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Assessing the interaction effects of brain structure longitudinal changes and life environmental factors on depression and anxiety

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Abstract

Disrupted brain structures and several life environmental factors have been shown to influence depression and anxiety, but their interactions with anxiety and depression remain elusive. Genome-wide association study datasets of 15 brain structure longitudinal changes ($N = 15{,}640$) were obtained from the published study. Genotype and phenotype-related data of depression, anxiety, and life environmental factors (including smoking, alcohol drinking, coffee intake, maternal smoking, physical activity, vitamin D, insomnia, sleep duration, and family satisfaction) were collected from UK Biobank. We calculated the polygenic risk scores (PRS) of 15 brain structure changes and then conducted linear regression analyses to explore the interactions of brain structure changes and life environmental factors on depression and anxiety using 15 brain structure change-related PRS, life environmental factors and interactions of them as instrumental variables, and depression score or anxiety score as outcomes. Sex stratification in all analyses was performed to reveal sex-specific differences in the interactions. We found 14 shared interactions related to both depression and anxiety in total sample, such as alcohol drinking × cerebellum white matter 3 (WM; beta = −.003, $p = .018$ for depression; beta = −003, $p = .008$ for anxiety) and maternal smoking × nucleus accumbens 2 (beta = .088, $p = .002$ for depression; beta = .070, $p = .008$ for anxiety). We also observed sex-specific differences in the interactions, for instance, alcohol drinking × cerebellum WM 3 was negatively associated with depression and anxiety in males (beta = −.004, $p = .020$ for depression;

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beta = −.005, p = .002 for anxiety). Our study results reveal the important interactions between brain structure changes and several life environmental factors on depression and anxiety, which may help to explore the pathogenesis of depression and anxiety.

KEYWORDS
anxiety, brain structure changes, depression, interaction, life environmental factor

1 | INTRODUCTION

Depression and anxiety account for a large part of the growing global burden of mental disorders in modern society. Depression is characterized by lack of pleasure, fatigue, worthlessness and even suicidal thoughts, and self-harm (Maurer et al., 2018). Anxiety refers to a series of mental disorders ranging from generalized anxiety disorder to phobia-related diseases, which may be mediated by the norepinephrine, serotonin, dopamine, and γ-aminobutyric acid in the central nervous system and sympathetic nervous system (Ströhle et al., 2018). According to the latest report of the World Health Organization, it is estimated that 322 million people (4.4% of the world population) suffer from depression, and more than 260 million people (3.6% of the global population) are affected by anxiety disorders (World Health Organization, 2017). Moreover, these two disorders are highly comorbid and are correlated with aggravated psychopathology and serious obstacles in daily life, which can cause huge social and economic burden and mental health problems (Johansson et al., 2013).

The etiology and pathogenesis of the two disorders are complicated and may be determined by genetic and lifestyle factors (Sund et al., 2021). The heritability of depression and anxiety is roughly 31%–42% and 20%–60%, respectively (Ask et al., 2021; Sullivan et al., 2000). In addition, numerous life environmental factors were reported to be associated with depression and anxiety. For example, smoking (Byeon, 2015), alcohol drinking (Bahorik et al., 2016), and insomnia (Li et al., 2016) may induce the development of depression and anxiety, while high family satisfaction (Novak et al., 2020), physical activity (Philippot et al., 2022), and vitamin D (VD; Casseb et al., 2019) could play beneficial roles in both disorders. Concretely, individuals with smoking are more likely to suffer from depression and anxiety than those with nonsmoking or quit smoking (Baiardini et al., 2014; Byeon, 2015). Study exhibited that continuous alcohol drinking can aggravate the symptoms of anxiety and depression, while reducing alcohol drinking can improve these symptoms (Bahorik et al., 2016). In addition, researchers found that increased family satisfaction was significantly correlated with decreased depression in both male and female, and reduced anxiety in female (Novak et al., 2020). The frequency of physical activity was inversely related to depressive and anxiety symptoms in both sexes (McMahon et al., 2017). VD deficiency was reported to be closely correlated with increased risk for depression and anxiety, and VD supplementation may have potential protection effects on mental health (Casseb et al., 2019). Interestingly, these life environmental factors were also demonstrated to exert important roles in brain structure and function. Ever smoked and smoking duration were correlated with smaller gray matter volume (GMV; Gray et al., 2020). Heavy drinking can lead to brain injury, and neurological impairment related to working memory and cognitive processing of emotional signals (Cargiulo, 2007). The brain imaging showed that the volume of various neurologic structures in people with chronic alcohol dependence was smaller than that in nonalcoholic subjects (Cargiulo, 2007). Moreover, a study showed that hippocampal volume and memory performance were better in athletic subjects than that in age-matched but sedentary individuals (Chaddock et al., 2010). The deficiency of VD was exhibited to be associated with impairment of brain physiological function leading to adverse effects on anatomy and behavior (Anastasiou et al., 2014).

