996716	G	A	-0.69	0.12	5.58E-09	-0.01	0.03	6.20E-01

*Two SNPs (rs10928827, rs7083345) are duplicated in the original article, we kept the variant with lowest p-value in the MR analysis.

RA, rheumatoid arthritis; SNP, single nucleotide polymorphism; a1, effect allele; a2, other allele; Beta, beta coefficient; SE, standard error.

Supplementary Table2. SNPs associated with individual bacterial abundance from gut microbiome and RA GWASs.

Bacterial Traits	SNP	a1	a2	Exposure (gut microbiome)			Outcome (RA)		
				Beta	SE	p-value	Beta	SE	p-value
Enterobacteriaceae family/Enterobacteriales order	rs35275482	C	A	-0.54	0.08	3.72E-11	0.00	0.03	9.10E-01
Escherichia Shigella	rs13096731	A	G	-0.43	0.08	2.55E-08	0.02	0.03	4.50E-01
OTU13305 Fecalibacterium Species-level	rs597205	T	C	-0.62	0.11	7.68E-09	-0.02	0.03	6.20E-01
OTU15355 Dialister Species-level	rs12442649	G	A	-1.49	0.27	3.72E-08	-0.06	0.06	2.60E-01
Proteobacteria phylum	rs9323326	A	G	-0.21	0.03	8.76E-10	-0.02	0.02	2.20E-01
Unclassified Erysipelotrichaceae	rs11626933	G	A	-0.24	0.04	1.83E-08	0.02	0.02	4.10E-01
Blautia genus	rs4669413	T	C	-0.18	0.03	1.20E-08	0.02	0.02	4.20E-01
	rs79387448	C	T	-0.31	0.05	7.68E-11	-0.02	0.02	3.40E-01
Erysipelotrichaceae family/Erysipelotrichales	rs11877825	G	T	-0.27	0.04	2.82E-11	-0.04	0.02	1.60E-01
order/Erysipelotrichia class	rs17421787	C	G	-0.30	0.05	3.60E-08	0.02	0.03	4.80E-01
Gammaproteobacteria class	rs4621152	C	T	-0.29	0.05	1.40E-08	0.00	0.02	8.60E-01
	rs9300430	C	T	-0.61	0.10	1.30E-09	-0.03	0.04	4.80E-01
Unclassified Porphyromonadaceae	rs7656342	A	G	0.39	0.07	2.80E-09	-0.04	0.02	2.60E-02
	rs9291879	C	T	-0.58	0.10	3.51E-09	0.03	0.03	4.00E-01
Marinilabiliaceae family/Unclassified Marinilabiliaceae	rs11722967	G	A	-0.97	0.15	2.44E-10	-0.08	0.03	1.50E-02
	rs11915634	T	C	-1.30	0.21	2.99E-10	0.02	0.04	5.20E-01
	rs9831278	C	T	-1.16	0.21	2.53E-08	0.00	0.05	9.70E-01
	rs9996716	G	A	-0.69	0.12	5.58E-09	-0.01	0.03	6.20E-01
Unclassified Acidaminococcaceae	rs17661843	T	C	-1.40	0.18	3.72E-14	-0.05	0.04	1.60E-01
	rs56006724	A	G	-0.88	0.14	6.35E-10	0.00	0.03	9.20E-01
	rs75036654	C	T	-1.39	0.22	4.94E-10	0.05	0.04	2.50E-01
	rs986417	C	T	-1.40	0.24	2.63E-09	-0.07	0.04	3.50E-02

Bacilli class	rs10928827	G	A	-0.22	0.04	1.02E-08	-0.05	0.02	1.50E-02
	rs148330122	C	T	-0.48	0.08	1.32E-09	0.05	0.04	2.00E-01
	rs2071199	T	C	-0.32	0.06	1.24E-08	0.00	0.02	9.90E-01
	rs479105	T	C	-0.22	0.04	1.21E-08	0.02	0.02	4.00E-01
	rs7083345	T	C	0.25	0.04	3.38E-10	-0.05	0.02	1.80E-02
	rs7646786	T	C	-0.22	0.04	2.29E-08	-0.03	0.03	1.20E-01
Lactobacillales order	rs10928827	G	A	-0.23	0.04	4.19E-09	-0.05	0.02	1.50E-02
	rs1362404	T	G	0.23	0.04	1.56E-08	-0.02	0.02	3.90E-01
	rs59042687	T	G	-0.23	0.04	6.22E-09	0.01	0.02	6.90E-01
	rs62295801	G	T	-0.27	0.04	5.32E-10	0.02	0.03	4.80E-01
	rs7083345	T	C	0.24	0.04	2.89E-09	-0.05	0.02	1.80E-02
	rs7113056	C	T	-0.50	0.07	1.72E-13	0.00	0.03	9.40E-01
OTU10032 unclassified Enterobacteriaceae	rs1009634	G	A	-1.31	0.23	7.12E-09	-0.02	0.05	7.40E-01
	rs12149695	A	T	0.61	0.10	1.82E-09	0.02	0.02	3.90E-01
	rs13276516	A	G	-0.61	0.10	5.54E-09	0.00	0.02	8.70E-01
	rs17085775	C	T	-1.03	0.18	2.06E-08	-0.03	0.03	3.80E-01
	rs2318350	T	C	-1.15	0.19	3.65E-09	0.01	0.04	8.50E-01
	rs249733	T	C	-0.65	0.10	4.74E-10	0.01	0.02	5.30E-01
	rs3925158	C	G	-1.00	0.17	6.29E-09	0.01	0.03	8.10E-01

