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Interactions between *FKBP5* variation and environmental stressors in adolescent Major Depression

Charlotte Elisabeth Piechaczek[a,*], Ellen Greimel[a], Lisa Feldmann[a], Verena Pehl[a], Antje-Kathrin Allgaier[a,b], Michael Frey[a], Franz Joseph Freisleder[c], Thorhildur Halldorsdottir[d,e], Elisabeth B. Binder[d,f], Marcus Ising[g,1], Gerd Schulte-Körne[a,1]

[a] Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, University Hospital, LMU Munich, Nußbaumstr. 5A, 80336 Munich, Germany
[b] Faculty of Social Sciences, Department of Psychology, University of the German Armed Forces, Werner-Heisenberg-Weg 39, 85577 Neubiberg, Germany
[c] KBO Heckscher-Klinikum, Deisenhofenerstr. 28, 81539 Munich, Germany
[d] Department of Translational Research in Psychiatry, Max-Planck Institute of Psychiatry, Kraepelinstr. 2-10, 80804 Munich, Germany
[e] Centre of Public Health Sciences, Faculty of Medicine, University of Iceland, Vatnsmýrarvegur 16, 101 Reykjavík, Iceland
[f] Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, 12 Executive Park Dr NE #200, Atlanta, GA 30329, USA
[g] Max Planck Institute of Psychiatry, Kraepelinstr. 2-10, 80804 Munich, Germany

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ABSTRACT

Objective: Major Depression (MD) results from a complex interplay between environmental stressors and biological factors. Previous studies in adults have shown that adverse life events interact with genetic variation in *FKBP5*, a gene implicated in the stress-response system, to predict depressive symptoms and MD. This is the first study to investigate interactions between *FKBP5* variants and a range of environmental stressors in adolescents with a clinical diagnosis of MD.

Method: 148 male and female adolescents with MD and 143 typically developing (TD) controls (13-18 years) were included in the present study. For self-reported environmental stressors, subjective severity was assessed to allow a classification of these factors as mild, moderate and severe. Sociodemographic stressors were assessed via parental-report.

Results: With a heightened number of sociodemographic, moderate and total number of stressors, participants carrying at least one copy of the *FKBP5* CATT haplotype or at least one minor allele of various *FKBP5* SNPs had the highest risk for being in the MD group. No genetic main effects were found. Sociodemographic stressors as well as self-reported mild, moderate, and severe stressors were more common in depressed than in TD adolescents.

Conclusion: This is the first study to show interactions between genetic variation in *FKBP5* and environmental stressors in a sample of clinically depressed adolescents. The current study provides important starting-points for preventive efforts and highlights the need for a fine-grained analysis of different forms and severities of environmental stressors and their interplay with genetic variation for understanding the complex etiology of (youth) MD.

1. Introduction

Adolescence is a developmentally sensitive period characterized by marked changes in biological systems, heightened brain plasticity and the maturation of stress systems. These changes render adolescents vulnerable for psychiatric diseases including Major Depression (MD; Andersen and Teicher, 2008). Additionally, a large body of research shows that youth MD is elicited by a substantial increase in stressors in the (social) environment, such as changes at home/school and experiences of violence and loss (Brent et al., 2009; Ge et al., 2006; Hussey et al., 2006; Kaltiala-Heino et al., 2001; Margolin and Gordis, 2000; McCarty et al., 2008; Sund et al., 2003; Thapar et al., 2012). In addition, sociodemographic stressors (e.g., low parental education) are known to be implicated in youth MD (Kaltiala-Heino et al., 2001; Sund

* Corresponding author at: Charlotte Elisabeth Piechaczek, Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, University Hospital, LMU Munich, Pettenkoferstr. 8A, D-80336 Munich, Germany.
E-mail address: Charlotte.Piechaczek@med.uni-muenchen.de (C.E. Piechaczek).
[1] These authors have shared senior authorship.

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et al., 2003). In this context, it is generally assumed that youth from families with a lower socioeconomic status (SES) experience more adverse life events than peers from families with a higher SES. The experience of a heightened amount of stress, in turn, may increase the risk for developing an episode of MD (Bradley and Corwyn, 2002; Hackman et al., 2010).

As MD is often precipitated by stress, the disorder can be conceptualized as being stress-related (Chrousos and Gold, 1992; Holsboer, 2000; Ising and Holsboer, 2006). In line, it has been claimed that environmental stressors can lead to a disruption of the stress-response system with the hypothalamic-pituitary-adrenal (HPA)-axis as a main component (Chrousos and Gold, 1992; Holsboer, 2000; Ising and Holsboer, 2006). Upon stress exposure, glucocorticoids (e.g., cortisol) are released. They activate the glucocorticoid receptor (GR), which initiates a negative feedback loop of the HPA-axis. This feedback loop aims at terminating the physiological stress response. In MD, this negative feedback loop has been suggested to be impaired, leading to a prolonged physiological stress response (Baumeister et al., 2014; Del Rey et al., 2008). However, studies exclusively investigating stressors implicated in youth MD fall short in addressing the complex etiology of the disease.

According to the diathesis-stress model, some people are equipped with a heightened biological risk for psychiatric disorders. However, a disorder may not develop until this diathesis converges with the experience of stressors of a certain intensity (Ingram and Luxton, 2005; Monroe and Simons, 1991). It is well acknowledged that a biological diathesis, including genetic factors, contributes to MD risk and may interplay with environmental stressors (e.g., Colodro-Conde et al., 2017). Given the relationship between experiences of stressors and an altered HPA-axis functioning in MD, it seems pertinent to study genes related to the HPA-axis, such as the *FKBP5* gene (Chrousos and Gold, 1992; Holsboer, 2000; Ising and Holsboer, 2006; Matosin et al., 2018).

