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Evaluating the interactive effects of dietary habits and human gut microbiome on the risks of depression and anxiety

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Original Article

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Abstract

Background. Gut microbiome and dietary patterns have been suggested to be associated with depression/anxiety. However, limited effort has been made to explore the effects of possible interactions between diet and microbiome on the risks of depression and anxiety.

Methods. Using the latest genome-wide association studies findings in gut microbiome and dietary habits, polygenic risk scores (PRSs) analysis of gut microbiome and dietary habits was conducted in the UK Biobank cohort. Logistic/linear regression models were applied for evaluating the associations for gut microbiome-PRS, dietary habits-PRS, and their interactions with depression/anxiety status and Patient Health Questionnaire (PHQ-9)/Generalized Anxiety Disorder-7 (GAD-7) score by R software.

Results. We observed 51 common diet–gut microbiome interactions shared by both PHQ score and depression status, such as overall beef intake × genus *Sporobacter* [hurdle binary (HB)] ($P_{PHQ} = 7.88 \times 10^{-4}$, $P_{depression\ status} = 5.86 \times 10^{-4}$); carbohydrate × genus *Lactococcus* (HB) ($P_{PHQ} = 0.0295$, $P_{depression\ status} = 0.0150$). We detected 41 common diet–gut microbiome interactions shared by GAD score and anxiety status, such as sugar × genus *Parasutterella* (rank normal transformed) ($P_{GAD} = 5.15 \times 10^{-3}$, $P_{anxiety\ status} = 0.0347$); tablespoons of raw vegetables per day × family *Coriobacteriaceae* (HB) ($P_{GAD} = 6.02 \times 10^{-4}$, $P_{anxiety\ status} = 0.0345$). Some common significant interactions shared by depression and anxiety were identified, such as overall beef intake × genus *Sporobacter* (HB).

Conclusions. Our study results expanded our understanding of how to comprehensively consider the relationships for dietary habits–gut microbiome interactions with depression and anxiety.

Introduction

Anxiety and depression are two important disorders contributing to the global burden of the diseases. It has been reported that 32% of the adolescents meet the criteria for subthreshold-anxious and 5.8% anxiety, 29.2% subthreshold-depressed and 10.5% depression (Balázs et al., 2013). Anxiety frequently co-occurs with depression, sharing several common risk factors and highly correlated symptoms. Approximately, 57% of depression patients possess anxiety, and 28% of patients with clinically significant anxiety suffer from depression (Almeida et al., 2012).

The risks of depression and anxiety are determined by genetic and environmental factors. Twin studies showed that the heritability of major depression disorder (MDD) and generalized anxiety disorder (GAD) was 37% (Sullivan, Neale, & Kendler, 2000) and 32%, respectively (Hettema, Neale, & Kendler, 2001). Many factors may alter overall vulnerability to depression-like and anxiety-like symptoms such as early-life events, immune system, comorbid psychiatric disorders, history of substance abuse or trauma and chronic medical illnesses, and peripheral cytokine production (DeMartini, Patel, & Fancher, 2019; Ménard, Hodes, & Russo, 2016).

The composition of the gut microbiome was suggested to be strongly associated with brain activity and mental health, including depression and anxiety (Knudsen et al., 2021; Simpson et al., 2021). This association appears to stem from the gut–brain axis, a communication channel between the central and enteric nervous system (Carabotti, Scirocco, Maselli, & Severi, 2015). There was evidence that patients with MDD had a different fecal microbiome composition compared with healthy controls: *Eggerthella*, *Atopobium*, and *Bifidobacterium* increased in the MDD patients, whereas *Faecalibacterium* significantly reduced (Knudsen et al., 2021). In addition, the severity of anxiety was negatively correlated with

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Eubacterium_coprostanoligenes_group, *Ruminococcaceae_UCG014*, and *Prevotella_9*, and positively correlated with *Bacteroides* and *Escherichia-Shigella* (Chen et al., 2019).

Previous studies have reported potential associations between dietary patterns and depression/anxiety disorder (Dharmayani, Juergens, Allman-Farinelli, & Mihrshahi, 2021; Fatahi et al., 2021). For example, systematic reviews indicated that dietary pattern characterized by a high intake of fruit, vegetables, and dietary fibers could reduce the risk of depression (Dharmayani et al., 2021; Fatahi et al., 2021). The associations of habitual diet quality and mental disorders were also supported by another cross-sectional study (Jacka et al., 2010). However, limited effort has been made to explore the effects of possible interactions between diet and microbiome on the risks of depression and anxiety. It is well-known that diet plays a significant role in the microbiome composition and gut microbiome can rapidly respond to altered diet within 24 h (David et al., 2014). Thus, it is important to comprehensively research the relationships between diet, gut microbiome, and mental disease for future applications of diet therapy for depression and anxiety.