RA, rheumatoid arthritis; SNP, single nucleotide polymorphism; a1, effect allele; a2, other allele; Beta, beta coefficient; SE, standard error.

Supplementary Table3. Mendelian randomization analysis of the risk of RA and individual bacterial traits.

Bacterial Traits	Method	nSNPs	Beta	SE	OR (95%CI)	p-value
Enterobacteriaceae family/Enterobacteriales order	Wald ratio	1	0.00	0.05	1.00(0.91-1.09)	1.000
Escherichia Shigella	Wald ratio	1	-0.05	0.06	0.95(0.84-1.07)	0.440
OTU13305 Fecalibacterium Species-level	Wald ratio	1	0.03	0.05	1.03(0.93-1.14)	0.531
OTU15355 Dialister Species-level	Wald ratio	1	-0.04	0.04	0.96(0.88-1.03)	0.281
Proteobacteria phylum	Wald ratio	1	0.10	0.10	1.10(0.90-1.30)	0.342
Unclassified Erysipelotrichaceae	Wald ratio	1	0.08	0.09	1.09(0.92-1.25)	0.332
Blautia genus	IVW	2	-0.08	0.06	0.93(0.81-1.04)	0.188
Erysipelotrichaceae family/Erysipelotrichales order/Erysipelotrichia class	Wald ratio	1	-0.15	0.08	0.86(0.70-1.02)	0.060
Gammaproteobacteria class	IVW	2	-0.03	0.05	0.97(0.88-1.06)	0.548
Unclassified Porphyromonadaceae	IVW	2	-0.02	0.08	0.98(0.83-1.13)	0.770
Marinilabiliaceae family/Unclassified Marinilabiliaceae	Weighted median	4	-0.02	0.02	0.98(0.94-1.03)	0.486
	MR Egger	4	-0.02	0.10	0.98(0.78-1.19)	0.893
	Weighted mode	4	-0.01	0.03	0.99(0.93-1.04)	0.666
	IVW	4	-0.03	0.02	0.97(0.93-1.01)	0.084
Unclassified Acidaminococcaceae	Weighted median	4	0.02	0.02	1.02(0.99-1.05)	0.263
	MR Egger	4	0.02	0.12	1.02(0.78-1.25)	0.899
	Weighted mode	4	0.03	0.03	1.03(0.98-1.09)	0.313
	IVW	4	0.01	0.02	1.01(0.96-1.05)	0.806
Bacilli class	Weighted median	6	-0.03	0.05	0.97(0.87-1.08)	0.585
	MR Egger	6	0.26	0.21	1.30(0.90-1.70)	0.272
	Weighted mode	6	0.01	0.07	1.01(0.87-1.14)	0.933
	IVW	6	-0.05	0.06	0.95(0.84-1.07)	0.412
Lactobacillales order	Weighted median	6	-0.05	0.04	0.95(0.87-1.04)	0.277

	MR Egger	6	0.12	0.15	1.13(0.83-1.42)	0.476
	Weighted mode	6	-0.03	0.06	0.97(0.85-1.08)	0.612
	IVW	6	-0.07	0.04	0.93(0.85-1.02)	0.101
OTU10032 unclassified Enterobacteriaceae	Weighted median	5	-0.02	0.02	0.98(0.95-1.02)	0.396
	MR Egger	5	-0.03	0.05	0.97(0.87-1.07)	0.603
	Weighted mode	5	-0.01	0.02	0.99(0.94-1.03)	0.584
	IVW	5	-0.01	0.02	0.99(0.96-1.02)	0.343

RA, rheumatoid arthritis; nSNPs, number of single nucleotide polymorphisms; IVW, Inverse variance weighted; Beta, beta coefficient; SE, standard error; OR, odd ratio; CI, confidence interval.

