The effect of childhood adversity on 4-year outcome in individuals at ultra-high risk FOR psychosis

8.

in the Dutch Early Detection and Intervention Evaluation (EDIE-NL) Trial

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Abstract

Background

Childhood adversity is associated with a range of mental disorders, functional impairment and higher health care costs in adulthood. In this study we evaluated if childhood adversity was predictive of adverse clinical and functional outcomes and health care costs in a sample of patients at ultra-high risk (UHR) for developing a psychosis.

Method

Structural Equation Modeling was used to examine the effect of childhood adversity on depression, anxiety, transition to psychosis and overall functioning at 4-year follow-up. In addition, we evaluated economic costs of childhood adversity in terms of health care use and productivity loss. Data pertain to 105 UHR participants of the Dutch Early Detection and Intervention Evaluation (EDIE-NL).

Results

Physical abuse was associated with higher depression rates (b=0.381, p=0.012) and lower social functional outcome (b=-0.219, p=0.017) at 4-year follow-up. In addition, emotional neglect was negatively associated with social functioning (b=-0.313, p=0.018).

Conclusion

We did not find evidence that childhood adversity was associated with transition to psychosis, but the experience of childhood adversity was associated with excess health care costs at follow-up. The data indicate long-term negative effects of childhood adversity on depression, social functioning and health care costs at follow-up in a sample of UHR patients.

Introduction

The experience of childhood adversity has been associated with a range of mental disorders, social functional impairment and health care costs in adulthood (1). For instance, two recent meta-analyses showed that childhood adversities were associated with post-traumatic stress disorder (PTSD), depression, panic disorder, social phobia, generalized anxiety disorder, drug and alcohol abuse (2) and psychotic disorders (3). These mental disorders and impaired functioning may subsequently impact on health care costs by direct (use of mental health care) and/or indirect costs (work productivity loss). Hence, childhood adversity is associated with more severe psychopathology in adulthood.

One of the outcomes of childhood adversity that now has been recognized is psychosis (3). Since the establishment of criteria to detect individuals at ultra-high risk (UHR) for psychosis an increasing number of studies have focused on the association between childhood adversity and psychotic symptoms within these cohorts (4–6). Overall, these studies indicate that childhood adversity is more prevalent in UHR individuals than in the general population (4,7). To date, studies on the effect of childhood adversity on transitioning to psychosis are inconsistent. While two studies reported a significant association between the experience of sexual abuse during childhood and higher transition rates (5,8), two more recent UHR studies could not confirm these findings (9,10).

Irrespective of transitioning to a first episode of psychosis a large number of UHR subjects that do not transition to psychosis experience persistent subclinical psychotic symptoms, depression, general symptoms and poor social functioning at follow-up (9,11–13). These findings raise the question whether childhood adversity increases the risk for transition to psychosis in UHR subjects, or whether childhood adversity is associated with poor clinical and social functional outcome in this stage. However, the association between childhood adversity and clinical outcomes other than psychosis in UHR subjects has yet to be explored. Therefore, the present study aimed to examine the association between childhood adversity and various clinical and functional outcomes in a prospective UHR cohort. Our aims were to (i) examine the association between childhood adversity and transition to psychosis, (ii) examine whether childhood adversity is similarly associated with psychotic symptoms as with depression or social anxiety, (iii) examine whether childhood adversity is associated with poor functional outcome, and (iv) examine whether childhood adversity is associated with health care costs.

Method

Study design

Data pertain to 105 participants of a multi-centered randomized controlled trial examining a cognitive behavioral intervention aimed at the prevention of psychosis Early Detection and Intervention Evaluation (EDIE-NL) (14,15). In the EDIE-NL trial participants were randomized to either the experimental or control group. Participants from both groups were included in the present study. Clinical and functional assessments took place at baseline, 6, 12, 18, and 48-month follow-up. In the present study, we used baseline and 4-year follow-up data. The 4-year follow-up assessments were conducted between June 2012 and January 2014. Participants were first contacted by telephone and asked if they would consent to a face-to-face interview. If participants did not consent to a face-to-face interview, they were asked if they would consent to a brief telephone assessment, enabling a minimal set of clinical and functional outcome data to be collected. Participants were included after providing written informed consent. Participants who consented to a brief telephone assessment provided informed consent by mail. The Dutch Central Committee on Research Involving Human Subjects approved the study design.

