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Assessing the effect of interaction between gut microbiome and inflammatory bowel disease on the risks of depression

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ABSTRACT

Background: Gut microbiome and inflammatory bowel disease (IBD) are implicated in the development of depression, but the effect of their interactions on the risk of depression remains unclear. We aim to analyze the effect of interactions between gut microbiome and IBD on the risk of depression, and explore candidate genes involving the interactions.

Methods: Using the individual genotype and depression traits data from the UK Biobank, we calculated the polygenetic risk scores (PRS) of 114 gut microbiome, ulcerative colitis (UC), Crohn's disease (CD), and total IBD (CD + UC) respectively. The effects of interactions between gut microbiome and IBD on depression were assessed through a linear regression model. Moreover, for observed significant interactions between gut microbiome PRS and IBD PRS, PLINK software was used to test pair-wise single nucleotide polymorphisms (SNPs) interaction of corresponding gut microbiome PRS and IBD PRS on depression.

Results: We found 64 candidate interactions between gut microbiome and IBD on four phenotypes of depression, such as *F_Lachnospiraceae (RNT)* × (CD + UC) for patient health questionnaire-9 (PHQ-9) score ($P = 1.48 \times 10^{-3}$), *F_Veillonellaceae (HB)* × UC for self-reported depression ($P = 2.83 \times 10^{-3}$) and *P_Firmicutes (RNT)* × CD for age at first episode of depression ($P = 8.50 \times 10^{-3}$). We observed interactions of gut-microbiome-associated SNPs × IBD-associated SNPs, such as *G_Alloprevotella (HB)*-associated rs147650986 (*GPM6A*) × IBD-associated rs114471990 (*QRICH1*) ($P = 2.26 \times 10^{-4}$).

Conclusion: Our results support the effects of interactions between gut microbiome and IBD on depression risk, and reported several novel candidate genes for depression.

1. Introduction

Depression is a common mental illness characterized by persistent low mood and diminished interest (Chand et al., 2021). The prevalence of depression has increased over the past few decades. It is estimated that 322 million people are suffering from depression, and the World Health Organization has identified it as one of the most significant contributors to global disability (Moreno-Agostino et al., 2021). Depression also seriously affects the life and employment of patients and brings heavy burdens to their families and society (Malhi and Mann, 2018).

The gut microbiome consists of a diverse consortium of bacteria, archaea, fungi, protozoa, viruses, and their collective genome found on and within the body (Barko et al., 2018), which play a crucial role in

Abbreviations: IBD, Inflammatory bowel disease; PRS, Polygenetic risk scores; UC, Ulcerative colitis; CD, Crohn's disease; SNPs, Single nucleotide polymorphisms; PNT, Rank normal transformed; HB, Hurdle binary; SCFAs, Short-chain fatty acids; GWAS, Genome-wide associations study; CI, Confidence interval; PHQ-9, Patient health questionnaire-9; HRC, Haplotype reference consortium; QC, Quality control; PCs, Principal components; FGFP, Flemish gut flora project; LD, Linkage disequilibrium; TDI, Townsend deprivation index; HPA, Hypothalamic-pituitary-adrenal; ASD, Autism spectrum disorders; SCZ, Schizophrenia; ENS, Enteric nervous system; CNS, Central nervous system; ER, Endoplasmic reticulum.

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maintaining normal intestinal physiology and health (Gomaa, 2020). A growing number of researches have demonstrated that gut microbiome dysbiosis is an influential factor in depression (Capuco et al., 2020). The brain-gut axis is a bidirectional communication channel between gut microbiome and the brain, involving neuroimmune, endocrine and inflammatory mechanisms (Osadchiy et al., 2019). A lot of evidence indicated that the abundance and diversity of gut microbiota were altered in depression patients. For example, the abundance of the family *Prevotellaceae*, genus *Coprococcus*, and genus *Faecalibacterium* were significantly decreased in patients with depression (Sanada et al., 2020). In addition, Simpson et al. found a higher abundance of proinflammatory species (e.g., family *Enterobacteriaceae* and genus *Desulfovibrio*), and lower short-chain fatty acids (SCFAs) producing-bacteria (e.g., genus *Faecalibacterium*) in depression and anxiety (Simpson et al., 2021). Inflammatory bowel disease (IBD) is a chronic and recurrent inflammatory disease of the gastrointestinal tract, including ulcerative colitis (UC), which involves continuous inflammation of the colonic mucosa, and Crohn's disease (CD), which can cause ulceration anywhere in the gastrointestinal tract (McDowell et al., 2021). According to previous studies, IBD was correlated with depression. A cohort study based on the UK population found that depressive disorders were more prevalent in people with IBD than in those without IBD (CD patients: 12.9% vs. 17.5%, UC patients: 12.4% vs.14.2%) (Irving et al., 2021). Patients with depression were 2.11 times more likely to develop CD (95% confidence interval [CI]: 1.65–2.70) and 2.23 times more likely to develop UC (95%CI: 1.92–2.60) than those without depression (Frolkis et al., 2019). Inflammatory responses, autoimmunity, and the microbiome-gut-brain axis were identified as shared pathogenic mechanisms for IBD and depression by Martin-Subero et al. (2016).

Gut microbiome dysbiosis can lead to IBD, and IBD can in turn disrupt the gut microbiome. Much evidence suggests that transferring fecal microbiota from mice with IBD to healthy mice could result in colitis (Schirmer et al., 2019). Furthermore, compared with the microbiome of healthy participants, patients with IBD had reduced diversity of the gut microbiome and abundance of phylum *Firmicutes*, fewer bacteria with anti-inflammatory capacity, and more bacteria with an inflammatory ability (Glassner et al., 2020). Ni et al. suggested that chronic inflammation could alter the oxidative and metabolic environment in the gut, leading to dysbiosis of the intestinal microbes (Ni et al., 2017). Although there are interactions between the gut microbiome and IBD, few studies focused on the effect of their interactions on the risk of depression, which needs to be further investigated.

Polygenic risk scores (PRS) can provide an overall estimate of the genetic propensity of a trait at the individual level by calculating the sum of the effects of risk alleles (Crouch and Bodmer, 2020; Dudbridge, 2016). Estimates for each of these risk alleles were derived from the effect size weighting of single nucleotide polymorphisms (SNPs) found by an independent large-scale genome-wide associations study (GWAS) (Crouch and Bodmer, 2020). The effect sizes of multiple SNPs are combined into a single aggregated score that can be used to predict disease risk in humans (Dudbridge, 2016). The PRS has been used to estimate an individual's risk of inflammatory bowel disease (Chen et al., 2017), and the potential use of the microbiome in human disease (Wang et al., 2022). However, limited efforts were made to explore the effect of the interaction between the gut microbiome and IBD on the risk of depression through the application of PRS analysis. SNPs are the major genetic variants in GWAS, and most GWAS analyses follow a single-locus test procedure for SNP marginal effects (Zhang et al., 2019a). SNP-SNP interactions are very important in biological systems (Wang et al., 2019a), several studies conducted using SNP-SNP interactions to determine the genetics of diseases including atherosclerotic ischemic stroke (Shen et al., 2021), schizophrenia (Lee et al., 2020a) and CD (Dinu et al., 2012), whereas some SNPs with weak marginal effects but strong interaction effects cannot be found by marginal effect detection (Zhang et al., 2019a). PLINK software performs a series of basic, large-scale analyses in a computationally efficient manner and is well able to assess SNP interaction effects (Purcell et al., 2007).

In this study, we calculated the PRS for gut microbiome and IBD using published GWAS datasets, and subsequently applied linear regression models to assess the effect of interactions between gut microbiome PRS and IBD PRS on the risk of depression. Finally, for the top 10 gut microbiome PRS × IBD PRS interactions, the PLINK software was used to perform SNPs interactions analysis. We aim to analyze the association between gut microbiome × IBD interactions and depression, and further explore the corresponding genetic mechanisms underlying depression.

2. Methods

2.1. UK biobank cohort

This study used the genotype and phenotype data from the UK Biobank prospective cohort (Application 46478), which collected genome-wide data and health-related information from approximately 500,000 individuals aged 40–69 from all over the UK in 2006–2010 (Bycroft et al., 2018). The information of participants was collected through self-completed touch-screen questionnaires, computer-assisted interviews, and anthropometric measurements. All participants signed an electronic consent and allowed the UK Biobank to access their health-related records and agreed to use their anonymous data and samples in any health-related research (Sudlow et al., 2015).

2.2. Definition of depression phenotypes

In this study, we defined four depression phenotypes. The phenotype of patient health questionnaire-9 (PHQ-9) score was measured according to the PHQ-9 (Davis et al., 2019). PHQ-9 is a classification algorithm with a total score of 0–27 that focuses on nine signs and symptoms of depression (Kroenke et al., 2010). Self-reported depression was defined based on self-reported disease status in the UK Biobank (Davis et al., 2019). Age at first episode of depression was defined based on the age at which participants first experienced depressive symptoms for two weeks or more. Depression possibly related to childbirth was defined by the presence of depressive symptoms within months of giving birth or post-natal depression. The detailed definitions are provided in the Supplementary materials.

