Mania symptoms in a Swedish longitudinal population study: the roles of childhood trauma and neurodevelopmental disorders

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Abstract

Background: Adult psychiatric disorders are associated with both childhood traumatic experiences (CTEs) and neurodevelopmental disorders (NDDs). CTEs and NDDs frequently co-occur in childhood, but their combined risk effect on the emergence of juvenile mania symptoms has not yet been examined.

Methods: In a population-representative Swedish twin study, CTEs and NDDs were assessed in 3,348 nine-year old twins born between 1998 and 2001, and treated as dichotomous predictors (any CTEs, any NDDs). Follow-up data were gathered at age 15 through parental reports of mania symptoms, yielding a symptom count score.

Results: Both CTEs and NDDs at age 9 contributed uniquely to an increase in mania symptoms at age 15. Children with both risk factors had 1.6 times the rate of mania symptoms as children with CTEs-only (Incidence rate ratio [IRR]: 1.63, 95% CI 1.37-1.93), and 1.3 times the rate of mania symptoms as children with NDDs-only (IRR: 1.26, 95% CI 1.06-1.50). There was no evidence for an interactive effect. NDDs showed a trend towards having a larger effect on mania symptoms than CTEs (IRR: 1.29, 95% CI 0.99-1.68).

Limitations: Although it is a strength of the study that the data on exposures and outcome were collected prospectively, parental recall of CTEs was required and CTEs may be under-reported.

Conclusions: NDDs are at least as important as CTEs in the development of mania symptoms, and their risk is additive. Those with a history of *both* CTEs and NDDs should be monitored closely for the development of more severe psychiatric presentations.

Keywords Neurodevelopmental disorders, Childhood traumatic experiences, Mania symptoms, Bipolar disorder

Abbreviations:

ADHD: Attention deficit/Hyperactivity Disorder

ASD: Autism Spectrum Disorder

BD: Bipolar disorder

CATSS: Child and Adolescent Twin Study in Sweden

CMRS-P: Child Mania Rating Scale–Parent Version

CTEs: Childhood traumatic experiences

DCD: Developmental coordination disorder

GEE: Generalized estimating equations

IRR: Incidence rate ratio

NDDs: Neurodevelopmental disorders

SES: Socio-economic status

Highlights

- Childhood traumatic experiences (CTEs) and Neurodevelopmental disorders (NDDs) have separately been associated with increased risk for juvenile mania
- We found that these risk effects are additive: Adolescents with both exposures had more mania symptoms than adolescents with only one exposure
- CTEs and NDDs often occur together
- Patients presenting with one risk factor should be examined for the other risk factor
- These patients should be monitored for potentially increased risk of juvenile mania

Background

Psychiatric disorders such as schizophrenia and bipolar disorder (BD) have well established links with childhood neurodevelopmental disorders (NDDs) such as Autism Spectrum Disorder (ASD) and Attention Deficit Hyperactivity Disorder (ADHD) (Larsson et al., 2013; Selten et al., 2015). It is now well known that these neurodevelopmental disorders overlap and almost certainly have a common genetic underpinning (Pettersson et al., 2013). Psychiatric disorders also have established links with childhood traumatic experiences, especially abuse and neglect (Scott et al., 2012; Taillieu et al., 2016). Despite the knowledge that trauma and NDDs are crucial in the development of severe mental illness in adults, their combined effect has never been examined. We have previously shown that abuse/neglect and NDDs overlap significantly: individuals who have experienced childhood trauma are much more likely to also have NDDs such as ASD and ADHD (Dinkler et al., 2017). Childhood trauma and NDDs are highly likely to overlap and it is unclear whether having both risk factors increases the risk for severe mental illness more than having either one of them would. If there is an additive (or even interactive) risk effect of CTEs and NDDs, is makes it even more important that both are considered in clinical practice. The recent research findings that children with a trauma history are much more likely to also have

NDDs (Danese et al., 2016; Dinkler et al., 2017), have not yet translated into clinical practice. Currently in both child/adolescent and adult psychiatry, there is an intense service focus on trauma (Sweeney et al., 2018). Service development for NDDs such as ASD and ADHD, now known to be lifelong conditions, is occurring in parallel yet separate specialist services/clinics (Eke et al., 2019). If findings of NDDs and childhood traumatic experiences significantly co-occurring hold true across the lifespan, that is, if *adults* with a trauma history are also more likely to have NDDs, then this could mean that psychiatric patients with severe mental illness and a trauma history might have undiagnosed, treatable NDDs.

In this study we have chosen to focus on juvenile mania symptoms as mania usually emerges for the first time in adolescence and is an important first sign of severe "adult-type" mental illness such as BD (Faedda et al., 2015; Findling et al., 2018; Van Meter et al., 2016). Our study aimed to investigate, in a prospective design, the relative contribution of childhood traumatic events (CTEs) and NDDs to symptoms of mania in adolescence, and whether children who have experienced CTEs and have NDDs are at a greater risk of developing mania symptoms than the children who have experienced either CTEs or NDDs (i.e., whether the risk associated with CTEs and NDDs is additive).