Sample

Participants, aged 14–35 years, were eligible for the study if they met criteria for at least one of the UHR groups as defined by the PACE clinic (16): (1) Vulnerability Group: a first-degree relative with a psychotic disorder or diagnosed with schizotypal personality disorder, (2) Attenuated Psychotic Symptoms (APS) Group: the presence of sub-threshold positive psychotic symptoms for at least one month during the past year, or (3) Brief Limited Intermittent Psychotic Symptoms (BLIPS) Group: an episode of frank psychotic symptoms that lasted no longer than one week, which abated spontaneously. In addition, in all three groups functioning had to be chronically impaired, or there had to be a significant drop in functioning during at least one month in the previous year.

Exclusion criteria were: (1) presence of a current or past psychotic disorder, (2) severe learning impairment (3) known organic cause for presentation, (4) insufficient mastery of the Dutch language and (5) current or previous use of antipsychotic medication equivalent to a total cumulative haloperidol equivalent of ≥15 mg.

Instruments

The Comprehensive Assessment of At Risk Mental State (CAARMS) (17) was used to assess subclinical psychotic symptoms in the year prior to assessment. The CAARMS is a semi-structured interview conducted to determine presence, severity (0–6), frequency (0–6), distress (0–100) and type of UHR symptoms. The CAARMS consists of seven subscales: 4 posi-

tive symptoms items, 2 cognitive symptom items, 3 emotional disturbance items, 3 negative symptoms items, 4 behavioral change items, 4 motor changes items and 8 general psychopathology items. Criteria for UHR are based on the 4 positive symptoms items only (unusual thought content, non-bizarre ideas, perceptual abnormalities and disorganized speech). This instrument uses the severity and frequency of UHR symptoms to discriminate between status groups (UHR criteria, psychosis, or not at risk).

Childhood adversity was retrospectively assessed with the Childhood Trauma Questionnaire-Short Form (CTQ-SF) (18). This self-report questionnaire consists of 25 items about traumatic events before the age of 17 years and 3 items about minimization and denial. The three items about minimization and denial were not included in our analyses. The 25 trauma items consist of five domains: emotional abuse, emotional neglect, sexual abuse, physical abuse and physical neglect. All items range from 1 (never) to 5 (almost always). For each of the five domains sum scores were calculated. An overall total trauma score was calculated as the sum of the five subscales (range 25–125). The CTQ was administered at the 4-year follow-up assessment.

The Beck Depression Inventory-II (BDI-II) was used to assess depression (19). Scores of the BDI-II range from 0 to 63, with higher scores reflecting more depressive symptoms.

Social anxiety was assessed with the Social Interaction Anxiety Scale (SIAS) (20). This is a self-report questionnaire in which items are ranged from 0 (not at all characteristic to me) to 4 (extremely characteristic to me).

The Social and Occupational Functioning Scale (SOFAS) (21) is a semi-structured questionnaire that assessed social impairment and global functioning in the previous year. The questionnaire provides a score ranging from 0 to 100, with higher scores indicating better functioning.

Health care costs were evaluated with the Trimbos Institute and Institute of Medical Technology Assessment Questionnaire for Costs associated with Psychiatric Illness (TiCP) (22). The present study included: (1) intervention costs, (2) direct medical costs (other than the intervention), and (3) participants' travel costs. See Ising et al. (23) for a detailed description on health care cost calculations at 4-year follow-up in the EDIE-NL trial.

Statistical analysis

Structural equation models (SEM)

Analyses involving multiple independent and/or dependent variables were performed within a SEM framework. SEM is a multivariate analysis in which a set of regression equations is tested simultaneously. It allows for incorporating multiple independent variables in a model, like standard linear regression, but also allows for incorporating multiple dependent variables in the same model. For all SEM analyses, the R statistical computing environment (24), together with the R package lavaan (25) was used.

