Investigating the Role of TNF-Alpha through Blood-Brain Barrier Integrity in Stress-Induced Depression

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Background: Major depressive disorder (MDD) is a complex psychiatric condition significantly impacted by environmental stress and inflammation. Previous research suggests that stress-induced alterations in the blood-brain barrier (BBB) may allow pro-inflammatory cytokines like interleukin-6 (IL-6) to enter the brain, contributing to depression. Tumor necrosis factor-alpha (TNF-α) is another prominent cytokine implicated in depression, but its role in the context of BBB integrity and stress-mediated depression remains unclear. **Objectives:** This study aimed to investigate whether TNF-α plays a similar role as IL-6 in the development of depression through interactions with environmental stress and BBB integrity. Specifically, we examined the interaction between environmental stress, genetic variants of *CLDN5* (the gene of the Claudin-5, a protein critical for BBB integrity), and *TNF* (the gene encoding the TNF-α protein) genetic variants on depressive symptoms. **Methods:** We utilized data from the UK Biobank, comprising genetic, health, and lifestyle information from approximately 500,000 participants aged 40 to 69. Depressive symptoms were assessed using the Patient Health Questionnaire-9 (PHQ-9) and a composite Current Depressive Symptoms (CDS) score based on self-reported questionnaire items. Environmental stress was quantified through participants' reports of significant life events in the past two years. Genetic analysis focused on 15 single nucleotide polymorphisms (SNPs) within the *TNF* gene (after linkage disequilibrium pruning) and a functional polymorphism in *CLDN5* (rs885985). Linear regression models were used to assess main effects, gene-gene interactions, gene-environment interactions, and three-way interactions on depressive symptoms, adjusting for covariates and applying Bonferroni correction for multiple testing. **Results:** No significant associations were found between *TNF* genetic variants and depressive symptoms after correcting for multiple testing. While some *TNF* SNPs showed nominal significance in interaction models – most notably rs3093546, which showed nominal significance in both depressive phenotypes – the findings were not robust enough to confirm a significant role. Unlike previous findings with *IL6, TNF* did not exhibit significant interactions with environmental stress and *CLDN5* variants affecting depression risk. **Conclusions:** The study does not support a significant role for *TNF* genetic variants interacting with environmental stress and BBB integrity in influencing depression risk. These findings suggest that IL-6 and BBB integrity may be more critical targets for understanding and treating stress-related depression, highlighting the complexity of depression's pathophysiology.

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Keywords: major depression, TNF-alpha, IL-6, blood-brain-barrier, CLDN5, stress, genetic interaction, proinflammatory citoknes, depression symptoms

INTRODUCTION

Major depressive disorder (MDD) is a complex psychiatric disorder that imposes a significant burden on individuals and society. Despite the wide variety of available medications, around 30% of MDD patients still do not achieve remission after several pharmacotherapeutic trials (Li et al., 2020; Nuñez et al., 2022) – warranting the identification of potential novel therapeutic targets. For this purpose, we selected two key contributing factors in depression: environmental stress and inflammation. We focused on their recently suggested interaction through alterations in the blood-brain barrier (BBB), a selective barrier that regulates the passage of substances between the bloodstream and the central nervous system (CNS) (Kealy et al., 2020; Wu et al., 2022).

Claudin-5 (encoded by the CLDN5 gene) is a tight junction protein essential for maintaining blood-brain barrier (BBB) integrity. Animal studies have shown that stress may downregulate Claudin-5 levels, leading to a higher permeability of the BBB, which can result in increased infiltration of pro-inflammatory cytokines, such as interleukin-6 (IL-6), into the brain (Dudek et al., 2020; Gal et al., 2023; Menard et al., 2017). Hypothesis-free genomic approaches also confirmed the important role of BBB in stress-associated depression (Gal et al., 2024). Our research group found a significant three-way interaction between recent stressful life events and genetic variants of *CLDN5* and *IL6* genes in humans (Gal et al., 2023), further supporting the idea that the depressogenic effect of IL-6 may depend on a stress-induced dysfunction of the BBB.