Methods

Participants

This study is based on the Child and Adolescent Twin Study in Sweden (CATSS), an ongoing longitudinal study targeting all twins born in Sweden since 1992 (Anckarsäter et al., 2011), used here as it is population representative and has a prospective design, and not because of its genetic sensitivity. All 9-year-old twins are identified through the Swedish twin registry (the first three years of the study also included 12-year-old twins) and their parents are invited to participate in a telephone interview about the somatic and mental health of the twins (*CATSS-9/12*, response rate

68%). The present study is based on 3,348 twins born between July 1, 1998, and December 31, 2001, whose parents also participated in the follow-up questionnaire at twin age 15 *(CATSS-15,* response rate 60%). The CATSS has ethical approval from the Regional Ethical Review Board in Stockholm.

Risk factors

Childhood Traumatic Experiences at age 9

Childhood Traumatic Experiences were assessed with the Life Stressor Checklist-Revised (LSC-R) (Wolfe and Kimerling, 1997), a screening measure of potentially traumatic life events according to DSM-IV criteria for posttraumatic stress disorder and other seriously stressful life events with good criterion-related validity (Brown et al., 1999; Kimerling et al., 1999). Parents reported if their children had ever been exposed to emotional neglect, physical neglect, physical abuse, sexual abuse, domestic or other violence, bullying, substance abuse in the family or other potentially traumatic life events. Free text answers were evaluated by the authors for inclusion, for example, the experience of war or natural disaster was rated as a CTE (see Supplement 1).

Neurodevelopmental disorders at age 9

A screening diagnosis of neurodevelopmental disorders were assessed with the Autism–Tics, AD/HD, and other Comorbidities inventory (A-TAC), a fully-structured 96-item parental telephone interview designed for large-scale epidemiological research. The A-TAC screens for neurodevelopmental and other psychiatric disorders in childhood based on symptom criteria and well-known clinical features and has been validated against clinical diagnoses cross-sectionally (Hansson et al., 2005; Larson et al., 2010) and longitudinally (Larson et al., 2013; Marland et al., 2017).

This study included five NDDs: ADHD, ASD, developmental coordination disorder (DCD), learning disability, and tic disorders. Items are scored with "no" (0), "yes, to some extent" (0.5), or "yes" (1) and summed up to yield scale scores for each NDD (Anckarsäter et al., 2011). The internal consistencies (Cronbach's α) in the current sample were good to excellent for ADHD (.91, 19 items) and ASD (.81,17 items), acceptable for learning disability (.72, 3 items), and modest for tic disorders (.57, 3 items). DCD was assessed with one item only. We applied validated cutoffs with high specificity to identify NDDs as proxies to the clinical diagnoses: ASD (cut-off ≥8.5, sensitivity .71/specificity .95), ADHD (≥12.5, .52/.95), DCD (≥1, .28/.95), learning disability (≥3, .23/.96), tic disorders (≥1.5, .92/.90) (Larson et al., 2010).

We considered investigating a dose-response effect of number of CTEs and number of NDDs on juvenile mania symptoms. However, we did not have sufficient power to do so, as few children had three or more CTEs (n = 12), or three or more NDDs (n = 14). Therefore, both risk factors were treated as dichotomous predictors (any CTEs, any NDDs).

Outcome

Mania symptoms at age 15

The 10-item Child Mania Rating Scale–Parent Version (CMRS-P) (Henry et al., 2008; West et al., 2011) was used to screen for juvenile mania symptoms including elated mood, irritability, grandiosity, decreased need for sleep, excess of energy, racing thoughts, extremely fast talking, sexually inappropriate behavior, rage attacks and hearing voices. According to a meta-analysis, the CMRS-P is one of the top tier measures in terms of discriminative validity for pediatric BD (Youngstrom et al., 2015). Whilst mania-like symptoms can sometimes occur in other disorders, the CMRS-P has high specificity of 0.94 and sensitivity of 0.82 in screening for bipolar disorder in studies that also assessed for other disorders such as ADHD and depression (Pavuluri et al., 2006). Items are scored on a four-point scale: 0 (never/rarely), 1 (sometimes), 2 (often), and 3

(very often). The internal consistency of the scale was acceptable (Cronbach's α = .72). A sum score of all ten items was calculated (CMRS score, total scale range 0-30). A cut-off score of 10 differentiates well between children with BD and healthy children (Henry et al., 2008). We used this cut-off score to determine the prevalence of juvenile mania in our sample. For the main analysis we used the CMRS score, as the number of children above the cut-off score for juvenile mania in each exposure group was very low.

Covariates

Socio-economic status (SES) may be associated with CTEs, NDDs, and juvenile mania symptoms and was therefore included as a covariate. The highest educational level of both parents was used as a proxy for SES on a 10-point scale from "compulsory school less than 9 years" to "doctoral degree/licentiate".