SEM - models

A first SEM was estimated to examine the effect of childhood adversity on transition to psychosis. The independent variables were continuous scores on the CTQ subscales (emotional abuse, physical abuse, sexual abuse, emotional neglect and physical neglect) (26). The dependent variables were statistically controlled for the linear effects of sex, age, condition and cannabis use. In addition to this analysis, CTQ scales were dichotomized by the following cut-off scores: physical abuse >=8, sexual abuse >=6, emotional abuse >=9, physical neglect >=8 and emotional neglect >=10 (27). The subscales were considered as present when scores were above low to moderate.

The dependent variable, transition to psychosis at 4-year follow-up, was binary. Therefore, diagonally weighted least squares (DWLS) estimation was used for parameter estimation in which a probit regression model is estimated. In probit regression, the binary outcome variable Y is modeled as a function of an underlying continuous variable Y*, which is regressed on the predictor variables and assumed to be normally distributed. The probability of Y taking a value of 1 is determined by the value of the continuous underlying variable Y*, and the normal cumulative distribution function. Probit regression coefficients can be interpreted in a similar fashion as linear regression coefficients: the estimated coefficient for predictor variable Xi represents the expected increase (or decrease, when the coefficient is negative) in Y*, given an unit increase in Xi. Also, standardized regression coefficients can be calculated, where a value of 1 (or –1) indicates a perfect linear association between the predictor variable and Y*, and a value of 0 indicates the absence of a linear association. The standardized regression coefficients can be used to compare the magnitude of the association with the outcome variable Y between predictor variables.

A second SEM model was estimated in which the effects of several types of childhood adversity and baseline severity of psychopathology, on the severity of psychopathology at 4-year follow-up were assessed. In this model, independent variables were total scores on the CTQ subscales (emotional abuse, physical abuse, sexual abuse, emotional neglect and physical neglect), baseline CAARMS total score, baseline SIAS total score, baseline BDI-II total score and baseline SOFAS score. Dependent variables were total score on the positive symptoms subscale of the CAARMS, SOFAS score, BDI-II total score and SIAS total score, all at 4-year follow-up. Additionally these analyses were repeated with the dichotomized CTQ scores. All dependent variables were controlled statistically for the linear effects of sex, age, cannabis use at baseline and condition.

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Because the dependent variables in this model were continuous, the second SEM model was estimated using Full Information Maximum Likelihood (FIML). Standard Maximum Likelihood (ML) estimation would result in list wise deletion of all observations with missing

values. With FIML estimation, all available data is used in the estimation of the model. FIML estimates have been shown to be more accurate than ML estimates when data are missing at random (28).

Because several dependent and independent variables in the analysis had skewed distributions, robust standard errors (SEs) were computed, both for DWLS and FIML estimation. Robust standard errors are not biased downwards under conditions of non-normality (29). In addition, Enders (30) has shown that the combined use of FIML estimation and robust standard errors can substantially reduce negative impact of non-normally distributed and missing data.

To evaluate the effect of childhood adversity on health care costs, first the mean health care costs were estimated. See Ising et al. (23) for a detailed description on estimating health care costs in the EDIE-NL trial. Subsequently, health care costs were evaluated for each form of childhood adversity. Childhood adversity was divided into percentiles to estimate the effect of subjects with moderate adversity (25th percentile) versus those with more severe adversity (75th percentile) on health care costs. Then, these costs were subtracted from the mean health care costs to evaluate excess health care costs by childhood adversity.

Results

Baseline sample characteristics

Of the 201 patients included in the original trial, 113 subjects (57.7%) agreed to participate in the 48-month follow-up. Of these, 108 had a face-to-face interview, while 5 were interviewed by a telephone interview. Of the 113 subjects with 4-year follow-up data, 105 subjects had data on childhood adversity available (see Fig. 1). The percentages of subjects who experienced any of the categorical sub domains of childhood adversity were: emotional abuse (46.7%), physical abuse (20.9%), sexual abuse (24.8%), emotional neglect (66.7%) and physical neglect (41.9%). Participants without follow-up data available were slightly younger than participants with follow-up data available (p=0.02, see Table 1). The mean time to follow-up was 4.15 years (SD=0.48). The total number of subjects who transitioned to psychosis was 23 (21.9%).