The human brain structure or function not only exists interindividual differences, but also changes in the whole life. The alterations of brain growth or decline rates are related to various mental illnesses and neurodegenerative diseases (Brouwer et al., 2022). The magnetic resonance imaging is widely used for depicting brain structure (Zhang et al., 2018). Based on the magnetic resonance imaging, depression and anxiety were reported to be associated with the disrupted brain structure. For example, researches of brain structure changes in depressed subjects have demonstrated that orbitofrontal cortex volume was significantly reduced in the population with depression than that in the controls (Ballmaier et al., 2004; Bremner et al., 2002). Study found that amygdala volume was negatively related to anxiety symptom (Hu et al., 2020). Collectively, previous studies mainly focused on the relationship of lifestyle or brain structure with depression and anxiety. There seems to be a lack on the interactive roles of brain structure change and life environmental factors in these two disorders.

Additionally, sex differences exist in the relationship between life environmental factors with depression / anxiety and brain structures. Females with a history of smoking had a higher risk of depression than males (Husky et al., 2008). Even women exhibited greater perceived risks from smoking cessation involving decreased concentration, greater negative effect, and the loss of enjoyment (McKee et al., 2005). Evidence indicated that higher frequency of comorbid depression and anxiety could be observed in alcohol-dependent females compared with males (Karpyak et al., 2019). Moreover, study reported sex differences in alterations of brain GMV in patients with depression. Male depression patients showed increased GMV in left cerebellum, and decreased GMV in bilateral middle temporal gyrus

and left ventromedial prefrontal cortex, while female patients exhibited reduced GMV in left lingual gyrus and dorsal medial prefrontal gyrus (Yang et al., 2017). Harrewijn and his colleagues found that anxious men had increased right ventral diencephalon volume compared with controls, whereas anxious women did not differ from healthy controls (Harrewijn et al., 2021).

Polygenic risk score (PRS) is a sum of phenotype-related risk alleles across numerous genetic loci, which is weighted by the risk allele effect sizes estimated by a genome-wide association study (GWAS; Euesden et al., 2015). The PRS analysis is capable of assessing the effects of susceptibility loci on risks of disease (Euesden et al., 2015). It has been widely applied to numerous complex diseases, such as Alzheimer disease (Escott-Price et al., 2017) and schizophrenia (Stauffer et al., 2021). The interactions between various life environmental factors and PRS of brain structure change rate on depression and anxiety need to be clarified.

Here, the GWAS summary statistics of brain structure change rate and UK Biobank data were employed to explore the influence of interactions between life environmental factors and PRS of brain structure change rate on the risk of depression and anxiety, which can provide novel dimension for the etiology research of depression and anxiety.

2 | MATERIALS AND METHODS

2.1 | UK Biobank cohort

The data used for this study was obtained from the UK Biobank cohort that is a large-scale population-based prospective cohort recruiting over half a million participants living across the United Kingdom aged from 40 to 69 years between 2006 and 2010 (Sudlow et al., 2015). The health-related information, baseline socioeconomic characteristics, and lifestyle of all individuals were collected via questionnaire, interview, and anthropometric measurements. Biological samples of subjects were collected and used for biochemical tests and genome-wide genotyping. All subjects signed their informed consent prior to participation. The present study was approved by the UK Biobank and obtained health-related information of 34,316–85,247 subjects including genotypic data and several phenotypes, such as depression, anxiety, and life environmental factors.

2.2 | UK Biobank genotyping, imputation, and quality control

The genotyping process, array design, and quality control were described in detail elsewhere (Bycroft et al., 2018). Briefly, totally 488,377 participants were genotyped through either the UK Bileve array or the UK Biobank axiom array. Then the genotyping data were imputed using Haplotype Reference Consortium reference panel (McCarthy et al., 2016) and a merged UK10K and 1000 Genomes Phase 3 reference panels (Bycroft et al., 2018). The processes of quality control included sample-based quality control and marker-based quality control. For instance, excluding single nucleotide polymorphisms (SNPs) with Hardy–Weinberg equilibrium < 0.001, minor allele frequencies <0.01; removing subjects who reported sex were inconsistent with genetic sex, who were genotyped but not imputed, who withdrew their consents and who were "non-white British" based on self-reported ethnicity (UK Biobank field ID: 21000). The genetically related subjects were also removed using KING in the UK Biobank study (Bycroft et al., 2018).

2.3 | Definitions of depression and anxiety in UK Biobank

The depression and anxiety were assessed based on the Patient Health Questionnaire (PHQ-9; Kroenke et al., 2001) and Generalized anxiety disorder-7 (GAD-7; Spitzer et al., 2006), respectively. In brief, PHQ-9 scale is a reliable tool for evaluating the severity of depressive disorder and has high sensitivity and specificity for identifying possible depression. It mostly includes nine symptoms and signs of depression, with a total depression score of 0–27 (Kroenke et al., 2001). GAD-7 scale is based on the DSM-IV diagnostic criteria, and it has been demonstrated to have good specificity and sensitivity for screening the possible anxiety disorders. It involves seven symptoms and signs of anxiety, with a total anxiety score of 0–21 (Spitzer et al., 2006). The detailed information could be obtained in Supplementary Material S1.