As the above mechanism may not be restricted to IL-6, other pro-inflammatory cytokines may also infiltrate the brain in a similar way and increase the risk of depression. Tumor necrosis factor-alpha (TNF-α), encoded by the *TNF* gene another prominent pro-inflammatory cytokine, may represent a good candidate. Elevated serum levels of TNF-α have been associated with depressive symptoms in multiple studies (Brymer et al., 2019; Young et al., 2014), and selective TNF-α antagonists, especially infliximab and etanercept, showed antidepressant effects, at least among specific patient subgroups (e.g., those with elevated levels of inflammatory markers) (Uzzan & Azab, 2021). Additionally, TNF-α is one of the key pro-inflammatory cytokines that were suggested to specifically promote stress-induced depression through the interconnectedness of stress, high levels of pro-inflammatory cytokines, and depression (J. Chang et al., 2024). Unlike IL-6, TNF-α exists in both soluble and transmembrane forms and interacts with specific receptors, potentially leading to different inflammatory responses (Horiuchi et al., 2010). Moreover, TNF-α levels have been linked to obesity, type 2 diabetes, and C-reactive protein levels, further indicating a distinct role in systemic inflammation compared to IL-6 (Popko et al., 2010).

The primary aim of this study is to investigate whether TNF-α plays a similar role as IL-6 in the development of depression risk through mechanisms involving stress and BBB integrity. Specifically, we aim to examine the interaction between environmental stress, and genetic variants of Claudin-5 and TNF-α on depressive symptoms.

METHODS

Study Population

Study data were sourced from the UK Biobank, a comprehensive biomedical database comprising genetic, health, and lifestyle information from approximately 500,000 participants aged 40 to 69 at recruitment between 2006 and 2010. The UK Biobank received ethical approval from the North West Multi-Centre Research Ethics Committee (REC reference: 16/NW/0274), and all participants provided informed consent.

Phenotype Measures

Depressive symptoms were assessed using two measures: (i) the Patient Health Questionnaire-9 (PHQ-9), which is a validated instrument for measuring depression severity, and (ii) Current Depressive Symptoms (CDS), which is a composite score (Hullam et al., 2019) derived from self-reported questionnaire items assessing mood, interest, and energy levels. Because of the different coverage of the two phenotypes, two overlapping cohorts were analysed. Using both phenotypes allowed us to extend the overall sample size and explore complementary aspects of depressive symptomatology.

The severity of environmental stress was assessed based on participants' responses to questionnaire items about significant life events they experienced in the past two years (UK Biobank data-field 6145), a composite score was determined as a sum of such events. These events included: (i) serious illness, injury, or assault to oneself; (ii) serious illness, injury, or assault to a close relative; (iii) the death of a close

Table 2.

	Sample Size	Mean	Standard Deviation
Current Depressive Symptoms (CDS)	333 398	1.4	0.53
Age	-	56.87	7.99
Female	-	54%	-
Recent Stressful Events	-	0.57	0.76
PHQ-9	109 426	1.31	0.41
Age	-	56.19	7.67
Female	-	56%	-
Recent Stressful Events	-	0.54	0.75

The table provides descriptive statistics for the study sample, detailing sample size, mean, and standard deviation for key variables: depressive symptoms (Current Depression Symptoms, PHQ-9), age, sex, and number of stressors in the last two years.

relative; (iv) the death of a spouse or partner; (v) marital separation or divorce; and (vi) financial difficulties. The data were collected as part of the UK Biobank's touchscreen questionnaire on psychological factors and mental health, specifically under data-field 6145. The age (data-field 21022) and sex (data-field 31) variables were also collected by UK Biobank.

