1 **Online-Only Material**
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3 **Interaction of Variants in the *FKBP5* Gene and Adverse Life Events in Predicting the**
4 **First Depression Onset: Results from a Ten-Year Prospective**
5 **Community Study**
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Methods

Sociodemographic characteristics of the EDSP Sample
47.7% of the 996 EDSP respondents were males and 52.3% females aged between 21 and 34 years (md=26) at the time of T3. 7.8% attended secondary general school, 23.6% intermediate secondary school, and 67.2% grammar school. At T3, 0.6% were still at school, 2.7% made an apprenticeship, 34.9% attended university, 46.8% were employed, and 4.2% unemployed. 19.6% were living with their parents, 27.1% alone, and 42.7% with their partner/spouse. The majority of the respondents were classified as middle (58.7%) or upper middle class (26.7%) reflecting the population of Munich. When comparing the 996 individuals participating in the molecular-genetic project with the rest of the T3-sample (n=1214), we found no difference in the prevalence of mental disorders, adverse events, or sociodemographic factors but one; respondents with a lower educational level were less likely to participate (OR=0.7; 95%CI=0.47-0.91). To exclude a selection bias of our findings, we tested for an association between educational level and 'incident MDE' in the total sample of T3 (N=2210) and found no association (OR=1.1; 95%CI=0.81-1.40).

Definition of the covariates
The category "anxiety disorder" included the following DSM-IV diagnoses: panic disorder, agoraphobia, specific phobia, phobia NOS, social phobia, generalized anxiety disorder, obsessive compulsive disorder, PTSD). "Substance use disorders (SUD" was composed of DSM-IV alcohol abuse/dependence, nicotine dependence and illicit drug abuse/dependence.

Frequency of traumatic events
The following 7 traumatic events were assessed: 1) "war" (n=2; 0.2%), 2) "physical threat/violence" (n=49; 5.5%), 3) "rape" (n=7; 0.8%), 4) "sexual abuse as child" (n=12; 1.4%), 5) "natural disaster" (n=4; 0.5%), 6) "serious accident" (n=56; 6.3%), and 7) "being kidnapped" (n=1; 0.1%). "Any trauma" comprises all traumatic events (n=118; 13.4%). "

Power calculation
Power calculation for the GxE analysis was conducted using Quanto Version 1.2.3 (http://hydra.usc.edu/gxe/). Model estimates were derived from the present data set (population disease risk: .20; prevalence of adverse events: .30; minor allele frequency: .3; alpha level of significance: .005, 2-sided). Following a log-additive model and assuming genetic and environmental main effects with a relative risk of 1.5 and 2.0, respectively, we calculated a power of 80% to detect GxE effects with a relative risk of at least 1.55, which is between the limit of a small (1.22) and medium effect (1.86) according to the classification by Cohen[1].

Diagnostic assessment in the replication samples
In the Dunedin study, MDE was evaluated with the Diagnostic Interview Schedule (DIS)[2,3] when study members were ages 18, 21, 26, and 32 years. At ages 18 and 21 years diagnoses followed the then-current DSM-III-R, and at ages 26 and 32 years diagnoses followed DSM-IV.
In the E-Risk study, MDE was evaluated with the Diagnostic Interview Schedule (DIS)[3] following DSM-IV criteria when study members were ages 33, 35, 38, and 40 years.

Results

Associations between MDE and adverse events
Compared to respondents without baseline adversity, respondents with exposure to any adverse event prior to baseline were more likely to report the first onset of MDE during follow-up (21.1% vs. 16.4%; OR=1.5; 95%CI=1.01-2.09; p=0.039). Associations with separation events (21.5% vs. 16.8%; OR=1.4; 95%CI=0.97-2.09; p=0.071) and trauma (22.9% vs. 17.2%; OR=1.6; 95%CI=0.96-2.52; p=0.067) were not significant, but severe trauma was associated with MDE onset (26.7% vs. 17.0%; OR=1.9; 95%CI=1.16-3.22; p=0.011) withstanding correction for multiple testing (for two independent event categories; $p_{corrected}$=0.022).

Associations between genotype and adverse events
Presence of potential gene-environment correlations (rGE) were tested by evaluating the association between *FKBP5* polymorphisms and the exposure to adverse events (**eTable 1**). Associations at the nominal level of significance were almost exclusively found for rs4713916 with carriers of the major allele (AG/GG) being less frequently exposed to adverse events compared to non-carriers (AA). No effect withstood correction for multiple testing.