Genome-wide association studies (GWASs) have successfully mapped thousands of common genetic variants associated with complex diseases, however, each loci having little individual effect on the phenotype (Hindorff, Gillanders, & Manolio, 2011). Polygenic risk scores (PRSs) can provide an overall estimate of the genetic propensity to a trait at the individual level by computing the sum of the effects of risk alleles, where each risk allele estimates the phenotype from an independent GWAS. PRS can account for a significant proportion of phenotypic variance (Crouch & Bodmer, 2020). Recently, a human host–microbiome GWAS was performed in the Flemish Gut Flora Project (n = 2223) and two German cohorts [Food-Chain Plus (FoCus), n = 950; PopGen, n = 717] and showed an association between human host genotype and gut microbiome variation using fecal 16S ribosomal RNA gene sequences (Hughes et al., 2020). Cole, Florez, and Hirschhorn (2020) performed GWAS with multiple complementary phenotyping approaches to examine dietary habits, including 85 single food intake and 85 principal component-derived dietary patterns (PC-DPs) according to food frequency questionnaires (FFQ) in UK Biobank. Similarly, another GWAS conducted by Meddens et al. (2020) identified several genetic associations involving relative intake from the macronutrients fat, protein, carbohydrates, and sugar in over 235 000 individuals of European ancestries. These previous studies enable us to explore the correlations for PRS of gut microbiome, PRS of dietary habit, and their interactions with mental traits. PRS has been used in the present depression study to identify traits whose genetic architecture is shared with major depression (Shen et al., 2020).

In this study, we calculated the PRS of gut microbiome and dietary habits in the UK Biobank cohort firstly and then constructed linear/logistic regression interaction analysis models. Our findings may help to understand the role of diet–gut microbiome interactions in the development of depression and anxiety.

Materials and methods

Ethical approval

UKB has ethical approval derived from Northwest Multi-Center Research Ethics Committee (reference 11/NW/0382).

UK Biobank cohort and definition of depression and anxiety

The genotype data from 488 377 participants were obtained from the UK Biobank under UKB application 46478 (http://www.ukbiobank.ac.uk/about-biobank-uk/). The UK Biobank project is a large-scale prospective cohort study with deep genetic and health information from half a million UK participants since 2006, aged between 40 and 69 at recruitment (Bycroft et al., 2018). We have excluded the non-European subjects of UK Biobank in this study. The genotype data of the UK Biobank was restricted to only 'white British' based on self-reported ethnicity (UK Biobank field ID: 21000) in this study. Genotyping was performed using two similar genotyping arrays (UK BiLEVE Axiom Array and UK Biobank Axiom Array). Quality control (QC), imputation, and post-imputation cleaning were performed centrally by the UK Biobank. The genetically related subjects were excluded using the KING software (Manichaikul et al., 2010). Details regarding the UK Biobank's genotyping, QC, and imputation are provided in online Supplementary material 1 and can be found in the published study (Bycroft et al., 2018).

Two common psychiatric disorders were analyzed in this study, including depression [based on self-reported depression and the Patient Health Questionnaire (PHQ-9) scores] and anxiety [based on self-reported anxiety and the Generalized Anxiety Disorder-7 (GAD-7) scores]. For depression, the present study included 119 637 participants (66 703 females, 56.24 ± 7.61 years) having PHQ-9 data, and 121 191 participants (58 043 self-reported depression patients and 63 148 controls, 56.47 ± 7.65 years) having self-reported depression status data. For anxiety, this study consisted 120 202 participants (67 010 females, 56.23 ± 7.61 years) having the GAD-7 data, and 107 947 participants (21 713 self-reported anxiety patients and 86 234 controls, 56.49 ± 7.57 years) having self-reported anxiety status data. Self-reported depression and anxiety were defined as binary variables (the case group and the control group), and the PHQ and GAD scores were defined as continuous variables. Criteria for the diagnoses of anxiety and depression were derived from the definition of Davis et al. (2019), which was based on PHQ-9, GAD-7 (Kroenke, Spitzer, Williams, & Löwe, 2010), and the World Health Organization Composite International Diagnostic Interview Short Form (CIDI-SF) (Kessler, Andrews, Mroczek, Ustun, & Wittchen, 1998; Kroenke et al., 2010). The detailed definition and criteria of selected participants from the dataset are provided in online Supplementary material 1.

GWAS summary data of gut microbiome

The gut microbiome-associated SNPs were derived from a recently published GWAS (Hughes et al., 2020). Hughes et al. (2020) performed 16S ribosomal RNA sequencing in fecal samples to explore the associations between host genetic variations and gut microbiome. Three independent studies were used in this study, including an expanded release of the FGFP cohort (n = 2223) and two German cohorts [FoCus (n = 950) and the PopGen cohort (n = 717)]. Microbial taxa were described as relative abundance profiles using rank normal transformed (RNT) model, while those with zero-inflated abundance distributions were described using a HB model. In total, 1056 LD-independent lead SNPs significantly associated with microbial traits were identified and used to calculate the PRSs of gut microbiome in this study. A detailed description of sample characteristics, array design, QC, and statistical analysis can be found in the previous study (Hughes et al., 2020).

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Table 1. The basic characteristics of study samples

	Depression		Anxiety	
	PHQ score	Depression status	GAD score	Anxiety status
Participants	119 637	121 191	120 202	107 947
Case	–	58 043	–	21 713
Control	–	63 148	–	86 234
Females, *n* (%)	66 703 (55.75)	68 067 (56.17)	67 010 (55.75)	59 243 (54.88)
Age (years): mean (s.d.)	56.24 (7.61)	56.47 (7.65)	56.23 (7.61)	56.49 (7.57)

PHQ, Patient Health Questionnaire; GAD, Generalized Anxiety Disorder.