Genetic Data

Candidate genes and SNPs were selected based on their relevance to BBB integrity and cytokine function:

- *CLDN5 (Claudin-5):* rs885985, a functional polymorphism where the G allele codes an amino acid, but the A allele forms a stop codon. Our previous article also used this variant to analyse interactions with IL6 (Gal et al., 2023)
- *TNF (Tumor Necrosis Factor):* 74 SNPs were pre-selected based on their location inside the extended *TNF* gene boundaries (extended by 10,000 base pairs up and downstream).

To reduce collinearity and ensure robust analysis, we performed linkage disequilibrium (LD) pruning on the pre-selected *TNF* SNPs using PLINK 2.0 (C. C. Chang et al., 2015) for the two phenotype cohorts (CDS and PHQ-9) separately. The pruning was conducted with the following parameters: a sliding window size of 50 variants, a step size of 5, and an LD threshold of r2=0.2. For both cohorts, the same 15 SNPs survived pruning, and these were used in the subsequent analyses.

Genotyping and imputation were performed by UK Biobank, and we followed the recommended quality control guidelines (Bycroft et al., 2018).

Statistical Analysis

We used linear regression to assess the association between genetic variants, environmental stress and depressive symptoms. The analyses included separate models for main effects of *TNF* SNPs, epistasis (GxG), GxE and three-way (GxGxE) interactions on depression.

The formulae for the four models were:

Main effect: Depression Phenotype ~ *TNF* SNP + Covariates

GxE: Depression Phenotype ~ Stress * *TNF* SNP + Covariates

GxG: Depression Phenotype ~ *CLDN5* SNP * *TNF* SNP + Covariates

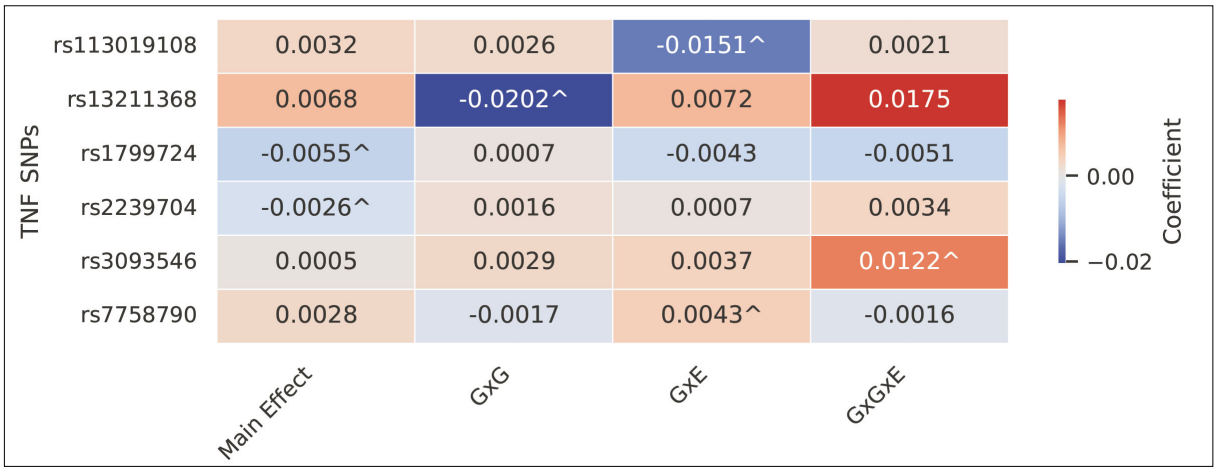
GxGxE: Depression Phenotype ~ Stress * *CLDN5* SNP * *TNF* SNP + Covariates

where the asterisk (*) corresponds to full factorial expansion, meaning that the 2-way interaction models also contain all main effects; the GxGxE model in addition to all main effects also contains all 2-way interactions.

Covariates included (i) age; (ii) sex; (iii) genotyping array type (to account for batch effects) and (iv) the first ten principal components (PC1–PC10) to control for population stratification.