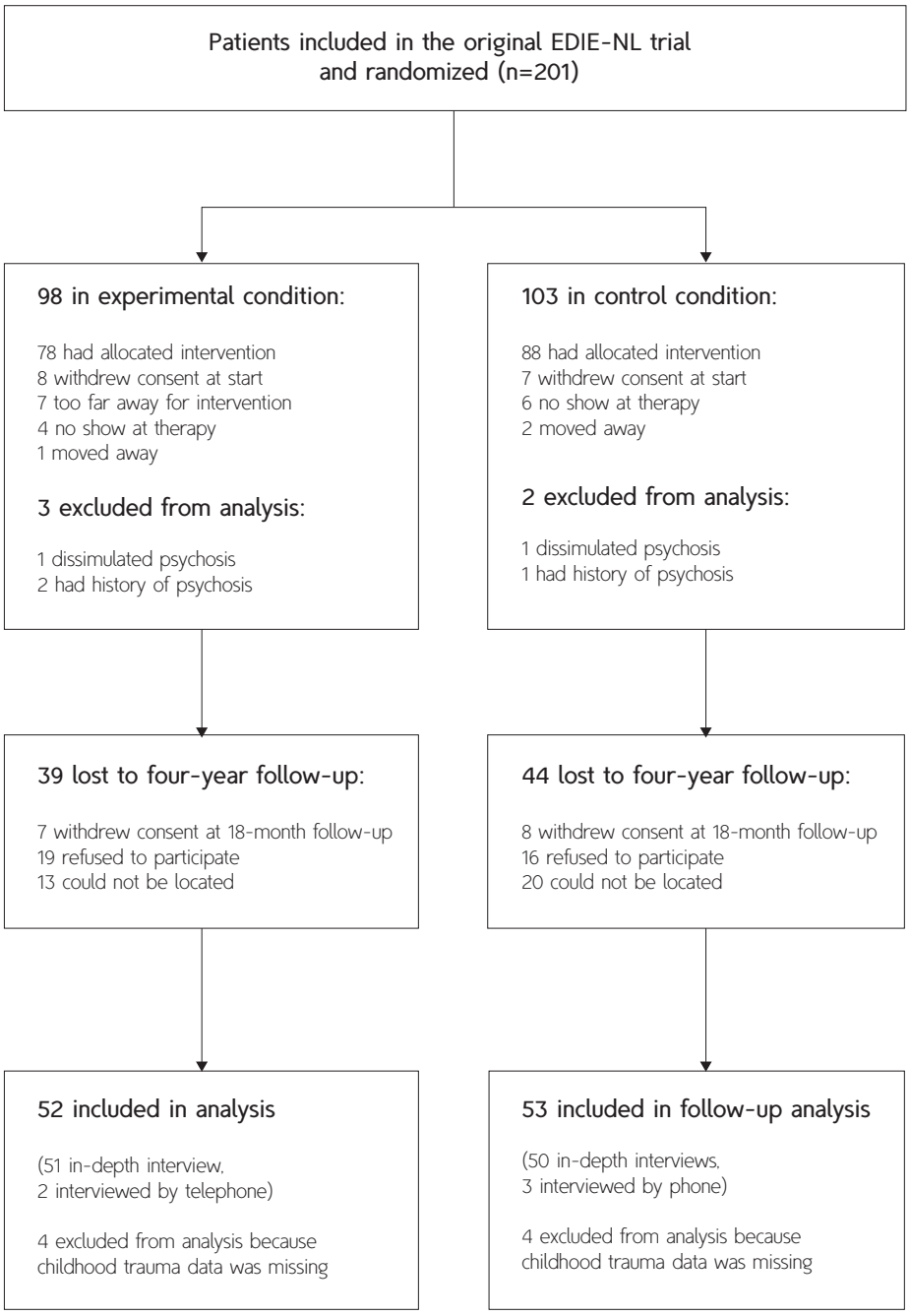

Figure 1. Flowchart of the study participants of the long-term follow-up trial.

Childhood adversity and transition to psychosis

A SEM analysis was conducted to examine the role of childhood adversity on transition to psychosis.