2.3. Genotyping, imputation and quality control

The UK Biobank cohort included genotypic data for 488,377 participants (Bycroft et al., 2018). Genotyping was performed by two very similar genotyping arrays, the UK BiLEVE Axiom array and the UK Biobank Axiom array (Bycroft et al., 2018). Imputation was carried out with the IMPUTE4 program, and the Haplotype Reference Consortium (HRC) and UK10K and 1000 Genomes phase 3 as imputation reference panels (McCarthy et al., 2016; UK 10K Consortium et al., 2015). Quality control (QC) included two parts: mark-based quality control and sample-based quality control (Bycroft et al., 2018). Briefly, statistical tests for batch effects, plate effects, departures from Hardy-Weinberg equilibrium, sex effects, array effects, and discordance across control replicates were performed to identify poor-quality markers. Poor-quality samples were detected using deletion rates and heterozygosity calculations. For sex chromosomes, specific quality controls were performed using 15,766 high-quality markers on the X and Y chromosomes. Principal components (PCs) were calculated by the UK Biobank from genome-wide genotypic data and could be representative of an individual's ethnic background (Bycroft et al., 2018). FastPCA (Galinsky et al., 2016) was applied to calculate PCs using a set of 407,219 unrelated, high-quality samples and 147,604 high-quality SNPs. Individuals with similar principal component scores have similar self-reported ethnic backgrounds (Bycroft et al., 2018). For example, the first two principal components separate out individuals with sub-Saharan African

ancestry, European ancestry and East Asian ancestry (Bycroft et al., 2018). In this study, we chose the first 10 PCs as covariates because they can explain sufficient ancestry genetic characteristics for the UK Biobank participants (Frank et al., 2020). Detailed information about genotyping, imputation and QC could be found in the published study (Bycroft et al., 2018).

2.4. GWAS data of gut microbiome

The gut microbiome GWAS data were derived from a large-scale study, which performed genomic analysis on 2,223 individuals from Flemish Gut Flora Project (FGFP) cohort (Hughes et al., 2020). In brief, DNA was extracted from the collected fecal samples, and was sequenced after amplifying the V4 region of 16rRNA. A total of 499 taxa were counted, 139 of which met the standards of association analysis, and 92 taxa were finally analyzed after removing the correlation coefficients greater than 0.985. Genotyping was performed on two different arrays of Human Core Exome v1.0 and v1.1. Microbial taxa were described as relative abundance curves using the rank normal transformed (RNT) model, whereas those taxa with zero abundance distribution were described using the hurdle binary (HB) model. The α-diversity, abundance, and presence/absence correlation of microbiome were analyzed using snptest.2.5.0. Finally, 3,321 linkage disequilibrium (LD) independent loci were identified to be associated with 16S gut microbiome phenotypes. In our study, we selected SNPs loci with $P < 1.0 \times 10^{-4}$ for subsequent PRS analysis, and finally calculated the PRS of 114 gut-microbiome-associated traits. Detailed information about the human gut microbiome GWAS has been published in previous study (Hughes et al., 2020).

2.5. GWAS data of IBD

The IBD GWAS summary data were derived from subjects recruited at the outpatient IBD clinic of the University Hospitals Leuven, Belgium (Vancamelbeke et al., 2017). Briefly, 1,696 patients with CD, 884 patients with UC and 849 controls were genotyped by Immunochip. SNPs located within 50 kb up- or downstream of the transcription start/end site were extracted, and highly correlated SNPs (SNPs in high linkage disequilibrium, $r^2 > 0.7$) were excluded. Finally, correlated SNPs were identified and used for PRS calculation. Detailed information of genetic data for IBD was described in the published study (Vancamelbeke et al., 2017).

2.6. PRS calculation

We calculated gut microbiome PRS and IBD PRS using GWAS data from gut microbiome and IBD and genotype data from UK Biobank cohort. The PRS was calculated by PLINK2.0 (Purcell et al., 2007; Lewis and Vassos, 2020). Let PRS*n* denote the PRS value of gut microbiome for the *n*th subject, defined as:

$$PRS_n = \sum_{i=1}^{l} E_i D_{in}$$

Where l denotes the total number of gut microbiome analyzed in this study; *Ei* denotes the effect size of the significant gut microbiome associated SNP *i*; *Din* denotes the dosage of the risk allele of the *ith* SNP for the *nth* individual (0 is coded for homozygous protective genotype, 1 for heterozygous and 2 for homozygous polymorphic genotypes). CD PRS, UC PRS, and total PRS (CD + UC) were calculated in the same way.

2.7. Gut microbiome PRS × IBD PRS interaction analysis

The linear regression model was developed using R software to evaluate the effects of interactions between gut microbiome PRS and IBD PRS on the depression phenotypes.

Table 1
The basic characteristics of study participants.

	PHQ-9 score	Self-reported depression	Age at first episode of depression	Depression possibly related to childbirth
Participants	84,805	85,073	43,664	26,696
Females, n (%)	45,866 (54.1)	46,457 (54.6)	27,358 (62.7)	26,696 (100.0)
Age (years)	56.23 ± 7.58	56.44 ± 7.62	55.63 ± 7.55	55.44 ± 7.45
Alcohol frequency weekly	10.02 ± 9.17	10.02 ± 9.88	9.76 ± 9.18	7.92 ± 7.05
Smoking frequency daily	5.68 ± 9.86	6.14 ± 10.23	6.01 ± 10.03	4.94 ± 8.60
Townsend deprivation index	−1.97 ± 2.67	−1.79 ± 2.77	−1.82 ± 2.74	−1.88 ± 2.69

Notes: PHQ: Patient Health Questionnaire. Age, Alcohol frequency weekly, Smoking frequency daily and Townsend deprivation index were described as Mean ± standard deviation.

$$Y \sim \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_1 X_2 + \varepsilon$$

Where Y stands for depressive phenotypes; X_1 represents PRS of the gut microbiome, X_2 denotes UC PRS, CD PRS, or CD + UC PRS, and $X_1 \times X_2$ denotes the interaction of gut microbiome × IBD.

Age, sex, townsend deprivation index (TDI), smoking frequency daily, alcohol frequency weekly and top 10 PCs of population structure were set as covariates in the analysis of PHQ-9 score, self-reported depression, and age at first episode of depression. The analysis for depression possibly related to childbirth was only conducted in females, and age, TDI, smoking frequency daily, alcohol frequency weekly and top 10 PCs were set as covariates. Furthermore, we performed subgroup analysis by sex and age respectively. For the age subgroup analysis, we divided the subjects into three age groups: youth group (<50 years old), middle-aged group (50–59 years old) and elderly group (≥60 years old), and age was not set as a covariate. For the sex subgroup analysis, sex was not set as a covariate. In this study, the significant threshold was set as $P = 0.05$.

2.8. SNP × SNP interaction analysis

According to the results of PRS, the top 10 significant interactions of gut microbiome PRS × IBD PRS were further selected for SNP × SNP interactions analysis. The "epistasis" command of PLINK was used to test the interactions of gut-microbiome-associated SNPs and IBD-associated SNPs, according to the regression model:

$$y \sim b_0 + b_1 A + b_2 B + b_3 AB + e$$

Where y represents depression phenotypes; A and B denote the SNPs associated with corresponding gut microbiome and IBD respectively. The depression phenotypes were adjusted by age, sex, TDI, smoking frequency daily, alcohol frequency weekly and top 10 PCs of population structure. The interactions with $P < 0.05$ were considered as significant.

3. Results

3.1. Characteristics of study participants

Totally, 84,805, 85,073, 43,664 and 26,696 individuals were included in analyses for PHQ-9 score, self-reported depression, age at first episode of depression and depression possibly related to childbirth, respectively. For depression possibly related to childbirth, the study samples were all females. The basic characteristics of study subjects are presented in Table 1.

Table 2
The top ten significant interactions of gut microbiome PRS and IBD PRS on depression.

Depression phenotypes	IBD phenotypes	Gut microbiome	Gut microbiome PRS		IBD PRS		Interaction	
			T	P	T	P	T	P
PHQ-9 score	CD + UC	*F_Lachnospiraceae_RNT*	2.684	0.007	3.365	0.001	−3.179	0.001
Self-reported depression	UC	*F_Veillonellaceae_HB*	−3.101	0.002	3.173	0.002	2.986	0.003
PHQ-9 score	CD	*G_Dialister_HB*	−2.022	0.043	2.619	0.009	−2.963	0.003
Age at first episode of depression	CD + UC	*G_Coprobacter_RNT*	2.100	0.036	−1.009	0.313	−2.900	0.004
Self-reported depression	UC	*G_Alloprevotella_HB*	−2.603	0.009	−0.118	0.906	2.791	0.005
Age at first episode of depression	UC	*G_Aestuariispira_HB*	2.226	0.026	1.503	0.133	−2.772	0.006
PHQ-9 score	CD + UC	*G_Acidaminococcus_RNT*	2.395	0.017	2.429	0.015	−2.752	0.006
Age at first episode of depression	CD + UC	*P_Firmicutes_RNT*	−2.635	0.008	0.661	0.508	2.738	0.006
Age at first episode of depression	CD	*P_Firmicutes_RNT*	0.149	0.882	0.720	0.471	2.632	0.009
PHQ-9 score	CD	*F_Lachnospiraceae_RNT*	−0.982	0.326	2.355	0.019	−2.626	0.009

Notes: P: Phylum. F: Family. G: Genus. PRS: Polygenic risk scores. PHQ: Patient Health Questionnaire. IBD: Inflammatory bowel disease. UC: Ulcerative colitis. CD: Crohn's disease.

