Associations of *FKBP5* Polymorphisms and Methylation and Parenting Style With Depressive Symptoms Among Chinese Adolescents

Lan Guo  
Sun Yat-sen University

Wanxin Wang  
Sun Yat-sen University

Yangfeng Guo  
Health Promotion Centre for Primary and Secondary Schools of Guangzhou Municipality

Xueying Du  
Health Promotion Centre for Primary and Secondary Schools of Guangzhou Municipality

Guangduoji Shi  
Sun Yat-sen University

Ci Yong Lu ( luciyong@mail.sysu.edu.cn )  
Sun Yat-sen University

Research Article

**Keywords:** FKBP5 polymorphism and methylation, parenting style, depressive symptoms, Chinese adolescents, nested case-control study.

**Posted Date:** August 30th, 2021

**DOI:** https://doi.org/10.21203/rs.3.rs-728266/v1

**License:** 📈 This work is licensed under a Creative Commons Attribution 4.0 International License.  [Read Full License](https://creativecommons.org/licenses/by/4.0/)
Abstract

Background

Genetic factors may interplay with environmental stressors to contribute to risks of depressive symptoms. This study aimed to investigate the association of FKBP5 polymorphisms and DNA methylation with depressive symptoms among Chinese adolescents, considering the role of parenting style.

Methods

This study used a nested case-control study design based on a cohort study, and the case (n = 120) and control groups (n = 118) were matched with age. Depressive symptoms, parenting style, and other demographics were measured. Fourteen potential polymorphisms and one promoter region in the FKBP5 gene were selected for genotyping and methylation analysis.

Results

In the adjusted models, a significant association between FKBP5 rs7757037 and depressive symptoms was found in the codominant model (AG vs. GG; adjusted odds ratio [AOR] = 2.37, 95% CI = 1.07–5.28) and dominant model (AA + AG vs. GG; AOR = 2.22, 95% CI = 1.05–4.69); rs2817032 polymorphism was associated with depressive symptoms in the codominant model and dominant model. Significant interactions between rs7757037 and the father’s parenting style were found in the codominant model (P = 0.037) and dominant model (P = 0.038), but the gene-environment interactions were not significant after correcting for multiple testing. The main and interactive effects of FKBP5 methylation status on depressive symptoms were not observed, and no significant mediations were found in the association between FKBP5 polymorphisms and depressive symptoms through the methylation mechanism.

Conclusions

Further studies are required to confirm the effect of FKBP5 polymorphisms and methylation as well as their interactions with parenting styles in larger samples.

Background

Depressive symptoms were one of the major mental health problems worldwide and are the main contributor to the global burden of disease in young people [1]. Adolescence represents a developmental transition period between childhood and adulthood, characterized by marked changes in biological systems and physical maturation of the body and brain, rendering adolescents vulnerable to mental health problems, including depressive symptoms [2]. However, the onset of depressive symptoms in adolescence has long-lasting effects on the adolescents’ physical and brain development and may be a significant risk factor for clinical depression later, leading to serious social and educational impairments [3]. Although the pathological mechanism of depressive symptoms remains unclear, both genetic factors and environmental stressors play a role in its pathogenesis. It has been widely reported that a positive family history of depression is the most critical risk factor for developing
depressive symptoms and is often observed in patients with an earlier onset age [4]. A recent study showed the heritability of 40% for depression in a young adult cohort [5], suggesting genetic factors may interplay with environmental stressors to contribute to risks of depressive symptoms.

Given that the hypothalamic-pituitary-adrenal (HPA) axis is the primary stress response system [6], it seems that environmental stressors may activate glucocorticoid receptor (GR) and then results in a prolonged dysfunction and dysregulation of HPA axis activity, which has been one of the potential biological mechanism for depression [7]. The FK506 binding protein 51 (FKBP51) is the co-chaperone of heat shock protein (Hsp) 90 and GR, which can inhibit GR sensitivity to regulate the HPA axis [8]. The FKBP5 gene (encoding FKBP51) has attracted significant attention, and several studies have suggested that some FKBP5 single nucleotide polymorphisms (SNPs) might be associated with the increased risk of depressive symptoms [9–12]. However, other studies did not observe a significant association between FKBP5 SNP and depressive symptoms, even though several included SNPs have been reported with significant associations before [13, 14]. The inconsistency of these findings might be explained by methodological variations, modulating environmental stressors, and the epigenetic mechanism. For instance, previous evidence suggests that the interactions between environmental stressors and FKBP5 rs3800373/ rs9296158/ rs1360780/ rs9470080 were statistically significant in a sample of clinically depressed adolescents [14], and the interaction effects of childhood physical abuse and FKBP5 rs3800373/ rs1360780/ rs4713916 on depressive symptoms in Chinese adolescents were significant [15].

Although adolescents may experience many environmental stressors, parenting style (referring to general patterns of parental behavior) is critically important for adolescent health [16], especially in a developmental period characterized by a rapid elevation in depressive symptoms. Based on Baumrind’s theory, negative parenting style (e.g., authoritarian or neglectful parenting style) can be categorized as a major environmental stressor. Previous evidence also suggested that authoritarian and neglectful parenting styles were associated with higher depressive symptoms in adolescents [17, 18]. However, few studies considered the interaction effects between parenting style and FKBP5 SNPs on depressive symptoms, particularly among adolescents. Additionally, DNA methylation is an epigenetic mechanism related to gene silencing or gene transcription activation [19]. There is also evidence that the effects of DNA methylation of the FKBP5 gene on depressive symptoms and environmental stressors (e.g., childhood trauma) may modify the effects [20]. However, scarce studies examined the role of parenting style in influencing FKBP5 DNA methylation and depressive symptoms in adolescents. Therefore, the aims of this nested case-control study among Chinese adolescents were twofold. First, to investigate the association of FKBP5 genetic and epigenetic variation with depressive symptoms among Chinese adolescents. Second, to investigate the potential role of parenting style on these associations.

Methods

Study design and participants

We used a nested case-control study design based on the Longitudinal Study of Adolescents’ Mental and Behavioral well-being Research (LSAMBR) in Guangzhou, China (Registration No. ChiCTR1900022032). The LSAMBR is a prospective follow-up study, which adopted a multi-stage, stratified cluster, random sampling method to include 1957 students as eligible participants from nine high schools at baseline (April to July 2019; response rate: 99.03%) and followed up at one-year later (retention rate: 93.8%) [21, 22]. Exclusion criteria included: 1) diagnosis of depressive disorder, severe psychiatric disorder, and/or alcohol or drug dependence
disorder; 2) non-fluency in mandarin; 3) inability to understand questionnaires or provide consent for themselves.

