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DOI:

[10.1016/j.cpr.2018.08.002](https://doi.org/10.1016/j.cpr.2018.08.002)

Document Version

Peer reviewed version

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Citation for published version (APA):

Hoppen, T. H., & Chalder, T. (2018). Childhood adversity as a transdiagnostic risk factor for affective disorders in adulthood: A systematic review focusing on biopsychosocial moderating and mediating variables. *Clinical Psychology Review*, 65, 81-151. <https://doi.org/10.1016/j.cpr.2018.08.002>

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Childhood Adversity as a Transdiagnostic Risk Factor for Affective Disorders in Adulthood:
A Systematic Review Focusing on Biopsychosocial Moderating and Mediating Variables

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Childhood Adversity as a Transdiagnostic Risk Factor for Affective Disorders in Adulthood: A Systematic Review Focusing on Biopsychosocial Moderating and Mediating Variables

Affective disorders such as Major Depressive Disorders (MDD), Post-Traumatic Stress Disorder (PTSD), Generalized Anxiety Disorder (GAD) or Social Anxiety Disorder (SAD) are among the leading contributors to the global disease burden (McCrone, Dhanasiri, Patel, Knapp, & Lawton-Smith, 2008). Worryingly, this tendency is rising (Prince et al., 2007). A well-recognized risk factor for developing affective disorders is childhood adversity (Felitti et al., 1998; Kessler, Davis, & Kendler, 1997). According to the National Centre of Child Abuse and Neglect, approximately 1.5 million verified cases of child maltreatment are reported annually in the US alone, of which more than half of the cases represent instances of neglect and about 700.000 sexual, physical, or emotional abuse (Sedlak & Broadhurst, 1996). Early parental loss (Agid, Kohn, & Lerer, 2000) and bullying (Tunnard et al., 2014) have also been reported as common adverse events during childhood that might have repercussions in adulthood. Notably, adverse experiences during childhood have been shown to be inter-dependent in the sense that the likelihood of suffering additional adversity after experiencing one increases dramatically (Dong et al., 2004).

The pioneering Adverse Childhood Experience (ACE) study (Felitti et al., 1998) was among the first to reveal the devastating and long-lasting consequences of childhood adversity. In two subsequent studies the same group illustrated that childhood adversity accounted for 54% of the Population Attributable Risk Fraction (PARF) for current episodes of depression and 67% of the PARF for suicide attempts in their large retrospective cohort (Dube et al., 2001; Dube et al., 2003). However, childhood adversity is not just linked to depression; it has been shown to have little predictive specificity across affective disorders and hence presents a transdiagnostic risk factor (Brewin, Andrews, & Valentine, 2000; Green et al., 2010; Kessler et al., 1997; Kessler et al., 2010).

Various epidemiological studies have confirmed a firm link between childhood

adversity and the development of affective disorders in adulthood (Danese et al., 2009; Fergusson, Horwood, & Lynskey, 1996; Kessler & Magee, 1993; Kessler et al. 1997; Mullen, Martin, Anderson, Romans, & Herbison, 1996). While the vast majority of research involves retrospectively assessed childhood adversity, which has been criticized for questionable validity due to negative memory biases during affective episodes, prospective accounts come to the same conclusions (Li, D'Arcy & Meng, 2016). Furthermore, the relationship between childhood adversity and later affective disorders seems dependent on the doses (Anda et al., 2006; Chapman et al., 2004; Felitti et al. 1998), severity (Hovens et al., 2010; Norman et al., 2012) and age of exposure (Dunn, McLaughlin, Slopen, Rosand, & Smoller, 2013; Kaplow & Widom, 2007; Keiley, Howe, Dodge, Bates, & Pettit, 2001; Schroedl et al., 2010). Related to the age of exposure, childhood adversity has particularly detrimental and long-lasting effects during early stages of brain development (Andersen et al., 2008; Khan et al., 2015; see also a comprehensive review by Lupien, McEwen, Gunnar & Heim, 2009). As such, the effects of childhood adversity on mental health have been shown to last for a lifetime (Clark, Caldwell, Power, & Stansfeld, 2010). Furthermore, childhood trauma has also been linked to treatment-resistance in affective disorders (Angst, Gamma, Rössler, Ajdacic, & Klein, 2011; Nanni, Uher, & Danese, 2012; Tunnard et al., 2014; Wiersma et al., 2009) as well as greater functional impairment (Arnold, 2004; McLaughlin et al., 2010). Consequently, some scholars have claimed that childhood-maltreatment-related affective disorders should be considered a clinically distinct subtype (Teicher & Samson, 2013).

Meanwhile, a thorough understanding of the mechanisms involved in the link between childhood adversity and affective disorders in adulthood is only slowly emerging. Some scholars have proposed influential neurobiological models involving a deregulated Hypothalamic-Pituitary-Adrenal (HPA) axis (De Kloet et al., 2005; Heim & Nemeroff, 2001; Heim et al., 2008; Perry et al., 1995). Others have focused on the dysregulation of the immune system (Danese et al., 2009; Salvich & Irwin, 2014; Tursich et al., 2013). In fact, there is a

vast plethora of studies proposing various other potential moderators and mediators such as neuroticism (Roy, 2002), insecure attachment styles (Styron & Janoff-Bulman, 1997), emotional dysregulation (Dvir et al., 2014), sensitization to stressors (Hammen et al., 2000; McLaughlin, Conron, Koenen, & Gilman, 2010), revictimization in adulthood (Gladstone et al., 2004), and gene-environment interactions (Hornung & Heim, 2014; Karg et al., 2011) to name just a few. Some reviews have examined multiple potential moderators and mediators simultaneously but none took a holistic, biopsychosocial stance (Ehlert, 2013; Heim & Nemeroff, 2001; Lupien et al., 2009).

To the knowledge of the authors only one review has been conducted to date without a restriction on the nature of potential moderating and mediating variables and this review focused on stress in general rather than childhood adversity in particular (Gunnar & Quevedo, 2007). Therefore, the present systematic review will take a holistic, biopsychosocial stance in analysing which moderators and mediators seem to play a role in the link between adversities in childhood and the development of affective disorders in adulthood. To date, this review is the first review which systematically examines the current literature base from both a transdiagnostic as well as biopsychosocial perspective. Accordingly, this review tries to shed light on the poorly understood mechanisms involved in the trajectory from troubled childhoods to severe affective disturbances in later life.

As Baron and Kenny (1986) pointed out, the terms 'moderator' and 'mediator' have often been used interchangeably in the social sciences which created erroneous claims and unnecessary confusion. In this review, a moderating variable is defined as "a qualitative (e.g. sex, race, class) or quantitative (e.g. level of reward) variable that affects the direction and/or strength of the relation between an independent or predictor variable and a dependent or criterion variable" (Baron & Kenny, 1986, p. 1174), while a mediator is defined as a variable that "accounts for the relation between the predictor and the criterion" (p. 1176). Thus,

"moderator variables specify when certain effects will hold, mediators speak to how or why such effects occur" (p.1176).

Method

Search Strategy and Selection Criteria

This systematic review was designed in accordance with the preferred reporting items for systematic reviews and meta analyses (PRISMA) guidelines (Liberati et al., 2009), although the PRISMA checklist and a formal review protocol were not entirely used due to the breadth of the aim and the wide-ranging nature of the material under consideration. Three electronic databases (i.e. Embase, MEDLINE & PsycINFO) were systematically searched for studies published from inception to October 2017, which examined at least one potential moderating, mediating or otherwise associated (e.g. correlated) variable in the relationship between childhood adversity and affective disorders in adulthood. Search terms were the same across databases and involved combining all field searches for four affective disorders (i.e. major depressive disorder, posttraumatic stress disorder, generalized anxiety disorder and social anxiety disorder) and terms for childhood adversity (e.g. childhood adversity, childhood trauma, childhood maltreatment). This systematic review was limited to affective disorders for conceptual reasons as well as reasons of feasibility. Conceptually, affective disorders share a high overlap in terms of comorbidity (Kessler et al., 1994) as well as symptomatology (American Psychiatric Association, 2013). In terms of feasibility, this systematic review is limited to the mentioned four affective disorders for two reasons. On the one hand, an even broader transdiagnostic analysis, transcending the field of affective disorders (e.g. also including schizoaffective disorder), would have gone beyond the possible scope of the authors' endeavours. On the other hand, the authors saw a trade-off between giving a comprehensive transdiagnostic overview and being concise; they prioritized the latter.

Inclusion and Exclusion Criteria

Empirical studies were included if they met the following inclusion criteria: (1) Empirical quantitative research reports published in a peer-reviewed journal which examined at least one potential moderating, mediating or otherwise associated variable in the relationship between childhood adversity and affective disorders in adulthood (i.e. above the age of 18 years), (2) Written in English language, (3) Involving human subjects. Studies were excluded if one or more of the following criteria was met: (1) Review article, (2) Conference abstract, (3) Animal study, (4) Letter to editors. Uncertainties concerning whether a study should be included or excluded were resolved through discussions between the authors.

Data Extraction and Synthesis

After the removal of duplicates and non-English language articles, paper titles were analysed by the first author. The majority of articles excluded at this stage had titles referring to either completely unrelated topics or did not meet the inclusion and exclusion criteria as listed above (e.g. subjects below the age of 18, animal study etc.). The abstracts of the remaining articles were then checked by the first author. All papers potentially meeting inclusion and exclusion criteria were included for full text scrutiny. The systematic literature research, conducted in October 2017, yielded a total of 5679 articles, 3062 when duplicates were removed and 583 when ineligible articles had been removed after the title screening. After a thorough screening of the 583 abstracts, 214 articles remained for inclusion of which none was excluded after full-text analysis (see Figure 1 below).

Figure 1. PRISMA Flower Depicting the Article Abstraction Procedure.

Quality Assessment

The quality of the included articles was judged on the basis of 12 items (see List A1 in the Appendix), which analysed various methodological and study design matters, most importantly the validity and reliability of the operationalization of childhood adversity, the affective disorder(s) as well as the moderator(s) and mediator(s). The 12 items sum up to a maximum score of 40. However, since certain items were not applicable to all articles, the obtained total score of the studies was divided by the respective potential total score and multiplied by 100 to give an estimate in percentage. Prospective studies received the highest study design score based on empirical evidence indicating a superiority in terms of validity and reliability of prospective childhood adversity reports over retrospective reports (Widom, Raphael, & DuMont, 2004). Clinical and public records received the highest quality score for the childhood adversity operationalization as there are various problems with retrospective self-reports such as negative memory biases particularly during affective episodes (Maughan & Rutter, 1997) or amnesia (Briere & Conte, 1993). Nevertheless, retrospective self-reports have also been shown to yield satisfactory validity (Hardt & Rutter, 2004) and hence received the moderate score of 3 and 4 if multiple validated measures were utilized. The quality score criteria for the operationalization of affective disorder(s) are based on the intention to focus on clinically relevant affective disturbances. As such, the clinically validated diagnoses and guideline-based, clinical assessments were favoured. The scoring of the other items is thought to be straightforward.

Definition of transdiagnostic vs. disorder-specific moderator/mediator

As soon as a moderator or mediator was shown to moderate or mediate the relationship between childhood adversity and at least two affective disorders in adulthood it was classified in the present review as transdiagnostic. While other

authors have chosen four (Harvey, Watkins, & Mansell, 2004), the authors of the present review decided to classify a moderator or mediator as transdiagnostic as soon as its moderating or mediating effect had been empirically shown beyond the scope of one diagnostic category. Consequently, a moderator or mediator has been classified as disorder-specific if the respective moderator or mediator has only been shown to mediate the relationship between childhood adversity and one affective disorder.

Results

Overall Quality of the Included Studies

The overall quality of the 214 included studies was moderate and approximately normally distributed with a mean of 50.01%, median of 51.35%, a standard deviation of 11.69% and a range from 17.50% to 82.5% (see Table A1 in the Appendix for details).

Of the total 214 studies, 47 (i.e. approx. 22%) included a formal mediation analysis, 30 (i.e. approx. 14%) included a formal moderation analysis and the remaining 137 (i.e. approx. 64%) consisted of associational studies utilizing various different statistical methodologies such as regression analyses, chi square tests or correlation analyses to name just a few (see Figure 2 below).

Figure 2. Proportions of studies investigating mediating, moderating or some form of association variable (pie chart).

However, studies were further subdivided into cross-sectional and non-cross-sectional as the distribution of quality scores became clearer (see Figure 3 and Table 1 for descriptive statistics below). In the present review, the term 'non-cross-sectional' refers to studies that did not investigate cross-sectionally but chose another study design instead (i.e. prospective cohorts, retrospective cohorts, matched-controls, case-control, RCTs or single-blind non-randomized placebo-controlled repeated-measures designs).

Figure 3. Proportions of cross-sectional vs. non-cross-sectional studies investigating mediating, moderating or some form of association variable (pie chart).

Table 1					
<i>Descriptive Statistics Concerning Quality Scores (in %) of the Six Subgroups</i>					
<u>Group</u>	<u>N</u>	<u>M</u>	<u>SD</u>	<u>Min</u>	<u>Max</u>
Non-Cross-Sectional-Association	56	49.3	9.9	35	65
Cross-Sectional-Association	81	39.4	6.5	17.5	46
Non-Cross-Sectional-Mediation	17	55	8.9	45	82.5
Cross-Sectional-Mediation	30	46	7.7	34.3	65.7
Non-Cross-Sectional-Moderation	13	68.8	7.5	65	80
Cross-Sectional-Moderation	17	45	7.1	40	55
Total	214	50.6	7.9	17.5	82.5

As this is primarily a systematic review about moderators and mediators in the relationship between childhood adversity and affective disorders in adulthood studies with a formal moderation and mediation analysis will be scrutinized in more depth compared to the associational studies. It is worth mentioning that this review involves large heterogeneities due to its inclusiveness. The operationalization of the exposure, the outcomes as well as the moderating, mediating or associated variable(s) differed considerably across studies. The advantage of such an inclusive approach is heightened sensitivity which might come at the cost of specificity. In other words, the holistic perspective taken gives a comprehensive overview of potential moderating and mediating variables involved in the relationship

between adversity suffered during childhood and affective disturbances in adulthood. However, some studies, particularly those with low quality, might present false positives.

Specific Shortcomings in the Quality of the Included Studies

The operationalization of childhood adversity varied substantially. Of the 214 studies, 161 studies (i.e. approx. 75%) utilized one validated, retrospective, self-report questionnaire to operationalize childhood adversity. The most commonly chosen questionnaire was the Childhood Trauma Questionnaire (CTQ) developed by Bernstein and colleagues (1997). While three out of four utilized questionnaires have been validated, the childhood adversities they probe into differ considerably. Arguably, the CTQ, is one of the most holistic inquiry tools but fails to identify childhood adversities such as bullying and prolonged financial constraints. In short, no gold standard questionnaire has been established which does not miss important potential adversities in early life. The remaining studies included either the authors' invalidated questions (i.e. approx. 13%), multiple validated, retrospective, self-report measures (i.e. approx. 7%) or expert observation and/or public records (i.e. approx. 5%).

The operationalization of the affective disorder(s) also varied substantially. Of the 214 studies, 94 studies (i.e. 44%) received the highest or second-highest score indicating that about 4 in 10 of the included studies fulfilled the standard requirements to detect clinically significant affective disturbances. Thirty-nine studies (i.e. approx. 18%) utilized at least one validated diagnostic tool but either did not specify whether it was administered by a trained specialist or used the social-desirability-prone self-report version and hence received a medium quality score. The remaining 81 studies (i.e. approx. 38%) used one or more validated symptom questionnaires such as the Beck Depression Inventory (BDI) often in convenience samples (e.g. undergraduate students) or invalid, self-chosen questions and received low quality scores. This was due to the fact that symptom questionnaires have not been developed for diagnostic purposes and on the other hand because this review primarily focuses on clinically significant affective disorders.

As mentioned above, 137 of the 214, about two in three of the included studies, did not perform a formal moderation or mediation analysis but utilized some form of associational statistical analysis. These studies were included in an effort to give a more comprehensive overview of potential moderators and mediators. It cannot be understated that the famous 'correlation does not imply causation' notion applies to these circumstances. As such, the results of the associational studies are to be scrutinized with caution and the proposed variables have to stand the test of future empirical rigour.

Non-Cross-Sectional Mediation studies

Of the 17 non-cross-sectional mediation studies, eight analysed psychological mediators (i.e. approx. 47%), five analysed social mediators (i.e. 29%), two focused on biopsychosocial mediators (i.e. 12%) and two investigated a biological mediator (i.e. 12%). Of the total studies, eleven analysed mediators for MDD (i.e. 65%), five analysed MDD and anxiety (i.e. 29%) and one focused on anxiety (i.e. 6%). Throughout this review, the term 'biopsychosocial' will refer to a combination of multiple biological, psychological or social mediators or to variables that do not neatly fit into one of these categories. References will include the Quality Score (QS) of the respective study. Details regarding the quality ratings and general information about these studies are presented in Table A1 and Table A5 in the Appendix, respectively. For convenience, the proposed moderators and mediators will be displayed in italics.

Major Depressive Disorders.

Biological Mediators. The only non-cross-sectional study on mediators for depression revealed that FKBP5 DNA methylation could not be shown to mediate the association between childhood maltreatment and depression symptom severity (Bustamante et al. 2018, QS = 72.22%),

Psychological Mediators. Two studies investigated the mediating effects of *maladaptive cognition*. Both studies found that a *negative cognitive style* mediated the relationship between measures of childhood adversity and MDD in adulthood (Gibb et al., 2001, QS = 60%; Liu, Choi, Boland, Mastin, & Alloy, 2013, QS = 68.6%). In terms of personality, one high quality study suggested that *personality disorder symptoms* seemed to serve as a partial mediator in the relationship between childhood trauma and adult MDD (Kounou et al., 2013, QS = 72.5%). In this vein, another high quality study reported that *borderline psychopathology as well as acceptance of pleasant emotions* mediated the association between childhood emotional abuse and self-reported depressive symptomatology (Schulz et al., 2017, QS = 77.5). Another study reported a mediating effect of *rejection sensitivity* between childhood emotional abuse and depressive symptoms in adulthood (Massing-Schaffer, Liu, Kraines, Choi, & Alloy, 2015, QS = 62.9%).

Social Mediators. These three medium-quality studies revealed that *intimate partner violence* (Brown, Craig, Harris, & Handley, 2008, QS = 57.1%), *chronic interpersonal stress in adulthood* (Kessler & Magee, 1994, QS = 55%) and *physical abuse in adulthood* (Stein, Leslie, & Nyamathi, 2002, QS = 54.1%) mediated the relationship between childhood adversity and unipolar depressive disorders in adulthood.

Biopsychosocial Mediators. Korkeila and colleagues (2005, QS = 50%) illustrated that *risk factors in adulthood* such as living alone, lack of education, alcohol consumption, lack of social support and negative affectivity partially mediated the effect of childhood adversity on depressive symptoms in a representative sample from the working-aged general Finish population. Hankin (2005, QS = 51.4%) demonstrated that *negative events in adulthood, an insecure attachment style and a negative cognitive style* proved to be significant mediators in the relationship between childhood maltreatment and depressive symptoms in a sample of young adults.

Anxiety.

Biological Mediators. The one study on anxiety illustrated that *reduced hippocampal and medial prefrontal gray matter volumes* mediated the relationship between reported childhood maltreatment and trait anxiety in adulthood (Gorka, Hanson, Radtke, & Hariri, 2011, QS = 55%).

Across Affective Disorders.

Psychological Mediators. McLaughlin and colleagues (2010 b, QS = 62.5%) found that *heightened emotional reactivity to daily stressors* mediated the relationship between childhood environments characterized by greater conflict and adversity and adult mood and anxiety disorders. One of the highest quality studies focused on personality as a potential mediating variable. Spinhoven, Elzinga, Van Hemert, de Rooij and Penninx (2016, QS = 70%) reported that *maladaptive personality types* (e.g. high neuroticism in combination with low agreeableness and low conscientiousness) mediated the effects of childhood maltreatment on psychological distress in adulthood.

Social Mediators. The best quality study revealed that *social support* functioned as a mediator between childhood maltreatment and depressive and anxiety disorders in adulthood particularly for male subjects (Sperry & Widom, 2013, QS = 82.5%). Similarly, another study found that *quantity and quality of social support* significantly mediated the association between childhood adversity and psychological distress in adulthood (Sheikh, 2018, QS = 46%)

Biopsychosocial Mediators. Fossion and collaborators (2013, QS = 60%), introduced a mediator model that illustrated how *retraumatizations in adulthood* in those who have suffered childhood trauma could have led to *diminished resilience* which in turn may have sensitized individuals to develop depressive and anxiety disorders in adulthood.

Cross-sectional Mediation Studies

Fifteen of the 30 cross-sectional mediation studies analysed psychological variables (i.e. approx. 50%), nine investigated biopsychosocial mediators (i.e. approx. 30%), four social mediators (i.e. approx. 13%) and two biological mediators (i.e. approx. 7%). Likewise, 15 analysed mediators for MDD (50%), 10 for PTSD (i.e. approx. 33%), four focused trans-diagnostically across affective disorders (i.e. approx. 13%) and one on anxiety (i.e. approx. 4%). Details regarding the quality ratings and general information about these studies are presented in Table A1 and in Table A6 in the Appendix, respectively.

Major Depressive Disorders.

Biological Mediators. Grant, Cannistraci, Hollon, Gore and Shelton (2011, QS = 68.6%) focused on functional neurological changes and yielded that *heightened amygdala responses* seem to mediate the link between early adversity, physical abuse in particular, and MDD in adulthood.

Psychological Mediators. Concerning psychological mediators, most research analysed cognitive mediation. The highest quality study on cognition was performed by Kaysen, Scher, Mastnak and Resick (2005, QS = 65.7%) and pointed out that *maladaptive cognitions* about self and others mediated the link between childhood sexual abuse and both current depressive symptoms and diagnosis of major depressive disorder. This finding was replicated by three studies which extended the mediation from sexual abuse to childhood adversity more generally (Cukor & McGinn, 2006, QS = 54.3%; Lumley & Harkness, 2009, 59.5%; Wells, Vanderlind, Selby, & Beevers, 2014, QS = 45.7%). Similarly, a particular subtype of rumination called *brooding* was also shown to mediate the relationship between childhood emotional abuse and depressive symptoms in adulthood (Raes & Hermans, 2008, QS = 45%). Another study highlighted a significant mediation by *emotion-focused coping* in

the relationship between childhood trauma and later depressive symptoms in a sample of adult First Native Americans (McQuaid, Bombay, McInnis, Matheson, & Anisman, 2015, QS = 48.6%).

With regard to personality, Gamble and co-workers (2006, QS = 52.5%) reported a partial mediation by *neuroticism* in the link between severe childhood sexual abuse and depressive symptom severity in adulthood. Another study yielded that childhood emotional abuse was associated with depressive symptomatology in adulthood in a low-income African-American sample and that *emotional dysregulation* served as a mediator in this relationship (Crow, Cross, Powers, & Bradley, 2014, QS = 45.7%). Moreover, Dunlop and colleagues (2015, QS = 48.6%) discussed that childhood sexual abuse predicted lower relationship quality and sexual satisfaction in adulthood with *anxious arousal* as the most important mediator in this relationship. Similarly, *attachment anxiety* was found to mediate the relationship between childhood maltreatment and maternal depression while maternal depression also served as a mediator in the relationship between childhood maltreatment and parental self-efficacy (Caldwell, Shaver, Li, & Minzenberg, 2011, QS = 52.5). These last results point towards a trans-generational transmission of psychopathological risk, a point that will be elaborated upon in more detail in the discussion.

Social Mediators. Another low quality study reported that *adverse events in adulthood*, defined as real or perceived threat to physical integrity, sexual coercion or emotional abuse, played a mediating role in the depressogenic effects of childhood adversity (LaNoüe, Graeber, de Hernandez, Warner, & Helitzer, 2012, QS = 34.3%).

Biopsychosocial Mediators. A slightly higher profile study replicated these findings and added that, particularly in combination with *low self esteem and early onset of disorder*, stress in adulthood functioned as a mediator in childhood adversity's depressogenic effects (Turner & Butler, 2003, QS = 45%). Another group of researchers revealed that different

types of childhood maltreatment predicted different depressotypic characteristics (O'Mahen, Karl, Moberly, & Fedock, 2015, QS = 57.5%). Childhood emotional abuse was predictive of rumination, whereas childhood emotional neglect was predictive of behavioural avoidance. *Rumination and behavioural avoidance* in turn functioned both as mediators in a path analysis in the link between childhood adversity and later depressive symptomatology.

Posttraumatic Stress Disorder.

Psychological Mediators. With regard to psychological mediators for PTSD, Weiss, Tull, Lavender and Gratz (2013, QS = 45.7%) demonstrated that *emotional dysregulation* mediated the relationship between childhood abuse and probable PTSD in a sample of substance abusers. Contrary to expectations, another group illustrated a partial mediation of *attentional bias toward happy faces* in the relationship between childhood maltreatment and the avoidance and numbing symptoms of PTSD in a sample of traumatized, economically disadvantaged adults (Fani, Bradley-Davino, Ressler, & McClure-Tone, 2011, QS = 51.4%). Finally, a partial mediation by *psychoform dissociation* was found in the relationship between complex childhood trauma and PTSD symptoms in a sample of adult psychiatric inpatients (van Dijke, Ford, Frank, & Van der Hart, 2015, QS = 62.9%).

Social Mediators. Lang et al. (2008, QS = 40%) reported that both *adult sexual assault as well as combat-related retraumatizations* served as mediators between childhood trauma and PTSD in adulthood. Interestingly, they also found that PTSD served as a mediator in the link between childhood trauma and poor physical health functioning in adulthood.

