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Childhood trauma as a transdiagnostic risk factor for major psychiatric conditions: A meta-analysis

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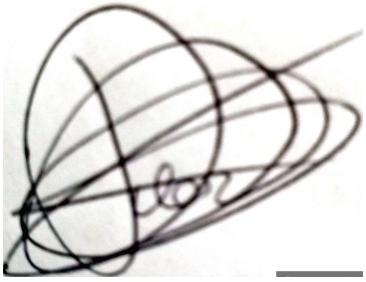

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List of Abbreviations

ALX	Alexithymia
BD	Bipolar Disorder
BDI	Bipolar Disorder Type 1
BDII	Bipolar Disorder Type 2
CAQ	Childhood Abuse Questionnaire
CATS	Childhood Abuse and Trauma Scale
CECA	Childhood Experience of Care and Abuse
CEQ-58	Childhood Experiences Questionnaire
CI	Confidence Interval
CT	Childhood Trauma
DSM	Diagnostic and Statistical Manual of Mental Disorders
EBDI	Early Bipolar Disorder Type 1
EA	Emotional Abuse
EDD	Episodic Depressive Disorder
EHEI	Early Home Environment Interview
ELSQ	Early Life Stress Questionnaire
EN	Emotional Neglect
ETI	Early Trauma Inventory
ETISR-SF	Early Trauma Inventory Self Report-Short Form
HDS	Hamilton Depression Scale
HPA	Hypothalamic-Pituitary-Adrenal axis
ICD	International Classification of diseases
LEQ	Life Experience Questionnaire
MACE	Maltreatment Abuse and Exposure Scale
MADRS	Montgomery–Åsberg Depression Rating Scale
MD	Major Depression
NA	Not Available
PA	Physical Abuse
PANSS	Positive and Negative Syndrome Scale
PDD	Persistent Depressive Disorder
PN	Physical Neglect
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PTSD	Posttraumatic Stress Disorder
RFQ	Risky Families Questionnaire

SA	Schizoaffective Disorder
SD	Standard Deviation
SE	Standard Error
SMD	Standardized Mean Difference
SQ-SF	Schema Questionnaire-Short Form
TAQ	Traumatic Antecedents Questionnaire
TRMD	Treatment-resistant Major Depression
TS	Total Score
TSMD	Treatment-sensitive Major Depression
UNT	Untreated
WHO	World Health Organization

1. Zusammenfassung

Hintergrund: Kindheitstraumata erhöhen die Anfälligkeit für die Entwicklung schwerwiegender psychischer Störungen im Erwachsenenalter einschließlich einer bipolaren Störung, Depression und Schizophrenie-Spektrum-Störungen. Zahlreiche Studien haben zugrundeliegende Mechanismen des Zusammenhangs zwischen Kindheitstraumata und Psychopathologien im Erwachsenalter identifiziert, welche nicht störungs- bzw. diagnosespezifisch sind. Transdiagnostische Ansätze gehen über die bisherige kategoriale Diagnostik hinaus und bieten eine neue, störungsübergreifende Perspektive zum Thema Kindheitstraumata und psychischem Erkrankungsrisiko. Transdiagnostische Risikofaktoren sind psychopathogene Prozesse, die an der Entstehung und Aufrechterhaltung verschiedener psychischer Störungen beteiligt sind.
Die vorliegende Meta-Analyse untersucht, ob Kindheitstraumata und die verschiedenen Traumatisierungsformen (wie körperliche Misshandlung (PA), emotionale Misshandlung (EA), sexuelle Misshandlung (SA), körperliche Vernachlässigung (PN) und emotionale Vernachlässigung (EN)) transdiagnostische Risikofaktoren für schwerwiegende psychiatrische Erkrankungen (bipolare Störung, Depression und Schizophrenie-Spektrum-Störungen) darstellen.

Methodik: Die systematische Literaturrecherche erfolgte in zwei bibliographische Datenbanken: *PubMed* und *Web of Science*. Eingeschlossen wurden Fall-Kontrollstudien, die Kindheitstraumata bei Patienten mit schwerwiegenden psychiatrischen Diagnosen (Depression, bipolare Störung oder Schizophrenie-Spektrum-Störung) und gesunden Probanden erfassten. Wir berechneten die Effektstärken der Kindheitstraumata-Gesamtscores und der verschiedenen Traumatisierungsformen (PA, EA, SA, EN, PN) bei diesen drei Diagnosen mittels Zufallseffektmodell. Für die Analyse transdiagnostischer Aspekte führten wir Subgruppenanalysen durch.

Ergebnisse: Insgesamt wurden 97 Studien eingeschlossen. Für die Kindheitstraumata-Gesamtscores zeigten sich bei Schizophrenie-Spektrum-Störungen (g=0.83, 95%-CI: 0.70-0.97), Depression (g=0.91, 95%-CI: 0.76-1.05) und bipolarer Störung (g=0.84, 95%-CI: 0.69-0.98) signifikant große Effektstärken ohne signifikante transdiagnostische Unterschiede in der Subgruppenanalyse.
Alle Traumatisierungsformen wiesen mittlere bis große, signifikante Effekte bei allen psychiatrischen Diagnosen im Vergleich zu gesunden Probanden auf. Die Effektstärken von emotionalem Missbrauch (EA) und emotionaler Vernachlässigung

(EN) waren signifikant größer in Depression als in Schizophrenie-Spektrum-Störungen.

Schlussfolgerung: Kindheitstraumata wiesen vergleichbare signifikant große Effektstärken bei schwerwiegenden psychischen Störungen auf und stellen somit einen wichtigen transdiagnostischen Risikofaktor für die Entwicklung psychischer Erkrankungen dar. Die Ergebnisse unserer Meta-analyse sind relevant für zukünftige Forschung, klinische Praxis und Public-Health Ansätze.

2. Summary

Background: Childhood trauma (CT) was shown to increase the risk for multiple forms of adult psychiatric disorders, such as bipolar disorder, major depression (MD), and schizophrenia spectrum disorder. Previous research points to general mechanisms linking childhood traumatic experiences and adult psychopathology, which are not specific for psychiatric diagnostic entities. A transdiagnostic approach that cuts across traditional diagnostic categories provides an inclusive picture for understanding research in this field. Transdiagnostic risk factors are factors occurring across multiple disorders that contribute to the aetiology and/ or maintenance of a range of pathologies.

This meta-analysis aims to determine if CT can be considered a transdiagnostic risk factor for the development of severe mental disorders: schizophrenia spectrum disorder, bipolar disorder, and major depression (MD); and analysing the role of different CT domains: physical abuse (PA), emotional abuse (EA), sexual abuse (SA), emotional neglect (EN), and physical neglect (PN).

Methods: We conducted a systematic literature search in two bibliographic databases: *PubMed* and *Web of Science*. We included articles reporting CT among patients with major psychiatric disorders (schizophrenia spectrum disorder, bipolar disorder, and MD) and healthy controls (HC). We calculated Hedge's g effect sizes of the CT total scores and the CT domains (PA, EA, SA, EN, and PN) in the three pathologies using random-effects models. To examine the transdiagnostic aspects, we conducted subgroup analyses comparing the effect sizes of CT and its subtypes in the three major psychiatric conditions.

Results: In total, 97 studies met our inclusion criteria. We found that the effect sizes of CT total scores were large in schizophrenia spectrum disorder (g=0.83, 95%-CI: 0.70-0.97), bipolar disorder (g=0.84, 95%-CI: 0.69-0.98), and MD (g=0.91, 95%-CI: 0.76-1.05) with no significant transdiagnostic differences in the subgroup analysis.

All CT domains had moderate to large effects in the three psychiatric diagnoses compared to healthy controls. In the transdiagnostic comparison, we found significantly higher effect sizes for EA and EN in MD than in schizophrenia spectrum disorder.

Conclusions: Our results provide strong evidence of the link between CT and adult psychopathology, identifying CT as a powerful transdiagnostic risk factor for the development of psychiatric disorders. The findings of our meta-analysis bear

important implications for future research, clinical practice, and public health approaches.

3. Introduction

Childhood trauma (CT) is a major public health concern with serious life-long consequences[1]. The term CT covers five different subcategories of trauma exposure: physical abuse (PA), emotional abuse (EA), sexual abuse (SA), physical neglect (PN), and emotional neglect (EN)[2,3].

The negative impact of CT on adult physical and mental health is supported by overwhelming evidence[1,4]. World Health Organization (WHO) surveys estimated that one-third of the global population has experienced some form of CT[5], making CT a public health problem[6]. The estimated economic burden of child maltreatment in the United States based on 2015 substantiated incident cases was $428 billion[7].

An extensive body of literature links CT to development, persistence, and severity of adult psychopathology and impairment[8-11]. Traumatic experiences in childhood have particularly detrimental and long lasting effects due to the great neurodevelopmental plasticity during this period. Early exposure to CT might negatively affect childhood brain development and cause a dysregulation in stress response systems, which in turn result in an increased risk of psychopathological symptoms[12]. The exact underlying pathophysiological mechanisms leading to the psychological impact of CT are still a subject of investigation[13].

While several studies have linked CT with risk trajectories for specific disorders such as schizophrenia[14], major depression (MD)[15], bipolar disorder[16], anxiety disorders[17] and posttraumatic stress disorder (PTSD)[18], recent research shows that certain risk factors might not be disorder-specific, but share common mechanisms that lead to psychopathology. Transdiagnostic research aims to elucidate the common processes that link, or differentiate among, multiple disorders. A key point of the transdiagnostic approach is that the risk, protective, and maintenance factors and processes implicated in mental health problems (biological, socio-environmental, or psychological variables) show no specificity for particular diagnostic disorders but rather appear to operate across traditional nosological boundaries[19].

MD, bipolar disorder, and schizophrenia spectrum disorder are among the leading contributors to the global disease burden[20]. For each of these disorders, several comprehensive reviews and meta-analyses have demonstrated the important role of CT in their onset and severity[14,21,22]. Descriptively, the reported effect sizes in the literature are comparably large for these three diagnoses. However, a quantitative analysis comparing the effect sizes of CT in different psychiatric disorders is yet

lacking. Additionally, the different domains of CT represent considerably different adverse experiences that have distinct effects on neurobiological, socio-emotional, and cognitive development and, in turn, psychopathology[23,24]. Research on the psychopathological impact of specific CT subtypes presents study heterogeneity and yielded inconsistent results.

Meta-analyses offer the opportunity to critically evaluate and statistically combine results of a large number of studies providing a more precise estimate of the underlying effects and improving the generalizability of the results[25]. The aim of the present work was to provide a quantitative review and meta-analysis of the available literature examining the magnitude of the effects of CT and its subtypes (PA, EA, SA, PN and EN) in major psychiatric conditions with a transdiagnostic approach.

3.1 CT: Concept and subtypes

The lack of a consistent definition across disciplines constitutes an important limitation for surveillance of CT[26]. In its Report of the Consultation on Child Abuse Prevention, the World Health Organization (WHO) proposes the following definition[27]:

"Child abuse or maltreatment constitutes all forms of physical and/or emotional ill-treatment, sexual abuse, neglect or negligent treatment or commercial or other exploitation, resulting in actual or potential harm to the child's health, survival, development or dignity in the context of a relationship of responsibility, trust or power"

For the current project, the CT subtypes were defined according to the Childhood Trauma Questionnaire (CTQ) as follows[3]:

PA	Bodily assaults on a child by an adult or older person that posed a risk of or resulted in injury
EA	Verbal assaults on a child's sense of worth or well-being or any humiliating or demeaning behaviour directed toward a child by an adult or older person
SA	Sexual contact or conduct between a child younger than 18 years of age and an adult or older person
PN	Failure of caretakers to provide for a child's basic physical needs, including food, shelter, clothing, safety, and health care"
EN	Failure of caretakers to meet children's basic emotional and psychological needs, including love, belonging, nurturance, and support

Table 1*:* Definition of CT subtypes

Childhood abuse and neglect often causes a deficiency in basic human needs, which can have lasting effects on the individual's thinking and behaviour. The consequences of CT depend on the severity, frequency, nature, and pattern of the traumatic experience itself. Moreover, children's perception, reaction, and subsequent processing of traumatic experiences are modulated by several developmental and environmental risk and protective factors[28].

While some studies found that subtypes of CT may have nonspecific, widespread effects on mental health, other studies found differences in the neurobiological and psychopathological impact of distinct CT domains[29,30]. Based on the neurodevelopmental impact of CT, a distinction of early traumatic experiences into core dimensions of deprivation (absence of expected environmental inputs and complexity) and threat (presence of experiences that represent a threat to one's physical integrity) has been proposed[28].

The concept of CT refers to abuse and neglect experiences that occur to a child before the age of 18. At this point, it is important to highlight the relevance of timing aspects of CT such as duration (single episode or chronic), age of trauma onset, and stage of development[31]. Several studies examine "sensitive periods" when the developing human brain is particularly sensitive to the effects of traumatic experiences[32]. Young children might be especially trauma-vulnerable as they undergo an exceptionally rapid period of physiological and emotional development, have limited coping strategies, and are strongly dependent on their caregivers to protect them physically and emotionally.

Another important aspect is the high interrelation and frequent co-occurrence of multiple subtypes of CT[33]. In this context, the "cumulative risk hypothesis" assumes that the accumulation of adverse experiences has a high predictive power for negative health outcomes in a dose-response relationship. In this framework, recent studies reported that increasing number of CT experiences result in higher adult risk for psychopathological complexity and severity[34].

Epidemiologic information is crucial for CT research and public health policy[35]. Obtaining precise estimates of the prevalence and incidence of different CT subtypes is problematic. As discussed previously, rates vary extremely due to different definitions, but also methodological factors like small sample sizes, geographical regions, or non-random designs[36].

The early detection of CT is inherently difficult, because frequently only the perpetrators and the children have knowledge of the events and do not reveal them for different reasons. These rationales for underreporting include, *inter alia*, the victim's fear of the offender, shame, a sense of stigmatization, and offender's fear of the legal consequences. All of the listed aspects are in turn modulated by cultural factors, gender or ethnicity[35].

PA in childhood is an important cause of paediatric morbidity and mortality. In some developing countries, child corporal punishment is culturally and socially accepted[37]. SA had most research and public interest[36]. Overall, females seem to be more often affected by SA than males and the geographical origin of the samples was shown to influence the prevalence[38]. EA and EN are highly prevalent, but often overlooked forms of maltreatment, perhaps because of the less visible immediate impact (i.e. no physical injury or outward signs of abuse) and typically accompany all other forms of abuse and neglect[39].

3.1.1 CT assessment

The accurate detection and assessment of CT is crucial to define the magnitude of the problem, estimate variations over time, and evaluate the effectiveness of prevention and intervention programs[40].

The method used to screen for CT in studies can have major effects on its results. Prospective and retrospective measures may be used to detect and estimate the occurrence of CT. For the purpose of our research, we will focus on retrospective assessment methods of CT in adulthood.

In the last decades, a wide variety of instruments have been designed for the assessment and evaluation of CT. This ample array of instruments includes self- and clinician-rated questionnaires and interviews. These vary considerably in the types of abuse and neglect assessed, psychometric properties, and amount of evaluated parameters (i.e. severity of trauma, frequency, number of perpetrators etc.)[41].

The CTQ is the most widely employed instrument to assess CT in research[42], which has undergone most examinations of validity proving to have strong psychometric properties. In its original version, the questionnaire assessed 70 items[2]. In subsequent years, the authors developed the short version of the CTQ providing a more rapid screening and thus contributing to the usability of this tool in research.

This brief CTQ version is a retrospective self-report standardized 28-item instrument that assesses the frequency of five CT subtypes (PA, EA, SA, PN and EN) on a 5-point Likert scale[3].

Retrospective assessment of CT has some methodological limitations that warrant attention, such as recall or memory bias. This error occurs when participants do not remember previous events or experiences accurately or omit details, which might involve a substantial rate of false negatives and measurement errors and in rare cases, false positive reports[43].

3.2 The transdiagnostic approach

Traditional diagnostic systems are long established and have a profound influence over the way we conceptualize, understand, and manage mental health[19]. In the last decades, the classification of mental disorders has largely focused on differentiating psychopathology into categories, an approach represented in the Diagnostic and Statistical Manual of Mental Disorders (DSM; currently in its 5th edition)[44] and the International Classification of Diseases (ICD; now in its 11th edition)[45].

There is a growing consensus that psychiatric nosology and diagnostic boundaries generate important limitations in research and clinical utility, which has led to the emergence and rapid development of the transdiagnostic approach. The transdiagnostic approach is expected to cut across categorical diagnoses and go beyond them to improve classification, prevention, and treatment of mental disorders[46].

An important benefit over disorder-specific approaches is the identification of core mechanisms that might play a role in many different forms of psychopathology[8]. Findings of transdiagnostic research have broad applicability across a range of disorders and open up a new way of understanding psychiatric conditions depending on their underlying mechanisms[47]. The frequent phenomenon of comorbidity in psychiatry might be partially explained by these commonalities in the causal background of different disorders.

Transdiagnostic research can provide key targets for interventions that might be used to prevent or treat multiple types of psychopathology[48]. Transdiagnostic prevention and treatment programs have the potential to maximize public health impact.

3.2.2 CT as a transdiagnostic risk factor

In the last years, transdiagnostic mechanisms underlying the strong link between CT and adult psychopathology have been postulated. These include alterations in biological systems, psychological and social processes.

Among the neurobiological aspects, research has identified dysregulation of the Hypothalamic-Pituitary-Adrenal (HPA) axis, abnormalities in the prefrontal-limbic system, genetic polymorphisms, alterations in the immune system, and accelerated biological aging as mechanisms through which CT may confer risk for transdiagnostic psychopathology[12,49].

Transdiagnostic psychosocial mechanisms include alterations in social and emotional information processing, difficulties in emotion regulation, insecure attachment styles, and a damaged self-worth concept[8,50]. Patterns of prioritization of threat-related information with elevated emotional reactivity to these stimuli have been observed in children who experienced trauma. Furthermore, an impaired ability to regulate and tolerate negative emotional states has been identified[51].

On the other hand, recent research aimed to determine potential independent effects of the different subtypes of CT in triggering psychopathology in adults, as they represent vastly different adverse experiences[23,33]. In this line, recent studies argued that different types of adverse environments in childhood have distinct influences on cognitive, emotional, and neurobiological development as a result of the plasticity mechanisms that allow the child to adapt to the environment[28].

CT is considered one of the most important preventable causes of adult psychopathology[52]. Transdiagnostic prevention programs with common early intervention components have been proved as effective, high impact strategies to reduce psychopathology[53-55].

3.3 Research aim and objectives

The aim of the present research project was to provide a quantitative review and meta-analysis of the available empirical literature examining the magnitude of the effects of CT and its subtypes in major psychiatric conditions focusing on transdiagnostic aspects.

Our research objectives were:

1) To perform a meta-analysis of the effect sizes of CT total scores in bipolar disorder, MD, and schizophrenia spectrum disorder.

2) To elucidate the effect sizes of the five CT subtypes (PA, EA, SA, EN, and PN) in the three psychiatric disorders.

3) To explore transdiagnostic overlaps and differences in CT total scores and CT subtypes (PA, EA, SA, EN, and PN) in schizophrenia spectrum disorder, MD, and bipolar disorder.

4. Methods

The systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[56].

4.1 Search procedure

We conducted a comprehensive systematic literature search to identify eligible studies investigating the role of CT as a risk factor for major psychiatric conditions in two electronic bibliographic databases: *PubMed* and *Web of Science.*

The respective search terms were defined as follows: (“psychosis” OR “schizophrenia” OR “schizophrenic” OR “psychotic”) AND (“childhood trauma”) for patients with a schizophrenia spectrum disorder, ("bipolar disorder" OR "bipolar" OR "affective disorder") AND ("childhood trauma") for patients with bipolar disorder and (“major depression” OR “depressive” OR "affective disorder") AND (“childhood trauma”) for patients with a diagnosis of MD.

We included articles published before the 31st January 2019. In addition, we conducted a manual search by screening the full texts of the systematic reviews and meta-analyses that were identified during the literature search for further suitable studies**.** The full text of all included studies was also screened for additional references with subsequent assessment of potential eligible studies following the in- and exclusion criteria.