The *FKBP5* gene encodes for the FK506 binding protein-51 (FKBP51), which is a co-chaperone protein to the heatshock protein HSP90, both playing a key role in regulating the sensitivity of the GR (Pratt and Toft, 1997). During acute stress, the cortisol-activated GR attaches to strands of the DNA, called glucocorticoid response elements (GREs). These elements are implicated in gene transcription. Binding of the GR to GREs has been associated with an enhanced transcription of *FKBP5* and increased levels of FKBP51 (de Kloet et al., 2005). FKBP51 binds to the GR upon stress exposure, impeding its activation and translocation, resulting in a disinhibition of the HPA-axis (Scammell et al., 2001; Scharf et al., 2011; Vermeer et al., 2003; Wochnik et al., 2005). The *FKBP5* single nucleotide polymorphism (SNP) rs1360780 is suggested to be the relevant variant being particularly involved in HPA-axis dysregulation as observed in MD (Binder, 2009; Klengel and Binder, 2013). Carriers of the rs1360780 minor allele show changes in chromatin structure, which has been found to facilitate *FKBP5* transcription via GR-binding to GREs (Klengel et al., 2013). In addition, exposure to stress during vulnerable developmental periods, i.e. childhood and youth, may lead to a demethylation of GREs in rs1360780 minor allele carriers. This, in turn, is thought to result in an increased transcription of *FKBP5* and a related increase of FKBP51 levels and, as a consequence, a further exacerbation of HPA-axis dysregulation in *FKBP5* rs1360780 minor allele carriers (Klengel et al., 2013). Over time and with repeated exposure to stress, a continued and potentially stable demethylation of GREs takes place, which further sensitizes the GR to future stress. This can result in long-lasting alterations in the physiological stress response (Klengel et al., 2013).

In line with the diathesis-stress model, there is increasing evidence suggesting that *FKBP5* SNPs (e.g., rs1360780) interact with stressors to elicit MD (Matosin et al., 2018), although there are also some indications for main effects of these SNP on occurrence of MD (e.g., Zobel et al., 2010). Interactions between stressors and *FKBP5* variants in the context of depression have predominantly been examined in adults and mainly focused on traumatic experiences and other serious life events (Matosin et al., 2018). Results from these studies have shown that adult minor allele carriers, as compared with major allele carriers of various *FKBP5* SNPs (e.g., rs1360780, rs3800373, rs9296158, 9470080, rs4713916) and *FKBP5* haplotypes including minor alleles of various SNPs, who experienced adverse events, had higher levels of depressive symptoms/a heightened risk for MD (Appel et al., 2011; Kohrt et al., 2015; Lahti et al., 2016; Lavebratt et al., 2010; Zimmermann et al., 2011, but see de Castro-Catala et al., 2017).

Studies investigating interactions of stressors and variants in *FKBP5* in adolescence are scarce. In addition, to date, no studies in this field of research have been conducted in adolescents with MD. Only one study included preschoolers and reported an interaction between various *FKBP5* polymorphisms (e.g., rs3800373) and higher levels of mild to moderate adverse events in predicting case-control status (depression/anxiety diagnosis vs. healthy children). Children carrying at least one minor allele of various *FKBP5* SNPs had a higher risk for having a depression/anxiety diagnosis as compared with homozygous major allele carriers (Scheuer et al., 2016). Interestingly, these SNPs did not interact with severe stressors in predicting depression/anxiety diagnoses, possibly because severe stressors per se might be potent enough to elicit an episode of depression independent of the presence of at least one minor *FKBP5* allele of the respective SNPs studied.

Further insight into gene-environment interactions including *FKBP5* variants in adolescents comes from two studies. In these studies, heightened levels of depressive symptoms were found in the context of increased peer victimization in girls/adverse life events in boys who carried at least one minor allele of two SNPs (rs1360780, rs3800373), as compared with adolescents who were homozygous for the major allele (Comasco et al., 2015; van Zomeren-Dohm et al., 2015).

It needs to be stressed that results from studies investigating depressive symptoms as measured with self-report questionnaires in youth may not be comparable to results from studies investigating a clinical cohort consisting of adolescents with the diagnosis of MD (Coyne and Whiffen, 1995). Therefore, it seems highly relevant to study gene-environment interactions including variation in the *FKBP5* gene in a well characterized sample of clinically depressed adolescents.

Adolescence is considered an especially vulnerable developmental period as it is associated with an increase of stressors, a heightened emotional responsiveness in reaction to these stressors and yet not fully developed capacities to cope with stress (Dahl and Gunnar, 2009; Paus et al., 2008). Moreover, during this age period, the stress systems are subject to marked maturational changes (Andersen and Teicher, 2008). These factors have been proposed to contribute to the high prevalence rate of youth MD of about 7.5% (Avenevoli et al., 2015). In addition, youth MD is characterized by high recurrence rates in adulthood, a more serious course and a worse prognosis as compared with an age of onset during adulthood (Kim-Cohen et al., 2003; Thapar et al., 2012). This stresses the need for a better understanding of the biological mechanisms and environmental factors implicated in youth MD in order to be able to inform prevention and treatment efforts. Despite heightened risk, adolescence is also seen as a chance for positive development. In line, an early identification of youth at risk with subsequent preventive and treatment efforts might pave the way for more beneficial outcomes for adolescents with MD/heightened depressive symptoms (Fergus and Zimmerman, 2005). Given the scarcity of studies and the importance of investigating a youth sample, more insight into the role of genetic variation in *FKBP5* in modulating the association between environmental stressors and MD in adolescence is needed. Therefore, it seems particularly promising to investigate whether variants in the HPA-axis related gene *FKBP5* interact with stressors of various types and severities.

In the current study, we investigated variation in a single gene. To address concerns regarding the candidate-gene approach (e.g., Dick et al., 2015; Duncan and Keller, 2011), we followed recommendations for conducting candidate-gene studies (Dick et al., 2015). Among other aspects, by focusing on *FKBP5*, we selected a gene for which there is

strong evidence that it interacts with adversity in the context of depression (e.g., Matosin et al., 2018).

The present study aims to extend previous work investigating G × E-interactions in the realm of depression. To achieve this, this study is the first to (1) examine adolescents with a MD diagnosis as well as typically developing (TD) youth and (2) focus on variation in the *FKBP5* gene (the CATT haplotype, as well as individual SNPs) and their interaction with stressors differing in type and severity (mild, moderate, severe, sociodemographic stressors, the total number of stressors experienced). We expected interactions between the *FKBP5* CATT haplotype as well as its constituent SNPs, respectively, and stressors of different types and severities in predicting case-control status. More specifically, we hypothesized that youth carrying at least one copy of the CATT haplotype or at least one minor allele of the selected *FKBP5* SNPs would have the highest risk for being in the MD group depending on the number of stressors experienced (e.g., Scheuer et al., 2016; Comasco et al., 2015). Furthermore, we expected main effects of the different stressors investigated. We did not state a hypothesis for the main effects of the CATT haplotype/individual SNPs due to inconsistent results concerning these main effects in previous studies (see e.g., Zobel et al., 2010; but see Zimmermann et al., 2011).

