The Interplay of Familial Depression Liability and Adverse Events in Predicting the First Onset of Depression During a 10-Year Follow-up

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Background: The aim of the present article is to explore interaction and correlation effects between familial depression liability and selected adverse (separation and traumatic) events in predicting the first onset of a major depressive episode (MDE) in a 10-year prospective longitudinal community survey.

Methods: Analyses are based on 1982 subjects (14 to 24 years at baseline) without baseline MDE who participated during the whole study period and for whom diagnostic information about psychopathology in both parents was available. The offspring's familial depression liability was determined by aggregating information on parental depressive symptoms obtained from family history data and direct interviews with parents. Data were assessed with the Munich-Composite International Diagnostic Interview according to its DSM-IV algorithms.

Results: Adverse events predicted a substantially increased incidence of MDE among respondents with familial liability but not in those without familial liability. There was a significant interaction between familial liability and traumatic events with the strongest effect for the number of severe traumatic events (risk difference = 11.3%; 95% confidence interval = 3.55–19.15). Associations with familial liability were most pronounced for separation events.

Conclusions: Adverse events are particularly pathogenic in individuals with familial liability. The involvement of interactions and correlations between familial liability and adversity might depend on type, severity, and number of events. Both processes are suggested to be concomitant rather than exclusive.

Key Words: Biological synergism, depression, depression liability, gene-environment interaction, trauma, vulnerability

The gene-environment interplay involved in the risk for unipolar depressive disorders is still an unresolved issue. While molecular-genetic studies select a specific candidate gene to investigate its interplay with environmental risks and restrict their findings to this specific gene (1–3), studies globally estimating existence, kind, and magnitude of a gene-environment interplay and dealing with the overall effects of genetic vulnerability on environmental pathogens are additionally important. These studies using twin and family data to indirectly determine genetic vulnerability are the focus of the present article.

Concerning a gene-environment interplay, three models have been described (4,5): 1) independence of both factors, meaning that the impact of adversity on depression risk is similar in individuals with and without familial risk (additive effect of risk factors); 2) gene-environment interaction or genetic control of sensitivity for stressful life events (effect modification, biological synergism); and 3) gene-environment correlation or genetic control of exposure to the environment (effect mediation). The validity of these relationship models has been examined predominantly in twin studies. Results from the Virginia Twin Study of

Adolescent Behavioral Development (VTSABD) (6,7), the Cardiff Study of All Wales and North West of England Twins (CaStANET) (8), or the Virginia Twin Registry (9,10) suggested gene-environment interactions regarding various stressful life events and adverse conditions. However, in line with the correlation model, twin studies also provide support that some adverse events and genetic risk are not independent (11–15).

The abovementioned relationship models also have been addressed in family studies but without having the possibility to separate genetic and shared familial environment influences. Most of them are high-risk studies (16–20) and/or based on clinical samples (16,18,19,21–23) with sample sizes ranging between 100 and 250 individuals. Few family studies are based on community data, larger samples size, and a cross-sectional design (24–26) and just one study has a prospective cohort design but the diagnosis of major depression and its age of onset are not prospectively assessed (27). Some of these studies provided evidence for the interaction model (16,24,26) and some did not (17,18,20,27). One study encouraged the correlation model (18), but others did not (21,23).

To summarize previous research, there is an essential lack of studies based on representative community samples with a prospective follow-up. Findings from twin, high-risk, and clinical studies could be biased by sample selection and might not be representative for the community. While many studies, mostly those with adolescents, investigate depressive symptoms rather than clinical diagnoses (24,26), studies with adults often do not separate between recurrent depression and the onset of a first episode (10,18). Interplay processes vary depending on the kind of event (28). While a wide range of stressors has been examined, the explicit role of traumatic events in their interplay with familial vulnerability is still unclear. Many studies analyze adverse events in close temporal proximity to the onset of a depressive episode as a direct trigger (6,10). Only a few studies investigate the medium and long-term impact of traumatic events on depression development, assuming that trauma exposure can induce a vulnerable phenotype (29,30).

The present study explores various processes of interplay between familial depression liability and adverse life events in predicting the first onset of a major depressive episode (MDE). Highlighting the long-term impact of traumatic and separation events on depression development in a 10-year prospective-longitudinal community study based on a sample of 3021 individuals shall add important information to existing research.