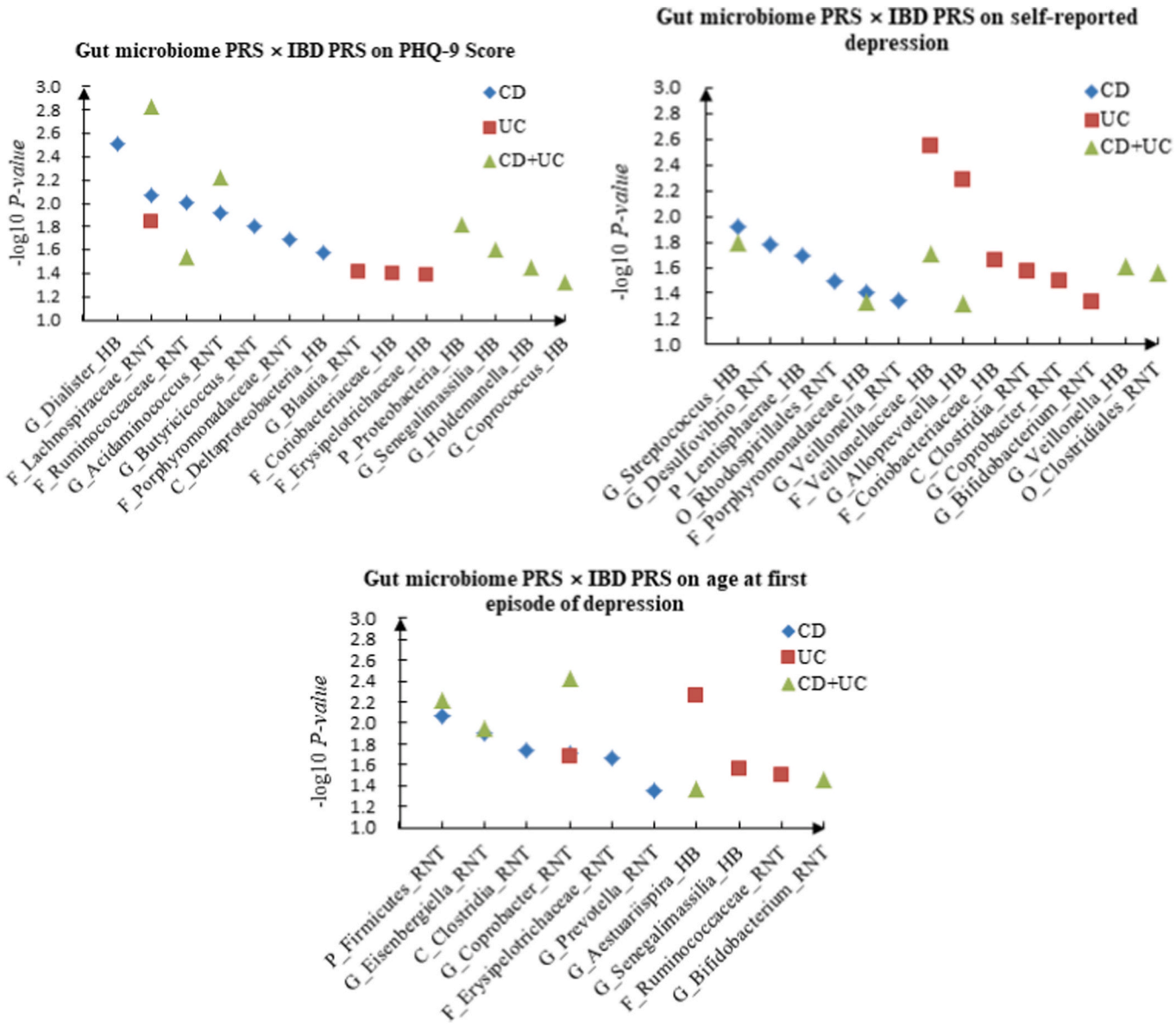

Fig. 1. **A** The scatter plot of the interactions of gut microbiome PRS and IBD PRS on PHQ-9 Score. **B** The scatter plot of the interactions of gut microbiome PRS and IBD PRS on self-reported depression. **C** The scatter plot of the interactions of gut microbiome PRS and IBD PRS on age at first episode of depression.

Table 3
The top ten significant interactions of gut microbiome PRS and IBD PRS on depression in different sex.

	Depression phenotypes	IBD phenotypes	Gut microbiome	Gut microbiome PRS		IBD PRS		Interaction	
				T	P	T	P	T	P
Male									
	PHQ-9 score	CD + UC	*F_Ruminococcaceae_RNT*	2.844	0.004	3.210	0.001	−3.202	0.001
	Self-reported depression	UC	*G_Phascolarctobacterium_RNT*	−3.053	0.002	3.062	0.002	3.027	0.002
	Age at first episode of depression	CD	*G_Streptococcus_RNT*	0.666	0.506	−2.111	0.035	2.854	0.004
	Age at first episode of depression	CD + UC	*G_Faecalitalea_HB*	2.520	0.012	−2.483	0.013	−2.781	0.005
	PHQ-9 score	UC	*F_Ruminococcaceae_RNT*	2.582	0.010	2.683	0.007	−2.725	0.006
	Self-reported depression	CD	*C_Gammaproteobacteria_HB*	0.757	0.449	−0.922	0.357	−2.724	0.006
	Age at first episode of depression	UC	*F_Erysipelotrichaceae_HB*	−2.335	0.020	−2.254	0.024	2.614	0.009
	Age at first episode of depression	UC	*C_Actinobacteria_RNT*	−2.603	0.009	−1.644	0.100	2.534	0.011
	Self-reported depression	CD + UC	*G_Acidaminococcus_HB*	2.288	0.022	2.695	0.007	−2.514	0.012
	Age at first episode of depression	UC	*G_Faecalitalea_HB*	2.376	0.018	−1.897	0.058	−2.464	0.014
Female									
	Self-reported depression	UC	*G_Sporobacter_HB*	−2.996	0.003	−2.423	0.015	3.419	0.001
	Age at first episode of depression	CD	*G_Eisenbergiella_RNT*	−1.712	0.087	2.230	0.026	−2.868	0.004
	Self-reported depression	CD	*F_Erysipelotrichaceae_RNT*	0.190	0.849	−1.016	0.310	−2.776	0.006
	Self-reported depression	CD + UC	*F_Erysipelotrichaceae_RNT*	2.736	0.006	−0.290	0.771	−2.689	0.007
	PHQ-9 score	CD + UC	*G_Intestinibacter_HB*	2.309	0.021	0.502	0.616	−2.679	0.007
	PHQ-9 score	CD + UC	*O_Bacteroidales_HB*	2.051	0.040	1.026	0.305	−2.663	0.008
	Depression possibly related to childbirth	CD	*G_Anaerostipes_RNT*	1.079	0.281	−0.273	0.785	−2.628	0.009
	PHQ-9 score	CD	*G_Intestinibacter_HB*	−0.652	0.514	0.696	0.487	−2.599	0.009
	Age at first episode of depression	UC	*G_Barnesiella_HB*	−2.208	0.027	−2.234	0.025	2.566	0.010
	Self-reported depression	CD + UC	*G_Sporobacter_HB*	−1.860	0.063	−2.039	0.041	2.529	0.011

Notes: C, Class. O, Order. F, Family. G, Genus. PRS: Polygenic risk scores. PHQ: Patient Health Questionnaire. IBD: Inflammatory bowel disease. UC: Ulcerative colitis. CD: Crohn's disease.

3.2. Interactions of gut microbiome PRS and IBD PRS

We detected multiple interactions between gut microbiome PRS and IBD PRS for depression phenotypes. The details were shown in Supplementary Table 1. For PHQ-9 score, we identified 7 candidate interactions of gut microbiome PRS and CD PRS, such as *G_Dialister (HB)* × CD ($P = 3.05 \times 10^{-3}$) and *F_Ruminococcaceae (RNT)* × CD ($P = 9.80 \times 10^{-3}$). Four candidate interactions of gut microbiome PRS and UC PRS were detected, such as *G_Blautia (RNT)* × UC ($P = 3.86 \times 10^{-2}$) and *F_Coriobacteriaceae (HB)* × UC ($P = 4.02 \times 10^{-2}$). We also discovered 7 significant interactions between gut microbiome PRS and CD + UC PRS, such as *F_Lachnospiraceae (RNT)* × CD + UC ($P = 1.48 \times 10^{-3}$) and *G_Acidaminococcus (RNT)* × CD + UC ($P = 5.92 \times 10^{-3}$).

For self-reported depression, 6 candidate interactions between gut microbiome PRS and CD PRS were detected, such as *G_Streptococcus (HB)* × CD ($P = 1.21 \times 10^{-2}$) and *G_Desulfovibrio (RNT)* × CD ($P = 1.66 \times 10^{-2}$), and 6 promising candidate interactions between gut microbiome PRS and UC PRS were observed, such as *F_Veillonellaceae (HB)* × UC ($P = 2.83 \times 10^{-3}$), *G_Alloprevotella (HB)* × UC ($P = 5.25 \times 10^{-3}$). In addition, we identified 6 interactions between gut microbiome PRS and CD + UC PRS, such as *G_Streptococcus (HB)* × CD + UC ($P = 1.62 \times 10^{-2}$) and *F_Veillonellaceae (HB)* × CD + UC ($P = 1.94 \times 10^{-2}$).

For age at first episode of depression, we discovered 6 candidate interactions of gut microbiome PRS and CD PRS, such as *P_Firmicutes (RNT)* × CD ($P = 8.50 \times 10^{-3}$) and *G_Eisenbergiella (RNT)* × CD ($P = 1.26 \times 10^{-2}$). Four candidate interactions of gut microbiome PRS and UC PRS were identified, such as *G_Aestuariispira (HB)* × UC ($P = 5.58 \times 10^{-3}$) and *G_Coprobacter (RNT)* × UC ($P = 2.11 \times 10^{-2}$), and 5 interactions between gut microbiome PRS and CD + UC PRS were detected, such as *G_Coprobacter (RNT)* × CD + UC ($P = 3.74 \times 10^{-3}$), *P_Firmicutes (RNT)* × CD + UC ($P = 6.18 \times 10^{-3}$). Table 2 summarized the top 10 significant interactions, and Fig. 1 showed the scatter plots of the interactions.

3.3. Interactions of gut microbiome PRS and IBD PRS in males

We tested the effects of the gut microbiome PRS × IBD PRS interactions on depression phenotypes in males. The details could be seen in Supplementary Table 2. For PHQ-9 score, 7 candidate interactions between gut microbiome PRS and CD PRS were identified, such as *F_Ruminococcaceae (RNT)* × CD ($P = 1.75 \times 10^{-2}$) and *G_Collinsella (RNT)* × CD ($P = 2.38 \times 10^{-2}$). *F_Ruminococcaceae (RNT)* × UC ($P = 6.43 \times 10^{-3}$) and *F_Lachnospiraceae (RNT)* × UC ($P = 2.24 \times 10^{-2}$) were detected as candidate interactions between gut microbiome PRS and UC PRS. We also discovered 6 potential interactions between gut microbiome PRS and CD + UC PRS, such as *G_Collinsella (RNT)* × CD + UC ($P = 2.12 \times 10^{-2}$) and *F_Porphyromonadaceae (RNT)* × CD + UC ($P = 2.71 \times 10^{-2}$).