2. Method

2.1. Participants

The current sample includes participants who were recruited since November 2009 in two studies investigating genetic factors and environmental stressors implicated in youth MD. 148 currently depressed and 143 age- and sex-matched TD adolescents aged 13-18 years were included in the present study. Table 1 depicts the age and sex distribution in the two groups.

The MD group was recruited from two child and adolescent psychiatry clinics in Munich, Germany (Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, University Hospital, LMU Munich; KBO Heckscher Klinikum, Munich). The TD group was recruited via address lists of former study participants and the hospitals' websites. Inclusion criteria for both groups were sufficient language skills of the participants and parents to complete questionnaires and clinical interviews, and an age between 13 and 18 years.

In the patient group, a diagnosis of a current MD episode and comorbid disorders according to ICD-10 were assessed based on the Kinder-DIPS (Schneider et al., 2008), which was administered to the participant and to one parent. The Kinder-DIPS is a well-established, standardized, semi-structured German diagnostic interview for which high test-retest reliabilities have been reported (Cohen's κ = .85-.94 for the parent-version and κ = .48-.94 for the child-version for psychiatric diagnoses; Adornetto et al., 2008). Interviewers were psychologists who had earned an official certificate after having completed an extensive Kinder-DIPS training and who were regularly supervised by experienced clinicians. Thirty-three participants had currently a mild depression, 46 a moderate depression and 69 a severe depression according to ICD-10 (Remschmidt et al., 2009). Seventy-seven patients currently suffered from a first-onset episode of MD. Seventy-one patients experienced a recurrent episode. The age of the first-onset of MD was M = 13.15 years (SD = 2.36). With regard to comorbidities, patients with a current or past attention deficit/hyperactivity disorder (ADHD), schizophrenic disorder or bipolar disorder were excluded. Patients with other psychiatric diagnoses were not excluded if MD was the primary diagnosis. Frequencies of comorbid disorders are displayed in Supplementary Table S.1.

To be included in the TD group, participants had to be free of any past or current mental illnesses based on the Kinder-DIPS. None of the MD or TD participants suffered from neurological or somatic disorders based on the clinical examination by the child and adolescent psychiatrists in the respective clinics.

Participants obtained a 20 Euro voucher as compensation for their effort. The study procedure was approved by the local ethics committee. The study was in accordance with the guidelines laid down in the Declaration of Helsinki. All participants were informed in detail about the design and aims of the study and gave written assent to participate in the study. Written informed consent was also obtained by at least one parent/legal custodian, after the parent(s)/legal custodian (s) had been informed about all aspects of the study.

Table 1
Demographic characteristics of the study sample.

	MD group (n = 148)	TD group (n = 143)	p
Age (M, SD)	15.75 (*1.43*)	15.82 (*1.50*)	.694[a]
Age range	13–18	13–18	
Sex (m/f)	37/111	36/107	.973[b]

Abbreviations: MD = Major Depression. TD = Typically developing. Note that sociodemographic factors were conceptualized as stressors and are depicted in supplementary Table S.2.
Note.
[a] t-test.
[b] χ^2-test.

2.2. Measures

Environmental stressors (for items, see Supplementary Table S.2) were assessed via a comprehensive questionnaire adapted from the Life Event Survey (Adams and Adams, 1991) and the Munich Event List (test-retest reliability: κ = 0.85; Maier-Diewald et al., 1983; Wittchen et al., 1989). Face and content validity were assumed by investigating stressors which are common and relevant during adolescence (Kohn and Milrose, 1993). As with most questionnaires assessing life events, calculating internal consistency is not appropriate (for methodological reasons see Streiner, 2003). One part of the questionnaire was administered to the participants (self-report questionnaire) and the other (sociodemographic) part to one of the parents (parental-report questionnaire). Answers were coded dichotomously ("yes"/"no").

The timeframe of the individual stressors for which we also assessed the subjective severity referred to participants' lifetime. In the self-report questionnaire, youths first had to indicate whether an individual stressor occurred or not. If they endorsed the respective individual stressor, they rated its subjective severity on a scale ranging from 0 to 3 ("not at all severe" to "very severe"). Across all participants, the median of this severity rating was subsequently calculated for each individual stressor. These were then categorized as "mild" (median = 1), "moderate" (median = 2) and "severe" (median = 3) based on their median severity rating (see Supplementary Table S.2). No stressors were identified with a median of 0. We followed this median-based approach instead of a mean-based approach as (1) the severity ratings of the individual stressors were not normally distributed, (2) the response categories have a Likert-scale format (Jamieson, 2004; Sullivan and Artino, 2013) and (3) individual stressors could be categorized exactly since they directly map onto the severity response categories of the respective stressors. A novelty of our study is that we assessed many qualitatively different stressors based on self-report, which we then classified based on perceived stressfulness. Adopting this approach, we accomodate the well-established view that not the occurrence of stressors per se, but the appraisal of these stressors determines the individual's experience of stress (Lazarus, 1974).

The parental-report questionnaire included items on sociodemographic data of the parents and the youth (see Supplementary Table S.2). No information regarding subjective severity was gathered for sociodemographic stressors assessed via the parental-report questionnaire.

The individual stressors assessed based on self- and parental-report

were summed up to create the following stress scores: “Mild stressors”, “Moderate stressors”, “Severe stressors”, and “Sociodemographic stressors”. In addition, a composite stress score “All stressors” was created by summing all individual stressors, which were assessed via self- and parental-report. Supplementary Table S.2 depicts the assignment of all individual stressors to the respective stress scores.

2.3. SNP selection and genotyping

In total, 92.1% of the participants provided a blood sample collected in EDTA coated tubes and the remaining 7.9% of the participants provided a saliva sample. We did not expect that the use of different DNA sample methods would have an impact on our results since these samples show high concordance with regard to genotyping results (Abraham et al., 2012; Hu et al., 2012). The extraction of DNA from EDTA blood was accompanied using the automated system from the chemagic 360 instrument from Perkin-Elmer, USA, which applies a magnetic bead-based method for extraction/purification of nucleic acids from different tissues. Saliva samples were collected using Oragene Saliva kits. Blood and saliva samples were genotyped as part of a larger genotyping project using the Infinium Global Screening Array protocol (www.illumina.com). Call rates in the MD and TD group were ≥ 93.90%.