Biopsychosocial Mediators. With regard to biopsychosocial mediators, Lilly, London and Bridgett (2014, QS = 45.7%) found that beyond a direct effect of childhood abuse on PTSD symptoms, *emotion regulation difficulties and intimate partner violence* also mediated this relationship. A well-performed study found that younger *age of first consensual sexual*

intercourse mediated the link between childhood physical abuse and maladaptive posttraumatic cognitions, one of the core symptoms of PTSD (Marshall & Leifker, 2014, QS = 62.2%). The authors suggested that younger age of sexual intercourse initiation was important in the recovery process from physical abuse in childhood. A low quality study argued that three variables mediated the association between childhood adversity and PTSD in adulthood, of which low *social support* as opposed to *low self-esteem and being bullied at school* had the strongest mediational influence (Murphy, Shevlin, Armour, Elklit, & Christoffersen, 2014, QS = 37.5%). As a side-note, being bullied at school arguably can be considered a childhood adversity itself. Another study found that a multiple mediator model, consisting of *low social support, emotional dysregulation and adult interpersonal violence* explained 63% of the variance in childhood-abuse-related PTSD symptoms (Stevens et al., 2013, QS = 45.7%). In a different model, two mediators namely *trauma-related guilt and domestic violence victimization in adulthood* accounted for 39% of the variance in childhood-trauma-related PTSD symptomatology in a female sample (Street, Gibson, & Holohan, 2005, QS = 54.3%). Lastly, *existential well-being and recent nonphysical intimate partner violence* were shown to mediate childhood maltreatment's influence on PTSD symptomatology in another multiple mediator analysis (Zhang et al., 2015, QS = 51.4%).

Anxiety.

Psychological Mediators. The only cross-sectional study on anxiety showed that *emotional dysregulation* mediated the relationship between emotional abuse in childhood and analogue generalized anxiety disorder in a sample of undergraduate students (Soenke, Hahn, Tull, & Gratz, 2010, QS = 45.7%).

Across Affective Disorders.

Psychological Mediators. A low quality study found that *maladaptive coping* mediated the association between childhood trauma and major depression and PTSD in a sample of pregnant South African females (Choi et al., 2015, QS = 42.9%). Similarly, McGinn, Cukor and Sanderson (2005, QS = 57.5%) pointed out that a *dysfunctional cognitive style* mediated the link between rating one's parents as being abusive and neglectful (i.e. childhood adversity measure) and depressive and anxious symptomatology in an adult clinical sample. Another study illustrated that *self-criticism* served as a mediator between parental verbal abuse and internalizing disorders in adulthood (Sachs-Ericsson, Verona, Joiner, & Preacher, 2006, QS = 59.5%). Lastly, Philippe, Laventure, Beaulieu-Pelletier, Lecours and Lekes (2011, QS = 57.1%) showed that *ego resiliency*, which was defined as the ability to adapt one's responses to changing, challenging situations and demands without being stressed or frustrated, mediated the influence of childhood trauma on anxiety, depression, and self-harm behaviours in an outpatient sample.

Social Mediators. In terms of social mediators, one cross-sectional study reported that *adult inter-personal abuse* functioned as a mediator between childhood abuse and depressive and anxious symptomatology in a sample of individuals with extreme obesity (Salwen, Hymowitz, Vivian, & O'Leary, 2014, QS = 45.7%).

Non-cross-sectional Moderation Studies

Of the 13 non-cross-sectional moderation studies, eleven analysed biological moderators (i.e. approx. 85%) and two investigated psychological moderators (i.e. approx. 15%). Of these, eleven analysed moderators for MDD (i.e. approx. 85%), one investigated PTSD (i.e. approx. 7.5 %) and one analysed trans-diagnostically across affective disorders (i.e. approx. 8%). Quality ratings and general information concerning these studies are displayed in Table A1 and Table A7 in the Appendix, respectively.

Major Depressive Disorders.

Biological Moderators. Concerning biological moderators, one of the highest quality studies showed that the *SS genotype of the serotonin transporter gene* (i.e. 5-HTT) moderated childhood maltreatment's effects on persistent but not single-episode depression (Uher et al., 2011, QS = 80%). This was replicated by two more studies (Fisher et al., 2013, QS = 70.3%; Haberstick et al., 2016, QS = 65%). Furthermore, this genotype has also been investigated in combination with other polymorphisms. Gutriérrez et al. (2015, QS = 82.5%) demonstrated that both the *SS genotype of the SERT gene as well as the Met allele of the BDNF gene* significantly moderated the relationship between childhood adversity and the risk of suffering major depression in adulthood. Similarly, it was observed that the *SS genotype of 5-HTTLPR and the GG genotype of the TPH2 gene* significantly interacted in predicting adult depressive symptoms in subjects with a history of childhood abuse (Van der Auwera et al., 2014, QS = 67.5%). Another study investigated the BDNF polymorphism Val66Met alone, and also concluded that it moderated the relationship between childhood adversity and the development of depression and notably the effect appeared to be time-dependent (Webb et al., 2016, QS = 66%). The moderation was found at baseline but not at any of the follow-up measurements. Given the novelty of time-dependent findings in this line of research, the authors call out for replications. Another *polymorphism in the CRHR1 gene* was also identified to moderate childhood adversity's effect on depressive symptoms in young adults (Laucht et al., 2013, QS = 70%). In this vein, Wichers and colleagues (2009, QS = 75.7%), more generally, illustrated that *genetic variation* served as a moderator in potentiating the detrimental effects of adverse experiences in childhood and the development of MDD in adulthood in a well-designed twin-study. Lastly, it has also been reported that *alterations in medial prefrontal cortex-amygdala connectivity* (i.e. the emotion processing circuitry) moderated the effect of early-life-trauma on later MDD (Grant et al. 2014, QS = 68.6%).

Psychological Moderators. The only non-cross-sectional study on psychological moderators revealed that *low self-esteem* functioned as a moderator in the relationship between parental maltreatment and adult chronic depression (Brown, Craig, & Harris, 2008 b, QS = 62.9%).

Biopsychosocial Moderators. Vinkers and colleagues (2015, QS = 74.3%) demonstrated a sex-dependent moderation (i.e. for male subjects) of the *mineralocorticoid receptor CA haplotype* in the relationship between childhood maltreatment and depression susceptibility in adulthood.

Posttraumatic Stress Disorder.

Psychological Moderators. The only non-cross-sectional moderation study on PTSD reported that *romantic attachment avoidance* moderated the effect of childhood abuse on PTSD in a sample of mothers in their third trimester of pregnancy (Busuito, Huth-Bocks, & Puro, 2014, QS = 54.3%).

Across Affective Disorders.

Biological Moderators. One non-cross-sectional study investigated transdiagnostic affective disorders and showed that *genetic variation at the ADCYAP1R1 locus* moderated the link between childhood maltreatment and PTSD but not MDD (Uddin et al., 2013, QS = 70%).

Cross-sectional Moderation Studies

Of the 17 cross-sectional moderation studies, 11 analysed biological moderators (i.e. approx. 65%), five investigated biopsychosocial moderators (i.e. approx. 29%) and one a psychological moderator (i.e. approx. 6%). Likewise, ten analysed moderators for MDD (i.e. approx. 58%), three for PTSD (i.e. approx. 18%), three transdiagnostic affective disorders

(i.e. approx. 18%) and one for anxiety (i.e. approx. 6%). Quality ratings and general information concerning these studies are displayed in Table A1 and Table A8 in the Appendix, respectively.

Major Depressive Disorders.

Biological Moderators. As in the previous sections, a cross-sectional study observed that the *SS-genotype of the serotonin transporter gene* moderated the effect between childhood adversity and chronic depression (Brown et al., 2013, QS = 52.5%). Similarly, Gibb, McGeary, Beevers and Miller (2006, QS = 60%) reported that this genotype moderated the relationship between childhood physical and sexual, but not emotional abuse, and adult psychiatric inpatients' histories of suicide attempts, which in turn was linked to major depressive episodes. Another study investigated whether the *SS genotype of the SERT gene* moderated the effect of early life stress and cognitive endophenotypes of depression but did not find significant moderation (Kruijt, Putman, & Van der Does, QS = 54.1%). In line with the findings discussed above, Aguilera and collaborators (2009, QS = 54.3%) indicated that the *SS genotype of the SERT gene in combination with the BDNF Val66Met polymorphism* moderated the relationship between childhood adversity and depressive symptoms. Other genes have also been investigated. One study concluded that the *rs1360780 polymorphism in the FKBP5 gene* moderated the effects of childhood physical abuse and individual susceptibility to depression in a general population sample (Appel et al., 2011, QS = 50%). Two studies focused on the *CRHR1 gene*. Firstly, specific *polymorphisms in the CRHR1 gene* were found to moderate the relationship between abuse in childhood and depressive symptoms in adulthood in a mainly African American, low socioeconomic status group with high rates of lifetime trauma as well as in an independent second mainly Caucasian, less-deprived sample (Bradley et al., 2008, QS = 54.3%). However, Kranzler et al. (2011, QS = 51.4%) concluded that the *TAT-haplotype of the CRHR1 gene* only had a protective,

moderating role between adverse childhood experiences and risk of depression in African American women but not in African American men nor in European American women or men. Lastly, *a polymorphism in the OXTR gene* was also shown to be a significant moderator in the association between childhood maltreatment and depressive symptomatology in a sample of university students (McQuaid, McInnis, Stead, Matheson, & Anisman, 2013, QS = 57.1%).

Psychological Moderators. The only cross-sectional study on moderators for MDD revealed that *psychological resilience* moderated the effect of childhood adversity on adulthood depression (Poole, Dobson, & Pusch, 2017, QS = 51.4%).

Biopsychosocial Moderators. One study investigated biopsychosocial moderators and observed that *limbic irritability and two copies of the CATT haplotype of the FKBP5 gene* moderated the effect of childhood maltreatment on adult depression in a sample of low-income, high-risk women (Dackis, Rogosch, Oshri, & Cicchetti, 2012, QS = 45.7%).

Posttraumatic Stress Disorder.

Biological Moderators. Two of the three PTSD moderation studies investigated genetic moderators. Again, four single-nucleotide *polymorphisms of the FKBP5 gene* moderated the effect of childhood abuse and PTSD in a sample of non-psychiatric clinic patients (Binder et al., 2008, QS = 45%). In the second study, Xie, Kranzler, Farrer and Gelernter (2012, QS = 62.9%) reported that *one or two copies of the short variant of the serotonin transporter gene* moderated the effects of childhood adversity on risk of suffering PTSD in adulthood in European Americans but not in African Americans.

Biopsychosocial Moderators. Lastly, the same group (Xie et al., 2010, QS = 62.9%) identified that the single-nucleotide *polymorphism rs9470080 of the FKBP5 gene* moderated the association between childhood abuse and PTSD in adult African Americans but not in

adult European Americans. Moreover, they indicated that alcohol dependence interacted with childhood adversity and FKBP5 polymorphisms in predicting increased risk of suffering PTSD in European Americans only.

Anxiety.

Biopsychosocial Moderators. The only cross-sectional moderation study on anxiety found a sex-specific (i.e. only in females) moderation of the *BDNF Val-66Met polymorphism* in the relationship between childhood maltreatment and anxiety in a sample of healthy, young Korean adults (Min et al., 2013, QS = 51.4%).

Across Affective Disorders.

Biopsychosocial Moderators. In line with most studies above, the *SS genotype of the serotonin transporter gene* was shown to moderate the effect of childhood emotional abuse on cognitive vulnerability to depression (Antypa & Van der Does, 2010, QS = 40%). Further, one study reported that *alcohol consumption* moderated the link between childhood exposure to trauma and adult symptoms of depression and PTSD (Ertl, Saile, Neuner, & Catani, 2016, QS = 34%). Lastly, *gender* has also been analysed and found to moderate the relationship between childhood abuse and internalizing as well as substance use disorders in adulthood (Meng & D'Arcy, 2016, QS = 60%).

Summary of the Mediation and Moderation Studies

Table 2 below gives an overview of the reviewed studies.

Table 2						
<i>Overview of the Analysed Studies on Moderators and Mediators</i>						
<u>Analysed variable(s)</u>	<u>Which is proposed as (with number of studies in brackets if multiple)</u>	<u>For the following affective disorder (with number of studies in brackets)</u>	<u>Number of studies</u>	<u>Total sample size</u>	<u>Unweighted average quality score</u>	<u>Notes</u>

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Biological

Genetics

SS genotype 5-HTT gene	Moderator	MDD (9), PTSD (1) and Transdiagnostic (1)	11	20.617	57.6%	Two studies found a moderation in combination with the Met polymorphism of the BDNF gene and one study in combination with the GG genotype of the TPH2 gene -One study did not find a moderating effect (Kruijt et al., 2014, QS = 54.1%)
Polymorphism in the FKBP5 gene	Moderator	MDD (3) and PTSD (2)	5	5.694	57.86%	One study only found moderation in African American subjects but not in European Americans (Xie et al., 2010, QS = 62.9%) and another study found no moderating effect (Bustamante et al, 2018, QS = 72.2%)
CRHR1 gene polymorphism	Moderator	MDD	3	3.877	54.97%	Protective effect - one study only found moderation in African American females
Mineralocorticoid receptor CA haplotype	Moderator	MDD	1	2.304	68.57%	Limited to male sex
GG/GA polymorphism in the OXTR gene	Moderator	MDD	1	288	51.43%	
General genetic variation	Moderator	MDD	1	621	70%	
Genetic variation at ADCYAP1R1	Moderator	PTSD	1	495	65%	Not for MDD
BDNF Val-66Met polymorphism	Moderation	Depressive symptoms	1	310	65.7%	Time-dependent (only at baseline not follow-up)
Total genetic studies:	Transdiagnostic moderation		23	29.266	57.65%	Some genotypes/ polymorphisms seem transdiagnostically relevant others disorder-specific but future research is necessary to verify/falsify these claims

Neuro-cognitive

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Heightened amygdala responses	Mediator	MDD	1	36	57.15%	Proposed moderator for MDD and mediators for MDD and anxiety but too few studies to draw firm conclusions
Reduced connectivity in emotion processing circuitry	Moderator	MDD	1	39	62.86%	
Reduced hippocampal and medial prefrontal gray matter volumes	Mediator	Anxiety	1	906	45%	
Total neurological studies	Transdiagnostic mediation and moderation in major depressive disorders		3	981	55.00%	
Psychological						
Emotional dysregulation	Mediator	MDD (1), PTSD (1), Anxiety (1) and transdiagnostic (1)	4	4.659	45.63%	Authors suggest: mediator for MDD and moderator for PTSD
Rejection sensitivity/attachment anxiety	Mediator (2) and moderator (1)	MDD (2) and PTSD (1)	3	381	47.30%	
Maladaptive cognitive style	Mediator	MDD	10	6.980	50.42%	
Emotion-focused coping	Mediator	MDD	1	359	42.86%	
Low self esteem	Moderator	MDD	1	175	57.14%	
Attentional bias toward happy faces	Mediator	PTSD	1	129	45.95%	Some cognitive factors seem transdiagnostically relevant others disorder-specific but future research is necessary to verify/falsify these claims
Psychoform dissociation	Mediator	PTSD	1	472	57.14%	
Total cognitive studies	Transdiagnostic mediation and moderation		23	13.461	49.59%	
<i>Personality</i>						
Maladaptive personality types	Mediator	MDD (1) and General psychological distress (1)	2	3.052	58.75%	
Personality disorder symptoms	Mediator	MDD	1	181	67.5%	Protective factor
Anxious arousal	Mediator	MDD	1	808	43.24%	
Psychological resilience	Mediator (PTSD) & moderator (MDD)	PTSD & MDD	2	4.124	51.43%	
Borderline psychopathology	Mediator	MDD	1	123	77.5%	

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Total personality studies	Transdiagnostic mediation		7	8.288	55.23%	Personality may be a transdiagnostic mediator in the aetiology of MDD and PTSD for the better (i.e. resilience) or worse (i.e. increasing chances to suffer affective disorders after childhood adversity)
Social						
Intimate partner violence	Mediator	MDD (1) and PTSD (1)	2	274	45.72%	Seems to interact with emotional dysregulation
Retraumatization in adulthood	Mediator	MDD (1), PTSD (1), depressive and anxiety disorder (1)	3	968	41.22%	
Chronic interpersonal stress in adulthood	Mediator	MDD	3	3.659	43.10%	Particularly in combination with low self esteem
Low social support	Mediator	Depressive and anxious disorders	1	696	82.5%	
Friendship	Mediator	Psychological Distress	1	4.530	45.7	Protective effect
Total social studies	Transdiagnostic mediation		10	10.127	53.14%	
Biopsychosocial						
Retraumatizations and diminished resilience	Mediators	Depressive and anxious disorders	1	65	60%	Further adversity in adulthood and a lack of social resources appear to be transdiagnostic mediators
Living alone, lack of education, alcohol consumption, lack of social support and negative affectivity	Partial mediators	MDD	1	16.877	50%	
Alcohol abuse	Moderator	Transdiagnostic	1	669	34.3%	
Emotional dysregulation and intimate partner violence	Mediators	PTSD	1	99	40%	
Negative events in adulthood in combination with insecure attachment style and negative cognitive style	Mediators	MDD	1	885	40.54%	
Rumination and behavioural avoidance	Mediators	MDD	1	140	52.5%	
Age of first	Mediator	PTSD	1	128	56.76%	

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consensual sexual intercourse						
Low social support, low self-esteem and being bullied at school	Mediators	PTSD	1	2.980	37.5%	
Social support, emotional dysregulation and adult interpersonal violence	Mediators	PTSD	1	139	40%	
Trauma-related guilt and domestic violence victimization in adulthood	Mediators	PTSD	1	63	48.57%	
Existential well-being and recent nonphysical intimate partner violence	Mediators	PTSD	1	192	45.71%	
Gender	Moderator	Internalizing disorders	1	23.395	60%	
Total biopsychosocial studies	Mediation across depressive and anxious disorders and various moderations and mediations for MDD and PTSD in isolation		9	45.632	47.95%	Some biopsychosocial studies underline findings above, others introduce new moderators and mediators. All remind us that a multiple moderator/mediator model is required for this complex relationship

Associational Studies - Potential Moderators and Mediators

The non-cross-sectional and cross-sectional associational studies are only briefly described in the Tables 3-6 below because of comparably low quality as discussed earlier (see Tables A2-A4 in the Appendix). Of the total 137 associational studies, 62 analysed biological associations (i.e. approx. 45%), 38 investigated biopsychosocial associations (i.e. approx. 28%), 21 psychological associations (i.e. approx. 15%) and 16 focused on social associations (i.e. approx. 12%). Of all studies, 79 analysed associations for MDD (i.e. approx. 58%), 35 for PTSD (i.e. approx. 26%), 20 analysed transdiagnostically across affective disorders (i.e. approx. 14%) and three focused on associations for anxiety (i.e. approx. 2%). Quality ratings

and general information concerning these studies are displayed in Table A1, A9 (i.e. non-cross-sectional studies) and A10 (cross-sectional studies) in the Appendix, respectively.

Table 3

Associational Studies on Major Depressive Disorders

<u>Analysed variable(s)</u>	<u>Number of studies</u>	<u>Total sample size</u>	<u>Unweighted average quality score</u>	<u>Notes</u>	<u>References (first author only) including Quality Score (in %) when multiple</u>
Biological					
<i>Genetics</i>					
S-variant of the 5-HTTLPR gene and the met-variant of the BDNF gene	2	472	43.6%		(Carver et al., 2011, 37.1%) (Harkness et al., 2015, 50%)
TAT-haplotype of the CTRH1 gene	2	3.791	61.25%	Protective effect with mixed findings - may be limited to females	(Grabe et al., 2010, 57.5%) (Polanczyk et al., 2009, 65%)
The A allele of the MR gene	1	298	51.4%		(Vrijssen et al., 2015)
T-allele of the MTHFR gene	1	124	57.5%		(Lok et al., 2013)
APOE-omega-4 genotype	1	137	34.3%		(Park et al., 2015)
GR 22/23EK and 9beta	1	906	36.1%	Elderly sample	(Bet et al., 2009)
MAOA-L variant	1	1.668	37.1%	Female sample	(Melas et al., 2013)
Polygenetic risk scores	1	1.985	62.9%		(Peyrot et al., 2014)
Higher SLC6A4 promoter methylation status	1	102	40%		(Kang et al., 2013)
Increased telomerase activity	1	40	51.4%		(Chen et al., 2014)
Immunogenetic risk - IL-6 (rs1818879) and CRP (rs3093077)	1	593	60		Cohen-Woods et al., in press
<i>Neuro-cognitive</i>					
Decreased gray matter volume in the hippocampus	4	354	52.8%	One study did not find a significant association	(Chaney et al., 2014, 54.1%) (Lenze et al., 2008, 54.1%) (Opel et al., 2014, 54.3%) (Vythilingam et al., 2002, 48.6%)
Reduced volume of brain regions related to emotional processing	3	203	48.6%		(Carballedo et al., 2012, 48.6%) (Jaworska et al.,

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more generally					2014, 48.6%) (Zhao et al., 2015, 48.6%)
Decreased functional connectivity and increased fractional anisotropy in brain regions related to emotional processing	5	293	48.6%		(Cisler et al., 2013, 42.9%) (Frodl et al., 2012, 42.9%) (Ugwu et al., 2015, 54.3%) (Wang et al., 2014, 48.6%) (Peng et al., 2013, 54.1%)
Decreased 5-HTT BPP levels	1	66	45.7%		(Miller et al., 2009)
Increased platelet BDNF levels	1	155	57.1%		(Jeon et al., 2012)
Increased cerebrospinal fluid NPY-LI levels	1	81	22.9%		(Soleimani et al., 2015)
<i>Physical comorbidity</i>					
Cardiovascular disease	1	5.308	42.5%		(Batten et al., 2004)
Chronic pain conditions	1	1.475	52.5%		(Gonzalez et al., 2012)
Metabolic syndrome	1	373	48.6%		(McIntyre et al., 2012)
Migraine	1	949	28.6%		(Tietjen et al., 2007)
<i>Immunology</i>					
Increased C-reactive protein levels	1	972	67.5%		(Danese et al., 2008)
Increased pro-inflammatory profile	1	65	57.1%		(Lu et al., 2013)
more generally					
Enhanced inflammatory responsiveness	1	28	48.6%		(Pace et al., 2006)
Increased fibrinogen levels	1	22	51.4%		(Zeugmann et al., 2013)
<i>Endocrinology</i>					
Decreased MR reactivity	1	30	54.3%		(Baes et al., 2014)
Increased HPA axis reactivity	4	250	51.4%	In one study the association was limited to low emotional neglect cases and one study found the opposite (i.e. blunted cortisol responses)	(Heim et al., 2008, 54.3%) (Peng et al., 2014, 54.1%) (Suzuki et al., 2014, 48.6%) (Watson et al., 2007, 48.6%)
Thyroid auto-antibodies and a concomitant disturbance in the HPT axis	2	339	44.3%		(Plaza et al., 2010, 51.4%) (Plaza et al., 2012, 37.1%)
Psychological					
<i>Cognition</i>					
Mood-congruent biases in emotion processing and memory	3	627	42.9%		(Günther et al., 2015, 48.6%) (Johnson et al., 2011, 28.6%) (Vrijnsen et al., 2014, 51.4%)
Low resilience	1	203	40%		(Soffer et al., 2008)

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<i>Personality</i>				
Trait impulsivity and aggression	1	136	31.4%	(Brodsky et al., 2001)
Low self-directedness	1	69	45.7%	(Perna et al., 2014)
Depressive, irritable and anxious temperament	1	100	45.7%	(Gündogar et al., 2014)
Avoidant personality disorder	1	279	54.3%	(Klein et al., 2015)
Social				
Adult negative life events/ revictimization	4	26.533	47.4%	(Korkeila et al., 2010, 37.5%) (Ouellet-Morin et al., 2015, 52.5%) (Patten, 2013, 42.5%) Power et al., 2013, 57.1%) (Roh et al., 2015)
Low social support	1	233	35.1%	(Roh et al., 2015)
Biopsychosocial				
SS- and SL-genotype of the 5-HTTLPR gene in combination with adult traumatic experiences	1	1.974	50%	(Grabe et al., 2012)
Attentional bias for angry faces and the 5-HTTLPR short allele	1	86	40%	(Johnson et al., 2010)
5-HTTLPR long allele interacted with poverty, and excessive sharing of parental problems	1	942	56.8%	(Ritchie et al., 2009)
SL and LL genotype of the SERT gene, recent life stress and low resilience	1	120	34.3%	(Sharpley et al., 2013)
T allele of rs1360780 and structural differences in brain areas involved in emotional perception	1	83	48.6%	(Tozzi et al., 2016)
3 or 4 risk alleles (BDNF and COMT combined) and decreased positivity bias for happy faces	1	325	51.4%	(Vrijssen et al., 2014 b)
Lower BDNF levels, psychological morbidity and decreased memory performance	1	49	62.9%	(Grassi-Oliveira et al., 2008)
Decreases in right Rostral Anterior Cingulate volume and cortisol levels	1	38	56.8%	(Treadway et al., 2009)
Increased inflammatory profile and clustering of metabolic risk markers	1	972	67.5%	(Danese et al., 2009)
Alcoholism	3	13.319	39.2%	One study found predominant effect for males (Anda et al., 2002, 40%) (Colman et al., 2013, 28.9%) (Roy, 1999,

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Alexithymia and somatisation	1	150	48.6%		48.6%) (Gülec et al., 2013)
Dysfunctional attitudes and self-criticism	1	808	51.4%		(Klein et al., 2009)
Sleep disturbances	1	173	31.4%		(Swanson et al., 2014)
Disturbed mother-child relationship and neurotic symptoms in childhood	1	1.000	57.5%	Only found in female subjects	(Veijola et al., 1998)
Race/ethnicity and gender	1	13.328	27%		(Roxburgh et al., 2014)
Socio-demographic strata	1	2.265	40%		(Schulz et al., 2014)
Inter-personal violence and poor general health	1	1.521	37.5%		(Barrios et al., 2015)
Revictimization and low self-esteem	1	253	28.6%		(Fox et al., 1994,)
Deliberate self-harm and revictimization	1	125	48%		(Gladstone et al., 2004)
Insufficient social support, poor subjective health and financial difficulties	1	835	35%		(Honkalampi et al., 2005)
Parental divorce and being raised in a relative's house due to financial strain	1	11.526	50%	Only found in female subject	(Kim et al., 2013)

Table 4

Associational Studies on Posttraumatic Stress Disorder

<u>Analysed variable(s)</u>	<u>Number of studies</u>	<u>Total sample size</u>	<u>Unweighted average quality score</u>	<u>Notes</u>	<u>References including Quality Score (QS) when multiple</u>
Biological					
<i>Genetics</i>					
The A allele (rs2400707) of the ADRB2 gene	1	2.893	48.6%	Protective effect	(Liberzon et al., 2014)
Shorter age-adjusted Leukocyte Telomere Length	1	88	51.4%		(O'Donovan et al., 2011)
SS genotype of 5-HTTLPR	1	682	37.1%	Contrary to other findings, protective effect (in African American only)	(Walsh et al., 2014)
<i>Neuro-cognitive</i>					
Smaller global and subfield hippocampal volumes	2	112	50.9%	One study did not find volumetric differences	(Chalavi et al., 2015, QS = 51.4%) (Pederson et al., 2004, 50%)
Increased dorsal anterior cingulate cortex gray matter thickness	1	61	59.5%		(Demers et al., 2015)