The self-reported questionnaires were distributed in the classrooms with the absence of teachers to protect the privacy of the students and reduce information bias. The blood sample (5 ml) of the students were collected at baseline. In the current nested case-control study, students without depressive symptoms at baseline and follow-up were randomly selected as the control group (n = 118), and those with depressive symptoms at baseline and follow-up were treated as the case group (n = 120). The case and control groups were matched with age (Figure 1). All participants and their legal guardians were informed in detail about the design and aims of the study and gave written assent to participate in the study, and written informed consent was obtained from each participant and one of the student’s legal guardians.

Measures

Depressive symptoms

Depressive symptoms were assessed by the Center for Epidemiologic Studies Depression Scale (CES-D) in Chinese. The Chinese version of this scale has been validated and widely utilized in Chinese studies [23], and shows satisfactory reliability (the total Cronbach’s alpha = 0.88) among Chinese adolescents [24]. The respondents were asked to rate the frequency of 20 symptoms of depression by selecting one of four response options ranging from ‘rarely or none of the time’ to ‘most or all of the time’. The CES-D score ranges from 0 to 60, with higher scores indicating more severe depressive symptomatology [25]. In this study, a score of 28 or higher was applied to identify students with depressive symptoms, and the cutoff score has been used in previous studies among Chinese adolescents [26, 27].

Parenting style

Parenting style was measured by asking students their perceptions of their father’s and mother’s parenting style. Based on Baumrind’s theory, the responses included four types of parenting styles (1 = Authoritative, 2 = Authoritarian or disciplinarian, 3 = Permissive or indulgent, 4 = Neglectful or uninvolved) [28, 29]. Moreover, the explanations of different parenting styles have also been provided as below. Authoritative parenting means high demandingness and responsiveness; although authoritative parents have high expectations for achievement and maturity, they are also warm and responsive. Authoritarian parenting means high demandingness and low responsiveness; high levels of parental control and low levels of responsiveness are the main two characteristics of authoritarian parents. Permissive parenting means low demandingness and high responsiveness; permissive parents set very few rules and boundaries, and they are reluctant to enforce rules. Neglectful parenting means low demandingness and low responsiveness, and neglectful parents are indifferent to their children’s needs or uninvolved in their lives.

Demographic information

Demographic information including age, sex (1 = boy, 2 = girl), living arrangement was also collected. Living arrangement was assessed by asking who lived in the student’s primary home (responses were coded as living with both parents = 1, living with a single parent = 2, living with others = 3).

SNP selection and genotyping
Genomic DNA was extracted from blood samples with the DNA extraction kit (BioTeke Corporation, Beijing, China) according to the manufacturer's instructions. DNA concentration was measured at the wavelength of A260 nm by a NanoDrop 2000C spectrophotometer (Thermo Scientific, Waltham, MA, USA). Haploview v.4.2 was used to select tagSNPs in linkage disequilibrium (LD) ($r^2 > 0.8$) with the remaining SNPs at minor allele frequency (MAF) > 0.1 in Han Chinese in Beijing (CHB). Functional SNP (rs3800373 and rs2817035) and SNPs most commonly associated with depressive symptoms or depressive disorder from the literature (rs7748266, rs9470080, rs4713902, rs1360780, rs9380524, rs9394309, rs7757037, rs1043805, rs2766533, rs4713916, rs9296158, rs2817032) [9–12] were prioritized as tagSNPs. In total, 14 SNPs were selected (Table S1). Assay Design 4.0 software (Agena Bioscience, Inc., San Diego, CA, USA) was used to design the primers. SNP genotyping was determined following the MassARRAY Nanodispenser (Agena Bioscience) protocols and MassARRAYiPLEX platform (Agena Bioscience) recommended by the manufacturer. None of the selected SNPs had more than 10% genotyping errors or were in severe Hardy-Weinberg disequilibrium ($P < 0.001$).

**FKBP5 promoter methylation analysis**

The CpG island in the promoter region of the *FKBP5* gene was selected as the target for methylation analysis. The sequences of CpG island (chr6: 35728998–35729370) were determined through the CpG Island Online Prediction website (http://www.ebi.ac.uk/Tools/seqstats/emboss_cpgplot/) based on the CpG island determination criteria (%GC > 50, length > 200 bp, Obs/Exp CpG > 0.6). The methylation of 14 CpG units, encompassing 20 CpG sites, was quantified using the SEQUENOM MassARRAY EpiTYPER platform [30]. Further quality control was performed, including excluding CpG units with less than 80% of available methylation data to ensure that spurious data were not analyzed [31]. Moreover, significantly deviating data points were also excluded [32]. A total of 14 CpG units were ultimately qualified for analysis (Table S2).

**Statistical analysis**

All statistical analyses were conducted using SPSS (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY). Descriptive analyses were used to describe the sample characteristics. Continuous and categorical data were reported in the form of proportions and means (SD). Student t-tests for continuous variables and chi-square tests for categorical variables were conducted to test the differences between the cases and control groups. The distribution of the observed genotype frequencies of *FKBP5* polymorphisms and *FKBP5* methylation levels in the cases and control group was described, and multiple inheritance models were applied to analyze genotype data. Conditional logistic regression models were performed to test the main effects of *FKBP5* polymorphisms and parenting styles on depressive symptoms first. Considering we had no hypothesis regarding main genetic effects, we did not adjust the two-sided $\alpha$-levels of 0.05 for the respective tests. To investigate interactions between *FKBP5* polymorphisms/methylation status and parenting styles on depressive symptoms, the interaction items between *FKBP5* polymorphisms/methylation status and the parenting style of father/mother were added into the multivariate conditional logistic regression models along with single variables, respectively. To control potential type I errors, the two-sided $\alpha$-level of 0.05 was corrected into 0.025 (0.05/2 for two-way interaction items of *FKBP5* SNPs × the parenting style of father/mother). Moreover, we also did mediation analyses by using the *FKBP5* methylation status as the mediating variable to investigate the mediating effects of *FKBP5* promoter CpG sites on the associations between *FKBP5* polymorphisms and depressive symptoms; the methods proposed by Preacher and Hayes were performed using PROCESS 3.0 in SPSS, with the 1500 bootstrap samples for bias correction and 95% confidence interval [33].
Results

