

Genome-wide environmental interaction analysis identifies dietary habit related risk loci for depression and intelligence in UK Biobank

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Research

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Abstract

Background

Dietary habits have considerable impact on brain development and mental health. Our aim is to explore the possible association of dietary habits with depression and intelligence.

Methods

A total of 814 independent loci from a genome-wide association study (GWAS) of dietary habits were utilized to calculate the individual polygenic risk score (PRS) for 143 dietary habits related traits. The individual genotype data were obtained from UK Biobank cohort. Regression analyses were then conducted to evaluate the possible association of dietary habits with depression (including 153,549 subjects) and intelligence (including 160,121 subjects), respectively. Using dietary habits related PRSs as covariates, PLINK 2.0 was utilized to detect the SNP × dietary habit interaction effect on the risks of depression and intelligence, respectively.

Results

We detected 32 and 41 candidate dietary habits related traits for depression and intelligence, respectively, such as never eat sugar vs. no sugar restrictions ($P = 1.09 \times 10^{-2}$) for depression, and coffee type: decaffeinated vs. any other ($P = 8.77 \times 10^{-3}$) for intelligence. We also detected 22 common dietary habits related traits shared by depression and intelligence, such as red wine glasses per month ($P_{\text{depression}} = 8.75 \times 10^{-3}$, $P_{\text{intelligence}} = 3.35 \times 10^{-19}$), and overall alcohol intake ($P_{\text{depression}} = 3.60 \times 10^{-2}$, $P_{\text{intelligence}} = 8.31 \times 10^{-8}$). Interaction analysis of depression detected OLFM1 with 9 significant SNPs interacted with champagne/white wine glasses per month. Interaction analysis of intelligence detected SYNPO2 with 3 significant SNPs interacted with coffee type: decaffeinated vs. any other.

Conclusions

Our study results provide novel useful information for understanding how eating habits affecting the intelligence and the risk of depression.

Background

Depression is one of the most common and debilitating mental disorders that severely restricts psychosocial functioning and reduces life quality [1]. The lifetime prevalence of major depression around the world is between 1.0% and 16.9% [2]. Fluid intelligence describes the capacity to solve problems that require logic and reasoning ability independent of acquired knowledge [3]. The affecting factors of

depression and fluid intelligence are related to environmental and genetic factors. Several risk factors have been proposed to explain the mechanisms of depression, such as substance abuse disorders and poor physical health [4–6]. Some investigators have confirmed that the intelligence level was influenced by brain size, neural efficiency and genetic factors [7, 8]. The risk factors of depression and fluid intelligence may be overlapped. For instance, depression symptom has been demonstrated to have significant negative genetic correlation with fluid intelligence [9, 10]. Researchers found that low fluid intelligence at a given age predicted higher depressive symptoms across the following 3-year interval [11]. In contrast, higher fluid intelligence in childhood predicted lower depression risk in adults [12].

Dietary habits have considerable impact on brain development and mental health [13]. Recently, an increasing number of studies provided evidence for dietary habits as a kind of modifiable affecting factors for mental traits. For example, a study examined the association between intelligence and dietary habits at preschool children, and suggested that poor food choices at preschool age characterized by foods with high fat, salt and sugar were associated with reduced scores in verbal and cognitive ability [14]. Velten et al. found that high consumption of alcohol could contribute to a deficient nutritional intake, which might lead to mental disorders [15]. There was a clear genetic component to diet demonstrated by significant heritability and individual genetic associations [16]. However, the relevance between detailed dietary habits and depression and intelligence remains unclear now.

To date, genome-wide association study (GWAS) has succeeded in revealing causal loci that contribute to the risk of psychiatric traits, such as anorexia nervosa and depression [17]. Nevertheless, GWAS result shows that the effect sizes of individual causal loci are relatively small. To solve this dilemma, researchers proposed the polygenic risk score (PRS), a score reflecting the sum of all known risk loci [18]. PRS is an individual-level score calculated based on the number of risk variants, and weighted by SNP effect sizes derived from an independent large-scaled discovery GWAS [18]. The effect sizes of multiple SNPs are combined into a single polymerized score that can be used to predict the risks of human diseases [19]. PRS has contributed to the genetic architecture of psychiatric traits by its ability to predict disease status [20].