Analyses revealed no significant association between total childhood adversity scores and any of the childhood adversity subscales and transition to psychosis at 4-year follow-up (see Table 2). The results remained non-significant when the analyses were repeated with categorical trauma scores. There were no significant differences in findings between men and women.

Childhood adversity and severity of psychopathology

A SEM analysis was conducted to examine the association between childhood adversity and severity of psychopathology. First, analyses between childhood adversity and depression at baseline revealed no significant associations. Then, as shown in Table 3, higher scores on the physical abuse subscale were associated with aggravation of depression scores at 4-year follow-up (b=0.381, p=0.012). In addition, severity of depression at baseline (b=0.456, p=0.001) was significantly associated with depression at 4-year follow-up.

There were no significant associations between childhood adversity and anxiety symptoms at baseline and at follow-up. Only severity of social anxiety at baseline (b=0.385, p=0.001) was significantly predictive of social anxiety symptoms at 4-year follow-up.

We also examined the effects of the childhood adversity subscales on severity of positive symptoms at baseline and at 4-year follow-up, but found no significant associations.

These analyses were repeated with categorical trauma scores. For depression, the findings were no longer significant when categorical trauma scores were analyzed. The effect of childhood adversity using categorical measures on social anxiety and severity of positive symptoms remained non-significant. Stratified analyses revealed no significant differences between men and women.

Childhood adversity and impaired social functioning

A SEM analysis was conducted to examine the effect of childhood adversity on social functioning. First the effect of childhood adversity of social functioning at baseline was analyzed. None of the subscales of childhood adversity were related to social functioning at baseline. Examining associations at 4-year follow-up, physical abuse (b=−0.219, p=0.017) and emotional neglect (b=−0.313, p=0.018) were negatively associated with deterioration of level of social functioning. Depression at baseline (b=−0.300, p=0.022) negatively affected social functioning at 4-year follow-up (b=0.209, p=0.023). In addition, higher levels of social functioning at baseline (b=0.209, p=0.023) were associated with better social functioning at 4-year follow-up. No significant findings were found for the categorical measures of childhood adversity and level of social functioning.

Table 1. Socio-demographic characteristics of UHR subjects

		Subjects without 4-year assessment	Subjects with 4-year assessment	
		N=83	N=113	Chi-square test P-value
Condition, N (%)	Experimental	39 (47)	56 (49.6)	0.72
	Control	44 (53)	57 (50.4)	
Transition, N (%)	No	74 (89.2)	88 (78.8)	0.08
	Yes	9 (10.8)	25 (21.2)	
Ethnicity, N (%)	Dutch	55 (66.3)	61 (54.0)	0.58
	Minority	28 (33.7)	52 (46.0)	
Job/Education, N (%)	Paid work	30 (37.5)	50 (44.2)	0.16
	Unpaid work	2 (2.5)	11 (9.7)	
	School	26 (32.5)	32 (28.3)	
	Unemployment	16 (19.3)	14 (12.4)	
	Other	6 (7.5)	6 (5.3)	
CAARMS intake group, N (%)	Familiar vulnerability	18 (21.7)	15 (13.3)	0.04
	Sub threshold intensity	58 (69.9)	96 (85.0)	
	Sub threshold frequency	5 (6.0)	1 (0.9)	
	BLIPS	2 (2.4)	1 (0.9)	
Site, N (%)	The Hague	33 (39.8)	57 (50.4)	0.09
	AMC Amsterdam	16 (19.3)	24 (21.2)	
	Friesland	17 (20.5)	12 (10.6)	
	Leiden	14 (16.9)	10 (8.8)	
	PsyQ Amsterdam	3 (3.6)	8 (7.1)	
	Utrecht	0 (0)	2 (1.8)	
Cannabis use lifetime[a], N (%)	No cannabis use	41 (49.4)	51 (45.1)	0.49
	Ca nnabis use	38 (45.8)	58 (51.3)	
	Missing	4 (4.8)	4 (3.5)	
Cannabis use at 4-year follow-up, N (%)	No cannabis use	N/A	80 (70.8)	
	Cannabis use	N/A	31 (27.4)	
	Missing	N/A	2 (1.8)	
Gender, N (%)	Male	47 (56.6)	50 (44.2)	0.09
	Female	36 (43.4)	63 (55.8)	
		Subjects without 4-year assessment	Subjects with 4-year assessment	