Methods and Materials

Design and Sample

Data come from the prospective-longitudinal Early Developmental Stages of Psychopathology (EDSP) study comprising a baseline and three follow-up waves that cover a period of 10 years. Onset, persistence, and correlates of DSM-IV mental disorders are assessed in a community sample of adolescents and young adults in Munich, Germany. The baseline sample was drawn randomly from the 1994 government registries of residents aged 14 to 24 years in metropolitan Munich and surrounding counties. Due to a special interest in early stages of psychopathology, the 14- to 15-year-olds were sampled at twice and the 22- to 24-year-olds at half the probability of the individuals 16 to 21 years of age. A total of 3021 respondents were interviewed at baseline (T0) (response rate = 71%). The complete sample consists of white Europeans with German nationality. At baseline, almost three quarters of the participants were students, 36% at the secondary level and 26% at the university level. Twenty percent of the participants were employed. Sixty-two percent of the participants were

living with their parents, 23% were living alone, and 12% were living with their partner/spouse. Nearly all (96.3%) were unmarried. The majority of the respondents belonged to the middle class (59%) or upper middle class (28.3%), reflecting the population of Munich.

The first follow-up (T1), on average 20 months after baseline, was conducted only for 14- to 17-year-olds at baseline ($n = 1228$; response rate = 88%), whereas the second and third follow-ups (T2, T3) were conducted for all subjects (T2: ~42 months after baseline; $n = 2548$; T0–T2 response rate = 84%; T3: ~101 months after baseline; $n = 2210$; T0–T3 response rate = 73%). The most frequent reasons for nonresponse at baseline or T3 were refusal/lack of time (21.5% and 17.7%, respectively) and failure to contact (3.1% and 8.3%, respectively). Changes in sociodemographic characteristics between baseline and T3 occurred for school/employment status (T3: secondary school: .3%, employed: 58%) and living arrangements (T3: with parents: 12%; with partner: 50%). We did not find selective attrition between baseline and T3 due to age, gender, geographic distribution, major depressive episode (MDE), and adverse events, with two exceptions for individuals with divorced parents (odds ratio [OR] = 1.2; 95% confidence interval [CI] = 1.00 –1.52; $p = .047$) and those exposed to violence (OR = 1.6; 95% CI = 1.20 –2.18; $p = .002$). Detailed descriptions of the EDSP sample and design have been presented elsewhere (31,32).

In the EDSP family supplement, direct diagnostic interviews were conducted with the mothers of the younger cohort (14- to 17-year-olds at baseline) (33,34). Fathers were interviewed if the mother was dead or not locatable. Besides familial psychopathology, childhood information about the respondents was obtained ($n = 1053$: 1026 mothers/27 fathers; response rate: 86%).

The EDSP project and its family genetic supplement have been approved by the Ethics Committee of the Medical Faculty of the Technische Universität Dresden (No: EK-13811). All participants provided informed consent.

Analyses are based on 1982 respondents who completed T3, who did not fulfill lifetime criteria for MDE at baseline, and for whom diagnostic information about psychopathology in both parents was available (direct and/or family history information).

Diagnostic Assessment

Diagnostic assessment was based on the computer-assisted version of the Munich-Composite International Diagnostic Interview (DIA-X/M-CIDI) (35). The M-CIDI allows for the standardized assessment of symptoms, syndromes, and diagnoses of DSM-IV disorders along with information about onset, duration, and severity (36). Acceptable ($\kappa .4 - .6$) to good ($\kappa .6$ and higher) reliability and validity for the variables considered in the current investigation have been reported elsewhere (37–39). Highly trained clinical interviewers carried out the interviews face-to-face mostly in respondents' homes. The M-CIDI (lifetime version) was also used to assess diagnoses among parents in the direct interview.

Assessment of Separation and Traumatic Events. To assess lifetime separation events, death of a parent ($n = 108$ of total $N = 1982$; 6.2%) and divorce of parents ($n = 470$; 24.3%), M-CIDI items at baseline were used (family history section). The category “any separation event” covers death and divorce in any parent ($n = 555$; 29.1%).