For self-reported depression, we found 5 candidate interactions between gut microbiome PRS and CD PRS, such as *C_Gammaproteobacteria (HB)* × CD ($P = 6.45 \times 10^{-3}$) and *P_Firmicutes (HB)* × CD ($P = 1.58 \times 10^{-2}$), and 3 candidate interactions between gut microbiome PRS and UC PRS, such as *G_Phascolarctobacterium (RNT)* × UC ($P = 2.47 \times 10^{-3}$) and *G_Escherichia_Shigella (RNT)* × UC ($P = 1.41 \times 10^{-2}$). In addition, we detected 3 interactions of gut microbiome PRS and CD + UC PRS, such as *G_Acidaminococcus (HB)* × CD + UC ($P = 1.19 \times 10^{-2}$) and *O_Selenomonadales (RNT)* × CD + UC ($P = 3.23 \times 10^{-2}$).

For age at first episode of depression, *G_Streptococcus (RNT)* × CD ($P = 4.33 \times 10^{-3}$) and *G_Coprobacter (RNT)* × CD ($P = 2.28 \times 10^{-2}$) were found as candidate interactions between gut microbiome PRS and CD PRS. We identified 12 candidate interactions between gut microbiome PRS and UC PRS, such as *F_Erysipelotrichaceae (HB)* × UC ($P = 8.97 \times 10^{-3}$), *C_Actinobacteria (RNT)* × UC ($P = 1.13 \times 10^{-2}$). We also detected 6 interactions between gut microbiome PRS and CD + UC PRS, such as *G_Faecalitalea (HB)* × CD + UC ($P = 5.44 \times 10^{-3}$) and *G_Paraprevotella (RNT)* × CD + UC ($P = 2.14 \times 10^{-2}$). Table 3 summarized the top 10 significant interactions in different sex, and Fig. 2 showed the scatter plots of the interactions in males.

3.4. Interactions of gut microbiome PRS and IBD PRS in females

In females, for PHQ-9 score, we identified 2 candidate interactions between gut microbiome PRS and CD PRS: *G_Intestinibacter (HB)* × CD ($P = 9.35 \times 10^{-3}$) and *G_Coprobacter (RNT)* × CD ($P = 3.62 \times 10^{-2}$), and 7 candidate interactions between gut microbiome PRS and UC PRS, such as *F_Prevotellaceae (RNT)* × UC ($P = 1.42 \times 10^{-2}$) and *O_Bacteroidales (HB)* × UC ($P = 2.25 \times 10^{-2}$). We also found 3 interactions between gut microbiome PRS and CD + UC PRS, such as *G_Intestinibacter (HB)* × CD

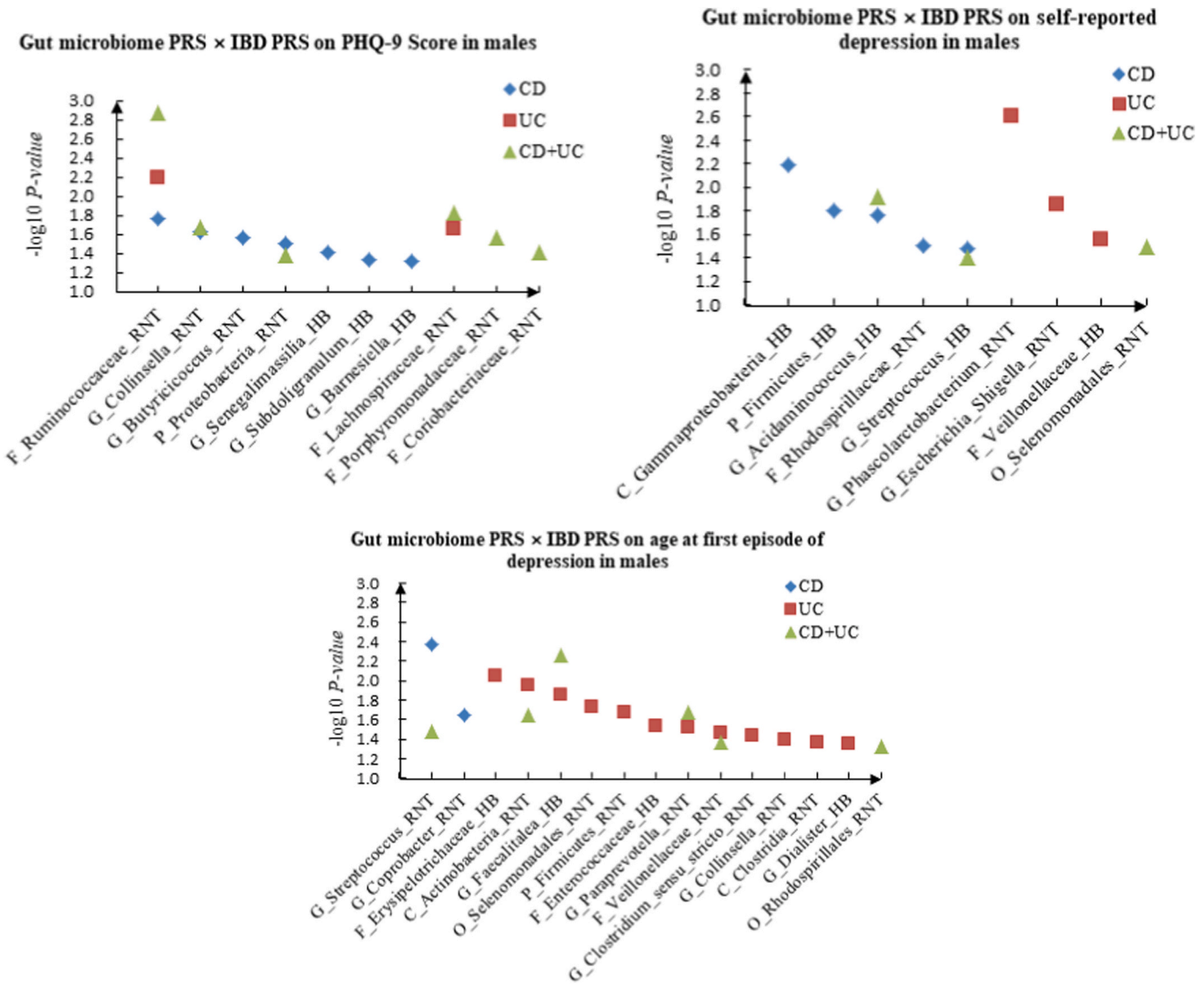

Fig. 2. **A** The scatter plot of the interactions of gut microbiome PRS and IBD PRS on PHQ-9 Score in males. **B** The scatter plot of the interactions of gut microbiome PRS and IBD PRS on self-reported depression in males. **C** The scatter plot of the interactions of gut microbiome PRS and IBD PRS on age at first episode of depression in males.

+ UC ($P = 7.39 \times 10^{-3}$) and *O_Bacteroidales (HB)* × CD + UC ($P = 7.74 \times 10^{-3}$).

For self-reported depression, 5 candidate interactions between gut microbiome PRS and CD PRS were discovered, such as *F_Erysipelotrichaceae (RNT)* × CD ($P = 5.50 \times 10^{-3}$) and *G_Paraprevotella (RNT)* × CD ($P = 1.94 \times 10^{-2}$). We also observed 6 candidate interactions between gut microbiome PRS and UC PRS, such as *G_Sporobacter (HB)* × UC ($P = 6.31 \times 10^{-4}$), *G_Holdemanella (HB)* × UC ($P = 1.60 \times 10^{-2}$), and 3 interactions between gut microbiome PRS and CD + UC PRS, such as *F_Erysipelotrichaceae (RNT)* × CD + UC ($P = 7.17 \times 10^{-3}$) and *G_Sporobacter (HB)* × CD + UC ($P = 1.15 \times 10^{-2}$).

For age at first episode of depression, we found 7 candidate interactions between gut microbiome PRS and CD PRS, such as *G_Eisenbergiella (RNT)* × CD ($P = 4.14 \times 10^{-3}$) and *G_Phascolarctobacterium (RNT)* × CD ($P = 1.76 \times 10^{-2}$). Seven candidate interactions between gut microbiome PRS and UC PRS were identified, such as *G_Barnesiella (HB)* × UC ($P = 1.03 \times 10^{-2}$) and *G_Butyrivibrio (RNT)* × UC ($P = 1.62 \times 10^{-2}$), and 7 interactions between gut microbiome PRS and CD + UC PRS were detected, such as *G_Barnesiella (HB)* × CD + UC ($P = 1.22 \times 10^{-2}$) and *G_Eisenbergiella (RNT)* × CD + UC ($P = 1.35 \times 10^{-2}$).

For depression possibly related to childbirth, we observed 6 candidate interactions between gut microbiome PRS and CD PRS, such as *G_Anaerostipes (RNT)* × CD ($P = 8.59 \times 10^{-3}$) and *G_Prevotella (RNT)* × CD ($P = 1.28 \times 10^{-2}$), and 3 candidate interactions between gut microbiome PRS and UC PRS, such as *P_Firmicutes (RNT)* × UC ($P = 2.57 \times 10^{-2}$) and *G_Veillonella (RNT)* × UC ($P = 3.88 \times 10^{-2}$). We also detected 4 interactions between gut microbiome PRS and CD + UC PRS, such as *G_Anaerostipes (RNT)* × CD + UC ($P = 1.86 \times 10^{-2}$) and *G_Prevotella (RNT)* × CD + UC ($P = 2.49 \times 10^{-2}$). The scatter plots of the interactions in females are shown in Fig. 3.