Statistical Analysis

Stata 15.0 (StataCorp, 2017b) was used for statistical analyses. Type I error rate was set to α = .05. In order to investigate the relative contribution of CTEs and NDDs to CMRS score and to test potential additive and interactive effects, we included both predictors and their interaction into a model to predict CMRS score, thus accounting for their covariance and testing their unique effects on CMRS score. Twins of a pair are correlated to each other, that is their observations are not independent (Carlin et al., 2005). In order to account for this dependence when testing our hypothesis, we used generalized estimating equations (GEE), treating twin pairs as clusters. The robust sandwich estimator *vce(robust)* within the *xtgee* procedure in Stata allows for intragroup correlation and produces valid standard errors even if the within-group correlations are mis-specified (StataCorp, 2017a). Furthermore, CMRS score is not a continuous variable, but rather a count variable taking only positive, discrete values. We therefore used a count distribution in the GEE model. In count models, parameter estimates are generally

expressed and discussed as incidence rate ratios (IRR). In our case of dichotomous predictor variables, the IRR can be interpreted as the ratio of the CMRS score in one category (e.g., any CTEs) to the CMRS score in the other category (e.g., no CTEs). Due to the low case number in the group with both risk factors (CTEs and NDDs, 32 males, 10 females), we collapsed both sexes for the main analyses. However, in Table S1 we present models 1 to 3 stratified by sex.

Results

About 7 % of the children experienced any of the assessed CTEs, and about 5.7 % of the children experienced any of the assessed NDDs (Table 1, Figure 1). The prevalence of CTEs was similar for males and females ($\chi^2(1) = 3.35$, $p = .076$). NDDs were more common in males compared to females ($\chi^2(1) = 16.59$, $p < .001$). The mean CMRS score was 1.92 ($SD = 2.50$) with a maximum score of 20. The prevalence of juvenile mania was twice as high in females (2.6%) compared to males (1.3%, $\chi^2(1) = 7.55$, $p = .006$, Table 1).

Insert Figure 1 about here

Insert Table 1 about here

CMRS score

CMRS score was over-dispersed (variance greater than mean) and the Poisson distribution was not a good fit for the data (Pearson $\chi^2 = 10870.7$, $p <.0001$). We therefore used a negative binomial distribution with a dispersion parameter of $\alpha = 1.28$ in the GEE model. The results of the GEE model are presented in Table 2. The interaction CTEs x NDDs was not significant (p=.4078) and was therefore excluded from the model. The final model revealed significant unique effects of both CTEs and NDDs on mania symptoms. Children with both CTEs and NDDs had a 1.6 times higher CMRS score than children with CTEs-only (IRR = 1.63, 95% CI

1.37-1.93), and a 1.3 times higher CMRS score than children with NDDs-only (IRR = 1.26, 95% CI 1.06-1.50; Table 2 & Figure 2). Children with both CTEs and NDDs had a 2.1 times higher CMRS score than children with neither risk factor (95% CI 1.65-2.55). Contrasting the effects of NDDs-only and CTEs-only showed a trend towards NDDs having a larger effect on mania symptoms than CTEs (IRR = 1.29, 95% CI 0.99-1.68).

Insert Table 2 about here

Insert Figure 2 about here

Discussion

In this study, we investigated the relative contribution of CTEs and NDDs at age 9 to symptoms of mania at age 15, and whether the risk associated with CTEs and NDDs is additive (i.e., whether having both risk factors leads to a higher increase in mania symptoms than having either one of them). We found that CTEs and NDDs at age 9 both uniquely contributed to an increase in mania symptoms at age 15, that is, their risk is additive. Our data did not support an interactive (multiplicative) effect of CTEs and NDDs on mania symptoms beyond the sum of their unique contributions. Clinically what this means is that CTEs and NDDs are different risk factors, explaining different parts of the variance of mania symptoms, and having both risk factors is associated with a higher risk for mania symptoms than having only one of the risk factors. This also implies that if both risk factors are present and only one risk factor is "treated", it might reduce risk of mania, but not "eliminate" it. There was a trend towards a larger effect of NDDs than of CTEs, showing that NDDs are *at least* an equally important predictor of juvenile mania symptoms as CTEs.

Our findings regarding the longitudinal association between CTEs at age 9 and mania symptoms at age 15 extend the findings of a recent meta-analysis on the links between CTEs and BD

(Palmier-Claus et al., 2016). Mechanisms for the role of NDDs in the development of adult psychiatric disorders such as BD are not well-known, but could operate through shared genetic factors, increased environmental risk (e.g., through NDD symptoms precipitating harsh parenting (Sullivan and Knutson, 2000) or shared symptomatology (Larsson et al., 2013). We have previously found, using a genetically sensitive design, that both child maltreatment and neurodevelopmental symptom load are underpinned by common genetic factors (Dinkler et al., 2017). This has led us to speculate whether these genetic factors could be unidentified neurodevelopmental symptoms in the parent, which could have an important role in the intergenerational problems of vulnerable families.