Lifetime exposure to a trauma until baseline was assessed within the M-CIDI section for posttraumatic stress disorder. A list of seven traumatic event categories was presented. Items

covered categories of 1) war (n = 5; .3%); 2) physical threat/violence (n = 154; 8.1%); 3) rape (n = 15; .9%); 4) sexual abuse as child (n = 26; 1.8%); 5) natural disaster (n = 7; .4%); 6) serious accident (n = 126; 6.8%); and 7) being kidnapped (n = 2; .1%). The category “any trauma” comprises all traumatic events (n = 297; 16.2%). The category “any severe trauma” only includes qualified traumatic events, defined as events that meet the DSM-IV A2 criterion; this means that respondents reported intense fear, helplessness, or horror on experiencing the respective traumatic event (n = 224; 12.2%).

Exposure to any separation or traumatic event was indicated by the category “any adverse event” (n = 745; 39.5%). Due to small case numbers, the presented results are based on aggregated event categories.

Assessment of Familial Depression Liability. To determine offspring’s familial depression liability, broadly defined as presence of at least subthreshold parental depression, two sources of reported information were used.

First, family history items about first-degree relatives were developed according to a modified version of the Family History- Research Diagnostic Criteria (40). At baseline, to obtain family history information, M-CIDI stem questions for DSM-IV diagnoses were used and respondents were additionally asked whether the relative sought professional help because of the respective symptoms. At T2 and T3, an extended version of the family history module was applied that covers M-CIDI/DSM-IV-criteria. Second, parents of the younger cohort were independently assessed with the M-CIDI in the EDSP family supplement. Interviewers were blind to the diagnostic findings from offspring. The parent M-CIDI contained a module providing family history data also for the noninterviewed parent (33).

Offspring’s familial liability for depression was defined by using all available diagnostic information about the occurrence of any major depressive episode in parents on an at least subthreshold level with either five depression symptoms (A criterion) with/without impairment or four symptoms plus the impairment criterion (C criterion). This procedure was chosen due to a rather low sensitivity of family history information (see below). For parents of the older cohort, family history information from the respondent interview (T0, T2, T3) was used; for parents of the younger cohort, both the direct M-CIDI information and family history data from respondents and parents were used. The overall rate for familial depression liability in offspring in the present sample was 53.2% (n = 1054 of total N = 1982).

To evaluate the accuracy of the family history information, the direct information from mothers was compared with data obtained from respondents about their mothers; the family history information obtained from respondents about their fathers was compared with the information about fathers given by mothers. Overall, only moderate sensitivity (48% for detection in mothers, 63% for detection in fathers) but acceptable to high specificity (68% for mothers; 85% for fathers) were found for major depression (34).

Assessment of Major Depressive Episode and Other DSM-IV Mental Disorders in Offspring. Major depressive episode and other mental disorders used as control variables such as anxiety disorders (panic disorder with and without agoraphobia; agoraphobia without panic disorder; specific phobia; phobia, not otherwise specified; social phobia; generalized anxiety disorder; obsessive-compulsive disorder; and posttraumatic stress disorder) and substance use disorders (SUD) (alcohol abuse and dependence, nicotine dependence, and illicit drug abuse and dependence) were assessed with the DSM-IV/M-CIDI algorithms. Incident MDE was defined as meeting DSM-IV criteria for MDE for the first time during follow-up (T1–T3).

Statistical Analyses

All associations were calculated with ORs based on logistic regressions.

To determine the biological synergism between familial liability and adversity on incident MDE, an additive statistical interaction model was used (41–43). Given the absence of any biases, a superadditive risk difference (RD) interaction (i.e., the combined effect of two factors exceeds the sum of their individual effects) indicates causal synergy at least in some individuals (44,45). The RD has been proposed as an appropriate measure in terms of the standard models of causality (counterfactual causality and the sufficient component cause model) (45,46). We used the BINREG procedure in the STATA software package (Stata-Corp., College Station, Texas) to compute RDs (47).

All analyses were performed twice: first, controlling for age and gender only, and second, additionally controlling for baseline anxiety and SUD. Control variables were chosen a priori guided by previous research (34).

Age-specific cumulative lifetime incidences for MDE were estimated with the Kaplan-Meier method (48) using age of onset information. This was done in four mutually exclusive groups defined by familial depression liability (with vs. without) and exposure to any adverse event prior to baseline (with vs. without). Few cases reported MDE for the first time at one of the follow-ups (T1, T2, T3) but dated the age of onset before their age at T0; as age of onset reports can easily be affected by recall biases even if a severe MDE had developed, we decided to put more weight on baseline reports and defined the age of onset for these cases as their age at baseline plus 1 year. Differences between the four mutually exclusive groups were tested with hazard ratios (HR) from Cox regression (stratified Cox regression) (48).