Complex human diseases were considered to involve the interaction between environmental and lifestyle factors, as well as inherited susceptibility [21]. The genome-wide environmental interaction (GWEI) study aims to describe the interactions between genetic and environmental factors and the effects on human diseases [21]. The risk of psychosis increased with the accumulation of many genetic risk variants and the exposure of multiple adverse environmental factors. Additionally, the impact of environmental exposure likely depends on individual susceptibility, influenced by gene-environment interactions [22]. The great performance of GWEI makes it widely used in many brain related researches. For example, the GWEI analysis of early life stress supported the risk of depression outcomes [23]. Caroline et al. suggested that genetic variations in FKBP5, CRH, or CRHR1 and SLE genes possibly moderate the effects of stressful life event in depression [24].

In this study, UK Biobank data were utilized to calculate individual PRSs for 143 dietary habits related traits. The linear regression and logistic regression of PLINK 2.0 were used to analyze the correlation between each dietary habit related PRS with intelligence (including 160,121 participants) and depression (including 153,549 participants), respectively. Using the calculated dietary habit related PRSs as covariates, GWEI analyses were performed to explore the effects of gene-dietary habits interactions on the development of depression and intelligence, respectively.

Methods

Definition of depression and intelligence in UK Biobank samples

The summary statistics from UK Biobank cohort was used in this study [25]. The UK Biobank including approximately 500,000 candidates from UK, aged between 40 and 69 years, who have had whole-genome genotyping undertaken and have allowed the linkage of these data with their patient records [25]. Briefly, the patient health questionnaire (PHQ-9) and composite international diagnostic interview short-form (CIDI-SF) were used to define the comprehensive and accurate dataset of depression [26, 27]. The case group of depression was selected based on depression phenotype, which was defined according to the code 1286 from ID 20002, code 3, 4 or 5 from ID 20126 and code 11 from ID 20544. The control group of depression was selected with PHQ score ≤ 5 , excluding participants with core symptoms of depression (ID 20446 and 20441), and the case group defined in our study and depression single episode defined in Davis et al. research [28]. After removing the participants without the calculated dietary habit related PRS, 153,549 participants of depression were included for association analysis (Table 1).

Table 1
Descriptive characteristics for intelligence and depression participants

	Intelligence	Depression
Participants	160,121	153,549 (case = 74,579)
Sex (female)	86,818 (54.22%)	87,265 (56.83%)
Age (years)	56.70 \pm 8.15	56.12 \pm 7.78
Note: Age is described as Mean \pm standard deviation; Sex is described as N (%).		

The data field 20016 of fluid intelligence score has four UK Biobank categories including cognitive function (100026), cognitive function summary (1005), fluid intelligence/reasoning (100027), and UK Biobank assessment centre (100000). Fluid intelligence phenotype was defined using fluid intelligence measurement, a simple unweighted sum of the number of correct answers given to the 13 fluid intelligence questions (Resource 100231). Participants who failed to answer all of the questions within the two minutes limit were scored as zero for each of the unattempted questions

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participants were classified from 0 to 13. After removing the participants without the calculated dietary habit related PRS, 160,121 participants of intelligence were included for association analysis (Table 1).

Genotyping, imputation and quality control in UK Biobank

Genotyping, imputation and quality control (QC) for 487,409 individuals were performed by the UK Biobank group [25]. Briefly, the UK BiLEVE Axiom array and UK Biobank Axiom array which share over 95% of their marker content were used for genotyping. IMPUTE4 was used for imputation in chunks of about 50,000 imputed markers with a 250 kb buffer region. Marker-based QC was performed using statistical tests designed primarily to check for consistency of genotype calling across experimental factors. Sample-based QC was performed using the metrics of missing rate, heterozygosity, and a set of 15,766 high quality markers on the X and Y chromosomes [25]. More information about genotyping, imputation, QC and physical measurements has been described previously [25].

GWAS summary data of dietary habits

A recent large-scale GWAS data of dietary habits was used here [29]. Briefly, the phenotype derivation and genomic analysis were conducted on a homogenous population of 455,146 participants of European ancestry. BOLT-Imm software (v.2.3.2) was used to obtain the measures of heritability [30]. The estimated relatedness matrix was utilized to explain the pseudo-heritability measurement representing the fraction of phenotypic variance. In GWAS, linear mixed model association was conducted by BOLT-Imm software (v.2.3.2) to account for relatedness in all variables [30, 31]. Additional covariates included in BOLT-Imm analysis for both heritability and GWAS included genotyping array and the first 10 genetic principal components (PC) derived on the subset of unrelated individuals using FlashPCA2, followed by projection of related individuals on to the PC space [32]. LDstore v1.157 was used to calculate linkage disequilibrium (LD) and identify SNPs in high LD ($r^2 \geq 0.80$) with any of the 77,229 95% credible set SNPs [33]. PC analysis were conducted of the single food intake quantitative traits (FI-QTs) to generate 85 PC-dietary patterns (DPs) that capture correlation structure among intake of single foods. The linear mixed models of GWAS were conducted on the 143 significantly heritable dietary habits in up to 449,210 participants. In total, 814 LD independent loci were identified surpassing genome wide significance ($P < 5.0 \times 10^{-8}$). The detailed information of phenotype derivation, heritability, GWAS, and genetic correlation analyses is described elsewhere [29].