Our finding of additive effects of CTEs and NDDs on the development of mania symptoms seems simple, on the surface. However, by screening regularly and robustly for neurodevelopmental symptom profiles across the lifespan, in those with mental health problems, may help to detect often 'hidden' vulnerabilities associated with more stable and treatable conditions such as ADHD, Tics, LD and ASD. Mania tends not to be considered in adolescents with newly emerging psychiatric disorder (Jauhar et al., 2019). Services for the assessment of NDDs such as ASD and ADHD tend to be "stand alone" so that these disorders are considered in isolation (Arim et al., 2017; Eke et al., 2019; Murphy et al., 2016). An assessment for NDDs is often overlooked in those with a history of abuse and neglect (Woolgar and Baldock, 2015). Our clinical experience is that, if NDDs are assessed for at all, they are rarely considered as part of the overall formulation, *especially* if there is a history of trauma.

Considering that CTEs and NDDs often co-occur (Dinkler et al., 2017), we therefore propose that children/adolescents and adults presenting with a history of *either* CTEs or NDDs should always be offered a holistic assessment encompassing both CTEs and NDDs. Those with a history of *both* CTEs and NDDs should be monitored closely for the development of more severe psychiatric presentations such as mania since our findings show they are at a higher risk for

mania than children/adolescents with one risk factor only and early intervention in mania is crucial (Jauhar et al., 2019).

For a very long time there have been discussions about the "neurodevelopmental model of schizophrenia" with recent preliminary evidence for the combined effect of trauma and neurodevelopmental risk in psychosis (Liu et al., 2019). Although our study focusses on symptoms of known neurodevelopmental disorders, it could well be the underlying "general factor" that is responsible for the associations with later mania symptoms (Brikell et al., 2018). This study provides important new findings by its focus on symptoms of recognized NDDs rather than non-specific neurodevelopmental risk.

Our findings also suggest that both CTEs and NDDs should be considered in adult patients with complex psychiatric presentations. Mania symptoms are prevalent in a range of mental health constructs such as borderline personality disorder (Paris et al., 2007) and psychosis (Boks et al., 2007). The associations between some NDDs (i.e., ASD and ADHD) and mania are already robustly established in children (Biederman et al., 1996; McGough et al., 2008; Weissman and Bates, 2010) and in adults between ADHD and BD (for a review see (Skirrow et al., 2012)). It is therefore plausible that additive effects of CTEs and NDDs might be implicated in other psychiatric disorders, since there is a common genetic factor for psychopathology that accounts for a substantial part of the variance across BD, schizophrenia, depression, anxiety, alcohol use disorder and drug abuse (Pettersson et al., 2016).

We suggest that future research should focus on a) testing the longitudinal effects of CTEs and NDDs in larger/pooled samples (Rocha et al., 2020) with a range of clinical outcomes, including psychosis and personality disorders, and b) examining risk specific mechanisms (i.e., emotional dysregulation, inflammatory markers, stress responsivity) along the pathways from CTEs and NDDs to mania and potentially other severe psychiatric disorders.

Strengths and limitations

The major strengths of this paper are the relatively large prospective sample and the use of validated instruments. The study also has limitations. First, mania diagnosis might have been a clinically more meaningful concept to investigate than a continuous mania symptom score but statistical power was not sufficient to analyse the categorical variable (CMRS score above/below cutoff). Whilst categorical diagnosis of Neurodevelopmental disorders is useful for clinical practice, we have previously shown that it is the neurodevelopmental symptom load that is associated with CTE's (Dinkler et al 2017). Second, symptoms of ADHD and juvenile mania are partly overlapping and the study is limited in not assessing ADHD again at age 15, however whilst mania-like symptoms can sometimes occur in other disorders, the CRMS-P has been shown to have excellent specificity for mania.(Pavuluri et al., 2006). The and differentiate well between ADHD and paediatric BD (Henry et al., 2008). Third, although the prospective examination of mania symptoms at age 15 is predicted by CTE and NDD data that had been collected previously at age 9: however retrospective parental recall of CTEs was still required at age 9 if the CTE had occurred before that date. We have extensively discussed the validity of the measurement of CTEs in this sample elsewhere and that they may be underreported (Dinkler et al., 2017). Fourth, given that all measures were parent-reported we cannot exclude that variance attributable to the measurement method, i.e. common method variance, may have influenced our results by amplifying the reported estimates. Fifth, at age 9, small differences have been reported between responders and non-responders: non-responders were more likely to belong to a lower socio-economic strata (26.6% vs 21.9%), being assigned a clinical ADHD diagnosis (2.1% vs 1.6%), and to have a parent treated in psychiatric settings (9.6% vs 6.3%, Anckarsäter et al.,

2011). While no systematic study has been conducted on responders in CATSS-15, it seems reasonable to assume that individuals with mental health problems are overrepresented in non-responders. Having less individuals with mental health problems and/or traumatic events in the sample might have attenuated associations found in our study.