3.5. Interactions of gut microbiome PRS and IBD PRS in age subgroups

In this study, the age range of participants was 38–71 years old. Thus, we divided the subjects into three age groups: youth group (<50 years old), middle-aged group (50–59 years old) and elderly group (≥60 years old). Totally, we found 193 interactions between gut microbiome PRS and IBD PRS associated with four depression phenotypes in all age groups. The details are shown in Supplementary Table 3. Table 4 summarized the top 10 significant interactions in different ages. Scatter plots of significant interactions across age groups were shown in Figs. 4–6.

For PHQ-9 score, 21 interactions were discovered in the youth group,

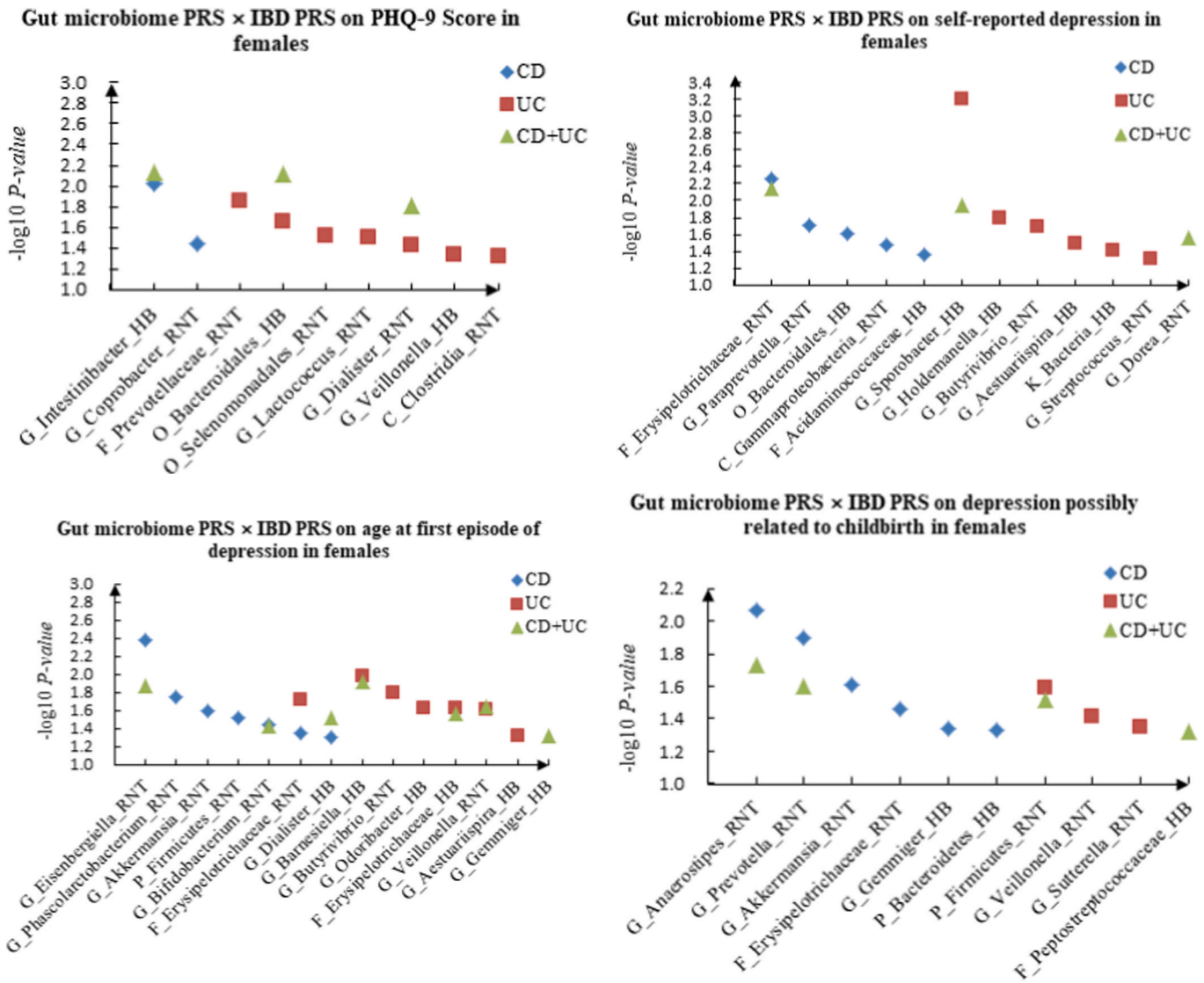

Fig. 3. **A** The scatter plot of the interactions of gut microbiome PRS and IBD PRS on PHQ-9 Score in females. **B** The scatter plot of the interactions of gut microbiome PRS and IBD PRS on self-reported depression in females. **C** The scatter plot of the interactions of gut microbiome PRS and IBD PRS on age at first episode of depression in females. **D** The scatter plot of the interactions of gut microbiome PRS and IBD PRS on depression possibly related to childbirth in females.

such as *C_Alphaproteobacteria (RNT)* × CD ($P = 2.67 \times 10^{-2}$), *F_Desulfovibrionaceae (HB)* × UC ($P = 5.01 \times 10^{-3}$) and *C_Alphaproteobacteria (RNT)* × CD + UC ($P = 4.23 \times 10^{-2}$). Thirteen correlations were identified in the middle-aged group, such as *C_Deltaproteobacteria (HB)* × CD ($P = 1.48 \times 10^{-3}$), *C_Gammaproteobacteria (RNT)* × UC ($P = 2.31 \times 10^{-2}$) and *F_Lachnospiraceae (RNT)* × CD + UC ($P = 3.60 \times 10^{-2}$), and we observed 16 candidate interactions in the elderly group, such as *F_Coriobacteriaceae (RNT)* × CD ($P = 8.17 \times 10^{-3}$), *F_Streptococcaceae (HB)* × UC ($P = 2.45 \times 10^{-2}$) and *G_Intestinibacter (RNT)* × CD + UC ($P = 4.46 \times 10^{-2}$).

For self-reported depression, 16 candidate interactions were discovered in the youth group, such as *F_Acidaminococcaceae (HB)* × CD ($P = 4.20 \times 10^{-2}$), *F_Desulfovibrionaceae (HB)* × UC ($P = 1.88 \times 10^{-2}$) and *F_Erysipelotrichaceae (RNT)* × CD + UC ($P = 4.34 \times 10^{-2}$). We also observed 22 interactions in the middle-aged group, such as *C_Deltaproteobacteria (HB)* × CD ($P = 1.05 \times 10^{-2}$), *G_Aestuariispira (RNT)* × UC ($P = 3.40 \times 10^{-2}$) and *F_Peptostreptococcaceae (HB)* × CD + UC ($P = 2.47 \times 10^{-2}$), and 11 interactions in the elderly group, such as *C_Alphaproteobacteria (RNT)* × CD ($P = 6.86 \times 10^{-3}$), *C_Gammaproteobacteria (RNT)* × UC ($P = 1.30 \times 10^{-2}$) and *G_Ruminococcus (RNT)* × CD + UC ($P = 3.63 \times 10^{-2}$).

For age at first episode of depression, we found 13 candidate interactions in the youth group, such as *F_Peptostreptococcaceae (HB)* × CD ($P = 3.89 \times 10^{-2}$), *G_Acidaminococcus (RNT)* × UC ($P = 2.85 \times 10^{-2}$) and *G_Aestuariispira (RNT)* × CD + UC ($P = 1.24 \times 10^{-2}$). Sixteen interactions were identified in the middle-aged group, such as *C_Gammaproteobacteria (HB)* × CD ($P = 7.31 \times 10^{-3}$), *G_Dialister (RNT)* × UC ($P = 3.77 \times 10^{-2}$) and *G_Alistipes (RNT)* × CD + UC ($P = 3.58 \times 10^{-2}$). Furthermore, we also detected 22 interactions in the elderly group, such as *C_Gammaproteobacteria (RNT)* × CD ($P = 2.75 \times 10^{-2}$), *F_Acidaminococcaceae (RNT)* × UC ($P = 4.29 \times 10^{-2}$) and *G_Acidaminococcus (HB)* × CD + UC ($P = 5.54 \times 10^{-3}$).

For depression possibly related to childbirth, we observed 11 interactions in the youth group, such as *F_Acidaminococcaceae (RNT)* × CD ($P = 2.20 \times 10^{-2}$), *F_Enterobacteriaceae (HB)* × UC ($P = 3.78 \times 10^{-2}$) and *P_Bacteroidetes (HB)* × CD + UC ($P = 4.51 \times 10^{-2}$), and 17 candidate interactions were detected in the middle-aged group, such as *F_Veillonellaceae (RNT)* × CD ($P = 5.84 \times 10^{-3}$), *G_Desulfovibrio (RNT)* × UC ($P = 3.84 \times 10^{-2}$) and *G_Acidaminococcus (RNT)* × CD + UC ($P = 3.60 \times 10^{-3}$). We also found 15 interactions in the elderly group, such as *G_Coprococcus (HB)* × CD ($P = 8.52 \times 10^{-3}$), *F_Peptostreptococcaceae (HB)* × UC ($P = 4.14 \times 10^{-2}$) and *G_Acidaminococcus (HB)* × CD + UC

Table 4
The top ten significant interactions of gut microbiome PRS and IBD PRS on depression in different ages.