Dietary habit related PRS calculation and association analysis

According to the standard approach, PLINK 2.0 was used to calculate dietary habits related PRS of each study subject using individual genotype data of UK Biobank. (<http://www.cog-genomics.org/plink/2.0/>) [34]. Briefly, we set PRS_n denotes the PRS value of dietary habits for the n th subject, defined as:

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

where l denotes the total number of dietary habit associated SNPs; E_j denotes the effect size of significant dietary habits associated SNP i ; D_{in} 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). R software (<https://www.r-project.org/>) was used to establish linear and logistic regression model to evaluate the possible associations between each dietary habit PRS and target traits of intelligence and depression. The PRSs of dietary habits were set as instrumental variables, while age and sex were set as covariates.

Genome-wide environmental interaction (GWEI) study

The command 'glm' of PLINK 2.0 was used to analyze the interaction between SNPs and the PRS of significant dietary habits for depression and intelligence, setting PRSs as covariates (<http://www.cog-genomics.org/plink/2.0/>) [34]. For quality control, we removed the SNPs with call rates < 90%, Hardy-Weinberg equilibrium (HWE) < 0.001, or minor allele frequencies (MAF) < 0.01. The kinship coefficients were estimated by KING software (<http://people.virginia.edu/~wc9c/KING/>) to remove the genetically related subjects [25]. Rectangular Manhattan plot and QQ plot were produced using the "CMplot" package (<https://github.com/YinLiLin/R-CMplot>) in R platform. Locus zoom plots were generated using the LocusZoom web interface tool (<http://locuszoom.sph.umich.edu/>) [35].

Results

Associations of dietary habits with depression and intelligence

We detected 32 candidate dietary habits associated with depression in UK Biobank, such as champagne/white wine glasses per month ($P = 6.56 \times 10^{-4}$), total drinks of alcohol per month ($P = 6.86 \times 10^{-4}$), and never eat sugar vs. no sugar restrictions ($P = 1.09 \times 10^{-2}$) (Table 2). In addition, we detected 41 candidate dietary habits associated with intelligence, such as coffee type: decaffeinated vs. any other ($P = 8.77 \times 10^{-3}$), overall beef intake ($P = 2.33 \times 10^{-2}$), and overall cheese intake ($P = 1.20 \times 10^{-22}$) (Table 3).

Table 2
The dietary habits associated with depression

Dietary habits	OR	P
Cereal type: cornflakes/frosties vs. any other	0.96	5.66×10^{-12}
Among current drinkers, drinks usually with meals: yes vs. no	0.97	4.24×10^{-7}
Coffee type: decaffeinated vs. any other	0.98	1.78×10^{-6}
Bread type: white vs. any other	0.98	1.82×10^{-6}
Never eat wheat vs. no wheat restrictions	0.98	7.40×10^{-6}
Overall cheese intake	0.98	1.70×10^{-5}
Frequency of adding salt to food	1.02	1.79×10^{-4}
Among current drinkers. Drinks usually with meals: yes vs. no	1.02	3.45×10^{-4}
Among current drinkers, drinks usually with meals: yes, it varies, no	0.98	3.57×10^{-4}
Cups of tea per day	1.02	5.07×10^{-4}
Champagne/white wine glasses per month	0.98	6.56×10^{-4}
Total drinks of alcohol per month	0.98	6.86×10^{-4}
Bowls of cereal per week	0.98	8.66×10^{-4}
Bread type: white vs. wholemeal/wholegrain + brown	1.02	1.42×10^{-3}
Tablespoons of vegetables per day	0.99	3.94×10^{-3}
Bread type: wholemeal/wholegrain vs. white + brown	0.99	4.88×10^{-3}
Slices of bread per week	0.99	6.76×10^{-3}
Among current drinkers, drinks usually with meals: yes + it varies vs. no	0.99	7.41×10^{-3}
Overall oily fish intake	0.99	8.04×10^{-3}
Red wine glasses per month	0.99	8.75×10^{-3}
Milk type: soy milk vs. never	0.99	8.76×10^{-3}
Never eat sugar vs. no sugar restrictions	1.01	1.09×10^{-2}
Never eat wheat vs. no eggs, dairy, wheat, or sugar restrictions	0.99	1.14×10^{-2}