To summarise, the prospective nature of this measurement is likely to be considerably more robust than the way childhood trauma is measured in most published studies, that is retrospective self-report, which is subject to recall bias. We were not powered to examine individual neurodevelopmental disorders and this would be unlikely to reap benefits because of the high degree of overlap between these disorders and the underlying "general factor" that seems to underpin them (Pettersson et al., 2013). Also, it would have been beneficial to consider some additional potential confounders such as child neurocognitive profile, parental psychopathology and/or parental neurodevelopmental disorders, had these data been available. There was no measure of mania symptoms at age 9 so we cannot be certain that CTEs and NDDs were associated with new onset mania, but since mania symptoms rarely occur before adolescence, this is unlikely (Harrington and Myatt, 2003).

Clinical Implications

Psychiatric problems have traditionally been conceptualized as *either* rooted in CTEs *or* in NDDs such as ASD or ADHD. Our finding that CTEs and NDDs at age 9 each uniquely contribute to mania symptoms in adolescence suggests that both should be considered simultaneously: clinicians should consider mania in young people with psychiatric disorder *especially* if there is a history of childhood trauma and/or NDDs. It is also important to note that manic symptoms are generally assessed by self-report and the involvement if parents as informant may be useful to consider clinically. Secondly, clinicians should carefully assess individuals who have mania symptoms for *both* a potential history of childhood trauma *and* for the potential existence of NDDs including ASD and ADHD. The presence of CTEs and/or NDDs

may indicate that additional treatments (e.g., targeted trauma-focused psychotherapies or stimulant medication) may be necessary alongside/subsequent to treatment directed at mania symptoms.

Ethical Considerations

The CATSS has ethical approval from the Regional Ethical Review Board in Stockholm. Oral consent has been obtained from all subjects participating in the telephone interview.

Author contributions

RG, LD, SL, CG, and HM designed the study. LD conducted the data analyses. RG, LD and HM drafted the manuscript. HM supervised the study. All authors contributed to the interpretation of results. All authors critically revised the manuscript for important intellectual content and approved the final manuscript.

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The funding sources had no involvement in the study design, collection, analysis, and interpretation of the data, preparation of the manuscript, or the decision to submit this manuscript for publication.

Conflict of Interest

The authors have declared that they have no competing or potential conflicts of interest.

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Table 1 Descriptive statistics of childhood traumatic experiences (CTEs) and neurodevelopmental disorders (NDDs) at age 9, and juvenile mania at age 15 in *n* = 3,348 twins (all zygosities)

	All		Males		Females	
Variable	N	%	N	%	N	%
Sex (male)	3348	100	1574	47.0	1774	53.0
Childhood traumatic experiences (CTEs)						
Any CTE	231	6.9	122	7.8	109	6.1
Emotional Neglect/Abuse	100	3.0	67	4.3	33	1.9
Physical Neglect	13	0.4	5	0.3	8	0.5
Physical Abuse	36	1.1	23	1.5	13	0.7
Sexual Abuse	21	0.6	7	0.4	14	0.8
Witnessed Violence	47	1.4	20	1.3	27	1.5
Domestic Violence	51	1.5	25	1.6	26	1.5
Substance Abuse in Family	5	0.1	2	0.1	3	0.2
Bullied	9	0.3	7	0.4	2	0.1
Other	9	0.3	3	0.2	6	0.3
Number of CTEs						
0	3117	93.1	1452	92.2	1665	93.9
1	186	5.6	93	5.9	93	5.2
2	33	1.0	22	1.4	11	0.6
3	9	0.3	6	0.4	3	0.2
4	3	0.1	1	0.1	2	0.1
Neurodevelopmental Disorders (NDDs)						
Any NDD	189	5.7	116	7.4	73	4.1
DCD	50	1.5	34	2.2	16	0.9
ADHD	50	1.5	31	2.0	19	1.1
ASD	20	0.6	12	0.8	8	0.5
LD	40	1.2	20	1.3	20	1.1
TD	91	2.7	57	3.6	34	1.9
Number of NDDs						
0	3159	94.4	1458	92.6	1701	95.9
1	146	4.4	88	5.6	58	3.3
2	29	0.9	20	1.3	9	0.5
3	11	0.3	7	0.4	4	0.2
4	1	0.0	0	0.0	1	0.1
5	2	0.1	1	0.1	1	0.1
Neither CTEs nor NDDs	2971	88.7	1369	87.0	1602	90.3
CTEs-only	188	5.6	89	5.7	99	5.6
NDDs-only	146	4.4	83	5.3	63	3.6
Both CTEs and NDDs	43	1.3	33	2.1	10	0.6
Child Mania Rating Scale-Parent Version (CMRS)						
Juvenile Mania (CMRS score >= 10)	66	2.0	20	1.3	46	2.6