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Various structural and functional differences in brain areas associated with emotion processing	1	33	48.6%		(Fonzo et al., 2013)
Decreases in right amygdala volumes	1	24	54.3%		(Veer et al., 2015)
Reduced functional connectivity within default network	1	32	42.9%		(Bluhm et al., 2009)
<i>Physical comorbidity</i>					
Weight extremes (i.e. under- and overweight)	1	2.981	30%		(Roehndt et al., 2012)
Increased cardiovascular, immune, musculoskeletal, neurologic, and reproductive symptoms	1	86	17.5%	Included female subjects only	(Farley et al., 2001)
<i>Endocrinology</i>					
Lower cortisol levels	3	281	53.3%	One study also found an absence of the usual decline in cortisol after awakening	(Santa Ana et al., 2006, 54.3%) (Van Vorhees et al., 2014, 51.4%) (Yehuda et al., 2001, 54.3%)
Psychological					
Negative body image and negative body-related emotions	2	230	40%		(Dyer et al., 2012, 40%) (Dyer et al., 2015, 40%)
Impairments in theory of mind	1	51	48.6%		(Nazarov et al., 2014)
Impairments in identifying emotional prosody	1	50	48.6%		(Nazarov et al., 2015)
Alterations in empathic functioning	1	49	51.4%		(Parlar et al., 2014)
Increased attentional bias towards body related stimuli	1	91	48.6%	Limited to subjects with a comorbid borderline personality disorder	(Witthöft et al., 2015)
Social					
Retraumatization in adulthood	3	1.151	41,3%		(Breslau et al., 2013, 52.5%) (Daalder et al., 2013, 28.6%) (Goldberg et al., 2005, 42.9%)
Combat exposure	3	9.714	44.4%		(LeardMann et al., 2010, 67.5%) (Van Vorhees et al., 2012, 37.1%) (Zaidi et al., 1994, 28.6%)
Biopsychosocial					
Severe substance misuse/dependence	4	1.010	46.9%	Also associated with earlier age of	(Farrugia et al., 2011, 60%)

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				first intoxication	(Khoury et al., 2010, 28.6%) (Lu et al., 2008, 51.4%) (Triffleman et al., 1995, 47.5%) (Cloitre et al., 2005) (Grassi-Oliveira et al., 2008 b) (Dietrich, 2007)
Emotion dysregulation and interpersonal problems	1	164	34.3%		
Emotional distress and low income	1	115	31.4%		
Revictimization and female sex	1	207	29.7%		
Intimate partner violence, smoking and immune status	1	138	37.1%		(Wood et al., 2005)
Lower rank, leaving service, having had a serious accident and holding a combat role	1	8.261	47.5%		(Jones et al., 2013)

Table 5

Associational Studies on Anxiety

<u>Analysed variable(s)</u>	<u>Number of studies</u>	<u>Total sample size</u>	<u>Unweighted average quality score</u>	<u>References including Quality Score (QS)</u>
Biological				
<i>Genetics</i>				
SS 5-HTTLPR genotype	1	247	34.3%	(Stein et al., 2008)
<i>Neuro-cognitive</i>				
Alterations in configuration of neurometabolites in the rostral prefrontal cortex and premotor cortex	1	32	54.3%	(Raparia et al., 2016)
<i>Physical comorbidity</i>				
Sexual dysfunctions	1	113	51.4%	(Tekin et al., 2015)
Psychological				
<i>Personality</i>				
Paranoid, histrionic and self-defeating personality styles	1	50	60%	(Prigerson et al., 1996)

Table 6)

Associational Studies Across Affective Disorders

<u>Analysed variable(s)</u>	<u>Number of studies</u>	<u>Total sample size</u>	<u>Unweighted average quality score</u>	<u>Notes</u>	<u>References including Quality Score (QS) when multiple</u>
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Biological						
<i>Genetics</i>						
FKBP5 tag-SNP rs9296158	1	682	47.5%	Only for MDD not PTSD	(Kohrt et al., 2015)	
Transcriptional control of stress-responsive pathways	1	60	40%		Schwaiger et al. 2016	
<i>Endocrinology</i>						
Dexamethasone non-suppression and higher salivary cortisol levels	1	126	54.3%	Analysed across Axis 1 disorders	(Faravelli et al., 2010)	
<i>Physical comorbidity</i>						
Decreased sexual desire, arousal and orgasm	1	81	31.4%		(Bakim et al., 2011)	
Psychological						
<i>Cognition</i>						
Dissociative symptoms	2	501	55.7%	Associated with MDD, borderline personality disorder and PTSD	(Mueller-Pfeiffer et al., 2013, 57.1%) (Wingenfeld et al., 2014, 54.3%)	
Decreased positive affect	1	173	47.5%	MDD, PTSD and general psychopathology	(Etter et al., 2013)	
<i>Personality</i>						
High neuroticism, low extraversion	1	2.402	62.5%	MDD, PTSD and anxiety	(Spinoven et al., 2014)	
Social						
Combat-exposure	3		39.8%	Mood and anxiety disorders	(Cabrera et al., 2007, 34.3%) (Owens et al., 2009, 42.5%) (Sareen et al., 2013, 42.5%)	
Current distress and current conflicts in relationships	3	12.034	45.7%	MDD, PTSD and anxiety	(Ford et al., 2012, 45%) (Lang et al., 2004, 37.1%) (Van Veen et al., 2013, 55%)	
Biopsychosocial						
Substance misuse/dependence	5	1.166	37.1%	Across affective disorders - also associated with suicidal ideation, low self-esteem, sex work, medical problems, and poor quality of life in these studies	(Banducci et al. 2014, 40%) (Brockie et al., 2015, 31.4%) (Ekinici et al., 2015, 37.1%) (Sacco et al., 2007, 51.4%) (Wu et al., 2010, 40%)	

Discussion

In summary, the relationship between childhood adversity and affective disorders is immensely complex, multifactorial and, most likely, involving a number of dynamically interacting biopsychosocial moderating and mediating variables. While some moderating and mediating variables have been shown to be transdiagnostically relevant (see a proposed model in Figure 6 below), there also seem to be some disorder-specific moderators and mediators (e.g. genetic variation at *ADCYAP1R1* and psychoform dissociation for PTSD exclusively). However, some of these moderators and mediators might only appear disorder-specific due to a lack of transdiagnostic research. Future research is necessary to disentangle which of these truly are only relevant to one affective disorder.

Figure 6. Transdiagnostic Model of Biological Moderation and Psychosocial Mediation.

Moreover, it is important to stress that the current systematic review leaves the reader with many uncertainties and interpretations. Due to the substantial timeframe between exposure and outcome in the phenomena at hand, it is extremely difficult to pinpoint the exact influence of a certain variable let alone establish causality. The reviewed studies do not speak to the issue of causality and its direction. On this note, it has long been thought and taught that the only way to establish (the direction of) causality would be an RCT. However, this is currently under debate and a more diverse plethora of research methodologies have been

advocated (Carey, Tai, Mansell, Huddy, Griffiths, & Marken, 2017). Furthermore, it remains questionable as to whether causal factors should be the best focus of interventions. For example, blood injury phobia is a highly heritable phenomenon and therefore presumably has a strong genetic 'cause'. Yet, it is highly treatable using applied tension (Öst, Fellenius, & Sterner, 1991). This is considered to be a psychological intervention which changes reversible physiological and psychological processes to achieve homeostasis.

Another uncertainty concerns the third variable problem. For instance, it could be argued that evocative gene-environment interactions play a central role in the development of childhood maltreatment in the first place and that these very same genes are also involved in the development of the psychopathology in adulthood rather than childhood adversity itself (Jaffee, & Price, 2007). Moreover, the affective disorder itself may function as a moderator or mediator between childhood abuse and one or more of the moderator or mediators discussed. Kulkarni, Pole and Timko (2013), for instance, found that PTSD severity partially mediated the link between childhood victimization and negative mood regulation in adulthood. However, confidence in the proposed claims is given by the fact that independent groups came to similar conclusions while utilizing various research designs. Particularly the high quality prospective cohort studies enabled researchers to tease apart to some extent which variables changed first.

Next to these conceptual difficulties inherent in the field of research, the present review comes with its own intrinsic limitations. Only four affective disorders have been studied. It would have been interesting to include other affective disorders such as the bipolar disorder spectrum (Etain et al., 2013) or other disorders beyond the affective disorder spectrum such as psychotic disorders (Bendall, Jackson, Hulbert, & McGorry, 2007) or borderline personality disorder (Herman, Perry, & Van der Kolk, 1989). We limited this review to affective disorders for reasons of feasibility as well as conciseness. In addition to

this limitation, moderators and mediators were classified as biological, psychological, social or mixed rather arbitrarily. For instance, substance misuse and dependence was classified as mixed moderator or mediator as the authors were not comfortable classifying it neatly into biological, psychological or social. Related to this issue, the current review did not integrate the biopsychosocial findings in an overarching theory such as the biopsychosocial model based on negative feedback and control proposed by Carey, Mansell, and Tai (2014). As such, authors would like to remind readers to interpret results cautiously and encourage future research to develop our ideas further. It remains difficult to specify the dynamics of an effect of a proposed moderator or mediator in this line of research due to the mentioned large timescale between exposure and outcome and the associated complexities in terms of number of variables involved, potential interactions as well as third variables. Nevertheless, the present evidence base suggests that childhood adversity constitutes an important risk factor in the aetiology of affective disorders in adulthood and that this link seems to be moderated and mediated biopsychosocially by multiple variables.

With regard to clinical implication, it is generally understood that mediators are more amenable to change than moderators (Baron & Kenny, 1986). For instance, one's cognitive style is an easier target for clinical interventions than one's genetic makeup. This review illustrated that maladaptive cognitive styles and predisposing personality dimensions appear to be important transdiagnostic mediators. Particularly the former, but also to some extent the latter, can be targeted in evidence-based psychological intervention such as cognitive-behavioural-therapy (Butler, Chapman, Forman, & Beck, 2006; Gould, Otto, Pollack, & Yap, 1997). When childhood adversities are suffered outside the family context and the family constitutes a stable environment, family therapy may also be a promising alternative (Rutter, 1999). The transdiagnostic mediational effects of interpersonal problems may best be addressed by interpersonal therapy (Cuijpers et al., 2011). Furthermore, severe emotional dysregulation has been shown to respond to dialectic behavioural therapy (Kliem, Kröger, &

Kosfelder, 2010). Retraumatizations in adulthood can be aimed at in trauma-focused CBT or Eye Movement Desensitization and Reprocessing (EMDR), which have been shown to have comparable efficacy (Seidler & Wagner, 2006). Also combat-related retraumatization can be focused upon in individual or group trauma-focused therapy (Schnurr et al., 2003). A lack of empirical evidence precludes recommendations with regards to trauma-focused therapies for children and adolescents (Cohen, Mannarino, Berliner, & Deblinger, 2000). Because childhood adversity is associated with severe clinical presentations (e.g. early onset, severe functional impairment, suicidal ideation etc.) as discussed earlier, high-intensity and long-term psychological interventions seem to be most appropriate. In terms of pharmacological treatment, childhood trauma-related depression has been associated with poor response to antidepressants (Nanni et al., 2012; Nemeroff et al., 2003). Hence, the authors recommend psychological therapies over drug treatment. Similarly, influential treatment guidelines for anxiety disorders recommend psychological interventions over pharmacological ones (Foa, Keane, Friedman, & Cohen, 2008; Forbes et al., 2007; Katzman et al., 2014; see also Barlow et al., 2010 for transdiagnostic recommendations). Nevertheless, childhood adversity is linked to increased utilization of psychotropic medications across disorders (Anda et al., 2007). In terms of timing, it appears that interventions should be implemented as early as possible to avoid the increased sensitization to stressors with increasing numbers of previous episodes commonly referred to as the 'kindling effect' (Kendler, Thornton & Gardner, 2000; Post & Weiss, 1998).

From a political perspective, governments are well advised to set up legal and regulatory means to prevent childhood adversities as much as possible. This is a moral advice as much as an economic one. As indicated in the introduction, affective disorders are among the main contributors to the global disease burden with rising tendencies prevalence rates (McCrone et al., 2008). Childhood maltreatment-related affective disorders in particular are associated with high medical and psychiatric costs as well as high functional impairment and

associated lost economic output (Anda et al., 2007; Cuijpers et al., 2011; Simon, Ormel, VonKorff, & Barlow, 1995). In the light of limited national health care budgets, cost-effective solutions to national mental health threats like these have to be found.

Next to prevention, early interventions for affected individuals should also be prioritized. While the evidence base remains slim, initial findings show that programs can be successful (Reynolds, Mathieson, & Topitzes, 2009). A study conducted after Reynold et al.'s review reported that after a video feedback intervention for mothers, dyads of severely mentally ill mothers and their offspring were significantly more sensitive, cooperative and responsive than control dyads in which mothers did not receive training (Kenny, Conroy, Pariante, Seneviratne, & Pawlby, 2013). Interventions studies like these show that families at high risk may be helped by teaching parents to meet the needs of their offspring more appropriately.

The numerous transdiagnostic as well as disorder-specific moderations by genetic polymorphisms give rise to an exciting new field of personalized psychiatry. Hopefully, psychiatry will be able to keep up with the rest of medicine in the relatively near future, for instance by developing prediction models which calculate with high accuracy which individuals may respond to a certain psychotropic or psychological therapy based on objective biomarkers (e.g. genetic profile). However, it needs to be pointed out that the single gene polymorphism-childhood adversity interactions discussed in this review are usually associated with relatively small effect sizes. This is in line with the notion that the aetiology of complex mental disorders such as MDD most probably involves hundreds if not thousands of genes (Flint & Kendler, 2014). Moreover, some genes might present plasticity genes rather than risk genes per se (Belsky et al., 2009).

As indicated before, it has been argued that childhood adversity-related pathology presents a clinically distinct subpopulation. Childhood adversity and the numerous mentioned moderators and mediators may be utilized in stratifying the heterogeneous clusters which

currently have to be lumped together despite the numerous drawbacks (van Praag, 2000).

Although not conclusive yet, it seems that several bodily systems involved in emotion processing (i.e. central nervous circuitry), the stress response (i.e HPA axis) and the immune response (i.e. immune system) suffer long-term dysregulation as a consequence of childhood adversity. While this adds a lot of complexity, it also offers many potential targets for diagnostics, preventions, treatments and outcome measures. Ultimately, affective disorders are complex, multifactorial, biopsychosocial phenomena that require complex, multifactorial, biopsychosocial treatments.

Future studies need to address the methodological weaknesses present in many of the analysed studies. Ideally childhood adversity should be measured prospectively and comprehensively with a combination of expert observations and validated self-report measures. The affective disorders should be measured with validated diagnostic tools administered by trained professionals. Moreover, studies need to have sufficient power to detect at least a medium-sized effect and also report on their power calculations. Lastly, the moderating and mediating variables need to be properly operationalized with valid and reliable measures. In obeying these methodological standards chances are maximized that clinically relevant moderators and mediators will be found which hopefully can be utilized in prediction modelling, prevention, intervention and evaluation.

As briefly mentioned before, some scholars have proposed to take a closer look at transgenerational transmissions in order to better understand the influence of childhood adversity on affective disturbances in adulthood. Childhood adversity afterall might not be the starting point, but only one element in a long history of transgenerational adversity. Pawlby, Hay, Sharp, Waters and Pariante (2012), illustrated that maternal, antenatal depression increases the risk of childhood maltreatment by almost four times and when children were exposed to both, antenatal depression as well as childhood maltreatment their risk of

developing psychopathology in later life was almost 12-fold compared to unexposed children (see also Betts, Williams, Najman, & Alati, 2015; Stein et al., 2014).

Given the array of biopsychosocial mediators and moderators identified, it is important to consider how these factors can be understood within an overarching theory. We tend to agree with Carey, Mansell, and Tai (2014) that the perceptual control theory (PCT) which takes into account biochemical, psychological and social processes and has negative feedback and control at its heart is a possible candidate. Negative feedback is purported to establish control at increasing levels of perceptual complexity and has been implicated in the regulation of emotions. In this context, a neural organization of control systems occur at all levels of complexity. Although the evidence for how negative feedback and control processes are integrated to understand how a mature functioning system works is lacking it is time we became more divergent in the models we use to assess complex distal relationships.

Another largely neglected but clinically important area concerns resilience. Masten and colleagues (1990, 1999) have repeatedly shown that children with good intellectual functioning (e.g. high intelligence quotient), high self-efficacy and one or more positive relationships with adults show high rates of recovery even from chronic adversity. Similarly, Collishaw et al., (2007) found that perceived parental care and in general harmonious relationships in adolescence and adulthood as well as personality style (i.e. particularly low neuroticism) may build resilience against the potentially detrimental effects of childhood trauma. These findings are clinically relevant as some scholars have argued that resilience might be amenable to change and should therefore be focused upon in interventions (Wingo et al., 2010). Indeed some programs have verified this claim in non-clinical samples (Arnetz, Nevedal, Lumley, Backman, & Lublin, 2009; Reivich, Seligman, & McBride, 2011). It seems plausible that extending resilience on top of minimizing risk factors seems more promising than either alone in both the prevention of and intervention for childhood adversity-related psychopathology.

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The long-term consequences of adversity in childhood on affective regulation in adulthood are undeniable but not inevitable. By means of methodologically sound research and evidence-based interventions on various levels (i.e. biopsychosocial) the detrimental effect of early maltreatment may be counteracted and hopefully enable those who have been slaves of their pasts to master their future.

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Appendix

List A1. Quality Assessment Items.

- (1) Study design (i.e. cross-sectional design → score 1; matched-controls design, retrospective cohort, case-control design, RCT or single-blind, non-randomized, placebo-controlled, repeated-measures design → score 3; Prospective cohort → score 5)
- (2) Information about the sampling procedure - if applicable (i.e. insufficient → score 0; minimally sufficient → score 1; sufficient → score 2)
- (3) Inclusion and exclusion criteria - judged on the appropriateness for the aims of this systematic review (i.e. insufficient → score 0; minimally sufficient → score 1; sufficient → score 2)
- (4) Response rate - if applicable (i.e. below 50% → score 0; 50-70% → score 1 - 70-80% → score 2; >80% → score 3)
- (5) Attrition documented - if applicable (i.e. not or insufficiently documented → score 0; minimally documented → score 1; sufficiently documented → score 2)
- (6) Operationalization of childhood adversity (i.e. unvalidated measure(s) → score 0; one validated measure → score 3; several validated measures → score 4; clinical/public records → score 5)
- (7) Operationalization of emotional disorder(s) (i.e. unvalidated measure(s) → score 0; one validated symptom questionnaire → score 1; multiple, validated symptom questionnaires → score 2; diagnostic interview by an untrained interviewer / patient version /not specified by whom → score 3; diagnostic interview by a trained specialist → score 4; several, validated

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measures including a diagnostic interview by a trained specialist or in- or outpatient status → score 5)

(8) Operationalization of moderator(s)/mediator(s) (i.e. unvalidated operationalization - score 0; minimally valid operationalization → score 1; valid operationalization → score 2)

(9) Formal moderation/mediation analysis (i.e. no → score 0; yes but not hypothesis driven / no prior model → score 3; yes and hypothesis driven / with prior model → score 5)

(10) Appropriate statistical analysis (i.e. inappropriate → score 0; appropriate but insufficient information (e.g. whether assumptions were met) → score 1; appropriate → score 2)

(11) Effect size (i.e. no effect size reported → score 0; effect size reported without CI → score 1; effect size reported with CI → score 2)

(12) Power (i.e. power calculation not mentioned/insufficient power to detect a small effect size → score 0; sufficient power to detect a small-moderate effect size → score 3; sufficient power to detect a large effect size → score 5)

Table A1							
<i>Quality Scores For All Included Studies</i>							
<u>Quality items</u>	<u>Aguilera et al. 2009</u>	<u>Anda et al. 2002</u>	<u>Antypa et al. 2010</u>	<u>Appel et al. 2010</u>	<u>Baes et al. 2014</u>	<u>Bakim et al. 2011</u>	<u>Banducci et al. 2014</u>
Study design (out of 5)	1	3	1	1	3	1	1
Sampling procedure appropriately reported (if applicable - out of 2)	1	2	0	2	2	1	1
Appropriate inclusion and exclusion criteria (if applicable - out of 2)	1	1	0	1	2	1	1
Response rate (if applicable - out of 3)	NA	2	NA	1	NA	NA	NA
Attrition documented (if applicable - out of 2)	NA	1	NA	2	NA	NA	NA
ACE(s) operationalization (out of 5)	3	3	3	3	3	3	3
Emotional disorder(s) (out of 5) operationalization	1	1	1	1	5	3	5
Formal moderation/mediation analysis (out of 5)	5	0	5	5	0	0	0
Moderators and mediators operationalization (out of 2)	2	1	2	2	2	1	1
Appropriateness of statistical analysis used (out of 2)	1	1	1	1	1	1	1
Power (out of 5)	3	0	0	0	0	0	0
Effect size(s) reported (out of 2)	1	1	1	1	1	0	1
Obtained score	19	16	14	20	19	11	14
Potential score	35	40	35	40	35	35	35
Quality Score ((obtained score/potential score) x 100)	54,3	40,0	40,0	50,0	54,3	31,4	40,0

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<u>Barrios et al. 2015</u>	<u>Batten et al. 2004</u>	<u>Bet et al. 2009</u>	<u>Binder et al. 2008</u>	<u>Bluhm et al. 2009</u>	<u>Bradley et al. 2008</u>	<u>Breslau et al. 2013</u>	<u>Brockie et al. 2015</u>	<u>Brodsky et al. 2001</u>	<u>Brown et al. 2008</u>
1	1	5	1	3	1	5	1	1	3
1	2	NA	2	0	2	1	2	0	2
1	1	NA	0	2	1	NA	1	1	1
3	3	1	1	NA	NR	3	NA	NA	NA
2	1	2	1	NA	NR	1	NA	NA	NA
3	3	0	3	3	3	5	3	3	3
1	3	1	1	3	3	3	1	3	3
0	0	0	5	0	5	0	0	0	5
1	1	2	2	2	2	1	1	1	1
1	1	1	1	1	1	1	1	1	1
0	0	0	0	0	0	0	0	0	0
1	1	1	1	1	1	1	1	1	1
15	17	13	18	15	19	21	11	11	20
40	40	36	40	35	35	40	35	35	35
37,5	42,5	36,1	45,0	42,9	54,3	52,5	31,4	31,4	57,1

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<u>Brown et al. 2008 b</u>	<u>Brown et al. 2013</u>	<u>Bustamante et al. 2018</u>	<u>Busuito et al. 2014</u>	<u>Cabrera et al. 2007</u>	<u>Caldwell et al. 2011</u>	<u>Carballedo et al. 2012</u>	<u>Carver et al. 2011</u>	<u>Chalavi et al. 2015</u>	<u>Chaney et al. 2014</u>
5	1	5	5	1	1	3	1	3	3
2	2	2	1	1	2	2	0	2	1
1	1	1	1	1	2	2	1	2	2
NA	1	NA	NA	NA	3	NA	NA	NA	NA
NA	1	NA	NA	NA	1	NA	NA	NA	NA
3	3	4	3	3	3	3	3	3	3
3	3	1	1	1	1	3	4	4	5
5	5	5	5	0	5	0	0	0	0
1	2	2	1	2	1	2	2	2	2
1	1	2	1	2	1	1	1	1	1
0	0	3	0	0	0	0	0	0	0
1	1	1	1	1	1	1	1	1	1
22	21	26	19	12	21	17	13	18	18
35	40	36	35	35	40	35	35	35	35
62,9	52,5	72,2	54,3	34,3	52,5	48,6	37,1	51,4	51,4

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<u>Chen et al. 2014</u>	<u>Choi et al. 2015</u>	<u>Cisler et al. 2013</u>	<u>Cloitre et al. 2005</u>	<u>Cohen-Woods et al., in press</u>	<u>Colman et al. 2013</u>	<u>Crow et al. 2014</u>	<u>Cukor et al. 2006</u>	<u>Daalder et al. 2013</u>	<u>Dackis et al. 2012</u>
3	1	1	1	5	1	1	1	1	1
1	1	2	0	1	2	2	1	1	1
2	1	2	1	2	NA	1	1	1	1
NA	NA	NA	NA	NA	0	NA	NA	NA	NA
NA	NA	NA	NA	NA	2	NA	NA	NA	NA
3	3	3	4	3	0	3	3	3	3
5	1	3	3	4	3	1	5	1	1
0	5	0	0	0	0	5	5	0	5
2	1	2	1	2	1	1	1	1	2
1	1	1	1	2	1	1	1	1	1
0	0	0	0	0	0	0	0	0	0
1	1	1	1	2	1	1	1	1	1
18	15	15	12	21	11	16	19	10	16
35	35	35	35	35	38	35	35	35	35
51,4	42,9	42,9	34,3	60,0	28,9	45,7	54,3	28,6	45,7

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<u>Danese et al. 2008</u>	<u>Danese et al. 2009</u>	<u>Demers et al. 2015</u>	<u>Dietrich 2007</u>	<u>Dunlop et al. 2015</u>	<u>Dyer et al. 2012</u>	<u>Dyer et al. 2015</u>	<u>Ekinci et al. 2015</u>	<u>Ertl et al. 2016</u>	<u>Etter et al. 2013</u>
5	5	3	1	1	1	1	3	1	1
2	2	1	1	2	2	2	1	1	1
2	2	2	1	2	2	2	1	1	2
3	3	NA	NA	NA	NA	NA	NA	NA	2
2	2	2	1	1	NA	NA	NA	NA	1
5	5	3	3	3	3	3	3	3	4
3	3	4	1	1	3	3	1	1	5
0	0	0	0	5	0	0	0	0	0
2	2	1	1	1	1	1	2	2	1
1	1	1	1	1	1	1	1	2	1
0	0	3	0	0	0	0	0	0	0
2	2	2	1	1	1	1	1	1	1
27	27	22	11	18	14	14	13	12	19
40	40	37	37	37	35	35	35	35	40
67,5	67,5	59,5	29,7	48,6	40,0	40,0	37,1	34,3	47,5