4.2 Inclusion and exclusion criteria

For a systematic screening of the studies, we defined the following hierarchically organized inclusion criteria:

1. Published in English language
2. Published in a peer-reviewed journal
3. Report of original data (no systematic reviews or meta-analyses)
4. Group of patients (n>3) with one of the following diagnoses according to international classification systems such as the DSM or the ICD: bipolar disorder, MD or a schizophrenia spectrum or other primary psychotic disorder (schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, brief psychotic disorder, unspecified schizophrenia spectrum, and other psychotic disorder). We excluded patients with substance induced psychotic disorders, patients in psychotic prodromal phases, and patients with psychotic disorders due to another medical condition such as neurodegenerative diseases or toxic/metabolic disorders.

5. Control groups with non-psychiatric healthy controls (HC).
6. Childhood traumatic experiences assessed by standardized questionnaires with reported validity.

When two or more studies reported data from the same cohort, we selected the publication with the biggest sample size for our meta-analysis. Studies were excluded as soon as one inclusion criterion was not sufficiently met.

The types of CT included in the meta-analysis were PA, EA, SA, EN, and PN. These categories were established in accordance with the descriptions found in seminal studies on the subject[2,3]. We screened the definition of each CT subtype in the included questionnaires and checked for comparability. CT "Total Score" (TS) represents a global measure of CT or a combination of abuse and neglect trauma types. We focused on the above mentioned definition of CT[2] and excluded other psychosocial adversities (abandonment, family dysfunction, divorce of parents, migration financial disadvantage, etc.), consistent with other work in this area[57].

4.3 Study selection

In the first stage of the study selection, two investigators (H.M. and P.A.P) independently screened the abstracts of all articles retrieved from the search. Afterwards, the same authors reviewed the full text of the potentially eligible articles. Intercoder disagreements were discussed with a third investigator (L.B., N.P.) until consensus was reached.
The overview of the selection procedure and inclusion criteria is given in the PRISMA flow diagrams in Figure 1 and Figures 1-3 in the supplementary material.

4.4 Data extraction

A standardized form was used for the data extraction. For each included study, the following information was extracted:

- First author's name and year of publication.
- Demographic characteristics of the samples: Mean age (+SD), gender distribution (percentage of men and women), and geographical location.
- Clinical variables: psychiatric diagnoses with available specifications (i.e. bipolar type I/II), specifications on non-affective/ non-psychotic comorbidities, and symptom severity scales (Young Mania Rating Scale (YMRS), Hamilton Depression Scale (HDS), Montgomery–Åsberg Depression Rating Scale (MADRS), and Positive and Negative Syndrome Scale (PANSS))

- Measurement scale used to assess CT.
- Statistical measures to estimate the effect sizes quantifying the association between CT scores and psychiatric diagnoses.

In cases in which relevant information to calculate an effect size was not available, the authors of the respective studies were contacted via email and further information was requested. After two weeks, we repeated the procedure with the authors who did not provide a response. If no sufficient information could be obtained to calculate relevant effect sizes, studies were excluded for the meta-analysis.

The data extraction was conducted by two authors (H.M., P.A.P) independently and checked randomly for consistency by a third investigator (L.B., N.P.) for approximately 30% of all data entries.

4.5 Study quality

The methodological quality of the included studies was explored using the Newcastle–Ottawa Quality Assessment Scale (NOQAS). This tool evaluates 3 quality aspects of the studies: the selection procedure, the comparability of samples as well as the suitability of adversity exposures[58]. The maximum achievable points are four points for selection, two points for comparability, and three points for outcomes, assigning up to a maximum of nine points. In case of disagreement, a consensus was reached through discussion.

2.6 Statistical analysis

In basic terms, an effect size is a number that encodes the magnitude of the relationship between two variables. A standardized mean difference (SMD) is an effect size that expresses the difference between the means of two groups.

The main outcome measure of our meta-analysis was defined as the Hedge's g SMD, which expresses an estimation of the difference in CT scores between psychiatric patients and HC in the pooled standard deviation (SD). A Hedge's g of 0.2 indicates a small effect size, of 0.5 a medium effect size, and of or above 0.8 a large effect size[59]. All effect estimates are presented with an estimate of precision using 95% confidence intervals (CI).

In some studies, CT assessments were reported as dichotomous data (presence/ absence of trauma). To allow comparability, we calculated the odds ratios (OR) based

on the dichotomous data and transformed these OR into Hedge's g SMD using the formulae of Cochrane's Handbook for Meta-Analyses[60].

The meta-analyses were conducted using the random effects model. The random effects model assumes that the variability of the observed estimated effects is due to real differences in the effects across studies as well as sampling variability[61]. We used this modelling strategy as we expected that study effect sizes would vary due to differences in the CT exposure, study populations, and outcomes assessed.

In the first step, we conducted random-effects meta-analyses to assess the effect sizes of total CT scores in the three psychiatric diagnoses. Subsequently, individual effect size estimates were derived for separate diagnoses and for the five separate domains of CT (PA, EA, SA, PN, and EN). We calculated the effect sizes and 95% CI for all diagnoses and CT domains.

Effect sizes of CT total scores and CT subtypes were compared between diagnoses conducting subgroup analyses using mixed-effects meta-regression models. A "mixed effects model" is a statistical model containing both fixed effects and random effects[62]. In our case, the psychiatric diagnosis was considered the categorical moderator.

All statistic analyses were carried out employing R, version 3.6.2, using the package "*metafor*", version 2.4-0[63].

4.6.1 Heterogeneity, risk of bias, and moderator analysis

We performed additional analyses to explore the effect of various potential sources of artefact or bias on our results.

Between-study heterogeneity was estimated using the standard Cochran's Q Test and the I^2 statistic according to the guidelines proposed in Cochrane's Handbook for Meta-Analyses. The Q test is computed by summing the squared deviations of each study's effect estimate from the overall effect estimate, weighting the contribution of each study by its inverse variance. A P-value lower than 0.05 indicates a significant heterogeneity. The I^2 statistic describes the percentage of variation across-studies that is due to heterogeneity rather than chance with values of 25, 50, and 75% that can be considered low, moderate, and high, respectively. An important advantage compared to the Cochran's Q test is that the I^2 statistic has no reliance on the number of studies used in the analysis[64] .

"Publication bias" is defined by the dictionary of epidemiology as "an editorial predilection for publishing particular findings, e.g., positive results, which leads to the failure of authors to submit negative findings for publication"[65]. The effect of this bias is that published studies may not be truly representative of all valid studies undertaken, leading to possible distortions in meta-analyses.

The potential presence of publication bias was assessed using visual inspection of funnel plots and by calculating Egger's coefficients for funnel plot asymmetry. Funnel-plots are scatter plots where the X-axis represents the mean result (in our meta-analysis, the SMD) and the Y-axis shows an index of precision (in our case, the SE). The plot should ideally resemble a pyramid or inverted funnel, with scatter due to sampling variation. Severe asymmetry to either side might be an indicator for the presence of publication bias. As the visual examination is usually subjective, we quantified the funnel plot asymmetry performing the Egger's test. This method tests the asymmetry in the funnel graph by carrying out a simple lineal regression of y_i (the effect size in study i divided by its SE) on x (the inverse of the SE) and testing whether the intercept significantly differs (at $P < 0.1$)[66].
In case of detection of significant funnel plot asymmetry, we applied the "trim-and-fill method" to adjust the results for potential publication bias[67]. The trim-and-fill method aims at estimating potentially missing studies due to publication bias in the funnel plot and adjusting the overall effect estimate[68]. It should be noted that the trim-and-fill procedure needs to be interpreted with caution in cases where significant heterogeneity is present.

The potential effect of methodological and demographic study-level variables was investigated using moderator analysis. We analysed the influence of age, gender, and publication year of the articles implementing meta-regression with mixed-effects models.

4.6.2 Outlier analysis

An additional factor that can negatively affect the validity of the results in a meta-analysis and distort its conclusions is the presence of outliers, defined as extreme values that deviate from the other observations in a dataset[69]. An outlier case might be irrelevant if it exerts little influence on the results. However, if the exclusion of the particular study from the analysis leads to considerable changes in the model, the study may be considered to be influential[70].

We performed an analysis to detect the studies that influenced the overall estimates of our meta-analysis the most and evaluated if this large influence distorted our pooled effect performing post-hoc sensitivity analyses, computing how the overall effect size would change removing one study at a time.

5. Results

5.1 Descriptive characteristics of the studies

Our literature search yielded a total of 97 studies that reported outcomes on the relationship between CT and any of the three investigated psychiatric diagnoses, and met all our inclusion criteria. This included 35 studies reporting data in schizophrenia spectrum disorder, 21 studies reporting data in bipolar disorder, and 41 studies reporting data in MD. The included studies were published between 1995 and 2019 and had population samples of 25 different countries.

An overview of the study selection procedure is provided in Figure 1. Separate PRISMA-diagrams of the study selection in each diagnostic category is provided in the supplementary material (see Supplementary figures 1,2 and 3).

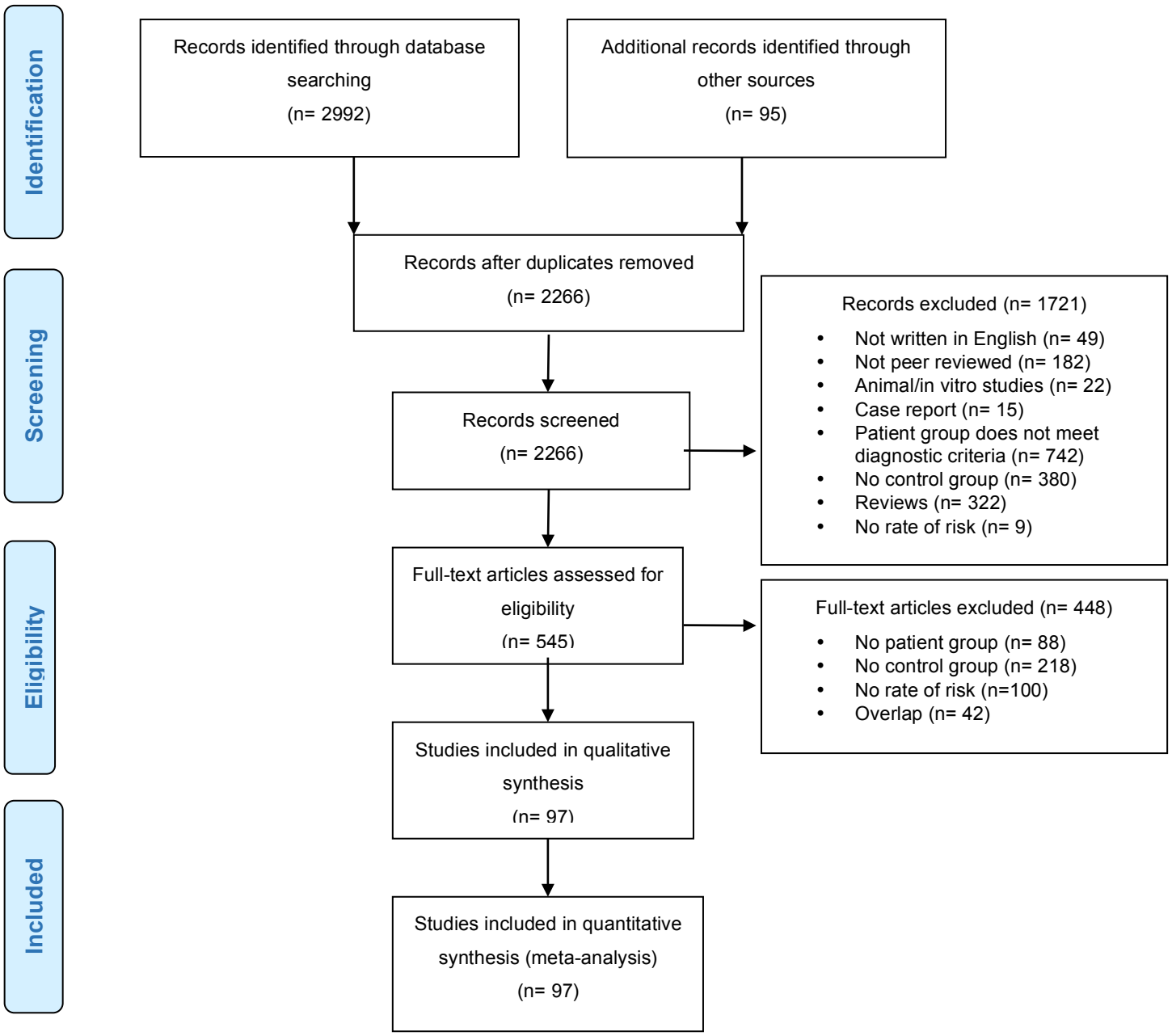


Figure 1- Identification of studies for inclusion in meta-analysis (PRISMA flowchart)

A total of twelve authors provided clarification or additional information that allowed the calculation of effects sizes. The number of studies reporting CT total scores was 74, and ranged from 66 for SA to 57 for PN for the CT domain scores.

The total number of patients included in the meta-analysis was n= 9851. There were 1494 patients diagnosed with bipolar disorder, 5763 patients with MD, 2594 patients with a schizophrenia spectrum disorder, and a total of 7253 non-psychiatric HC.

The mean age of all included patients was 36.1 years (range: 15.1-60.8): 35.8 years (range: 20.7-47.9) in patients with bipolar disorder, 36.9 (range: 15.1-60.8) years in patients with MD, and 34.5 years (range: 20.6-48.7) in patients with schizophrenia spectrum disorder. Gender was differently distributed in the thee diagnostic groups with male ratios of 38.7% in bipolar disorder, 38.2% in MD, and 61.5% in schizophrenia spectrum disorder.

The quality assessment on the NOQAS ranged from 5 to 8 and showed the best scores for selection and exposure. The least well-met quality criterion was the comparability, due to studies not controlling for covariates or not employing matching criteria.

All demographic and descriptive characteristics of the studies that were included in the meta-analysis are detailed in Tables 3, 4 and 5.

5.1.1. CT assessment instruments

Included studies used a total of 13 different instruments assessing CT. 81,4% (n=79) of all articles included in the meta-analysis used the short version of the CTQ.

Six different questionnaires were used in MD: CTQ, Early Life Stress Questionnaire (ELSQ), Early Trauma Inventory (ETI), Early Trauma Inventory Self Report- Short Form (ETIST-SF), Childhood Experience of Care and Abuse (CECA), and Early Home Environment Interview (EHEI); two in bipolar disorder: CTQ and Lifetime of Experiences Questionnaire (LEQ), and nine in schizophrenia spectrum disorder: CTQ, ETI, Childhood Abuse Questionnaire (CAQ), the Reflective Functioning Questionnaire (RFQ), Schema Questionnaire-Short Form (SQ-SF), Maltreatment Abuse and Exposure Scale (MACE), childhood experiences questionnaire (CEQ58), Traumatic Antecedents Questionnaire (TAQ), and Child Abuse and Trauma Scale (CATS).

A total of 5 articles reported dichotomous data: 2 studies in schizophrenia spectrum disorder (Schalinski et al., 2016; Green et al., 2015) and 3 studies in MD (Williams et al., 2016; Jansen et al., 2016; Jeon et al., 2012).

Instrument	Type of assessment	N of Studies
CTQ[2,3]	Self-report	79
ELSQ[71]	Self-report	2
ETI[72]	Semi-structured interview	1
ETISR-SF[73]	Self-report	2
CECA[74]	Semi-structured interview	1
EHEI[75]	Semi-structured interview	1
LEQ[76]	Self-report	1
CAQ[77]	Self-report	1
RFQ[78]	Self-report	1
MACE[79]	Self-report	1
TAQ[80]	Self-report	1
SQ-SF[81]	Self-report	1
CEQ58[82]	Self-report	1
CATS[71]	Self-report	2

Table 2*:* CT assessment instruments

First author	CT scale	Country	CT domains	N Patients	N HC	Patients age Mean(SD)	HC age Mean(SD)	Men (%) Patients/HC	Diagnoses	Quality
He et al. (2019)[83]	CTQ	Netherlands	*TS*	50	91	43.5 (12.8)	33.5 (15.7)	50/ 51.6	BDI/BDII	6
Tunc et al. (2019)	CTQ	Turkey	*TS,EN,PN*	59	69	33.4 (11.2)	33.4 (10.4)	50/ 51.6	BD	7
Boen et al. (2018)[84]	CTQ	Norway	*TS*	22	21	32.6 (6)	29.3 (5.6)	22.7/ 33.3	BDII	6
Larsen et al. (2018) [85]	CTQ	USA	*TS,PA,EA,SA,PN,EN*	62	27	38.3 (12.6)	35.1 (10.8)	38.7/ 40.7	BDI/BDII	6
Richard-Lepouriel et al. (2018)[86]	CTQ	Switzerland	*TS,PA,EA,SA,PN,EN*	168	47	32.7 (10.4)	39.6 (11.2)	7.2/ 51	BD	5
Aas et al. (2018)[87]	CTQ	Norway	*TS,PA,EA,SA,PN,EN*	132	234	33.5 (11.7)	32.8 (9.6)	NA	BD	6
Mazer et al. (2018)[88]	CTQ	Brasil	*TS,PA,EA,SA,PN,EN*	16	15	37.3 (10.3)	30.8 (7.1)	0/ 0	BD	6
Xie et al. (2017)[89]	CTQ	China	*TS, PA,EA,SA,PN,EN*	102	132	25.5 (9.4)	27.9 (4.8)	52.9/ 40.9	BD	6
Ozdin et al. (2017)[90]	CTQ	Turkey	*TS, PA,EA,SA,PN,EN*	60	60	33.9 (10.7)	33.6 (6.9)	30/ 33.3	BD	8
Souza-Queiroz et al. (2016)[91]	CTQ	France	*TS, PA,EA,SA,PN,EN*	32	47	35.8 (11.2)	36.4 (11.3)	62.5/ 46.8	BD	6
Watson et al. (2013)[92]	CTQ	New Zealand	*TS, PA,EA,SA,PN,EN*	60	55	47.9 (9.4)	45.1 (13.1)	53.3/ 54.5	BDI/BDII	8
Pavlova et al. (2011)[93]	CTQ	UK	*TS*	24	24	46.1 (11.7)	43.29 (11.91)	45.8/ 45.8	BDI/BDII	8
Erylmaz et al. (2015)[94]	CTQ	Turkey	*TS, PA,EA,SA,PN,EN*	33	50	32.4 (7)	30.5 (7)	63.6/ 40	BDII	6
Quidé et al. (2018)[95]	CTQ	Australia	*TS, PA,EA,SA,PN,EN*	84	75	37.5 (12.2)	36.1 (11.5)	36.9/ 54.6	BDI	6
Leclerc et al. (2017)[96]	CTQ	Brazil	*TS, PA,EA,SA,PN,EN*	39 (EBD) 73 (LBD)	85	33.1 (12.2) 47.9 (8.2)	34.87 (11.1)	20.5/ 60 68.4/ 60	EBDI/LBDI	8
Janiri et al. (2015)[97]	CTQ	Italy	*TS, PA,EA,SA,PN,EN*	58 (BDI) 46 (BDII)	103	43.9 (13.55)	44.26 (15.7)	67.2-50/ 52.4	BDI/BDII	7
Fowke et al. (2011)[98]	CTQ	UK	*TS, PA,EA,SA,PN,EN*	35	35	35.57 (9.89)	46.2 (12.8)	37.1/ 37.1	BD	8
Moraes et al. (2017)[99]	CTQ	Brazil	*PA,EA,SA,PN,EN*	30	31	41.8 (10.8)	42.4 (12.3)	0/ 0	BD	5
Kefeli et al. (2017)[100]	CTQ	Turkey	*PA,EA,SA,PN,EN*	40	40	33.1 (9.9)	33.7 (10.2)	52.5/ 52.5	BDI	6
Hosang et al. (2018)[101]	CTQ	UK	*PA,EA,SA,PN,EN*	72	354	48.4 (9.4)	47.73 (9.2)	22.2/ 42.1	BD	6
Neeren et al. (2008)[102]	LEQ	USA	*PA,EA,SA*	217	219	20.7 (1.9)	21 (2.1)	40.6/ 39.7	BD	6

Table 3: Demographic information of included studies in bipolar disorder

Note: TS Total Score, BD Bipolar Disorder, BDI Bipolar Disorder Type 1, BDII Bipolar Disorder Type 2, EBDI Early Bipolar Disorder Type 1, LBD1 Late Bipolar Disorder Type 1