Note. DCD: Developmental Coordination Disorder, ADHD: Attention Deficit/Hyperactivity Disorder, ASD: Autism Spectrum Disorder, LD: Learning Disorder, TD: Tic Disorders

Table 2. Impact of childhood traumatic experiences (CTEs) and neurodevelopmental disorders (NDDs) at age 9 on Childhood Mania Rating Scale score at age 15 in 3,327 twins, controlling for socio-economic status (SES)

	IRR (95 % CI)	*SE*	*z*	*p*
Model 1				
CTEs	1.36 (1.14, 1.63)	0.12	3.41	.0006
SES	0.96 (0.94, 0.98)	0.01	-3.82	.0001
Constant	2.50 (2.15, 2.91)	0.19	11.88	<.0001
Model 2				
NDDs	1.69 (1.42, 2.01)	0.15	6.01	<.0001
SES	0.96 (0.94, 0.98)	0.01	-3.83	.0001
Constant	2.46 (2.11, 2.87)	0.19	11.56	<.0001
Model 3a				
CTEs	1.23 (1.01, 1.49)	0.12	2.06	.0392
NDDs	1.57 (1.29, 1.92)	0.16	4.42	<.0001
CTEsx NDDs	1.17 (0.81, 1.68)	0.22	0.83	.4078
SES	0.96 (0.94, 0.98)	0.01	-3.74	.0002
Constant	2.41 (2.07, 2.80)	0.18	11.43	<.0001
Model 3b – Final model				
CTEs	**1.26 (1.06, 1.50)**	**0.11**	**2.64**	**.0083**
NDDs	**1.63 (1.37, 1.93)**	**0.14**	**5.50**	**<.0001**
SES	**0.96 (0.94, 0.98)**	**0.01**	**-3.73**	**.0002**
Constant	**2.40 (2.06, 2.79)**	**0.18**	**11.41**	**<.0001**
Contrasts Model 3b				
NDDs-only vs CTEs-only	**1.29 (0.99, 1.68)**	**0.18**	**1.86**	**.0636**
Both vs Neither	**2.05 (1.65, 2.55)**	**0.23**	**6.44**	**<.0001**

Note. IRR: Incidence Rate Ratio, CI: Confidence Interval. Outcome: Count of score points on CMRS. Statistical method: Generalized estimating equations (GEE) with negative binomial distribution (dispersion parameter $\alpha = 1.28$), log link function, and exchangeable within-cluster correlation structure; standard errors adjusted for 1,687 clusters (i.e., twin pairs). Estimates were adjusted for SES. The final model is printed in bold. The correlation between twins in a pair in the final model was $r = .46$. Model statistics of the final model: Wald $\chi^2(3) = 57.11$, $p < .0001$.