Dietary habits	OR	P
Overall non-oily fish intake	0.99	1.17×10^{-2}
Milk type: skimmed vs. never	0.99	1.66×10^{-2}
Cereal type: muesli vs. any other	1.01	2.83×10^{-2}
Tablespoons of cooked vegetables per day	1.01	2.87×10^{-2}
Overall alcohol intake	0.99	3.60×10^{-2}
Alcohol drinker status: current + former vs. never	0.99	4.15×10^{-2}
Slices of bread per week	0.99	4.21×10^{-2}
Overall poultry intake	0.99	4.41×10^{-2}
Cereal type: muesli vs. any other	0.99	4.87×10^{-2}

Table 3
The dietary habits associated with intelligence

Dietary habits	Beta	P
Bread type: white vs. any other	0.03	1.30×10^{-32}
Bread type: whole grain/whole meal vs. white bread	0.02	3.13×10^{-23}
Overall cheese intake	0.02	1.20×10^{-22}
Red wine glasses per month	0.02	3.35×10^{-19}
Among current drinkers. drinks usually with meals: yes vs. no	-0.02	1.21×10^{-13}
Cereal type: cornflakes/frosties vs. any other	0.01	8.36×10^{-10}
Overall alcohol intake	0.01	8.31×10^{-8}
Champagne/white wine glasses per month	0.01	1.07×10^{-6}
Temperature of hot drinks	-0.01	1.18×10^{-6}
Among current drinkers, drinks usually with meals: yes vs. no	0.01	2.85×10^{-6}
Never eat sugar vs. no sugar restrictions	0.01	6.91×10^{-6}
Bread type: wholemeal/wholegrain vs. any other	0.01	9.75×10^{-6}
Overall non-oily fish intake	0.01	1.24×10^{-5}
Bread type: wholemeal/wholegrain vs. white + brown	0.01	1.51×10^{-5}
Spread type: flora + benecol vs. never	0.01	4.50×10^{-5}
Overall oily fish intake	-0.01	7.96×10^{-5}
Spread type: tub margarine vs. never	-0.01	1.96×10^{-4}
Never eat wheat vs. no wheat restrictions	0.01	3.43×10^{-4}
Spread type: butter and butter-like spreads vs. oil-based spreads	0.01	3.99×10^{-4}
Never eat sugar vs. no sugar restrictions	-0.01	5.99×10^{-4}
Spread type: butter and margarine spreads vs. oil-based spreads	-0.01	7.58×10^{-4}
Bowls of cereal per week	0.01	8.10×10^{-4}
Cups of tea per day	-0.01	1.43×10^{-3}

Dietary habits	Beta	P
Tablespoons of vegetables per day	0.01	3.54×10^{-3}
Cereal type: comflakes/frosties vs. any other	0.01	5.97×10^{-3}
Spread type: low fat spread vs. never	-0.01	5.97×10^{-3}
Beer/cider glasses per month	-0.01	7.68×10^{-3}
Cereal type: biscuit cereal vs. any other	0.01	8.49×10^{-3}
Coffee type: decaffeinated vs. any other	0.01	8.77×10^{-3}
Never eat wheat vs. no eggs, dairy, wheat, or sugar restrictions	0.01	9.77×10^{-3}
Among current drinkers, drinks usually with meals: yes, it varies, no	0.01	1.09×10^{-2}
Bread type: white vs. any other	-0.01	1.16×10^{-2}
Pieces of dried fruit per day	0.01	1.49×10^{-2}
Milk type: skimmed vs. never	0.01	1.53×10^{-2}
Overall non-oily fish intake	-0.01	1.63×10^{-2}
Slices of bread per week	0.01	1.98×10^{-2}
Alcohol drinker status: current + former vs. never	0.01	2.09×10^{-2}
Overall beef intake	-0.01	2.33×10^{-2}
Cups of tea per day	-0.01	2.33×10^{-2}
Total drinks of alcohol per month	0.01	2.92×10^{-2}
Overall lamb/mutton intake	0.01	3.07×10^{-2}

We further compared above association analysis results, and found 22 candidate dietary habits shared by depression and intelligence, such as red wine glasses per month ($P_{\text{depression}} = 8.75 \times 10^{-3}$, $P_{\text{intelligence}} = 3.35 \times 10^{-19}$), overall alcohol intake ($P_{\text{depression}} = 3.60 \times 10^{-2}$, $P_{\text{intelligence}} = 8.31 \times 10^{-8}$), and overall cheese intake ($P_{\text{depression}} = 1.70 \times 10^{-5}$, $P_{\text{intelligence}} = 1.20 \times 10^{-22}$).