Depression phenotypes	IBD phenotypes	Gut microbiome	Gut microbiome PRS		IBD PRS		Interaction	
			T	P	T	P	T	P
<50 years old								
PHQ-9 score	CD	*G_Clostridium_sensu_stricto_HB*	0.867	0.386	−1.864	0.062	3.787	<0.001
PHQ-9 score	UC	*G_Akkermansia_RNT*	−3.479	0.001	−2.648	0.008	3.613	<0.001
PHQ-9 score	CD + UC	*G_Clostridium_sensu_stricto_HB*	−2.812	0.005	−1.068	0.285	3.195	0.001
Self-reported depression	CD + UC	*F_Porphyromonadaceae_RNT*	3.082	0.002	2.535	0.011	−3.138	0.002
Age at first episode of depression	UC	*G_Veillonella_HB*	3.275	0.001	−0.452	0.651	−2.919	0.004
PHQ-9 score	UC	*F_Desulfovibrionaceae_HB*	−3.003	0.003	−2.578	0.010	2.807	0.005
Self-reported depression	CD	*F_Rhodospirillaceae_HB*	0.495	0.621	1.250	0.211	2.774	0.006
PHQ-9 score	CD	*F_Ruminococcaceae_RNT*	0.852	0.394	1.792	0.073	−2.651	0.008
PHQ-9 score	CD + UC	*G_Akkermansia_RNT*	−2.408	0.016	−1.872	0.061	2.644	0.008
Age at first episode of depression	CD	*P_Bacteroidetes_HB*	−1.678	0.093	1.664	0.096	−2.644	0.008
50–59 years old								
PHQ-9 score	CD	*C_Deltaproteobacteria_HB*	−0.022	0.982	1.321	0.187	−3.179	0.001
Depression possibly related to childbirth	CD + UC	*G_Acidaminococcus_RNT*	−2.289	0.022	−0.674	0.500	2.912	0.004
Depression possibly related to childbirth	CD	*G_Acidaminococcus_RNT*	1.438	0.151	−1.029	0.304	2.874	0.004
Depression possibly related to childbirth	CD + UC	*G_Intestinibacter_RNT*	3.151	0.002	−0.339	0.734	−2.844	0.004
Age at first episode of depression	CD + UC	*G_Eisenbergiella_RNT*	1.570	0.116	0.922	0.357	−2.837	0.005
Depression possibly related to childbirth	CD	*F_Veillonellaceae_RNT*	−0.394	0.693	0.959	0.338	2.757	0.006
Self-reported depression	UC	*P_Lentisphaerae_HB*	−2.237	0.025	−0.237	0.812	2.742	0.006
Depression possibly related to childbirth	UC	*G_Clostridium_sensu_stricto_RNT*	−2.653	0.008	−0.382	0.702	2.686	0.007
Age at first episode of depression	CD	*C_Gammaproteobacteria_HB*	1.184	0.237	1.308	0.191	2.683	0.007
PHQ-9 score	UC	*F_Erysipelotrichaceae_HB*	−2.002	0.045	−2.392	0.017	2.678	0.007
≥60 years old								
Self-reported depression	UC	*G_Alloprevotella_HB*	−2.911	0.004	−1.380	0.168	3.390	0.001
PHQ-9 score	UC	*F_Ruminococcaceae_RNT*	2.772	0.006	1.737	0.082	−3.035	0.002
Age at first episode of depression	CD + UC	*P_Firmicutes_RNT*	−3.048	0.002	0.678	0.498	2.911	0.004
PHQ-9 score	CD + UC	*O_Lactobacillales_HB*	2.747	0.006	−1.573	0.116	−2.866	0.004
Age at first episode of depression	CD	*C_Clostridia_RNT*	1.299	0.194	−2.272	0.023	−2.846	0.004
Age at first episode of depression	CD	*P_Firmicutes_RNT*	−0.390	0.697	0.777	0.437	2.813	0.005
Age at first episode of depression	CD + UC	*C_Gammaproteobacteria_RNT*	−2.468	0.014	−2.379	0.017	2.808	0.005
PHQ-9 score	UC	*O_Lactobacillales_HB*	2.771	0.006	−0.628	0.530	−2.784	0.005
Age at first episode of depression	CD + UC	*G_Acidaminococcus_HB*	2.666	0.008	−0.057	0.955	−2.774	0.006
Self-reported depression	CD	*C_Alphaproteobacteria_RNT*	1.465	0.143	−2.840	0.005	−2.704	0.007

Notes: P, Phylum. C, Class. O, Order. F, Family. G, Genus. PRS: Polygenic risk scores. PHQ: Patient Health Questionnaire. IBD: Inflammatory bowel disease. UC: Ulcerative colitis. CD: Crohn's disease.

($P = 4.18 \times 10^{-2}$).

3.6. SNP interaction analysis results

For identified candidate PRS interactions, we further conducted single SNP interaction analysis between the top 10 gut microbiome PRS × IBD PRS interactions for depression phenotypes. And we identified several candidate genes corresponding to the SNP locus through GWAS4D (http://mulinlab.org/gwas4d).

For PHQ-9 score, we detected 3 interactions between gut-microbiome-associated SNP × IBD-associated SNP, such as *G_Alloprevotella (HB)*-associated rs147650986 (*GPM6A*) × IBD-associated rs114471990 (*QRICH1*) ($P = 2.26 \times 10^{-4}$), *G_Aestuariispira (HB)*-associated rs10882795 (*TLL2*) × IBD-associated rs2517523 (*HCG22*) ($P = 1.01 \times 10^{-4}$).

For self-reported depression, we identified 3 interactions between gut-microbiome-associated SNP × IBD-associated SNP, such as *G_Alloprevotella (HB)*-associated rs181338468 (*4q31.21*) × IBD-associated rs911359 (*LINC01620*) ($P = 2.35 \times 10^{-4}$) and *G_Aestuariispira (HB)*-associated rs140132254 (*FER1L6*) × IBD-associated rs9262636 (*HCG22*) ($P = 5.14 \times 10^{-4}$).

For age at first episode of depression, two interactions between gut-microbiome-associated SNP × IBD-associated SNP were discovered: *G_Alloprevotella (HB)*-associated rs147377160 (*2q14.3*) × IBD-associated rs9308261 (*1p13.2*) ($P = 1.41 \times 10^{-4}$), *F_Veillonellaceae (HB)*-associated rs117748831 (*16p13.2*) × IBD-associated rs11168249 (*HDAC7*) ($P = 5.39 \times 10^{-4}$).

For depression possibly related to childbirth, we found 3 interactions between gut-microbiome-associated SNP × IBD-associated SNP, such as *G_Alloprevotella (HB)*-associated rs116712055 (*WDR64*) × IBD-associated rs117987337 (*12q12*) ($P = 1.06 \times 10^{-4}$) and *G_Dialister (HB)*-associated rs11001120 (*10q22.2*) × IBD-associated rs3213673 (*DLD*) ($P = 1.40 \times 10^{-4}$). The detailed results are shown in Table 5.

4. Discussion

Previous studies have revealed that gut microbiome and IBD involve in the development of depression (Barandouzi et al., 2020; Abautret-Daly et al., 2018). However, the biological mechanisms behind the impact of interactions between gut microbiome and IBD on depression risk remain to be elucidated. In this study, we examined the interactions between IBD and the gut microbiome, and then observed the effects of the interactions on depression risk. We also reported several novel candidate genes for depression through SNPs interaction analysis.

We found a significant association between the interactions of gut microbiome × IBD and depression. Previous studies have illustrated that gut microbiome and IBD can influence the pathogenesis of depression. The gut microbiome plays a direct role in mental disorders and can affect the brain and behavior through the microbiome-gut-brain axis (Liang et al., 2018; Lima-Ojeda et al., 2020). Communication between the gut microbiome and the brain includes modulation of the hypothalamic-pituitary-adrenal (HPA) axis, activation of the immune system and the inflammatory response system (Abautret-Daly et al., 2018). IBD can affect the pathogenesis of depression through immune inflammation, gut-brain pathways, tryptophan catabolites, and oxidative and nitrosating stress (Martin-Subero et al., 2016; Abautret-Daly et al., 2018). In addition, IBD can influence the composition of the microbiome, while microorganisms can influence the occurrence of IBD. For example, people with CD or UC have different gut microbiota with healthy individuals (Guarner, 2011). In contrast, the gut microbiota