First author (Year)	CT scale	Country	CT domains	N Patients	N HC	Patients age	HC age	Men (%) Patients/HC	Diagnoses	Quality
Aas et al. (2018)[87]	CTQ	Norway	*TS,PA,EA,SA,PN,EN*	263	234	30.0(9.8)	32.8(9.6)	NA	SZ (100%)	6
Li et al. (2018)[103]	CTQ	China	*TS,PA,EA,SA,PN,EN*	56	49	25.9(6.8)	26.2(3.9)	39.2/51	FEP (100%)	6
Schürr et al. (2018)[104]	CTQ	Netherlands	*TS,PA,EA,SA,PN,EN*	13	51	40.1(15)	43.4(15.9)	53.8/47	SZ(100%)	6
Quidé et al. (2018)[105]	CTQ	Australia	*TS,PA,EA,SA,PN,EN*	79	75	45.5(11.1)	36.1(11.5)	57/54.7	SZ(63%)/ SA	6
Lee et al. (2018)[106]	CTQ	USA	*TS,PA,EA,SA,PN,EN*	114	101	48.3(10.1)	49.4(11.3)	56.1/46.5	SZ(100%)	8
Xie et al. (2017)[89]	CTQ	China	*TS,PA,EA,SA,PN,EN*	216	132	23.8(6.2)	25.1(6.8)	19.4/26.5	SZ(100%)	6
Schalinski et al. (2017)[107]	MACE	Germany	*TS*	180	70	23.8(6.2)	25.1(6.8)	73.3/NA	F20.0(75%)	6
Lange et al. (2017)	CTQ	Switzerland	*TS,PA,EA,SA,PN,EN*	25	25	41.2(11.1)	18(16)	72/64	SZ(92%)/ SA	6
Bilgi et al. (2017)	CTQ	Turkey	*TS,PA,EA,SA,PN,EN*	36	36	38.3(13.5)	33.8(9.6)	80.5/80.5	SZ(100%)	8
Catalan et al. (2017)[108]	CTQ	Spain	*TS*	61	173	36.1(12.5)	31.9(11.6)	59/54.3	FEP	6
Seidenfaden et al. (2016)[109]	CATS	Denmark	*TS*	37	39	32.3(10.7)	31.7(9.7)	78.3/74.3	SZ(100%)	6
Aydin et al. (2016)[110]	CTQ	Turkey	*TS,PA,EA,SA,PN,EN*	35	35	29.9(7.4)	31.1(7.9)	62.9/40	SZ(100%)	6
Green et al. (2015)[111]	CAQ	Australia	*TS*	454	502	NA	NA	NA	SZ(79.8%)	6
Misiak et al. (2015)	ETI	Poland	*TS,PA,SA,EA*	48	48	25.9(5.2)	26.1(2.8)	43.8/48	SZ(100%)	6
Cancel et al. (2015)[112]	CTQ	France	*TS,PA,EA,SA,PN,EN*	21	30	32.1(8.3)	32.9(7.2)	71.4/66.7	SZ(100%)	6
Alvarez et al. (2014)[113]	CTQ	Spain	*PA,EA,SA,PN,EN*	45	78	41.1(NA)	36.1(NA)	55.5/43.5	SZ/SA(NA)	6
Michail et al. (2014)[114]	CTQ	UK	*PA,EA,SA,PN,EN*	60 20	24	24.0(4.5) 24.2(5.1)	24.2(5)	76.7-35/ 45.8	FEP(100%)	6
Bortolon et al.(2013) [115]	SQ-SF	France	*EN*	48	44	37(10.3)	37(13.4)	66.6/63.6	SZ(100%)	8
Sahin et al. (2013)[116]	CTQ	Turkey	*TS,PA,EA,SA,PN,EN*	83	69	23.1(NA)	23.9(NA)	72.3/42	SZ(100%)	6
Phassouliotis et al. (2012)[117]	CTQ	Australia	*TS,PA,EA,SA,PN,EN*	21	20	20.6(2.9)	22.4(2.3)	57.2/60	FEP(100%)	6
Styla et al. (2016)[82]	CEQ58	Poland	*TS,PA,EA,SA,PN,EN*	30	28	48.7(11.6)	50.7(10.6)	63.3/71.4	SZ(100%)	5
Andreou et al. (2015)[118]	CTQ	Germany	*TS,PA,EA,SA,PN,EN*	36	38	32.4(11.4)	21.9(12.6)	55.6/42.1	SZ(100%)	6
Varese et al. (2012)[119]	CATS	UK	*TS,PA,EA,SA,PN,EN*	15 14 16	20	45.6(12.2) 39.6(13.3) 48.3(12.2)	39.5(14.6)	40-50/55	SZ(75.5%)	6
DeRosse, et al. (2014)[120]	CTQ	USA	*TS,PA,EA,SA,PN,EN*	184	447	41(11.1)	41.1(17.1)	69/61.5	SZ/SA	6
Saleptsi et al. (2004)[121]	TAQ	Germany	*EN,EA,PA,SA*	52	63	38.0(16.5)	33(10)	59.6/39.7	SZ/SA	6
Benedetti et al. (2011)[122]	RFQ	Italy	*TS*	20	20	33.2(7.6)	38.8(10.9)	70/60	SZ(100%)	7

Chiappelli et al. (2018)[123]	CTQ	USA	*TS*	23	21	38.0(13.8)	37.6(15.2)	60.9/57.1	SZ(91.3%)	6
Dennison et al. (2012)[124]	CTQ	Ireland	*TS*	40	40	38.3(1.7)	37.2(1.8)	60/32.5	SZ(100%)	6
Hoffmann et al. (2018)[125]	CAQ	Australia	*TS,PA,SA,PN,EN*	153	96	38.2(NA)	41.8(NA)	71.2/42.7	SZ(75.8%) /SA	6
Huang et al. (2019)[126]	CTQ	China	*TS,PA,EA,SA,PN,EN*	61	53	26.5(8.5)	31.3(7.9)	66.1/52.5	FEP (100%)	6
Speck et al. (2019)[127]	CTQ	Germany	*PA,EA,SA,PN,EN*	35	35	40.4(8.8)	36.0(10.4)	65.7/65.7	SZ(100%)	8

Table 4: Demographic information of included studies in schizophrenia spectrum disorder

Note: FEP first episode psychosis, SA schizoaffective disorder, SZ schizophrenia

First author (Year)	CT scale	Country	CT domains	N Patients	N HC	Patients age	HC age	Men (%) Patients/HC	Diagnoses	Quality
Klein et al. (2018)[128]	CTQ	Germany	*TS,PA,EA,SA,PN,EN*	30 (ED) 47(PDD)	31	39.2(10.3) 36.15(8.0)	35.2(13.1)	46.6-31.2/ 41.9	ED/PDD	8
Hosang et al. (2018)[101]	CTQ	UK	*PA,EA,SA,PN,EN*	248	354	45.4(12.8)	47.7(9.2)	26.2/42.1	MD	6
Gander et al. (2018)[129]	CTQ	Austria	*PA,EA,SA,PN,EN*	30	60	15.1(1.5)	16.1(1.2)	10/26.7	MD	6
Adams et al. (2018)[130]	CTQ	Canada	*TS,PA,EA,SA,PN,EN*	44 56	62	28.7(7.1) 29.6(8.6)	26.1(5.6)	27.3-32.1/ 27.4	MD/ MD+SAD	6
Ferrer et al. (2018)[131]	CTQ	Spain	*TS*	89	126	60.8(11.8)	49(15.9)	33.7/43.7	MDD	5
Miller et al. (2018)[132]	CTQ	USA	*TS*	10	13	32.6(6.5)	34.8(10)	50/53.8	MDD	5
Chamberlain et al. (2018)[133]	CTQ	UK	*PA,EA,SA,PN,EN*	48 102 48	54	35.9(NA) 36.5(NA) 35.1(NA)	34.2(NA)	29.2- 38.2- 29.2/31.5	TSMD TRMD MD-UNT	6
Munjiza et al. (2018)[134]	CTQ	Serbia	*TS,PA,EA,SA,PN,EN*	64	53	46(10.3)	46(10.2)	20.3/18.9	MD	8
Xie et al. (2017)[89]	CTQ	China	*TS,PA,EA,SA,PN,EN*	229	132	27.8(8.1)	27.8(4.8)	55.5/40.9	MD	8
Dannehl et al. (2017)[135]	CTQ	Germany	*TS,PA,EA,SA,PN,EN*	91	40	37.4(12.4)	34.3(11.6)	36.3/35	MD	7
Ernst et al. (2017)[136]	CTQ	Germany	*TS*	20	22	31.8(11.3)	30.5(10.1)	0/0	MD	5
Saleh et al. (2016)[137]	ELSQ	USA	*TS*	64	65	35.1(8.9)	29.7(9.2)	39/33.8	MD	6
Grosse et al. (2016)[138]	CTQ	Germany	*TS,PA,EA,SA,PN,EN*	214	180	41(12)	36(12)	43.9/36.6	MD	8
Tatham et al. (2016)[139]	CTQ	Canada	*TS,PA,EA,SA,PN,EN*	44	17	36.4(10.5)	33.2(10.2)	NA	MD	6
Williams et al. (2016)[140]	ELSQ	USA	*PA,SA,EA*	1008	336	NA	NA	NA	MD	6
Du et al. (2016)[141]	CTQ	China	*TS,PA,EA,SA,PN,EN*	18	18	39.3(12.9)	35.33(10.0)	27.8/55.6	MD	7
Jansen et al. (2016)[142]	CTQ	Brazil	*PA,EA,SA,PN,EN*	82	94	21.8(2)	22.5(2.7)	23.2/41.5	MD	7
Karacoç et al. (2015)[143]	CTQ	Turkey	*PA,SA,EA*	100	30	39.1(10.2)	41.9(11.3)	0/0	MD	6
Mullins et al. (2015)[144]	CTQ	UK	*TS*	240	272	NA	NA	NA	MD	6
Bailer et al. (2014)[145]	CTQ	Germany	*TS PA,EA,SA,PN,EN*	52	52	42.7(11.6)	42.1(12.9)	44.2/40.4	MD	6
Peyrot et al. (2014)[146]	CTQ	Netherlands	*TS*	1645	340	42.2(2.5)	43.3(14.5)	32/43	MD	6
Opel et al. (2014)[147]	CTQ	Germany	*TS,PA,EA,SA,PN,EN*	85	85	37.6(12)	37.2(11.6)	36.5/40	MD	8
Carvalho-Fernando et al. (2013)[148]	CTQ	Germany	*PA,EA,SA,PN,EN*	48	63	33.15(8.89)	31.44(10)	45.8/35	MD	6
Wingenfeld et al. (2011)[149]	ETI	Germany	*PA,SA,EA*	47	108	NA	NA	NA	MD	6
Güleç et al. (2012)[150]	CTQ	Turkey	*TS,PA,EA,SA,PN,EN*	48 52	50	40.2(12.6) 40.3(11.4)	39.3 11.7	33.3-15.4/ 40	MD+ALX. MD	8
Jeon et al. (2012)[151]	ETISR-SF	Korea	*TS*	105	50	46.3(12.7)	40.3(12.7)	25.7/36	MD	6
Horesh et al. (2008)[152]	CTQ	Israel	*TS*	19	20	16.26(1)	17.5(2.3)	31.6/45	MD	7

Grassi-Oliveira et al. (2009)[153]	CTQ	Brazil	*TS*	30	19	39.2(11.6)	37.4(5.5)	0/0	MD	7
Bremner et al. (2007)[73]	ETISR-SF	USA	*TS,PA,SA,EA*	51	83	45(13)	42(11)	21.6/20.5	MD	6
Wessel et al. (2001)[154]	CTQ	Netherlands	*PA,EA,SA,PN,EN*	17	24	40.9(8.8)	25.1(10.4)	35.3/50	MD	6
Bernet et al. (1999)[155]	CTQ	USA	*TS,PA,EA,SA,PN,EN*	47	41	39(11)	45(9.8)	49/51.2	MD	6
Kounou et al. (2012)[156]	CTQ	Togo	*TS ,PA,EA,SA,PN,EN*	91	90	29.2(7.2)	28.8(6.2)	34/33.3	MD	6
Kaczmarczy et al. (2018)[157]	CTQ	Germany	*TS,PA,EA,SA,PN,EN*	68	75	37.4(9.3)	35.1(9.2)	45.6/34.7	MD	8
Farrell et al. (2018)[158]	CTQ	Ireland	*TS,PA,EA,SA,PN,EN*	33	34	28.3(8.8)	28.2(7.5)	27.3/38.2	MD	6
Herane-Vives et al. (2018)[159]	CTQ	UK	*TS*	44 27	40	34.5(11.7) 31.9(8.3)	33.2(8.9)	36.4-25.9/ 27.5	MD	8
Kiliç et al. (2017)[160]	CTQ	Turkey	*TS,PA,EA,SA,PN,EN*	30	91	15.26(NA)	15.15(NA)	30/58.2	MD	6
Bauriedl-Schmidt et al. (2017)[161]	CTQ	Germany	*PA,EA,SA,PN,EN*	29 23	29	46.7(14.2) 43.1(11.5)	46.3(13.6)	58.6-43.5/ 51.7	MD	8
Hsu et al. (2010)[162]	CTQ	USA	*TS*	23	20	41.3(11.7)	40.6(10.4)	34.8/35	MD	6
Harkness et al. (2006)[163]	CECA	Canada	*TS,PA,SA,EA*	30 24	49	15.2(1.3)	15.3(1.3)	20-41.7/ 40.8	MD	6
Frodl T et al. (2010)[164]	CTQ	Germany	*TS,PA,EA,SA,PN,EN*	43	44	44.3(12.2)	41.1(12.5)	39.5/45.5	MD	8
Lizardi et al. (1995)[75]	EHEI	USA	*TS*	45	45	31.6(9.2)	33.4(10.1)	33.3/17.7	MD	8
Özdin et al (2017)[90]	CTQ	Turkey	*TS,PA,EA,SA,PN,EN*	60	60	32.8(10.9)	33.9(10.7)	28.3/33.3	MD	8
Peterfalvi et al. (2019)[165]	CTQ	Hungary	*EN*	21	20	35.4(9.7)	35.8(8.5)	19/35	MD	6

Table 5: Demographic information of included studies in MD

Note: ALX Alexithymia, EDD Episodic depressive disorder, PDD Persistent depressive disorder, SAD Social Anxiety Disorder, TSMD Treatment-sensitive major depression, TRMD Treatment-resistant major depression, MD-UNT Major depression untreated

5.2 Meta-analytic results

An overview of the results of our meta-analysis is provided in Figure 2 and summarized in Tables 6-8. The effect sizes of CT total scores were large for bipolar disorder (g=0.84), MD (g=0.91), and schizophrenia spectrum disorder (g=0.83) and did not show significant differences between diagnoses in the subgroup analysis.

We found significant effect sizes for all CT subtypes in bipolar disorder, MD, and schizophrenia spectrum disorder. The strength of the effect sizes varied by type of CT, meaning that the difference of reported trauma scores between patients and non-psychiatric HC was higher for some CT subtypes than for others. The results of our meta-analysis show that the effect size for the different trauma subtypes ranged from g=0.35 (95%-CI: 0.13-0.56) for PA in bipolar disorder to g=0.86 (95%-CI: 0.76-0.96) for EN in MD.

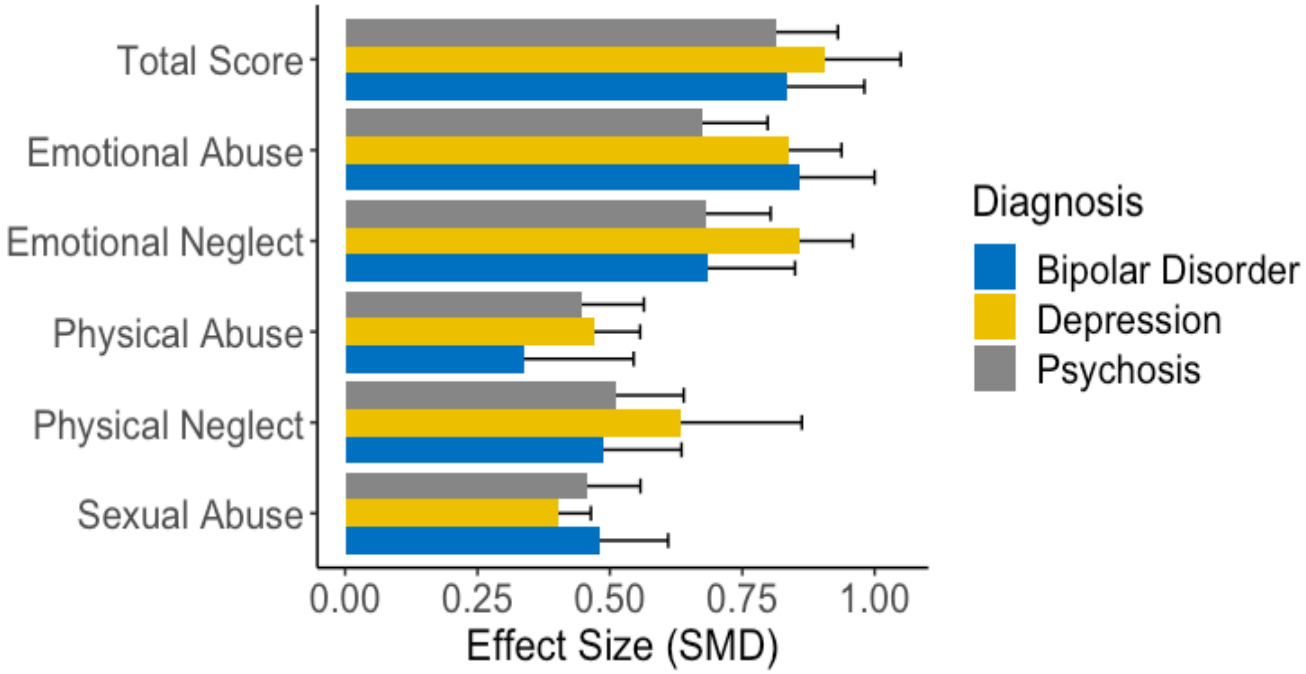


Figure 2- Overview plot of the meta-analytic results

The forest plots of CT total scores are provided in Figures 3-6, additional forest plots for each CT subtype can be found in the supplementary material (Supplementary figures 4-18).