2.4 | Definitions of environmental factors in UK Biobank

The present study analyzed life environmental factors that may be associated with depression and anxiety including smoking, alcohol drinking, coffee intake, maternal smoking, physical activity, VD, insomnia, and sleep duration as well as family satisfaction. In short, the cigarettes (or pipes/cigars) consumed daily were used to define the frequency of smoking (UK Biobank field IDs: 20116, 2887, and 3456). The total consumption of different kinds of alcohol per week was taken as the frequency of alcohol drinking (UK Biobank field ID: 20117). Coffee intake (cups/day) was assessed by the UK Biobank field ID: 1498. Maternal smoking was evaluated by the UK Biobank field ID: 1787. Physical activity was evaluated with a revised version of International Physical Activity Questionnaire that captured the frequency (d/wk; UK Biobank field IDs: 864, 884, and 904) and duration (min/d; UK Biobank field IDs: 874, 894, and 914) of three intensity levels of physical activity including walking, moderate and vigorous exercise (Craig et al., 2003). Serum VD concentration (nmol/L) was measured by chemiluminescent immunoassay on a DiaSorin Ltd. LIASON XL (UK Biobank field ID: 30890). Sleep duration, insomnia, and family satisfaction were assessed by the UK Biobank field ID: 1160, 1200, and 4559, respectively. The detailed definitions of life environmental factors were exhibited in Supplementary Material S1.

2.5 | GWAS summary statistics of brain structure change rate

The brain structure change rate-related SNPs and their genetic effects were derived from a large-scale GWAS meta-analysis of brain structure change rate (Brouwer et al., 2022). Briefly, this study included a total of 15,640 subjects (from 40 longitudinal cohorts) aged 4–99 years who had the genotyping data from blood or saliva and longitudinal magnetic resonance imaging data of 15 brain structures (8 global brain measures and 7 subcortical structures). The annual rates of brain structure change were calculated by subtracting brain measures at baseline from follow-up measures and dividing by the time interval. The genotyping data were imputed using the 1000 Genomes project dataset by the Michigan Imputation Server or the Sanger Imputation Server. Variants with a minor allele frequency <0.05 or variants with imputation R^2/info score <.75 were excluded. Subsequently, under three models, authors used meta-analysis and meta-regression methods to estimate the age-independent effect (Model 1), linear age effects (Model 2), and quadratic age effects of genetic loci (Model 3), respectively. The detailed description of sample characteristics, genotyping, and quality control could be obtained from the recently published study (Brouwer et al., 2022).

2.6 | PRS analysis of brain structure change rate

Using the brain change rate-associated SNPs and their genetic effects from the published GWAS ($p < 1 \times 10^{-5}$; Brouwer et al., 2022), PRS analysis of brain change rate was performed by PLINK (Purcell et al., 2007) following the formula: $PRS_n = \sum_{i=1}^{I} E_i D_{in}$, PRS_n represents the PRS value of brain change rate for the nth UKB sample; I denotes the total number of brain change rate-associated SNPs; E_i refers to the genetic effect size of significant brain change rate-associated SNP i; D_{in} represents the dosage (0, 1, 2) of the risk allele of the ith SNP for the nth subject.

2.7 | Statistical analysis

Linear regression model was applied to evaluate the roles of interactions between life environmental factors and PRS of brain structure change rate on the risk of depression and anxiety. The PRS of brain structure change, life environmental factors, and interactions of them were set as instrumental variables. Depression score or anxiety score were set as outcomes. Age, sex, smoking, alcohol drinking, coffee intake, and 10 genetic principal components (PC) of population structure were used as covariates. Additionally, sex stratification was conducted in all analyses to reveal sex-specific differences in interactions using age, smoking, alcohol drinking, coffee intake, and 10 PC of population structure as covariates. Smoking or alcohol drinking or coffee intake variable was removed when assessing the interactions between the three behaviors and PRS of brain structure change rate. The significant interaction effects were measured by $p < .05$. All analyses were performed using R 4.0.3.

3 | RESULTS

3.1 | Descriptive characteristics of subjects

There were 34,316–85,247 subjects included in our study. For depression score, a total of 84,892 (45,917 females and 38,975 males) individuals had the self-reported data on smoking, alcohol drinking, and coffee intake, and the mean ± SD of age was 56.23 ± 7.58. For anxiety score, a total of 85,247 (46,107 females and 39,143 males) subjects had the self-reported information about smoking, alcohol drinking, and coffee intake, and the mean ± SD of age was 56.22 ± 7.58. The more detailed characteristics of subjects could be obtained from Table S1.

3.2 | Interactions between life environmental factors and brain structure changes for depression

We observed several interactions between brain structure change-related PRS and life environmental factors that were associated with depression. Briefly, in the total samples, totally 42 interactions between brain structure change and life environmental factors appeared to be correlated with depression, such as alcohol drinking × cerebellum white matter 2 (WM; beta = −.004, $p = .001$), smoking × cerebellum gray matter 1 (GM; beta = .003, $p = .022$), coffee intake × putamen 1 (beta = .015, $p = .018$), maternal smoking × cerebellum GM 1 (beta = −.066, $p = .016$), physical activity × cerebellum WM 2 (beta = .033, $p = .024$) and family satisfaction × putamen 3 (beta = .257, $p = .002$; Table 1; Table S2).