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95 **References**
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eTable 1. Associations between baseline adverse events and SNPs of the *FKBP5* gene

Lifetime adverse event until baseline	Proportion of Respondents with Respective Adverse Event [c] among ...					
	Subjects Homozygous for the Minor Allele 'aa'	Heterozygous Subjects 'ab'	Subjects Homozygous for the Major Allele 'bb'	*ab vs aa*	*bb vs aa*	*ab vs bb*
	n (%) [a]	n (%) [a]	n (%) [a]	OR (95%CI) [a]	OR (95%CI) [a]	OR (95%CI) [a]
rs3800373 *(CC/CA/AA)* [b]						
Any adverse event	29 (40.3)	102 (33.4)	166 (32.9)	0.8 (0.46-1.36)	0.8 (0.45-1.28)	1.0 (0.76-1.41)
Any separation event	19 (26.4)	73 (23.9)	130 (25.8)	0.9 (0.51-1.68)	1.0 (0.57-1.78)	0.9 (0.65-1.29)
Any trauma	14 (19.4)	43 (14.1)	61 (12.1)	0.7 (0.37-1.46)	0.6 (0.31-1.17)	1.2 (0.79-1.87)
Any severe trauma	11 (15.3)	32 (10.5)	47 (9.3)	0.7 (0.33-1.49)	0.6 (0.29-1.23)	1.2 (0.72-1.90)
rs9296158 *(AA/AG/GG)* [b]						
Any adverse event	38 (42.7)	102 (31.5)	158 (33.6)	0.7 (0.40-1.07)	0.7 (0.44-1.13)	0.9 (0.68-1.26)
Any separation event	26 (29.2)	74 (22.8)	123 (26.1)	0.8 (0.44-1.29)	0.9 (0.53-1.47)	0.9 (0.61-1.20)
Any trauma	18 (20.2)	41 (12.7)	59 (12.5)	0.6 (0.33-1.16)	0.6 (0.33-1.09)	1.0 (0.67-1.60)
Any severe trauma	15 (16.9)	29 (9.0)	46 (9.8)	0.5 (0.26-1.04)	0.6 (0.29-1.07)	0.9 (0.57-1.53)
rs1360780 *(TT/CT/CC)* [b]						
Any adverse event	39 (43.3)	105 (32.1)	154 (33.0)	0.7 (0.40-1.06)	0.7 (0.41-1.07)	1.0 (0.72-1.33)
Any separation event	27 (30.0)	75 (22.9)	121 (25.9)	0.7 (0.43-1.24)	0.8 (0.51-1.39)	0.9 (0.62-1.22)
Any trauma	18 (20.0)	43 (13.2)	57 (12.2)	0.7 (0.35-1.22)	0.6 (0.32-1.06)	1.1 (0.72-1.72)
Any severe trauma	15 (16.7)	30 (9.2)	45 (9.6)	0.5 (0.27-1.07)	0.6 (0.29-1.06)	1.0 (0.59-1.60)
rs9470080 *(TT/CT/CC)* [b]						
Any adverse event	41 (39.8)	112 (31.4)	145 (34.2)	0.7 (0.45-1.14)	0.8 (0.51-1.27)	0.9 (0.65-1.21)
Any separation event	29 (28.2)	81 (22.7)	113 (26.7)	0.8 (0.47-1.28)	0.9 (0.58-1.54)	0.8 (0.58-1.14)
Any trauma	20 (19.4)	45 (12.6)	53 (12.5)	0.6 (0.35-1.14)	0.6 (0.34-1.10)	1.0 (0.66-1.58)
Any severe trauma	17 (16.5)	32 (9.0)	41 (9.7)	0.5 (0.27-0.99)*	0.6 (0.30-1.04)	0.9 (0.57-1.53)
rs4713916 *(AA/AG/GG)* [b]						
Any adverse event	39 (44.8)	109 (31.9)	150 (33.0)	0.6 (0.36-0.96) *	0.6 (0.38-0.99) *	1.0 (0.70-1.29)
Any separation event	29 (33.3)	79 (23.1)	115 (25.3)	0.6 (0.36-1.02) *	0.7 (0.41-1.13)	0.9 (0.64-1.24)
Any trauma	19 (21.8)	43 (12.6)	56 (12.3)	0.5 (0.28-0.97) *	0.5 (0.28-0.93) *	1.0 (0.67-1.58)
Any severe trauma	16 (18.4)	31 (9.1)	43 (9.5)	0.5 (0.23-0.88) *	0.5 (0.24-0.89) *	1.0 (0.59-1.57)

a   "n (%)" = number and percentage of respondents; "OR" = odds ratio of a multiple logistic regression; "CI" = confidence interval;
b   minor alleles: rs3800373: C; rs9296158: A; rs1360780: T; rs9470080: T; rs4713916: A;
c   reference group: without the respective adverse event until baseline;
* $p < 0.05$ for an OR controlled for age and gender;