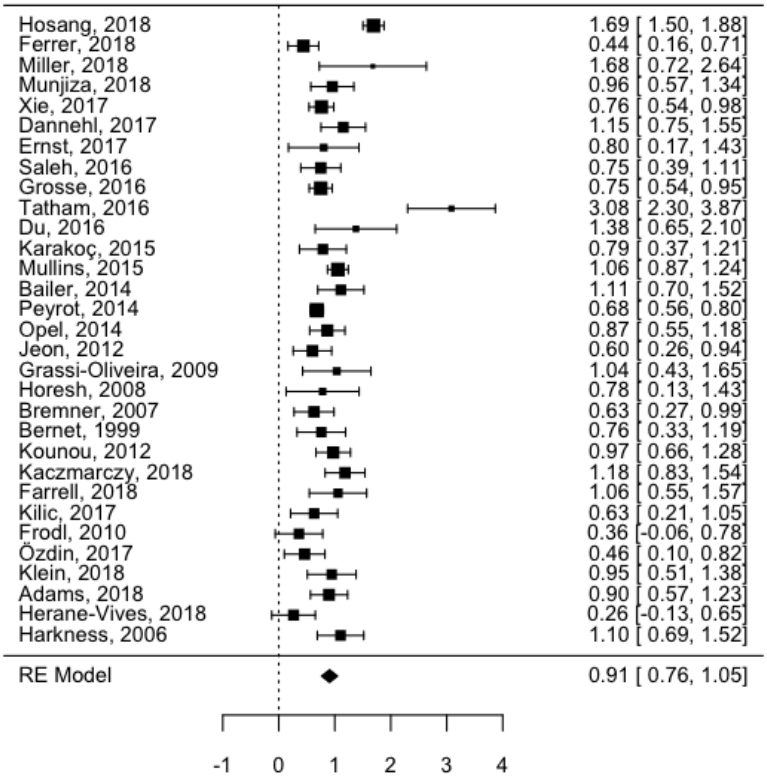


Figure 3: Forrest plot CT TS in MD

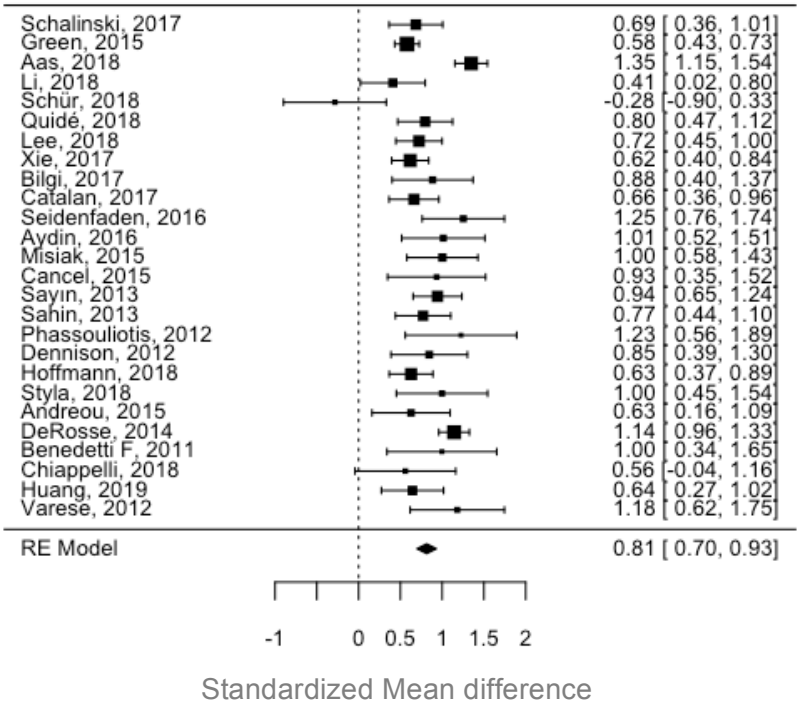


Figure 4: Forrest plot CT TS in schizophrenia spectrum disorder

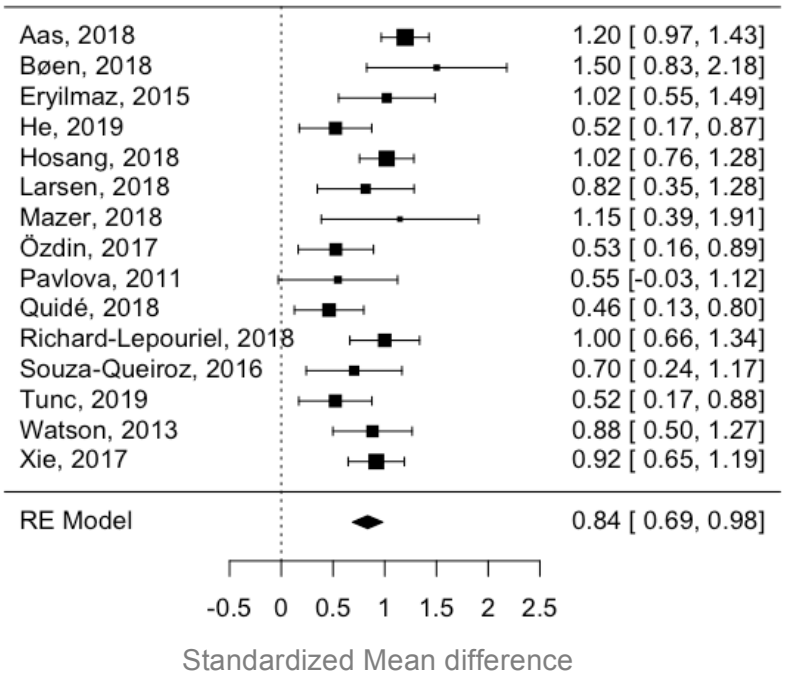


Figure 5- Forrest plot CT TS in bipolar disorder

Subgroup analyses were carried out to test the transdiagnostic effect of exposure to the specific types of adversity considered in this review (PA, EA, SA, PN, and EN).

5.2.1. PA

A total of 65 studies assessed the presence of PA in their samples (28 in MD, 13 in bipolar disorder, and 24 in schizophrenia spectrum disorder). In the subgroup analysis, no significant differences in the effect sizes across diagnoses were found.

5.2.2. EA

There were 65 studies reporting scores of EA (28 in MD, 13 in bipolar disorder, and 24 in schizophrenia spectrum disorder). We found significantly higher effect sizes for EA in MD than in schizophrenia spectrum disorder (p= 0.04).

5.2.3. SA

66 studies reported the scores of SA (29 in MD, 13 in bipolar disorder, and 22 in schizophrenia spectrum disorder). We did not find significant differences in the effect sizes across diagnoses.

5.2.4. PN

58 articles reported scores of PN in their samples (25 in MD, 13 in bipolar disorder, and 20 in schizophrenia spectrum disorder). There were no significant differences between the effect sizes across diagnoses.

5.2.5. EN

63 studies reported the scores of EN in their samples (26 in MD, 13 in bipolar disorder, and 24 in schizophrenia spectrum disorder). Effect sizes of EN were significantly higher in MD than in schizophrenia spectrum disorder ($p=0.03$).

	Effect size					Heterogenity			Egger's test	
	n	g	95%-CI	z	p	Q	p	I^2	z	p
TS	15	0.84	0.69-0.98	11.23	<.001	32.21	0.004	54.86%	0.30	0.77
PA	13	0.34	0.13-0.54	3.18	0.002	60.38		83.41%	-0.32	0.74
EA	13	0.86	0.72-1.00	11.80	<.001	44.33	<-001	55.43%	0.46	0.65
SA	13	0.48	0.35-0.61	7.34	<.001	23.6	0.02	48.20%	-0.48	0.63
PN	13	0.49	0.34-0.64	6.49	<.001	28.70	0.004	59.93%	0.04	0.97
EN	13	0.69	0.52-0.87	7.88	<.001	51.11	<.001	69.71%	1.70	0.09

	Effect size					Heterogenity			Egger's test	
	n	g	95%-CI	z	p	Q	p	I^2	z	p
TS	26	0.81	0.66-0.95	13.72	<.001	85.84	<.001 <.001	65.8%	-0.64	0.95
PA	24	0.45	0.33-0.56	7.42	<.001	69.30		61.68%	-0.08	0.94
EA	24	0.67	0.55-0.80	10.71	<.001	76.12	<.001	63.99%	-0.38	0.71
SA	24	0.46	0.35-0.56	8.76	<.001	46.91	0.001	48.60%	-1.46	0.14
PN	20	0.51	0.38-0.64	7.75	<.001	53.35	<.001	61.74%	-1.35	0.18
EN	24	0.68	0.56-0.80	10.90	<.001	73.18	<.001	63.32%	-0.42	0.68

Table 6- Meta-analytic results of CT domains in bipolar disorder

	Effect size	Heterogenity	Egger's test
		<.001	

Table 7- Meta-analytic results of CT domains in schizophrenia spectrum disorder

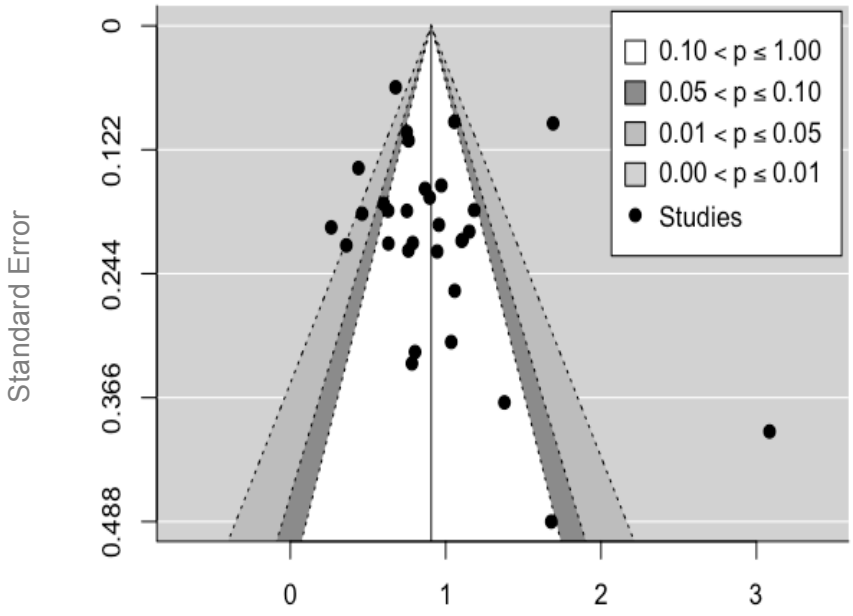
	n	g	95%-CI	z	p	Q	p	I^2	z	p
TS	31	0.91	0.77-1.05	12.50	<.001	169.04	<.001	82.32	2.19	0.03
PA	28	0.47	0.38-0.56	10.49	<.001	43.90		41.04	1.92	0.06
EA	28	0.84	0.74-0.94	16.71	<.001	58.83	<.001	52.50	0.68	0.50
SA	29	0.41	0.33-0.49	10.46	<.001	37.60	0.11 0.02	26.70	-2-00	0.05
PN	25	0.63	0.41-0.86	5.47	<.001	110.37	<.001	90.62	4.20	<.001
EN	26	0.86	0.76-0.96	17.00	<.001	46.88	0.005	45.78	1.21	0.22

5.3. Heterogeneity and risk of bias

There were high estimated proportions of heterogeneity with statistical significance for CT total scores and all CT domains in the three diagnoses ($p<0.01$), with the exception of SA in MD. Overall, heterogeneity of our analysis measured with the I^2 statistic ranged from moderate to high[64], indicating that the strength of the relationship between CT and psychiatric disease varied considerably across studies.

Table 8. Meta-analytic results of CT domains in MD

The funnel plots for CT total scores are provided in Figures 6-8. The funnel plots for all CT domains in the three diagnoses can be found in the supplementary material (Supplementary Figures 4-18). Egger's test indicated no significant funnel plot asymmetry ($p > 0.05$) for CT total scores in bipolar disorder and schizophrenia spectrum disorder, but detected significant funnel plot asymmetry in MD ($p= 0.03$). Trim and fill analysis showed no missing studies either side of the plot for CT total scores in MD.



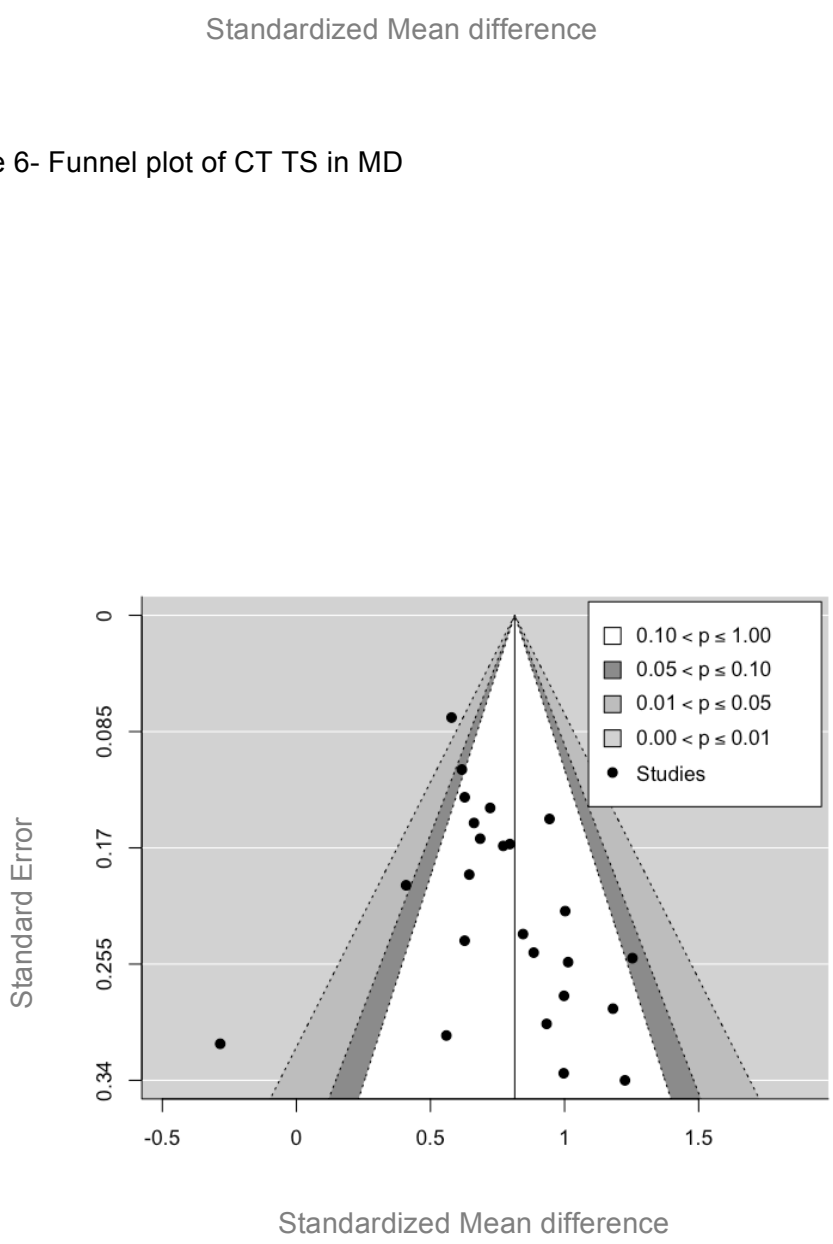


Figure 6- Funnel plot of CT TS in MD

Figure 7- Funnel plot: CT TS in schizophrenia spectrum disorder

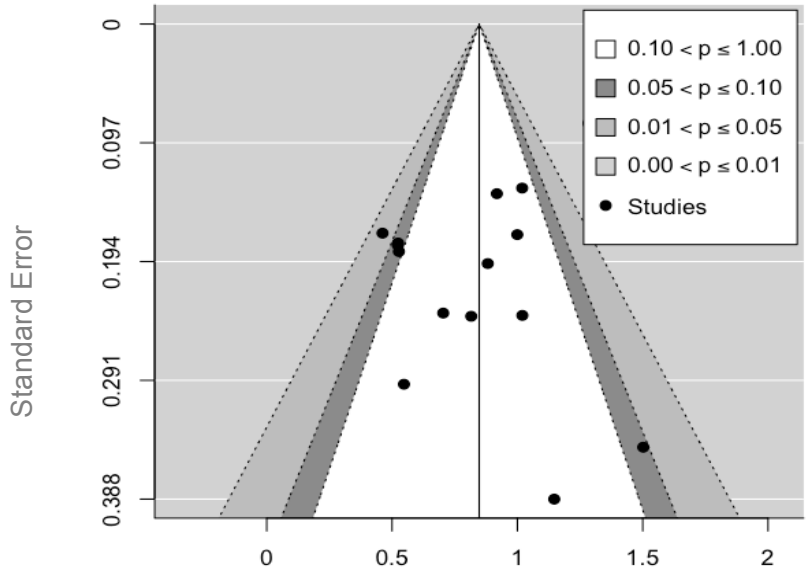


Figure 8- Funnel plot: CT TS in bipolar disorder

Egger's test indicated low risk of publication bias for most CT domains in the three psychiatric diagnoses. However, significant funnel plot asymmetry was found in SA and PN in MD (p= 0.05 and p<0.001, respectively). The trim and fill method identified 0 missing studies in PN in MD. For SA, the trim and fill procedure identified 6 missing studies on the right side (adjusted g=0.44, 95%-CI: 0.30-0.51).

5.4. Outlier analysis

Figure 9 provides an overview of the influential cases for each CT domain in the three psychiatric diagnoses and the estimated effect sizes and CI after excluding the data of these articles in the post-hoc sensitivity analysis.

	Influential cases	**Effect size**	**95%-CI**
MD			
TS	Tatham, 2016 Hosang 2018	0.81	0.72-0.91
PA	Williams, 2016	0.44	0.36-0.52
SA	Hosang, 2018	0.40	0.33-0.46
PN	Tatham, 2016	0.53	0.43-0.62
Schizophrenia spectrum disorder			
TS	Aas 2018	0.78	0.68-0.88
EA	Aas 2018	0.64	0.53-0.74
EN	Aas 2018	0.64	0.54-0.74
Bipolar disorder			
EA	Aas 2018	0.80	0.68-0.94

PA	Eryilmaz, 2015	0.44	0.31-0.57

Figure 9- Influential cases and corrected ES and CI

All effect sizes remained significant ($p<0.001$) after removal of the influential cases. For most CT domains, effect size estimates changed moderately after the exclusion of most outliers, suggesting that the pooled estimates were relatively stable.

In PA in bipolar disorder, the article of Eryilmaz (2015) was the only included article reporting a large negative effect size (see Supplementary Figure 6). Our effect size estimate for PA in bipolar disorder changed considerably after removal of this outlier from a small ($g=0.34$) to a moderate effect size ($g=0.44$).

5.5. Moderator analysis

Heterogeneity was moderate to high, indicating the appropriateness of moderator analyses. Neither the articles' year of publication, gender, nor the mean age of the patients did show significant moderator effects on the CT total scores in any of the major psychiatric disorders. We analyzed the influence of the potential moderators on the effect sizes for all CT subtypes. The year of publication of the article had a significant moderator effect for SA in bipolar disorder ($p=0.01$)

6. Discussion

We conducted a series of comprehensive meta-analyses to quantify the effects of CT in schizophrenia spectrum disorder, MD, and bipolar disorder compared with non-psychiatric HC focusing on transdiagnostic aspects on the basis of data of k=97 studies including n=17104 participants.

In summary, our results showed large effect sizes for CT total scores in patients with schizophrenia spectrum disorder (g=0.83, 95%-CI: 0.70-0.97), bipolar disorder (g=0.84, 95%-CI: 0.69-0.98), and MD (g=0.91, 95%-CI: 0.76-1.05) without significant transdiagnostic differences. Further, we found significant effect sizes for all CT subtypes (PA, EA, SA, PN, and EN) in the three diagnoses with magnitudes varying from moderate to large. Exploring transdiagnostic differences, we found statistically significant larger effect sizes for EA and EN in MD than in schizophrenia spectrum disorder. Despite significant heterogeneity in most of the analyses, these results were robust with respect to the inclusion of moderators, such as age, gender, and year of publication. The following section will discuss our findings in the context of the broader literature and highlight future research directions and clinical applications.

Our meta-analysis complements and substantially expands the evidence covered by previous reviews by synthesizing the growing number of studies focused on the effects of CT on adult psychopathology. Consistent with earlier systematic reviews and meta-analyses, our results indicate that CT and all its subtypes are substantially more prevalent in individuals with major psychiatric conditions compared to HC. The magnitude of the effect sizes of CT in major psychiatric conditions is comparable with the results reported in previous meta-analyses[14,15,166]. Most importantly, our findings show an overall comparable impact of CT in MD, bipolar disorder, and schizophrenia spectrum disorder pointing to the relevance of CT as a transdiagnostic risk factor for major psychiatric conditions.

The results of our meta-analyses reinforce the relevance of the investigation of transdiagnostic mechanisms linking CT and adult psychopathology. Recent research postulated different systems and pathways, which might act as driving factors of this relationship, such as the allostatic load, difficulties in emotion regulation, low emotional awareness, difficulties in social and emotional information processing, and accelerated biological aging, as well as neurobiological processes like frontal gray matter reductions[8].

An important focus of our meta-analysis was to examine the general versus the specific role of CT on adult psychopathology and determine whether specific CT types differed in their psychopathological impact. Overall, EA and EN had the largest effect sizes in the three psychiatric diagnoses, pointing to be stronger transdiagnostic predictors for adult psychopathology than SA, PA, and PN. In the transdiagnostic comparison, we found that EA and EN were significantly stronger associated with MD than schizophrenia spectrum disorder. In line with our findings, previous studies and a recent meta-analysis of Humphreys and colleagues[15] identified that EA and EN were most strongly associated with depression than other CT subtypes and hypothesized that individuals suffering from EA and EN are especially vulnerable to developing negative cognition musters, which increase the risk for MD. Precisely, children suffering from EA and EN by attachment figures might develop negative internal models of the self and others that might lead to a lack of trust and social avoidance that in turn increase the risk of MD. Another important aspect is that EA and EN tend to be more "chronic" abuse subtypes with longer exposition times[36], which might enhance the evolution of maladaptive thinking styles mentioned above.