All data were weighted by age, gender, geographic location, noncontact and nonresponse at T0 to match the distribution of the original sampling frame (32). All statistical analyses were carried out with the STATA software package (49). The Huber-White sandwich method for weighted data was used to adjust statistical inference for the weighting of the data (50).

Results

Association Between Familial Liability for Depression as well as Baseline Adverse Events and the First Onset of MDE During Follow-up

Familial liability for depression significantly predicts incident MDE during follow-up in offspring even after adjustment for age, gender, anxiety disorders, SUD, and adverse events (OR adjusted = 2.0; 95% CI = 1.45–2.63; $p = .001$). Of the respondents with familial depression liability ($n = 1054$), 20.5% developed an MDE compared with 10.7% of respondents without familial risk ($n = 928$).

Compared with respondents without any baseline adverse event, respondents with exposure to any adverse event prior to baseline were significantly more likely to report the first onset of MDE during follow-up (20.2% vs. 13.1%; OR = 1.8; 95% CI = 1.39–2.38; $p = .001$) (Table 1, upper part). Other adversity categories were also found to be associated with MDE with ORs ranging between 1.6 and 1.8. All associations could be replicated when additionally controlling for baseline anxiety, SUD, and familial depression liability.

The higher the number of reported baseline adverse events, the higher was the risk for the subsequent onset of MDE (Table 1, lower part). Strongest associations were found for the number of separation events (95% CI = 1.29–2.20; $p = .001$) and severe traumatic events (95% CI = 1.28–2.24; $p = .001$) with ORs of 1.7 per increase by one event.

Baseline Adverse Events and the Prediction of Incident MDE with Respect to Familial Liability for Depression

Comparing the subgroups with and without familial liability for depression, the association pattern is considerably different. Among those with familial liability, all adverse event categories significantly predicted the onset of MDE, even when ORs were adjusted for all control variables including anxiety and SUD. In contrast, among respondents without familial liability, no associations were found (Table 2, upper part).

The same pattern was shown concerning the number of adverse events. Significant associations were revealed only in the liability subgroup where respondents who reported a higher number of events were at increased risk for MDE with the strongest association for the number of severe traumatic events (OR adjusted = 1.7; 95% CI = 1.21–2.37; $p = .002$) (Table 2, lower part).

The Interplay Between Familial Depression Liability and Adverse Events for the Prediction of MDE

Table 3 illustrates the difference in incident MDE if only one of the two risk factors—familial depression liability or adverse events—was present, as well as the interaction of both factors expressed as RD. Whereas familial liability alone was consistently significant in predicting incident MDE, exposure to adverse events alone was not related to an increased risk for MDE when compared with the group with neither factor (neither liability nor adversity).

However, the model revealed additive interaction effects between familial liability and adverse events for the subsequent onset risk of MDE. This means that the sum of the RDs for the independent effects of both factors is exceeded by the joint effect of these factors in terms of the RD for interaction. For example, the RD for the group exposed to both factors—familial liability and any severe trauma—compared with the group exposed to neither factor significantly exceeded the sum of RDs of the single factors (7.3% + 5.9%) by 10.9 percentage points. Further significant RD interactions ranged between 5.9 and 11.3 percentage points. After additionally controlling for anxiety and SUD, most differences attenuated: any adverse event (RD adjusted = 6.9; 95% CI = [-.40]–14.18; $p = .064$), any trauma (RD adjusted = 8.0; 95% CI = [-1.34]–17.39; $p = .093$), number of adverse events (RD adjusted = 5.2; 95% CI = [-.33]–10.77; $p = .063$), and the number of any trauma (RD adjusted = 7.5; 95% CI = [-.42]–15.48; $p = .063$). The strongest RD interaction appeared for the number of severe traumatic events (RD adjusted = 9.2; 95% CI = .95–17.54; $p = .029$). No interaction effects were found for separation events.

Results are illustrated in Figure 1 in terms of age-dependent cumulative lifetime incidences. Highest cumulative incidences of MDE revealed for respondents with both familial liability and any adverse event prior to baseline (group 4). Cumulative incidences for group 3 (familial depression liability only) were slightly, but not significantly, higher than those for group 2 (adversity at T0 only) (HR = 1.3; 95% CI = .86–2.07; $p = .197$). The lowest incidence curve resulted for respondents with neither liability nor adverse events (group 1), reaching at no age a level over 12%.