Table 1 shows the characteristics of the sample. In the students with depressive symptoms (cases), the mean age was 13.45 (SD: 1.33) years, the proportion of females was 40.7%, and the proportion of students living with a single parent was 8.5%. In the students without depressive symptoms (controls), the mean age was 13.79 (SD: 1.52) years, the proportion of females was 66.7%, and the proportion of students living with a single parent was 17.5%. The differences between the cases and control group in sex and living arrangement distribution were statistically significant ($P < 0.05$). Regarding the parenting style, the proportion of students who reported suffering authoritarian parenting style of the father in cases was 3.4% and in the control group was 10.8%; the proportion of those who reported suffering authoritarian parenting style of the mother in cases was 1.7% and in the control group was 10.0%; the differences of reported parenting style between the cases and control group were statistically significant ($P < 0.05$).
Table 1
Sample characteristics between cases and control group.

| Variable                          | Non-depressive symptoms group (n, %) | Depressive symptoms group (n, %) | P value* |
|----------------------------------|-------------------------------------|---------------------------------|----------|
| Total                            | 118 (100)                           | 120 (100)                       |          |
| Age, mean (SD), year             | 13.45 (1.33)                        | 13.79 (1.52)                    | 0.065    |
| Sex                              |                                     |                                 |          |
| Boy                              | 70 (59.3)                           | 40 (33.3)                       | < 0.001  |
| Girl                             | 48 (40.7)                           | 80 (66.7)                       |          |
| Living arrangement               |                                     |                                 |          |
| Living with both parents         | 103 (88.0)                          | 86 (71.7)                       | 0.006    |
| Living with a single parent      | 10 (8.5)                            | 21 (17.5)                       |          |
| Living with others               | 4 (3.4)                             | 13 (10.8)                       |          |
| Missing data                     | 1                                   |                                 |          |
| Parenting style of the father    |                                     |                                 |          |
| Permissive                       | 81 (68.6)                           | 67 (55.8)                       | < 0.001  |
| Authoritative                    | 32 (27.1)                           | 25 (20.8)                       |          |
| Authoritarian                    | 4 (3.4)                             | 13 (10.8)                       |          |
| Neglectful                       | 1 (0.8)                             | 15 (12.5)                       |          |
| Parenting style of the mother    |                                     |                                 |          |
| Permissive                       | 100 (84.7)                          | 78 (65.0)                       | 0.001    |
| Authoritative                    | 16 (13.6)                           | 24 (20.0)                       |          |
| Authoritarian                    | 2 (1.7)                             | 12 (10.0)                       |          |
| Neglectful                       | 0                                   | 6 (5.0)                         |          |

*: The chi-square test was used for categorical variables, and the Wilcoxon rank test was used for age data.

The genotype frequency distributions of the FKBP5 polymorphisms in the cases and control group were shown in Table S1. As shown in Table 2, without adjusting for other variables, only rs7757037 and rs2817032 were associated with depressive symptoms under the codominant model and dominant model. After adjusting for age, gender, and living arrangement, a significant association between rs7757037 and depressive symptoms was found in the codominant model (AG vs. GG; adjusted odds ratio [AOR] = 2.37, 95% CI = 1.07–5.28) and the dominant model (AA + AG vs. GG; AOR = 2.22, 95% CI = 1.05–4.69); rs2817032 polymorphism was associated
with depressive symptoms in the codominant model (TT vs. CC; AOR = 3.08, 95% CI = 1.15–8.25 & TC vs. CC; AOR = 3.39, 95% CI = 1.21–9.56) and dominant model (TT + TC vs. CC; AOR = 3.19, 95% CI = 1.22–9.33). However, after further adjusting for the father’s or mother’s parenting style, there are no significant associations of rs7757037 and rs2817032 with depressive symptoms (P > 0.05).
Table 2
Main effects of the FKBP5 polymorphisms on depressive symptoms.

| Variable | Model 1 |                  | Model 2 |                  | Model 3 |                  | Model 4 |                  |
|----------|---------|------------------|---------|------------------|---------|------------------|---------|------------------|
|          | OR (95% CI) | P value | Adjusted OR (95% CI) | P value | Adjusted OR (95% CI) | P value | Adjusted OR (95% CI) | P value |
| rs7757037* |         |         |                     |         |                     |         |                     |         |
| Codominant model |         |         |                     |         |                     |         |                     |         |
| AA vs. GG | 2.01 (0.94–4.34) | 0.074 | 2.03 (0.89–4.65) | 0.095 | 1.93 (0.83–4.46) | 0.126 | 1.85 (0.80–4.27) | 0.150 |
| AG vs. GG | 2.35 (1.13–4.92) | 0.023 | 2.37 (1.07–5.28) | 0.034 | 2.11 (0.94–4.74) | 0.072 | 1.90 (0.85–4.28) | 0.120 |
| Dominant model |         |         |                     |         |                     |         |                     |         |
| AA + AG vs. GG | 2.20 (1.10–4.39) | 0.025 | 2.22 (1.05–4.69) | 0.038 | 0.49 (0.23–1.05) | 0.068 | 1.87 (0.88–3.99) | 0.101 |
| Recessive model |         |         |                     |         |                     |         |                     |         |
| AA vs. AG + GG | 1.09 (0.63–1.89) | 0.748 | 1.10 (0.61–1.98) | 0.761 | 1.14 (0.62–2.10) | 0.670 | 1.19 (0.64–2.19) | 0.585 |
| rs2817032* |         |         |                     |         |                     |         |                     |         |
| Codominant model |         |         |                     |         |                     |         |                     |         |
| TT vs. CC | 3.01 (1.18–7.70) | 0.022 | 3.08 (1.15–8.25) | 0.026 | 2.69 (0.99–7.29) | 0.051 | 2.44 (0.90–6.58) | 0.079 |
| TC vs. CC | 2.77 (1.04–7.35) | 0.041 | 3.39 (1.21–9.56) | 0.021 | 2.65 (0.92–7.60) | 0.070 | 2.58 (0.91–7.32) | 0.074 |
| Dominant model |         |         |                     |         |                     |         |                     |         |
| TT + TC vs. CC | 2.91 (1.17–7.27) | 0.022 | 3.19 (1.22–8.33) | 0.018 | 2.68 (1.01–7.08) | 0.047 | 2.49 (0.95–6.54) | 0.064 |

Abbreviations:

OR, odds ratio; 95% CI, 95% confidence interval; NA, not applicable or not available.