In the female, a total of 29 interactions between brain structure longitudinal changes and life environmental factors seemed to be associated with depression, for instance, alcohol drinking × cerebellum WM 2 (beta = −.010, $p = 5.52 \times 10^{-5}$), smoking × thalamus 3 (beta = −.005, $p = .008$), physical activity × nucleus accumbens 3 (beta = .068, $p = .004$) and VD × lateral ventricles 2 (beta = .002, $p = .021$) as well as family satisfaction × thalamus 2 (beta = .426, $p < .001$; Table 1 and Table S2).

Additionally, in the male, 46 interactions between brain structure longitudinal changes and life environmental factors were associated with depression, such as alcohol drinking × cerebellum WM 3 (beta = −.004, $p = .020$), coffee intake × caudate 2 (beta = −.023, $p = .004$), physical activity × cerebellum WM 2 (beta = .052, $p = .006$), VD × total brain 2 (beta = −.004, $p = 2.06 \times 10^{-5}$), sleep duration × surface area 3 (beta = .049, $p = .006$) and family satisfaction × total brain 1 (beta = .438, $p < .001$; Table 1 and Table S2).

3.3 | A comparison of the interactions of different environmental factors and brain structures change in depressed individuals

Moreover, common brain structure changes interacting with two or more life environmental factors were also identified (Table S3). In

TABLE 1 Interactions of brain structures and life environmental factors for depression meeting $p < .01$

	Lifestyle × brain structures	Beta	*p*
Total	Alcohol drinking × cerebellumWM 2	−.004	.001
Female	Alcohol drinking × cerebellum WM 2	−.010	5.52×10^{-5}
	Alcohol drinking × putamen 2	−.007	.005
Male	Alcohol drinking × surface area 1	.005	.003
Female	Smoking × thalamus 1	.006	.004
	Smoking × thalamus 3	−.005	.008
Male	Coffee intake × caudate 2	−.023	.004
Total	MS × nucleus accumbens 2	.088	.002
Total	PA × hippocampus 1	.038	.009
	PA × mean thickness 2	.043	.004
Female	PA × nucleus accumbens 3	.068	.004
Male	PA × cerebral WM 1	−.051	.008
	PA × hippocampus 1	.062	.001
	PA × putamen 1	.051	.007
	PA × cerebellum WM 2	.052	.006
Male	VD × total brain 2	−.004	2.06×10^{-5}
	VD × surface area 3	−.002	.007
Total	Sleep duration × Cortical GM 1	−.032	.009
	Sleep duration × mean thickness 2	−.038	.002
	Sleep duration × pallidum 2	.034	.005
Male	Sleep duration × surface area 3	.049	.006
Total	Family satisfaction × putamen 3	.257	.002
Female	Family satisfaction × amygdala 2	−.311	.007
	Family satisfaction × thalamus 2	.426	<.001
Male	Family satisfaction × cortical GM 1	.351	.002
	Family satisfaction × total brain 1	.438	<.001
	Family satisfaction × putamen 2	.306	.008
	Family satisfaction × putamen 3	.432	<.001

Note: 1, 2, and 3 separately denote the three models, of which Model 1 refers to the age-independent effect of genetic loci, Model 2 refers to linear age effects, and Model 3 refers to quadratic age effects.
Abbreviations: GM, gray matter; MS, maternal smoking; PA, physical activity; VD, vitamin D; WM, white matte.

brief, in the total population, we found that 10 common brain structure changes that can significantly interact with multiple life environmental factors, such as cerebellum WM interacting with alcohol drinking and physical activity (beta = −.004, p = .001 for alcohol drinking; beta = .033, p = .024 for physical activity), cerebellum GM interacting with smoking and maternal smoking (beta = .003, p = .022 for smoking; beta = −.066, P = .016 for maternal smoking).

In the female, 6 common brain structure changes that interacted with several life environmental factors, such as lateral ventricles interacting with smoking and VD (beta = −.004, p = .038 for smoking; beta = .002, p = .021 for VD), cortical GM interacting with alcohol drinking and VD (beta = −.005, p = .026 for alcohol drinking; beta = −.002, P = .021 for VD).

In the male, 11 common brain structure changes interacting with multiple life environmental factors. For example, putamen, caudate and surface area interacting with both coffee intake and physical activity (putamen: beta = .017, p = .038 for coffee intake; beta = .051, p = .007 for physical activity; caudate: beta = −.023, p = .004 for coffee intake; beta = .039, p = .044 for physical activity; surface area: beta = .018, p = .029 for coffee intake; beta = .049, p = .011 for physical activity).