Relationship Between Familial Depression Liability and Adverse Events

All adverse event categories were significantly associated with familial depression liability even after controlling for offspring's anxiety and SUD, MDE, age, and gender, with the highest OR found for separation events (OR adjusted $\square$ 2.2; 95% CI $\square$ 1.75–2.83; $p \square$.001) (Table 4, upper part). The same pattern was observed for the number of adverse events with significant associations between familial liability and all adversity categories (Table 4, lower part).

Discussion

The aim of the present investigation was to explore various processes of interplay between familial depression liability and separation and traumatic events in predicting the first onset of MDE in a family study that was based on a large community sample and a prospective-longitudinal design over 10 years. 1) Consistent with previous reports (51,52), familial depression liability and adverse events could be confirmed as risk factors for the first depression onset. 2) Additionally, we could demonstrate that the effect of adverse events on the new development of MDE was clearly evident only among those under familial risk and therefore seemed to be moderated by parental depression status. 3) Even without the occurrence of adverse events, individuals with a familial depression liability had an elevated risk of the first onset of MDE, but this was further increased by additional exposure to adverse events. Significant interactions indicate that on a familial vulnerable background, adverse, particularly traumatic events, contribute considerably to the development of depression as powerful triggers. 4) With increasing number of adverse events, the risk for the subsequent development of depression also increased in the sense of a dose-response relationship, indicating together with their temporal priority a possible causal role of adverse events. Strongest interaction effect was found for the number of severe traumatic events defined by DSM-IV A2 criterion (RD adjusted = 9.2), suggesting that contextual threat may have an additional malignant impact. 5) Found effects of adverse events can be characterized as long-term vulnerabilities for MDE, as we prospectively considered their impact on the depression development over a 10-year follow-up period. 6) Respondents with familial depression liability were more likely to experience separation and traumatic events, particularly accidents (data available on request), than those without familial depression liability. 7) The above reported results do not apply to traumatic events that are only witnessed but did not affect the person directly ($n = 99$; 5.6%). Witnessing traumatic events was associated with depression onset only among respondents without familial risk (number of any witnessed event: OR adjusted = 2.2; 95% CI = 1.03–4.89; $p = .041$). Neither interactions nor associations between these events and familial liability could be observed (data available on request). Accordingly, Foley et al. (11) showed that the exposure to most network events (occurring to someone in the respondent's social network) but not to personal events was mainly influenced by random factors. 8) Results could be replicated when additionally controlling for anxiety orders and SUD.

Before discussing found results, some limitations of our study should be mentioned. 1) Our family data do not allow separation of genetic factors from shared family environment with respect to the effects of familial liability. 2) In the older cohort, direct information about the parents' psychopathology was not available; in these cases, family history information was obtained from the offspring's interview. 3) The use of the prospective cohort design for the present analyses implied exclusion of individuals with lifetime MDE at baseline. This could have led to exclusion of cases with depression onset briefly after trauma exposure and thus the

strength of the association might be affected. 4) Even if our analyses were based on a large community sample, case numbers might be still too small for detecting interaction effects (53). Thus, it seems to be justified to consider interaction effects identified with approaching significance. 5) Some events, particularly separation events, were considerably (OR adjusted = 2.0) associated with familial liability. Here, the RD interaction might be biased upward. 6) We cannot exclude that familial depression liability had induced a reporting bias for adverse events.

Interplay of Familial Depression Liability and Adverse Events: Mechanisms of Risk

With these limitations in mind, we address the mechanisms of relationship between environmental and familial risk. In the present study, familial liability is assumed to be determined by genetic factors and shared family environment and therefore the following three hypothetical models could explain the results: 1) Within a genetic perspective, our results support the gene-environment interaction model in favor of a biological synergism (41,43) of familial depression liability and adverse, especially traumatic events in causing first depression onset. In this context, our results are in line with findings from twin and other family studies (7,10,24). 2) In addition to gene-environment interactions, we have to consider associations between a genetic and an adversity risk that could result from both being induced by a common (genetic) risk factor or that the familiarity of depression is due to the familiarity of events. According to a gene-environment correlation, our data show that primarily separation events (especially parental divorce) but also traumatic events (in particular accidents) are more common among individuals from depression vulnerable families, suggesting a possible influence of genetic factors on exposure to these events. These findings are again consistent with previous reports (11,12,18). 3) Based on the assumption that familial depression liability resulted from shared environmental factors, we interpret the presented results as environment-environment interactions as well as correlations. On the one hand, social support may be an example for an interaction effect insofar that coping styles in healthy families could buffer the effects of adverse events. On the other hand, a low socioeconomic background could increase exposure rate to traumatic events in the sense of a correlational model.