Interaction analysis of dietary habits with depression and intelligence

For depression, we detected 9 significant SNPs interacted with champagne/white wine glasses per month, such as rs7869470 ($P= 1.54 \times 10^{-8}$), rs34379422 ($P= 2.39 \times 10^{-8}$) and rs796938996 ($P= 6.33 \times 10^{-9}$) (Fig. 1.A and B). The nearest gene of the 9 SNPs was OLFM1 gene (Fig. 1.C). The analysis results ($P < 5.00 \times 10^{-8}$) of depression are detailed in Table 4.

Table 4
The significant SNPs interacted with champagne/white wine glasses per month for depression

SNP	ALT	A1	Beta	SE	P
rs7869470	A	G	0.062	0.011	1.54×10^{-8}
rs34379422	C	T	0.061	0.011	2.39×10^{-8}
rs796938996	G	GCG	0.067	0.011	6.33×10^{-9}
rs17493408	A	G	0.061	0.011	3.13×10^{-8}
rs11103643	T	C	0.060	0.011	4.94×10^{-8}
rs113597793	C	T	0.060	0.011	4.92×10^{-8}
rs7036368	A	C	0.061	0.011	3.87×10^{-8}
rs7049100	G	A	0.060	0.011	4.58×10^{-8}
rs7040385	T	A	0.060	0.011	4.43×10^{-8}
Note: ALT = alternate alleles; A1 = tested allele; SE = standard error; P = P-value.					

For intelligence, we detected 3 significant SNPs interacted with coffee type: decaffeinated vs. any other, including rs6846781 ($P= 4.22 \times 10^{-8}$), rs7690236 ($P= 3.28 \times 10^{-8}$) and rs28378450 ($P= 3.29 \times 10^{-8}$) (Fig. 2.A and B). The 3 SNPs located at SYNPO2 gene (Fig. 2.C). The analysis results ($P < 5.00 \times 10^{-8}$) of intelligence are summarized in Table 5.

Table 5
The significant SNPs interacted with coffee type: decaffeinated vs. any other for intelligence

SNP	ALT	A1	Beta	SE	P
rs6846781	T	T	0.051721	0.009435	4.22×10^{-8}
rs7690236	T	T	0.052089	0.009425	3.27×10^{-8}
rs28378450	A	A	0.052049	0.009419	3.29×10^{-8}
Note: ALT = alternate alleles; A1 = tested allele; SE = standard error; P = P-value.					

Discussion

In this study, a recent large-scale GWAS data was utilized to obtain 814 loci associated with dietary habits. The UK Biobank data were used to conduct PRS analysis for each individual of depression and intelligence, respectively. The GWEI analyses were performed to detect significant SNP × dietary habit interaction effects on depression and intelligence, respectively. Our study observed associations of dietary habit with depression and intelligence, and detected several candidate loci that interacted with dietary habits for depression and intelligence.

Multiple common dietary habits associated with depression and intelligence were observed in this study, such as overall alcohol intake and red wine glasses per month. Alcohol consumption has highly negative effects that contribute to the symptoms in many neuropsychiatric disorders [36]. Churchill et al. suggested that alcohol consumption might induce depression, and consistently related to several measures of drinking behavior, including alcohol consumption intensity, alcohol dependence and risk of dependence [37]. Interestingly, evidence about the relationship between intelligence and alcohol intake were complicated, with researchers reported evidence of a positive relationship [38] and a negative relationship [39]. Laust et al. assessed the association between intelligence and preferred beverage type in young Danish men, and found that high intelligence was associated with the preference for wine [40]. While the considerable associations of alcohol intake with depression and intelligence were reported, the causal relationships and biological mechanisms remain elusive now.

Never eat sugar vs. no sugar restrictions was detected to be associated with depression. Higher sugar consumption was linked to higher depression prevalence in several ecological and cross-sectional studies [41, 42]. Likewise, a western diet rich in sugar and fat might increase the risk of depression [43]. A recent meta-analysis also indicated that the consumption of sugar-sweetened beverages might associate with a modestly higher risk of depression [44]. Knüppel et al. performed a random effects regression to repeated measures, and suggested that high long-term consumption of carbohydrates has adverse effects on psychological health, even led to higher rate of depression [42]. In six countries, a highly significant correlation was detected between sugar consumption and the annual rate of depression [45]. The above studies strongly support our result that sugar consumption may closely relate to the risk of depression.