Multiple testing correction was applied using the Bonferroni method, adjusting the number of SNPs (15) and tests conducted in the overall analysis (8: two phenotypes, four models); the p-value threshold was approximately 0.00167 (=0.05 / [15 x 8]), where 0.05 was the limit for nominal significance.

Figure 1. Depression Phenotype: Current Depressive Symptoms (CDS)



Heatmap showing the coefficients of *TNF* SNPs and corresponding interaction terms from the regression models for the current depressive symptoms phenotype. Nominally significant (p<0.05) coefficients are indicated by '^'. Only SNPs with at least one nominally significant coefficient are shown.

Software

All statistical analyses were performed using Python, specifically the statsmodels library (version 0.14.0) for statistical modelling using the "ols" function. We used PLINK v2.00a5.10LM (C. C. Chang et al., 2015) for LD pruning.

RESULTS

Participant Characteristics

Based on the different coverage of the investigated phenotypes, the subcohorts differed in size and composition. The subcohort where the depressive phenotype was established based on current depressive symptoms (CDS) had a larger sample size, 333 398, compared to the PHQ-9 cohort with 109 426 participants; the CDS cohort overlapped the PHQ-9 cohort with 109 309 participants. The severity of recent stress exposure and distribution of sex was comparable in the two cohorts (Table 1).

Genetic Associations and Interaction Effects

We tested 15 SNPs of the *TNF* gene for association with the PHQ-9 and CDS phenotype with linear regression models, and looked at interaction effects with environmental stress, epistasis (with the *CLDN5* functional polymorphism) and 3-way interaction.

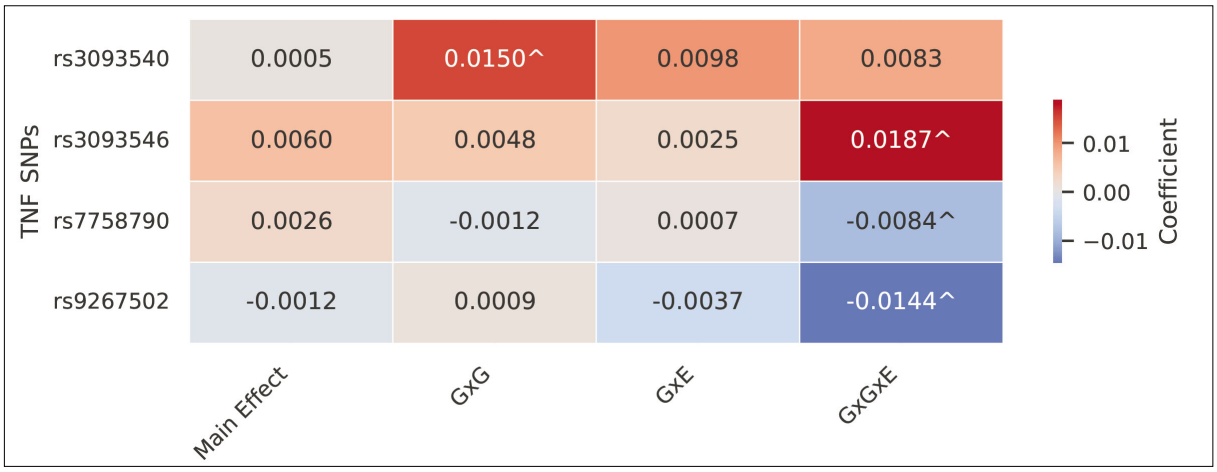
No significant associations were found after correction for multiple testing. Six SNPs reached nominal significance in at least one of the tested interactions for CDS (Figure 1), and 4 SNPs for PHQ-9 depression (Figure 2).

The nominally significant SNP coefficients for each phenotype and model type are summarized in Table 2. PHQ-9 had no significant SNPs in the main effect or GxE models, contrasting with the CDS phenotype, which showed nominal associations across all models. The GxGxE model produced the most consistent nominal associations, where the rs3093546 SNP was associated in both phenotypes, and its coefficients point in the same direction. Furthermore, a nominally significant association for the rs7758790 SNP was found in both phenotypes: in the GxE model for the CDS population and in the GxGxE model for the PHQ-9 population.