GWAS summary data of dietary habits

Our dietary habits associated SNPs were derived from two recently published GWAS (Cole et al., 2020; Meddens et al., 2020). Cole et al. (2020) performed GWAS to examine a wide array of dietary habits, including 85 single food intake, analyzed as single food intake quantitative traits (FI-QTs), and 85 PC-DPs from FFQ in the UK Biobank. PCs were derived from all 85 FI-QTs using PCA. PC-DPs could capture correlation structure among intake of single foods and represent independent components of real-world dietary habits using FFQ data. For example, PC1 is primarily defined by the type of bread consumed, and positive loadings include wholemeal/wholegrain bread, fruit, vegetable, oily fish, and water intake; negative loadings include white bread, butter and oil spread, processed meat and milk with full cream consumption, which can explain 8.63% of the total phenotypic variance in FI-QTs. For details of significantly single FI-QTs for each PC, please see Table S7 of online Supplementary material 2. GWAS identified 814 LD-independent significant loci (defined as >500 kb apart) for 143 heritable dietary habits. Similarly, the GWAS of four dietary composition phenotypes conducted by Meddens et al. (2020) were used in our study, including relative intake from fat, protein, carbohydrates, and sugar in over 235 000 European-ancestry individuals. In total, 235 391 individuals were included in sugar phenotype, while 268 922 individuals in fat, protein, and carbohydrate phenotypes. There were 6, 7, 10, and 13 LD-independent lead SNPs significantly associated with fat, protein, sugar, and carbohydrate. We selected the LD-independent lead SNPs identified in the two GWASs for calculating the PRSs of dietary habit in this study. The detailed information of phenotype derivation, heritability, GWAS, and genetic correlation analyses was described in the previous studies (Cole et al., 2020; Meddens et al., 2020).

PRS and statistical analysis

We calculated gut microbiome PRS and dietary habit PRS using GWAS data of gut microbiome and dietary habits as discovery sample and genotype data of UK Biobank cohort as target sample. PRS analysis was performed using the PLINK's '–score' command. For gut microbiome PRS, PRS_g denotes the PRS value of gut microbiota for the gth subject, defined as $PRS_g = \sum_i \beta_i SNP_{ig}$, β_i is the effect parameter of risk allele of the ith significant SNP related to each microbial trait, which is obtained from the published study (Hughes et al., 2020). SNP_{ig} is the dosage (0, 1, 2, 0 is coded for homozygous protective genotype, 1 for heterozygous and 2 for homozygous polymorphic genotypes) of the risk allele of the ith SNP for the gth subject. PRS of dietary habits were calculated in the same way. The diet–gut microbiota interactions were defined as gut microbiota PRS × dietary habits PRS. Logistic regression model was applied for evaluating the effects of gut microbiome, dietary habits, and their interactions on depression status and anxiety status. Linear regression model was used to research the effects of gut microbiome, dietary habits, and their interactions on PHQ and GAD scores. The analyses were conducted by R software. Gut microbiome PRS, dietary habits PRS, gut microbiome PRS × dietary habits PRS were selected as independent variables; PHQ score and depression status, GAD score and anxiety status were fitted as dependent variables; sex, age, 10 principle components of population structure, smoking, alcohol use, and Townsend deprivation index were used as covariates. Adding the top 10 principal components (PC1–10) of population structures as covariates in the logistic/linear regression moles can help to control the potential impact of ethnic background on our study results (Lotta et al., 2019; Luo, Au Yeung, Zhao, Burgess, & Schooling, 2019). Principal components were calculated by UK Biobank from genome-wide genotype data, and could represent the ethnic backgrounds of individuals. We set p value<0.05 for statistical significance.

Results

Basic characteristics of study samples

The basic characteristics of study subjects and detailed information are presented in Table 1.

Association analysis of depression

We found a series of interactions of gut microbiome-PRS and dietary habits-PRS that showed associations with depression PHQ score in linear regression model and self-reported depression status in logistic regression model, respectively (Table S1 of online Supplementary material 2). After integrating the two results, 51 common interactions were shared by both PHQ score and self-reported depression status, such as overall beef intake × genus *Sporobacter* (HB) ($P_{\text{PHQ score}} = 7.88 \times 10^{-4}$, $P_{\text{depression status}} = 5.86 \times 10^{-4}$); carbohydrate × genus *Lactococcus* (HB) ($P_{\text{PHQ score}} = 0.0295$, $P_{\text{depression status}} = 0.0150$); cups of tea per day × class *Gammaproteobacteria* (RNT) ($P_{\text{PHQ score}} = 9.46 \times 10^{-3}$, $P_{\text{depression status}} = 0.0121$); pieces of fresh fruit per day × family *Veillonellaceae* (HB) ($P_{\text{PHQ score}} = 3.51 \times 10^{-3}$, $P_{\text{depression status}} = 6.84 \times 10^{-4}$). Top 10 significant common interactions were presented in Table 2 and all results were presented in Table S2 of online Supplementary material 2.