Overall, interaction and correlational processes seem not to be exclusive but contribute concomitantly to this interplay (6). Even if gene-environment correlations are involved, exposure to events is not completely determined by genes (54). The extent to which both processes work seems to be dependent on the specific environmental pathogen (28) and on an individual's developmental stage (29).

Long-Term Impact of Adverse Events on First Depression Onset

While many studies had analyzed adverse events as direct triggers of MDE (6,10), it is remarkable that we could demonstrate strong effects of adversity during childhood up to young adulthood on subsequent depression onset in familial vulnerable individuals, even though we considered an extended time period of 10 years indicating medium and longterm effects of adverse events. Such long-term effects are explained, for instance, by the model of Heim et al. (29,55,56) proposing that a genetic predisposition, together with early adverse experiences during sensitive developmental phases, induce a persistent vulnerability to stress effects later in life. Stress vulnerability mediated by changes in stress-responsive neurobiological systems like the hypothalamic-pituitary-adrenal axis, in turn, increases the risk to develop mood disorders.

Future Directions

Studies according to an advanced genetic epidemiological paradigm like the present investigation indirectly determine genetic vulnerability by using twin and family data and thus globally estimate the kind and magnitude of a gene-environment interplay. They are effective tools to answer basic questions as, for example, which specific environmental pathogens do play a role, how do they work (e.g., short-term or prolonged effect), how does the action of these risk factors change as a function of developmental stages, what kind of interplay with a genetic vulnerability could be assumed for specific events, or how could personality traits play a role as pathways from genes to control sensitivity for stressful life events and from genes to event exposure as well, to mention only a few. This information should be combined with molecular genetic approaches investigating selected susceptibility genes to elucidate how these specific genes together with environmental factors could contribute to the development of depression (1,57,58).

Figure 1. Cumulative lifetime incidences of MDE by familial depression liability and any lifetime adverse event prior to baseline. MDE, major depressive episode.

Table 1. Associations Between Baseline Adverse Events and First Onset of MDE During Follow-up

Lifetime Adverse Event at Baseline ^b	Incident MDE (<i>N</i> = 330) During Follow-up (T1–T3) ^a Among Individuals							
	Without Adverse Event		With Adverse Event		OR	95% CI	OR adj.	95% CI
	<i>n</i>	% _w	<i>n</i>	% _w				
Any Adverse Event	175	13.1	155	20.2	1.8 ^d	1.39–2.38	1.5 ^d	1.16–2.02
Any separation event	212	13.9	118	20.8	1.7 ^d	1.26–2.22	1.4 ^d	1.05–1.88
Any trauma	265	15.0	65	20.4	1.6 ^d	1.16–2.31	1.4 ^c	.98–2.00
Any severe trauma	275	15.0	55	22.7	1.8 ^d	1.26–2.64	1.6 ^d	1.08–2.32
Mean Number of Adverse Events Among Individuals								
Number of Events ^b	Without Incident MDE		With Incident MDE		OR	95% CI	OR adj.	95% CI
	<i>m</i>	SD	<i>m</i>	SD				
Number of adverse events	.45	.66	.68	.85	1.5 ^d	1.33–1.90	1.4 ^d	1.18–1.71
Number of separation events	.28	.48	.41	.54	1.7 ^d	1.29–2.20	1.5 ^d	1.11–1.92
Number of traumatic events	.17	.42	.26	.61	1.6 ^d	1.23–2.07	1.4 ^d	1.08–1.85
Number of severe traumatic events	.12	.37	.22	.57	1.7 ^d	1.28–2.24	1.5 ^d	1.14–2.00

N = 1982.

%_w, weighted percentage; CI, confidence interval; *m*, mean number of adverse events; MDE, major depressive episode; *n*, number of respondents; OR, odds ratio of a multiple logistic regression including age and gender; OR adj., odds ratio of a multiple logistic regression including age, gender, baseline anxiety, and substance use disorders, and familial depression liability; SD, standard deviation.