DISCUSSION

This study aimed to determine whether tumor necrosis factor-alpha (TNF-α) plays a role similar to interleukin-6 (IL-6) in the development of depression through interactions with environmental stress and blood-brain barrier (BBB) integrity. Analyzing genetic variants of *TNF* and the BBB integrity gene *CLDN5* in the UK Biobank data, we found no significant associations after correcting for multiple testing.

Figure 2. Depression Phenotype: PHQ-9



Heatmap showing the coefficients of *TNF* SNPs and corresponding interaction terms from the regression models for the PHQ-9 phenotype. Nominally significant (p<0.05) coefficients are indicated by '^'. Only SNPs with at least one nominally significant coefficient are shown.

Table 2.

	Main Effect	GxG	GxE	GxGxE
Current Depressive Symptoms (CDS)	2 (2 neg.)	1 (neg.)	2 (1 pos., 1 neg.)	1 (pos.)
PHQ-9	0	1 (pos.)	0	3 (1 pos., 2 neg.)

The table shows the number and direction of nominally significant SNP coefficients for each phenotype and each model type.

Our results suggest that TNF-α does not interact with stress and BBB dysfunction in the same way as IL-6 does in influencing depression risk. Our previous study found a significant three-way interaction among stress, *IL6*, and *CLDN5* variants affecting depression risk (Gal et al., 2023). The lack of significant associations for *TNF* indicates that its role in depression may be indirect or operate through different mechanisms, possibly related to systemic inflammation rather than direct BBB permeability. Looking more closely at the nominally significant results, only one *TNF* SNP (rs3093546) affected both depression phenotypes – a risk effect was found in the three-way interaction model, similarly as in case of the previously detected IL-6 variant (Gal et al., 2023). Again, it has to be highlighted that while the IL-6 variant showed a highly significant effect, the result with the *TNF* SNP was not robust enough to reach statistical significance after Bonferroni correction, therefore we cannot conclude a similar role for TNF-α in stress-mediated depression.

Elevated TNF-α levels have been observed in depressed patients (Brymer et al., 2019; Young et al., 2014). However, the regulation and location of the synthesis of TNF-α and IL-6 differs both at the peripheral level and at the CNS which may also contribute to their differing roles in stress, and as a result in stress-related depression, e.g., IL-6 plays a more direct role in the acute stress response by activating the HPA axis possibly via IL-6 receptors in the paraventricular nucleus of the hypothalamus, while TNF-α is not known to exert such a direct stress-regulating function (Hughes et al., 2016). Previous animal studies also emphasized IL-6's role in stress-induced BBB permeability and depression-like behaviors (Dudek et al., 2020; Menard et al., 2017). The lack of similar findings for TNF-α suggests that IL-6 may have a more direct effect on neuroinflammation and BBB integrity in the context of stress-related depression.

Clinically, this implies that we should differentiate between stress-related proinflammatory cytokin targets. In case of stress-mediated depression, a focus on IL-6 signaling or BBB integrity is recommended. However, TNF-α should not be discounted, as it may influence depression through systemic inflammation, especially in individuals with metabolic comorbidities.

LIMITATIONS

Limitations of our study include the use of self-reported measures for stress and depressive symptoms, which may introduce bias. Despite controlling for population stratification, residual confounding could persist. The genetic variants studied may not capture the full functional diversity of the *TNF* gene, and other environmental or lifestyle factors were not considered. The cross-sectional design also limits causal interpretations.

CONCLUSION

In conclusion, our study does not support a significant role for *TNF* genetic variants interacting with environmental stress and BBB integrity in influencing depression risk, unlike IL6. These findings highlight the complexity of depression's pathophysiology and suggest that IL-6 and BBB integrity are more critical targets for understanding and treating stress-related depression.