Association analysis of anxiety

For anxiety, we detected a series of interactions of gut microbiome-PRS and dietary habits-PRS that showed associations

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Table 2. Top 10 significant common gut microbiome–dietary habits interactions for depression PHQ score and status

	PHQ score			Depression status		
Interaction	$B_{PHQ\ score}$	$S.E._{PHQ\ score}$	$P_{PHQ\ score}$	$B_{depression\ status}$	$S.E._{depression\ status}$	$P_{depression\ status}$
Overall beef intake × G_Sporobacter_HB	-9.54×10^{-3}	2.84×10^{-3}	7.88×10^{-4}	−0.0206	5.98×10^{-3}	5.86×10^{-4}
Never eat wheat *v.* no eggs, dairy, wheat, or sugar restrictions × F_Ruminococcaceae_RNT	8.89×10^{-3}	2.84×10^{-3}	1.76×10^{-3}	0.0170	6.00×10^{-3}	4.41×10^{-3}
PC7 × F_Sutterellaceae_RNT	8.44×10^{-3}	2.83×10^{-3}	2.88×10^{-3}	0.0146	5.93×10^{-3}	0.0137
PC13 × G_Ruminococcus_RNT	8.46×10^{-3}	2.85×10^{-3}	3.00×10^{-3}	0.0172	6.02×10^{-3}	4.21×10^{-3}
Pieces of fresh fruit per day × F_Veillonellaceae_HB	-8.26×10^{-3}	2.83×10^{-3}	3.51×10^{-3}	−0.0203	5.97×10^{-3}	6.84×10^{-4}
PC40 × G_Ruminococcus_RNT	-8.17×10^{-3}	2.84×10^{-3}	4.06×10^{-3}	−0.0146	5.93×10^{-3}	0.0141
PC31 × F_Veillonellaceae_HB	-7.75×10^{-3}	2.83×10^{-3}	6.22×10^{-3}	−0.0155	5.98×10^{-3}	9.73×10^{-3}
PC58 × G_Escherichia_Shigella_RNT	-7.55×10^{-3}	2.82×10^{-3}	7.33×10^{-3}	−0.0125	6.14×10^{-3}	0.0414
PC2 × G_Gemmiger_HB	-7.55×10^{-3}	2.84×10^{-3}	7.84×10^{-3}	−0.0119	5.97×10^{-3}	0.0465
Cups of tea per day × C_Gammaproteobacteria_RNT	-7.43×10^{-3}	2.86×10^{-3}	9.46×10^{-3}	−0.0151	6.02×10^{-3}	0.0121

PHQ, Patient Health Questionnaire; B, β value; S.E., standard error value. For details of significantly single FI-QTs for each PC, please see Table S7 of online Supplementary material 2.

with GAD score in linear regression model and self-reported anxiety status in logistic regression model, respectively (Table S3 of online Supplementary material 2). After integrating the two results, 41 common interactions were shared by both GAD score and self-reported anxiety status, such as sugar × genus *Parasutterella* (RNT) ($P_{GAD\ score} = 5.15 \times 10^{-3}$, $P_{anxiety\ status} = 0.0347$); tablespoons of raw vegetables per day × family *Coriobacteriaceae* (HB) ($P_{GAD\ score} = 6.02 \times 10^{-4}$, $P_{anxiety\ status} = 0.0345$); never eat wheat *v.* no wheat restrictions × family *Enterobacteriaceae* (HB) ($P_{GAD\ score} = 3.47 \times 10^{-3}$, $P_{anxiety\ status} = 0.0477$). Top 10 significant interactions were presented in Table 3 and all significant results were shown in Table S4 of online Supplementary material 2.

The common interactions of depression and anxiety

In addition, we discovered several common significant interactions shared by depression and anxiety. A total of 67 and 56 common interactions of gut microbiome-PRS and dietary habit-PRS were found to be significantly associated with PHQ and GAD score, as well as depression and anxiety status, respectively. For example, overall beef intake × genus *Sporobacter* (HB) ($P_{PHQ\ score} = 7.88 \times 10_{-4}$, $P_{GAD\ score} = 0.0358$, $P_{depression\ status} = 5.86 \times 10^{-4}$, $P_{anxiety\ status} = 0.0320$), PC40 × genus *Ruminococcus* (RNT) ($P_{PHQ\ score} = 4.06 \times 10^{-3}$, $P_{GAD\ score} = 1.56 \times 10^{-3}$, $P_{depression\ status} = 0.0141$, $P_{anxiety\ status} = 0.0479$) were found to be significantly associated with both PHQ/depression status and GAD/anxiety status. Top 10 significant common interactions were presented in Table 4 and Fig. 1, and all significant results were shown in Table S5 of online Supplementary material 2.