3.4 | Interactions between life environmental factors and brain structure changes for anxiety

We also found numerous interactions between brain structure changes and life environmental factors that were associated with anxiety. In the total sample, a total of 33 interactions between brain structure changes and life environmental factors seemed to be related to anxiety, such as alcohol drinking × surface area 2 (beta = .003, p = .018), smoking × cerebellum GM 1 (beta = .003, p = .014), maternal smoking × nucleus accumbens 2 (beta = .070, p = .008), physical

TABLE 2 Interactions of brain structures and life environmental factors for anxiety meeting $p < .01$

	Lifestyle × brain structures	Beta	*p*
Total	Alcohol drinking × cerebellum WM 3	−.003	.008
Female	Alcohol drinking × putamen 3	.006	.007
Male	Alcohol drinking × surface area 1	.007	1.97×10^{-6}
	Alcohol drinking × surface area 2	.004	.003
	Alcohol drinking × cerebellum WM 3	−.005	.002
Male	Smoking × thalamus 3	.004	.008
Male	Coffee intake × cortical GM 1	.021	.005
	Coffee intake × mean thickness 1	.022	.004
	Coffee intake × putamen 1	.022	.002
	Coffee intake × surface area 2	.023	.002
Total	MS × nucleus accumbens 2	.070	.008
Male	PA × cerebral WM 1	−.055	.002
	PA × hippocampus 1	.046	.009
Total	VD × cortical GM 2	.002	.007
	VD × lateral ventricles 2	.002	.006
	VD × surface area 3	−.002	2.15×10^{-4}
Female	VD × lateral ventricles 2	.003	.002
Male	VD × cortical GM 2	−.004	1.28×10^{-6}
	VD × total brain 2	−.003	3.76×10^{-5}
	VD × surface area 3	−.003	2.70×10^{-4}
Total	Sleep duration × mean thickness 2	−.035	.003
	Sleep duration × surface area 2	.034	.003
Female	Sleep duration × caudate 2	−.045	.007
	Sleep duration × mean thickness 2	−.045	.007
Total	Family satisfaction × lateral ventricles 1	.230	.003
Female	Family satisfaction × thalamus 2	.343	.003
Male	Family satisfaction × cortical GM 1	.303	.002
	Family satisfaction × lateral ventricles 1	.391	<.001
	Family satisfaction × lateral ventricles 3	−.361	<.001

Note: 1, 2, and 3 separately denote the three models, of which Model 1 refers to the age-independent effect of genetic loci, Model 2 refers to linear age effects, and Model 3 refers to quadratic age effects. Abbreviations: GM, gray matter; MS, maternal smoking; PA, physical activity; VD, vitamin D; WM, white matter.

activity × nucleus accumbens 2 (beta = −.031, $p = .033$), VD × surface area 3 (beta = −.002, $p = 2.15 \times 10^{-4}$) and sleep duration × mean thickness 2 (beta = −.035, $p = .003$) as well as family satisfaction × lateral ventricles 1 (beta = .230, $p = .003$; Table 2 and Table S4).

In the female, totally 20 interactions between brain structure changes and life environmental factors appeared to be related to anxiety, for instance, coffee intake × caudate 3 (beta = .018, $p = .036$), maternal smoking × nucleus accumbens 1 (beta = .075, $p = .043$), physical activity × thalamus 1 (beta = −.051, $p = .027$) and VD × cerebral WM 1 (beta = −.002, $p = .025$), sleep duration × caudate 2 (beta = −.045, $p = .007$) and family satisfaction × thalamus 2 (beta = .343, $p = .003$; Table 2 and Supplementary Table 4).

In addition, in the male, 44 interactions between brain structure changes and life environmental factors were correlated with anxiety, such as an alcohol drinking × cerebellum WM 3 (beta = −.005, $p = .002$), smoking × thalamus 3 (beta = .004, $p = .008$), coffee intake × surface area 2 (beta = .023, $p = .002$), maternal smoking × cerebellum WM 2 (beta = .082, $p = .018$), physical activity × nucleus accumbens 2 (beta = −.041, $P = .022$) and VD × cortical GM 2 (beta = −.004, $p = 1.28 \times 10^{-6}$) as well as family satisfaction × lateral ventricles 3 (beta = −.361, $p < .001$). The detailed information could be found in Table 2 and Table S4.

3.5 | A comparison of the interactions of different environmental factors and brain structures change in anxious individuals

Besides, we also identified several common brain structures interacting with two or more life environmental factors for anxiety (Table S5).

In the total population, 6 common brain structures interacting with several life environmental factors seemed to be related to risk of anxiety, such as, nucleus accumbens interacting with maternal smoking and physical activity (beta = .070, p = .008 for maternal smoking; beta = −.031, p = .033 for physical activity), surface area interacting with alcohol drinking, coffee intake, and sleep duration as well as family satisfaction (beta = .003, P = .018 for alcohol drinking; beta = .012, p = .042 for coffee intake; beta = .034, p = .003 for sleep duration; beta = −.168, p = .026 for family satisfaction) and mean thickness interacting with alcohol drinking and maternal smoking (beta = −.003, p = .010 for alcohol drinking; beta = −.056, p = .029 for maternal smoking).