Table 1. Continued

		Subjects without 4-year assessment	Subjects with 4-year assessment	
		Mean (SD)	Mean (SD)	t-test P value
Age baseline		21.6 (5.5)	23.5 (5.4)	0.02
SOFAS baseline		45.4 (5.4)	46.5 (4.6)	0.12
Baseline clinical characteristics	CAARMS Positive symptoms	10.1 (2.9)	10.41 (2.7)	0.37
	CAARMS Negative symptoms	7.1 (3.8)	7.1 (3.2)	0.97
	BDI-II Depression	22.0 (13.8)	21.4 (11.3)	0.74
	SIAS Anxiety	31.7 (17.2)	29.9 (16.6)	0.46
Childhood adversity data	Total adversity	N/A	43.51 (15.76)	
	Emotional abuse	N/A	10.03 (5.12)	
	Physical abuse	N/A	6.65 (3.12)	
	Sexual abuse	N/A	6.89 (4.49)	
	Emotional neglect	N/A	17.57 (5.23)	
	Physical neglect	N/A	12.02 (1.99)	

Note. CAARMS: Comprehensive Assessment of At Risk Mental State, BLIPS: Brief Limited Intermittent Psychotic Symptoms, SOFAS; Social and Occupational Functioning Assessment Scale, SD: Standard Deviation.

[a] Cannabis use, lifetime was assessed at the baseline interview. Cannabis use was defined as 'yes' when cannabis had been used for at least 5 times lifetime

Table 2. Regression coefficients of associations between childhood adversity and transition to psychosis

Dependent variable	Independent variable	Unstand. coeff.	Stand. coeff.	z-value	SE	p-value
Transition to psychosis	Total adversity score	-0.010	-0.129	-0.704	0.014	0.481
	Emotional abuse	-0.031	-0.139	-0.653	0.048	0.514
	Physical abuse	0.024	0.063	0.276	0.085	0.782
	Sexual abuse	0.015	0.057	0.291	0.051	0.771
	Emotional neglect	-0.006	-0.027	-0.137	0.044	0.891
	Physical neglect	-0.033	-0.078	-0.365	0.089	0.715

Note. Transition to psychosis was controlled statistically for the linear effects of sex, age, condition and cannabis use. SE, standard error. CTQ scales were treated as continuous measures.

Table 3. Regression coefficients of associations between childhood adversity and clinical and functional outcome

Dependent variable	Independent variable	Unstand. coeff.	Stand. coeff.	z-value	SE	p-value
SOFAS	Total adversity	-0.140	-0.166	0.076	0.076	0.066
	Emotional abuse	0.344	0.132	0.991	0.347	0.322
	Physical abuse	-0.937	-0.219	-2.383	0.393	0.017
	Sexual abuse	-0.138	-0.047	-0.464	0.298	0.642
	Emotional neglect	-0.801	-0.313	-2.356	0.340	0.018
	Physical neglect	0.882	0.187	1.312	0.672	0.189
	Social anxiety baseline	0.009	0.008	0.080	0.117	0.936
	Depression baseline	-0.326	-0.300	-2.295	0.142	0.022
	SOFAS baseline	0.562	0.209	2.266	0.248	0.023
	CAARMS pos. symptoms baseline	-0.250	-0.052	-0.595	0.420	0.552
Depression	Total adversity	0.038	0.056	0.634	0.060	0.526
	Emotional abuse	-0.469	-0.228	-1.981	0.237	0.048
	Physical abuse	1.283	0.381	2.500	0.513	0.012
	Sexual abuse	0.077	0.033	0.283	0.272	0.777
	Emotional neglect	0.102	0.051	0.439	0.232	0.660
	Physical neglect	-0.217	-0.059	-0.498	0.436	0.618
	Social anxiety baseline	0.029	0.032	0.355	0.083	0.723
	Depression baseline	0.390	0.456	3.278	0.119	0.001
	SOFAS baseline	-0.241	-0.114	-1.301	0.185	0.193
	CAARMS pos. symptoms baseline	0.051	0.014	0.162	0.318	0.872
Social anxiety	Total adversity	0.062	0.060	0.592	0.104	0.554
	Emotional abuse	0.069	0.022	0.176	0.390	0.860
	Physical abuse	0.363	0.070	0.480	0.756	0.631
	Sexual abuse	0.295	0.082	0.714	0.413	0.475
	Emotional neglect	0.115	0.037	0.328	0.351	0.743
	Physical neglect	-0.547	-0.096	-0.777	0.704	0.437
	Social anxiety baseline	0.544	0.385	3.336	0.163	0.001
	Depression baseline	0.280	0.214	1.521	0.184	0.128
	SOFAS baseline	-0.322	-0.099	-1.046	0.308	0.296