^aReference group: without incident MDE during follow-up.

^bReference group: without respective adverse event until baseline.

^c*p* < .10.

^d*p* < .05.

Table 2. Associations Between Baseline Adverse Events and Incident MDE by Familial Depression Liability

Lifetime Adverse Event at Baseline ^b	Incident MDE (<i>N</i> = 330) During Follow-up (T1–T3) ^a Among Individuals											
	Without Familial Liability for Depression						With Familial Liability for Depression					
	Without Adverse Event		With Adverse Event		OR	OR adj.	Without Adverse Event		With Adverse Event		OR	OR adj.
	<i>n</i>	% _w	<i>n</i>	% _w			<i>n</i>	% _w	<i>n</i>	% _w		
Any Adverse Event	71	10.3	33	11.5	1.2	1.1	104	16.3	122	25.0	1.9 ^c	1.8 ^c
Any separation event	80	10.1	24	13.0	.73–1.96	.69–1.87	132	18.2	94	24.4	1.35–2.63	1.28–2.51
Any trauma	91	10.9	13	9.5	1.3	1.3	174	19.0	52	27.1	1.6 ^c	1.5 ^c
Any severe trauma	92	10.6	12	11.4	.77–2.32	.74–2.23	174	19.0	52	27.1	1.10–2.18	1.05–2.09
					1.0	.9					1.8 ^c	1.7 ^c
					.47–1.94	.43–1.92					1.18–2.68	1.09–2.51
					1.2	1.1	183	19.0	43	29.7	2.0 ^c	1.8 ^c
					.56–2.43	.52–2.41					1.25–3.04	1.16–2.85
Mean Number of Events Among Individuals												
Number of events ^b	Without Incident MDE				OR	OR adj.	Without Incident MDE				OR	OR adj.
	<i>m</i>	SD	<i>m</i>	SD			<i>m</i>	SD	<i>m</i>	SD		
Number of Adverse Events	.35	.59	.40	.65	1.2	1.2	.56	.70	.80	.89	1.6 ^c	1.6 ^c
Number of separation events	.20	.43	.26	.48	.80–1.79	.76–1.76	.36	.50	.48	.56	1.29–1.97	1.25–1.92
Number of traumatic events	.14	.39	.13	.39	1.3	1.3	.19	.45	.32	.67	1.6 ^c	1.6 ^c
Number of severe traumatic events	.11	.34	.10	.31	.79–2.25	.77–2.16	.14	.39	.28	.65	1.17–2.24	1.12–2.17
					1.0	1.0					1.7 ^c	1.6 ^c
					.52–2.02	.48–2.03					1.23–2.24	1.16–2.14
					1.0	1.0					1.8 ^c	1.7 ^c
					.56–1.93	.52–1.91					1.28–2.49	1.21–2.37

N = 1982.

%_w, weighted percentage; CI, confidence interval; *m*, mean number of adverse events; MDE, major depressive episode; *n*, number of respondents; OR, odds ratio of a multiple regression including age and gender; OR adj., odds ratio of a multiple logistic regression including age, gender, baseline anxiety, and substance use disorders; SD, standard deviation.

^aReference group: without incident MDE during follow-up.

^bReference group: without respective adverse event until baseline.

^c*p* < .05.

Table 3. Additive Interactions Between Familial Depression Liability and Adverse Events