Supplementary Table4. SNPs related with bacterial traits at the phylum level from gut microbiome and RA GWASs.

Phylum	SNP	a1	a2	Exposure(gut microbiome)			Outcome(RA)		
				beta	se	p-value	beta	se	p-value
Bacteroidetes	rs11722967	G	A	-0.97	0.15	2.44E-10	-0.08	0.03	1.50E-02
	rs11915634	T	C	-1.30	0.21	2.99E-10	0.02	0.04	5.20E-01
	rs7656342	A	G	0.39	0.07	2.80E-09	-0.04	0.02	2.60E-02
	rs9291879	C	T	-0.58	0.10	3.51E-09	0.03	0.03	4.00E-01
	rs9831278	C	T	-1.16	0.21	2.53E-08	0.00	0.05	9.70E-01
	rs9996716	G	A	-0.69	0.12	5.58E-09	-0.01	0.03	6.20E-01
Firmicutes	rs10928827	G	A	-0.22	0.04	1.02E-08	-0.05	0.02	1.50E-02
	rs11626933	G	A	-0.24	0.04	1.83E-08	0.02	0.02	4.10E-01
	rs11877825	G	T	-0.27	0.04	2.82E-11	-0.04	0.02	1.60E-01
	rs12442649	G	A	-1.49	0.27	3.72E-08	-0.06	0.06	2.60E-01
	rs1362404	T	G	0.23	0.04	1.56E-08	-0.02	0.02	3.90E-01
	rs148330122	C	T	-0.48	0.08	1.32E-09	0.05	0.04	2.00E-01
	rs17661843	T	C	-1.40	0.19	3.72E-14	-0.05	0.04	1.60E-01
	rs2071199	T	C	-0.32	0.06	1.24E-08	0.00	0.02	9.90E-01
	rs4669413	T	C	-0.18	0.03	1.20E-08	0.02	0.02	4.20E-01
	rs479105	T	C	-0.22	0.04	1.21E-08	0.02	0.02	4.00E-01
	rs56006724	A	G	-0.88	0.14	6.35E-10	0.00	0.03	9.20E-01
	rs59042687	T	G	-0.23	0.04	6.22E-09	0.01	0.02	6.90E-01
	rs597205	T	C	-0.62	0.11	7.68E-09	-0.02	0.03	6.20E-01
	rs62295801	G	T	-0.27	0.04	5.32E-10	0.02	0.03	4.80E-01
	rs7083345	T	C	0.25	0.04	3.38E-10	-0.05	0.02	1.80E-02