Discussion

Previous studies demonstrated that the composition of the gut microbiome and dietary patterns had potential associations with depression and anxiety (Dharmayani et al., 2021; Fatahi et al., 2021; Knudsen et al., 2021; Simpson et al., 2021). Diet plays an important role in the composition of microbiome, which in turn may affect host immune and metabolism, and has broad implications for mental health (Singh et al., 2017). However, the influence of gut microbiome, diet, and their interactions on depression/anxiety is poorly understood. In the present study, the latest GWASs of gut microbiome and dietary habits were used to calculate gut microbiome-PRS and dietary habits-PRS in UK Biobank samples. We found multiple significant diet–gut microbiome interactions associated with depression/anxiety using linear/logistic regression models. Our study contributes to better understanding how to comprehensively consider gut microbiome and diet habit as a new approach to prevent psychological disorders.

For depression, several common candidate interactions of gut microbiome-PRS and dietary habit-PRS were detected in both PHQ score and self-reported depression status, such as overall beef intake × genus *Sporobacter* (HB); carbohydrate × genus *Lactococcus* (HB). Overall beef intake × genus *Sporobacter* (HB) is the most significant interaction of gut microbiome and dietary habit for depression. Red meat category, defined as the sum of red meats (beef, lamb), and organ meats (beef liver, kidney, and heart, ruminant meat), is recognized to be positively related to the prevalence of depressive symptoms (Darooghegi Mofrad, Mozaffari, Sheikhi, Zamani, & Azadbakht, 2021; Li et al., 2017). In particular, high intake of red and processed meat is one of the characteristics of the typical Western dietary pattern, red and processed meats are rich in saturated fats and its high consumption may be associated with pro-inflammatory states (Norde, Collese, Giovannucci, & Rogero, 2021). Significantly lower abundance of *Sporobacter* genus was reported in patients with immune-mediated inflammatory diseases, such as Crohn's disease, ulcerative colitis, and multiple sclerosis (Forbes et al., 2018). In a clinical case of successful fecal microbiota transplantation (FMT) treatment for antibiotic-induced, non-*Clostridium difficile* infection colitis, an assembly of post-FMT bacterial species may restore normal gastrointestinal function by attenuating the mild, on-going inflammation, *Sporobacter termitidis* was one of them (Satokari et al., 2014). Although the function of the

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Table 3. Top 10 significant common gut microbiome–dietary habits interactions for anxiety GAD score and status

	GAD score			Anxiety status		
Interaction	$B_{GAD\ score}$	$S.E._{GAD\ score}$	$P_{GAD\ score}$	$B_{anxiety\ status}$	$S.E._{anxiety\ status}$	$P_{anxiety\ status}$
PC8 × C_Deltaproteobacteria_RNT	−0.0124	2.88×10^{-3}	1.70×10^{-5}	−0.0192	7.81×10^{-3}	0.0139
Tablespoons of raw vegetables per day × G_unclassified_F_Coriobacteriaceae_HB	-9.83×10^{-3}	2.87×10^{-3}	6.02×10^{-4}	−0.0162	7.64×10^{-3}	0.0345
PC40 × G_Ruminococcus_RNT	-9.09×10^{-3}	2.87×10^{-3}	1.56×10^{-3}	−0.0151	7.64×10^{-3}	0.0479
PC7 × G_Eisenbergiella_RNT	-8.85×10^{-3}	2.88×10^{-3}	2.12×10^{-3}	−0.0186	7.76×10^{-3}	0.0168
Never eat wheat *v.* no wheat restrictions × F_Enterobacteriaceae_HB	-8.39×10^{-3}	2.87×10^{-3}	3.47×10^{-3}	−0.0153	7.75×10^{-3}	0.0477
PC4 × G_Lactococcus_RNT	8.31×10^{-3}	2.88×10^{-3}	3.91×10^{-3}	0.0185	7.71×10^{-3}	0.0163
Spread type: any oil-based spread *v.* never × O_Selenomonadales_RNT	-8.16×10^{-3}	2.89×10^{-3}	4.78×10^{-3}	−0.0258	8.02×10^{-3}	1.31×10^{-3}
Sugar × G_Parasutterella_RNT	-8.07×10^{-3}	2.88×10^{-3}	5.15×10^{-3}	−0.0164	7.76×10^{-3}	0.0347
PC52 × F_Ruminococcaceae_RNT	7.87×10^{-3}	2.85×10^{-3}	5.81×10^{-3}	0.0163	7.77×10^{-3}	0.0360
PC11 × C_Actinobacteria_RNT	-7.56×10^{-3}	2.86×10^{-3}	8.35×10^{-3}	−0.0160	7.67×10^{-3}	0.0372

GAD, Generalized Anxiety Disorder; B, β value; S.E., standard error value. For details of significantly single FI-QTs for each PC, please see Table S7 of online Supplementary material 2.