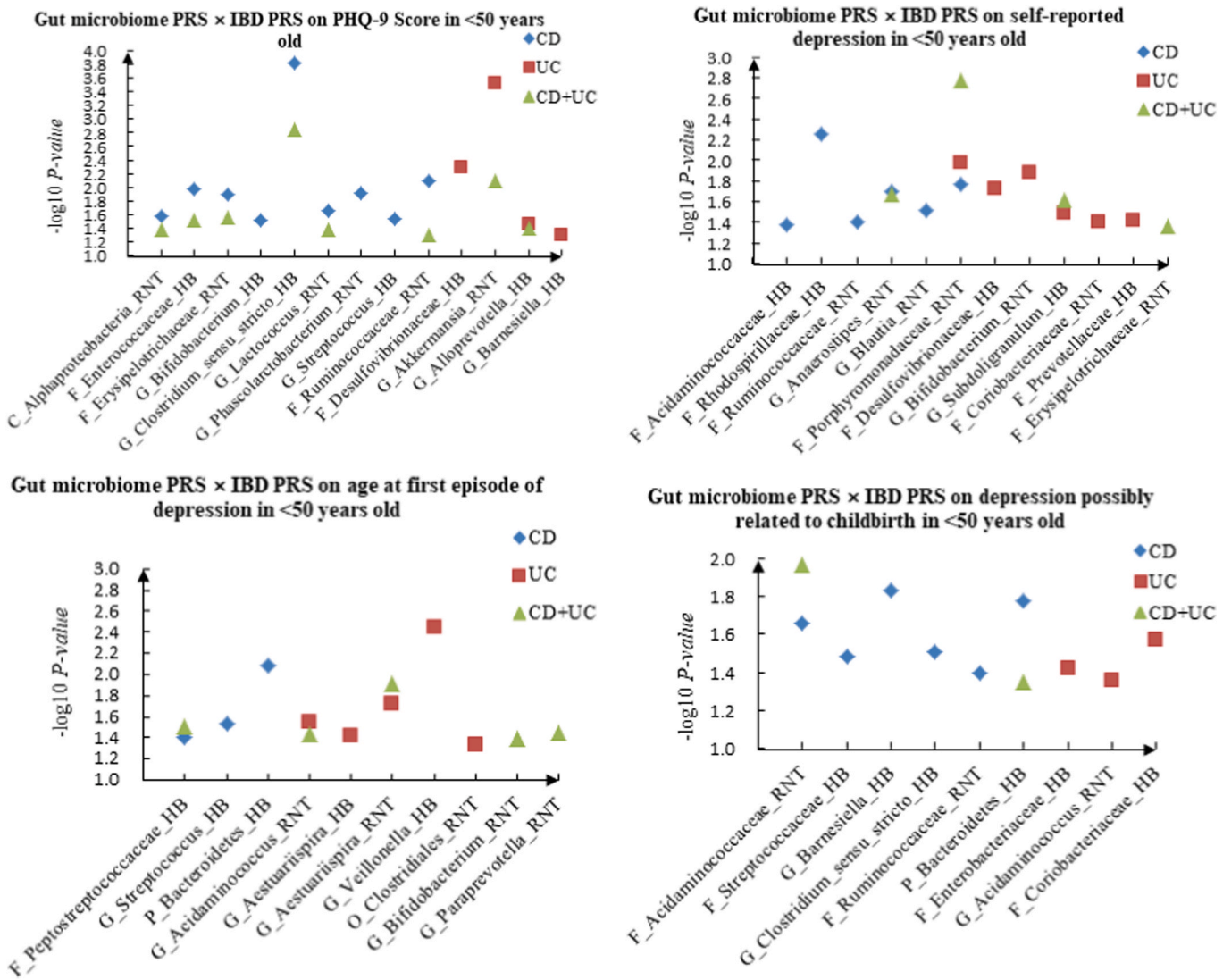

Fig. 4. **A** The scatter plot of the interactions of gut microbiome PRS and IBD PRS on PHQ-9 Score in <50 years old. **B** The scatter plot of the interactions of gut microbiome PRS and IBD PRS on self-reported depression in <50 years old. **C** The scatter plot of the interactions of gut microbiome PRS and IBD PRS on age at first episode of depression in <50 years old. **D** The scatter plot of the interactions of gut microbiome PRS and IBD PRS on depression possibly related to childbirth in <50 years old.

metabolizes complex dietary carbohydrates through a wide range of enzymes, resulting in the production of organic acids, gases, and large amounts of SCFAs (Martin-Gallausiaux et al., 2021), SCFAs promote the differentiation of naive T lymphocytes in the intestine into Treg cells (Martin-Gallausiaux et al., 2021). When the number of SCFAs-producing microorganisms is reduced, the number of Treg cells is reduced, which can lead to IBD (Martin-Gallausiaux et al., 2021; Dalile et al., 2019; Yan et al., 2020; Ueno et al., 2018). However, whether the relationship between gut microbiota and IBD is related to the pathogenesis of depression remains uncertain and requires further investigation.

We identified several significant gut microbiome and IBD interactions, such as *G_Dialister (HB)* × CD, *G_Anaerostipes (RNT)* × CD, *G_Alloprevotella (HB)* × UC, *F_Veillonellaceae (HB)* × UC and *F_Lachnospiraceae (RNT)* × CD + UC. Previous studies showed an increased abundance of genus *Anaerostipes* (Cheung et al., 2019) and family *Lachnospiraceae* (Cheung et al., 2019; Chen et al., 2018a) and decreased abundance of genus *Alloprevotella* (Zheng et al., 2021), family *Veillonellaceae* (Barandouzi et al., 2020) and genus *Dialister* (Cheung et al., 2019; Valles-Colomer et al., 2019) in depressed patients compared to non-depressed patients, suggesting that depression may be associated with specific gut microbiome phenotypes (Liang et al., 2018). Interestingly, genus *Dialister* decreased in CD patients (Kowalska-Duplaga et al., 2019) and family *Veillonellaceae* decreased in UC patients (Lee et al., 2020b), which may act through the microbiome-gut-brain axis, leading to the psychiatric disorders of autism spectrum disorders (ASD) and schizophrenia (SCZ), respectively (Andreo-Martinez et al., 2020; Zheng et al., 2019). In addition, family *Lachnospiraceae* and genus *Anaerostipes* can alleviate intestinal inflammation in IBD patients by producing butyrate and inhibiting proinflammatory cytokines (Vacca et al., 2020; Lee et al., 2021). Wang et al. observed that the increase of genus *Alloprevotella* was not conducive to the relief of intestinal inflammation (Wang et al., 2019b).

The effect of the gut microbiome PRS × IBD PRS interactions on depression risk differed across sex and age. Some pieces of evidence suggested that sex can affect gut microbiota diversity and may play a role in depression (Manosso et al., 2021). For example, the relative abundance of *Actinobacteria* increased in female-depressed individuals, while that of *Bacteroidetes* decreased in male-depressed individuals (Chen et al., 2018b). Notably, there appears to be a reciprocal interaction between gut microbiota and sex hormones, and sex differences in gut microbiota do not appear until puberty (Kim et al., 2020; Jaggar et al., 2020). In addition, the composition of the gut microbiome and the

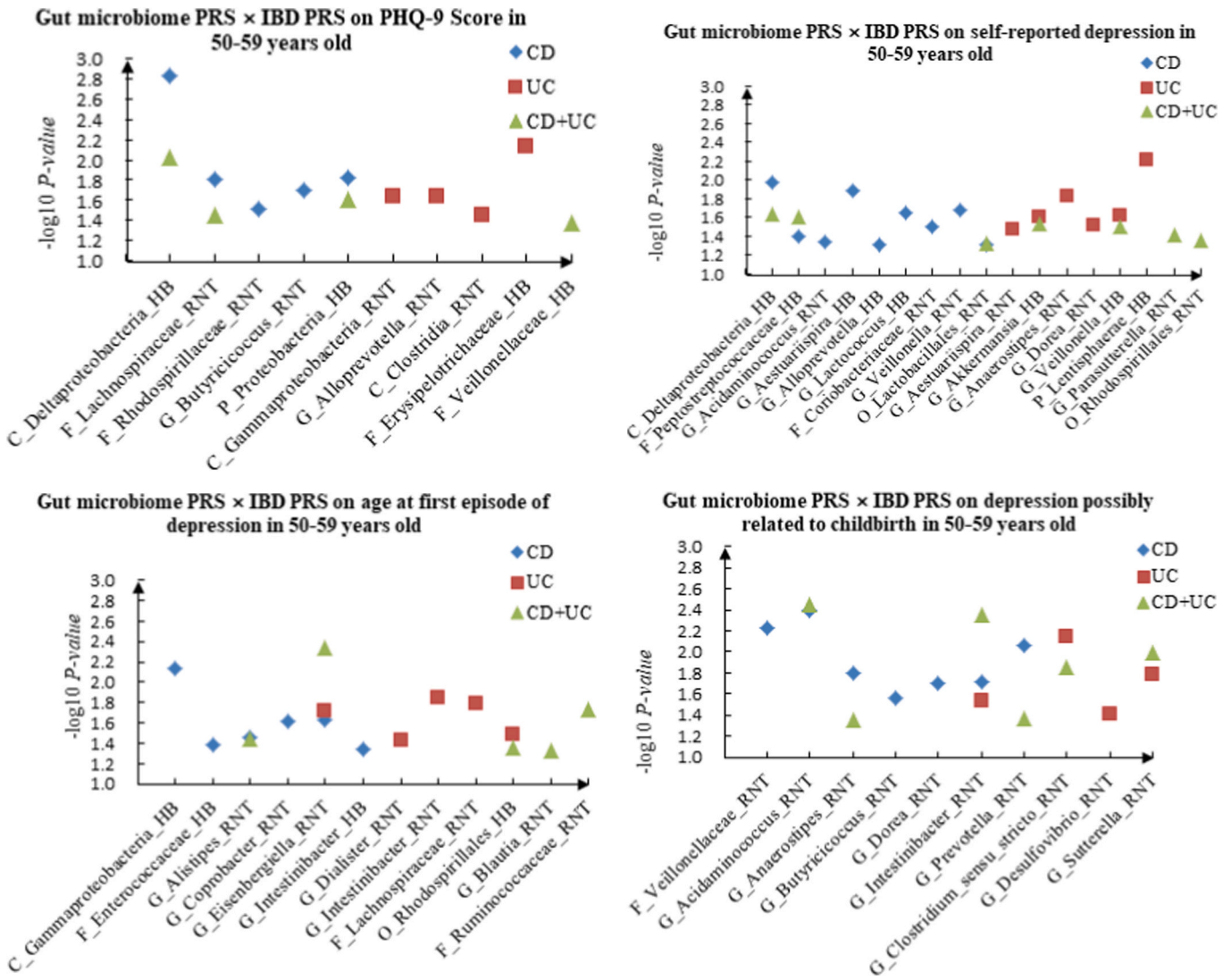

Fig. 5. **A** The scatter plot of the interactions of gut microbiome PRS and IBD PRS on PHQ-9 Score in 50–59 years old. **B** The scatter plot of the interactions of gut microbiome PRS and IBD PRS on self-reported depression in 50–59 years old. **C** The scatter plot of the interactions of gut microbiome PRS and IBD PRS on age at first episode of depression in 50–59 years old. **D** The scatter plot of the interactions of gut microbiome PRS and IBD PRS on depression possibly related to childbirth in 50–59 years old.

relative abundance of specific bacterial taxa are affected with age (Ratto et al., 2022). Specifically, changes in microbiota composition could be caused by maladaptive and dysbiosis conditions in the gut microbiota in the delicate balance between inflammation, immune senescence and ecological homeostasis, such as changes in the relative abundance of *Lachnospiraceae* and *Ruminococcaceae* (DeJong et al., 2020). It was believed that increasing age can affect the gut-brain axis by causing alterations in the gut microbiome, thereby impeding neural, endocrine, nutritional and immune signals between the gut and brain via the enteric nervous system (ENS), and may play a role in central nervous system (CNS) disorders such as depression and anxiety (Nagpal et al., 2018).