SNP rs1360780 was selected for the analyses because it is suggested to play an important role in HPA-axis functioning via genotypic as well as epigenetic effects in the context of stress, as well as effects on neural circuitry (e.g., functional changes in the amygdala; Klengel et al., 2013; Matosin et al., 2018). These effects have also been implicated in MD (Matosin et al., 2018). In addition, this SNPwas previously identified in gene-environment interactions related to the experience of stressful life events in the context of depression (e.g., Appel et al., 2011; Lahti et al., 2016; Matosin et al., 2018; van Zomeren-Dohm et al., 2015; Zimmermann et al., 2011). We additionally included the following adjacent SNPs in our analyses, as previous studies have found interactions between these SNPs and adverse events in depression: rs3800373, rs9296158, rs9470080, and rs4713916 (e.g., Kohrt et al., 2015; Lahti et al., 2016; Scheuer et al., 2016; Zimmermann et al., 2011). Furthermore, in line with previous work (e.g., Halldorsdottir et al., 2017), we investigated the CATT haplotype consisting of minor alleles of SNPs rs3800373, rs9296158, rs1360780 and rs9470080, which have been reported to be in high linkage disequilibrium (LD) with each other (e.g., Halldorsdottir et al., 2017; Scheuer et al., 2016; Zimmermann et al., 2011). Since we investigate multiple stressors and SNPs, examining the CATT haplotype in a first step allows testing gene-environment interactions on a more global level, which then justifies following-up significant results in further steps.

Genotype frequencies in the MD and the TD group, respectively, did not deviate from Hardy-Weinberg Equilibrium (HWE; *p*s ≥ .133). Minor allele frequencies (MAF) were ≥ 0.24 in both groups. Detailed information on the genotyped SNPs, such as call rates, HWE *p*-values and MAF in the MD and TD group can be found in Supplementary Table S.3. Using Haploview 4.2 (Barrett et al., 2004), one LD block was identified, consisting of the SNPs rs3800373, rs9296158, rs1360780, rs9470080 ($r^2 \geq .76$ for all SNPs within this block). SNP rs4713916 was in modest LD with the LD block ($r^2 \geq .55$). This LD structure has also been found in previous studies (e.g., Halldorsdottir et al., 2017; Scheuer et al., 2016; Zimmermann et al., 2011) and is depicted in Supplementary Fig. S.1. The CATT haplotypes derived from the four SNPs forming a LD block (rs3800373, rs9296158, rs1360780, rs9470080) were computed using PLINK and the number of copies (0, 1, 2) of the CATT haplotype was calculated for each participant. Principal components (PCs) to account for population stratification were calculated using genome-wide complex trait analysis (Yang et al., 2013).

2.4. Data analysis

Statistical analyses were run with SPSS. To compare sex distribution and age between the MD and the TD group, χ^2- and *t*-tests were conducted. In a first explorative step, χ^2-tests were computed to examine group differences in *individual* stressors. In a next step, we examined whether the five stress scores “All stressors”, “Mild stressors”, “Moderate stressors”, “Severe stressors”, and “Sociodemographic stressors” predicted case-control status (MD/TD group). Therefore, we ran five logistic regression analyses with group as the dependent variable and one of the five stress scores as the independent variable. First, we tested the main effect of the stress score “All stressors”. In case of a significant effect, we conducted follow-up analyses with the stress scores “Mild stressors”, “Moderate stressors”, “Severe stressors”, and “Sociodemographic stressors”. Applying the Bonferroni-correction, α was set to .0125 (α = .05/4). The analyses were controlled for age and sex due to well-known sex differences in MD and an increase of MD during adolescence (Avenevoli et al., 2015).

To examine main effects of the CATT haplotype on case-control status, logistic regression analyses were conducted with group as the dependent and the CATT haplotype as the independent variable. Next, the contribution of each individual SNP (rs3800373, rs9296158, rs1360780, rs9470080, rs4713916) was tested conducting logistic regression analyses with group as the dependent and each one of the five SNPs as the independent variable. Because we had no hypothesis regarding genetic main effects, we did not adjust the α-levels for the respective tests. Due to the existence of three clusters, as identified in the genome-wide complex trait analysis, the first three PCs were included as covariates in these analyses to control for population stratification (in addition to age and sex).

To investigate interactions between *FKBP5* variants and the five stress scores, we followed a stepwise approach to account for multiple testing in the logistic regression analyses. We first conducted a logistic regression analysis with group as the dependent variable, the stress score “All stressors” and the CATT haplotype, as well as their interaction term as the independent variables. In case of a significant interaction between the CATT haplotype and the stress score “All stressors”, we conducted follow-up logistic regression analyses to investigate the interplay between the individual SNPs with the stress score “All stressors” with α set to .025 (α = .05/2) due to the existence of two LD-blocks (see Supplementary Fig. S.1). Next, these analyses were followed-up by conducting analyses including the interactions between the five SNPs and the four remaining stressors (“Mild stressors”, “Moderate stressors”, “Severe stressors”, “Sociodemographic stressors”). In the case the SNPs significantly interacted with “All stressors”, α was set to .05/4 = .0125 (α divided by four stressors) for the subsequent analyses of interactions between individual SNPs and the four remaining stressors. As a last step, it was tested whether the CATT haplotype interacted with the four stressors (“Mild stressors”, “Moderate stressors”, “Severe stressors”, “Sociodemographic stressors”); for these analyses, α was set to .0125 (α = .05/4).

All logistic regression analyses on interactions were controlled for age, sex, the first three PCs, as well as interactions between *FKBP5* variants/stress scores and age, sex and the PCs, respectively (Keller, 2014).

When investigating interactions conducting logistic regression analyses, we entered the variables in a hierarchical manner to examine how much the models including gene-environment interactions contributed over the previous models including main effects of the stressors and the polymorphisms, the covariates as well as their interactions. First, we entered all covariates (age, sex, three PCs), and main effects of the respective *FKBP5* polymorphisms and stress scores tested in the model, as well as interactions between the covariates and the *FKBP5* polymorphisms and stress scores, respectively. Next, we added the respective *FKBP5* polymorphism × stress score interaction.