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A TNF-alfa szerepének vizsgálata a vér-agy gát integritásán keresztül stressz által kiváltott depresszióban

Háttér: A major depressziós zavar (MDD) összetett pszichiátriai betegség, amelyre jelentős hatást gyakorol a környezeti stressz és a gyulladás. Korábbi kutatások alapján a stressz által kiváltott változások a vér-agy gátban (BBB) lehetővé tehetik, hogy a proinflammátoros citokinek, mint például az interleukin-6 (IL-6), bejussanak az agyba, hozzájárulva a depresszió kialakulásához. A tumor nekrózis faktor-alfa (TNF-α) egy másik kiemelten fontos citokin, amelyet összefüggésbe hoztak a depresszióval, de szerepe a BBB integritásának és a stressz által közvetített depresszió kontextusában továbbra sem egyértelmű. **Célkitűzések:** A kutatás célja annak vizsgálata volt, hogy a TNF-α hasonló szerepet játszik-e a depresszió kialakulásában a környezeti stresszel és a BBB integritásával való kölcsönhatások révén, mint az IL-6. Konkrétan, a környezeti stressz, a *CLDN5* (a BBB integritása szempontjából kritikus Claudin-5 fehérjét kódoló gén) genetikai variánsai és a *TNF* (a TNF-α fehérjét kódoló gén) genetikai variánsai közötti interakciót vizsgáltuk a depressziós tünetekre gyakorolt hatásuk tekintetében. **Módszerek:** A UK Biobank adatbázisát használtuk fel, amely körülbelül 500 000, 40 és 69 év közötti résztvevő genetikai, egészségügyi, és életmódbeli információit tartalmazza. A depressziós tüneteket a 9 tételes Patient Health Questionnaire-9 (PHQ-9), és egy kompozit, jelenlegi depressziós tüneteket (CDS) mérő pontszám alapján értékeltük, önbevallásos kérdőívtételek felhasználásával. A környezeti stresszt a résztvevők által az elmúlt két évben jelentős életeseményekről szóló beszámolók alapján számszerűsítettük. A genetikai elemzés a *TNF* gén 15 polimorfizmusára (SNP) fókuszált , valamint a CLDN5 egy funkcionális polimorfizmusára (rs885985). Lineáris regressziós modelleket alkalmaztunk a fő hatások, gén-gén interakciók, gén-környezet interakciók, és háromirányú interakciók kiértékelésére a depressziós tünetekre vonatkozóan. **Eredmények:** A *TNF* genetikai variánsai és a depressziós tünetek között nem találtunk szignifikáns összefüggést a többszörös tesztelésre történt korrekció után. Bár néhány *TNF* SNP névleges szignifikanciát mutatott az interakciós modellekben, az eredmények nem voltak elég erősek a jelentősebb szerep kimutatásához; megemlítendő azonban az rs3093546, amely mindkét depressziós fenotípusban azonos irányú koefficienst és névleges szignifikanciát mutatott. A korábbi IL6-tal kapcsolatos eredményekkel ellentétben a *TNF* gén nem mutatott szignifikáns interakciókat a környezeti stresszel és a depresszió kockázatát befolyásoló CLDN5 variánsokkal. **Következtetések:** A kutatás nem támasztja alá azt, hogy a depresszió kockázatának befolyásolásában jelentős szerepe lenne a *TNF* genetikai variánsai, a környezeti stressz és a BBB integritás interakciójának. Ezek az eredmények azt sugallják, hogy az IL-6 és a BBB integritása kritikusabb célpontok lehetnek a stressz-kapcsolt depresszió megértésében és kezelésében.

Kulcsszavak: major depresszió, TNF-alfa, IL-6, vér-agy gát, CLDN5, környezeti stressz, genetikai interakció, proinflammatorikus citokinek, depressziós tünetek.