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<u>Fani et al.</u> <u>2011</u>	<u>Faravelli et</u> <u>al. 2010</u>	<u>Farley et</u> <u>al. 2001</u>	<u>Farrugia et</u> <u>al. 2011</u>	<u>Fisher et</u> <u>al. 2013</u>	<u>Fonzo et</u> <u>al. 2013</u>	<u>Ford et al.</u> <u>2011</u>	<u>Fossion et</u> <u>al. 2013</u>	<u>Fox et al.</u> <u>1994</u>
1	3	1	3	2	1	3	3	1
2	2	1	2	2	2	2	2	1
1	2	0	2	2	2	1	2	1
NA	NA	0	3	NA	NA	2	NA	NA
2	NA	1	1	2	NA	1	NA	NA
3	3	0	3	3	3	5	5	3
1	5	1	5	5	5	1	1	1
5	0	0	0	5	0	0	5	0
2	2	1	2	2	2	1	1	1
1	1	1	1	1	1	1	1	1
0	0	0	0	0	0	0	0	0
1	1	1	2	2	1	1	1	1
19	19	7	24	26	17	18	21	10
37	35	40	40	37	35	40	35	35
51,4	54,3	17,5	60,0	70,3	48,6	45,0	60,0	28,6

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<u>Frodl et al. 2012</u>	<u>Gamble et al. 2006</u>	<u>Gibb et al. 2001</u>	<u>Gibb et al. 2006</u>	<u>Gladstone et al. 2004</u>	<u>Goldberg et al. 2005</u>	<u>Gonzalez et al. 2012</u>	<u>Gorka et al. 2014</u>	<u>Grabe et al. 2010</u>	<u>Grabe et al. 2012</u>
2	1	5	1	1	1	5	5	5	5
2	2	1	1	1	1	2	1	2	2
2	2	1	2	2	2	2	1	2	2
NA	1	3	NA	NA	NA	1	0	0	0
NA	1	2	NA	NA	NA	2	1	2	2
3	3	3	3	0	3	3	3	3	3
2	3	1	5	5	5	3	1	1	1
0	5	5	5	0	0	0	5	0	0
2	1	1	2	1	1	1	2	2	2
1	1	1	1	1	1	1	1	1	1
0	0	0	0	0	0	0	0	3	0
1	1	1	1	1	1	1	2	2	2
15	21	24	21	12	15	21	22	23	20
35	40	40	35	25	35	40	40	40	40
42,9	52,5	60,0	60,0	48,0	42,9	52,5	55,0	57,5	50,0

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<u>Grant et al.</u> <u>2011</u>	<u>Grant et al.</u> <u>2014</u>	<u>Grassi-</u> <u>Oliveira et</u> <u>al. 2008</u>	<u>Grassi-</u> <u>Oliveira et</u> <u>al. 2008 b</u>	<u>Gülec et al.</u> <u>2013</u>	<u>Gündogar</u> <u>et al. 2014</u>	<u>Günther et</u> <u>al. 2015</u>	<u>Gutierrez</u> <u>et al. 2015</u>	<u>Haberstick</u> <u>et al. 2016</u>
1	3	3	1	3	1	1	5	5
2	2	2	2	1	2	2	2	2
2	2	2	1	2	2	2	2	1
NA	NA	NA	NA	NA	NA	NA	3	2
NA	NA	NA	NA	NA	NA	NA	2	1
3	3	3	3	3	3	3	3	0
5	5	5	1	5	5	5	3	1
5	5	0	0	0	0	0	5	5
2	2	2	1	1	1	2	2	2
1	1	1	1	1	1	1	1	2
0	0	3	0	0	0	0	3	3
1	1	1	1	1	1	1	2	2
22	24	22	11	17	16	17	33	26
35	35	35	35	35	35	35	40	40
62,9	68,6	62,9	31,4	48,6	45,7	48,6	82,5	65,0

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<u>Hankin 2005</u>	<u>Harkness et al. 2015</u>	<u>Heim et al. 2008</u>	<u>Honkalampi et al. 2005</u>	<u>Jaworska et al. 2014</u>	<u>Jeon et al. 2012</u>	<u>Johnson et al. 2010</u>	<u>Johnson et al. 2011</u>	<u>Jones et al. 2013</u>
5	3	1	5	1	5	1	1	5
1	1	1	1	1	1	1	0	2
0	2	2	1	2	2	2	1	2
NA	0	NA	1	NA	NA	NA	NA	1
1	2	NA	1	2	NA	NA	NA	1
3	3	3	0	3	3	3	3	3
1	5	5	1	5	5	3	1	1
5	0	0	0	0	0	0	0	0
1	2	2	1	2	2	2	2	1
1	1	1	1	1	1	1	1	1
0	0	3	0	0	0	0	0	0
1	1	1	2	1	1	1	1	2
19	20	19	14	18	20	14	10	19
37	40	35	40	37	35	35	35	40
51,4	50,0	54,3	35,0	48,6	57,1	40,0	28,6	47,5

CHILDHOOD ADVERSITY AND AFFECTIVE DISORDERS

<u>Kang et al. 2013</u>	<u>Kaysen et al. 2005</u>	<u>Kessler et al. 1994</u>	<u>Khoury et al. 2010</u>	<u>Kim et al. 2013</u>	<u>Klein et al. 2009</u>	<u>Klein et al. 2015</u>	<u>Kohrt et al. 2015</u>	<u>Korkeila et al. 2005</u>	<u>Korkeila et al. 2010</u>
1	1	5	1	5	1	3	1	5	5
1	2	2	1	2	2	1	2	2	2
2	2	2	1	2	2	2	2	2	2
NA	NA	2	NA	3	NA	NA	3	0	0
NA	NA	1	NA	2	NA	NA	2	1	1
0	5	0	3	0	4	3	3	0	0
3	5	1	1	1	5	5	1	1	1
0	5	5	0	0	0	0	0	5	0
2	1	1	1	2	1	2	2	1	1
1	1	1	1	1	1	1	1	1	1
3	0	0	0	0	0	0	0	0	0
1	1	2	1	2	2	2	2	2	2
14	23	22	10	20	18	19	19	20	15
35	35	40	35	40	35	35	40	40	40
40,0	65,7	55,0	28,6	50,0	51,4	54,3	47,5	50,0	37,5

CHILDHOOD ADVERSITY AND AFFECTIVE DISORDERS

<u>Kounou et al. 2013</u>	<u>Kranzler et al. 2011</u>	<u>Kruijt et al. 2014</u>	<u>Lang et al. 2004</u>	<u>Lang et al. 2008</u>	<u>LaNoue et al. 2012</u>	<u>Laucht et al. 2013</u>	<u>LeardMann et al. 2010</u>	<u>Lenze et al. 2008</u>
3	1	1	1	1	1	5	5	3
1	2	1	1	1	1	2	2	2
2	2	1	2	1	1	2	2	2
3	NA	NA	NA	0	NA	2	3	NA
2	1	1	NA	1	NA	2	1	1
3	0	3	5	3	0	3	4	3
5	3	1	1	1	1	1	5	5
5	5	5	0	5	5	5	0	0
2	2	2	1	1	1	1	2	2
1	1	1	1	1	1	1	1	1
0	0	3	0	0	0	3	0	0
2	2	1	1	1	1	1	2	1
29	19	20	13	16	12	28	27	20
40	37	37	35	40	35	40	40	37
72,5	51,4	54,1	37,1	40,0	34,3	70,0	67,5	54,1

CHILDHOOD ADVERSITY AND AFFECTIVE DISORDERS

<u>Liberzon et al. 2014</u>	<u>Lilly et al. 2014</u>	<u>Liu et al. 2013</u>	<u>Lok et al. 2013</u>	<u>Lu et al. 2008</u>	<u>Lu et al. 2013</u>	<u>Lumley et al. 2009</u>	<u>Marshall et al. 2014</u>	<u>Massing-Schaffer et al. 2015</u>
5	1	5	5	1	3	1	1	5
2	2	1	2	2	2	2	2	0
2	1	2	2	2	2	2	2	0
NA	NA	NA	0	NA	NA	NA	NA	NA
1	NA	NA	1	NA	NA	1	1	NA
3	3	3	4	4	3	3	3	3
1	1	5	5	5	5	5	5	5
0	5	5	0	0	0	5	5	5
2	1	1	2	1	2	1	1	1
1	1	1	1	1	1	1	1	1
0	0	0	0	0	0	0	0	0
1	1	1	1	2	2	1	2	2
18	16	24	23	18	20	22	23	22
37	35	35	40	35	35	37	37	35
48,6	45,7	68,6	57,5	51,4	57,1	59,5	62,2	62,9

CHILDHOOD ADVERSITY AND AFFECTIVE DISORDERS

<u>McGinn et al. 2005</u>	<u>McIntyre et al. 2012</u>	<u>McLaughlin et al. 2010</u>	<u>McQuaid et al. 2013</u>	<u>McQuaid et al. 2015</u>	<u>Melas et al. 2013</u>	<u>Meng et al. 2016</u>	<u>Miller et al. 2009</u>	<u>Min et al. 2013</u>
1	1	5	1	1	3	1	1	1
2	2	2	1	2	2	2	1	1
2	2	2	1	1	2	2	2	1
1	NA	0	NA	NA	NA	2	NA	NA
1	NA	2	NA	NA	NA	2	NA	NA
3	3	0	3	3	0	3	3	3
5	5	5	1	1	1	3	5	3
5	0	5	5	5	0	5	0	5
1	2	1	2	1	2	2	2	2
1	1	1	1	1	1	2	1	1
0	0	0	3	0	0	0	0	0
1	1	2	2	2	2	0	1	1
23	17	25	20	17	13	24	16	18
40	35	40	35	35	35	40	35	35
57,5	48,6	62,5	57,1	48,6	37,1	60,0	45,7	51,4

CHILDHOOD ADVERSITY AND AFFECTIVE DISORDERS

<u>Mueller-Pfeiffer et al. 2013</u>	<u>Murphy et al. 2014</u>	<u>Nazarov et al. 2014</u>	<u>Nazarov et al. 2015</u>	<u>O'Donovan et al. 2011</u>	<u>O'Mahen et al. 2015</u>	<u>Opel et al. 2014</u>	<u>Ouellet-Morin et al. 2015</u>	<u>Owens et al. 2009</u>
1	1	1	1	1	1	3	5	1
2	2	2	2	2	2	2	1	2
2	1	2	2	2	2	2	1	1
NA	1	NA	NA	NA	1	NA	3	3
NA	1	NA	NA	2	1	NA	1	1
3	0	3	3	3	3	3	3	3
5	1	5	5	5	5	5	2	2
0	5	0	0	0	5	0	0	0
2	1	2	2	2	1	2	2	2
1	1	1	1	1	1	1	1	1
3	0	0	0	0	0	0	0	0
1	1	1	1	1	1	1	2	1
20	15	17	17	19	23	19	21	17
35	40	35	35	37	40	35	40	40
57,1	37,5	48,6	48,6	51,4	57,5	54,3	52,5	42,5

CHILDHOOD ADVERSITY AND AFFECTIVE DISORDERS

<u>Pace et al.</u> <u>2006</u>	<u>Park et al.</u> <u>2015</u>	<u>Parlar et al.</u> <u>2014</u>	<u>Patten 2013</u>	<u>Pederson et</u> <u>al. 2004</u>	<u>Peng et al.</u> <u>2013</u>	<u>Perna et al.</u> <u>2014</u>	<u>Peyrot et al.</u> <u>2014</u>	<u>Philippe et</u> <u>al. 2011</u>
3	1	3	5	3	3	1	5	1
2	1	2	2	2	2	2	2	1
2	1	2	2	2	2	2	2	1
NA	NA	NA	2	1	NA	NA	NA	NA
NA	NA	NA	1	2	1	NA	NA	NA
3	3	3	0	4	3	3	4	3
3	1	5	3	3	5	5	5	5
0	0	0	0	0	0	0	0	5
2	2	1	0	1	2	1	2	1
1	1	1	1	1	1	1	1	1
0	0	0	0	0	0	0	0	0
1	2	1	1	1	1	1	1	2
17	12	18	17	20	20	16	22	20
35	35	35	40	40	37	35	35	35
48,6	34,3	51,4	42,5	50,0	54,1	45,7	62,9	57,1

CHILDHOOD ADVERSITY AND AFFECTIVE DISORDERS

<u>Plaza et al.</u> <u>2010</u>	<u>Plaza et al.</u> <u>2012</u>	<u>Polanczyk</u> <u>et al. 2009</u>	<u>Poole et al.</u> <u>2017</u>	<u>Power et al.</u> <u>2013</u>	<u>Prigerson et</u> <u>al. 1996</u>	<u>Raes et al.</u> <u>2008</u>	<u>Raparia et</u> <u>al. 2016</u>	<u>Reinelt et</u> <u>al. 2013</u>
1	1	5	1	3	5	1	3	1
2	2	2	2	2	2	1	2	2
2	1	2	1	2	2	1	2	2
NA	NA	3	NR	NA	NA	1	NA	0
NA	NA	1	NR	NA	NA	2	NA	2
3	3	5	3	3	3	3	3	3
5	1	3	1	5	5	1	5	3
0	0	0	5	0	0	5	0	5
2	2	2	2	2	2	1	2	2
1	1	1	2	1	1	1	1	1
0	0	0	0	0	0	0	0	0
2	2	2	1	2	1	1	1	2
18	13	26	18	20	21	18	19	23
35	35	40	35	35	35	40	35	40
51,4	37,1	65,0	51,4	57,1	60,0	45,0	54,3	57,5

CHILDHOOD ADVERSITY AND AFFECTIVE DISORDERS

<u>Ritchie et al. 2009</u>	<u>Roh et al. 2015</u>	<u>Roenholdt et al. 2012</u>	<u>Roxburgh et al. 2014</u>	<u>Roy 1999</u>	<u>Sacco et al. 2007</u>	<u>Sachs-Ericsson et al. 2006</u>	<u>Salwen et al. 2014</u>	<u>Santa Ana et al. 2006</u>
5	1	1	1	1	1	1	1	1
1	2	2	2	2	2	2	2	2
1	1	2	1	2	2	2	1	2
NA	NA	1	NA	NA	NA	NA	NA	NA
2	2	2	1	NA	2	2	NA	NA
4	3	0	0	3	3	3	3	5
3	1	0	1	5	5	3	1	5
0	0	0	0	0	0	5	5	0
2	1	2	2	2	2	1	1	2
1	1	1	1	1	1	1	1	1
0	0	0	0	0	0	0	0	0
2	1	1	1	1	1	2	1	1
21	13	12	10	17	19	22	16	19
37	37	40	37	35	37	37	35	35
56,8	35,1	30,0	27,0	48,6	51,4	59,5	45,7	54,3

CHILDHOOD ADVERSITY AND AFFECTIVE DISORDERS

<u>Sareen et al. 2013</u>	<u>Schulz et al. 2014</u>	<u>Schulz et al. 2017</u>	<u>Schwaiger et al. 2016</u>	<u>Sharpley et al. 2013</u>	<u>Sheik et al. 2018</u>	<u>Soenke et al. 2010</u>	<u>Soffer et al. 2008</u>	<u>Soleimani et al. 2015</u>
1	1	5	1	1	3	1	1	1
2	2	2	1	1	1	1	2	1
2	2	2	1	1	1	1	2	1
3	1	1	NA	NA	NA	NA	NA	NA
1	2	2	NA	NA	NA	NA	NA	NA
0	3	3	3	3	0	3	0	0
3	1	5	4	1	1	1	5	1
0	0	5	0	0	5	5	0	0
2	1	2	2	2	1	1	2	2
1	1	2	1	1	2	1	1	1
0	0	0	0	0	0	0	0	0
2	2	2	1	2	2	2	1	1
17	16	31	14	12	16	16	14	8
40	40	40	35	35	35	35	35	35
42,5	40,0	77,5	40,0	34,3	45,7	45,7	40,0	22,9

CHILDHOOD ADVERSITY AND AFFECTIVE DISORDERS

<u>Sperry et al. 2013</u>	<u>Spinhoven et al. 2014</u>	<u>Spinhoven et al. 2016</u>	<u>Stein et al. 2002</u>	<u>Stein et al. 2008</u>	<u>Stevens et al. 2013</u>	<u>Street et al. 2005</u>	<u>Suzuki et al. 2014</u>	<u>Swanson et al. 2014</u>
5	5	5	5	1	1	1	1	1
2	2	2	1	2	1	2	2	2
2	2	2	1	1	1	2	2	1
3	3	3	NA	NA	NA	NA	NA	NA
2	1	1	1	NA	NA	NA	NA	NA
5	4	4	0	3	3	3	3	3
5	3	3	3	1	1	1	5	1
5	0	5	5	0	5	5	0	0
1	2	2	2	2	1	2	2	0
1	1	1	1	1	1	1	1	1
0	0	0	0	0	0	0	0	0
2	2	2	1	1	2	2	1	2
33	25	30	20	12	16	19	17	11
40	40	40	37	35	35	35	35	35
82,5	62,5	75,0	54,1	34,3	45,7	54,3	48,6	31,4

CHILDHOOD ADVERSITY AND AFFECTIVE DISORDERS

<u>Tekin et al. 2015</u>	<u>Tietjen et al. 2007</u>	<u>Tozzi et al. 2016</u>	<u>Treadway et al. 2009</u>	<u>Triffleman et al. 1995</u>	<u>Turner et al. 2003</u>	<u>Uddin et al. 2013</u>	<u>Ugwu et al. 2015</u>	<u>Uher et al. 2011</u>
1	1	1	3	1	1	5	3	5
2	2	2	2	2	2	2	2	2
2	1	2	2	1	1	2	2	2
NA	NA	NA	NA	3	3	1	NA	3
NA	NA	NA	2	2	1	1	NA	2
3	0	3	3	3	0	4	3	5
5	1	5	5	2	1	3	5	3
0	0	0	0	0	5	5	0	5
2	2	2	2	2	2	2	2	2
1	1	1	1	1	1	1	1	1
0	0	0	0	0	0	0	0	0
2	2	1	1	2	1	2	1	2
18	10	17	21	19	18	28	19	32
35	35	35	37	40	40	40	35	40
51,4	28,6	48,6	56,8	47,5	45,0	70,0	54,3	80,0

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<u>Van der Auwera et al. 2014</u>	<u>Van Dijke et al. 2015</u>	<u>van Veen et al. 2013</u>	<u>Van Vorhees et al. 2012</u>	<u>Van Vorhees et al. 2014</u>	<u>Veer et al. 2015</u>	<u>Veijola et al. 1998</u>	<u>Vinkers et al. 2015</u>	<u>Vrijzen et al. 2014</u>	<u>Vrijzen et al. 2014 b</u>	<u>Vrijzen et al. 2015</u>
5	1	1	1	1	3	5	5	1	1	1
2	2	2	2	2	2	2	2	2	2	2
2	2	2	2	2	2	2	2	2	2	2
2	NA	3	NA	NA	NA	2	NA	NA	NA	NA
1	NA	2	NA	NA	NA	2	NA	NA	2	2
3	3	4	3	3	3	0	3	3	3	3
2	5	5	1	5	5	5	5	5	5	5
5	5	0	0	0	0	0	5	0	0	0
2	1	1	2	2	2	2	2	2	2	2
1	1	1	1	1	1	1	1	1	1	1
0	0	0	0	0	0	0	0	0	0	0
2	2	1	1	2	1	2	1	2	1	1
27	22	22	13	18	19	23	26	18	19	19
40	35	40	35	35	35	40	35	35	37	37
67,5	62,9	55,0	37,1	51,4	54,3	57,5	74,3	51,4	51,4	51,4

CHILDHOOD ADVERSITY AND AFFECTIVE DISORDERS

<u>Vythilingam et al. 2002</u>	<u>Walsh et al. 2014</u>	<u>Wang et al. 2014</u>	<u>Watson et al. 2007</u>	<u>Webb et al. 2016</u>	<u>Weiss et al. 2013</u>	<u>Wells et al. 2014</u>	<u>Wichers et al. 2009</u>	<u>Wingenfeld et al. 2011</u>	<u>Witthöft et al. 2015</u>
1	3	1	1	5	1	1	5	1	1
2	1	2	2	1	1	1	2	2	2
2	1	2	2	2	1	1	2	2	2
NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA	NA	2	NA	1
3	3	3	3	3	3	3	3	3	3
5	1	5	5	2	1	1	5	5	5
0	0	0	0	5	5	5	5	0	0
2	2	2	2	2	2	1	2	1	2
1	1	1	1	2	1	1	1	1	1
0	0	0	0	0	0	0	0	3	0
1	1	1	1	1	1	2	1	1	1
17	13	17	17	23	16	16	28	19	18
35	35	35	35	35	35	35	37	35	37
48,6	37,1	48,6	48,6	65,7	45,7	45,7	75,7	54,3	48,6

CHILDHOOD ADVERSITY AND AFFECTIVE DISORDERS

<u>Woods et al. 2005</u>	<u>Wu et al. 2010</u>	<u>Xie et al. 2010</u>	<u>Xie et al. 2012</u>	<u>Yehuda et al. 2001</u>	<u>Zaidi et al. 1994</u>	<u>Zeugmann et al. 2013</u>	<u>Zhang et al. 2015</u>	<u>Zhao et al. 2015</u>
1	1	1	1	1	1	1	1	1
2	1	2	2	2	0	2	2	2
1	1	2	2	2	0	2	2	2
NA	NA	NA	NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA	2	NA	NA
3	3	3	3	5	3	3	3	3
2	3	4	4	5	2	5	1	5
0	0	5	5	0	0	0	5	0
2	2	2	2	2	2	2	1	2
1	1	1	1	1	1	1	1	1
0	0	0	0	0	0	0	0	0
1	2	2	2	1	1	1	2	1
13	14	22	22	19	10	19	18	17
35	35	35	35	35	35	37	35	35
37,1	40,0	62,9	62,9	54,3	28,6	51,4	51,4	48,6

Table A5

General information concerning the 17 non-cross-sectional mediation studies

Study	Study design	Inclusion criteria	Exclusion criteria	State	Sample source	N	%F	Age of exposure (in years)	Exposure assessed with	Mental health outcome	Mental health outcome assessed with	Age at outcome mean $\pm$ SD or range (years)	Mediator(s)
Bustamante et al. 2018	Prospective cohort	Adult (18 years or older) residing in Detroit	NA	US	Population-based representative sample	112	55.35	<17	CTS and CTQ	Depressive Symptoms	PHQ-9	50.74 $\pm$ 12.96	FKBP5 DNA methylation (null finding)
Brown et al. 2008	Retro-spective cohort	Sisters within five years of age living anywhere in the UK with whom they had been largely brought up - experimental sister pairs had high likelihood of ACEs - comparison sister pairs (n=80) were selected at random	Above 50 years old	UK	Pairs of sisters registered at two Islington health centres in North London	175	100	< 17	CECA	MDD	SCAN	35	Highly aversive partnerships

CHILDHOOD ADVERSITY AND AFFECTIVE DISORDERS

Fossion et al. 2013	Retro-spective cohort	Exposure group: Jewish, born between 1931 and 1942, hidden during the Nazi occupation in a Catholic Institution, in a Catholic foster family or with their parents under the protection of a Catholic family	NR	Bel	Recruited voluntary participants in Belgium through an announcement in the Belgian Bulletin of the Hidden Children	65	38.5	NR	Semi-structured interview	MDD and anxiety	HSC	73.28 ±3.74	Diminished resilience due to one or more retraumatizations in adulthood
Gibb et al. 2001	Pro-spective cohort	Freshmen of Temple University and the University of Wisconsin-Madison less than 30 years old	Any current or past episodic mood disorder except MDD or any other psychiatric disorder or serious medical illness that would preclude participation in a longitudinal study	US	Subset of those selected for inclusion in the Temple-Wisconsin Cognitive Vulnerability to Depression (CVD) Project (Alloy & Abramson, 1999)	297	68.4	< 15	LEQ	Depressive symptoms	BDI	19.1 ±2.41	Negative cognitive styles
Gorka et al. 2014	Prospective cohort	Non-patient, 18–22-year-old university students	Medical diagnoses of cancer, stroke, head injury with loss of consciousness, untreated migraine headaches, diabetes requiring insulin treatment, chronic kidney or liver disease, or lifetime history of psychotic symptoms, use of psychotropic, glucocorticoid, or hypolipidemic medication and conditions affecting cerebral blood flow and metabolism	US	Participants who had successfully completed the ongoing DNS at Duke University, a study which assesses a wide range of behavioural and biological traits	906	57.33	< 15	CTQ	Anxiety	STAI	19.62 ±1.24	Reduced hippocampal and medial prefrontal gray matter volumes
Hankin 2005	Prospective cohort	None	None	US	Undergraduate students from an Introduction to Psychology class	652 and 233	67.79 and 69.96	< 14	LEQ	Depressive symptoms	BDI	18.7 ±0.96 and 18.6 ±0.84	Insecure attachment style, a negative cognitive style, and negative events
Kessler et al. 1994	Prospective cohort	Non-institutionalized persons aged 25 and over living in the continental United States	Respondents who spoke neither English nor Spanish or who were physically or mentally incapable of being interviewed	US	General population	2800	NR	< 16	Own questions	MDD	DIS	48.85 ±15.9	Chronic interpersonal stress in adulthood
Korkeila et al. 2005	Pro-spective cohort	None	None	Finland	Working-aged respondents from the Health and Social Support in Finland (HeSSup) Study - representative of the general population	21101	58.45	NR	Own questions	Depressive symptoms	BDI	20-54	Alcohol abuse, poor social support, negative affectivity and recent negative life events
Kounou et al. 2013	Matched-controls	Experimental group: MDD DSM IV	Control group: psychiatric history; All: French illiteracy	Togo	Controls: paramedical staff (nurses, midwives, laboratory technicians, etc.) and students; Experimental group: recruited from psychiatric care centres	181	66.3	< 15	CTQ	MDD	DSM IV diagnosis	29.0 ±6.7	Personality Disorders
Liu et al. 2013	Prospective cohort	Lifetime history of depression - DSM-IV-TR	None	US	Data from a larger study examining the interrelations between negative life events and depressogenic risk factors in university undergraduates	66	77.3	< 15	CTQ	MDD	SADS-L and BDI-II	19.86 ±1.67	Negative cognitive styles