To explore potential gene-environment correlations, analyses of

covariance (ANCOVAs) were conducted with one of the five stress scores as the dependent variable and the CATT haplotype and one of the five SNPs, respectively, as the independent variable, including age, sex, and the PCs as covariates.

Only dominant models were tested. No recessive models were conducted due to the low number of homozygous minor allele carriers and due to problems inherent in multiple testing.

3. Results

3.1. Environmental stressors

Descriptive data for the five stress scores in the MD and TD group can be found in Table 2.

The results from the logistic regression analyses indicated that the five stress scores "All stressors "($p < .001$, OR = 1.45, $b = 0.37$, $SE(b) = 0.05$), "Mild Stressors "($p < .001$, OR = 1.98, $b = 0.682$, $SE(b) = 0.11$), "Moderate stressors "($p < .001$, OR = 1.65, $b = 0.50$, $SE(b) = 0.06$), "Severe stressors "($p < .001$, OR = 2.60, $b = 0.95$, $SE(b) = 0.15$), and "Sociodemographic stressors "($p < .001$, OR = 1.64, $b = 0.50$, $SE(b) = 0.13$) significantly predicted case-control status.

3.2. Genetic main effects and interactions

Table 3 depicts the frequency distribution of the CATT haplotype and the *FKBP5* SNPs in the MD and TD group.

No genetic main effects of the CATT haplotype and the five SNPs predicting case-control status were found (all $ps \geq .109$; see Table 4).

Table 5 depicts interactions between the five stress scores, the CATT haplotype and SNPs, respectively.

A significant gene-environment interaction was found between "All stressors" and the CATT haplotype ($p = .006$, OR = 1.40, $b = 0.34$, $SE(b) = 0.12$; p for the previous step = .003[2]). With a higher number of "All stressors", carriers of at least one copy of the CATT haplotype were shown to have the highest risk for being in the MD group. Following up these results by inspecting interactions between individual SNPs and "All stressors", significant interactions were found with SNPs rs3800373 ($p = .005$, OR = 1.42, $b = 0.35$, $SE(b) = 0.12$; p for the previous step = .002[2]), rs9296158 ($p = .010$, OR = 1.34, $b = 0.29$, $SE(b) = 0.11$; p for the previous step = .006[2]), rs1360780 ($p = .016$, OR = 1.30, $b = 0.26$, $SE(b) = 0.11$; p for the previous step = .012[2]), and rs9470080 ($p = .015$, OR = 1.30, $b = 0.27$, $SE(b) = 0.11$; p for the previous step = .011[2]), respectively, in predicting case-control status. The odds of being depressed increased to a greater extent in adolescent carriers of at least one minor allele of respective SNPs depending on the number of "All stressors". The results of the interaction between the stress score "All stressors" and SNP rs1360780 are exemplarily depicted in Supplementary Table S.4 and Supplementary Fig. S.2.

Investigating interactions between stressors and individual SNPs, significant interactions were found between moderate stressors and SNPs rs3800373 ($p = .004$, OR = 1.64, $b = 0.50$, $SE(b) = 0.17$; p for the previous step = .002[2]) and rs1360780 ($p = .011$, OR = 1.48, $b = 0.39$, $SE(b) = 0.16$; p for the previous step = .008[2]), respectively, in predicting case-control status. With a higher number of moderate stressors, carriers of at least one minor allele of the respective SNPs had the highest risk for being in the MD group. The results of the interaction between the stress score "Moderate stressors" and SNP rs1360780 are exemplarily depicted in Supplementary Table S.5 and Supplementary Fig. S.3. Furthermore, significant interactions were found between sociodemographic stressors and SNPs rs3800373 ($p = .002$, OR = 2.51, $b = 0.92$, $SE(b) = 0.30$; p for the previous step = .002[2]), rs9296158 ($p = .001$, OR = 2.60, $b = 0.96$, $SE(b) = 0.30$; p for the previous step = .001[2]) and rs9470080 ($p = .007$, OR = 2.18, $b = 0.78$, $SE(b) = 0.29$; p for the previous step = .006[2]), respectively, in predicting case-control status. The odds for being depressed increased to a greater

Table 2
Means (*M*), standard deviations (*SD*), odds ratios (*OR*) and *p*-values for the five stress scores in the MD and TD group.

Stress scores	MD group ($n = 148$) *M* (*SD*)	TD group ($n = 143$) *M* (*SD*)	OR	*p*
All stressors[a]	12.14 (*4.41*)	6.40 (*3.48*)	1.45	< .001
Mild stressors[b]	2.18 (*1.37*)	1.17 (*1.06*)	1.98	< .001
Moderate stressors[b]	7.11 (*2.59*)	4.07 (*2.29*)	1.65	< .001
Severe stressors[b]	1.59 (*1.64*)	0.36 (*0.75*)	2.60	< .001
Sociodemographic stressors[c]	1.27 (*1.05*)	0.80 (*0.90*)	1.64	< .001

Note.
[a] The stress score "All stressors" was calculated by summing all individual stressors endorsed by the youths.
[b] Based on severity ratings of the individual stressors, stressors were classified as mild, moderate and severe. Individual stressors were subsequently summed to create each stress score.
[c] The stress score "Sociodemographic stressors" was calculated by summing all individual stressors assessed via parental-report.

Table 3
Frequency distribution (n/%) of the CATT haplotype and the *FKBP5* SNPs in the MD and the TD group.

	MD group ($n = 148$)		TD group ($n = 143$)	
CATT haplotype/SNPs	*n*	%	*n*	%
CATT haplotype				
0 copy	69	46.6	81	56.6
1 copy	67	45.3	56	39.2
2 copies	9	6.1	6	4.2
rs3800373				
AA	71	48.0	81	56.6
AC	68	45.9	56	39.2
CC	9	6.1	6	4.2
rs9296158				
GG	65	43.9	71	49.7
GA	70	47.3	62	43.3
AA	11	7.4	10	7.0
rs1360780				
CC	66	44.6	72	50.3
CT	70	47.3	61	42.7
TT	12	8.1	10	7.0
rs9470080				
CC	60	40.5	66	46.2
CT	69	46.6	66	46.2
TT	10	6.8	11	7.7
rs4713916				
GG	68	45.9	72	50.3
GA	65	43.9	62	43.4
AA	7	4.7	7	4.9

Table 4
Main effects of the FKBP5 CATT haplotype and the five SNPs under a dominant model in predicting case-control status.