Interaction analysis of depression indicated that OLFM1 (olfactomedin 1) had interaction effects with champagne/white wine glasses per month. OLFM1 is a glycoprotein highly expressed in human brain, and may have an essential role in nerve tissue [46]. Nakaya et al. confirmed that OLFM1 participated in neural progenitor maintenance and cell death in brain [47]. OLFM1 was also demonstrated to be related to amyotrophic lateral sclerosis due to its regulation of motor cortex and spinal cord [48]. Our result suggests that OLFM1 gene expression may be involved in the mechanism between champagne/white wine and depression. Additionally, several suggestively significant SNP-dietary interactions were observed in depression GWEI, such as interaction between rs117916244 (PTPRJ) and total drinks of alcohol per month, and interaction between rs62169868 (KYNU) and red wine glasses per month. The regulation of

the ephrin-Eph-c-Abl axis by PTPRJ plays a vital role in the proper central projection of retinal axons during development [49]. Wigner et al. confirmed that venlafaxine modulated the expression and methylation level of KYNU in brain when rats exposed to the chronic mild stress model of depression [50]. The SNP-dietary interactions suggest that PTPRJ and KYNU may play a role in alcohol-induced depression.

Caffeine was detected for intelligence in this study. The cognitive enhancing properties of caffeine were facilitated by its indirect effects on mood and attention [51]. A memory and intelligence test supported that intelligence was declined by small dose of caffeine, while associative reproduction of idea was improved by caffeine [52]. Corley et al. collected intelligence quotient data from 923 healthy participants at age 11 and assessed their cognitive function at age 70, and found that higher cognitive scores were associated with caffeine consumption [53]. Likewise, Rees et al. assessed the influence of age on the effects of caffeine on a variety of psychomotor and cognitive tests, and observed that the psychomotor performance and cognitive function in participants were improved after caffeine consumption [54]. A recent systematic review highlighted the benefit of caffeine on memory, crystallized intelligence, physical and occupational performance [55]. In genetic perspective, our research may suggest an effect of caffeine intake on intelligence.

Our interaction analysis of intelligence highlighted SYNPO2 (synaptopodin-2) was a significant gene interacted with dietary habit-coffee type: decaffeinated vs. any other. SYNPO2 is mainly expressed in human brain tissue and has been demonstrated to associate with several mental disorders [56]. For example, Zhang et al. observed that SYNPO2 was one of the differentially expressed genes in schizophrenia [57]. The GWASdb SNP-Phenotype association dataset showed that SYNPO2 was associated with the schizophrenia phenotype in GWAS datasets [58]. SYNPO2 was demonstrated to closely associate with cognitive development in mice brain [59]. Chronic variable stress in mice induced significantly down-regulation of SYNPO2 which was necessary for synaptic plasticity, learning and memory [59]. Although there is less evidence to link caffeine consumption to SYNPO2 expression change, our result suggests that caffeine may influence the intelligence by affecting the expression of SYNPO2 in human brain.

Notably, there are also two limitations in this study. Although the dietary habits and GWEI reported in this study are significantly related to depression and intelligence, and consistent with some previous evidences, further experimental studies are needed to explore and confirm the underlying molecular biological mechanisms. In addition, the GWAS and dietary habits data in this study were obtained from European ancestry, which should be careful to apply on other race.

Conclusions

Taken together, we performed the PRS and GWEI analysis to evaluate the associations between dietary habits and depression and intelligence utilizing UK Biobank data. Our results provide useful information of how our eating habits causally relate to the risk of depression and intelligence. Genetically

investigation of the cause-and-effect relationship between dietary habits and brain healthy could have enormous public health implications.

Abbreviations

GWAS: genome-wide association study; PRS:polygenic risk score; GWEI:genome-wide environmental interaction; PHQ:the patient health questionnaire; CIDI-SF:composite international diagnostic interview short-form; QC:quality control; PC:principal components; LD:linkage disequilibrium; FI-QTs:food intake quantitative traits; DPs:dietary patterns; HWE:Hardy-Weinberg equilibrium; MAF:minor allele frequencies.

Declarations

Ethics approval and consent to participate

The study does contain human participants. The consent was obtained by the UK Biobank.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

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FZ and BC designed and planned the study. BC, JY, SC and LL selected the phenotype of depression and intelligence. BC and XC analyzed the UK Biobank data. YW and YJ processed GWAS summary data of dietary habits. BC, CL, and YY performed polygenic risk score (PRS) calculation. FZ and BC performed the genome-wide environmental interaction (GWEI) analysis. All authors read and approved the final manuscript.

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Not applicable.