*: Only the FKBP5 polymorphisms observed with a significant association of depressive symptoms in the unadjusted model were reported here.

Model 1: unadjusted models.

Model 2: adjusted for age, gender, and living arrangement.

Model 3: adjusted for age, gender, living arrangement, and parenting style of the father.

Model 4: adjusted for age, gender, living arrangement, and parenting style of the mother.
| Variable                  | Model 1                         | Model 2                         | Model 3                         | Model 4                         |
|---------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
|                           | OR (95% CI) P value              | Adjusted OR (95% CI) P value    | Adjusted OR (95% CI) P value    | Adjusted OR (95% CI) P value    |
| **Recessive model**       |                                 |                                 |                                 |                                 |
| TT vs. TC + CC            | 1.36 (0.81–2.28) 0.243          | 1.21 (0.70–2.10) 0.500          | 1.30 (0.73–2.30) 0.372          | 1.19 (0.67–2.10) 0.551          |
| rs2817035*                |                                 |                                 |                                 |                                 |
| **Codominant model**      |                                 |                                 |                                 |                                 |
| GG vs. AA                 | 2.55 (1.03–6.32) 0.043          | 2.54 (0.98–6.60) 0.056          | 2.18 (0.82–5.75) 0.117          | 2.03 (0.77–5.37) 0.155          |
| GA vs. AA                 | 2.07 (0.80–5.37) 0.135          | 2.21 (0.81–6.05) 0.123          | 1.76 (0.63–4.93) 0.283          | 1.74 (0.62–4.84) 0.291          |
| **Dominant model**        |                                 |                                 |                                 |                                 |
| GG + GA vs. AA            | 2.36 (0.98–5.72) 0.056          | 2.41 (0.95–6.12) 0.063          | 2.02 (0.78–5.20) 0.146          | 1.92 (0.74–4.93) 0.178          |
| **Recessive model**       |                                 |                                 |                                 |                                 |
| GG vs. GA + AA            | 1.47 (0.87–2.47) 0.151          | 1.40 (0.80–2.44) 0.242          | 1.43 (0.80–2.55) 0.228          | 1.34 (0.75–2.37) 0.324          |
| **Parenting style of the father** |                       |                                 |                                 |                                 |
| Authoritarian             | 1.00 (reference) NA             | 1.00 (reference) NA             | NA                              | NA                              |
| Permissive                | 0.26 (0.08–0.82) 0.021          | 0.19 (0.06–0.66) 0.009          | NA                              | NA                              |

**Abbreviations:**

OR, odds ratio; 95% CI, 95% confidence interval; NA, not applicable or not available.

*: Only the *FKBP5* polymorphisms observed with a significant association of depressive symptoms in the unadjusted model were reported here.

**Model 1:** unadjusted models.

**Model 2:** adjusted for age, gender, and living arrangement.

**Model 3:** adjusted for age, gender, living arrangement, and parenting style of the father.

**Model 4:** adjusted for age, gender, living arrangement, and parenting style of the mother.
| Variable                          | Model 1                          | Model 2                          | Model 3                          | Model 4                          |
|----------------------------------|----------------------------------|----------------------------------|----------------------------------|----------------------------------|
|                                  | OR (95% CI)                      | P value                          | Adjusted OR (95% CI)              | P value                          | Adjusted OR (95% CI)              | P value                          | Adjusted OR (95% CI)              | P value                          |
|----------------------------------|----------------------------------|----------------------------------|----------------------------------|----------------------------------|----------------------------------|----------------------------------|----------------------------------|----------------------------------|
| Authoritative                    | 0.24 (0.07–0.83)                 | 0.024                            | 0.22 (0.06–0.82)                 | 0.023                            | NA                               | NA                               | NA                               | NA                               |
| Neglectful                       | 4.62 (0.46–46.67)                | 0.195                            | 3.15 (0.29–34.59)                | 0.348                            | NA                               | NA                               | NA                               | NA                               |
| Parenting style of the mother    |                                  |                                  |                                  |                                  |                                  |                                  |                                  |                                  |
| Authoritarian                    | 1.00 (reference)                 | 1.00 (reference)                 | NA                               | NA                               | NA                               | NA                               | NA                               | NA                               |
| Permissive                       | 0.13 (0.03–0.60)                 | 0.009                            | 0.11 (0.02–0.53)                 | 0.006                            | NA                               | NA                               | NA                               | NA                               |
| Authoritative                    | 0.25 (0.05–1.27)                 | 0.095                            | 0.22 (0.04–1.21)                 | 0.081                            | NA                               | NA                               | NA                               | NA                               |
| Neglectful                       | NA                               | NA                               | NA                               | NA                               | NA                               | NA                               | NA                               | NA                               |

Abbreviations:

OR, odds ratio; 95% CI, 95% confidence interval; NA, not applicable or not available.

*: Only the $FKBP5$ polymorphisms observed with a significant association of depressive symptoms in the unadjusted model were reported here.

Model 1: unadjusted models.

Model 2: adjusted for age, gender, and living arrangement.

Model 3: adjusted for age, gender, living arrangement, and parenting style of the father.

Model 4: adjusted for age, gender, living arrangement, and parenting style of the mother.

Table 3 depicts the interaction effects between $FKBP5$ polymorphisms and parenting style on depressive symptoms. After adjusting for age, gender, and living arrangement, significant interactions between rs7757037 and the father’s parenting style were found in the codominant model (AG vs. GG; $P = 0.037$) and dominant model (AA + AG vs. GG; $P = 0.038$). However, the gene-environment interactions were not significant after correcting for multiple testing.
Table 3
Interaction effects between FKBP5 polymorphisms and parenting style on depressive symptoms.