CATT haplotype/SNPs	OR	*p*
CATT haplotype	1.47	.109
rs3800373	1.37	.143
rs9296158	1.27	.322
rs1360780	1.27	.325
rs9470080	1.27	.328
rs4713916	1.20	.448

[2] Improvement of the model including gene-environment interactions over the previous model including main effects of the stressors and polymorphisms and covariates, as well as their interactions.

Table 5
Interactions between the stress scores and FKBP5 CATT haplotype/SNPs under a dominant model in predicting case-control status.

Environmental stressors in interaction with the CATT haplotype/ SNPs	OR	*p*
All Stressors		
CATT haplotype	1.40	.006[a]
rs3800373	1.42	.005[a]
rs9296158	1.34	.010[a]
rs1360780	1.30	.016[a]
rs9470080	1.30	.015[a]
rs4713916	1.22	.057
Mild stressors		
CATT haplotype	1.13	.625
rs3800373	1.15	.574
rs9296158	1.13	.615
rs1360780	1.18	.495
rs9470080	1.05	.849
rs4713916	0.99	.981
Moderate stressors		
CATT haplotype	1.58	.008[a]
rs3800373	1.64	.004[a]
rs9296158	1.41	.028
rs1360780	1.48	.011[a]
rs9470080	1.40	.029
rs4713916	1.45	.013
Severe stressors		
CATT haplotype	2.35	.023
rs3800373	2.41	.019
rs9296158	1.94	.062
rs1360780	2.10	.033
rs9470080	1.88	.059
rs4713916	1.87	.068
Sociodemographic stressors		
CATT haplotype	2.64	.001[a]
rs3800373	2.51	.002[a]
rs9296158	2.60	.001[a]
rs1360780	1.96	.019
rs9470080	2.18	.007[a]
rs4713916	1.90	.023

Note.
[a] Gene-environment interactions, which remained significant after correcting for multiple testing.

extent for carriers of at least one minor allele of the respective SNPs depending on the number of sociodemographic stressors. The results of the interaction between the stress score "Sociodemographic stressors" and SNP rs9296158 are exemplarily depicted in Supplementary Table S.6 and Supplementary Fig. S.4. Furthermore, significant interactions were found between the CATT haplotype and moderate stressors (p = .008, OR = 1.58, b = 0.46, $SE(b)$ = 0.17; p for the previous step = .004[2]) and sociodemographic stressors (p = .001, OR = 2.64, b = 0.97, $SE(b)$ = 0.31; p for the previous step = .001[2]), respectively, in predicting case-control status. Depending on the number of moderate and sociodemographic stressors, respectively, carriers of at least one copy of the CATT haplotype had the highest risk for being in the MD group.

Nominal significant interactions emerged between severe stressors, the CATT haplotype (p = .023, OR = 2.35, b = 0.855, $SE(b)$ = 0.376; p for the previous step = .017[2]), rs3800373 (p = .019, OR = 2.41; b = 0.877; $SE(b)$ = 0.374; p for the previous step = .013[2]), and rs1360780 (p = .033, OR = 2.10, b = 0.741, $SE(b)$ = 0.348; p for the previous step = .028[2]), respectively, in predicting case-control status. The odds of being depressed increased to a greater extent in adolescent carriers of at least one copy of the CATT haplotype/at least one minor allele of respective SNPs depending on the number of severe stressors. Note, however, that these results did not withstand correction for multiple testing.

No significant gene-environment correlations were found ($ps \geq$ .091).

4. Discussion

Our study provides evidence for a moderating role of *FKBP5* variants on the relationship between a) sociodemographic stressors, b) moderate stressors, and c) the total number of stressors experienced based on self- and parental-report, and MD in adolescence. We are not aware of other studies that investigated interactions between variation in the *FKBP5* gene and environmental stressors in a youth clinical MD sample. In more detail, the odds for being depressed increased to a greater extent in adolescent carriers of at least one copy of the CATT haplotype or at least one minor allele of respective *FKBP5* SNPs depending on the number of sociodemographic, moderate, and total number of stressors. While no genetic main effects of the *FKBP5* haplotype and the respective SNPs on case-control status were found, self-reported stressors ranging from mild to severe, as well as sociodemographic stressors were more common in MD than in TD adolescents.

Extending previous work, a novel aspect of our study was that we included sociodemographic stressors and their interaction with *FKBP5* variants in the context of youth depression. Evidence from previous studies suggests that a lower overall socioeconomic status (SES) is associated with an impairment of the HPA-axis, potentially mediated by higher levels of exposure to environmental stressors (e.g., child abuse; Bradley and Corwyn, 2002; Cohen et al., 2006). Since the *FKBP5* gene has a well-documented role in the regulation of the HPA-axis and is implicated in MD (Binder, 2009), it seems pertinent to study variation in this gene in the context of sociodemographic stressors. We expand previous studies by showing that not only single or repeatedly occurring stressful life events, but also more stable background variables (such as low parental education) interacted with genetic risk in the form of genetic variation in *FKBP5*. Sociodemographic stressors affect the maturation of the HPA-axis and socio-affective development (Baum et al., 1999; Bradley and Corwyn, 2002). This might be further aggravated by genetic variation in *FKBP5*, which may ultimately lead to MD in adolescents from families with a lower SES.