Table 4. Top 10 significant common gut microbiome–dietary habits interactions for anxiety and depression

	PHQ score		Depression status	
Interaction	$P_{PHQ\ score}$	$P_{GAD\ score}$	$P_{depression\ status}$	$P_{anxiety\ status}$
Cereal type: muesli *v.* any other × F_Ruminococcaceae_RNT	9.10×10^{-5}	0.0396	–	–
Overall non-oily fish intake × F_Sutterellaceae_HB	7.38×10^{-4}	0.0330	–	–
Overall beef intake × G_Sporobacter_HB	7.88×10^{-4}	0.0358	5.86×10^{-4}	0.0320
PC31 × O_Lactobacillales_RNT	1.03×10^{-3}	0.0345	–	–
PC4 × G_Akkermansia_HB	1.65×10^{-3}	0.0110	–	–
PC44 × G_Faecalitalea_HB	–	–	9.03×10^{-4}	0.0138
Carbohydrate × G_unclassified_P_Firmicutes_RNT	–	–	1.04×10^{-3}	0.0033
Sugar × G_unclassified_P_Firmicutes_RNT	–	–	1.38×10^{-3}	0.0073
Cups of tea per day × G_unclassified_F_Ruminococcaceae_RNT	–	–	1.67×10^{-3}	0.0190
PC4 × G_Lactococcus_RNT	–	–	1.80×10^{-3}	0.0163

PHQ, Patient Health Questionnaire; GAD, Generalized Anxiety Disorder. For details of significantly single FI-QTs for each PC, please see Table S7 of online Supplementary material 2.

Sporobacter genus is not well known, *Sporobacter* seems to have anti-inflammatory effects. Inflammatory response may play an important role in the pathogenesis of depression (Miller & Raison, 2016). Although the specific mechanisms of the link between gut microbiota, diet, and depression characteristics need further clarification, our results suggested that *Sporobacter* may be associated with beef intake and linked to the lower symptoms of depression. *Sporobacter* may serve as a target of dietary modification for treatment of depression.

Our results also showed that the association of *Lactococcus* and carbohydrate linked to the higher symptoms of depression. Recent studies have suggested that high carbohydrate consumption is associated with increased circulating inflammatory markers (Karimi et al., 2021). Mice fed with carbohydrate-enriched diet showed higher levels of obesity, which may also facilitate the development of depressive-like behaviors after the stress (Santos et al., 2018). In contrast, a low carbohydrate diet, defined as a diet with lower intakes of carbohydrates and higher intakes of proteins and fats, suggests a protective long-term effect on psychological health in adults with obesity and type 2 diabetes (Kakoschke et al., 2021). A typical ketogenic diet consists of ~225 g fats and 75 g proteins, with no more than 25 g of carbohydrates per day in an individual with an uptake of ~2300 cal/day. It may be an option for MDD treatment due to its strong relationship with increased γ-aminobutyric acid (GABA)/glutamate ratio (Włodarczyk, Cubała, & Stawicki, 2021). *Lactococcus* is one of the strains of probiotics, which is widely used as starter bacterial species in dairy fermentations. *Lactococcus lactis* can synthesize GABA from dietary glutamate and can be used for the manufacture of functional GABA-enriched foods (Redruello et al., 2021).

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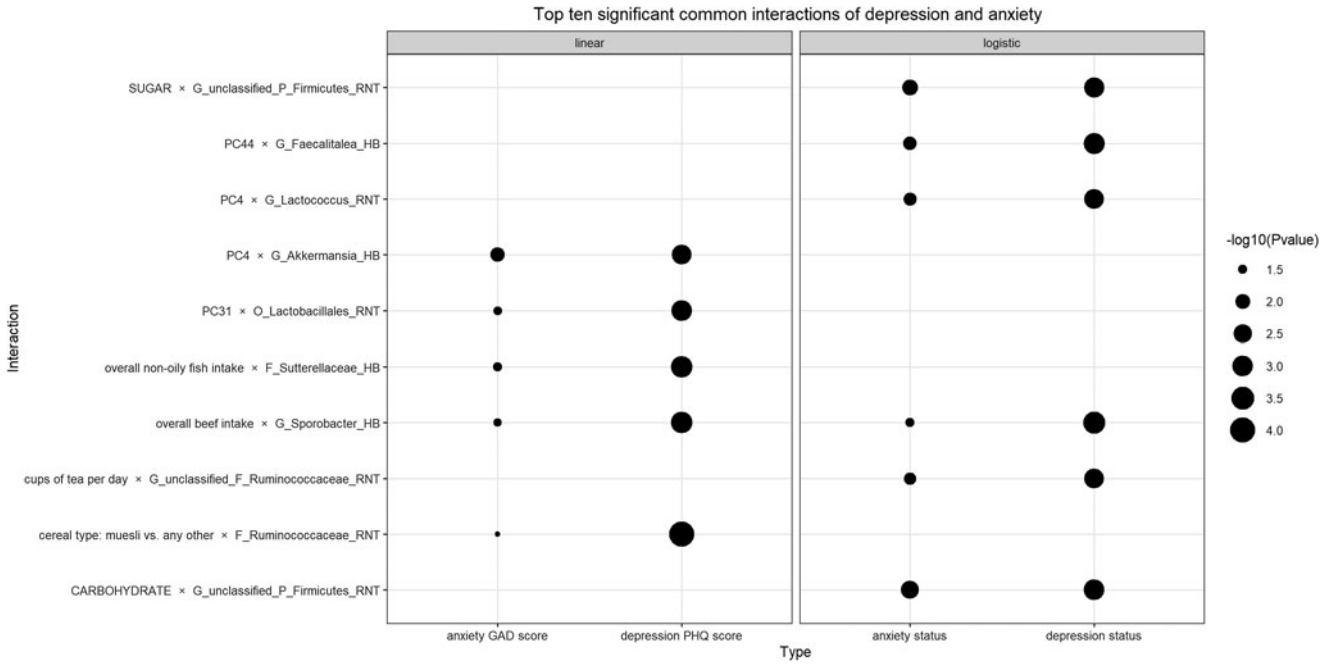