In the female, 3 common brain structures interacting with multiple life environmental factors, such as cerebral WM interacting with both alcohol drinking and smoking (beta = .006, p = .015 for alcohol drinking; beta = .005, p = .017 for smoking).

In the male, 11 common brain structures interacting with multiple life environmental factors appeared to be correlated with risk of anxiety, such as nucleus accumbens interacting with smoking, maternal smoking, and physical activity (beta = −.003, p = .028 for smoking; beta = .084, p = .019 for maternal smoking; beta = −.041, p = .022 for physical activity), surface area interacting with alcohol drinking, coffee intake and insomnia (beta = .004, p = .003 for alcohol drinking; beta = .023, p = .002 for coffee intake; beta = .069, p = .029 for insomnia) and thalamus interacting with alcohol drinking and smoking (beta = −.003, p = .029 for alcohol drinking; beta = .004, p = .008 for smoking).

3.6 | Comparison of the interactions of depression and anxiety

Interestingly, we observed several common interactions of depression and anxiety (Table 3). In the total sample, 14 common interactions were both associated with depression and anxiety, such as, alcohol drinking × cerebellum WM 3 (beta = −.003, p = .018 for depression; beta = −.003, p = .008 for anxiety), VD × surface area 3 (beta = −.002, p = .007 for depression; beta = −.003, $p = 2.70 \times 10^{-4}$ for anxiety), and family satisfaction × thalamus 2 (beta = .192, p = .022 for depression; beta = .181, p = .022 for anxiety).

In the female, a total of 7 common interactions were identified, for instance, smoking × cerebral WM 3 (beta = .004, p = .046 for depression; beta = .005, p = .017 for anxiety), VD × lateral ventricles 2 (beta = .002, p = .021 for depression; beta = .003, p = .002 for anxiety), and family satisfaction × surface area 3 (beta = −.248, p = .033 for depression; beta = −.229, p = .043 for anxiety).

In the male, 19 common interactions were correlated with depression and anxiety, such as alcohol drinking × surface area 1 (beta = .005, p = .003 for depression; beta = .007, $p = 1.97 \times 10^{-6}$ for anxiety), VD × surface area 3 (beta = −.002, p = .007 for depression; beta = −.003, $p = 2.70 \times 10^{-4}$ for anxiety), sleep duration × surface area 3 (beta = .049, p = .006 for depression; beta = .036, p = .024 for anxiety) and family satisfaction × surface area 1 (beta = −.287, p = .014 for depression; beta = −.248, p = .016 for anxiety).

4 | DISCUSSION

This study comprehensively explored interactions between brain structure change rate-related PRS and life environmental factors on the risk of depression and anxiety by using the GWAS summary data of brain structure change rate from the published study (Brouwer et al., 2022) and phenotype and genotyping data extracted from the UK Biobank. We found that numerous interactions were associated with depression and anxiety, which could provide novel clues for etiology, prevention and treatment of depression, and anxiety.

Our study results showed that the interaction between cerebellum and multiple life environmental factors (smoking, alcohol drinking, and physical activity) was associated with depression and anxiety. Cerebellum has long been considered to be responsible for motor learning and reflex adaptation, but recently its roles in cognition and emotion processing have received substantial attention (D'Angelo, 2019). Multidisciplinary evidence suggests that the abnormality of cerebellum is associated with several psychiatric disorders, such as depression (Peng et al., 2011), anxiety disorders (Schutter et al., 2012), and autism (Stoodley, 2014). Peng et al. (2011) found that the GM density of cerebellum was reduced in the depression patients compared with the healthy controls, suggesting that the cerebellum dysfunction may be involved in the pathogenesis of depression. Cerebellum volume was also reported to be inversely associated with the anxiety-related traits, and the cerebellum GM and WM subserved equally to the associations. (Schutter et al., 2012). Moreover, numerous studies reported that some life environmental exposure, such as alcohol drinking (Fitzpatrick & Crowe, 2013) and smoking (Sutherland et al., 2016), could lead to the cognitive and emotional deficits mediated by cerebellum. Fitzpatrick & Crowe, (2013) observed that the cognitive and emotional regulation and affect processing were poorer in the alcohol group than those in the control group, indicating cognitive and emotional deficits occurred in the chronic alcoholics, which may partly be mediated by cerebellum. When compared with nonsmokers, the smokers had smaller cerebellar volumes and performed worse on the neurocognitive measures (Sutherland et al., 2016). The GABA system and hypothalamic–pituitary–adrenal axis (HPA) were demonstrated to play vital roles in the pathogenesis of depression and anxiety. The GABAergic deficits and HPA axis dysregulation could contribute to depression and anxiety-related behaviors (Fiksdal et al., 2019; Smith & Rudolph, 2012). The alteration of GABAA receptor-dependent neurotransmission was regarded as an important mechanism of cerebellum dysfunction induced by alcohol (Luo, 2015). Besides, nicotine exposure could also change the GABA levels in the brain (Esterlis et al., 2009), and it has been considered to be a strong stimulator of the HPA axis with impact on the chronic modifications of the HPA axis in smokers (Rohleder & Kirschbaum, 2006). Thus, we speculate that smoking and alcohol