Much of the existing literature on gene-environment interactions involving genetic variation in *FKBP5* in the context of depressive symptoms or MD focused on traumatic or other severe adverse life events (but see Scheuer et al., 2016). A unique aspect of our study was the classification of different stressors according to their perceived stressfulness as indicated by the adolescents. A major finding of our study was the interaction between moderate stressors and variation in *FKBP5*, including an interaction between moderate stressors and variant rs1360780. Our findings can be brought in line with the results from a study by Scheuer et al. (2016), which found interactions between mild to moderate stressors and *FKBP5* SNPs in the occurrence of depression and anxiety diagnoses in preschoolers. When coupled with a diathesis in the form of *FKBP5* SNPs, moderate stressors might be severe enough to elicit an episode of MD in adolescence by crossing a critical threshold in the diathesis-stress model. Concerning adverse experiences during childhood, there exists strong evidence that early life stress (ELS) can have long-lasting effects on the developing brain (Heim et al., 2004) and may lead to epigenetic changes (e.g., changes in methylation levels) of genes implicated in HPA-axis dysregulation, including *FKBP5* (Matosin et al., 2018). Importantly, the minor allele of the *FKBP5* SNP rs1360780 is likely associated with an increased expression of *FKBP5*, which has been related to a dysregulation of the HPA-axis (i.e., a lack of HPA-axis inhibition, heightened cortisol levels) in the context of repeated stress. Epigenetic changes, as induced by stress exposure, may further enhance this dysregulation in carriers of at least one minor rs1360780 allele, leading to a prolonged stress response when encountering future stressors (Klengel et al., 2013; Matosin et al., 2018). Furthermore, a heightened (epi-)genetically-mediated expression of *FKBP5* has been proposed to be related to functional changes in the

amygdala and the hippocampus, which are also implicated in (risk for) MD (Matosin et al., 2018). In line with this suggestion, it has been shown that minor allele carriers of various HPA-axis related genes, including *FKBP5*, exhibit a heightened amygdala reactivity when experiencing early life stress/emotional neglect (Di Iorio et al., 2017; White et al., 2012).

In the present study, interactions between severe environmental stressors and *FKBP5* variants did not significantly predict case-control status when correcting for multiple testing. It needs to be taken into account, however, that some of the interactions (e.g., including rs1360780) reached nominal significance. Considering the small sample size of the present study, it would be important to follow-up these trends in future studies including larger samples. In this vein, our results can be brought in line with previous studies, which found interactions between traumatic events and *FKBP5* SNPs in predicting MD/depressive symptoms in adulthood (Appel et al., 2011; de Castro-Catala et al., 2017; Kohrt et al., 2015; Lavebratt et al., 2010; Zimmermann et al., 2011).

An alternative account for our non-significant results regarding the interplay between *FKBP5* variation and severe stressors is that these types of stressors did not occur very frequently in the current sample. It might thus be the case that these stressors add to more frequent moderate environmental stressors and need to accumulate across a prolonged period of time in order to ultimately elicit an episode of MD. Thus, single severe environmental stressors may not be potent enough to elicit an episode of MD in adolescence, but the risk may increase if the single stressor is paralleled by other, e.g., moderate and sociodemographic stressors. In line with this suggestion, we found interactions between variation in *FKBP5*, including the variant rs1360780, and the total number of stressors experienced (including severe stressors). These findings suggest that stressors of different types and severities likely accumulate and interact with each other and with *FKBP5* variants to elicit an episode of MD.

Results from the current study indicate that mild environmental stressors did not interact with *FKBP5* variants to predict case-control status in adolescents. In line with the diathesis-stress model, mild environmental stressors might not be potent enough to induce long-lasting changes in biological systems, and thus, do not contribute to MD risk when not paralleled with other stressors. As opposed to mild stressors, severe negative experiences, which are perceived as uncontrollable, threatening and loss-related may exceed adolescents' capabilities for coping with these stressors (Zimmer-Gembeck and Skinner, 2008). In contrast, single mild environmental stressors might be buffered via coping behavior, averting possible negative consequences of these events.

In agreement with most previous studies, no genetic main effects predicting case-control status were found (e.g., Scheuer et al., 2016; Zimmermann et al., 2011). These findings are in line with the assumption that genetic factors have to interact with environmental stressors to elicit MD (e.g., Colodro-Conde et al., 2017). However, we found main effects of sociodemographic, mild, moderate, and severe environmental stressors as well as the total number of stressors experienced predicting case-control status. Our findings highlight the importance of not only focusing on severe stressors but also investigating stressful experiences, which are often part of everyday life in adolescence.

The present study is unique in several ways. First, previous studies in the field of gene-environment interactions including genetic variation in *FKBP5* predominantly focused on adults. In our present study, we focused on adolescence and thus on a particularly sensitive developmental period characterized by marked biological and social changes (Andersen and Teicher, 2008; Paus et al., 2008). Second, previous studies investigated the role of *FKBP5* variants in the context of traumatic childhood events and other serious adverse experiences. The current study, however, focused on a range of environmental stressors of different types and severities, which have so far been largely neglected (but see Scheuer et al., 2016). Third, conceptualizing MD as a stress-related disorder, we focused not only on environmental stressors known to elicit an episode of MD. We also investigated the biological diathesis, i.e., variation in the *FKBP5* gene. Investigating the complex interplay between environmental stressors and variants in the HPA-axis related *FKBP5* gene may help to identify starting-points for preventive efforts for youth MD. In this context, it needs to be stressed that we identified stressors, which frequently occur during adolescence and which can be targeted in prevention approaches. For example, one possibility would be to identify adolescents who experience many of these stressors and to train them in adaptively coping with them. Another fruitful approach would be to include adolescents from high-risk families (e.g., with a high number of sociodemographic stressors) in prevention programs specifically targeting vulnerability factors associated with MD. Another promising avenue is that the *FKBP5* gene might prove to be an important target for psychopharmacological treatment (Binder et al., 2004; Kirchheiner et al., 2008).