| Interaction item | Model 1 | Model 2 |   |   |   |   |
|------------------|---------|---------|---|---|---|---|
|                  | OR (95% CI) | P value | Adjusted OR (95% CI) | P value |
| rs7757037        |          |         |   |   |   |   |
| rs7757037×parenting style of the father |         |         |   |   |   |   |
| Codominant model | AA vs. GG | 5.35 (1.15–24.8) | 0.032 | 4.60 (0.92–23.12) | 0.064 |
|                  | AG vs. GG | 6.04 (1.36–26.94) | 0.018* | 5.31 (1.11–25.46) | 0.037 |
| Dominant model   | AA + AG vs. GG | 5.78 (1.34–24.96) | 0.019* | 5.03 (1.09–23.20) | 0.038 |
| Recessive model  | AA vs. AG + GG | 1.05 (0.51–2.18) | 0.890 | 1.03 (0.46–2.31) | 0.938 |
| rs7757037×parenting style of the mother |         |         |   |   |   |   |
| Codominant model | AA vs. GG | 0.70 (0.11–4.43) | 0.702 | 0.25 (0.03–1.85) | 0.175 |
|                  | AG vs. GG | 0.72 (0.12–4.21) | 0.715 | 0.30 (0.05–2.02) | 0.217 |
| Dominant model   | AA + AG vs. GG | 0.71 (0.13–4.02) | 0.703 | 0.29 (0.05–1.83) | 0.187 |
| Recessive model  | AA vs. AG + GG | 0.87 (0.32–2.36) | 0.783 | 0.67 (0.22–2.03) | 0.473 |
| rs2817032        |          |         |   |   |   |   |
| rs2817032×parenting style of the father |         |         |   |   |   |   |
| Codominant model | TT vs. CC | NA | NA | NA | NA |
|                  | TC vs. CC | NA | NA | NA | NA |
| Dominant model   | TT + TC vs. CC | NA | NA | 0.95 (0.66–1.36) | 0.773 |
| Recessive model  | TT vs. TC + CC | 1.10 (0.56–2.15) | 0.784 | 1.09 (0.52–2.29) | 0.825 |

Abbreviations: OR, odds ratio; 95% CI, 95% confidence interval; NA, not applicable or not available.

Model 1: unadjusted models.

Model 2: adjusted for age, gender, and living arrangement.

*: Gene-environment interactions, which remained significant after correcting for multiple testing.
| Interaction item | Model 1 | | | | Model 2 | | | |
|-----------------|--------|--------|--------|--------|--------|--------|--------|
| | OR (95% CI) | P value | Adjusted OR (95% CI) | P value |
|________________|---------|---------|-----------------|---------|
| rs2817032×parenting style of the mother | | | | |
| Codominant model | TT vs. CC | NA | NA | NA | NA | NA | NA |
| | TC vs. CC | NA | NA | NA | NA | NA | NA |
| Dominant model | TT + TC vs. CC | NA | NA | NA | NA | NA | NA |
| Recessive model | TT vs. TC + CC | 0.98 (0.37–2.57) | 0.969 | 0.62 (0.22–1.80) | 0.380 |
| rs2817035 | | | | |
| rs2817035×parenting style of the father | | | | |
| Codominant model | GG vs. AA | 7.60 (0.71–81.21) | 0.094 | 10.16 (0.89–116.17) | 0.062 |
| Dominant model | GG + GA vs. AA | 7.43 (0.71–77.64) | 0.094 | 9.95 (0.89–111.06) | 0.062 |
| Recessive model | GG vs. GA + AA | 1.10 (0.56–2.14) | 0.787 | 1.18 (0.56–2.49) | 0.662 |
| rs2817035×parenting style of the mother | | | | |
| Codominant model | GG vs. AA | NA | NA | NA | NA | NA | NA |
| | GA vs. AA | NA | NA | NA | NA | NA | NA |
| Dominant model | GG + GA vs. AA | NA | NA | NA | NA | NA | NA |
| Recessive model | GG vs. GA + AA | 1.19 (0.46–3.05) | 0.722 | 0.90 (0.32–2.55) | 0.847 |

Abbreviations: OR, odds ratio; 95% CI, 95% confidence interval; NA, not applicable or not available.

Model 1: unadjusted models.

Model 2: adjusted for age, gender, and living arrangement.

*: Gene-environment interactions, which remained significant after correcting for multiple testing.

As shown in Table S2, we observed no significant differences in the methylation levels of the selected FKBP5 CpG sites between the cases and the control group (all $P > 0.05$). Additionally, there were no significant interaction effects between FKBP5 gene methylation status and parenting styles on depressive symptoms observed in this study (all $P > 0.05$, Table 4). Moreover, no significant mediations were found in the association
between FKBP5 polymorphisms and depressive symptoms through differential methylation at the detected CpG sites of the FKBP5 promoter region (Table S3).
### Table 4
Interaction effects between *FKBP5* gene methylation status and parenting style on depressive symptoms.

| Interaction | *P* value<br>\(^*\) |
|-------------|-----------------|
| **Parenting style of the father**<br>
| *FKBP5*-12 CpG 1 | 0.653 |
| *FKBP5*-12 CpG 2 | 0.974 |
| *FKBP5*-12 CpG 3 | 0.414 |
| *FKBP5*-12 CpG 4 | 0.761 |
| *FKBP5*-12 CpG 5.6.7 | 0.951 |
| *FKBP5*-12 CpG 8 | 0.630 |
| *FKBP5*-12 CpG 9 | 0.887 |
| *FKBP5*-12 CpG 10.11 | 0.942 |
| *FKBP5*-12 CpG 12 | 0.232 |
| *FKBP5*-12 CpG 13 | 0.463 |
| *FKBP5*-12 CpG 14 | 0.599 |
| *FKBP5*-12 CpG 15 | 0.491 |
| *FKBP5*-12 CpG 17.18.19 | 0.505 |
| *FKBP5*-12 CpG 20 | 0.761 |
| **Parenting style of the mother**<br>
| *FKBP5*-12 CpG 1 | 0.951 |
| *FKBP5*-12 CpG 2 | 0.661 |
| *FKBP5*-12 CpG 3 | 0.575 |
| *FKBP5*-12 CpG 4 | 0.211 |
| *FKBP5*-12 CpG 5.6.7 | 0.230 |
| *FKBP5*-12 CpG 8 | 0.217 |
| *FKBP5*-12 CpG 9 | 0.852 |
| *FKBP5*-12 CpG 10.11 | 0.818 |
| *FKBP5*-12 CpG 12 | 0.063 |
| *FKBP5*-12 CpG 13 | 0.205 |

*:\ The interaction items between *FKBP5* methylation status and the parenting style of father/mother were added into the multivariate conditional logistic regression models along with single variables, respectively. Considering the 95% confidence intervals of the odds ratios were too wide, only *P* values were reported.
| Interaction                  | Pr-value* |
|-----------------------------|-----------|
| FKBP5-12 CpG 14             | 0.486     |
| FKBP5-12 CpG 15             | 0.498     |
| FKBP5-12 CpG 17-18-19       | 0.766     |
| FKBP5-12 CpG 20             | 0.211     |

*: The interaction items between FKBP5 methylation status and the parenting style of father/mother were added into the multivariate conditional logistic regression models along with single variables, respectively. Considering the 95% confidence intervals of the odds ratios were too wide, only P values were reported.