The data obtained in this study is consistent with previous data reported in literature. Three previous meta-analyses studied the effect sizes of CT in major psychiatric conditions with a disorder-specific approach. The meta-analysis performed by Varese and colleagues analyzing the role of childhood adversities in the development of psychotic disorders did not find any evidence that any specific type of trauma has a bigger effect size for psychosis than any other[14]. As mentioned above, in the meta-analysis performed by Humphreys and colleagues EA and EN showed higher effect sizes than other CT subtypes in individuals with MD[15]. In the case of bipolar disorder, a systematic review performed by Palmier-Claus and colleagues, indicated that EA might be a more specific risk factor for bipolar disorder than other trauma subtypes[166].

The statistical analysis revealed high levels of heterogeneity, which is understandable in the context of the methodological and analytical variances in the identified studies. Even though previous studies have consistently reported that certain moderator

variables are implicated and meaningful in the association between CT and severe psychiatric disease[167], we found no significant evidence that the effect sizes of the CT total scores were explained by the age, gender, or year of publication. To date, research on the potential moderators of this relationship is methodologically heterogeneous and does not allow generalizable conclusions.

6.1 Limitations

Several limitations may affect the interpretations of our meta-analysis and are discussed in the following section.

Firstly, our meta-analysis included studies employing different retrospective CT assessments including self-report questionnaires and (semi) structured interviews. Despite checking the definitions of each CT subtype and their consistency between instruments, slight differences in the concept and the scoring might be present, which limit the generalizability of the results. Furthermore, the employed retrospective measures of CT could imply recall bias, which might involve a substantial rate of false negatives and measurement errors and in rare cases, false positive reports[43]. However, several studies sustain reliability in retrospective evaluation of CT and support the relevance of the subjective assessment of the traumatic experience showing its stability across time, low variability by current symptoms, and concordance with other sources of information[168].

Second, we performed our meta-analysis based on cross sectional, case-control studies. For this reason we cannot establish the direction of the causality between CT and psychopathology. In the future, research on this field should be extended by studies with a prospective design. The recent meta-analysis by McKay and colleagues[169] synthetized the evidence of longitudinal cohort studies on CT and adult mental disorders and provides evidence for temporal causality.

Third, the difficulty of a clear separation into the role of different subtypes of trauma should be highlighted, since they show high levels of co-occurrence and the design of our study did not allow us to consider the potential cumulative risk[28]. Thus, it is unclear to what degree our estimated effect sizes for different CT subtypes reflect unique effects rather than a compound of this high co-occurrence. Since CT experiences tend to accumulate over time and the exposure to one type of CT increases the risk of exposure to another, further research on a potential dose-response relationship is needed.

Forth, we could not assess the timing (onset) and duration of the trauma exposure, which might have relevance in the understanding of the transdiagnostic mechanisms leading to psychopathology[32].

Finally, it should be noted that our study focused on three major psychiatric disorders, but did not analyze the role of CT in other diagnoses, such as personality disorders, anxiety disorders, and posttraumatic stress disorder. Previous research analyzed the effects of CT in those pathologies with disorder-specific approaches[9], but future studies might quantitatively analyze the transdiagnostic effect between diagnoses.

6.2 Implications for future research and practice

The results of this meta-analysis have several implications for future research, clinical practice, and public health.

First, our findings imply that exposure to CT should be regarded as a strong transdiagnostic risk factor for the development of adult psychopathology. Thus, clinicians should routinely assess and recognize CT.

Assuming a causal link, our work highlights the importance of additional research to increase the understanding of the transdiagnostic mechanisms linking CT and adult psychopathology. This field has the potential to guide the development of more efficient transdiagnostic interventions, which might specifically target these mechanisms.

Our findings also have implications for the field of prevention in mental health. CT is a major and potentially modifiable contributor to the global burden of disease[170]. Population-based interventions (e.g. educational programs) should be undertaken to increase public awareness of this problem. Transdiagnostic preventive approaches focusing on CT as a common risk factor for development of severe mental disorders could bear larger benefits enhancing the efficacy and cost-effectiveness of disorder-specific preventive approaches and potentially prevent victims of CT from developing major psychiatric disorders over time.

7. References

1. Chapman DP, Dube SR, Anda RF. Adverse childhood events as risk factors for negative mental health outcomes. *Psychiatric Annals* 2007; **37**(5): 359-64.
2. Bernstein DP, Ahluvalia T, Pogge D, Handelsman L. Validity of the Childhood Trauma Questionnaire in an adolescent psychiatric population. *J Am Acad Child Adolesc Psychiatry* 1997; **36**(3): 340-8.
3. Bernstein DP, Stein JA, Newcomb MD, et al. Development and validation of a brief screening version of the Childhood Trauma Questionnaire. *Child Abuse Negl* 2003; **27**(2): 169-90.
4. Roberts SJ, Chandler GE, Kalmakis K. A model for trauma-informed primary care. *J Am Assoc Nurse Pract* 2019; **31**(2): 139-44.
5. Kessler RC, McLaughlin KA, Green JG, et al. Childhood adversities and adult psychopathology in the WHO World Mental Health Surveys. *Br J Psychiatry* 2010; **197**(5): 378-85.
6. Copeland WE, Shanahan L, Hinesley J, et al. Association of Childhood Trauma Exposure With Adult Psychiatric Disorders and Functional Outcomes. *JAMA Netw Open* 2018; **1**(7): e184493.
7. Peterson C, Florence C, Klevens J. The economic burden of child maltreatment in the United States, 2015. *Child Abuse Negl* 2018; **86**: 178-83.
8. McLaughlin KA, Colich NL, Rodman AM, Weissman DG. Mechanisms linking childhood trauma exposure and psychopathology: a transdiagnostic model of risk and resilience. *BMC Med* 2020; **18**(1): 96.
9. Weber K, Rockstroh B, Borgelt J, et al. Stress load during childhood affects psychopathology in psychiatric patients. *BMC Psychiatry* 2008; **8**: 63.
10. Haidl TK, Hedderich DM, Rosen M, et al. The non-specific nature of mental health and structural brain outcomes following childhood trauma. *Psychol Med* 2021: 1-10.
11. Tiwari A, Gonzalez A. Biological alterations affecting risk of adult psychopathology following childhood trauma: A review of sex differences. *Clin Psychol Rev* 2018; **66**: 69-79.
12. De Bellis MD, Zisk A. The biological effects of childhood trauma. *Child Adolesc Psychiatr Clin N Am* 2014; **23**(2): 185-222, vii.
13. Liu RT. Childhood Adversities and Depression in Adulthood: Current Findings and Future Directions. *Clin Psychol (New York)* 2017; **24**(2): 140-53.
14. Varese F, Smeets F, Drukker M, et al. Childhood adversities increase the risk of psychosis: a meta-analysis of patient-control, prospective- and cross-sectional cohort studies. *Schizophr Bull* 2012; **38**(4): 661-71.
15. Humphreys KL, LeMoult J, Wear JG, Piersiak HA, Lee A, Gotlib IH. Child maltreatment and depression: A meta-analysis of studies using the Childhood Trauma Questionnaire. *Child Abuse Negl* 2020; **102**: 104361.
16. Aas M, Henry C, Andreassen OA, Bellivier F, Melle I, Etain B. The role of childhood trauma in bipolar disorders. *Int J Bipolar Disord* 2016; **4**(1): 2.
17. Lindert J, von Ehrenstein OS, Grashow R, Gal G, Braehler E, Weisskopf MG. Sexual and physical abuse in childhood is associated with depression and anxiety over the life course: systematic review and meta-analysis. *Int J Public Health* 2014; **59**(2): 359-72.
18. Kessler RC, Sonnega A, Bromet E, Hughes M, Nelson CB. Posttraumatic stress disorder in the National Comorbidity Survey. *Arch Gen Psychiatry* 1995; **52**(12): 1048-60.
19. Dalgleish T, Black M, Johnston D, Bevan A. Transdiagnostic approaches to mental health problems: Current status and future directions. *J Consult Clin Psychol* 2020; **88**(3): 179-95.
20. Gore FM, Bloem PJ, Patton GC, et al. Global burden of disease in young people aged 10-24 years: a systematic analysis. *Lancet* 2011; **377**(9783): 2093-102.

21. Agnew-Blais J, Danese A. Childhood maltreatment and unfavourable clinical outcomes in bipolar disorder: a systematic review and meta-analysis. *Lancet Psychiatry* 2016; **3**(4): 342-9.
22. Hosang GM, Fisher HL, Uher R, et al. Childhood maltreatment and the medical morbidity in bipolar disorder: a case-control study. *Int J Bipolar Disord* 2017; **5**(1): 30.
23. Betz LT, Penzel N, Rosen M, Kambeitz J. Relationships between childhood trauma and perceived stress in the general population: a network perspective. *Psychol Med* 2020: 1-11.
24. Cecil CA, Smith RG, Walton E, Mill J, McCrory EJ, Viding E. Epigenetic signatures of childhood abuse and neglect: Implications for psychiatric vulnerability. *J Psychiatr Res* 2016; **83**: 184-94.
25. Walker E, Hernandez AV, Kattan MW. Meta-analysis: Its strengths and limitations. *Cleve Clin J Med* 2008; **75**(6): 431-9.
26. Arias I, Leeb RT, Melanson C, Paulozzi LJ, Simon TR. Child maltreatment surveillance; uniform definitions for public health and recommended data elements. 2008.
27. Global Forum for Health Research Omdls. Report of the consultation on child abuse prevention, 29-31 march 1999, WHO, Geneva. Geneva: World Health Organization, Violence Injury Prevention, Social Change and Mental Health; 1999.
28. McLaughlin KA, Sheridan MA, Lambert HK. Childhood adversity and neural development: deprivation and threat as distinct dimensions of early experience. *Neurosci Biobehav Rev* 2014; **47**: 578-91.
29. Vachon DD, Krueger RF, Rogosch FA, Cicchetti D. Assessment of the Harmful Psychiatric and Behavioral Effects of Different Forms of Child Maltreatment. *JAMA Psychiatry* 2015; **72**(11): 1135-42.
30. Cassiers LLM, Sabbe BGC, Schmaal L, Veltman DJ, Penninx B, Van Den Eede F. Structural and Functional Brain Abnormalities Associated With Exposure to Different Childhood Trauma Subtypes: A Systematic Review of Neuroimaging Findings. *Front Psychiatry* 2018; **9**: 329.
31. Croft J, Heron J, Teufel C, et al. Association of Trauma Type, Age of Exposure, and Frequency in Childhood and Adolescence With Psychotic Experiences in Early Adulthood. *JAMA Psychiatry* 2019; **76**(1): 79-86.
32. Dunn EC, Nishimi K, Gomez SH, Powers A, Bradley B. Developmental timing of trauma exposure and emotion dysregulation in adulthood: Are there sensitive periods when trauma is most harmful? *J Affect Disord* 2018; **227**: 869-77.
33. Carr CP, Martins CM, Stingel AM, Lemgruber VB, Juruena MF. The role of early life stress in adult psychiatric disorders: a systematic review according to childhood trauma subtypes. *J Nerv Ment Dis* 2013; **201**(12): 1007-20.
34. Hamby S, Elm JHL, Howell KH, Merrick MT. Recognizing the cumulative burden of childhood adversities transforms science and practice for trauma and resilience. *Am Psychol* 2021; **76**(2): 230-42.
35. Saunders BE, Adams ZW. Epidemiology of traumatic experiences in childhood. *Child Adolesc Psychiatr Clin N Am* 2014; **23**(2): 167-84, vii.
36. Stoltenborgh M, bakermans-kranenburg M, Alink L, van Ijzendoorn M. The Prevalence of Child Maltreatment across the Globe: Review of a Series of Meta-Analyses. *Child Abuse Review* 2014; **24**.
37. Akmatov MK. Child abuse in 28 developing and transitional countries--results from the Multiple Indicator Cluster Surveys. *Int J Epidemiol* 2011; **40**(1): 219-27.
38. Stoltenborgh M, van Ijzendoorn MH, Euser EM, Bakermans-Kranenburg MJ. A global perspective on child sexual abuse: meta-analysis of prevalence around the world. *Child Maltreat* 2011; **16**(2): 79-101.
39. Kumari V. Emotional abuse and neglect: time to focus on prevention and mental health consequences. *Br J Psychiatry* 2020; **217**(5): 597-9.
40. Georgieva S, Tomas JM, Navarro-Perez JJ. Systematic review and critical appraisal of Childhood Trauma Questionnaire - Short Form (CTQ-SF). *Child Abuse Negl* 2021; **120**: 105223.

41. Thabrew H, de Sylva S, Romans S. Evaluating childhood adversity. *Adv Psychosom Med* 2012; **32**: 35-57.
42. Schmidt MR, Narayan AJ, Atzl VM, Rivera LM, Lieberman AF. Childhood maltreatment on the Adverse Childhood Experiences (ACEs) scale versus the Childhood Trauma Questionnaire (CTQ) in a perinatal sample. *Journal of Aggression, Maltreatment & Trauma* 2020; **29**(1): 38-56.
43. Hardt J, Rutter M. Validity of adult retrospective reports of adverse childhood experiences: review of the evidence. *J Child Psychol Psychiatry* 2004; **45**(2): 260-73.
44. Diagnostic and statistical manual of mental disorders : DSM-5™. 5th edition. ed. Washington, DC ;: American Psychiatric Publishing, a division of American Psychiatric Association; 2013.
45. World Health O. ICD 11. Zurich, Switzerland: World Health Organization; 2018.
46. Nolen-Hoeksema S, Watkins ER. A Heuristic for Developing Transdiagnostic Models of Psychopathology: Explaining Multifinality and Divergent Trajectories. *Perspect Psychol Sci* 2011; **6**(6): 589-609.
47. Sauer-Zavala S, Gutner CA, Farchione TJ, Boettcher HT, Bullis JR, Barlow DH. Current Definitions of "Transdiagnostic" in Treatment Development: A Search for Consensus. *Behav Ther* 2017; **48**(1): 128-38.
48. Martin P, Murray L, Darnell D, Dorsey S. Transdiagnostic treatment approaches for greater public health impact: Implementing principles of evidence-based mental health interventions. *Clinical Psychology: Science and Practice* 2018; **25**: e12270.
49. Begemann MJH, Schutte MJL, van Dellen E, et al. Childhood trauma is associated with reduced frontal gray matter volume: a large transdiagnostic structural MRI study. *Psychol Med* 2021: 1-9.
50. Midolo L, Santoro G, Ferrante E, et al. Childhood trauma, attachment and psychopathology: A correlation network approach. *Mediterranean Journal of Clinical Psychology* 2020; **8**: 1-25.
51. Dvir Y, Ford JD, Hill M, Frazier JA. Childhood maltreatment, emotional dysregulation, and psychiatric comorbidities. *Harv Rev Psychiatry* 2014; **22**(3): 149-61.
52. Teicher MH, Samson JA. Annual Research Review: Enduring neurobiological effects of childhood abuse and neglect. *J Child Psychol Psychiatry* 2016; **57**(3): 241-66.
53. Newby JM, McKinnon A, Kuyken W, Gilbody S, Dalgleish T. Systematic review and meta-analysis of transdiagnostic psychological treatments for anxiety and depressive disorders in adulthood. *Clin Psychol Rev* 2015; **40**: 91-110.
54. Ishikawa SI, Kishida K, Oka T, et al. Developing the universal unified prevention program for diverse disorders for school-aged children. *Child Adolesc Psychiatry Ment Health* 2019; **13**: 44.
55. Mei C, Nelson B, Hartmann J, Spooner R, McGorry P. Transdiagnostic early intervention, prevention, and prediction in psychiatry. 2020: 27-37.
56. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009; **6**(7): e1000097.
57. Liu RT. Childhood Maltreatment and Impulsivity: A Meta-Analysis and Recommendations for Future Study. *J Abnorm Child Psychol* 2019; **47**(2): 221-43.
58. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol* 2010; **25**(9): 603-5.
59. Lin LF, Aloe AM. Evaluation of various estimators for standardized mean difference in meta-analysis. *Stat Med* 2021; **40**(2): 403-26.
60. Higgins JP, Li T, Deeks JJ. Choosing effect measures and computing estimates of effect. Cochrane Handbook for Systematic Reviews of Interventions; 2019: 143-76.
61. Spineli LM, Pandis N. Meta-analysis: Random-effects model. *Am J Orthod Dentofacial Orthop* 2020; **157**(2): 280-2.

62. Borenstein M, Hedges LV, Higgins JP, Rothstein HR. A basic introduction to fixed-effect and random-effects models for meta-analysis. *Res Synth Methods* 2010; **1**(2): 97-111.
63. Viechtbauer W. Conducting Meta-Analyses in R with the metafor Package. *Journal of Statistical Software* 2010; **36**(3): 1 - 48.
64. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003; **327**(7414): 557-60.
65. Porta MS, International Epidemiological Association. A dictionary of epidemiology. 5th ed. Oxford ; New York: Oxford University Press; 2008.
66. Thornton A, Lee P. Publication bias in meta-analysis: its causes and consequences. *J Clin Epidemiol* 2000; **53**(2): 207-16.
67. Duval S, Tweedie R. Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics* 2000; **56**(2): 455-63.
68. Shi L, Lin L. The trim-and-fill method for publication bias: practical guidelines and recommendations based on a large database of meta-analyses. *Medicine (Baltimore)* 2019; **98**(23): e15987.
69. Matsushima Y, Noma H, Yamada T, Furukawa TA. Influence diagnostics and outlier detection for meta-analysis of diagnostic test accuracy. *Res Synth Methods* 2020; **11**(2): 237-47.
70. Viechtbauer W, Cheung MW. Outlier and influence diagnostics for meta-analysis. *Res Synth Methods* 2010; **1**(2): 112-25.
71. Sanders B, Becker-Lausen E. The measurement of psychological maltreatment: early data on the Child Abuse and Trauma Scale. *Child Abuse Negl* 1995; **19**(3): 315-23.
72. Bremner JD, Vermetten E, Mazure CM. Development and preliminary psychometric properties of an instrument for the measurement of childhood trauma: the Early Trauma Inventory. *Depress Anxiety* 2000; **12**(1): 1-12.
73. Bremner JD, Bolus R, Mayer EA. Psychometric properties of the Early Trauma Inventory-Self Report. *J Nerv Ment Dis* 2007; **195**(3): 211-8.
74. Bifulco A, Brown GW, Harris TO. Childhood Experience of Care and Abuse (CECA): a retrospective interview measure. *J Child Psychol Psychiatry* 1994; **35**(8): 1419-35.
75. Lizardi H, Klein DN, Ouimette PC, Riso LP, Anderson RL, Donaldson SK. Reports of the childhood home environment in early-onset dysthymia and episodic major depression. *J Abnorm Psychol* 1995; **104**(1): 132-9.
76. Gibb B, Alloy L, Abramson L, et al. History of Childhood Maltreatment, Negative Cognitive Styles, and Episodes of Depression in Adulthood. *Cognitive Therapy and Research* 2001; **25**: 425-46.
77. Rosenman S, Rodgers B. Childhood adversity in an Australian population. *Social psychiatry and psychiatric epidemiology* 2004; **39**: 695-702.
78. Taylor SE, Lerner JS, Sage RM, Lehman BJ, Seeman TE. Early environment, emotions, responses to stress, and health. *J Pers* 2004; **72**(6): 1365-93.
79. Teicher MH, Parigger A. The 'Maltreatment and Abuse Chronology of Exposure' (MACE) scale for the retrospective assessment of abuse and neglect during development. *PLoS One* 2015; **10**(2): e0117423.
80. Park K, Shim G, Jeong B. Validation of the Traumatic Antecedents Questionnaire using item response theory. *Brain and Behavior* 2020; **10**.
81. Oei TPS, Baranoff J. Young Schema Questionnaire: Review of psychometric and measurement issues*. *Australian Journal of Psychology* 2007; **59**(2): 78-86.
82. Styla R, Makoveychuk O. Psychometric properties of childhood experiences questionnaire (CEQ-58) used to assess the intensity of traumatic experiences from childhood and adolescence - Preliminary elaboration. *Postepy Psychiatrii i Neurologii* 2018; **27**: 15-30.
83. He Y, Vinkers CH, Houtepen LC, de Witte LD, Boks MP. Childhood Adversity Is Associated With Increased KITLG Methylation in Healthy Individuals but Not in Bipolar Disorder Patients. *Front Psychiatry* 2018; **9**: 743.