Moreover, we detected several candidate genes for depression phenotypes, such as *HDAC7*, *GPM6A*, *VDR*, and *QRICH1*. *HDAC7* is a major histone deacetylase, which can drive macrophage-mediated inflammatory response and increase the proinflammatory mediators IL-1β and Ccl2 (Das Gupta et al., 2020; Ramnath et al., 2021; Shakespear et al., 2013). *GPM6A* promotes the formation of synapses and is involved in the brain signaling pathways of psychiatric disorders such as depression and schizophrenia (Aparicio et al., 2020; Fuchsova et al., 2015). *GPM6A* mRNA level in the hippocampus of patients with depression is significantly decreased, and down-regulated *GPM6A* expression may be associated with morphological alterations in the depressed human brain (Fuchsova et al., 2015). Additionally, *VDR* has the function of regulating T cells and has been shown to influence the relationship between the intestinal flora and the host (Battistini et al., 2020). For example, mice knocked out of the *VDR* had severe colitis and increased intestinal mucosal permeability (Zhang et al., 2019b). *QRICH1* plays a key role in the unfolded response to endoplasmic reticulum (ER) stress through transcriptional control of protein status, and *QRICH1* variants contribute to neurodevelopmental disorders through dysregulation of the ER stress response (Kumble et al., 2022).

In this study, we conducted the first large-scale PRS-based analysis to detect the effect of gut microbiome × IBD interactions on depression. The PRS was generated using the latest GWAS summary data of gut microbiome and IBD, and genotype data from the UK Biobank cohort. We indicated significant gut microbiome PRS × IBD PRS interactions for depression. In addition, we conducted SNP × SNP interaction analysis and found a significant effect of interactions between gut-microbiome-associated SNPs and IBD-associated SNPs on depression. Our findings may contribute to a more detailed understanding of the pathogenesis of depression and provide novel therapeutic targets. However, certain

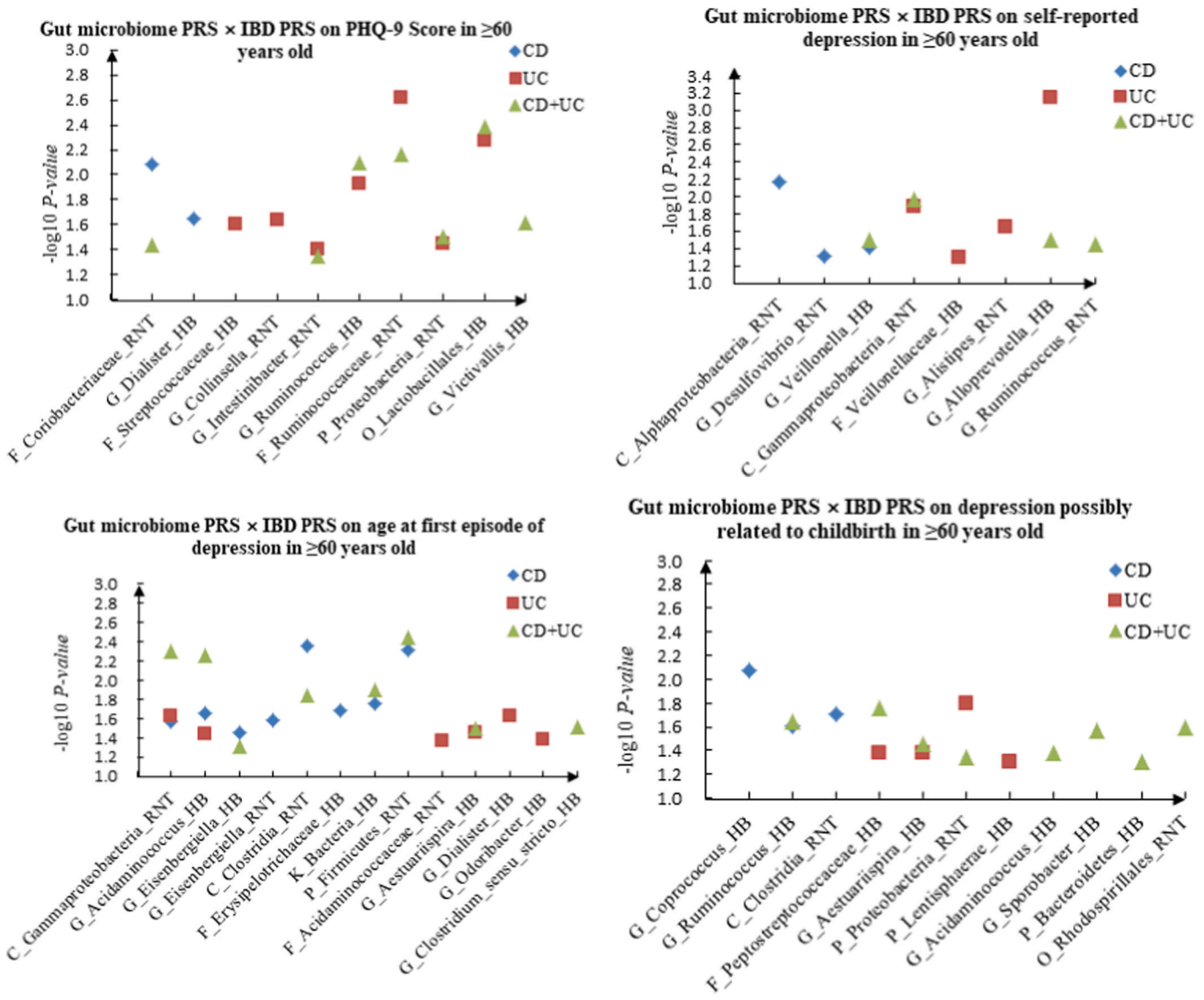

Fig. 6. **A** The scatter plot of the interactions of gut microbiome PRS and IBD PRS on PHQ-9 Score in ≥60 years old. **B** The scatter plot of the interactions of gut microbiome PRS and IBD PRS on self-reported depression in ≥60 years old. **C** The scatter plot of the interactions of gut microbiome PRS and IBD PRS on age at first episode of depression in ≥60 years old. **D** The scatter plot of the interactions of gut microbiome PRS and IBD PRS on depression possibly related to childbirth in ≥60 years old.

limitations should be noted. First, the samples in this study were drawn entirely from the European population aged 38–71 years old, so the findings should be extended with caution to other ethnic groups or other age groups. Second, given that our study is a cross-sectional study, we would be unable to prove a causal relationship between gut microbiome × IBD interactions and depression. Third, we focused on the interaction between IBD and 64 gut microbiota that significantly affect the risk of depression, and further experimental studies are needed to verify the underlying molecular biological mechanisms.

In conclusion, we conducted a comprehensive analysis to test the effect of gut microbiome × IBD on depression risk, and explore the potential role of SNPs interactions in the pathogenesis of depression. We detected multiple significant gut microbiome PRS × IBD PRS interactions and identified several candidate genes for depression. Our findings provide novel clues for the pathogenesis and therapy of depression. Further research is needed to elucidate and validate the biological mechanisms in the future.

Authors' contributions

XQ and FZ conceived and designed the study; XQ and CP wrote the manuscript; All authors collected the data and CP carried out the statistical analysis; QC, YZ, DH, WW, NZ, SS and XC made preparations for the manuscript at first. All authors reviewed and approved the final manuscript.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Table 5
The interactions of SNPs on depression.

Depression phenotypes	Gut microbiome	Gut microbiome related SNPs		IBD related SNPs		SNP × SNP interaction *P* value
		ID	Gene locus	ID	Gene locus	
PHQ-9 score						
	G_Alloprevotella_HB	rs139744914	OBP2B	rs911359	LINC01620	4.77×10^{-4}
		rs147650986	GPM6A	rs114471990	QRICH1	2.26×10^{-4}
		rs148583470	3p12.1	rs76970129	18p11.21	8.43×10^{-4}
		rs77408394	CACNA1C	rs28894977	6p21.33	7.00×10^{-4}
	G_Aestuariispira_HB	rs10882795	TLL2	rs2517523	HCG22	1.01×10^{-4}
				rs939983	15q13.1	1.25×10^{-4}
				rs9262636	HCG22	4.03×10^{-4}
				rs2517474	6p21.33	8.03×10^{-4}
		rs140132254	FER1L6	rs3809133	ESYT1, ZC3H10	4.89×10^{-4}
	G_Anaerostipes_RNT	rs117662630	14q21.1	rs114471990	QRICH1	1.02×10^{-4}
				rs147118406	C3orf84	1.61×10^{-4}
Self-reported depression						
	G_Alloprevotella_HB	rs181338468	4q31.21	rs911359	LINC01620	2.35×10^{-4}
				rs2844670	6p21.33	3.67×10^{-4}
	G_Aestuariispira_HB	rs140132254	FER1L6	rs9262636	HCG22	5.14×10^{-4}
	P_Firmicutes_RNT	rs11788336	ELP1	rs2254210	VDR	9.73×10^{-4}
Age at first episode of depression						
	G_Alloprevotella_HB	rs147377160	2q14.3	rs9308261	1p13.2	1.41×10^{-4}
		rs147650986	GPM6A	rs11564168	MUC19,AC107023.1	5.73×10^{-4}
		rs181338468	4q31.21	rs117987337	12q12	7.95×10^{-4}
	F_Veillonellaceae_HB	rs117748831	16p13.2	rs11168249	HDAC7	5.39×10^{-4}
Depression possibly related to childbirth						
	G_Alloprevotella_HB	rs116712055	WDR64	rs117987337	12q12	1.06×10^{-4}
		rs78681519	SLC13A3	rs1538580	9q21.11	4.87×10^{-4}
		rs9282699	CSHL1,GH1	rs2853564	VDR,AC121338.1	6.39×10^{-4}
	P_Firmicutes_RNT	rs11788336	ELP1	rs12179536	MUC22	9.88×10^{-4}
	G_Dialister_HB	rs10249533	PDE1C	rs10401439	SYMPK	3.06×10^{-4}
		rs11001120	10q22.2	rs3213673	DLD,LAMB1	1.40×10^{-4}

Notes: P, Phylum. F, Family. G, Genus. SNP: Single nucleotide polymorphisms. PHQ: Patient Health Questionnaire. IBD: Inflammatory bowel disease.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbih.2022.100557.

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