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Massin g-Schaff er et al. 2015	Prospect ive cohort	None	None	US	Recruited from introductory-level psychology courses at Temple University	185	75.1	< 15	CTQ	Depressive symptoms	SADS-L and BDI-II	19.65 ±1.48	Rejection sensitivity
McLaughlin et al. 2010	Pro-spective cohort	Male college sophomores	Indications of physical and mental health problems during a medical examination at college entrance	US	Data come from the Study of Adult Development, a longitudinal cohort of men first interviewed between 1939 and 1942 when they were college sophomores	268	0	NR	CCES	MDE and anxiety	IMDD S	20-50	Emotional reactivity
Schulz et al. 2017	Prospect ive cohort	Current MDD as primary diagnosis, 18–65 years of age and sufficient German skills	Current substance dependence (e.g., F10.2), bipolar and/or psychotic disorder, cognitive impairments due to neuropsychiatric disorders and treatment duration of less than four weeks.	Ger	Patients treated on a depression ward in the Clinic of Psychiatry and Psychotherapy of the Evangelisches Klinikum Bethel (Germany) between February 2013 and November 2015	123	40.65	< 15	CTQ	MDD	ICD-10	40.3±1.8	Borderline psychopathology and acceptance of pleasant emotions
Sheikh 2018	Retrospect ive cohort	Attending all follow-up surveys	NA	Nor	Representative adult population residing in the municipality of Tromsø, Norway	4530	59.2	NR	Own questions	Psychologic al distress	HSCL-10	Mediat or measur ed at: 54.7; Outco me measur ed at: 61.7	Quantity and quality of social support
Sperry et al. 2013	Pro-spective cohort	All: non-Hispanic White and Black ethnicity; Cases: documented history of child abuse or neglect; Controls: without documented histories of child abuse or neglect matched with cases on sex, race, date of birth (±1 week), and hospital of birth	Cases: Adoption of the subject as an infant; “involuntary” neglect only, usually resulting from the temporary institutionalization of the legal guardian; placement only; or failure to pay child support; All: missing data	US	Data from a larger research project based on a cohort design study (Widom, 1989) - substantiated cases of childhood physical and sexual abuse and neglect processed from 1967 to 1971 in the county juvenile (family) or adult criminal courts of a Midwestern metropolitan area	696	53	NR	Juvenile and adult criminal arrest records	Anxiety and depress-ive symptoms	BAI and CES-D	41.2 ±3.53	Social support
Spinho ven et al. 2016	Pro-spective cohort	All 18 to 65 years old ; Healthy controls: none; Case group 1; prior history of DSM IV depressive and anxiety disorders, Case group 2: current DSM IV depressive and/or anxiety disorder	Primary severe other psychiatric disorder that required specific other treatment (e.g. schizophrenia), not being fluent in Dutch	NL	Part of the Netherlands Study of Depression and Anxiety (NESDA) - controls recruited from the general population and cases via a screening procedure in general practice specialized health care centres	2947	66.4	1) < 15; 2) < 16	1) CTQ 2) CTI)	Depress-ive and anxiety disorders	CIDI and BAI	41.2 ±13.1	Maladapt-ive personality types
Stein et al. 2002	Prospect ive cohort	Being homeless and living in a shelter or a sober living recovery program for at least 1 week	Above 50 years of age and missing data	US	Homeless women residing in 35 shelters and sober living recovery programs in Los Angeles in 1995 through 1998	581	100	NR	Own questions	Depressive symptoms	DIS	33.5 (16 to 50)	Physical abuse in adulthood

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Note. UK = United Kingdom ; Bel = Belgium ; US = United States ; NL = The Netherlands ; CECA = Childhood experience of care and abuse questionnaire ; LEQ = Life events questionnaire ; CTQ = Childhood trauma questionnaire ; CCES = Composite childhood environment scale ; CTI = Childhood trauma index ; SCAN = Schedules for clinical assessment in neuropsychiatry ; HSC = Hopkins symptoms checklist ; BDI = Beck depression inventory ; STAI = State-trait anxiety inventory ; DIS = Diagnostic interview schedule ; DSM = Diagnostic and statistical manual of mental disorders ; SADS-L = Schedule for affective disorders and schizophrenia-lifetime interview ; IMDDS = Indicators of major depressive disorder scale ; BAI = Beck anxiety inventory ; CES-D = Centre for epidemiological studies-depression questionnaire ; CIDI = Composite international diagnostic interview

Table A6

General information concerning the 32 cross-sectional mediation studies

Study	Inclusion criteria	Exclusion criteria	State	Sample source	N	%F	Age of exposure	Exposure assessed with	Mental health outcome	Mental health outcome assessed with	Age at outcome mean, SD or range	Mediator(s)
Caldwell et al. 2011	Female gender, maternal age between 18 and 44, being a caregiver for one or more children under the age of 18	No substance abuse during the 6 months prior to the study, no prescription for psychiatric medications at the time of the study, and no history of developmental disorder, mental retardation, or neurological disorder	US	At-risk mothers and children in a small county in northern California in contact with several community programs	76	0	< 15	CTQ	MDD	SCL-90-R	28±6.91	Attachment anxiety
Choi et al. 2015	Current pregnancy, known HIV status and Xhosa, Afrikaans, or English fluency	No cognitive impairment	SA	Pregnant women seeking antenatal care in Cape Town, South Africa	84	100	< 15	CTQ-SF	Postnatal depression	EPDS	92% between 18 and 35	Maladaptive coping
Crow et al. 2014	From a low-income population and ability to give informed consent	None	US	Low-income population in Atlanta, Georgia recruited as part of the Grady Trauma Project	3902	68.9	< 15	CTQ	Depressive symptoms	BDI-II	39.3±13.8	Emotional dysregulation
Cukor et al. 2006	Women with a current diagnosis of a unipolar depressive or anxiety disorder, being between 18 and 65 years old, and basic fluency in English	None	US	Recruited from a larger study (McGinn, Cukor, & Sanderson, 2005) in the Outpatient Psychiatry Department at Montefiore Medical Centre	48	100	< 15	CTQ	MDD	Psych. diagnosis and BDI	42±9.6	Maladaptive cognitive schemas
Dunlop et al. 2015	MDE - DSM IV criteria plus and significant depressive symptoms that were present for at least the previous 2 years without a period of remission	Pregnancy, bipolar disorder, dementia, current psychotic disorder, unstable medical illness, and a primary diagnosis of PTSD, OCD, eating- or personality disorders and substance dependence (except nicotine)	US	Chronically depressed outpatients enrolled in the Research Evaluating the Value of Augmenting Medication with Psychotherapy study	808	55.9	< 15	CTQ	MDD	IDS-SR	44.2±12.4	Anxious arousal
Fani et al. 2011	Ability to give informed consent and understand English	Poor task performance (i.e., they skipped or made errors on more than 20% of trials)	US	Recruited through an ongoing NIMH funded study of risk factors for PTSD in a highly traumatized, low socioeconomic status, urban population in the southeastern United States	129	72	< 15	CTQ	PTSD	M-PSS	39.5±12.5	Attentional bias toward happy faces
Gamble et al. 2006	50 years of age and older, current MDD as defined by SCID/DSM-IV	Schizophrenia, schizoaffective disorder, dementia, or substance-induced mood disorder	US	Part of a larger investigation examining personality and suicidal behavior in middle aged and older adults in the US	105	58.1	< 15	CTQ-SF	MDD	SCID	58.87±9.1	Neuroticism

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Grant et al. 2011	Experimental group: score of 16 or higher on the HDRS and MDD according to SCID; Control group: score of six or less on the HDRS	Experimental group: no significant history of neurological disease, lifetime history of brain injury, psychosis, mania, substance dependence; or substance abuse within the previous six months; Control group: neurological disease and head injury, current or past mood disorders, as well as current or past history of Axis I disorders	US	Recruited through the Vanderbilt University Medical Centre Outpatient Psychiatry Clinic and through television advertisements in the community	36	58.3 3	< 15	CTQ-SF	MDD	HDRS and SCID	32.8±9.95	Heightened amygdala response
Kaysen et al. 2005	Victimization as reported by police, hospital, or victim service	Illiteracy and apparently psychotic, or intoxicated participants at the time of assessment	US	Recruited through police, hospital, and victim service agencies as part of a larger study examining recovery from assault	206	100	< 17	HVQ and Police reports	MDD	BDI and SCID	31.21±8.58	Maladaptive cognitions about self and others
Lang et al. 2008	Women seen in the Veterans' Affairs San Diego Healthcare System (VASDHS) primary care clinic	None	US	Recruited from the Veterans' Affairs San Diego Healthcare System (VASDHS) primary care clinic in 1998	200	100	< 15	CTQ	PTSD	PCL-C	46.6±14.6	Adult sexual assault
LaNoue et al. 2012	None	None	US	Collected as part of two pilot studies conducted between 2005 and 2006 aimed at developing and testing a comprehensive health assessment instrument which included items on childhood and adult adversity and current depressive symptoms	210	66.2	NR	Own questions	Depressive symptoms	PHQ-9	47.76±12.1	Adult adverse events
Lilly et al. 2014	Over the age of 18, fluent in English, and having had experienced at least one incident of physical IPV in the past 6 months	None	US	Recruited from a rural community in the Midwestern U.S. using fliers posted at local commercial locations, as well as newspaper advertisements	99	100	< 15	CTQ	PTSD	PDS	29.72±10.1	Emotion regulation difficulties and intimate partner violence
Lumley et al. 2009	Experimental group: past- or current MDD	Presence of a medical condition linked to depression symptoms (e.g., thyroid disorder), acute suicidality, Depressive Disorder NOS, marked lack of understanding of the computer task, significantly older than the rest of the sample and missing data	Canada	Recruited from a first year class in Introductory Psychology	91	76.9 2	< 17	CECA	Depressive symptoms	BDI and SCID	18.1±0.84	Depressotypic schema organization
Marshall et al. 2014	Married or cohabitating heterosexual couples in which at least one partner experienced a stressful life event (PCL-C cut-off score of 44)	Neither partner met criteria for probable PTSD, partners' combined income exceeded \$100,000 per year, either partner had more than 6 years of post-high-school education, end of relationship during the screening process	US	Recruited using newspaper and Internet advertisements, fliers placed in local businesses, and fliers placed in a local outpatient mental health clinic	128	50	< 18	TLEQ	PTSD symptoms	PCL-C and CAPS	36.2±12.83	Age of first consensual sexual intercourse
McGinn et al. 2005	Current diagnosis of a unipolar depressive or anxiety disorder, being between 18 and 65 years old, and basic fluency in English	None	US	Recruited from the Outpatient Psychiatry Department at Montefiore Medical Centre, a not-for-profit university hospital serving a primarily low-income population in the Bronx borough of New York City	55	89	< 15	CTQ	Unipolar depression or anxiety disorders	DSM IV, BDI, BAI	41.9±10	Dysfunctional cognitive style

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McQuaid et al. 2015	Both studies: First Nations adults	None	Canada	Recruited through Aboriginal community Centres and organizations	Study 1: 225; Study 2: 134	Study 1: 75.1; Study 2: 73.13	< 15	CTQ	Depressive symptoms	BDI-SF	Study 1: 35.8±10.9; Study 2: 35.6±10	Study 1: perceived discrimination Study 2: emotion-focused coping
Murphy et al. 2014	Children who had been in child protection where oversampled by stratifying	Refusal, illness, disability, and being uncontactable	Den	Data from a Danish national study conducted by The Danish National Centre for Social Research in 2008 and 2009 using a stratified random probability survey	2980	47.01	NR	Structured interview	PTSD	PC-PTSD	24	Low social support and low self-esteem
O'Mahen 2015	Age 18 or older, 24 or more weeks pregnant, scoring 12 or greater on the Edinburgh Postnatal Depression Screen (EPDS) at screen	Receiving any treatment for depression, did not speak English, did not plan to return to the clinic for additional care (e.g. moving out of the area), suffered from an intellectual disability or any psychotic disorder, or met criteria for current alcohol/drug abuse or dependence	US	Women were recruited from five obstetrics clinics in South-eastern Michigan	140	100	< 15	CTQ	Postnatal depression	SCID and EPDS	26.71±5.8	Behavioural avoidance and rumination
Philippe et al. 2011	Outpatients of a psychology clinic	NR	Canada	Recruited outpatients from a psychology clinic at a Canadian university and assessed before receiving a psychological treatment	118	29.66	< 15	CTQ	Anxiety and depressive symptoms	BAI and BDI	32.82±12.65	Ego resiliency
Raes et al. 2008	Students from introductory social work classes at the Katholieke Hogeschool Leuven, the Hogeschool Limburg, and the Provinciale Hogeschool Limburg	None	Bel	Belgian students from introductory social work classes at the Katholieke Hogeschool Leuven, the Hogeschool Limburg, and the Provinciale Hogeschool Limburg	101	82.18	< 15	CTQ	Depressive symptoms	BDI	19.64±3.39	Brooding
Sachs-Ericsson et al. 2006	NA	Incomplete data	US	Data from the the National Comorbidity Survey in the US - nationally representative sample	5877	50	NR	CIDI and dichotomous questions	Internalizing syndromes (incl. MDD, GAD, and PTSD)	DSM-III-R - CIDI	33.2±10.7	Self-criticism
Salwen et al. 2014	Bariatric surgery recipient	NR	US	Extremely obese individuals who underwent a psychological evaluation for clearance for bariatric surgery, during which they were administered	187	66.8	< 15	CTQ	Depressive and anxiety symptoms	DASS	43.58±12.98	Adult interpersonal abuse
Soenke et al. 2010	Undergraduate students	None	US	Recruited undergraduates at a large public university on the eastern coast of the United States	396	73.99	< 15	CTQ	GAD symptoms	GADQ-IV	20.26±2.45	Emotional dysregulation
Stevens et al. 2013	Patients at an outpatient obstetric-gynaecological clinic	Medical problems (e.g., immune conditions and acute infections)	US	Patients at an outpatient obstetric-gynaecological clinic at a large inner-city medical Centre in Chicago - representative of the general surrounding urban community	139	100	< 16	CTQ	PTSD symptoms	PSS-SR	28.46±7.76	Lower social support, emotional dysregulation and adult interpersonal violence

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Street et al. 2005	Seeking services from a battered-women shelter	None	US	Women seeking services from 23 battered-women shelters in the south-eastern United States	63	100	< 16	TSS	PTSD symptoms	PCL	32 (19 to 64)	Trauma-related guilt and domestic violence victimization in adulthood
Turner et al. 2003	College student	NR	UK	College students attending 1 of 3 colleges in New England - random samples of Liberal Arts students	649	59	<16	Own questions	Depressive symptoms	CES-D	18-29	Stress in adulthood and low self-esteem
Van Dijke et al. 2015	Adult psychiatric inpatients who were admitted to two Centres for clinical psychotherapy	Severe mental health disorder (i.e., psychotic disorder, severe mood disorder, neuro-cognitive disorders), those with severe behavioural problems (including but not limited to severe self-harm, suicidal urges, severe eating problems, and intermittent explosive behaviour), or participants who currently were homeless	NL	Adult psychiatric inpatients admitted to two Centres for clinical psychotherapy and referred from departments of medical psychology-psychiatry in somatic hospitals, outpatient psychotherapy facilities, or day care psychotherapy departments for intensive multimodal treatment	472	69.28	NR	TEC	PTSD symptoms	SIDES	34.7±10.1	Psychoform dissociation
Weiss et al. 2013	Being a substance use disorder patient in a residential substance abuse treatment facility in Central Mississippi	None	US	Recruited from a residential substance abuse treatment facility in Central Mississippi	93	23.7	< 15	CTQ	PTSD symptoms	PCL-C	40.62±9.68	Substance use disorder and emotion dysregulation
Wells et al. 2014	Taking an introductory psychology class at the University of Texas at Austin, CES-D scores of 15 or less	Presence of any current or past mood, anxiety, substance use, psychotic, or eating disorder	US	Recruited from introductory psychology classes at the University of Texas at Austin	155	53.5	< 15	CTQ	Depressive symptoms	CES-D	18.8±1.6	Cognitive vulnerability
Zhang et al. 2015	African American women with a history in the prior year of both a suicide attempt and intimate partner violence (IPV) exposure	None	US	Recruited from a public hospital that provides medical and mental health treatment to mostly low income patients - part of a large longitudinal study - data from the pre-intervention interview only	192	100	< 15	CTQ	PTSD symptoms	DTS	34.9±9.29	Existential well-being and recent nonphysical intimate partner violence
<p><i>Note.</i> US = United States ; SA = South Africa ; Den = Denmark ; Bel = Belgium ; NL = The Netherlands ; UK = United Kingdom ; CTQ = Childhood trauma questionnaire ; CMIS = Childhood maltreatment interview schedule ; HVQ = History of victimization questionnaire ; THQ = Trauma history questionnaire ; CECA = Childhood experience of care and abuse questionnaire ; TLEQ = Traumatic live events questionnaire ; CIDI = Composite international diagnostic interview ; TSS = Traumatic stress survey ; TEC = Traumatic events checklist ; SCL = Symptom checklist ; EPDS = Edinburgh postnatal depression scale ; SCID = Structured clinical interview for DSM disorders ; BDI = Beck depression inventory ; IDS = Inventory of depressive symptomatology ; M-PSS = Modified PTSD symptoms scale ; HDRS = Hamilton depression rating scale ; MPTSD = Mississippi scale for combat-related PTSD ; PCL = PTSD checklist ; PHQ = Physical health questionnaire ; PDS = Posttraumatic stress diagnostic scale ; CAPS = Clinician-administered PTSD scale ; DSM = Diagnostic and statistical manual for DSM disorders ; BAI = Beck anxiety inventory ; PC-PTSD = Primary care PTSD screen ; DASS = Depression and anxiety stress scales ; GADQ = Generalized anxiety disorder questionnaire ; PSS = PTSD symptom scale ; CES-D = Centre for epidemiological studies depression scale ; SIDES = Structured interview for disorders of extreme stress ; DTS = Davidson Trauma Scale</p>												

Table A7

General information concerning the 11 non-cross-sectional moderation studies

Study	Study design	Inclusion criteria	Exclusion criteria	State	Sample source	N	%F	Age of exposure	Exposure assessed with	Mental health outcome	Mental health outcome assessed with	Age at outcome mean or SD	Moderator (s)
Brown et al. 2008 b	Prospective cohort	Sisters within five years of age living anywhere in the UK, largely brought up together - experimental sister pairs had high likelihood	No older than 50 years old	UK	Pairs of sisters registered at two Islington health centres in North London	175	100	< 17	CECA	MDD	SCAN	35	Low self-esteem

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		of ACEs - comparison sister pairs (n=80) were selected at random												
Busuito et al. 2014	Prospective cohort	Low-income mothers in their third trimester of pregnancy, fluent in English	None	US	Local urban communities recruited via flier advertising and community-based health clinics	120	100	< 15	CTQ	PTSD	PCL	26±5.7	Romantic attachment avoidance	
Fisher et al. 2013	Matched-controls	Cases: at least 2 DSM IV MDE (unipolar); Controls: no history of psychiatric illness; All: Caucasian aged 18 years or over	History of mania or hypomania, mood-incongruent psychosis, and a first or second-degree relative with bipolar or psychotic disorder	UK	Recruited from the Cardiff and London sites of the Depression Case-Control (DeCC) multi-centre study (see Cohen-Woods et al.,2009)	455	71.8	<15	CTQ	MDD	SCAN	45.4±12.7	Serotonin transporter gene polymorphism	
Grant et al. 2014	Matched-controls	Experimental group: score of 16 or higher on the HDRS and MDD according to SCID; Control group: score of six or less on the HDRS	Experimental group: obsessive compulsive disorder, schizophrenia and other psychotic disorders, bipolar disorder, substance dependence, or substance abuse; Control group: neurological disease and head injury, current or past mood disorders, as well as current or past history of Axis I disorders	US	Recruited through the Vanderbilt University Medical Centre Outpatient Psychiatry Clinic and through television advertisements in the community	39	53.9	< 15	CTQ-SF	MDD	HDRS and SCID	32.9±9.95	Deregulation in emotion processing circuitry	
Gutierrez et al. 2015	Prospective cohort	Aged 18–75 years, fluency in Spanish	Organic mental disorder and/or any terminal illness	Spa	Sub-study nested in a larger cohort study, PredictD, whose main objective was to develop a risk algorithm for the onset of MDD in general practice attendees (41 health centres and 231 physicians throughout Spain)	2679	69.7	< 15	CTQ	MDD	CIDI	50±15	SERT and BDNF polymorphism	
Haberstick et al. 2016	Prospective Cohort	NA	NA	US	National Longitudinal Study of Adolescent to Adult Health (Add Health)	4724	47.2	< 12	Own questions	Depressive symptoms	CES-D	22±1.77	5HTTLPR serotonin transporter polymorphism	
Laucht et al. 2013	Prospective cohort	First born child, singleton births and German-speaking parent	Severe physical handicaps, obvious genetic defects, or metabolic diseases	Ger	Ongoing epidemiological cohort study recruited from two obstetric and six children's hospitals of the Rhine-Neckar Region of Germany	300	54.3	< 15	CTQ	Depressive symptoms	BDI	23	CRHR1 polymorphism	
Uddin et al. 2013	Prospective cohort	Age 18 years or older, female sex	NR	US	Female participants from the Detroit Neighbourhood Health Study - a population-representative cohort study of adult residents residing in Detroit	495	100	< 18	CTS, CTQ and Wyatt's (1985) eight-item interview guide	PTSD and depressive symptoms	CAPS and PHQ-9	NR	Genetic variation at the ADCYAP1 R1 locus	
Uher et al. 2011	2 Prospective cohorts	Dunedin: Infant born in Dunedin between April 1972 and March 1973; E-Risk: Mother of twins	NR	NZ and Eng and Wales	Men and women from the Dunedin Study - infants born in Dunedin, New Zealand, between	E-Risk : 930; Dunedin:	E-Risk : 100; Dunedin:	< 15 and < 11	E-Risk study: CTQ; Dunedin study:	MDD	DIS (both)	E-Risk: 33±5.8; Dunedin: 32±0	5-HTTLPR SS-variant	

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		born in England and Wales			April 1972 and March 1973 and women from the E-Risk Study - mothers of twins	847	48			prospective observation and retrospective self-reports				
Van der Auwera et al. 2014	Prospective cohort	20–83 years old	Missing data	Ger	Data from the “study of health in Pomerania (SHIP)” - representative sample of adult German residents in northeast Germany living in 3 cities and 29 communities, with a total population of 212,157	4504	51.7	< 15	CTQ	Depressive symptoms	BDI-II and PHQ-9	53.7±14.4	Interaction of the SS-variant of 5-HTTLPR and TPH2 GG	
Vinkers et al. 2015	Prospective cohort	All 18 to 65 years old; Cases: history of DSM IV depressive and anxiety disorders,	All: Primary severe other psychiatric disorder that required specific other treatment (e.g. schizophrenia), not being fluent in Dutch	NL	Data from the NESDA	2304	63.1	< 15	CTQ	MDD	CIDI 2.1	18 to 65	Male gender in combination with mineralocorticoid receptor CA haplotype BDNF Val66Met polymorphism (time-dependent effect)	
Webb et al. 2016	Prospective cohort	Aged 18–75 years, able to read English, and scored 16 or higher on the Center for Epidemiologic Studies Depression Scale (CES-D)	Terminally ill, and residing in a nursing home	Australia	Recruited from the Diagnosis, Management and Outcomes of Depression in Primary Care (diamond) study, an ongoing prospective cohort that commenced in 2005	310	71	NR	CMHS R	Depressive symptoms	CES-D and PHQ-9	48.9±11.9		
Wichers et al. 2009	Prospective twin study	Twin and non-twin sisters from East Flanders	Missing data, reports not filled in within 15 min of the beep, subjects with <17 valid reports (out of 50), subjects with a current MDD	Bel	Twins and non-twin sisters from Flanders, Belgium recruited from the East Flanders Prospective Twin Survey (EFPTS) and from birth registers of Flemish municipalities in Belgium	621	100	< 15	CTQ	MDD	SCID and SCL-90R	28±7.9	Genetic variation	
<i>Note.</i> UK = United Kingdom ; US = United States ; Spa = Spain ; Ger = Germany ; NZ = New Zealand ; Eng = England ; Bel = Belgium ; CTQ = Childhood trauma questionnaire ; CTS = Childhood trauma screener ; PCL = PTSD checklist ; SCAN = Schedules for clinical assessments in neuropsychiatry ; HDRS = Hamilton depression rating scale ; CIDI = Composite international diagnostic interview ; BDI = Beck depression inventory ; CAPS = Clinician-administered PTSD scale ; PHQ = Physical health questionnaire ; DIS = Diagnostic interview schedule ; SCL = Symptom checklist														

Table A8

General information concerning the 14 cross-sectional moderation studies

Study	Inclusion criteria	Exclusion criteria	State	Sample source	N	%F	Age range of exposure	Exposure assessed with	Mental health outcome	Mental health outcome assessed with	Age at outcome mean ± SD	Moderator(s)
Aguilera et al. 2009	NA	Major medical illness affecting brain function, current substance abuse (alcohol or any illicit drug), Neurological conditions, history of head injury and personal	Spa	General population in Barcelona and Casetelló	534	54.7	< 17	CTQ	MDD	SCL-90-R	22.9±5.4	BDNF and SERT polymorphisms