**Discussion**

This study was the first study investigating interactions between FKBP5 gene variation and parenting style on depressive symptoms in an adolescent sample. Our findings suggested that among the selected 14 SNPs, only FKBP5 rs7757037 and rs2817032 were associated with the increased risk of depressive symptoms in the codominant model and dominant model with and without adjusting for sociodemographic characteristics. Similarly, Piechaczek et al. reported that no main genetic effects of the five SNPs (rs3800373, rs9296158, rs1360780, rs9470080, and rs4713916) on depression were found [14]; Lou et al. reported that rs7757037 of FKBP5 was associated with depression in Chinese systemic lupus erythematosus patients [34] in dominant model. However, this finding was inconsistent with a study among patients with coronary artery disease, indicating rs2817032 was not associated with depressive symptoms among those patients [35]. The diversity of populations, which might result in various gene sensitivity, may explain the discrepancy of genotype models, while this study focused on Chinese adolescents. Moreover, while this study found that the significant genetic main effects of FKBP5 rs7757037 and rs2817032 were not significant after adjusting for the parenting style of the father or mother, respectively. These findings were in line with most prior studies, which demonstrated no main genetic effects predicting case-control status after adjusting for other variables [13, 14, 36]; indicating that genetic factors may have to interact with environmental stressors to elicit depressive symptoms [5].

Previous evidence has suggested that parenting style was one of the most significant environmental stressors influencing their child’s growth [16]. Consistent with prior studies [18, 37], the protective role of the father’s permissive and authoritative parenting style on the development of depressive symptoms among Chinese adolescents was observed. Considering the FKBP5 gene plays a vital role in regulating the HPA-axis and is implicated in depressive symptoms [38], it seems appropriate to study the effect of the FKBP5 gene in the context of parenting style as an environmental stressor. Extending previous evidence, a novel aspect of this study was that the influences of parenting style of father/mother (reflecting more stable living background) and their interactions with FKBP5 polymorphisms on adolescent depressive symptoms were explored; while much of the previous literature on the gene-environment interactions at the FKBP5 locus in the context of depressive symptoms mainly focused on adverse or traumatic life events [15, 36]. In this study, without adjusting for sociodemographic variables, significant interactions between FKBP5 rs7757037 and the father’s parenting style were first observed in the codominant and dominant model, even correcting for multiple testing. These results might be explained by the diathesis-stress model of depressive symptoms [39], which indicated that FKBP5 rs7757037 carriers might exhibit a heightened HPA response activity and be more likely to be implicated in the risk for depressive symptoms when experiencing negative parenting styles. However, based on multiple testing
corrections, these interaction effects did not significantly predict depressive symptoms after adjusting for sociodemographic variables. It needs to be considered that these interactions reached nominal significance, given the small sample size in the present study. It would be significant to follow up on this finding in future studies using larger sample sizes. Besides, this finding may also reflect that a single environmental stressor (i.e., parenting style in this study) may not be potent enough to elicit the development of depressive symptoms in adolescence, and other sociodemographic stressors may influence the effects of the single environmental stress.

Additionally, **FKBP5** epigenetic changes induced by environmental stressors have also been reported to be associated with the risk of depressive symptoms [40]. Considering parenting style may affect the developing brain through leading to changes in methylation levels of **FKBP5**, this study also compared the difference of **FKBP5** methylation levels between students with and without depressive symptoms and investigated the interactions between **FKBP5** methylation status and parenting style. However, no significant difference or association was observed. Similarly, Klinger-König et al. reported there were no significant effects of **FKBP5** methylation or the interaction between **FKBP5** methylation and childhood maltreatment on depressive symptoms [41]; Höhne et al. showed that no significant difference of **FKBP5** DNA methylation in intron 7 between subjects with a lifetime history of depression and healthy controls was observed [42]; Bustamante et al. also reportedly did not observe any association of **FKBP5** methylation levels in intron 7 or intron 2 with depressive symptoms [43]. Nevertheless, we also estimated the role of **FKBP5** methylation in the association of **FKBP5** polymorphisms and parenting style with depressive symptoms. In accordance with previous studies [41, 43], no significant interactions between parenting style and **FKBP5** methylation status were observed, and the mediating effect of **FKBP5** DNA methylation on the association between **FKBP5** polymorphism and depressive symptoms was also not statistically significant.

To our knowledge, the present study is the first nested case-control study to explore the associations of **FKBP5** genetic and epigenetic variation with depressive symptoms among Chinese adolescents in the context of parenting style. However, there were several limitations that should be noted. First, only the **FKBP5** gene was examined in this study by a hypothesis-driven approach, and other potential genes with implications in depressive symptoms (e.g., BDNF or NR3C1 gene) were not considered. However, depressive symptoms may have a polygenic nature. Second, although parenting style and depressive symptoms were measured by self-reported, which may lead to self-report bias, self-reports remain a common and accepted method. Third, the sample size is relatively small, which may imply insufficient statistical power of these findings.

**Conclusions**

This study suggests a significant relationship of **FKBP5** rs7757037 and rs2817032 with depressive symptoms without adjusting for parenting style and observes a nominally significant interaction between **FKBP5** rs7757037 and parenting style of the father on depressive symptoms. However, no significant association of **FKBP5** CpG methylation status with parenting style, **FKBP5** polymorphisms, or depressive symptoms was observed. Therefore, this work suggests that parenting style, almost experiencing by each adolescent, can be targeted in prevention strategies, and a particular focus should be placed on adolescents who suffered negative parenting styles. Moreover, this study also indicates that **FKBP5** variation, not DNA methylation, may be more sensitive in moderating the effects of parenting style stressors on depressive symptoms, especially for the negative parenting style of the father, even though the evidence under the mechanism is deficient now. Further studies to investigate the underlying mechanism are warranted.
Declarations

Ethical approval and consent to participate

The study procedures were carried out in accordance with the Declaration of Helsinki. The study obtained ethical approval from the Sun Yat-sen University, School of Public Health Institutional Review Board (Ethics Number: L201707060)

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 no conflict of interest.