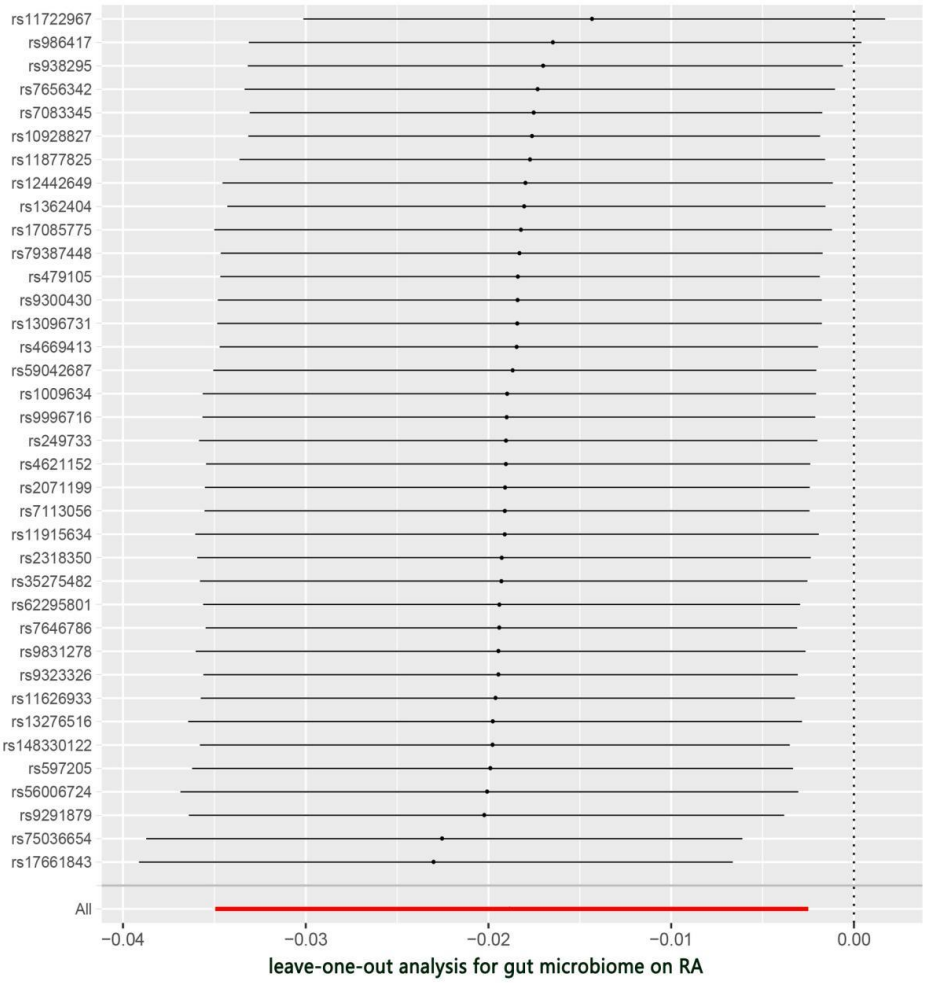
	rs7113056	C	T	-0.50	0.07	1.72E-13	0.00	0.03	9.40E-01
	rs75036654	C	T	-1.39	0.22	4.94E-10	0.05	0.04	2.50E-01
	rs7646786	T	C	-0.22	0.04	2.29E-08	-0.03	0.03	1.20E-01
	rs79387448	C	T	-0.31	0.05	7.68E-11	-0.02	0.02	3.40E-01
	rs986417	C	T	-1.40	0.24	2.63E-09	-0.07	0.04	3.50E-02
Proteobacteria	rs1009634	G	A	-1.31	0.23	7.12E-09	-0.02	0.05	7.40E-01
	rs13096731	A	G	-0.43	0.08	2.55E-08	0.02	0.03	4.50E-01
	rs13276516	A	G	-0.61	0.11	5.54E-09	0.00	0.02	8.70E-01
	rs17085775	C	T	-1.03	0.18	2.06E-08	-0.03	0.03	3.80E-01
	rs2318350	T	C	-1.15	0.20	3.65E-09	0.01	0.04	8.50E-01
	rs249733	T	C	-0.65	0.10	4.74E-10	0.01	0.02	5.30E-01
	rs35275482	C	A	-0.54	0.08	3.72E-11	0.00	0.03	9.10E-01
	rs4621152	C	T	-0.29	0.05	1.40E-08	0.00	0.02	8.60E-01
	rs9300430	C	T	-0.61	0.10	1.30E-09	-0.03	0.04	4.80E-01
	rs9323326	A	G	-0.21	0.03	8.76E-10	-0.02	0.02	2.20E-01
	rs938295	C	T	-0.49	0.09	2.34E-08	-0.04	0.02	1.30E-01

RA, rheumatoid arthritis; SNP, single nucleotide polymorphism; a1, effect allele; a2, other allele; Beta, beta coefficient; SE, standard error.

Supplementary Table5. Mendelian randomization results of the bacterial traits at the phylum level on the risk of RA.

Phylum	Method	nSNPs	Beta	SE	OR(95%CI)	p-value
Bacteroidetes	Weighted median	6	-0.02	0.02	0.99(0.94-1.03)	4.94E-01
	MR Egger	6	-0.01	0.06	0.99(0.88-1.10)	8.30E-01
	Weighted mode	6	-0.01	0.03	0.99(0.93-1.04)	6.39E-01
	IVW	6	-0.03	0.02	0.97(0.93-1.01)	9.82E-02
Firmicutes	Weighted median	20	0.00	0.02	1.00(0.97-1.03)	1.00E+00
	MR Egger	20	0.02	0.02	1.02(0.98-1.06)	3.86E-01
	Weighted mode	20	0.01	0.02	1.01(0.97-1.04)	6.93E-01
	IVW	20	-0.01	0.01	0.99(0.96-1.02)	4.90E-01
Proteobacteria	Weighted median	11	-0.02	0.02	0.98(0.95-1.02)	3.74E-01
	MR Egger	11	-0.03	0.03	0.97(0.91-1.03)	3.26E-01
	Weighted mode	11	-0.01	0.02	0.99(0.95-1.03)	6.13E-01
	IVW	11	-0.02	0.01	0.98(0.96-1.01)	1.21E-01

RA, rheumatoid arthritis; nSNPs, number of single nucleotide polymorphisms; IVW, Inverse variance weighted; Beta, beta coefficient; SE, standard error; OR, odd ratio; CI, confidence interval.



Supplementary Figure1. Leave-one-out plot of the effect of gut microbiome on rheumatoid arthritis.