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Figures

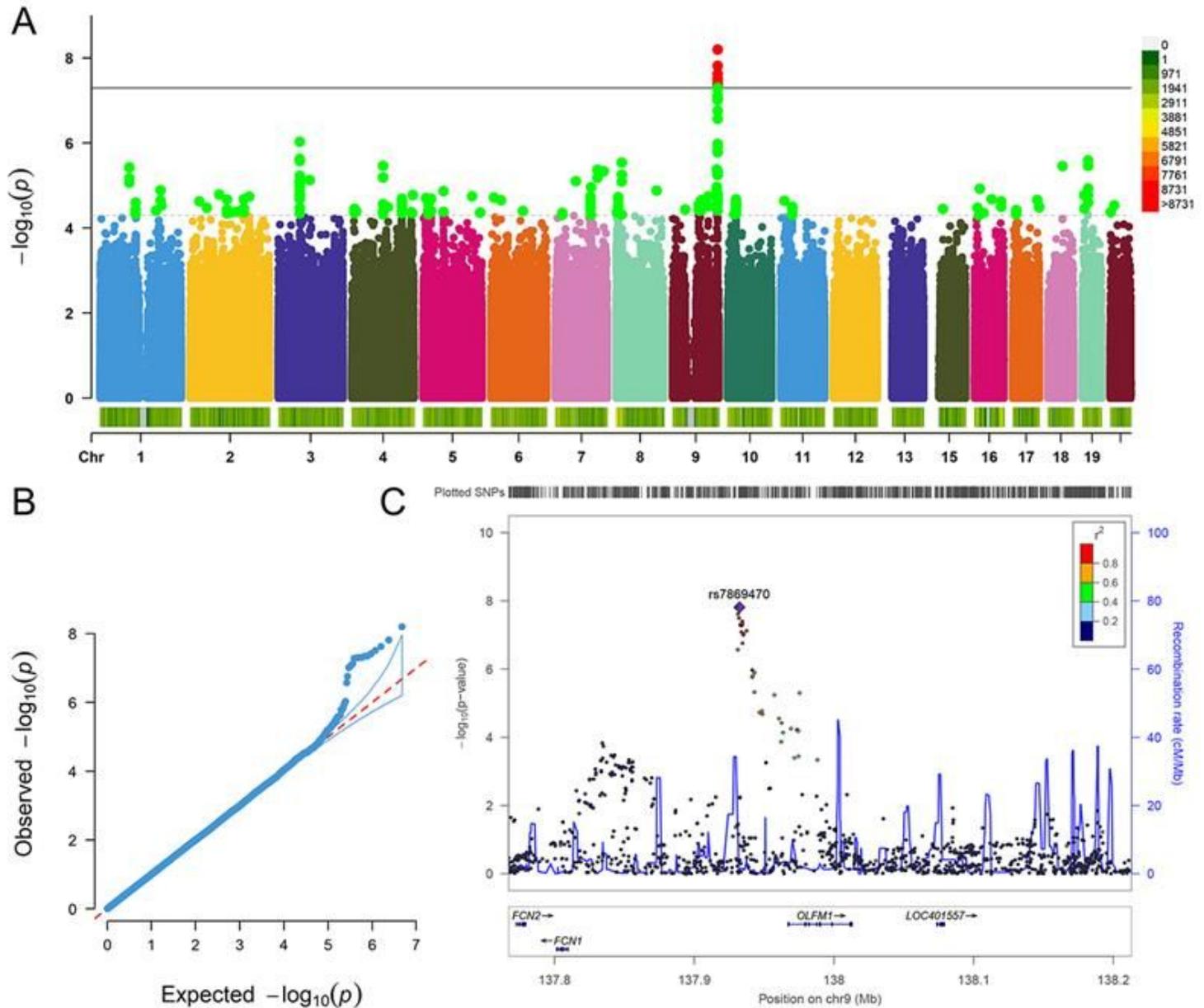


Figure 1

Genome-wide environmental interaction study in champagne/white wine glasses per month of depression A) Manhattan plot. The black solid line indicates the P value threshold for genome-wide significance ($P < 5 \times 10^{-8}$) while the black dotted line indicates P value threshold for suggestive significance ($P < 5 \times 10^{-5}$). B) QQ plot. A graphical representation of the deviation of the observed P values from the null hypothesis: the observed P values for each SNP are sorted from largest to smallest and plotted against expected values from a theoretical χ^2 -distribution. C) Locus Zoom plot for gene OLFM1. Association results for SNPs as a function of genomic distance for OLFM1. The display range is chr9: 137767088–138213030. Purple diamond indicates SNP at the locus with the strongest association evidence (*rs7869470*). Each point represents a SNP.