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history of psychiatric medical treatment												
Antypa et al. 2010	None	None	NL	Students from the University of Leiden	248	76.4	< 17	CTQ	Depression and anxiety symptoms	HADS and LEIDS-R	22	5-HTTLPR polymorphism and cognitive reactivity
Appel et al. 2011	None	Missing data, unreliable information or inconsistencies in the interview	Ger	General population - Study of Health in Pomerania (SHIP)	2157	52.7	< 17	CTQ	MDD	BDI-II	55.85	FKBP5 polymorphism
Binder et al. 2008	None	None	Geo	Patients in general medical care and obstetrics-gynaecology clinics of an urban public hospital in Atlanta, Georgia, between 2005 and 2007	762	57.3	< 14	TEI	PTSD symptoms	M-PSS	40.8±13.8	FKBP5 polymorphism
Bradley et al. 2008	18 years of age or older	None	Geo	Patients at a general medical clinics of a large, public, urban hospital and Emory University, Atlanta, Georgia	497	61	< 17	CTQ	MDD	SCID and BDI	38.4±13.3	CRHR1 polymorphism
Brown et al. 2013	Female adult with at least one of the following: low self-esteem, negative core relationship, and chronic subclinical depression or clinically relevant anxiety	Problems with the genetic material	UK	Genetic samples were collected in 2006–2009 from women who had previously taken part in four studies of the general British population systematically enriched for risk factors for depressive disorders and with comparable recruitment and assessment procedures	273	100	< 17	CECA	MDD	SCAN	37±7	Serotonin transporter gene polymorphism
Dackis et al. 2012	Low-income and female sex	None	US	Low-income women who were initially recruited as part of a larger study examining the impact of maltreatment on children's functioning; recruited at random through the Department of Human Services (DHS) liaison	236	100	< 15	CTQ-SF	Depressive symptoms	BDI-II	33.8±6.9	Limbic irritability and FKBP5 polymorphism
Ertl et al. 2016	NA	Acute psychotic symptoms and obvious mental retardation	Uganda	Second-grade students from two suburban and seven rural communities in Uganda	369	54.56	<17	ETI and CTQ	PTSD symptoms	PDS	Males: 41.46 ±11.44; Females: 38.37 ±11.04	Alcohol consumption
Gibb et al. 2006	Inpatient in a psychiatric hospital	Inability to understand English	US	Recruited from a general psychiatric inpatient unit at Butler Hospital in Providence, Rhode Island between May and August 2003	30	53.3	< 15	CTQ	MDD	NR	36.1±11.5	Serotonin transporter gene polymorphism
Kranzler et al. 2011	Complete genotype and phenotype data	None	US	Recruited at four sites: University of Connecticut Health Centre, Yale University, the Medical University of South Carolina, the University of Pennsylvania and McLean Hospital	3080	42.9	< 13	Own questions	MDE	DSM IV	42	TAT-halotype of the CRHR1
Kruijt et al. 2014	None	Major depressive episode during the past month, outliers with respect to error rate, response times below 200 or above 2000 ms	NL	General population recruited via posters and flyers	215	86.1	< 15	CTQ-SF	MDD	MDQ	20±2.5	Non-significant finding: SERT polymorphism
McQuaid et al. 2013	Student at the Carleton University	Inability to determine a genotype from the samples provided	Canada	First and second year students recruited through the online computerized recruitment system of Carleton University	288	74	< 18	CMQ-SF	Depressive symptoms	BDI	19.99±3.2	OXTR polymorphism

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Meng et al. 2016	Aged 18 and over	NA	Canada	Canadian Community Health Survey 2012, representative sample of respondents residing in the 10 provinces of Canada	23395	NR	< 16	CEVQ	MDD, GAD	CIDI	NR	Gender
Min et al. 2013	Young adults	lifetime or current diagnosis of any psychiatric disorders	SK	Recruited by newspaper advertisement	206	47.6	< 15	CTQ	Anxiety symptoms	SCID and HADS-A	23.1±3.2	BDNF Val-66Met polymorphism and gender
Poole et al. 2017	Aged 18 and over	NR	Canada	EmbrACE Study, adult primary care patients from 11 primary care clinics in Calgary, Alberta, Canada	4006	68	NR	ACEQ	Depressive symptoms	PHQ-9	44±16.98	Psychological resilience
Xie et al. 2010	Member of a family which includes at least one affected sibling pair for cocaine or opioid dependence	None	US	493 participants were recruited as members of families each of which included at least one affected sibling pair for cocaine or opioid dependence; The remaining samples were collected from cocaine, opioid or alcohol dependence cases and unaffected controls and recruited from Yale University School of Medicine, University of Connecticut Health Centre, Medical University of South Carolina and McLean Hospital of Harvard Medical School	2427	48.1	< 13	SSAD DA	PTSD	SSADDA	38.1±11.3	FKBP5 polymorphism and alcohol dependence
Xie et al. 2012	Member of a family which includes at least one affected sibling pair for cocaine or opioid dependence	None	US	Yale University School of Medicine (2,406 subjects), the University of Connecticut Health Centre (2,171 subjects) and the University of Pennsylvania School of Medicine (601 subjects)	5178	44	< 13	SSAD DA	PTSD	SSADDA	40.5±11.2	SS variant of 5-HTTLPR (only in European Americans)
<i>Note.</i> Spa = Spain ; NL = The Netherlands ; Ger = Germany ; Geo = Georgia ; UK = United Kingdom ; US = United States ; SK = South Korea ; CTQ = childhood trauma questionnaire ; TEI = Traumatic events inventors ; CECA = Childhood experience of care and abuse questionnaire ; CMQ-SF = Childhood maltreatment questionnaire - short form ; SSADDA = Semi-structured assessment for drug dependence and alcoholism												

Table A9

General information concerning the 55 non-cross-sectional association studies

Study	Study design	Inclusion criteria	Exclusion criteria	State	Sample source	N	%F	Age of exposure	Exposure assessed with	Mental health outcome	Mental health outcome assessed with	Age at outcome mean, SD or range (years)	Associated variable (+ statistical analysis)
Anda et al. 2002	Retrospective cohort	Kaiser Health Plan members	None	US	Patients at Kaiser Permanente's San Diego Health Appraisal Clinic between August 1995 and March 1996 - representative sample	9346	54	< 15	CTS	MDD	National Health Interview Survey and DIS	56.6±15.6	Alcoholism (odds ratio)
Baes et al. 2014	Single-blind non-randomized placebo-controlled repeated-measures	Current MDE for experimental group	History of hypersensitivity to corticosteroids or steroid use, heavy smoking (more than 25 cigarettes a day), a viral illness during the preceding 2 weeks, pregnancy or lactation, alcohol dependence and significant physical illness	Brazil	Inpatients and healthy controls (recruited from hospital staff, students and the local community via public advertisement)	30	74.2	< 17	CTQ	MDE	MINI HAM-D	38.35	Impaired mineralocorticoid receptor (MR) activity

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Bet et al. 2009	Prospective cohort	NA	NA	NL	Large population based sample of older men and women as part of the Longitudinal Aging Study Amsterdam (LASA)	906	69	< 18	Own questions	Depressive symptoms	CES-D	77±6.9	GR 22/23EK and 9beta (odds ratio)
Bluhm et al. 2009	Matched-controls	Experimental group: medicated and unmedicated female patients with chronic PTSD related to early-life trauma; Control group: healthy females	History of head injury or neurologic disorders or a history of drug or alcohol abuse in the 6months preceding the scan	Canada	Participants were recruited via advertisement in the community and within the health care network in London, Ontario	32	100	< 17	CTQ-SF	PTSD	CAPS and SCID	Experimental group: 39±9 ; Controls: 38±13	Alteration in default network connectivity (correlations)
Breslau et al. 2013	Prospective cohort	NA	NA	NZ	Dunedin Multidisciplinary Health and Development Study (DMHDS), children born in Dunedin during 1972–1973 South-West mental health services in Dublin	928	49.1	< 18	Interviews, expert observation and self-report CTQ	PTSD	DIS-IV	38	Retraumatization in adulthood (odds ratio)
Carballido et al. 2012	Matched-controls	20 healthy volunteers with first degree family history of depression and 20 healthy controls without family history for a psychiatric disease	Personal history of neurological or psychiatric disorder (Axis I or Axis II), neither a history of severe medical illness, head injury or substance abuse	IRE	South-West mental health services in Dublin	40	65	< 15	CTQ	Depressive symptoms	HDRS, BDI-II, MADRS and SCID-I	36.5±13	Structural changes in brain regions associated with emotional processing (F and t-tests)
Chalavi et al. 2015	Matched-controls	Controls were matched for sex, age, years of education and Western European ancestry	Healthy controls: a high score of dissociative symptoms, current or past psychiatric disorder; for all participants: age outside the range of 18–65, pregnancy, systemic or neurological illness, claustrophobia, presence of metal implants, and alcohol/drug abuse	NL	PTSD patients with a history of interpersonal traumatizing events and dissociative personality disorder patients were recruited via mental healthcare institutions and controls via internet advertisements	61	100	< 15	CTQ	PTSD	SCID	42.16	Decreased hippocampal volume (correlation)
Chaney et al. 2014	Matched-controls	Patient group: currently depressed; Controls: matched on age	Patients: History of neurologic or severe internal disorders, head injury, substance abuse or comorbid axis I or II disorder; Healthy controls: any psychiatric disorder (Axis I or Axis II)	IRE	Dublin South-West Mental Health Service	83	59	< 15	CTQ	MDD	HAMD, BDI and SCID-I	40±11.67	Decreased hippocampal volume (t-tests and r square)
Chen et al. 2014	Matched-controls	MDD for patients and controls matched on age ± 3 years, gender and ethnicity	Subjects with lifetime diagnoses of bipolar or psychotic illness or with diagnoses of alcohol or substance abuse within the preceding six months, symptoms of PTSD in the past month; Other comorbid anxiety diagnoses were permitted within the MDD group if MDD was considered the primary diagnosis	US	Clinical referrals (MDD patients) and general population (control group)	40	NR	< 18	ACE	MDD	SCID, QIDS and HDRS	NR	Increased telomerase activity (correlation)
Cohen-Woods et al. in press	Prospective cohort	MDD cases experienced a minimum of two DSM-IV/ICD-10 depressive episodes of moderate to severe severity	Cases: History of substance-related disorders, mania or hypomania, mood-incongruent psychosis, and a first or second-degree relative with bipolar or psychotic disorder; Controls: personal or first-degree relative with a history of any psychiatric disorder	UK	Individuals were drawn from the Radiant MDD cohort recruited in the United Kingdom from three sites (Birmingham, Cardiff, and London), described in detail previously (Fisher et al., 2013; Lewis et al., 2010)	262	72.52	<17	CTQ	MDD	SCID	47.49 ±9.24	Genetic prediction (risk difference)

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Demers et al. 2015	Matched-controls	For experimental group: DSM IV defined PTSD	Claustrophobia, PTSD symptom remission, neurological disease, left-handedness, no history of childhood maltreatment, medical conditions that might affect brain structure, current substance use disorder; current nicotine use, use of other psychotropic medication, structural abnormalities on MRI scan or a positive urine toxicology test	US	Recruited via advertisements in the local Boston community	61	60	< 18	TLEQ	PTSD	SCID-I	34.6±11.5	Dorsal anterior cingulate cortex gray matter thickness (correlations)
Danese et al. 2008	Prospective cohort	NA	Pregnant women	NZ	Infants born in Dunedin, New Zealand, between April 1972 and March 1973 and followed up at ages 3, 5, 7, 9, 11, 13, 15, 18, 21, 26 and 32 years	972	62	< 18	Self report, expert observation and parental reports	MDD	DIS	32	Pro-inflammatory markers (relative risk)
Danese et al. 2009	Prospective cohort	NA	Pregnant women	NZ	Infants born in Dunedin, New Zealand, between April 1972 and March 1973 and followed up at ages 3, 5, 7, 9, 11, 13, 15, 18, 21, 26 and 32 years	972	62	< 18	Self report, expert observation and parental reports	MDD	DIS	32	Pro-inflammatory markers and clustering of metabolic risk markers (incident rate ratio)
Ekinici et al. 2015	Matched-controls	Experimental group: met DSM IV criteria for substance dependence, able to read and write	Mental retardation or psychotic disorders	Turkey	The experimental group was admitted to the Balikh Rum Hospital in Istanbul between March 2012 and April 2013	95	9	< 15	CTQ	Depression and anxiety symptoms	BDI and BAI	25.1±6.2	Substance dependence and self-esteem (Chi square tests, correlations and t-tests)
Faraveli et al. 2010	Matched-controls	Aged between 18 and 65 years, any Axis I diagnosis as assessed by the SCID-I and acute phase of the illness	Substance abuse or dependence, organic mental disorder, physical illnesses altering HPA axis function such as Cushing disease, obesity, thyroid dysfunctions, chronic infections, pregnancy, breast-feeding, epilepsy etc.	Italy	Moderate to severely ill psychiatric out-patients of Florence and Pisa University Psychiatric Units and 33 healthy control subjects	126	49.4	< 15	CECA	Axis I disorders	SCID-I	41.9±14.7	Dexamethasone non-suppression and higher salivary cortisol levels (t-tests, chi square tests and logistic regression)
Farrugia et al. 2011	Part of an RCT	Substance use in the previous month, past-month diagnosis of PTSD according to the DSM-IV-TR or partial PTSD, aged 18 or over and fluency in English	Currently suicidal or self-harming, psychotic, or exhibiting cognitive impairment severe enough to impede treatment	AUS	The data were collected between October 2007 and June 2009 as part of a randomised controlled trial (RCT) examining the efficacy of an integrated psychological treatment for SUD+PTSD (Mills, Back et al., 2007)	103	62	NR	CIDI version 2.1	PTSD, depressive and anxiety symptoms	CAPS, BDI and STAI	33.7±7.9	Retraumatization, substance misuse and dependence (t-tests, odds ratios, Mann Whitney U tests)
Ford et al. 2012	Retrospective cohort	NA	NA	UK	Data from a large birth cohort study (the 1958 British birth cohort/National Child Development Study) which includes all births in one week in 1958 in England, Scotland and Wales	9377	50.3	< 16	Self-report, parental report, observation and medical records	Affective and anxiety disorders	CIS-R	45	Negative aspects of close relationships and decreased social network size
Frodl et al. 2012	Matched-controls	Experimental group: unaffected first-degree healthy relatives of patients with MDD; healthy controls: no family history of psychiatric disease	Diagnosed comorbidity of first-degree family members or personal history of neurologic or psychiatric disorders (Axis I or Axis II)	IRE	Recruited siblings or children of adult patients undergoing treatment for recurrent MDD in the mental health services department of the Adelaide and Meath Hospital in Ireland	45	60	< 15	CTQ	Depressive symptoms	BDI and HAM-D	36.4±12.8	Greater fractional anisotropy and structural changes in white matter tracts involved in cognitive-emotional processes (correlation)

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Gonzalez et al. 2012	Prospective cohort	Children (aged 4-16) born from January 1, 1966 through January 1, 1979, whose usual place of residence was a household in Ontario.	Living (i) on First Nation reserves; (ii) in collective dwellings such as institutions; and (iii) in dwellings constructed after June 1, 1981 (Census Day)	Canada	Data from the initial (1983) and third (2001) waves of the Ontario Child Health Study - population-based study	1475	51	< 16	CEVQ-SF	MDD	CIDI-SF	22-34	Chronic pain conditions (multinomial logistic regression and odds ratios)
Grabe et al. 2010	Prospective cohort	None	Bipolar disorder	Ger	Caucasian subjects from the German general population (Study of Health in Pomerania, SHIP)	1638	52.6	< 15	CTQ	Depressive symptoms	BDI-II	53.6±13.6	TAT-haplotype of the CRHR1 (Linear regression - interaction effects)
Grabe et al. 2012	Prospective cohort	None	Unreliable information or inconsistencies in the interview according to the judgment of the interviewer and the supervisor, missing genetic data, missing BDI-II values, missing values for childhood abuse	Ger	Caucasian subjects from the German general population (Study of Health in Pomerania, SHIP)	1974	52.3	< 15	CTQ	Depressive symptoms	BDI-II	56.1±13.8	Serotonin transporter gene polymorphism and adult traumatic experiences (Tobit regression-interactions)
Grassi-Oliveira et al. 2008	Matched-controls	Two patient groups: Female, stable dosage of antidepressant for at least 3 months prior to the experiment, diagnosis of recurrent MDD and childhood physical neglect present and absent (i.e. differentiating the two patient groups); Controls: matched for gender and age	Controls: any past or current Axis I disorder, any history of childhood maltreatment, severe or unstable clinical illness, neurological disorder, or any psychoactive substance use in the last 30 days (except nicotine and caffeine)	Brazil	Outpatients of an affective unit at the Hospital Presidente Vargas, Porto Alegre, Brazil	49	100	< 15	CTQ	MDD	SCID-I and BDI	38.5±7.9	Low brain-derived neurotrophic factor levels and memory performance (short-term and long-term) (ANOVA F-tests and correlations)
Gülec et al. 2013	Matched-controls	Patient group: MDD; Controls: matched for age, sex, and education	Patient group: comorbid psychiatric disorders, chronic somatic or physical diseases and use of psychotropic agents during the 15 days before assessment; Controls: no history of psychiatric disorders or medical diseases	Turkey	Patient group: outpatients; Controls: hospital staff members and their relatives	150	71.3	< 15	CTQ	MDD	HDRS and SCID	39.7±11.5	Alexithymia and somatisation (partial correlation analysis and linear regression)
Harkness et al. 2015	Case-control	Case group meeting DSM-IV criteria for a current unipolar depressive disorder and a non-psychiatrically ill group matched on sex, age, and ethnicity	Lifetime bipolar/psychotic/substance disorder	Canada	Recruited from advertisements and referrals to the University of Toronto or Queen's University between March, 2007 and March, 2013	339	78.2	< 17	CECA	MDD	SCID and BDI-II	22 to 33	SERT S-variant and BDNF Met-variant (odds ratios)
Honkalampi et al. 2005	Prospective cohort	Female	None	FIN	A stratified random sample of women from the general population living in the district of Kuopio in eastern Finland in 1999	835	100	NR	Own questions	Depressive symptoms	BDI	46.0±10.7	Insufficient social support, poor subjective health and financial difficulties (multinomial logistic regression analysis and odds ratios)

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Jeon et al. 2012	Prospective cohort	Experimental group: MDD defined by DSM-IV, HAM-D score > 16, and between 18 and 65 years old	Psychotic disorders, bipolar disorder, organic mental disorders, mental retardation, epilepsy or neurologic illness, alcohol or substance abuse or dependence, personality disorders, and serious medical illnesses, including cardiovascular, gastrointestinal, respiratory, endocrinologic, and genitourinary system diseases, antidepressant medication, antipsychotics, mood stabilizers, and acetylcholine esterase inhibitors	South Korea	Recruited from the outpatient clinic of the Department of Psychiatry and Depression Centre at the Samsung Medical Centre	155	71	< 18	ETISR-SF	MDD	MINI and HAM-D	43.3±12.7	High platelet BDNF levels (ANOVA, Tukey's post-hoc test and correlations)
Jones et al. 2013	Prospective cohort	Regular in the UK armed forces personnel	None	UK	Random sample of regular UK armed forces personnel who deployed to Iraq, Afghanistan or other operational areas or were not deployed contacted between 2004 and 2009	8261	9..3	NR	16-item scale derived from a factor analysis	PTSD	PCL-C	NR	Lower rank, leaving service, having had a serious accident and holding a combat role (odds ratios)
Kim et al. 2013	Prospective cohort	Living in South Korea	Respondents who were less than 18 years old, did not participate in the second wave of KOWEPS or had missing values for depressive symptoms, childhood abuse or any covariates	South Korea	Nationally representative longitudinal survey - data from the Korean Welfare Panel Study	11526	55.4	< 18	Own questions	Depressive symptoms	CES-D	18 to 98	Gender (odds ratios)
Klein et al. 2015	Retrospective cohort	MDE > 2 years, double depression or dysthymia - DSM IV, HAM-D score >9, above 18 years and stable psychiatric medication	Acute suicidality, history of psychosis, diagnosis of substance dependence and current psychotherapy	Ger	Recruited from an RCT in an outpatient psychotherapy centre over a period of 18 months from 2010 to 2012	279	63.8	< 15	CTQ-SF	MDD	SCID and BDI	38.7±10.6	Avoidant personality disorder (odds ratios)
Korkeila et al. 2010	Prospective cohort	None	None	FIN	Working-aged respondents from the Health and Social Support in Finland (HeSSup) Study - representative general population	16877	62	NR	Own questions	Depressive symptoms	BDI	20 to 54	Negative life events in adulthood (odds ratios)
Leardman et al. 2010	Prospective cohort	Cases: ICD-9-CM-coded diagnoses listed in the medical record within 24 months following deployment and prior to the end of the study period	Diagnosis of PTSD before or during first deployment, diagnosis for any of the mental health disorders prior to or during their first deployment, female sex or missing data	US	Part of the Recruit Assessment Program survey at Marine Corps Recruit Depot in San Diego who were deployed in support of military conflicts between September 2001 and June 2004	8391	0	< 17	CTQ, CTS and questions adapted from Wyatt (1985)	PTSD	Medical records	NR	Deployment (multivariable modelling adjusted for covariates)
Lenze et al. 2008	Matched-controls	A history of recurrent major depression, with at least one prior episode requiring psychiatric treatment, female gender, right-handed, and no medical illness potentially affecting the central nervous system	Current acute depression, acutely depressed within the past 4 months, more than three courses of electroconvulsive therapy, current or past neurological disorder, head trauma, uncontrolled hypertension, myocardial infarction or ischemia, diabetes, Cushing's Disease, steroid use, or drug/alcohol abuse and male sex	US	Cases recruited from an outpatient psychiatry service at Washington University School of Medicine, referrals from psychiatrists and advertisements to the general public; Control participants were recruited from the Aging and Development Project at Washington University and notices posted at the medical centre	55	100	< 18	CECA	MDD	HAM-D	48±14.5	Non-significant finding: hippocampal volume

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Liberzon et al. 2014	Prospective cohort	Prospective cohort: trauma exposure ; replication cohort: trauma-exposed	Prospective cohort: Non-European ancestry, no lifetime trauma exposure	US	Prospective cohort: Ohio National Guard Study of Risk and Resilience, a prospective longitudinal study of post-deployment psychological health; Replication cohort: trauma-exposed primarily African American women with low levels of income and education, enrolled in the Grady Trauma Project at Emory University	(1): 810 (2): 2083	(1): 15.7 (2): 69.9	NR	TEI	PTSD	PCL	NR	ADRB2 gene polymorphism (linear regression models adjusted for covariates)
Lok et al. 2013	Prospective cohort	Experimental group: top or bottom quintile of total scores of psychotic experiences	All: Random answers, failing to correctly complete the verification questions and incomplete data set; Controls: history of any psychotic disorder	NL	Recruited using a project website launched in 2006 targeted at Dutch young adults and adolescents from age 18 to 25 years - the Cannabis Quest cohort	124	74.2	< 16	CTQ and NLEQ	MDD	SCID-I and HAM-D	44.6±9.8	MTHFR polymorphism (Cox regression model)
Lu et al. 2013	Matched-controls	Experimental group: MDD - DSM IV, aged 18–45 years; 3) at least junior middle school level of education; 4) Han ethnicity; Controls: age- and gender-matched	Current infection, somatic trauma and autoimmune diseases, any other psychiatric axis-I or axis-II disorders (except MDD) after SCID screening, history of alcohol and drug dependence, family history of bipolar disorder, organic disease of brain and severe somatic disease, history of loss of consciousness, pregnancy or in lactation period, history of seizures or with a family history of epilepsy, receiving hormone for treatment	China	Experimental group: recruited from the psychiatric clinic of the Second Xiangya Hospital of Central South University, Changsha, Hunan, P.R. China from December, 2010 to July, 2011; Controls: recruited from the local community via advertisement	65	55.4	< 15	CTQ	MDD	SCID, SDS and HAM-D	29.3±6.71	Elevated cytokine levels (ANOVA, Kruskal–Wallis H analyses and Spearman rank correlations)
Melander et al. 2013	Case-control	Cases: diagnosed with major depression, mixed anxiety depression or dysthymia, in at least one of the two PART waves	Controls: no psychopathological symptom of depression, anxiety, social phobia, agoraphobia, obsessive-compulsive disorder, eating disorder, use of illicit drugs or social disability due to psychological problems, in either of the two PART waves	SWE	Derived from the PART study; a longitudinal population-based study of mental health, work and relations in Stockholm County, Sweden	1668	59.5	< 18	Own questions	MDD	MDI	29 to 74	MAOA-L variant (linear regression, odds ratios and chi square tests)
Opel et al. 2014	Matched-controls	Cases: inpatient treatment at the University Hospital of Münster, scores of >18 on the BDI ; Controls: age- and sex-matched, scores of < 10 on the BDI	All: history of severe neurological (e.g. concussion, stroke, tumour, neuro-inflammatory diseases) and medical (e.g. cancer, chronic inflammatory or autoimmune diseases, infections) conditions; Controls: history of psychiatric disorders or any psychotropic medication	Ger	Cases: inpatients receiving treatment at the University Hospital of Münster; Controls: recruited via newspaper advertisement	170	61.8	< 15	CTQ	MDD	SCID I, HAM-D and BDI	37.4±11.9	Reduced hippocampal volume (ANCOVA and partial correlations)
Ouellet-Morin et al. 2015	Prospective cohort	Women who gave birth to twins in England and Wales in 1994–1995	Lifetime history of depression prior to T1 (i.e. first measurement)	ENG Wales	Mothers involved in the Environmental Risk (E-Risk) Longitudinal Twin Study, a nationally representative cohort of women who gave birth to twins in England and Wales in 1994–1995	978	100	< 15	CTQ-SF	MDD	DIS	33 for T1, 38 for T2, 40 for T3	Intimate partner violence (bivariate and multivariate logistic regression - odds ratios)