The candidate-gene approach has been criticized for a number of reasons, including the reliance on small sample sizes and low statistical power, a non-stringent correction for multiple testing, an insufficient replicability of results, as well as a lack of confirmation of selected genes in genome-wide approaches (Dick et al., 2015; Duncan and Keller, 2011). For these reasons, we followed the recommendations for conducting candidate G × E-interaction studies as put forward by Dick et al. (2015) in several ways. First, we carefully selected the *FKBP5* gene because of its known role in the physiological stress-response and in stress-related phenotypes, including MD (e.g., Matosin et al., 2018). In our analyses, we focused on SNP rs1360780 as well as on adjacent SNPs. SNP rs1360780 is suggested to be the relevant variant underlying disruptions in HPA-axis functioning in MD, presumably due to allele-specific methylation changes in response to early adverse experiences (Klengel and Binder, 2013). Our group has shown that the *FKBP5* SNPs investigated in our study are implicated in the regulation of the HPA-axis (Binder et al., 2004; Ising et al., 2008), the (psychosocial) stress reactivity (Höhne et al., 2015; Ising et al., 2008), the response to antidepressant treatment in the context of MD (Binder et al., 2004), emotion regulation (Halldorsdottir et al., 2017), as well as depression risk as a consequence of traumatic and stressful life events (Scheuer et al., 2016; Zimmermann et al., 2011). Due to the large number and consistency of replicated findings, linking variation in *FKBP5* with stress-reactivity and stress-related disorders (including MD), we assume that the number of false positive signals is lower concerning findings for the *FKBP5* gene compared to other candidate genes. Second, we deliberately chose environmental stressors, which occur frequently and are of high relevance during adolescence (e.g., problems at school or interpersonal disputes; Kohn and Milrose, 1993). Third, we addressed multiple testing by conducting interactions in a stepwise approach and by adjusting the α-level. Although yet to be proven, we expect that these methodological aspects to overcome limitations of candidate-gene studies contribute to the replicability of our results. However, despite many efforts to overcome limitations of the candidate-gene approach, it clearly needs to be acknowledged that our sample size is small compared to other studies investigating gene-environment interactions including *FKBP5* (e.g., Appel et al., 2011; Zimmermann et al., 2011; but see Scheuer et al., 2016). Indeed, when considering that MD is a polygenic disorder in which individual genes have small genetic effects (Dick et al., 2015; Sullivan et al., 2018), the sample size of the present study was not sufficiently large (for details see Supplementary material 1). Therefore, results of our study should be interpreted in the context of the restricted sample size and a replication in larger samples is undoubtedly needed to strengthen confidence in the robustness of our results. This having said, well characterized clinical youth samples, which currently receive in- or outpatient treatment for MD, are particularly difficult to recruit. Among other challenges in youth samples, assent/consent from both adolescents and their parents is needed to collect very sensitive DNA and questionnaire data.

One promising alternative to the candidate-gene approach for the investigation of gene-environment interactions in psychiatry are biologically-informed multilocus profile scores (BIMPS; e.g., Di Iorio et al., 2017; Pagliaccio et al., 2015). By capturing variation in numerous genes/loci likely implicated in a certain biological system (e.g., the HPA-axis), BIMPS may outperform single SNPs in predicting outcome, in particular when genes have small effect sizes on phenotypic variation. This approach is also strictly hypothesis-driven and provides a biological rationale for selecting genes/loci. One of the limitations of this approach, however, is the heterogeneity in the methods used to calculate BIMPS (Bogdan et al., 2017; Di Iorio et al., 2017).

Some limitations of the current study have to be noted. In the present study, we strictly followed a hypothesis-driven approach by focusing on a gene with a well-established implication in MD (Matosin et al., 2018). As such, we did not examine other genes, such as the *BDNF* gene and did not take into account the polygenic nature of MD by investigating variation in only one gene (e.g., Hosang et al., 2014; Sullivan et al., 2018).As in other studies investigating stressful life events, the possibility of a recall bias in reporting environmental stressors cannot be ruled out. However, due to the shorter time span between experiences in the past and current age in adolescent samples, we assume this bias to be smaller in our sample than in samples investigating adults. Due to the cross-sectional design of our study, it cannot be ruled out that being in a depressed state might have resulted in more stressors (i.e., stress generation; Hammen, 2006; Williamson et al., 1995). However, we aimed to limit this aspect by investigating juvenile patients with MD, as this patient group typically has a shorter illness duration as compared to adult MD samples (Kovacs, 1996; Thapar et al., 2012). In line, we mainly included patients with a current first-onset MD. Furthermore, we included many stressors, which are unlikely to be the consequence of depression status (i.e., “fateful “events, whose occurrence individuals cannot control, such as loss events; see Hammen, 2006; Mazure, 1998). Future prospective longitudinal studies would be needed to replicate our findings and to disentangle the mutual effects of stress and MD in the context of gene-environment interactions.

5. Conclusion

In conclusion, this is the first study to investigate the interplay between various environmental stressors and genetic variation in the *FKBP5* gene in a clinically well characterized sample of currently depressed adolescent patients as well as TD youth. Extending previous work, these results highlight the need for a fine-grained analysis of different forms and severities of environmental stressors and their interplay with genetic variation for understanding the complex etiology of youth MD. Based on the present findings, future studies investigating gene-environment interactions including variation in the *FKBP5* gene in adolescent MD should investigate biological mechanisms implied in G × E-interactions, e.g. epigenetic variation, and biological marker for HPA-dysfunction, such as heightened cortisol levels, to further elucidate the complex etiology of adolescent MD.

Although a replication of our findings is clearly warranted in future studies investigating larger samples, our findings replicate and extend existing literature on gene-environment interactions including variation in *FKBP5* and add to the current knowledge of the role of *FKBP5* in stress-related disorders (e.g. Scheuer et al., 2016). Results from our study can thus contribute to a better understanding of the interplay between *FKBP5* variation and environmental stressors in youth MD.

Declaration of interest

Charlotte E. Piechaczek, Ellen Greimel, Lisa Feldmann, Verena Pehl, Antje-Kathrin Allgaier, Michael Frey, Franz Joseph Freisleder, Thorhildur Halldorsdottir, Marcus Ising and Gerd Schulte-Körne report no financial interests or potential conflicts of interest.

Elisabeth B. Binder is co-inventor on *FKBP5*: a novel target for antidepressant therapy, European Patent# EP 1687443 B1, and receives a research grant from Böhringer-Ingelheim for a collaboration on functional investigations of *FKBP5*.

Author contributions

Charlotte Piechaczek: Formal Analysis, Investigation, Visualization, Writing – original draft, writing – review & editing.

Ellen Greimel: Conceptualization, Project administration, Supervision, writing – review & editing.

Lisa Feldmann and Verena Pehl: Investigation, writing – review & editing.

Antje-Kathrin Allgaier: Conceptualization, Project administration, writing – review & editing.

Michael Frey: Conceptualization, writing – review & editing.

Franz Joseph Freisleder: Conceptualization, Funding acquisition, Supervision, writing – review & editing.

Thorhildur Halldorsdottir: Formal analysis, writing – review & editing.

Elisabeth B. Binder: Conceptualization, Resources, Supervision, writing – review & editing.

Marcus Ising: Conceptualization, Funding acquisition, Project administration, Supervision, writing – review & editing.

Gerd Schulte-Körne: Conceptualization, Funding acquisition, Project administration, Supervision, writing – review & editing.

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Appendix A. Supplementary data

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