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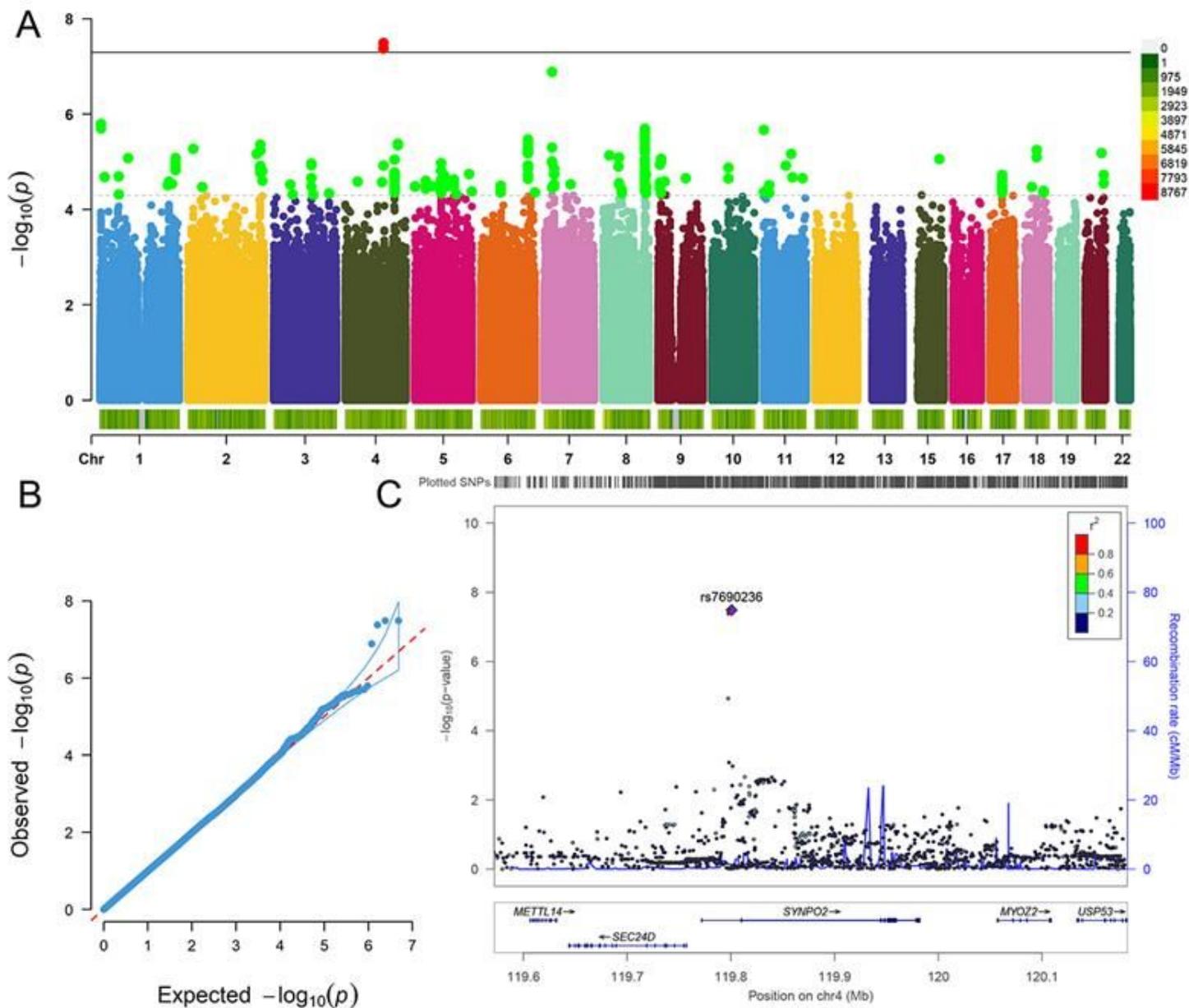


Figure 2

Genome-wide environmental interaction study in coffee type: decaffeinated vs. any other of intelligence

A) Manhattan plot. The black solid line indicates the P value threshold for genome-wide significance ($P < 5 \times 10^{-8}$) while the black dotted line indicates P value threshold for suggestive significance ($P < 5 \times 10^{-5}$). B) QQ plot. A graphical representation of the deviation of the observed P values from the null hypothesis: the observed P values for each SNP are sorted from largest to smallest and plotted against expected values from a theoretical χ^2 -distribution. C) Locus Zoom plot for gene SYNPO2. Association results for SNPs as a function of genomic distance for SYNPO2. The display range is chr4: 119571842–120182402. Purple diamond indicates SNP at the locus with the strongest association evidence (rs7690236). Each point represents a SNP.