Fig. 1. Top 10 significant common gut microbiome–dietary habits interactions for depression and anxiety. Bubble chart represents top 10 significant common gut microbiome–dietary habits interactions for depression and anxiety in linear regression model and logistic regression model, respectively. Circle size indicates the −log10 *p* value of each interaction. All the specific *p* values of interactions illustrated here can be found in Table 4 and Table S5 of online Supplementary material 2. For details of significantly single FI-QTs for each PC, please see Table S7 of online Supplementary material 2.

GABA is one of the inhibitory neurotransmitters robustly associated with neurological disorders, which exhibits anti-stress effects in humans and helps to improve depressive symptoms (Duman, Sanacora, & Krystal, 2019). The imbalance of GABA metabolism may play a role in the pathogenesis of depression (Averina et al., 2020). *Lactococcus lactis* is beneficial to cognitive reactivity to sad mood and prevention of depression in a placebo-controlled randomized study (Steenbergen, Sellaro, van Hemert, Bosch, & Colzato, 2015). The very low carbohydrate ketogenic diet incorporating probiotics may help to maintain proper gut health and better prevent neurological diseases (Paoli et al., 2019).

We also detected other common candidate interactions of gut microbiome-PRS and dietary habit-PRS for depression, such as cups of tea per day × class *Gammaproteobacteria* (RNT); pieces of fresh fruit per day × family *Veillonellaceae* (HB). Previous study supported the protective effects of tea consumption on the risk and severity of depression (Dong et al., 2015). The protective effect of tea may be mediated by a number of compounds, such as L-theanine, polyphenols, and polyphenol metabolites (Rothenberg & Zhang, 2019). Tea can change the type and quantity of gut microbiome, and enable gut microbiota to metabolize polyphenols and yield bioactive compounds (Bond & Derbyshire, 2019). Tea polyphenols can form complexes with the membranes of certain harmful bacteria, such as *Escherichia coli* (based on 16S rRNA sequencing, genus *Escherichia* belongs to the class *Gammaproteobacteria*), thereby destroying the membrane and suppressing the growth and proliferation of potentially pathogenic bacterial species (Xing, Zhang, Qi, Tsao, & Mine, 2019). Class *Gammaproteobacteria* was found to be enriched in the participants with MDD (Liu et al., 2020). Gram-negative *Gammaproteobacteria* is known to produce potent forms of lipopolysaccharide (LPS), which is an inflammatory endotoxin that stimulates the immune response through the release of pro-inflammatory cytokines and activates low-grade systemic inflammation (d'Hennezel, Abubucker, Murphy, & Cullen, 2017). The patients with depression have higher expression of pro-inflammatory cytokines and their receptors, increased levels of acute-phase proteins and their immune system is more active (Miller & Raison, 2016). And depressed patients have been found to have increased serum concentrations of IgM and IgA against the LPS of members of this class (Maes, Kubera, Leunis, & Berk, 2012). Previous evidence supported that greater consumption of fresh fruit, as an important factor within the Mediterranean diet, was inversely associated with the risk of depression, and even was postulated to improve depressive symptoms (Gibson-Smith et al., 2020). Lower abundance of family *Veillonellaceae* was found in the individuals with depression relative to healthy controls (Barandouzi, Starkweather, Henderson, Gyamfi, & Cong, 2020). Overall, in the present study, cups of tea per day × class *Gammaproteobacteria* (RNT) and pieces of fresh fruit per day × family *Veillonellaceae* (HB) showed negative associations with the risk and severity of depression.

For anxiety, our results identified multiple common candidate interactions of gut microbiome-PRS and dietary habit-PRS in both GAD score and self-reported anxiety status, such as sugar × genus *Parasutterella* (RNT). Sugar content in diet was reported to be correlated with anxiety. Rats fed a high fructose diet showed increased anxiety-like and depressive-like behaviors in their adulthood (Hu, Cheng, & Jiang, 2019; Peris-Sampedro et al., 2019). Another study reported that although a diet rich in fat and sugar can meliorate the increased anxiety-like behaviors in rodents induced by early life stress exposure, it also has significant adverse effects on hippocampal genes associated with mood regulation, neurogenesis, and brain development (Maniam, Antoniadis, Le, & Morris, 2016). Diet that is high in sugars affects the gut microbiome. *Parasutterella* was elevated in rodents fed an

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added-sugar diet during the juvenile and adolescent stages (Noble et al., 2017). Anxiety is more common in people with obesity (Amiri & Behnezhad, 2019). The relative abundance of *Parasutterella* was lower in high-fat diet (HFD)-induced obesity mice than in normal chow feeding mice (Zhang et al., 2012). *Parasutterella* is a symbiotic gut microbe, which may actively participate in bile acid metabolism and enhance the deamination and chain shortening procedure of tryptophan metabolism in the gut (Ju, Kong, Stothard, & Willing, 2019). Tryptophan is the precursor of 5-hydroxytryptamine (serotonin), which is involved in the physiological regulation of several behavioral and neuroendocrine functions (Höglund, Øverli, & Winberg, 2019). *Parasutterella* may play a beneficial role in the intestinal mucosal homeostasis (Ju et al., 2019). In this study, we found that sugar × genus *Parasutterella* (RNT) might be associated with lower anxiety symptom severity and anxiety status. More studies are needed to explore the relationship.