TABLE 3 Common interactions of depression and anxiety

	Lifestyle × brain structures	$Beta_{-dep}$	P_{-dep}	$Beta_{-anx}$	P_{-anx}
Total	Alcohol drinking × cerebellum WM 3	−.003	.018	−.003	.008
	Alcohol drinking × mean thickness 3	−.003	.010	−.003	.010
	Smoking × cerebellum GM 1	.003	.022	.003	.014
	MS × cerebellum WM 1	−.060	.027	−.061	.018
	MS × nucleus accumbens 2	.088	.002	.070	.008
	PA × cerebellum WM 1	.033	.025	.030	.033
	PA × lateral ventricles 1	−.037	.014	−.030	.036
	VD × cerebral WM 1	−.001	.029	−.001	.040
	VD × lateral ventricles 2	.001	.035	.002	.006
	VD × total brain 2	−.001	.027	−.001	.015
	VD × surface area 3	−.002	.007	−.003	2.70×10^{-4}
	Sleep duration × cortical GM 2	−.030	.013	−.027	.019
	Sleep duration × mean thickness 2	−.038	.002	−.035	.003
	Family satisfaction × thalamus 2	.192	.022	.181	.022
Female	Smoking × cerebral WM 3	.004	.046	.005	.017
	Coffee intake × caudate 3	.018	.045	.018	.036
	VD × lateral ventricles 2	.002	.021	.003	.002
	Sleep duration × mean thickness 2	−.040	.019	−.045	.007
	Sleep duration × lateral ventricles 3	−.037	.031	−.033	.044
	Family satisfaction × thalamus 2	.426	<.001	.343	.003
	Family satisfaction × surface area 3	−.248	.033	−.229	.043
Male	Alcohol drinking × surface area 1	.005	.003	.007	1.97×10^{-6}
	Alcohol drinking × cerebellum WM 3	−.004	.020	−.005	.002
	Smoking × cerebellum GM 1	.003	.038	.003	.046
	Coffee intake × putamen 1	.017	.038	.022	.002
	Coffee intake × surface area 2	.018	.029	.023	.002
	MS × nucleus accumbens 2	.079	.048	.084	.019
	PA × cerebral WM 1	−.051	.008	−.055	.002
	PA × hippocampus 1	.062	.001	.046	.009
	PA × cerebellum WM 2	.052	.006	.040	.018
	PA × hippocampus 2	.042	.035	.037	.041
	PA × mean thickness 2	.040	.040	.037	.035
	PA × nucleus accumbens 2	−.042	.037	−.041	.022
	VD × amygdala1	.002	.012	.001	.050
	VD × total brain 2	−.004	2.06×10^{-5}	−.003	3.76×10^{-5}
	VD × surface area 3	−.002	.007	−.003	2.70×10^{-4}
	Sleep duration × surface area 3	.049	.006	.036	.024
	Family satisfaction × cortical GM 1	.351	.002	.303	.002
	Family satisfaction × surface area 1	−.287	.014	−.248	.016
	Family satisfaction × putamen 2	.306	.008	.245	.018

Note: 1, 2, and 3 separately denote the three models, of which Model 1 refers to the age-independent effect of genetic loci, Model 2 refers to linear age effects, and Model 3 refers to quadratic age effects.
Abbreviations: GM, gray matter; MS, maternal smoking; PA, physical activity; VD, vitamin D; WM, white matter.

drinking could take part in the pathogenesis of depression and anxiety, which may partly be attributed to the cerebellum dysfunction induced by ethanol and nicotine exposure.

Additionally, we also observed other interactions associated with both depression and anxiety. For example, interactions of alcohol drinking and mean thickness were inversely related to depression and

anxiety, and interactions of VD and lateral ventricles, family satisfaction and thalamus, maternal smoking, and nucleus accumbens were positively correlated with depression and anxiety. Cortical thickness abnormality was related to depression and anxiety (Korom et al., 2021). Some researchers observed that cortices in frontal and occipital regions were significantly thinner in the depression group than that in the control group, whereas the left supramarginal gyrus was thicker in the depression individuals than that in the healthy participants (Suh et al., 2019). Study reported that increased alcohol consumption was related to thinned widespread cortical in a dose-dependent manner (Lange et al., 2017). Moreover, VD deficiency has been shown to be associated with an increased risk of depression and anxiety (Casseb et al., 2019). Given VD exerts important influences on the neuroplasticity and neuroimmunomodulation, as well as decreases oxidative stress, it has been widely investigated as a potential measure for the prevention and/or treatment of depression and anxiety (Casseb et al., 2019). Serum VD concentration was also negatively associated with lateral cerebral ventricles (Annweiler et al., 2013). Enlargement of lateral ventricles could occur in several psychiatric disorders such as bipolar disorder (Soares et al., 2005) and autism (Richards et al., 2020). In addition, maternal smoking was significantly associated with enhanced risk of anxiety and depressive disorders in offspring (Chu et al., 2021). Family satisfaction appeared to be important for an individual's mental health, and increased family satisfaction was significantly associated with reduced risk of depression and anxiety (Novak et al., 2020). Altogether, numerous interactions of life environmental factors and brain structures might be implicated in the pathogenesis of depression and anxiety, and the underlying biological mechanisms need to be clarified.