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Pace et al. 2006	Case-control	All: male subjects, medically healthy as determined by physical examination and laboratory testing; Cases: DSM IV MDD	Past or current psychotic symptoms, bipolar disorder, substance abuse/dependence within 1 year, current eating disorder, and use of psychotropic medication	US	Recruited between May 2003 and April 2005 as part of a study investigating the neurobiology of early life stress and major depression.	28	0	< 15	CTQ	MDD	SCID	29.65±8.8	Enhanced inflammatory responsiveness (ANOVA, Mann-Whitney-U test, correlations and multiple regression analyses)
Parlar et al. 2014	Matched-controls	Cases: DSM IV diagnosis of current chronic PTSD due to a history of childhood trauma; Controls: Age- and sex-matched	History of neurological disease, traumatic brain injury, and/or head injury with loss of consciousness (lasting more than 60 sec), substance abuse in the last 6 months, current or lifetime history of substance dependence, current or prior history of untreated significant medical illness, bipolar disorder or a psychotic disorder; Controls: history of psychotherapy	Canada	Cases were recruited from London Health Sciences Centre (LHSC) in London, Ontario, Canada; Controls were recruited from St. Joseph's Healthcare Hamilton, in Hamilton, Ontario and LHSC	49	100	< 15	CTQ	PTSD	CAPS	39.2±12.7	Impairments in empathic functioning (Mann-Whitney U-test, ANOVA, multiple linear regression analyses using stepwise entry)
Patten 2013	Prospective cohort	None	MDE at baseline, 12–18 year olds (in 2004), First Nation reserves and the Armed Forces	Canada	Data from the Canadian National Population Health Survey (NPHS) - nationally representative community sample assembled by Canada's national statistical agency in 1994/1995	8223	52.1	NR	Own questions	MDD	CIDI-SF	NR	Stressors in adulthood (bootstrapping, logistic and linear regression analysis)
Pederson et al. 2004	Matched-controls	All: right-handed women aged 20-40 years; PTSD group: prepubescently abused at least 5 years and diagnosis of PTSD; Abuse group: prepubescently abused at least 5 years and no diagnosis of PTSD; Controls matched on age, education, and exposure to alcohol, nicotine, and illicit drugs	All: serious medical condition, suffered a head injury that rendered her unconscious more than 5 min, attention deficit disorder or learning disabilities; Controls: history of abuse or PTSD	US	Phone interviews were completed with 7 19 potential participants who responded to advertisements	51	100	< 15	TSI and CTQ	PTSD symptoms	CAPS	25.13±5.8	Non-significant finding: memory performance and hippocampal volume (MANOVA, ANOVA and correlations)
Peng et al. 2013	Matched-controls	All: 18 to 45 years; Cases: MDD diagnosis and ≥15 for emotional neglect, ≥10 for physical neglect, or ≥20 for comorbid emotional and physical neglect sum score on CTQ subscale(s); Control MDD patients: MDD diagnosis and matched on age, gender, illness course, severity of depression, or treatments received; Healthy Controls: age- and sex-matched	Psychiatric axis-I or axis-II disorders, any other neurological disorder, any substance use within the past 6 months, electroconvulsive therapy (ECT), any kind of contraindication for magnetic resonance imaging (MRI), any other clinically relevant abnormalities in their medical history or laboratory examinations and CTQ subscale (other than neglect) scores < 8	China	Recruited from the inpatient and outpatient units at the Institute of Mental Health at the second Xiangya Hospital of Central South University; Healthy controls were recruited from the local community	60	NR	< 15	CTQ	Depressive symptoms	HAMD and SDS	18-45	White-matter microstructural abnormalities (ANOVA, post-hoc tests and correlations)

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Peng et al. 2014	Matched-controls	18 to 45 years	Psychiatric axis-I or axis-II disorders, any other neurological disorder, any substance use < 6 months, ECT, any kind of contraindication for magnetic resonance imaging (MRI), any other clinically relevant abnormalities in their medical history or laboratory examinations, CTQ subscale (other than neglect) scores < 8, salivary samples polluted by minor bleeding in the oral cavity, or samples that were collected after having breakfast, drinking something or brushing teeth during the first half hour after awakening	China	Recruited from inpatient and outpatient units of Guangzhou Psychiatric Hospital, Affiliated Hospital of Guangzhou Medical University	81	50.6	< 15	CTQ	Depressive symptoms	HAMD and SDS	28.4±6.3	Non-significant finding: HPA axis activity (ANOVA and correlations)
Peyrot et al. 2014	Prospective cohort	Cases: DSM IV lifetime diagnosis of MDD	Controls: diagnosis of a depressive, dysthymic, anxiety or other psychiatric disorder in their lifetime; All: not fluent in speaking Dutch or primary diagnosis of psychotic, obsessive-compulsive, bipolar or severe substance use disorder, genetic batch effect, data missing rate > 5%, excess genome-wide heterozygosity or inbreeding levels, contrast QC < 0.4, genotypic inconsistencies regarding reported gender or non-European/non-Dutch ancestry as indicated with principal component analysis	NL	Data from the Netherlands Study of Depression and Anxiety (NESDA) - participants recruited from mental healthcare settings, general practices and the general population in the period from 2004 to 2007	1985	66.1	< 16	CTI in an interview	MDD	CIDI	42.8±8.5	Polygenic risk scores (linear regression, logistic regression and bootstrapping)
Polanczyk et al. 2009	2 prospective cohorts	None	None	END, Wales and NZ	Sample 1 were women from the E-Risk Study and Sample 2 were men and women from the Dunedin Study	1116 and 1037	100 and 48	< 15; and < 11	E-Risk: CTQ; Dunedin : prospective observation and retrospective self-reports CTQ	MDD	DIS (both studies)	40±5.8 and 32	Protective Effect of CRHR1 TAT haplotype - mixed findings (logistic regression)
Power et al. 2013	Matched-controls	Cases: DSM-IV and/or ICD 10 recurrent MDD (i.e. at least two episodes of depression of at least moderate to severity, separated by 2 or more months of remission); All: parents and grandparents of white European origin	All: Below 18 years old; Cases: history of mania or hypomania, mood-incongruent psychosis, and a first or second-degree relative with bipolar or psychotic disorder; Controls: personal or first-degree relative with a history of any psychiatric disorder	ENG	Cases and healthy controls were drawn from the Cardiff and London sites of the Depression Case Control (DeCC) multi-centre study	455	66	< 15		Recurrent MDD	DSM IV and/or ICD 10	46.3±0.73	Stressful life events in adulthood (logistic regression model)

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Prigers on et al. 1996	Prospectiv e cohort	Age 60 or above and non-cognitively impaired spouses of the terminally ill (i.e., individuals whose life expectancy was estimated to be 6 months or less	None	US	Recruited as part of the Psychosocial Factors in Depression among Bereaved Elders study designed to prospectively investigate the long term effects of specific psychosocial factors on bereavement-related depression	50	62	< 17	CECA in a semi- structure d intervie w	Anxiety disorder s	SCID	70±9.1	Paranoid, histrionic and self- defeating personality style (logistic regressions)
Raparia et al. 2016	Matched- controls	Age between 18 and 55 years, negative urine toxicology at screening and day of scan, and, for females of reproductive age, use of an effective birth control method, including abstinence	Poor motion-degraded spectral quality of the lactate signal, history of psychotic disorder, bipolar disorder, OCD, neurological illness, structural heart disease, diabetes mellitus, hepatic disease, inflammatory bowel disease, primary sleep disorders, HIV, Lymedisease, systemic lupus erythematosus, mental retardation or learning disability, or any unstable medical condition	US	All subjects had participated in a neuroimaging study as psychiatric or healthy controls in a study of chronic fatigue syndrome (Mathew et al. ,2009)	32	65.6	< 15	CTQ	GAD	SCID, HAM-A and PSWQ	37.2±12.2	Configurati on of neurometab olites in the RPFC and functionally related PMC and SSC (correlations and omnibus general linear model)
Ritchie et al. 2009	Prospectiv e cohort	Aged 65 years and older	Severe disability, incomplete data	France	Community-dwelling persons were recruited by random selection from the 15 electoral roles of the Montpellier District, France, between March 1999 and February 2001 as part of the Esprit study of late life psychiatric disorder	942	58	NR	Question naire based on a review of existing instrume nts covering 25 adverse and 8 protectiv e factors	Depressi ve and sympto ms	MINI and CES-D	72 (65 to 92)	5-HTTLPR long allele and poverty (polytomous logistic regression models and Wald chi square tests)
Spinho ven et al. 2014	Prospectiv e cohort	All 18 to 65 years old ; Healthy controls: none; Case group 1; prior history of DSM IV depressive and anxiety disorders, Case group 2: current DSM IV depressive and/or anxiety disorder	Primary severe other psychiatric disorder that required specific other treatment (e.g. schizophrenia), not being fluent in Dutch	NL	Part of the Netherlands Study of Depression and Anxiety (NESDA) - controls recruited from the general population and cases via a screening procedure in general practice specialized health care centres	2402	66.4	< 15; and < 16	1) CTQ 2) CTI	Depressi ve and anxiety disorder s and PTSD	CIDI and PSS-I	46.0±13.1	High neuroticism and low extraversion (multivariab le logistic regression)
Treadw ay et al. 2009	Matched- controls	All: 18 and 55 years of age; Cases: DSM IV MDD, 16 or higher on the HDRS and antidepressant-free at the time of scanning; Controls: six or less on the HDRS	All: significant history of neurological disease or lifetime history of brain injury, psychosis, mania, substance dependence, substance abuse within the previous six months, missing data or statistical outliers; Cases: comorbid Axis I disorders; Controls: any Axis I disorder (except mild agoraphobia)	US	Recruited through the Vanderbilt University Medical Centre Outpatient Psychiatry Clinic or through television advertisements	38	52.6	< 15	CTQ	MDD	SCID and HDRS	32.8±9.6	Cortisol levels and decreased rACC volume (ANCOVA and partial correlations)
Ugwu et al. 2015	Matched- controls	Cases: DSM IV-TR MDD; Controls: age and gender- matched	All: personal history of neurological or psychiatric disorders (Axis I or Axis II) or a history of severe medical illness, head injury or substance abuse	IRE	Controls: recruited from the local community via announcements; Cases: undergoing treatment for first onset or recurrent MDD at the mental health services of the Adelaide and Meath Hospital	92	59.8	< 15	CTQ-SF	MDD	DSM IV-TR diagnosi s, SCID, HRDS and BDI-II	38.3±11.5	Microstruct ural anomalies in affective brain networks (ANCOVA, Pearson product moment correlations and RM- ANCOVA)

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Veer et al. 2015	Matched-controls	All: female sex, right-handed, fluency in Dutch, body mass index between 19 and 26 kg/m ² ; Cases: DSM IV PTSD and history of childhood maltreatment; Controls: age and years of education-matched	Cases: Repetitive psychotic episodes, use of antipsychotic medication; Controls: history of psychiatric disorders, score <145 on the Symptom Check List; All: presence or history of a major internal or neurological illness, MINI diagnosis of substance abuse and/or addiction, pregnancy and general MRI contraindications	NL	Patients were recruited within primary mental health care institutions (de Voorde, Leiden and Trauma Centre, PsyQ, The Hague) in the vicinity of the Leiden University Medical Centre; Female controls were recruited by means of advertisements	24	100	< 18	HTQ	PTSD	MINI	27.5±6.9	Smaller right amygdala volumes (correlations)
Veijola et al. 1998	Prospective cohort	Born between 1905 and 1954 in Uusikaupunki or Kemijärvi	NR	FIN	Uusikaupunki Kemijärvi Study (UKKI) Study consisted of 1000 subjects representative of the general population chosen from two small towns and the surrounding countryside in Finland	1000	49.9	< 16	Own questions	Psychotic and neurotic depression	ICD-8 and medical /insurance records	31 to 80	Gender and neuroticism (multivariate logistic regression)
Walsh et al. 2014	Prospective cohort (DNHS) and cross-sectional (GTP)	None	None	US	Data from the Detroit Neighbourhood Health Study (DNHS) and the Grady Trauma Project (GTP) - African American household residents from Detroit, MI and African American patients recruited from waiting-rooms in primary care clinics in Atlanta, GA	682	62.8	< 16	Emotional abuse subscale of the CTQ	PTSD symptoms	PCL-S	47.7±15.1	SS variant of 5-HTTLPR - protective (ANCOVA)

Note. US = United States ; NL = The Netherlands ; IRE = Ireland ; NZ = New Zealand ; Ger = Germany ; FIN = Finland ; SWE = Sweden ; ENG = England ; CTS = Childhood trauma screener ; CTQ = Childhood trauma questionnaire ; ACE = Adverse childhood experiences questionnaire ; TLEQ = Traumatic life events questionnaire ; CECA = Childhood experiences of care and abuse questionnaire ; CIDI = Composite international diagnostic interview ; CEVQ-SF = Childhood experiences of violence questionnaire-short form ; ETISR-SF = Early trauma inventory self report-short form ; TEI = Traumatic events inventory ; NLEQ = Negative life events questionnaire ; TSI = Trauma symptom inventory ; CTI = Childhood trauma inventory ; HTQ = Harvard trauma questionnaire ; MINI = Mini international neuropsychiatric interview ; HAM-D = Hamilton depression scale ; CES-D = Centre for epidemiological studies depression scale ; CAPS = Clinician-administered PTSD scale ; SCID = Structured clinical interview for DSM disorders ; DIS = Diagnostic interview schedule ; HDRS = Hamilton depression rating scale ; BDI = Beck depression inventory ; MADRS = Montgomery Asberg depression rating scale ; QIDS = Quick inventory of depressive symptomatology ; BAI = Beck anxiety inventory ; STAI = State-trait anxiety inventory ; CIS = Clinical interview schedule ; PCL = PTSD checklist ; SDS = Self-rating depression scale ; MDI = Major depression inventory ; DSM = Diagnostic and statistical manual for DSM disorders ; HAM-A = Hamilton anxiety scale ; PSWQ = Penn state worry questionnaire ; PSS = PTSD symptom scale ; ICD = International classification of diseases

Table A10

General information concerning the 80 cross-sectional association studies

Study	Inclusion criteria	Exclusion criteria	State	Sample source	N	%F	Age of exposure	Exposure assessed with	Mental health outcome	Mental health outcome assessed with	Age at outcome mean, mean ± SD or range (years)	Associated variable (and utilized statistical analyses)
Bakim et al. 2011	Panic Disorder as defined by DSM-IV-TR criteria	Mental retardation, dementia, general medical problems, history of alcohol/drug addiction and comorbid anxiety disorders	Turkey	Patients at Şişli Etfal Education and Research Hospital, Anxiety Disorders Outpatient Clinic between November 2006 and September 2007	81	71.6	< 17	CTQ	MDD and Panic Disorder	SCID-I	36±11.6	Sexual dysfunction (correlation)
Banducci et al. 2014	Negative urine drug screen	None	US	Inpatients in a residential substance use treatment Centre in Washington D.C.	280	30.3	< 17	CTQ-SF	Axis 1 and axis 2 disorders	SCID-I, HAM-D	43.3±9.8	Substance misuse and comorbid mental disorders (odds ratios)
Barrios et al. 2015	Women initiating prenatal care prior to 16 weeks gestation	Younger than 18 years of age, not being able to speak and read Spanish, or more than 16 weeks gestation	Peru	Women attending prenatal care clinics at the Instituto Nacional Materno Perinatal (INMP) in Lima, Peru	1521	100	< 18	CPSAQ	Depressive symptoms	PHQ-9	28.0±6.2	Inter-personal violence and poor general health (odds ratios)

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Batten et al. 2004	None	Childhood depressive disorders	US	National Comorbidity Survey - general population	5308	49.9	< 15	CTS	MDD	CIDI - DSM III	33.2±11	Cardiovascular disease and female sex (CVD) (odds ratio)
Brockie et al. 2015	15–24 year old tribal members, parental/guardian consent if below 18 years of age, and live within 1 h of the Indian Health Service	None	US	Reservation-based Native Americans	288	51	< 15	CTQ	PTSD and depressive symptoms	Short Screen for PTSD and BDI	19.3±2.9	Poly-drug use (odds ratio)
Brodsky et al. 2001	MDE - DSM III-R criteria	Current substance or alcohol abuse, neurological illness, or other active medical	US	Inpatients - The subjects were recruited at two university hospital sites, one in New York City (N=47) and the other in Pittsburgh (N=89)	136	66.5	< 15	CDTH I	MDD	SCID - DSM-III-R criteria and HAM-D	36.3±12	Impulsiveness and aggression (odds-ratio)
Cabrera et al. 2007	Male soldiers, no deployment	Female sex	US	Male soldiers who had not deployed to Iraq and/or Afghanistan surveyed in 2003	4529	0	< 15	M-CTQ	PTSD and depressive symptoms	PCL and PHQ	NR	Combat exposure (odds ratio)
Carver et al. 2011	None	None	US	College sample - undergraduate students from University of Miami	133	73.7	NR	Risky Families	MDD	SCID-I	18.71	SERT and BDNF polymorphism (interaction)
Cisler et al. 2013	1st arm: history of early life stress (ELS) and either past or current DSM-IV-defined MDD; 2nd arm: history of ELS but no diagnosis of current or past MDD; 3rd arm: history of neither ELS nor MDD	Significant medical illness, pregnancy or nursing, past or current presence of psychotic symptoms or bipolar disorder, current presence of psychoactive substance abuse/dependency or eating disorders, hormonal medication and psychotropic medication in the 2 weeks prior to study entry; For subjects assigned to the non-ELS groups, exclusion criteria were major stress experiences before the onset of puberty, such as abuse, neglect, parental death, accidents, or natural disaster	US	Recruited via advertisements in local newspapers and on public transport, and also through information flyers posted throughout the Metro Atlanta Area in highly frequented places such as coffee shops and grocery stores	38	100	< 13	ETI	MDD	HAM-D and SCID	18–44	Altered connectivity within emotion regulation neural networks (omnibus contrasts and linear multiple regression)
Cloitre et al. 2005	Treatment-seeking women	Current dissociative, bipolar, or substance dependence disorder, an eating disorder, psychotic symptoms, or acute suicidality requiring hospitalization	US	NR	164	100	< 18	CMIS and the SAAI VS	PTSD	M-PSS and SCID	34.1±9.4	Emotional regulation and interpersonal problems (hierarchical regression and correlations)
Colman et al. 2013	18 years old or above and suffered ACEs. Three groups: those who experienced no ACE, those who experienced one ACE and those who experienced two or more ACEs	NA	Can	National Population Health Survey	3930	56.5	< 18	Own questions	MDD	CIDI-SF	41.7±0.3	Heavy drinking (odds ratios)
Daalder et al. 2013	Indoor sex workers in the Netherlands	None	NL	Participants were indoor sex workers in the Netherlands, recruited in legal sex businesses only	123	100	< 15	CTQ	PTSD symptoms	SRIP	33.5±9.2	Retraumatization (correlations)

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Dietrich 2007	Prison inmates, or treatment-seeking or responding to the internet advertisement	None	Can	Prison inmates, a treatment-seeking community sample, and an internet sample - 19 persons from a local Community Counselling Centre (8.5%), 72 from Canada Corrections (32.1%), 38 from a provincial Correctional Centre for Women (17%), as well as 95 from the Internet (42.4%)	207	60.8	< 18	CMIS	PTSD	DAPS	37.9±10	Female gender and re-victimization (correlations and chi square tests)
Dyer et al. 2013	All: Females, of full legal age and fluent command of the German language; 1st group: DSM IV-PTSD (n=49); 2nd group: DSM-IV PTSD plus eating disorder (n=31); 3rd group: healthy controls (n=53)	All: Male sex; Healthy controls: no axis 1 or axis 2 disorder	Ger	Recruited via the outpatient section and inpatient unit of the Department of Psychosomatic Medicine and Psychotherapy at the Central Institute of Mental Health, Mannheim, Germany; Healthy controls were recruited via newspaper advertisement	133	100	<15	Sexual abuse subscale of the CTQ	PTSD	SCID	34.5±11	Negative body image (Mann-Whitney U tests and Kruskal-Wallis tests)
Dyer et al. 2015	All: Females, of full legal age and fluent command of the German language; 1st group: DSM IV-PTSD (n=23); 2nd group: borderline personality disorder (BPD) (n=25); 3rd group: both PTSD and BPD (n=22); 4th group: healthy controls (n=27)	All: Male sex; Healthy controls: no axis 1 or axis 2 disorder	Ger	Recruited at the inpatient and outpatient units of the Department of Psychosomatic Medicine and Psychotherapy at the Central Institute of Mental Health, Mannheim, Germany	97	100	<15	Sexual abuse subscale of the CTQ	PTSD	SCID	32.8±9.9	Negative body image and body-related emotions (Mann-Whitney U tests and Kruskal-Wallis tests)
Etter et al. 2013	Being admitted to a large, non-profit psychiatric hospital over a period of at least 3.5 years and approval from the admitting psychiatrist or psychologist	NR	US	Adult psychiatric inpatients recruited from another study (Carlson et al., 2001)	173	52	< 18	CTS, SI-SSC, and structured interview	Depressive symptoms and PTSD symptoms	Depression subscale of the SCL-90-R and SI-PTSD	37.7±5.0	Low positive affect (correlations)
Farley et al. 2001	Adult, female and member of a health maintenance organization	None	US	Randomly selected sample of adult female members of a health maintenance organization in northern California	86	100	NR	Own questions	PTSD	PCL	39±8	Cardiovascular, immune, musculoskeletal, neurologic, and reproductive symptoms (F-tests and post hoc analyses)
Fonzo et al. 2013	DSM-IV PTSD as a result of exposure to intimate violence	Substance abuse in the past year, history of greater than 2 years of alcohol abuse, use of psychotropic medications in the past 4 weeks, Fluoxetine in the past 6 weeks and irremovable ferromagnetic bodily material, pregnancy, claustrophobia, bipolar disorder, or schizophrenia	US	Participants with DSM-IV PTSD as a result of exposure to intimate violence were recruited through community advertisement to participate in functional magnetic resonance imaging	33	100	< 15	CTQ-SF	PTSD	CAPS	39.3±8.5	Alterations in limbic/prefrontal brain functions and connectivity and a reduction in prefrontal gray matter volumes (correlations)
Fox et al. 1994	Female, psychology undergraduate	NR	US	College women from introductory psychology classes at a large Midwestern university in the US	253	100	< 17	FCVQ	Depressive symptoms	BDI	19.3±2.9	Self-esteem and revictimization (MANOVA)
Gladstone et al. 2004	DSM IV MDD	None	Australia	Participants were consecutively referred to the Mood Disorders Unit at Prince of Wales Hospital in Randwick, New South Wales, Australia	125	100	< 16	Own questions	MDD	CIDI and HAM-D	37.8±12	Deliberate self-harm revictimization (path analysis)

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Goldberg et al. 2005	DSM-IV bipolar patients	None	US	Participants sought treatment from the Bipolar Disorders Research Clinic of the New York Presbyterian Hospital	100	49	< 15	CTQ	PTSD	SCID	39.6±12	Adult sexual assault (t-tests, Wilcoxon tests, chi square tests, fisher's exact tests, logistic regression and odds ratios)
Grassi-Oliveira et al. 2008 b	Between 17 and 40 years old, those who had at least 5 years of basic education, and those declaring low income	If the participant did not identify their gender where requested and if there was missing data of more than one item on any instrument used	Brazil	Participants were recruited while waiting for previously scheduled appointments in paediatric and gynaecology services of a public general hospital following convenience sampling technique	115	68.7	< 15	CTQ	PTSD	PCL-C	28.6±12	Low income and emotional distress (correlations and hierarchical multiple regression)
Gündoğar et al. 2014	MDD as defined by the DSM IV	Unreliable responses, comorbid diagnoses	Turkey	Participants were admitted to the outpatient clinic of Erenköy Psychiatry Education and Research Hospital between January 2012 and March 2012 for their regular follow-up interviews	100	57	< 13	ETI	MDD	DSM IV	32.7±13	Depressive, irritable and anxious temperament (Mann–Whitney U test and correlations)
Günther et al. 2015	MDD as defined by the DSM IV	History of bipolar or psychotic disorders and substance abuse or addiction within the previous six months as well as participants with trials with response errors and reaction times below 100 ms and greater than 1000 ms	Germany	Participants were recruited from a treatment program of the Department for Psychosomatic Medicine and Psychotherapy of the University of Leipzig	45	66.7	< 15	CTQ	MDD	SCID, HAM D and BDI	34±9.5	Mood-congruent bias in emotion processing (hierarchical regression and correlations)
Heim et al. 2008	4 groups: 1) subjects with no childhood abuse history or psychiatric disorder; 2) men with childhood abuse histories without current MDD; 3) men with childhood abuse histories with current MDD; 4) men with current MDD and no childhood abuse history	Current medical illness, lifetime psychosis or bipolar disorder, alcohol or substance abuse within 6 months, eating disorders within the past year, current psychiatric treatment or medication and heavy smoking (20 cigarettes/day)	US	Recruited from responses to advertising in newspaper and the local transportation system	49	0	<13	ETI	MDD	DSM IV and HRSD 21	18 to 60	HPA hyperactivity (ANCOVA and bonferroni post hoc tests)
Jaworska et al. 2014	Experimental group: HAM D score of ≥18; All participants: free of psychotropic medications for a minimum of three weeks	Bipolar disorder (BP-I/II or NOS), psychosis history, a clinically significant anxiety disorder, current (<6 months) substance abuse/dependence, neurological disorders, eating disorders, unstable medical condition, significant suicide risk, MRI contraindications (e.g., pregnancy, metal implants, and claustrophobia)	Canada	NR	90	60	< 15	CTQ	MDD	SCID and HAM D	19 to 58	Thinner frontal pole cortex, transverse temporal cortices and left inferior and right superior parietal cortex thickness (MANCOVA and ANOVA)
Johnson et al. 2010	Experimental group: lifetime criteria for at least one DSM-IV major depressive disorder (MDD) Control group: no lifetime history of any DSM-IV mood disorder	Schizophrenia, organic mental disorder, or history of bipolar I disorder	US	Recruited from a community who were part of a larger study of the intergenerational transmission of depression	86	100	< 15	CTQ	MDD	SADS-L and BDI	38.9±6.8	SERT polymorphism and attentional bias for angry faces (ANOVA)
Johnson et al. 2011	None	Response latencies longer than 10,000 ms	US	Undergraduate students (not otherwise specified)	201	100	< 15	CTQ	Depressive symptoms	BDI-II	18.9±1	Implicit associations with depression-relevant stimuli (D-scores)