Table 3. Continued

Dependent variable	Independent variable	Unstand. coeff.	Stand. coeff.	z-value	SE	p-value
Social anxiety	CAARMS pos. symptoms baseline	0.262	0.045	0.734	0.357	0.463
CAARMS pos. symptoms	Total adversity	-0.006	-0.023	-0.222	0.026	0.825
	Emotional abuse	0.030	0.038	0.230	0.131	0.818
	Physical abuse	0.113	0.087	0.993	0.113	0.321
	Sexual abuse	-0.130	-0.144	-1.634	0.080	0.102
	Emotional neglect	-0.005	-0.007	-0.058	0.089	0.954
	Physical neglect	-0.029	-0.020	-0.140	0.204	0.889
	Social anxiety baseline	0.016	0.044	0.401	0.039	0.688
	Depression baseline	0.018	0.054	0.419	0.043	0.675
	SOFAS baseline	-0.047	-0.057	-0.622	0.076	0.534
	CAARMS pos. symptoms baseline	0.348	0.237	2.080	0.167	0.038

Note. Dependent variables were controlled statistically for the linear effects of sex, age, condition and cannabis use. CAARMS: Comprehensive Assessment of At Risk Mental State, SOFAS: Social and Occupational Functioning Assessment Scale; SE, standard error. CTQ scales were treated as continuous measures.

Childhood adversity and health care costs

The average total health care costs per-person was $19.912,16 (95% CI=15,466.49–24,357.82). Table 4 presents excess health care costs when participants were exposed to childhood adversity. Table 4 shows that for all domains of childhood adversity, except for physical neglect, more severe childhood adversity (i.e. the 75th percentile of childhood adversity) is associated with higher health care costs at 4- year follow-up. In addition, Table 5 show that costs stemming from service use accounted for most of the total additional healthcare expenses in the group who experienced childhood adversity.

Table 4. Childhood adversity and health care costs

	Health care costs	Excess health care costs
Emotional abuse 25th %	$14,674.16	$-5,238.00
Physical abuse 25th %	$19,660.74	$-251.42
Sexual abuse 25th %	$16,016.41	$-3,895.75
Physical neglect 25th %	$26,515.32	$6,603.16
Emotional neglect 25th %	$17,190.44	$-2,721.72
Emotional abuse 75th %	$28,255.48	$8,343.32
Physical abuse 75th %	$24,662.30	$4,750.14
Sexual abuse 75th %	$31,435.43	$11,523.27
Physical neglect 75th %	$18,188.74	$-1,723.42
Emotional neglect 75th %	$20,729.25	$817.09

Note: Data are presented as mean.

Table 5. Estimated Per-participant Four-year Cumulative Costs (in 2014 US$)

	25th % of total adversity	75th % of total adversity
Service use costs, US$ (SD)	15,820.23	23,372.87
Antipsychotic medication, US$ (SD)	55.18	11.39
Travel costs, US$ (SD)	316.07	431.31
Total costs, US$ (SD)	**16,191.48**	**23,815.57**

Note: Data are presented as mean

Discussion

In the present study we examined the association between childhood adversity and clinical and functional outcome at 4 year follow-up in UHR individuals of the EDIE-NL trial. Our findings show that physical abuse was predictive of more severe depression and lower social functioning, but not with transition to psychosis. Importantly, our findings show that more severe childhood adversity is associated with higher health care costs at 4-year follow-up.