Interestingly, we also found subtle sex-specific differences in the interactions, such as interaction of smoking and cerebellum GM was associated with depression and anxiety in males. Study reported that individuals with nicotine dependence showed less GM volume in the cerebellum compared to the controls, whereas sex-specific analyses exhibited that this finding was stronger in males with nicotine dependence (Franklin et al., 2014). The major targets of nicotine in the brain are the neuronal nicotinic acetylcholine receptors (nAChRs; Picciotto et al., 2002). The primary reinforcing effects of nicotine are mediated by the β2-nAChR (Cosgrove et al., 2012). Sex-related differences in β2-nAChR availability could be observed. As expected, availability of β2-nAChR was significantly increased in the male smokers compared with the male non-smokers in the cerebellum and cortex, whereas there was no higher β2-nAChR availability in the female smokers compared with the female non-smokers in any brain region (Cosgrove et al., 2012). Except women, interactions between physical activity and several brain structures were correlated with both depression and anxiety in men. Physical activity and daily exercise are regarded as essential components for maintaining the brain health and cognition function (Sanders et al., 2021). Casaletto et al. (2020) found that males exhibited a tighter relationship between daily physical activity and larger parahippocampal volumes, and better visual memory as well as processing speed, whereas these effects seemed to be attenuated or absent in females. Study also indicated that compared with female mice, male mice have greater hippocampal long-term potentiation and improved memory following voluntary exercise (Barha et al., 2017). In females, the levels of estrogen decrease sharply at menopause, which may lead to the dysfunction of cognition in normal aging (Berchtold et al., 2001). Moreover, estrogen loss was not only associated with decreased voluntary physical activity, but related to the remarkably decreased beneficial effects of physical activity on hippocampal brain-derived neurotrophic factor expression (Berchtold et al., 2001). These results indicated that men might show greater neurobehavioral benefits following physical activity, which may be partly mediated by hormone levels. The biological mechanisms underpinning the sex-related differences in the interactions remain to be further investigation.

It is note that our study has some strengthens. Our analysis data were collected from a large-scale GWAS and a well-established prospective population-based cohort. Our study not only first explored the joint effects of brain structure change rate and life environmental factors on depression and anxiety, but also analyzed the common brain structures interacting with multiple environment factors as well as common interactions between depression and anxiety. Importantly, we observed sex-differences in the interactions, which may be partly modulated by hormone levels.

This study also has some limitations. GWAS summary statistics of brain structure changes rate included 15,640 individuals, 540 of whom were non-European ancestry, which may induce subtle bias into our study results. In addition, depression and anxiety may be correlated with some social factors and other life environmental factors, such as cohabitation status (Tani et al., 2015), education, employment status (Cook et al., 2021; Rizvi et al., 2015), and socioeconomic deprivation in the locality (Fernández-Niño et al., 2014), which should be considered and further determined. Study reported that individuals with more than 4 years of formal education complained more frequently of psychomotor disturbance than those with less education, suggesting that education level may exert important influence on depressive symptom profiles (da Costa Dias et al., 2021). Moreover, high rates of unemployment can be observed in individuals with depression or anxiety (Rizvi et al., 2015). Socioeconomic deprivation at the locality is significantly associated with symptom of depression and could be a vital risk factor for depression (Cook et al., 2021; Fernández-Niño et al., 2014). The potential biological mechanisms underlying these interactions deserve further exploration.

In summary, we observed that the interactions between brain structure changes and life environmental factors were associated with depression and anxiety by using the PRS analysis and regression analyses. Our findings may provide new direction for the etiology and pathogenesis of depression and anxiety.

AUTHOR CONTRIBUTIONS

Xuena Yang: writing – original draft and conceptualization. **Bolun Cheng:** writing – review and editing. **Jian Yang:** investigation. **Shiqiang Cheng:** software. **Yijing Zhao:** investigation. **Huijie Zhang:** conceptualization. **Li Liu:** visualization. **Peilin Meng:** visualization. **Chuyu Pan:** investigation. **Jingxi Zhang:** data curation. **Zhen Zhang:** data curation. **Chun'e Li:** conceptualization. **Yujing Chen:** investigation. **Dan He:**

investigation. **Yan Wen:** validation. **Yumeng Jia:** methodology and formal analysis. **Huan Liu:** validation. **Feng Zhang:** supervision and project administration.

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CONFLICT OF INTEREST

The author declares that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

DATA AVAILABILITY STATEMENT

The UKB data support the findings of this study are openly available in the UK Biobank Access Management System at https://www.ukbiobank.ac.uk/.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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