Funding: This work was supported by National Natural Science Foundation of China (grant No. 81761128030; grant No. 81903339), Natural Science Foundation of Guangdong Province (grant No. 2019A1515011091), and the Science and Technology Planning Project of Guangzhou (grant No. 202102020136).

Author’s Contributors: Lan Guo and Ciyong Lu designed the study. Lan Guo, Wanxin Wang, Yangfeng Guo, Xueying Du, and Guangduoji Shi managed the literature searches and summaries of previous related work. Xueying Du, Wanxin Wang, Yangfeng Guo, and Guangduoji Shi carried out the field research. Lan Guo did the statistical analyses and wrote the first draft of this manuscript. All authors reviewed the manuscript.

Acknowledgements: The authors gratefully acknowledge the contribution of participating schools, and also gratefully acknowledge technical support from the School of Public Health, Sun Yat-sen University.

References

1. Erskine HE, Moffitt TE, Copeland WE, Costello EJ, Ferrari AJ, Patton G, Degenhardt L, Vos T, Whiteford HA, Scott JG: A heavy burden on young minds: the global burden of mental and substance use disorders in children and youth. PSYCHOL MED 2015, 45(7):1551–1563.

2. National Academies Of Sciences EAM, Division HAM, Education DOBA, Board On Children YAF, Applications COTN, Backes EP BRE: The Promise of Adolescence: Realizing Opportunity for All Youth. Washington (DC): National Academies Press (US). 2, Adolescent Development. Available from: https://www.ncbi.nlm.nih.gov/books/NBK545476/; 2019.

3. Thapar A, Collishaw S, Pine DS, Thapar AK: Depression in adolescence. LANCET 2012, 379(9820):1056–1067.

4. Monroe SM, Slavich GM, Gotlib IH: Life stress and family history for depression: the moderating role of past depressive episodes. J PSYCHIATR RES 2014, 49:90–95.

5. Corfield EC, Yang Y, Martin NG, Nyholt DR: A continuum of genetic liability for minor and major depression. Transl Psychiatry 2017, 7(5):e1131.
6. Dunlavey CJ: *Introduction to the Hypothalamic-Pituitary-Adrenal Axis: Healthy and Dysregulated Stress Responses, Developmental Stress and Neurodegeneration*. *J Undergrad Neurosci Educ* 2018, 16(2):R59-R60.

7. van Bodegom M, Homberg JR, Henckens M: *Modulation of the Hypothalamic-Pituitary-Adrenal Axis by Early Life Stress Exposure*. *FRONT CELL NEUROSCI* 2017, 11:87.

8. Zannas AS, Binder EB: *Gene-environment interactions at the FKBP5 locus: sensitive periods, mechanisms and pleiotropism*. *GENES BRAIN BEHAV* 2014, 13(1):25–37.

9. Szczepankiewicz A, Leszczynska-Rodziewicz A, Pawlak J, Narozena B, Rajewska-Rager A, Wilkosc M, Zaremba D, Maciukiewicz M, Twarowska-Hauser J: *FKBP5 polymorphism is associated with major depression but not with bipolar disorder*. *J Affect Disord* 2014, 164:33–37.

10. Tozzi L, Carballedo A, Wetterling F, McCarthy H, O’Keane V, Gill M, Morris D, Fahey C, Meaney J, Frodl T: *Single-Nucleotide Polymorphism of the FKBP5 Gene and Childhood Maltreatment as Predictors of Structural Changes in Brain Areas Involved in Emotional Processing in Depression*. *NEUROPSYCHOPHARMACOL* 2016, 41(2):487–497.

11. Brandt J, Warnke K, Jörgens S, Arolt V, Beer K, Domschke K, Haverkamp W, Kuhlmann SL, Müller-Nordhom J, Rieckmann N et al: *Association of FKBP5 genotype with depressive symptoms in patients with coronary heart disease: a prospective study*. *J NEURAL TRANSM* 2020, 127(12):1651–1662.

12. Lekman M, Laje G, Charney D, Rush AJ, Wilson AF, Sorant AJ, Lipsky R, Wisniewski SR, Manji H, McMahon FJ et al: *The FKBP5-gene in depression and treatment response—an association study in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) Cohort*. *Biol Psychiatry* 2008, 63(12):1103–1110.

13. Zimmermann P, Bruckl T, Nocon A, Pfister H, Binder EB, Uhr M, Lieb R, Moffitt TE, Caspi A, Holsboer F et al: *Interaction of FKBP5 gene variants and adverse life events in predicting depression onset: results from a 10-year prospective community study*. *Am J Psychiatry* 2011, 168(10):1107–1116.

14. Piechaczek CE, Greimel E, Feldmann L, Pehl V, Allgaier AK, Frey M, Freisleder FJ, Halldorsdottir T, Binder EB, Ising M et al: *Interactions between FKBP5 variation and environmental stressors in adolescent Major Depression*. *PSYCHONEUROENDOCRINO* 2019, 106:28–37.

15. Kang C, Shi J, Gong Y, Wei J, Zhang M, Ding H, Wang K, Yu Y, Wang S, Han J: *Interaction between FKBP5 polymorphisms and childhood trauma on depressive symptoms in Chinese adolescents: The moderating role of resilience*. *J Affect Disord* 2020, 266:143–150.

16. Murphy DA, Brecht ML, Huang D, Herbeck DM: *Trajectories of Delinquency from Age 14 to 23 in the National Longitudinal Survey of Youth Sample*. *Int J Adolesc Youth* 2012, 17(1):47–62.

17. Lipps G, Lowe GA, Gibson RC, Halliday S, Morris A, Clarke N, Wilson RN: *Parenting and depressive symptoms among adolescents in four Caribbean societies*. *Child Adolesc Psychiatry Ment Health* 2012, 6(1):31.

18. Griffith JM, Crawford CM, Oppenheimer CW, Young JF, Hankin BL: *Parenting and Youth Onset of Depression Across Three Years: Examining the Influence of Observed Parenting on Child and Adolescent Depressive Outcomes*. *J Abnorm Child Psychol* 2019, 47(12):1969–1980.

19. Jiang S, Postnov L, Cattaneo A, Binder EB, Aitchison KJ: *Epigenetic Modifications in Stress Response Genes Associated With Childhood Trauma*. *FRONT PSYCHIATRY* 2019, 10.