84. Bøen E, Hjørnevik T, Hummelen B, et al. Patterns of altered regional brain glucose metabolism in borderline personality disorder and bipolar II disorder. *Acta Psychiatr Scand* 2019; **139**(3): 256-68.
85. Larsen EM, Ospina LH, Cuesta-Diaz A, et al. Effects of childhood trauma on adult moral decision-making: Clinical correlates and insights from bipolar disorder. *J Affect Disord* 2019; **244**: 180-6.
86. Richard-Lepouriel H, Kung AL, Hasler R, et al. Impulsivity and its association with childhood trauma experiences across bipolar disorder, attention deficit hyperactivity disorder and borderline personality disorder. *J Affect Disord* 2019; **244**: 33-41.
87. Aas M, Dieset I, Morch R, et al. Reduced brain-derived neurotrophic factor is associated with childhood trauma experiences and number of depressive episodes in severe mental disorders. *Schizophr Res* 2019; **205**: 45-50.
88. Mazer AK, Cleare AJ, Young AH, Juruena MF. Bipolar affective disorder and borderline personality disorder: Differentiation based on the history of early life stress and psychoneuroendocrine measures. *Behav Brain Res* 2019; **357-358**: 48-56.
89. Xie P, Wu K, Zheng Y, et al. Prevalence of childhood trauma and correlations between childhood trauma, suicidal ideation, and social support in patients with depression, bipolar disorder, and schizophrenia in southern China. *J Affect Disord* 2018; **228**: 41-8.
90. Özdin S, Sarısoy G, Şahin A, et al. Early maladaptive schemas in patients with bipolar and unipolar disorder. *International Journal of Psychiatry in Clinical Practice* 2017; **22**: 1-6.
91. Souza-Queiroz J, Boisgontier J, Etain B, et al. Childhood trauma and the limbic network: a multimodal MRI study in patients with bipolar disorder and controls. *J Affect Disord* 2016; **200**: 159-64.
92. Watson S, Gallagher P, Dougall D, et al. Childhood trauma in bipolar disorder. *Aust N Z J Psychiatry* 2014; **48**(6): 564-70.
93. Pavlova B, Uher R, Dennington L, Wright K, Donaldson C. Reactivity of affect and self-esteem during remission in bipolar affective disorder: an experimental investigation. *J Affect Disord* 2011; **134**(1-3): 102-11.
94. Gul Eryilmaz, Kesebir S, Gül I, Özten E, Karamustafalioglu O. Dissociative experiences in bipolar disorder II: Are they related to childhood trauma and obsessive-compulsive symptoms? *Revista de Psiquiatria Clinica* 2015; **42**: 38-40.
95. Quide Y, Bortolasci CC, Spolding B, et al. Association between childhood trauma exposure and pro-inflammatory cytokines in schizophrenia and bipolar-I disorder. *Psychol Med* 2019; **49**(16): 2736-44.
96. Leclerc E, Mansur RB, Grassi-Oliveira R, et al. The differential association between history of childhood sexual abuse and body mass index in early and late stages of bipolar disorder. *J Affect Disord* 2018; **227**: 214-8.
97. Janiri D, Sani G, Danese E, et al. Childhood traumatic experiences of patients with bipolar disorder type I and type II. *J Affect Disord* 2015; **175**: 92-7.
98. Fowke A, Ross S, Ashcroft K. Childhood maltreatment and internalized shame in adults with a diagnosis of bipolar disorder. *Clin Psychol Psychother* 2012; **19**(5): 450-7.
99. Moraes JB, Maes M, Barbosa DS, et al. Elevated C-reactive Protein Levels in Women with Bipolar Disorder may be Explained by a History of Childhood Trauma, Especially Sexual Abuse, Body Mass Index and Age. *CNS Neurol Disord Drug Targets* 2017; **16**(4): 514-21.
100. Kefeli MC, Turow RG, Yıldırım A, Boysan M. Childhood maltreatment is associated with attachment insecurities, dissociation and alexithymia in bipolar disorder. *Psychiatry Res* 2018; **260**: 391-9.
101. Hosang GM, Fisher HL, Hodgson K, Maughan B, Farmer AE. Childhood maltreatment and adult medical morbidity in mood disorders: comparison of unipolar depression with bipolar disorder. *Br J Psychiatry* 2018; **213**(5): 645-53.

102. Neeren A, Alloy L, Abramson L. History of Parenting and Bipolar Spectrum Disorders. *Journal of Social and Clinical Psychology - J SOC CLIN PSYCHOL* 2008; **27**: 1021-44.
103. Li XB, Bo QJ, Tian Q, et al. Impact of childhood trauma on sensory gating in patients with first-episode schizophrenia. *BMC Psychiatry* 2018; **18**(1): 258.
104. Schur RR, van Leeuwen JMC, Houtepen LC, et al. Glucocorticoid receptor exon 1F methylation and the cortisol stress response in health and disease. *Psychoneuroendocrinology* 2018; **97**: 182-9.
105. Quide Y, Cohen-Woods S, O'Reilly N, Carr VJ, Elzinga BM, Green MJ. Schizotypal personality traits and social cognition are associated with childhood trauma exposure. *Br J Clin Psychol* 2018; **57**(4): 397-419.
106. Lee EE, Martin AS, Tu X, Palmer BW, Jeste DV. Childhood Adversity and Schizophrenia: The Protective Role of Resilience in Mental and Physical Health and Metabolic Markers. *J Clin Psychiatry* 2018; **79**(3).
107. Schalinski I, Breinlinger S, Hirt V, Teicher MH, Odenwald M, Rockstroh B. Environmental adversities and psychotic symptoms: The impact of timing of trauma, abuse, and neglect. *Schizophr Res* 2019; **205**: 4-9.
108. Catalan A, Angosto V, Diaz A, et al. Relation between psychotic symptoms, parental care and childhood trauma in severe mental disorders. *Psychiatry Res* 2017; **251**: 78-84.
109. Seidenfaden D, Knorr U, Soendergaard MG, et al. The relationship between self-reported childhood adversities, adulthood psychopathology and psychological stress markers in patients with schizophrenia. *Compr Psychiatry* 2017; **72**: 48-55.
110. Aydin O, Balikci K, Tas C, et al. The developmental origins of metacognitive deficits in schizophrenia. *Psychiatry Res* 2016; **245**: 15-21.
111. Green MJ, Raudino A, Cairns MJ, et al. Do common genotypes of FK506 binding protein 5 (FKBP5) moderate the effects of childhood maltreatment on cognition in schizophrenia and healthy controls? *J Psychiatr Res* 2015; **70**: 9-17.
112. Cancel A, Comte M, Truillet R, et al. Childhood neglect predicts disorganization in schizophrenia through grey matter decrease in dorsolateral prefrontal cortex. *Acta Psychiatr Scand* 2015; **132**(4): 244-56.
113. Alvarez MJ, Masramon H, Pena C, et al. Cumulative effects of childhood traumas: polytraumatization, dissociation, and schizophrenia. *Community Ment Health J* 2015; **51**(1): 54-62.
114. Michail M, Birchwood M. Social anxiety in first-episode psychosis: the role of childhood trauma and adult attachment. *J Affect Disord* 2014; **163**: 102-9.
115. Bortolon C, Capdevielle D, Boulenger JP, Gely-Nargeot MC, Raffard S. Early maladaptive schemas predict positive symptomatology in schizophrenia: a cross-sectional study. *Psychiatry Res* 2013; **209**(3): 361-6.
116. Sahin S, Yüksel Ç, Güler J, et al. The history of childhood trauma among individuals with ultra high risk for psychosis is as common as among patients with first-episode schizophrenia. *Early Interv Psychiatry* 2013; **7**(4): 414-20.
117. Phassouliotis C, Garner BA, Phillips LJ, et al. Enhanced cortisol suppression following administration of low-dose dexamethasone in first-episode psychosis patients. *Aust N Z J Psychiatry* 2013; **47**(4): 363-70.
118. Andreou C, Kelm L, Bierbrodt J, et al. Factors contributing to social cognition impairment in borderline personality disorder and schizophrenia. *Psychiatry Res* 2015; **229**(3): 872-9.
119. Varese F, Barkus E, Bentall RP. Dissociation mediates the relationship between childhood trauma and hallucination-proneness. *Psychol Med* 2012; **42**(5): 1025-36.
120. DeRosse P, Nitzburg GC, Kompancaril B, Malhotra AK. The relation between childhood maltreatment and psychosis in patients with schizophrenia and non-psychiatric controls. *Schizophr Res* 2014; **155**(1-3): 66-71.
121. Saleptsi E, Bichescu D, Rockstroh B, et al. Negative and positive childhood experiences across developmental periods in psychiatric patients with different diagnoses - an explorative study. *BMC Psychiatry* 2004; **4**: 40.

122. Benedetti F, Radaelli D, Poletti S, et al. Emotional reactivity in chronic schizophrenia: structural and functional brain correlates and the influence of adverse childhood experiences. *Psychol Med* 2011; **41**(3): 509-19.
123. Chiappelli J, Shi Q, Wijtenburg SA, et al. Glutamatergic Response to Heat Pain Stress in Schizophrenia. *Schizophr Bull* 2018; **44**(4): 886-95.
124. Dennison U, McKernan D, Cryan J, Dinan T. Schizophrenia patients with a history of childhood trauma have a pro-inflammatory phenotype. *Psychol Med* 2012; **42**(9): 1865-71.
125. Hoffmann C, Van Rheenen TE, Mancuso SG, et al. Exploring the moderating effects of dopaminergic polymorphisms and childhood adversity on brain morphology in schizophrenia-spectrum disorders. *Psychiatry Res Neuroimaging* 2018; **281**: 61-8.
126. Huang ZH, Hou CL, Huang YH, et al. Individuals at high risk for psychosis experience more childhood trauma, life events and social support deficit in comparison to healthy controls. *Psychiatry Res* 2019; **273**: 296-302.
127. Speck LG, Schöner J, Bermpohl F, et al. Endogenous oxytocin response to film scenes of attachment and loss is pronounced in schizophrenia. *Soc Cogn Affect Neurosci* 2019; **14**(1): 109-17.
128. Klein JP, Stahl J, Hüppe M, et al. Do interpersonal fears mediate the association between childhood maltreatment and interpersonal skills deficits? A matched cross-sectional analysis. *Psychother Res* 2020; **30**(2): 267-78.
129. Gander M, Sevecke K, Buchheim A. Disorder-specific attachment characteristics and experiences of childhood abuse and neglect in adolescents with anorexia nervosa and a major depressive episode. *Clin Psychol Psychother* 2018; **25**(6): 894-906.
130. Adams GC, Wrath AJ, Mondal P, Asmundson GJG. Depression with or without comorbid social anxiety: Is attachment the culprit? *Psychiatry Res* 2018; **269**: 86-92.
131. Ferrer A, Costas J, Labad J, et al. FKBP5 polymorphisms and hypothalamic-pituitary-adrenal axis negative feedback in major depression and obsessive-compulsive disorder. *J Psychiatr Res* 2018; **104**: 227-34.
132. Miller JM, Zanderigo F, Purushothaman PD, et al. Kappa opioid receptor binding in major depression: A pilot study. *Synapse* 2018; **72**(9): e22042.
133. Chamberlain SR, Cavanagh J, de Boer P, et al. Treatment-resistant depression and peripheral C-reactive protein. *Br J Psychiatry* 2019; **214**(1): 11-9.
134. Munjiza Jovanovic A, Kostic M, Pesic D, Gajic M, Markovic I, Tosevski D. Higher concentration of interleukin 6 - A possible link between major depressive disorder and childhood abuse. *Psychiatry Research* 2018; **264**.
135. Dannehl K, Rief W, Euteneuer F. Childhood adversity and cognitive functioning in patients with major depression. *Child Abuse Negl* 2017; **70**: 247-54.
136. Ernst M, Mohr HM, Schött M, et al. The effects of social exclusion on response inhibition in borderline personality disorder and major depression. *Psychiatry Res* 2018; **262**: 333-9.
137. Saleh A, Potter GG, McQuoid DR, et al. Effects of early life stress on depression, cognitive performance and brain morphology. *Psychol Med* 2017; **47**(1): 171-81.
138. Grosse L, Ambree O, Jorgens S, et al. Cytokine levels in major depression are related to childhood trauma but not to recent stressors. *Psychoneuroendocrinology* 2016; **73**: 24-31.
139. Tatham EL, Ramasubbu R, Gaxiola-Valdez I, et al. White matter integrity in major depressive disorder: Implications of childhood trauma, 5-HTTLPR and BDNF polymorphisms. *Psychiatry Res Neuroimaging* 2016; **253**: 15-25.
140. Williams LM, Debattista C, Duchemin AM, Schatzberg AF, Nemeroff CB. Childhood trauma predicts antidepressant response in adults with major depression: data from the randomized international study to predict optimized treatment for depression. *Transl Psychiatry* 2016; **6**: e799.
141. Du L, Wang J, Meng B, et al. Early life stress affects limited regional brain activity in depression. *Scientific Reports* 2016; **6**: 25338.

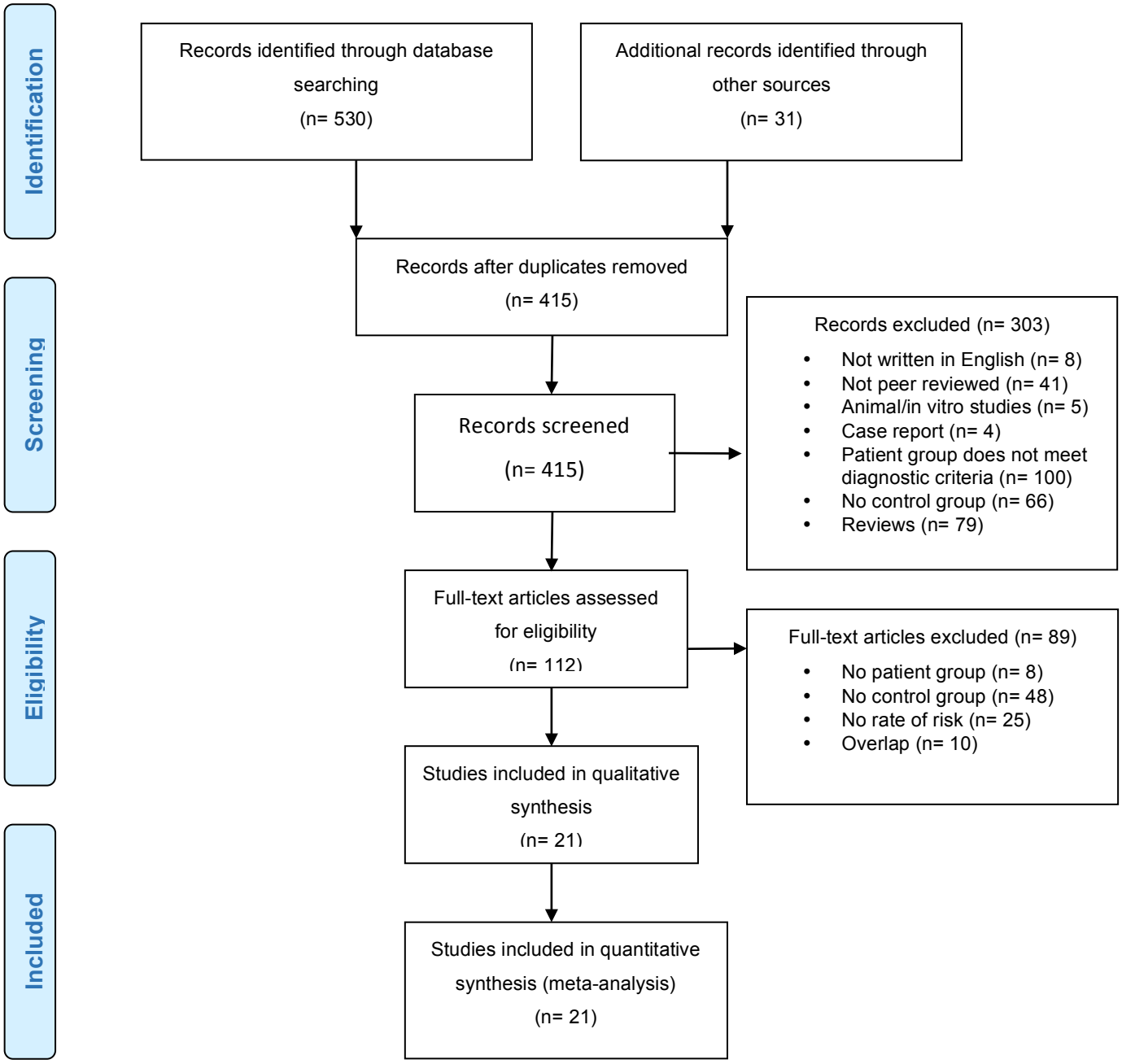
142. Jansen K, Cardoso TA, Fries GR, et al. Childhood trauma, family history, and their association with mood disorders in early adulthood. *Acta Psychiatr Scand* 2016; **134**(4): 281-6.
143. Karakoç B, Gülseren L, Çam B, Gulseren S, Tenekeci N, Mete L. Prevalence of Intimate Partner Violence and Associated Factors. *Arch Neuropsychiatr* 2015; **52**: 324-30.
144. Mullins N, Power RA, Fisher HL, et al. Polygenic interactions with environmental adversity in the aetiology of major depressive disorder. *Psychol Med* 2016; **46**(4): 759-70.
145. Bailer J, Witthöft M, Wagner H, Mier D, Diener C, Rist F. Childhood maltreatment is associated with depression but not with hypochondriasis in later life. *J Psychosom Res* 2014; **77**(2): 104-8.
146. Peyrot WJ, Milaneschi Y, Abdellaoui A, et al. Effect of polygenic risk scores on depression in childhood trauma. *Br J Psychiatry* 2014; **205**(2): 113-9.
147. Opel N, Redlich R, Zwanzger P, et al. Hippocampal atrophy in major depression: a function of childhood maltreatment rather than diagnosis? *Neuropsychopharmacology* 2014; **39**(12): 2723-31.
148. Carvalho Fernando S, Beblo T, Schlosser N, et al. The impact of self-reported childhood trauma on emotion regulation in borderline personality disorder and major depression. *J Trauma Dissociation* 2014; **15**(4): 384-401.
149. Wingenfeld K, Schaffrath C, Rullkoetter N, et al. Associations of childhood trauma, trauma in adulthood and previous-year stress with psychopathology in patients with major depression and borderline personality disorder. *Child Abuse Negl* 2011; **35**(8): 647-54.
150. Güleç MY, Altintaş M, İnanç L, Bezgin CH, Koca EK, Güleç H. Effects of childhood trauma on somatization in major depressive disorder: The role of alexithymia. *J Affect Disord* 2013; **146**(1): 137-41.
151. Jeon HJ, Kang ES, Lee EH, et al. Childhood trauma and platelet brain-derived neurotrophic factor (BDNF) after a three month follow-up in patients with major depressive disorder. *J Psychiatr Res* 2012; **46**(7): 966-72.
152. Horesh N, Ratner S, Laor N, Toren P. A comparison of life events in adolescents with major depression, borderline personality disorder and matched controls: a pilot study. *Psychopathology* 2008; **41**(5): 300-6.
153. Grassi-Oliveira R, Brietzke E, Pezzi JC, Lopes RP, Teixeira AL, Bauer ME. Increased soluble tumor necrosis factor-alpha receptors in patients with major depressive disorder. *Psychiatry Clin Neurosci* 2009; **63**(2): 202-8.
154. Wessel I, Meeren M, Peeters F, Arntz A, Merckelbach H. Correlates of autobiographical memory specificity: the role of depression, anxiety and childhood trauma. *Behav Res Ther* 2001; **39**(4): 409-21.
155. Bernet CZ, Stein MB. Relationship of childhood maltreatment to the onset and course of major depression in adulthood. *Depress Anxiety* 1999; **9**(4): 169-74.
156. Kounou KB, Bui E, Dassa KS, et al. Childhood trauma, personality disorders symptoms and current major depressive disorder in Togo. *Soc Psychiatry Psychiatr Epidemiol* 2013; **48**(7): 1095-103.
157. Kaczmarczyk M, Wingenfeld K, Kuehl LK, Otte C, Hinkelmann K. Childhood trauma and diagnosis of major depression: Association with memory and executive function. *Psychiatry Res* 2018; **270**: 880-6.
158. Farrell C, Doolin K, N OL, et al. DNA methylation differences at the glucocorticoid receptor gene in depression are related to functional alterations in hypothalamic-pituitary-adrenal axis activity and to early life emotional abuse. *Psychiatry Res* 2018; **265**: 341-8.
159. Herane-Vives A, de Angel V, Papadopoulos A, et al. Short-term and long-term measures of cortisol in saliva and hair in atypical and non-atypical depression. *Acta Psychiatr Scand* 2018; **137**(3): 216-30.