The present study confirms previous research, showing an association between physical abuse and depression (31,32) and between physical abuse and emotional neglect and lower social functioning (13). Interestingly, these findings were found while controlling for the effect of treatment condition. Also in an earlier study with psychotic patients, stronger associations were found between abuse, negative symptoms and depression than between abuse and psychotic symptoms (33). It is therefore not surprising that the experience of childhood adversity was associated with higher health care costs in our study; subjects with depressive symptoms are likely to seek help at mental health care institutions, resulting in higher health care costs.

In contrast to previous studies from the PACE clinic (5,8) we could not confirm the association between childhood sexual abuse and transition to psychosis. However, in the present study we confirmed earlier findings in other UHR cohorts, in which no associations between several domains of childhood adversity and higher transition rates were reported (9,10). This discrepancy between findings could potentially be attributed to our relatively small sample size. However, the findings might also suggest that while childhood adversity is associated with meeting UHR criteria (7), they do not subsequently constitute additional risk for psychotic de-compensation after UHR criteria are met. The high childhood adversity levels reported in UHR samples do suggest that a history of adversity may significantly increase the chance to present at mental health services with distressing subclinical psychotic symptoms in young adulthood.

The association between physical abuse and depression may be mediated by negative self-schemas and hopelessness (34). For instance, abusive events during childhood might result in persistent negative self-schemas. These schemas may in turn be associated with the emergence of depression. It has also been suggested that attribution styles, i.e. the way (potential) negative events are interpreted, may mediate the relationship between childhood adversity and depression (35,36). When negative events are interpreted as uncontrollable or when they are interpreted as being caused by a failure of the person (e.g. 'it is my fault'), they may result in the emergence of depression (36). Future studies should focus on why physical abuse was specifically associated with depression and poor social functioning.

Strengths and limitations

The major strength of this study is the long follow-up period of 4 years. Although previous research showed that transition to psychosis can occur up to 10 years after determining UHR status (37), most UHR patients convert to psychosis within the first three years (38). This study therefore displays a relatively good representation of the long-term outcome of UHR subjects in the EDIE-NL trial.

Several methodological limitations of our study need to be considered. The first limitation is that childhood adversity was assessed with the CTQ. This retrospective self-report question-

naire does not tap into specific details like frequency, impact and/or distress of the adversity. Second, the CTQ was administered at the 4-year follow-up assessment. Although previous research has shown that patients with psychotic disorders are reliable in their recollection of past experiences, we cannot rule out that the assessment has been influenced by recall bias (39). A third limitation is the substantial loss to 4-year follow-up assessment (42.4%). As Ising et al. (40) showed, participants lost to follow-up were functioning better at 18-month follow-up than participants included in the 4-year follow-up assessment. Therefore, the group participating in the 4-year follow-up assessment may consist of somewhat worse functioning participants of the EDIE-NL trial. Fourth, the present study did not examine associations between childhood adversity and DSM-IV disorders (41). Fifth, level of cognitive functioning, which has been associated with psychosis risk in previous reports (42), was not included as a confounding variable in our analyses. Sixth, most of the instruments that were used in the present study were self-report questionnaires. Seventh, because the mean age of participants at baseline was considerably young (40), participants might still be at risk for psychosis after the follow-up period. As a recent study showed, transition to psychosis can occur up to 10 years after baseline interview (37).

Conclusion

To the best of our knowledge, this was the first study examining the effect of childhood adversity on health care costs in an UHR cohort. Our findings suggest that childhood adversity has long-term negative effects on depression, social and occupational outcome and economic costs in UHR individuals. These findings indicate that the focus of future research in UHR populations should be broader than mere transition to psychosis. The high prevalence of childhood adversity in UHR populations indicates that adverse events during childhood should be assessed systematically in clinical settings. Importantly, clinical interventions for UHR patients should target a combination of psychotic symptoms, depressive symptoms, improvement of social functioning and posttraumatic stress events. Although previous research showed that PTSD and psychotic disorders often co-occur, trauma treatment is not standard care for patients with psychotic disorders (43,44). However, as the study of van den Berg (45), trauma treatment is safe and effective in patients with PTSD and psychotic disorder.

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