We also detected other common candidate interactions of gut microbiome-PRS and dietary habit-PRS for anxiety, such as tablespoons of raw vegetables per day × family *Coriobacteriaceae* (HB); never eat wheat *v.* no wheat restrictions × family *Enterobacteriaceae* (HB). As a typical healthy diet, non-refined grains and vegetables were inversely associated with depression and anxiety severity (Gibson-Smith et al., 2020). *Coriobacteriaceae* has previously been decreased in patients with inflammatory bowel diseases (Pittayanon et al., 2020). Kale is one of the cruciferous vegetables. *Coriobacteriaceae* has previously been shown to decrease when the high-density lipoprotein (HDL)/non-HDL increased in a hamster model (Martínez et al., 2009). Supplementing a HFD with kale could induce an increased family *Coriobacteriaceae* and prevent HFD-induced inflammation in adipose tissue (Shahinozzaman, Raychaudhuri, Fan, & Obanda, 2021). Participants with anxiety were reported to have a higher abundance of *Enterobacteriaceae*, which was associated with gastrointestinal inflammation and may also deteriorate anxiety through microbiota–gut–brain axis (Jang, Lee, Lee, & Kim, 2018; Simpson et al., 2021). Interventional studies suggested that whole-grain consumption could reduce pro-inflammatory *Enterobacteriaceae* and have modest positive effects on short-chain fatty acid (SCFA), effector memory T cells, and the acute innate immune response (Vanegas et al., 2017). SCFA, such as acetate, butyrate, and propionate, primarily derived from microbial fermentation of carbohydrates, are important immunomodulatory and anti-inflammatory molecules in the intestine that show promising effects against symptoms of depression and anxiety in mice (Bergman, 1990; van de Wouw et al., 2018). The current study results showed that the association of raw vegetables and family *Coriobacteriaceae*, wheat and family *Enterobacteriaceae* that would result in lower symptoms of anxiety.

Consideration of shared interactions in depression and anxiety is essential due to the high rates of comorbidity. In this study, we also identified multiple common significant interactions of gut microbiome and dietary habits overlapped in depression and anxiety. For example, overall beef intake × genus *Sporobacter* (HB) and PC40 × genus *Ruminococcus* (RNT) were found to be significantly negatively associated with both PHQ/depression status and GAD/anxiety status. PC40 is primarily defined by overall beef and pork intake. Beef consumption has the most significant positive loadings for PC40. As prior described, beef, as one of the red meat category, is rich in saturated fats and its high consumption may be associated with pro-inflammatory states, and is also recognized to be positively related to depressive symptoms (Darooghegi Mofrad et al., 2021; Norde et al., 2021). *Sporobacter* seems to have anti-inflammatory effects and might be associated with immune-mediated inflammatory diseases, such as Crohn's disease, ulcerative colitis, and multiple sclerosis (Forbes et al., 2018). Inflammatory response and immune system activation appear to play an important role in the brain function and pathogenesis of depression and anxiety (Peirce & Alviña, 2019). *Ruminococcus* can ferment anaerobes that lead to the production of SCFAs, which are known to be mediators in the microbiota–gut–brain axis crosstalk (Crost et al., 2013; Dalile, Van Oudenhove, Vervliet, & Verbeke, 2019). *Ruminococcus* was also reported to be decreased in chronic restraint stress-treated rodents and positively correlated with dopamine metabolism (Yang et al., 2021).

There are several strengths and limitations in the present study. We leveraged the latest GWAS data of gut microbiome and dietary habits and genotype data of the UK Biobank cohort, the results of which improved power for the detection of significant interactions. Interestingly, this approach found a number of novel interactions of gut microbiome and dietary habits associated with depression and anxiety. In addition, we found some common significant interactions of gut microbiome and dietary habits shared by both depression and anxiety. Although we found significant associations between gut microbiome–dietary habits interactions and the risk of depression/anxiety, further experimental studies were needed to explore and confirm the underlying molecular biological mechanisms. Our results could have been affected by a possible confounding bias because of the impact of various factors in mental disorders, such as early adversity and comorbid illness. Our results may not be generalized across ethnic groups since the GWASs and genotype data of UK Biobank in this study were from European ancestry.

To conclude, linear/logistic regression modules were constructed in this study to systematically explore the interactions of gut microbiome-PRS and dietary habits-PRS on depression/anxiety. Our findings revealed that different diet compositions could be one of the critical modifiable factors in regulating the gut microbiota and gut microbiome–dietary habits interactions could provide new insights for the prevention of depression and anxiety disorders.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291721005092

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Ethical standards. There is no ethical statement.

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