160. Kılıç F, Coşkun M, Bozkurt H, Kaya İ, Zoroğlu S. Self-Injury and Suicide Attempt in Relation with Trauma and Dissociation among Adolescents with Dissociative and Non-Dissociative Disorders. *Psychiatry Investig* 2017; **14**(2): 172-8.
161. Bauriedl-Schmidt C, Jobst A, Gander M, et al. Attachment representations, patterns of emotion regulation, and social exclusion in patients with chronic and episodic depression and healthy controls. *J Affect Disord* 2017; **210**: 130-8.
162. Hsu DT, Langenecker SA, Kennedy SE, Zubieta JK, Heitzeg MM. fMRI BOLD responses to negative stimuli in the prefrontal cortex are dependent on levels of recent negative life stress in major depressive disorder. *Psychiatry Res* 2010; **183**(3): 202-8.
163. Harkness KL, Bruce AE, Lumley MN. The role of childhood abuse and neglect in the sensitization to stressful life events in adolescent depression. *J Abnorm Psychol* 2006; **115**(4): 730-41.
164. Frodl T, Reinhold E, Koutsouleris N, Reiser M, Meisenzahl EM. Interaction of childhood stress with hippocampus and prefrontal cortex volume reduction in major depression. *J Psychiatr Res* 2010; **44**(13): 799-807.
165. Peterfalvi A, Nemeth N, Herczeg R, et al. Examining the Influence of Early Life Stress on Serum Lipid Profiles and Cognitive Functioning in Depressed Patients. *Front Psychol* 2019; **10**: 1798.
166. Palmier-Claus JE, Berry K, Bucci S, Mansell W, Varese F. Relationship between childhood adversity and bipolar affective disorder: systematic review and meta-analysis. *Br J Psychiatry* 2016; **209**(6): 454-9.
167. Zhang S, Lin X, Yang T, et al. Prevalence of childhood trauma among adults with affective disorder using the Childhood Trauma Questionnaire: A meta-analysis. *J Affect Disord* 2020; **276**: 546-54.
168. Widom CS. Commentary: A challenge for a higher bar in research on childhood trauma - reflections on Danese (2020). *J Child Psychol Psychiatry* 2020; **61**(3): 251-4.
169. McKay MT, Cannon M, Chambers D, et al. Childhood trauma and adult mental disorder: A systematic review and meta-analysis of longitudinal cohort studies. *Acta Psychiatr Scand* 2021; **143**(3): 189-205.
170. Sara G, Lappin J. Childhood trauma: psychiatry's greatest public health challenge? *Lancet Public Health* 2017; **2**(7): e300-e1.

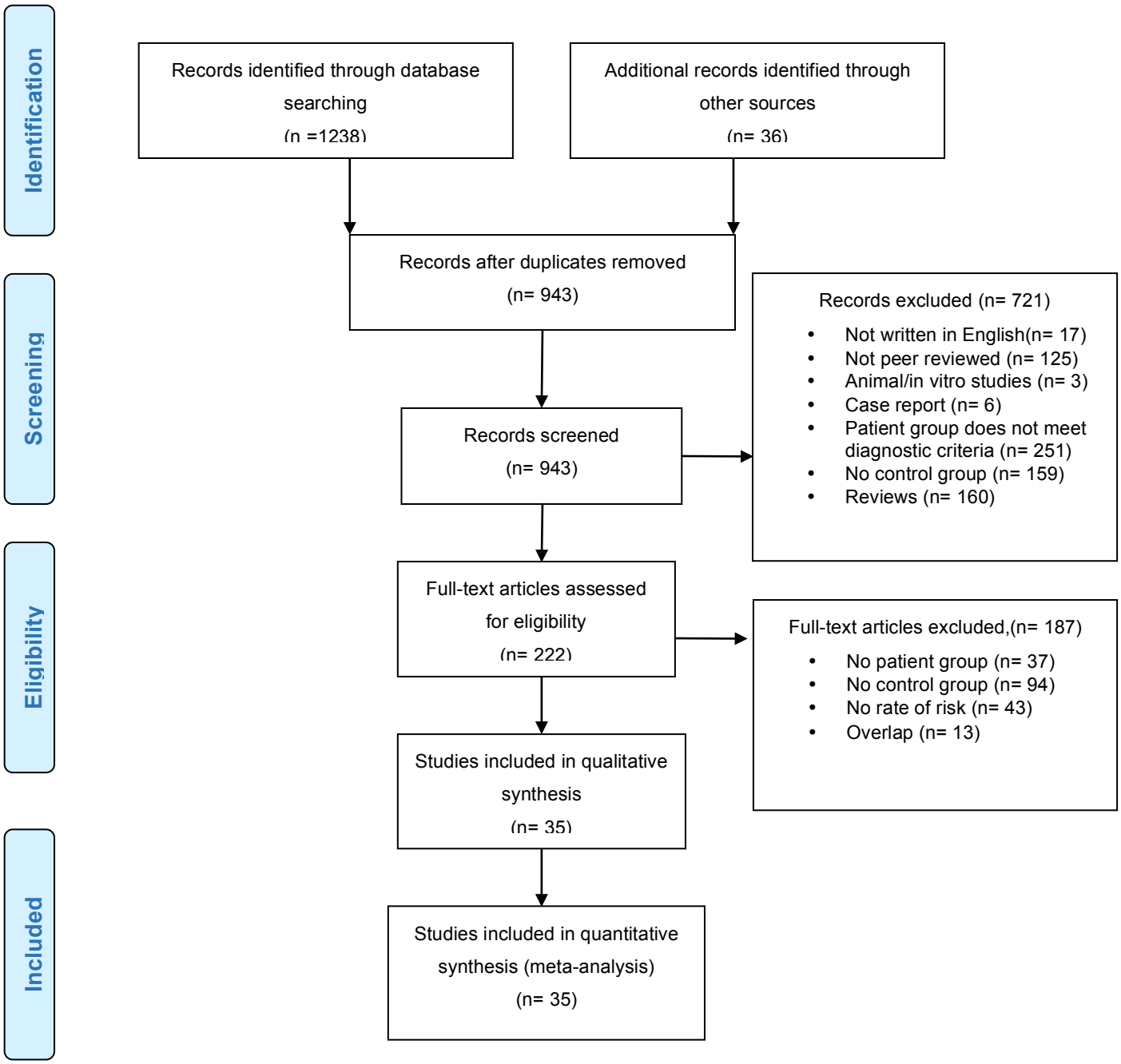
8. Appendix

8.1 Supplementary material

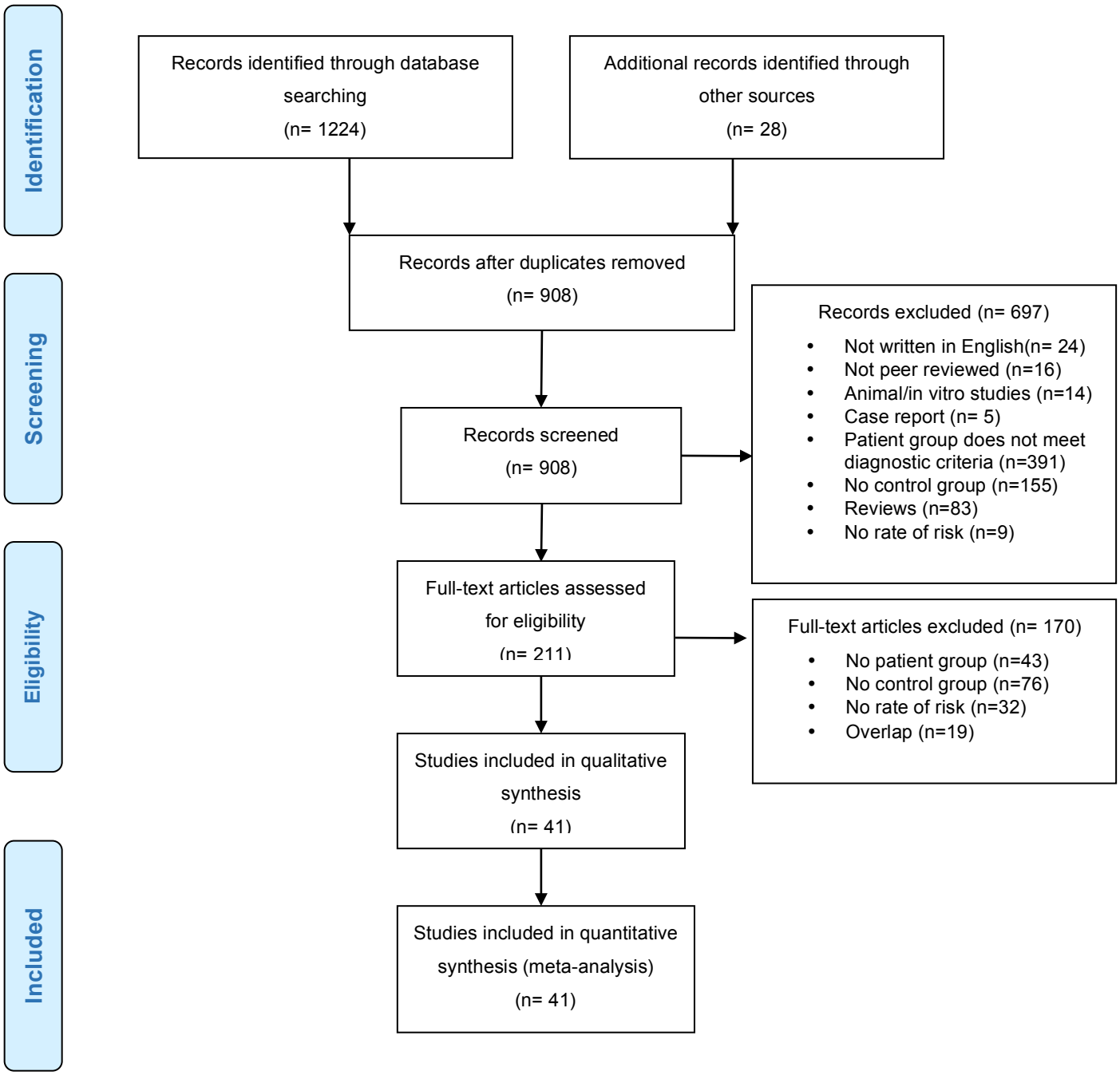
8.1.2 PRISMA flowcharts



Supplementary figure 1- PRISMA flowchart bipolar disorder

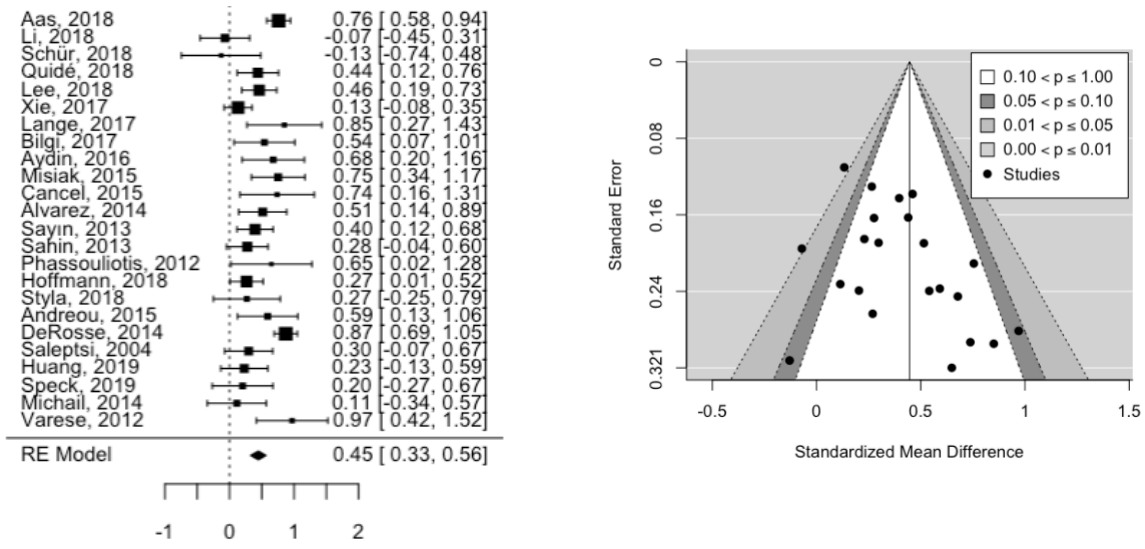


Supplementary figure 2- PRISMA flowchart schizophrenia spectrum disorder

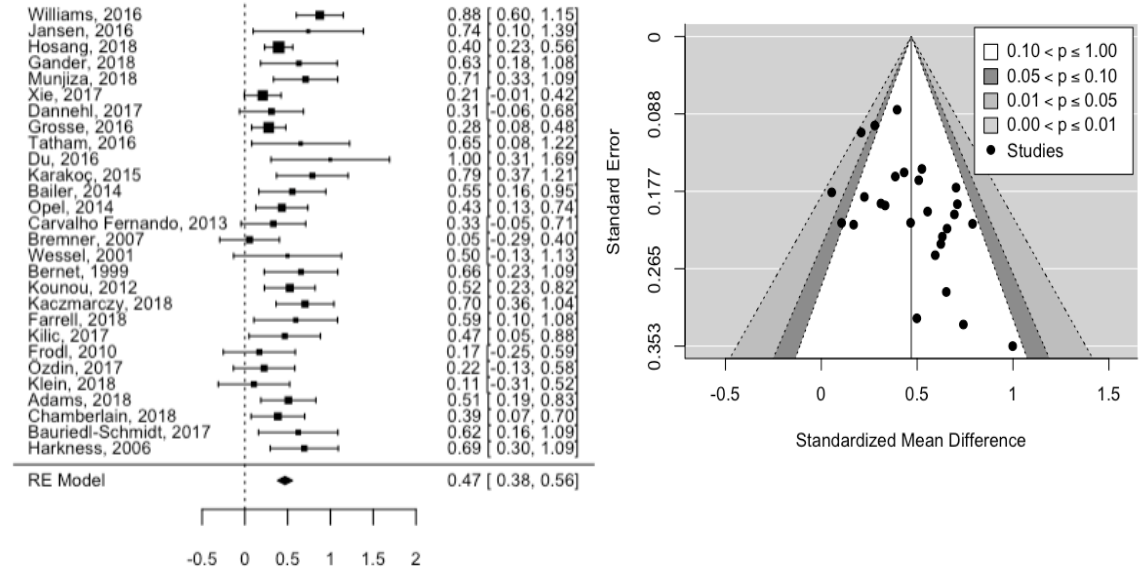


Supplementary figure 3- PRISMA flowchart MD

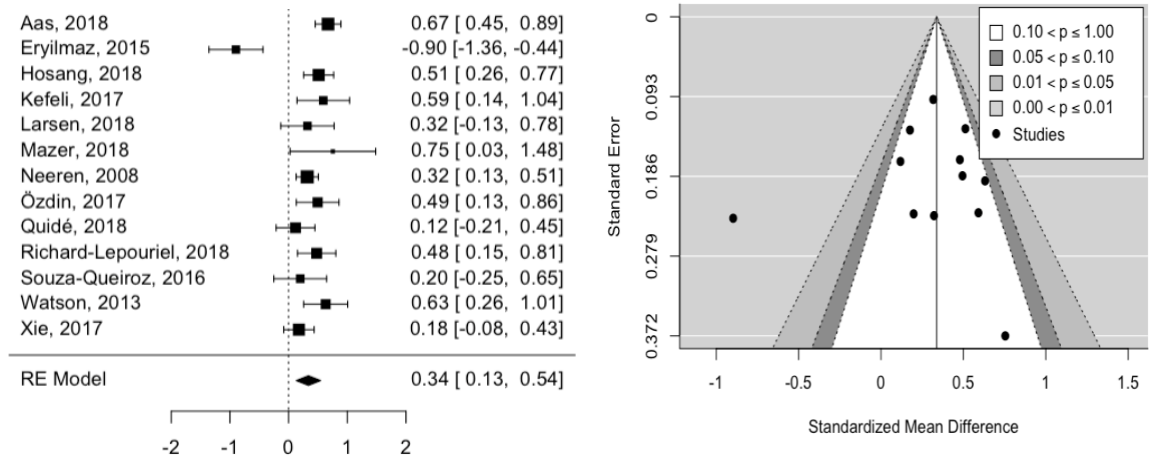
8.1.3 PA



Supplementary figure 4- Forest and funnel plot: PA in schizophrenia spectrum

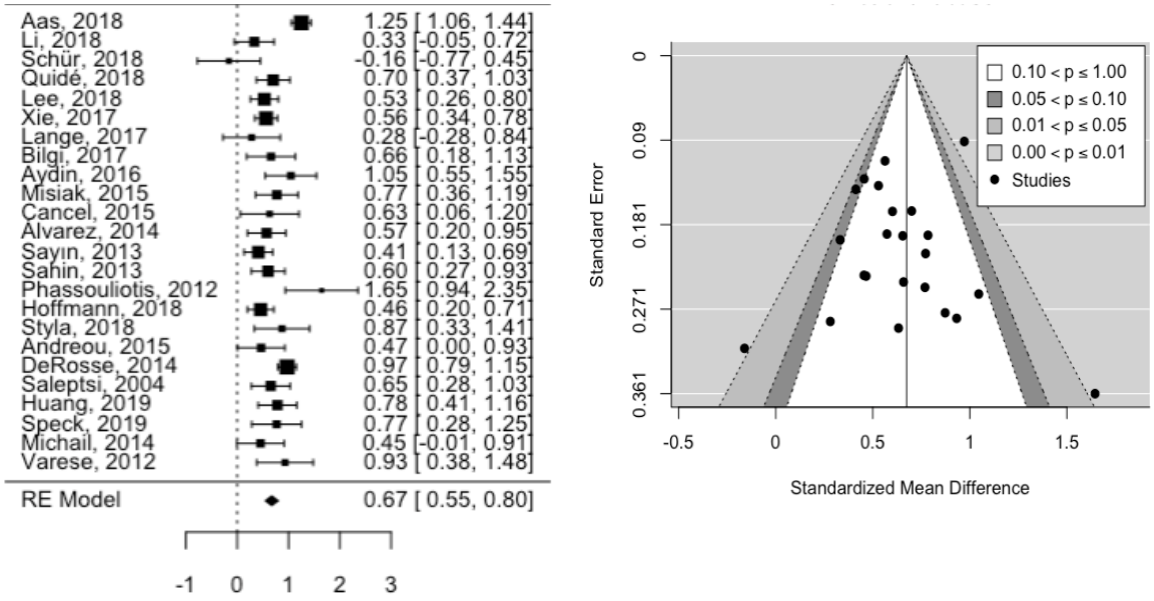


Supplementary figure 5- Forrest and funnel plot: PA in MD

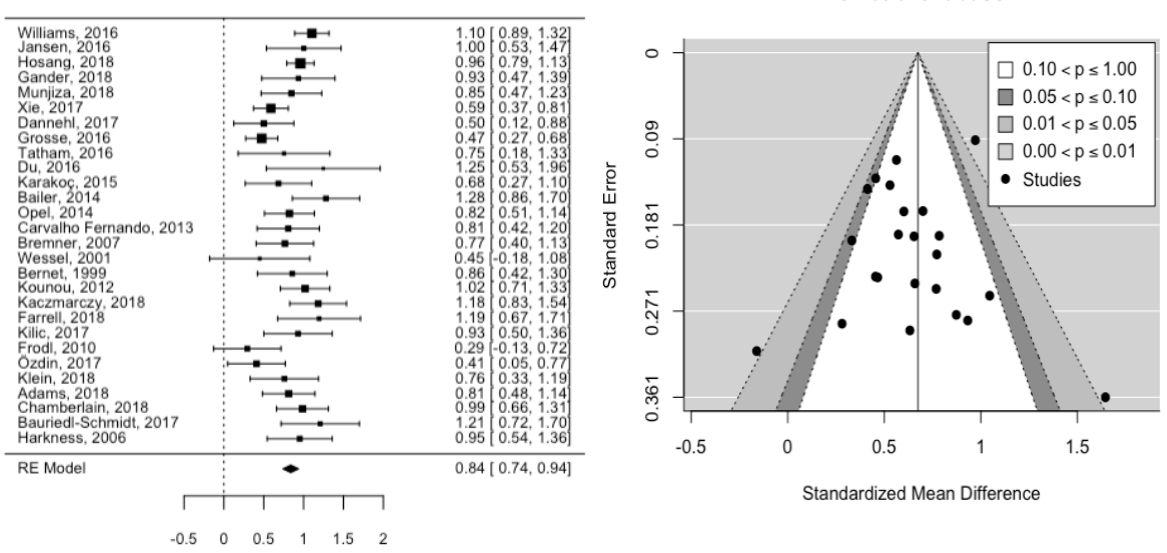


Supplementary figure 6- Forrest and funnel plot: PA in bipolar disorder

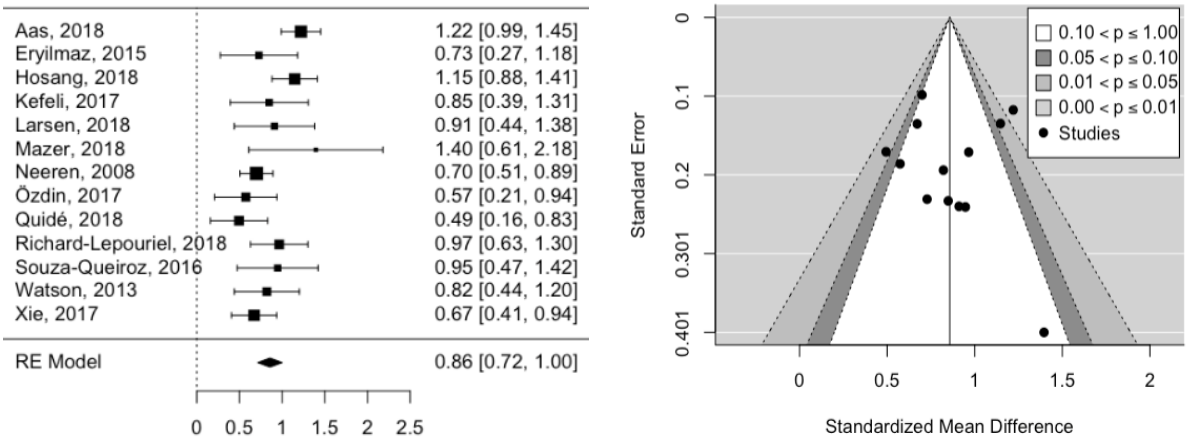
8.1.4 EA



Supplementary figure 7- Forest and funnel plot: EA in schizophrenia spectrum disorder