20. Klengel T, Binder EB: *Allele-specific epigenetic modification: a molecular mechanism for gene-environment interactions in stress-related psychiatric disorders?* *EPIGENOMICS-UK* 2013, 5(2):109–112.
21. Wang W, Du X, Guo Y, Li W, Zhang S, Zhang W, McIntyre RS, Tamura JK, Guo L, Lu C: Associations Among Screen Time, Sleep Duration and Depressive Symptoms Among Chinese Adolescents. *J Affect Disord* 2021, 284:69–74.

22. Wang W, Du X, Guo Y, Li W, Teopiz KM, Shi J, Guo L, Lu C, McIntyre RS: The associations between sleep situations and mental health among Chinese adolescents: A longitudinal study. *SLEEP MED* 2021, 82:71–77.

23. Lee SW, Stewart SM, Byrne BM, Wong JP, Ho SY, Lee PW, Lam TH: Factor structure of the Center for Epidemiological Studies Depression Scale in Hong Kong adolescents. *J Pers Assess* 2008, 90(2):175–184.

24. Zhi-yan C, Xiao-dong Y: Psychometric Features of CES-D in Chinese Adolescents (in Chinese). *Chinese Journal of Clinical Psychology* 2009, 17(4).

25. Radloff LS: The use of the Center for Epidemiologic Studies Depression Scale in adolescents and young adults. *J Youth Adolesc* 1991, 20(2):149–166.

26. YANG H: Using the CES-D in a two-phase survey for depressive disorders among nonreferred adolescents in Taipei: a stratum-specific likelihood ratio analysis. *J AFFECT DISORDERS* 2004.

27. Guo L, Xu Y, Deng J, Huang J, Huang G, Gao X, Li P, Wu H, Pan S, Zhang WH et al: Association between sleep duration, suicidal ideation, and suicidal attempts among Chinese adolescents: The moderating role of depressive symptoms. *J Affect Disord* 2017, 208:355–362.

28. Baumrind D: Patterns of parental authority and adolescent autonomy. *New Dir Child Adolesc Dev* 2005(108):61–69.

29. Baumrind D: The Influence of Parenting Style on Adolescent Competence and Substance Use. *The Journal of Early Adolescence* 1991, 11(1):56–95.

30. Coolen MW, Statham AL, Gardiner-Garden M, Clark SJ: Genomic profiling of CpG methylation and allelic specificity using quantitative high-throughput mass spectrometry: critical evaluation and improvements. *Nucleic Acids Res* 2007, 35(18):e119.

31. Okada S, Morinobu S, Fuchikami M, Segawa M, Yokomaku K, Kataoka T, Okamoto Y, Yamawaki S, Inoue T, Kusumi I et al: The potential of SLC6A4 gene methylation analysis for the diagnosis and treatment of major depression. *J Psychiatr Res* 2014, 53:47–53.

32. Lam D, Ancelin ML, Ritchie K, Freak-Poli R, Saffery R, Ryan J: Genotype-dependent associations between serotonin transporter gene (SLC6A4) DNA methylation and late-life depression. *BMC Psychiatry* 2018, 18(1):282.

33. Preacher KJ, Hayes AF: SPSS and SAS procedures for estimating indirect effects in simple mediation models. *Behav Res Methods Instrum Comput* 2004, 36(4):717–731.

34. Lou QY, Li Z, Teng Y, Xie QM, Zhang M, Huang SW, Li WF, Chen YF, Pan FM, Xu SQ et al: Associations of FKBP4 and FKBP5 gene polymorphisms with disease susceptibility, glucocorticoid efficacy, anxiety, depression, and health-related quality of life in systemic lupus erythematosus patients. *Clin Rheumatol* 2021, 40(1):167–179.

35. Wang H, Wang C, Song X, Liu H, Zhang Y, Jiang P: Association of FKBP5 polymorphisms with patient susceptibility to coronary artery disease comorbid with depression. *PeerJ* 2020, 8:e9286.

36. Scheuer S, Ising M, Uhr M, Otto Y, von Klitzing K, Klein AM: FKBP5 polymorphisms moderate the influence of adverse life events on the risk of anxiety and depressive disorders in preschool children. *J Psychiatr Res*
2016, 72:30–36.

37. Gorostiaga A, Aliri J, Balluerka N, Lameirinhas J: Parenting Styles and Internalizing Symptoms in Adolescence: A Systematic Literature Review. Int J Environ Res Public Health 2019, 16(17).

38. Zannas AS, Wiechmann T, Gassen NC, Binder EB: Gene-Stress-Epigenetic Regulation of FKBP5: Clinical and Translational Implications. NEUROPSYCHOPHARMACOL 2016, 41(1):261–274.

39. Colodro-Conde L, Couvy-Duchesne B, Zhu G, Coventry WL, Byrne EM, Gordon S, Wright MJ, Montgomery GW, Madden P, Ripke S et al: A direct test of the diathesis-stress model for depression. Mol Psychiatry 2018, 23(7):1590–1596.

40. Han KM, Won E, Sim Y, Kang J, Han C, Kim YK, Kim SH, Joe SH, Lee MS, Tae WS et al: Influence of FKBP5 polymorphism and DNA methylation on structural changes of the brain in major depressive disorder. Sci Rep 2017, 7:42621.

41. Klinger-Konig J, Hertel J, Van der Auwera S, Frenzel S, Pfeiffer L, Waldenberger M, Golchert J, Teumer A, Nauck M, Homuth G et al: Methylation of the FKBP5 gene in association with FKBP5 genotypes, childhood maltreatment and depression. NEUROPSYCHOPHARMACOL 2019, 44(5):930–938.

42. Hohne N, Poidinger M, Merz F, Pfister H, Bruckl T, Zimmermann P, Uhr M, Holsboer F, Ising M: FKBP5 Genotype-Dependent DNA Methylation and mRNA Regulation After Psychosocial Stress in Remitted Depression and Healthy Controls. INT J NEUROPSYCHOPH 2015, 18(4):u87.

43. Bustamante AC, Aiello AE, Guffanti G, Galea S, Wildman DE, Uddin M: FKBP5 DNA methylation does not mediate the association between childhood maltreatment and depression symptom severity in the Detroit Neighborhood Health Study. J PSYCHIATR RES 2018, 96:39–48.

Figures
Figure 1
The flowchart of the nested case-control study.

Supplementary Files
This is a list of supplementary files associated with this preprint. Click to download.

- Supplement.docx