	Effects on Incident MDE (<i>N</i> = 330) During Follow-up (T1–T3) ^a : Risk Differences (RD)					
	Independent Effect Familial Depression Liability ^b		Independent Effect Adverse Event ^b		Additive Interaction ^c	
	RD (%) 95% CI	RD (%) adj. 95% CI	RD (%) 95% CI	RD (%) adj. 95% CI	RD (pp) 95% CI	RD (pp) adj. 95% CI
Lifetime Adverse Event at Baseline						
Any Adverse Event	4.5 ^e .54–8.55	4.7 ^e .62–8.73	2.4 (–2.78)–7.59	2.3 (–2.78)–7.33	7.8 ^e .43–15.17	6.9 ^d (–.40)–14.18
Any separation event	6.9 ^e 3.06–10.81	6.6 ^e 2.69–10.45	3.8 (–2.87)–10.48	3.4 (–2.92)–9.72	3.5 (–5.28)–12.23	3.3 (–5.25)–11.78
Any trauma	6.9 ^e 3.16–10.64	7.0 ^e 3.22–10.69	–1.0 (–6.33)–4.43	.2 (–5.84)–6.20	10.5 ^e 1.46–19.59	8.0 ^d (–1.34)–17.39
Any severe trauma	7.3 ^e 3.68–11.02	7.3 ^e 3.64–10.99	5.9 (–5.76)–6.94	1.7 (–5.43)–8.76	10.9 ^e .44–21.42	8.4 (–2.45)–19.20
Number of Events						
Number of Adverse Events	4.7 ^e .82–8.50	4.8 ^e .94–8.71	2.3 (–2.01)–6.59	2.2 (–1.96)–6.40	5.9 ^e .27–11.51	5.2 ^d (–.33)–10.77
Number of separation events	6.8 ^e 3.03–10.71	6.5 ^e 2.67–10.36	3.8 (–2.54)–10.19	3.5 (–2.54)–9.49	3.9 (–4.43)–12.33	3.7 (–4.40)–11.89
Number of traumatic events	6.8 ^e 3.11–10.51	6.9 ^e 3.16–10.56	–.5 (–5.53)–4.50	.4 (–5.23)–6.11	9.5 ^e (–1.93)–17.12	7.5 ^d (–.42)–15.48
Number of severe traumatic events	7.1 ^e 3.48–10.75	7.1 ^e 3.44–10.72	–.5 (–5.27)–4.29	.5 (–5.11)–6.21	11.3 ^e 3.55–19.15	9.2 ^e .95–17.54

N = 1982.

CI, confidence interval; MDE, major depressive episode; pp, percentage points; RD, risk difference adjusted for age and gender; RD adj., risk difference adjusted for age, gender, baseline anxiety, and substance use disorders.

^aReference group: without incident MDE during follow-up.^bReference group: without familial depression liability and without respective adverse event until baseline.^cSum of RDs for independent effects of both factors (liability and adversity) is exceeded by the joint effect of these factors in terms of the RD for interaction by ...%.^d*p* < .10.^e*p* < .05.**Table 4.** Associations Between Baseline Adverse Events and Familial Depression Liability

Lifetime Adverse Event at Baseline	Proportion of Respondents with Respective Adverse Event ^a Among Individuals							
	Without Familial Depression Liability ^b		With Familial Depression Liability		OR	95 % CI	OR adj.	95% CI
	<i>n</i>	% _w	<i>n</i>	% _w				
Any Adverse Event (<i>N</i> = 745)	260	29.9	485	47.9	2.2 ^d	1.76–2.72	2.0 ^d	1.59–2.48
Any separation event (<i>N</i> = 555)	173	19.7	382	37.3	2.4 ^d	1.91–3.08	2.2 ^d	1.75–2.83
Any trauma (<i>N</i> = 297)	112	13.1	185	18.9	1.6 ^d	1.20–2.11	1.4 ^d	1.08–1.92
Any severe trauma (<i>N</i> = 224)	84	9.9	140	14.2	1.5 ^d	1.12–2.12	1.4 ^c	.99–1.90
Number of Events	Mean Number of Adverse Events Among Individuals							
	Without Liability		With Liability		OR	95% CI	OR adj.	95% CI
	<i>m</i>	SD	<i>m</i>	SD				
Number of Adverse Events	.35	.59	.61	.75	1.8 ^d	1.52–2.14	1.7 ^d	1.40–1.99
Number of separation events	.21	.44	.39	.52	2.2 ^d	1.72–2.77	2.0 ^d	1.57–2.54
Number of traumatic events	.14	.39	.22	.51	1.5 ^d	1.19–1.92	1.4 ^d	1.08–1.77
Number of severe traumatic events	.11	.34	.17	.46	1.5 ^d	1.14–1.93	1.3 ^d	1.03–1.76

N = 1982.%_w, weighted percentage; CI, confidence interval; *m*, mean number of adverse events; MDE, major depressive episode; *n*, number of respondents; OR, odds ratio of a multiple logistic regression including age and gender; OR adj., odds ratio of a multiple logistic regression including age, gender, anxiety, and substance use disorders, as well as MDE (lifetime, T3); SD, standard deviation.^aReference group: without respective adverse event until baseline.^bReference group: without familial depression liability.^c*p* < .10.^d*p* < .05.

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