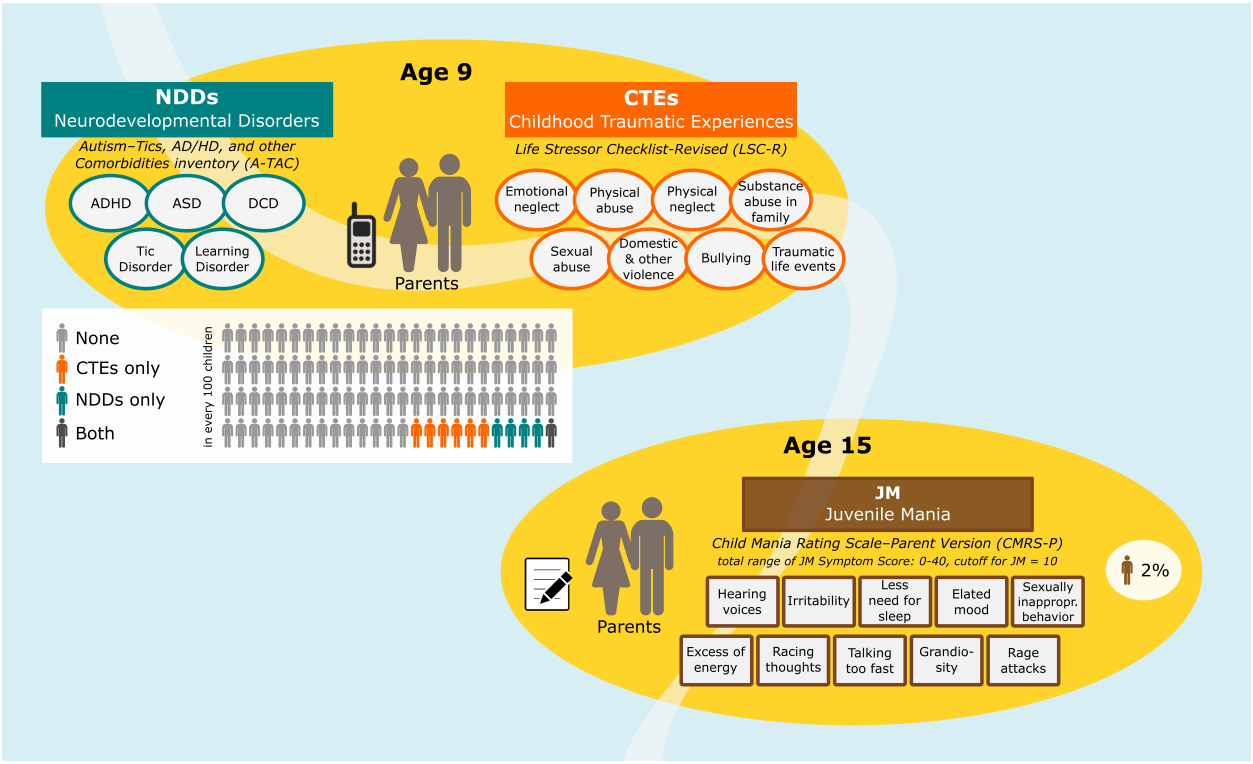

Figure 1. Assessment and prevalence of Childhood traumatic experiences (CTEs), Neurodevelopmental disorders (NDDs) and Juvenile mania (JM) symptoms in the current study

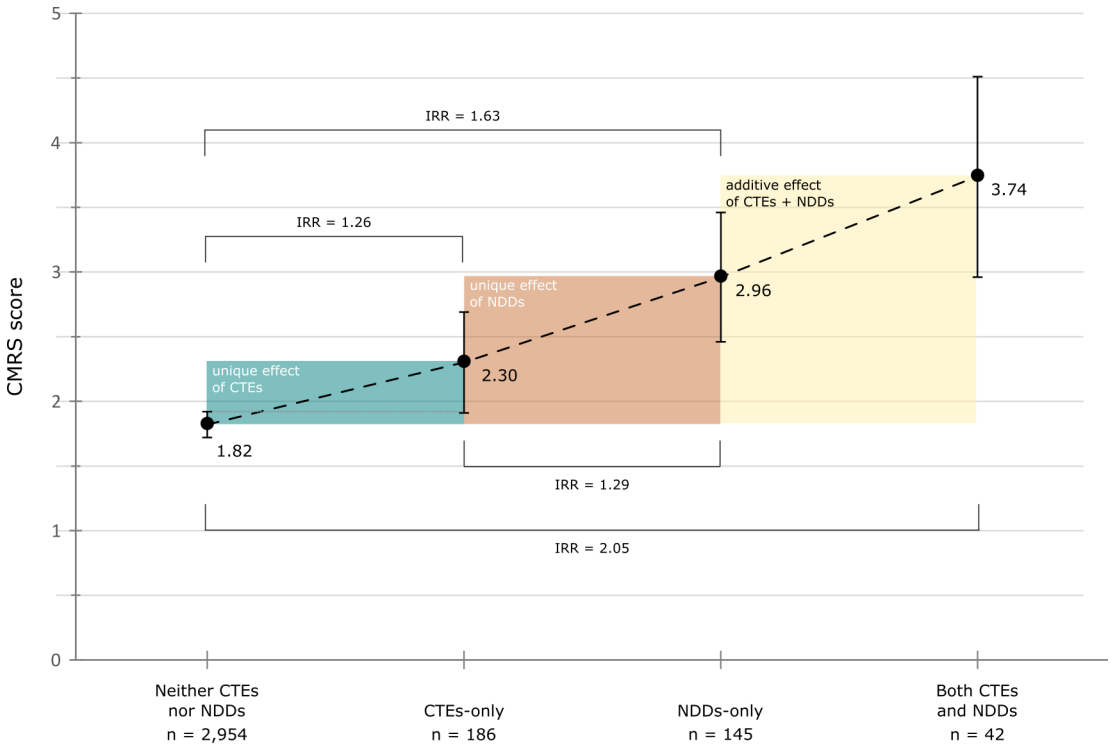

Figure 2. Average Childhood Mania Rating Scale (CMRS) score by exposure group based on the final regression model (without interaction)

Caption: Error bars present the 95% confidence intervals around the margins. The covariate socio-economic status is fixed at its mean (7.15). CTEs: Childhood traumatic experiences, NDDs: Neurodevelopmental disorders, IRR: Incidence rate ratio

Table S1. Impact of childhood traumatic experiences (CTEs) and neurodevelopmental disorders (NDDs) at age 9 on Childhood Mania Rating Scale score at age 15 by gender and controlling for socio-economic status (SES)