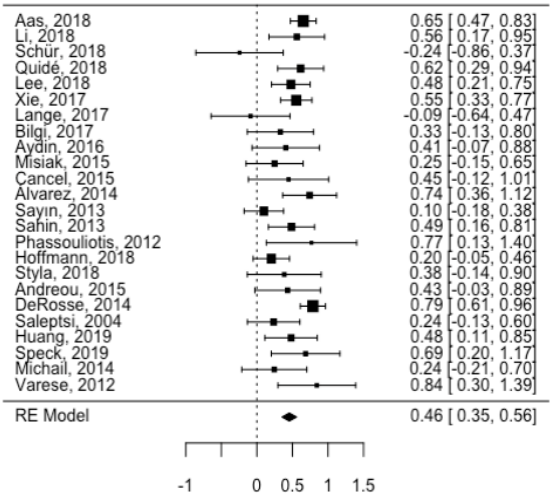


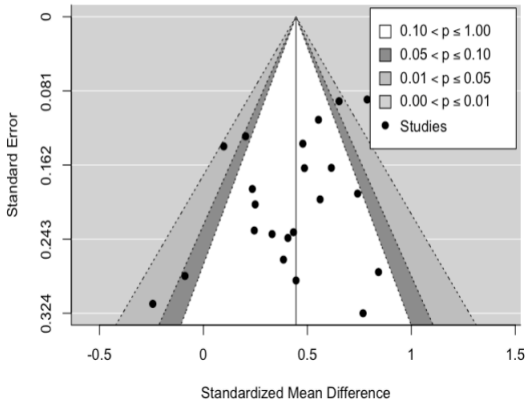
Supplementary figure 8- Forrest and funnel plot: EA in MD



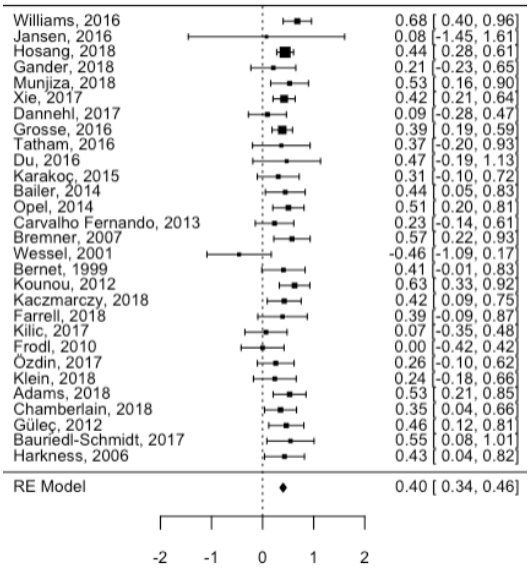
Supplementary figure 9- Forest and funnel plot: EA in bipolar disorder

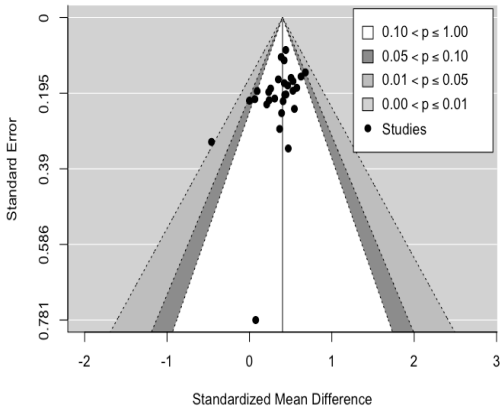
8.1.5 SA



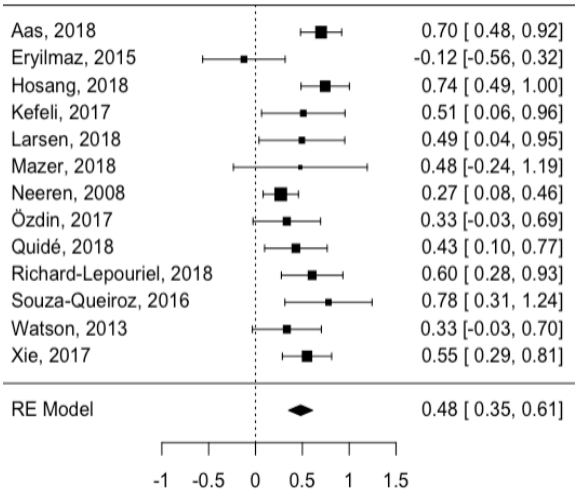


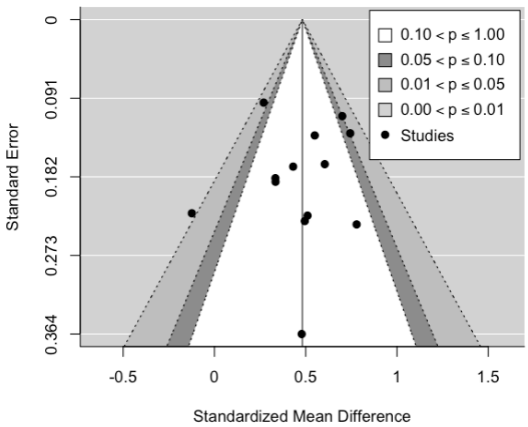
Supplementary figure 10- Forest and funnel plot: SA in schizophrenia spectrum disorder





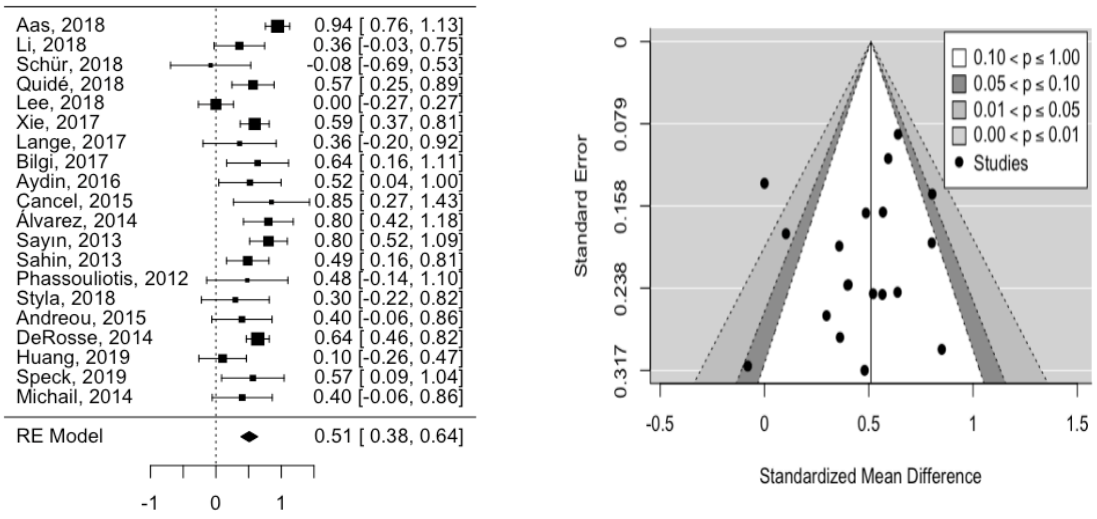
Supplementary figure 11- Forest and funnel plot: SA in MD



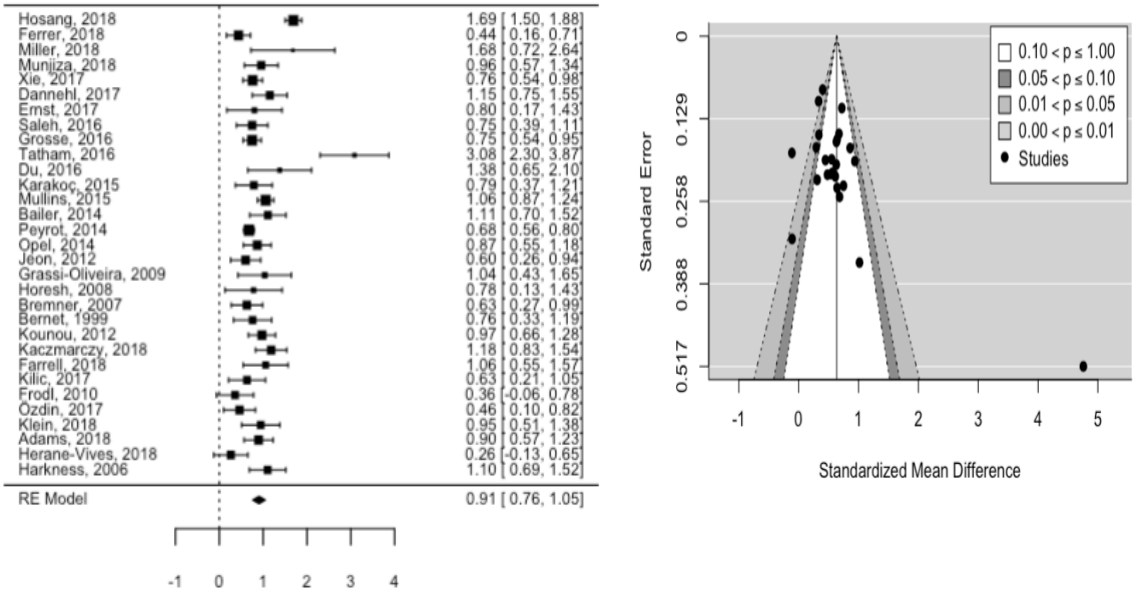


Supplementary figure 12- Forest and funnel plot: SA in bipolar disorder

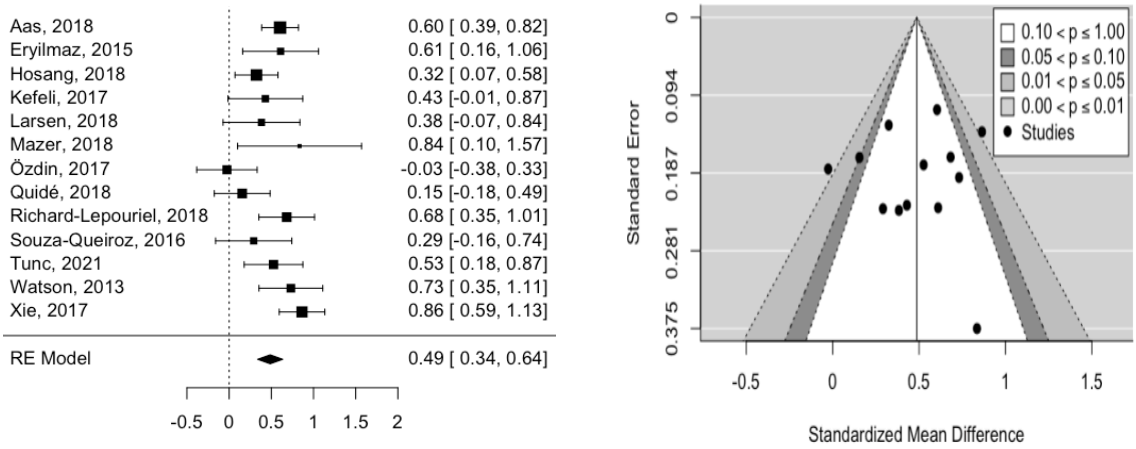
8.1.6 PN



Supplementary figure 13- Forest and funnel plot: PN in schizophrenia spectrum disorder

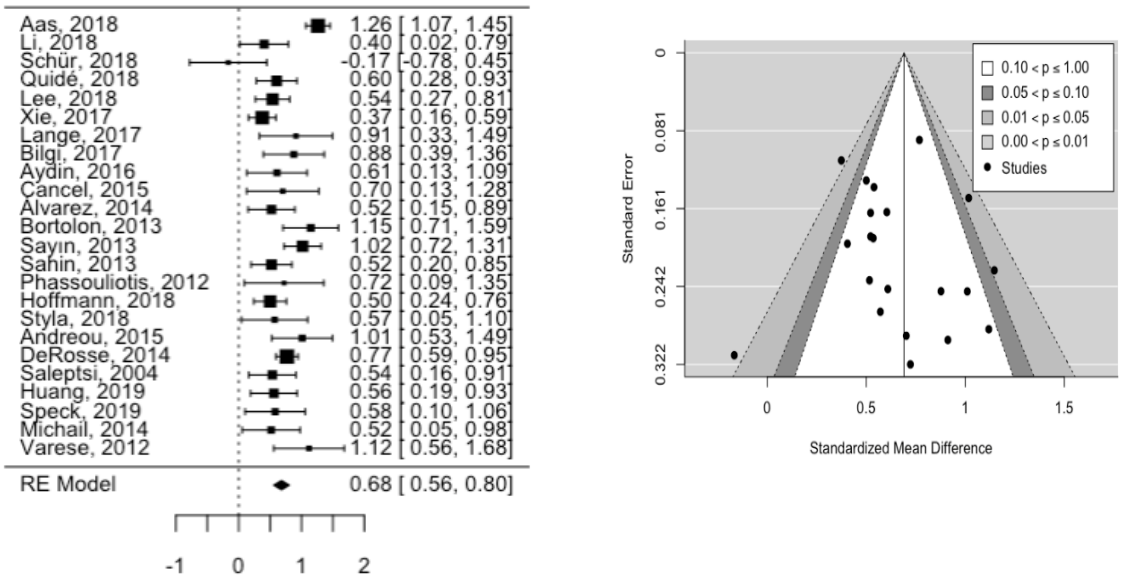


Supplementary figure 14- Forest and funnel plot: PN in MD

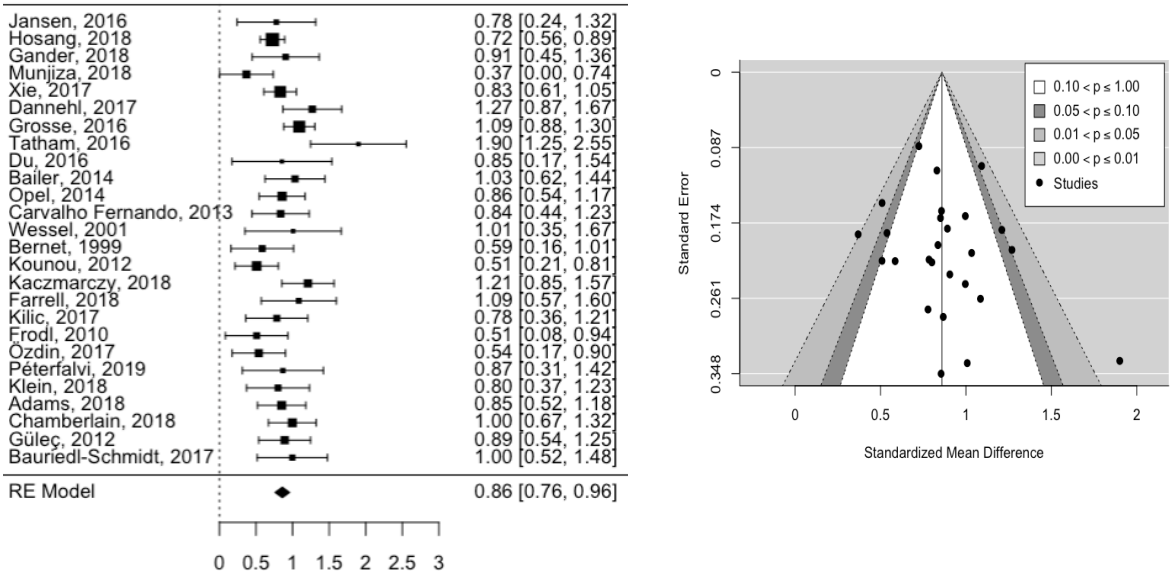


Supplementary figure 15- Forest and funnel plot: PN in bipolar disorder

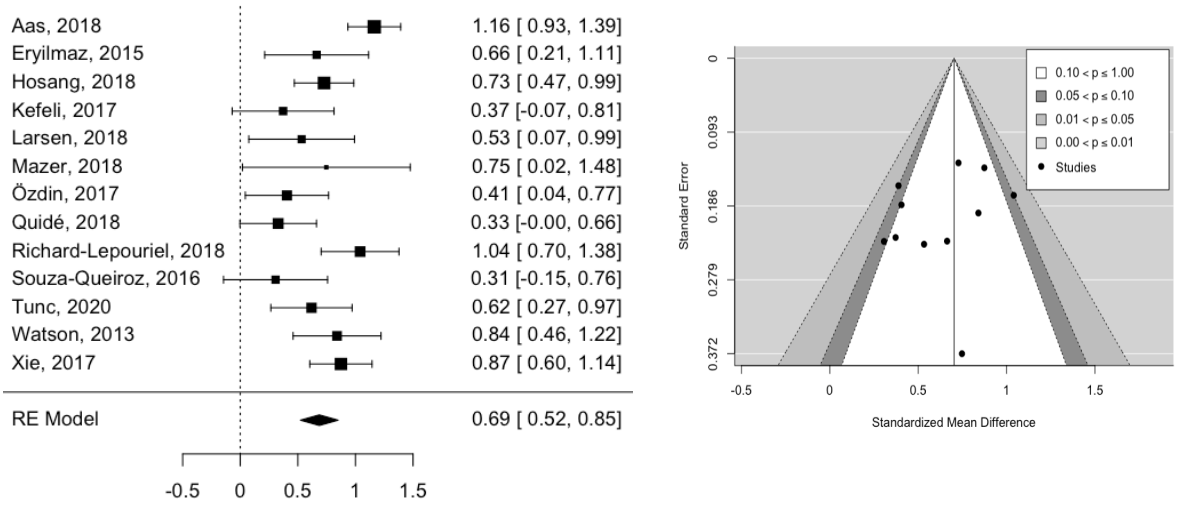
8.1.7 EN



Supplementary figure 16- Forest and funnel plot: EN in schizophrenia spectrum disorder



Supplementary figure 17- Forest and funnel plot: EN in MD



Supplementary figure 18- Forest and funnel plot: EN in bipolar disorder

8.2 List of tables

8.3 List of figures