	Males (n = 1,561)				Females (n = 1,766)			
	IRR (95 % CI)	*SE*	*z*	*p*	*IRR* (95 % CI)	*SE*	*z*	*p*
Model 1								
CTEs	1.40 (1.10, 1.77)	0.17	2.77	.0056	1.41 (1.11, 1.80)	0.17	2.79	.0053
SES	0.98 (0.94, 1.00)	0.01	-2.14	.0321	0.96 (0.93, 0.98)	0.01	-3.52	.0004
Constant	1.97 (1.58, 2.46)	0.22	6.08	<.0001	2.96 (2.48, 3.54)	0.27	11.92	<.0001
Model 2								
NDDs	1.73 (1.37, 2.19)	0.21	4.60	<.0001	1.90 (1.50, 2.41)	0.23	5.32	<.0001
SES	0.97 (0.94, 1.00)	0.02	-1.98	.0478	0.96 (0.93, 0.98)	0.02	-3.59	.0003
Constant	1.89 (1.51, 2.38)	0.22	5.50	<.0001	2.93 (2.45, 3.49)	0.26	11.95	<.0001
Model 3a								
CTEs	1.26 (0.95, 1.66)	0.18	1.62	.1058	1.24 (0.97, 1.59)	0.16	1.68	.0921
NDDs	1.67 (1.24, 2.26)	0.26	3.33	.0009	1.69 (1.32, 2.16)	0.21	4.17	<.0001
CTEs x NDDs	0.98 (0.63, 1.52)	0.22	-0.08	.9346	1.62 (0.91, 2.88)	0.48	1.63	.1037
SES	0.97 (0.94, 1.00)	0.02	-1.94	.0525	0.96 (0.94, 0.98)	0.01	-3.52	.0004
Constant	1.85 (1.48, 2.32)	0.21	5.38	<.0001	2.86 (2.40, 3.41)	0.26	11.79	<.0001
Model 3b – Final model								
CTEs	**1.25 (0.98, 1.60)**	**0.16**	**1.78**	**.0747**	**1.32 (1.05, 1.65)**	**0.15**	**2.38**	**.0171**
NDDs	**1.66 (1.29, 2.15)**	**0.22**	**3.91**	**.0001**	**1.83 (1.46, 2.29)**	**0.21**	**5.20**	**<.0001**
SES	**0.97 (0.94, 1.00)**	**0.02**	**-1.95**	**.0513**	**0.96 (0.94, 0.98)**	**0.01**	**-3.50**	**.0005**
Constant	**1.85 (1.48, 2.31)**	**0.21**	**5.43**	**<.0001**	**2.85 (2.39, 3.39)**	**0.25**	**11.73**	**<.0001**
Contrasts Model 3b								
NDDs-only vs CTEs-only	**1.33 (0.86, 2.04)**	**0.29**	**1.30**	**.1950**	**1.39 (1.01, 1.92)**	**0.23**	**1.99**	**.0464**
Both vs Neither	**2.08 (1.60, 2.70)**	**0.28**	**5.49**	**<.0001**	**2.40 (1.75, 3.30)**	**0.39**	**5.41**	**<.0001**

Note. IRR: Incidence Rate Ratio, CI: Confidence Interval. Outcome: Count of score points on CMRS. Statistical method: Generalized estimating equations (GEE) with negative binomial distribution (dispersion parameter α = 1.28), log link function, and exchangeable within-cluster correlation structure; standard errors adjusted for 1,088 (males)/1,189 (females) clusters (i.e., twin pairs). Estimates were adjusted for SES. Final models are printed in bold. The correlations between twins in a pair in the final models were r = .54 (males) and r = .43 (females). Model statistics of the final models: males: Wald $\chi^2(3) = 35.44$, $p < .0001$; females: Wald $\chi^2(3) = 43.89$, $p < .0001$.

Table S2. Impact of childhood traumatic experiences (CTEs) and neurodevelopmental disorders (NDDs) at age 9 on juvenile mania at age 15 by exposure group

Exposure	No juvenile mania (CMRS score <10) n (%)	Juvenile mania (CMRS score ≥10) n (%)	OR (95% CI)	p
Neither CTEs nor NDDs	2909 (98.5)	45 (1.5)	*base*	
CTEs-only	181 (97.3)	5 (2.7)	1.73 (0.68, 4.40)	.253
NDDs-only	135 (93.1)	10 (6.9)	4.53 (2.20, 9.31)	<.001
Both CTEs and NDDs	36 (85.7)	6 (14.3)	10.92 (4.51, 26.42)	<.001

Note. OR: Odds Ratio, CI: Confidence Interval. Outcome: Presence/absence of juvenile mania based on a score ≥ 10 on the Childhood Mania Rating Scale (CMRS). Statistical method: Generalized estimating equations (GEE) with binomial distribution, logit link function, and exchangeable within-cluster correlation structure; standard errors adjusted for 1,687 clusters (i.e., twin pairs). Estimates were adjusted for socio-economic status. The correlation between twins in a pair in the final model was $r = .04$. Model statistics: Wald $\chi^2(3) = 44.24$, $p < .0001$.