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Kang et al. 2013	MDD - DSM IV	Current or lifetime comorbid DSM-IV diagnosis of schizophrenia, other psychotic disorders, bipolar disorders, organic psychosis, or dementia; and a medical or neurological illness	South Korea	Recruited from Chonnam National University Hospital, Gwangju, Korea from January 2009 to July 2012	102	75	< 16	Own questions	MDD	SCID	54.9±15	Higher SLC6A4 promoter methylation status (t-tests, correlations and Bonferroni-corrected multiple comparisons)
Khoury et al. 2010	At least 18 years old, ability to give informed consent	Mental retardation or diagnosis of a psychotic disorder	US	Recruited from medical and OB/GYN clinic waiting rooms at Grady Memorial Hospital in Atlanta, GA	587	61.2	< 18	ETI	PTSD	M-PSS	42.4±13	Substance use (correlations and univariate analysis)
Klein et al. 2009	Chronic form of MDD (i.e. chronic MDD, double depression, or recurrent MDD with incomplete recovery between episodes and a total continuous duration of > 2 years), between ages 18 and 75, English speaking, Hamilton Depression Rating Scale score at intake > 20	Pregnancy, current psychotic disorder, bipolar disorder, dementia, PTSD, anorexia or bulimia nervosa, OCD, antisocial, schizotypal, or severe borderline personality disorder; and current substance dependence disorder (except nicotine), failed four treatment steps in the pharmacotherapy algorithm, unwilling to terminate other forms of treatment, or had an unstable or terminal medical illness	US	Recruited from eight academic Centres through clinician referrals and other sources (e.g. advertising, self-referral, referral by friends/family)	808	55	< 16	MOPS and CTQ-SF	MDD	SCID and HAM D	43.6±12	Higher levels of dysfunctional attitudes and self-criticism (correlations and backwards stepwise multiple linear and logistic regression analyses)
Kohrt et al. 2015	None	None	Nepal	Random-sampling frame of households was employed to recruit one adult per household in four village development committees in a rural mountainous district of north-western Nepal	682	49.1	< 15	CTQ	Depressive symptoms and PTSD	BDI and PCL	37±13	FKBP5 tag-SNP rs9296158 (general linear model and linear mixed model)
Lang et al. 2004	Victims of physical and/or sexual abuse by an intimate partner in the past 2 years but were not currently in an abusive relationship	Neurological illness, head injury involving loss of consciousness > 10 minutes, learning disability, psychosis, or meeting criteria for alcohol abuse, dependence > 2 years, use of psychotropic medication < 6 weeks, oral or intramuscular steroids < 4 months, or any illegal substances < past year	US	Recruited using flyers posted in community service agencies and medical clinics and advertisements placed in local newspapers or by word of mouth	42	100	< 15	CTQ	PTSD	LASC and SCID I	32.8±10	Current distress and conflicts in relationships (multiple linear regression))
Lu et al. 2008	Severe major depression or bipolar disorder	Incomplete data	US	Drawn from a larger investigation of risky behaviour and sexually transmitted diseases among persons with severe mental illness; participants were receiving treatment through the public mental health systems of Connecticut, Maryland, New Hampshire, or North Carolina or through the Durham, North Carolina, Department of Veterans Affairs Medical Centre	274	44.1	< 16	CTS, SAEQ and own questions	PTSD	PCL	42.9±11	High-risk behaviors, diagnosis of a substance use disorder, exposure to trauma in adulthood, psychiatric problems, younger age at first hospitalization, number of suicide attempts, medical service utilization, and homelessness (logistic regression)

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McIntyre et al. 2012	DSM-IV-defined MDD and bipolar disorder 1 or 2	Inability/unwillingness to give consent	US	Adult outpatients from the International Mood Disorders Collaborative Project from the University of Toronto and Cleveland Clinic enrolled between 2007 and 2010	373	61.7	< 15	Klein Trauma & Abuse-Neglect self-report scale	MDD	MINI Plus	42.9±14	Metabolic syndrome (chi square tests and t-tests)
Miller et al. 2009	age 18–65 years; DSM-IV MDE, 2-6week medication-free (depending on substance), capacity to provide informed consent	Pregnancy, current or lifetime history of alcohol or other drug abuse or dependence, lifetime exposure to MDMA, significant current medical conditions; Additionally for controls: no psychiatric history and no history of a mood or psychotic disorder in first-degree relatives	US	Data from a previous study of 5-HTT binding in depression, which contains details regarding the clinical sample and imaging methods (Parsey et al., 2006)	66	57.6	< 15	Semi-structured interview	MDD	SCID, BDI and HAM-D	39±14.5	Lower 5-HTT BPP levels (Linear mixed effects models, chi square, t-tests and Fisher's exact test)
Mueller-Pfeiffer et al. 2013	Outpatients and inpatients	Serious cognitive impairment or mental retardation, acute psychosis, severe substance abuse, affective disorder with psychotic symptoms, acute suicidal ideation, and lack of German language ability	Germany and Switzerland	Outpatient and inpatient units of seven psychiatric services in the German part of Switzerland and the federal state of Baden-Württemberg in Germany as well as referrals from several private psychiatry and psychotherapy practitioners	287	77.4	< 18	TEC	PTSD and MDD	ICD-10	37.4±14	Dissociative symptoms (linear multiple regression and correlations)
Nazarov et al. 2014	Cases: primary diagnosis of current DSM IV PTSD	Substance use-related disorder within the past 6 months, lifetime history of substance dependence, use of alcohol or illicit psychoactive substance within 48 h of testing, significant medical illness, history of head injury with loss of consciousness lasting more than 60s; and history of neurological disease	Canada	Cases: recruited by London Health Sciences Centre through outpatient programs; Controls: recruited through word of mouth and local advertisements by LHSC and St. Joseph's Healthcare Hamilton	51	100	< 15	CTQ	PTSD	SCID and CAPS	39±12.6	Impairments in theory of mind (partial correlation analysis and chi square tests)
Nazarov et al. 2015	Cases: primary diagnosis of current DSM IV PTSD related to childhood abuse; Controls: matched for age and sex	Controls: current or lifetime history of psychiatric illness; All: substance-use-related disorder within the past 6 months, use of alcohol or illicit psychoactive substance within 48 h of testing, significant medical illness, history of head injury with loss of consciousness lasting more than 60, history of neurological disease, and knowledge of the Hebrew language	Canada	Recruited through word of mouth and local advertisements at LHSC and St. Joseph's Healthcare Hamilton (Hamilton, ON, Canada)	50	100	< 15	CTQ	PTSD	SCID and CAPS	41±13.5	Slower identification of emotional prosody (mixed-effects model for nonparametric data, ANOVA, bonferroni post hoc test and correlations)

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O'Donovan et al. 2011	Cases: current chronic DSM IV PTSD	Neurologic disorders or systemic illness; use of anticonvulsant, anti-hypertensive, sympatho-mimetic, estrogens replacement therapy, steroidal, statin or other prescription medications; obesity; alcohol abuse or dependence < 2 years; substance abuse or dependence < year; any psychiatric disorder with psychotic features; bipolar disorder or OCD, pregnancy or statistical outliers; Additionally for controls: lifetime history of PTSD, MDD or panic disorder	US	Recruited through ads and flyers distributed in the community as well as through relevant local clinics for the PTSD sample	88	51.1	< 14	Five items from the LSC assessed in a structured interview conducted by trained clinical interviewers	Chronic PTSD diagnosis	CAPS	30.6±7.4	Shorter age-adjusted Leukocyte Telomere Length (ANCOVA and partial correlations)
Owens et al. 2009	Treatment-seeking male veterans who were either interested in being screened for the Veterans Administration Gulf War Registry and/or interested in obtaining treatment services from the PTSD unit at the local VA Medical Centre	None	US	Veterans from the Korean War, World War II, Vietnam, and the first Gulf War who were being screened for the Veterans Administration Gulf War Registry and/or admission to the PTSD unit at the local VA Medical Centre from November 2000 to December 2003	299	0	< 15	CTQ	PTSD and depressive symptoms	CAPS, MPTSD and HAM-D	51.7±9.1	Combat exposure (hierarchical multiple regression analyses)
Park et al. 2015	Aged 50 to 70	Dementia, or severe cognitive impairment	South Korea	Recruited from a community health centre in Seoul via advertisement	137	59.9	<18	ACE	Depressive symptoms	QIDS-SR	59.2±6.1	Apolipoprotein E omega-4 (multiple linear regression)
Perna et al. 2014	Depressive episode without suicide risk, current pharmacological treatment recommended for the disorders, and age of 18 years or higher	Relevant modifications of pharmacologic treatments in the last 4 weeks preceding hospitalization including addition or discontinuation of drug, current/previous history of schizophrenia/ other psychotic disorders, suspected or diagnosed (IQ < 70) mental retardation, neurological disease, or probable false-negative trauma reports	Italy	Recruited from the inpatients consecutively referred to Villa San Benedetto Menni Hospital, Albese con Cassano, Como, Italy, to undergo a 4-week hospitalization for a psychiatric rehabilitation program	69	81.2	< 15	CTQ	MDD	DSM-IV-TR	57.2±12	Low self-directedness (t-tests, linear regression and chi square tests)
Plaza et al. 2010	DSM IV major postpartum depressive diagnosis, female sex	Current treatment with drugs that can influence the thyroid function, history of alcohol or/and substance abuse within the past six months, previous thyroid disease, being illiterate and women, whose children died after birth	Spain	Recruited from the Perinatal Psychiatric Unit of a teaching hospital (October 2002–July 2007)	103	100	< 13	ETI	Postpartum depression	SCID	33±4.4	Thyroid auto-antibodies and concomitant hypothalamus-pituitary-thyroid axis disturbances (multivariate logistic regression with backward selection strategy)
Plaza et al. 2012	Caucasian, Spanish postpartum women, over 18 years of age, and able to understand and answer clinical questionnaires	Current treatment with drugs that can influence the thyroid function, history of alcohol or/and substance abuse within the past six months, previous thyroid disease, being illiterate and women, whose children died	Spain	Recruited from a Obstetrics Unit as part of a larger prospective multi-Centre study on postpartum depression that took place between December 2004 and July 2005	236	100	< 13	ETI	Depressive symptoms	EPDS	32.6±4.6	Postpartum thyroid dysfunction (hierarchical multivariate logistic regression)

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		after birth											
Roh et al. 2015	Aged 50 years and older and self-identify as an American Indian (AI)	Missing data	US	Convenience sampling of AI older adults in two Midwestern states: South Dakota and Minnesota recruited through a variety of off-reservation locations including AI churches, social service Centres, other religious organizations, senior housing facilities, senior centres, and three powwows	233	54.3	< 15	CTQ	Geriatric depression	GDS-SF	60.7±8.4	Low social support (hierarchical multivariate regression)	
Roehndt et al. 2012	None	Individuals who had previously refused to participate in national research, who were incarcerated, deemed to have learning difficulties and who had moved out of the country	Denmark	Stratified random probability survey was conducted in Denmark by the Danish National Centre for Social Research between 2008 and 2009 with 2,981 participants born in 1984	2981	47.8	NR	Own questions	PTSD	Core symptoms of PTSD	Born in 1984	Underweight and overweight/obesity (chi square, ANOVA and logistic regression)	
Roxburgh et al. 2014	State prison inmate or sentenced Federal inmate held in federally owned and operated facilities	Those identifying as mixed race, as well as those who identified as Asian, Hawaiian/Pacific Islander, American Indian/Alaskan Native, or 'other' race	US	Data from the 2004 Survey of Inmates in State and Federal Correctional Facilities (SI-SFCF) in the US - representative sample of the incarcerated (i.e. State prison inmates and sentenced Federal inmates held in federally owned and operated facilities)	13328	19.6	< 18	Own questions	Depressive symptoms	CES-D	35.4±10	Ethnicity and gender (ordinary least squares regression)	
Roy 1999	Cases: Abstinence from alcohol for a minimum period of at least 2 weeks, male sex and fulfilled DSM-III-R MDE criteria; Controls: recently abstinent alcoholic men	Controls: lifetime history of depression	US	Inpatients on the Abuse Treatment Program at the Veterans Administration Medical Centre, East Orange	43	100	< 15	CTQ	MDE	DSM III-R	44.7±8.5	Alcohol misuse and male sex	
Sacco et al. 2007	DSM IV Schizophrenia, Schizoaffective Disorder, Bipolar Disorder, MDD or PTSD, outpatients, psychiatrically stable at the time of interview, and if prescribed psychotropic medications, to be on a stable dose of medication >1 month	Positive urine drug screens for cocaine, opioids or marijuana, detectable breath alcohol levels at the screening visit, or suicidal ideation; Additionally for controls: current Axis I psychiatric disorder or substance abuse or dependence	US	Subjects were seeking enrolment in treatment and non-treatment studies in The Program for Research in Smokers with Mental Illness (PRISM) at The Connecticut Mental Health Centre (CMHC) in New Haven - chronically mentally ill populations (primarily schizophrenia, bipolar disorder, and MDD) and non-psychiatric controls	101	48.5	< 18	ACE	MDD and PTSD	SCID	41.3±11	Smoking (ANOVA and LSD post-hoc tests)	
Santa Ana et al. 2006	1) Individuals with PTSD as a result of an index trauma during childhood (i.e. before age 18) and 2) individuals with PTSD as a result of an index trauma as an adult	Pregnancy, current MDD or other primary axis I disorders, major medical disorders, use of psychotropic medications or steroid therapy, or DSM-IV criteria for any substance dependence other than alcohol or nicotine within the past 60 days	US	Recruited via newspaper and other media advertisements as part of a larger non-treatment study examining naltrexone and stress responding in PTSD and alcohol dependence	89	51.7	NR	Clinical records	PTSD	SCID	31.4±9.6	Hypocortisolism (mixed model repeated measures ANCOVA)	

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Sareen et al. 2013	Part of the Canadian Forces personnel aged 18-54	None	Canada	Data from the 2002 Canadian Community Health Survey – Canadian Forces Supplement - representative sample of serving forces	8340	30.7	< 18	Own questions	MDD, panic disorder, social phobia, GAD and PTSD	WHO-CIDI	18-54	Deployment-related traumatic exposures (adjusted logistic regression and population attributable fractions)
Schulz et al. 2014	German nationality, primary place of residence in the study region	None	Ger	Data from the Study of Health in Pomerania (SHIP) - adult German residents in north-eastern Germany living in three cities and 29 communities with a total population of 153,263	2265	52.5	< 15	CTQ	Depressive symptoms	BDI-II	46.3±14	Socio-demographic variables (Multiple group comparisons and chi square tests)
Schwai ger et al. 2016	Healthy adults aged between 45 and 60 years of age, Controls: scored below cutoff on all CTQ subscales, and were matched for gender, age, and current SES as well as childhood SES	Any mental disorder (axis I and II) at the time of assessment or during the preceding 12 months, intake of psychoactive, or cortisol-containing medication or oral contraceptives	Ger	Recruited via articles in local newspapers and community-posted flyers	60	66.7	< 15	CTQ	Past depression and anxiety	SKID-I& SKID II	Cases: 52.57±5.52; Controls: 51.47±4.64	Alterations in transcriptional control of stress-responsive pathways (correlations)
Sharpley et al. 2013	Aged 18 or above	None	Australia	Recruited from the general population of a large regional city of about 22,000 people in New South Wales, Australia	120	54.2	< 18	ACE	Depressive symptoms	ZSDS	32.5±14	SERT polymorphism and psychological resilience (MANOVA, ANOVA and hierarchical regression)
Soffer et al. 2008	Psychology undergraduates	Incomplete data	Israel	Introductory psychology undergraduates at the Ben-Gurion University of the Negev, as well as at Sapir and Achva colleges, were contacted through ads placed on bulletin boards	203	81.7	< 15	CTQ	Depressive symptoms	BSI	23.6±1.9	Psychological resilience (structural equation modeling)
Soleimani et al. 2015	All 18-70 years: Controls: medication free; Cases: DSM IV MDD, free from active medical illness and medication-free for at least two weeks period prior to the lumbar puncture (four weeks in the case of neuroleptics and six weeks for Fluoxetine)	Controls: no psychiatric history based on SCID, significant illness and history of a mood or psychotic disorder in their first-degree relatives; All: bipolar or schizophrenia spectrum disorders or family history of schizophrenia or schizoaffective disorder	US	Recruited through advertising and referrals and admitted to a university hospital for participation in mood disorders research	81	NR	< 15	Own questions	MDD	SCID and HDRS	37.67 (18 to 70)	Higher cerebrospinal fluid NPY-LI levels (correlations and ANOVA)
Stein et al. 2008	European-American (Caucasian) ancestry	None	US	Recruited from among undergraduate psychology students at San Diego State University (SDSU)	247	69.2	< 15	CTQ	Anxiety sensitivity	ASI	18.8±1.5	SERT polymorphism (linear and multivariate regression)
Suzuki et al. 2014	17 healthy participants with a history of childhood trauma and 24 without and 21 depressed patients with a history of childhood trauma and 18 without; All: between 20 and 65 years old	Neurological disorders, history of substance misuse within the previous 2 years and medication use that could affect the HPA axis (except antidepressants)	UK	Recruited from in- and out-patient facilities of the South London and Maudsley NHS Foundation Trust	80	65	< 15	CTQ	MDD	ICD 10 and QIDS-SR	48.4±12	Non-significant finding: hypocortisolism (three-way mixed model ANOVA and two-way ANCOVA)

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Swanson et al. 2014	18 years of age or older, non-psychiatrically referred, and English speaking	Use of illegal or non-prescription drugs during pregnancy, maternal history of bipolar and psychotic illness, child prematurity (<36-weeks term), or child developmental disability, severe illness (e.g. epilepsy), did not meet abuse or neglect criteria for childhood maltreatment	US	Women were recruited as part of a longitudinal study from pregnancy clinics in a Midwestern metropolitan area and through flyers posted in the community	173	100	< 15	CTQ	Postpartum depression	PDS	28.3±5.6	Sleeping problems (logistic regression analyses utilizing stepwise regressions)
Tekin et al. 2015	DSM IV Social anxiety disorder (SAD), 18 – 60 years old and at least primary school graduates	History of severe internal or neurological disease, diagnosed with psychotic disorders such as bipolar disorder or schizophrenia, those who abused alcohol or other substances, or who had been co-diagnosed with other anxiety disorders	Turkey	Social anxiety disorder patients recruited from Anxiety Disorders Outpatient Clinic of Psychiatry Department of Şişli Hamidiye Etfal Research and Training Hospital	113	48.7	< 15	CTQ	SAD, depressive and anxiety symptoms	SCID, BDI and BAI	27.7±9.4	Sexual dysfunction (chi square, Mann-Whitney U-test and multivariate logistic regression)
Tietjen et al. 2007	Women with ICHD-II primary headache disorder, 18 years and older, willingness to complete a self-administered electronic questionnaire	Not physically well enough to complete an electronic questionnaire on a personal digital assistant and not literate in English	US	Headache clinic patients from six Centres belonging to the research consortium of the American Headache Society Women's Issues Section	949	100	< 12	Own questionnaires	Depressive symptoms	PHQ-9	42±11	Migraine (multinomial logistic regression and odds ratios/Wald test)
Tozzi et al. 2016	Cases: DSM IV MDD	Age <18 or >65, history of neurological or comorbid psychiatric disorders (Axis I or Axis II), other severe medical illness, head injury, substance abuse or movement parameters in FMRI scan exceeded 3 mm	IRE	Cases: MDD patients from the mental health services of the Tallaght Hospital, Dublin or St James's Hospital, Dublin; Controls: from the local community	83	65.1	< 15	CTQ	Depressive symptoms	SCID, HRSD and BDI-II	38.9±12	T allele of rs1360780 and functional and structural differences in emotion-processing inhibition areas (general linear models)
Triffleman et al. 1995	Score 26 or above on the Mini-Mental State Examination and maintained abstinence during the time period of the study	Positive self report or urine toxicology test, incapacitation by intoxication, delirium, dementia, acute withdrawal or other concomitant physical conditions	US	Veterans admitted over an 8-month period to the San Francisco Department of Veterans Affairs Medical Centres Substance Abuse Inpatient Unit	46	0	<16	TAQ	PTSD	SCID, M-PTSD and IES-R	44.9±7	Substance dependence (correlations)
Van Veen et al. 2013	All: Between 18 and 65 years of age; Cases: DSM IV lifetime diagnosis of a depressive or anxiety disorder	Not being fluent in Dutch or the presence of a primary clinical diagnosis of psychotic disorder, OCD, bipolar disorder, or severe addiction disorder and missing data	NL	Data from the Netherlands Study of Depression and Anxiety (NESDA) - participants recruited from mental healthcare settings, general practices and the general population in the period from 2004 to 2007	2615	67.2	< 16	CTI in an interview	Anhedonic depression and anxious arousal	MASQ -D30	42.4±13	Recent life events (multivariate linear regression)
Van Vorhees et al. 2012	Veterans and active duty soldiers who have served in the US military since 9/11/2001	None	US	Part of a multi-site investigation conducted through the Department of Veterans Affairs (VA) VISN 6 Mid-Atlantic Mental Illness Research, Education, and Clinical Centre (MIRECC) recruited veterans and active duty soldiers who have served in the US military since 9/11/2001	1301	19	< 18	TLEQ	PTSD symptoms	DTS	36.8±10	Combat exposure (linear regression and nonparametric bootstrapping)

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Van Vorhees et al. 2014	Between 18 and 65 years of age, generally healthy, not currently seeking treatment for nicotine dependence, and currently smoking least 10 cigarettes/day	Blood draws not conducted between 10:00 am and 2:00pm, major unstable medical problems, using non-cigarette forms of nicotine, pregnancy, non-English speaking, current substance abuse/dependence, schizophrenia, current manic syndrome, lifetime but not current PTSD, and current bupropion or benzodiazepine use.	US	Data from a larger smoking cessation study investigating mechanisms of relapse in 55 smokers with PTSD and 68 smokers without PTSD	100	53	< 18	TLEQ)	PTSD symptoms	CAPS	41.9±10	Low cortisol levels (multiple regression)
Vrijzen et al. 2014	Cases: history of DSM IV MDE, Controls:	All: Current depressive episode, current or lifetime bipolar disorder, current psychotic symptoms, alcohol or substance abuse within the past 6 months, deafness, blindness, neurological disorder, sensorimotor handicaps, intellectual disability	NL	Cases: Recruited remitted depressed participants from the Department of Psychiatry of the Radboud University Medical Centre as well as other regional outpatient psychiatric services; Controls: recruited via local newspapers, online postings at the medical centre's website and a local training centre	381	66.5	< 16	LEQ	Depressive symptoms	BDI-II	45.5±12	Memory bias (logistic regression-odds ratios)
Vrijzen et al. b 2014	History of DSM IV MDE	Current depressive episode, current or lifetime bipolar disorder, current psychotic symptoms, alcohol or substance abuse within the past 6 months, deafness, blindness, neurological disorder, sensorimotor handicaps, intellectual disability and <55% correct on 2-back and/or no-go trials	NL	Recruited remitted depressed participants from the Department of Psychiatry of the Radboud University Medical Centre as well as other regional outpatient psychiatric services	325	68	< 16	LEQ	MDE	SCID I	45.2±12	BDNF and COMT polymorphisms and negative attentional biases (ANCOVA)
Vrijzen et al. 2015	History of DSM IV MDE	All: Current depressive episode, current or lifetime bipolar disorder, current psychotic symptoms, alcohol or substance abuse within the past 6 months, deafness, blindness, neurological disorder, sensorimotor handicaps, intellectual disability and did not adhere to the instructions	NL	Depressed patients in remission were recruited at the Department of Psychiatry of the Radboud University Medical Centre in Nijmegen, the Netherlands, as well as other regional outpatient psychiatric services	298	66	< 16	LEQ	Previous MDE and current depressive symptoms	SCID and BDI-II	47.8±12	The A variant of the mineralocorticoid receptor (MR) gene (ANCOVA)
Vythilingam et al. 2002	Group1: Women With MDD and Childhood Abuse Group 2: Women with MDD and No Childhood Abuse Group 3: Healthy Women With No Childhood Abuse	Major medical illness, significant head trauma, irregular menses, or any other axis I disorder, including bipolar disorder, schizophrenia, schizoaffective disorder and contraindication for an MRI, including having a cardiac pacemaker	US	Controls: recruited through newspaper advertisements and flyers; Cases were admitted as inpatients to the Emory University Hospital General Clinical Research Centre	46	100	NR	C-ETI	MDD	SCID, HDRS and ZSDS	31.3±6.3	Smaller hippocampal volume (ANOVA and Spearman's rho correlations)

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Wang et al. 2014	Group 1: DSM IV MDD patients without childhood neglect; Group 2: DSM IV MDD patients with childhood neglect; Controls: healthy controls	Axis I or Axis II disorders, histories of other forms of childhood trauma, previous ECT, neurological disorders, loss of consciousness, perinatal or neonatal complications, substance dependence, any contraindications for MRI or excessive head movements during scanning Controls: Family history of mood disorder	China	Patients were recruited from inpatient or outpatient Departments of Psychiatry, the Second Xiangya Hospital, Central South University, China; Healthy controls were recruited from the local area through poster advertisements	58	50	< 15	CTQ	MDD	SCID and HDRS	28.1±6.4	Reduction of functional connectivity strength primarily in brain regions within the prefrontal-limbic-thalamic-cerebellar circuitry (ANCOVA)
Watson et al. 2007	Cases: DSM IV MDD or bipolar disorder	Controls: Family history of mood disorder	UK	Patients were recruited from out-patient clinics in secondary and tertiary care in the North-East of England and had previously participated in a program of research into neurobiological abnormalities in mood disorder - healthy controls had also participated in this program	40	47.5	< 15	CTQ	MDD	DSM IV	49.7±7.2	Increased HPA axis response - limited to low emotional neglect cases
Wingenfeld et al. 2014	Potential diagnosis of major depressive disorder or borderline personality, and age over 18	Current pregnancy or significant medical condition, as ascertained by hospital physicians, diagnoses of concurrent anorexia nervosa, schizophrenia, schizoaffective disorder, bipolar disorder, MDD with psychotic features or clinical diagnoses of alcohol and/or drug dependence during the last 6 months; additionally for controls: any psychiatric disorder	Ger	Patients were recruited during their stay at a psychiatric hospital in Germany; control participants were recruited by advertisement in a local newspaper	214	67	< 13	ETI	Depressive and PTSD symptoms	SCID, BDI, PDS	30.8±12	Perceived stress (ANOVA and hierarchical multiple regression)
Witthöft et al. 2015	All: Female, over the age of 18, and fluent in German	Cases: diagnosis of BPD but not of PTSD; Controls: any axis I DSM IV disorder; All: sexual abuse defined by a score higher than five points on the corresponding subscale of the CTQ	Ger	Participants were recruited at the Department of Psychosomatic Medicine and Psychotherapy at the Central Institute of Mental Health, Mannheim, Germany; Healthy controls were recruited via newspaper ads	91	100	< 15	CTQ	PTSD	PDS	35±9.39	Attentional bias towards body related stimuli (ANOVA, correlations and linear regression)
Wood et al. 2005	Abused women	None	US	Abused women recruited over 10 months through bulletin board postings and pamphlets primarily in battered women's shelters in north-eastern Ohio	138	100	< 15	CTQ	PTSD symptoms	PSS and IES	35.5±11	Smoking, intimate partner violence and immune status (correlation, regression techniques and structural equation modelling)
Wu et al. 2010	Aged 18 years or older	None	US	Participants were sampled from August 1999 to April 2002 from 11 residential drug abuse treatment programs that provided publicly funded treatment to adults within Los Angeles County	402	47.2	< 16	LSC-R	Mood disorders and PTSD	BSI, SCID, and TSC	36.4±8.4	Injection drug use, tobacco use, sex work, medical problems, and poor quality of life (logistic regression)

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Yehuda et al. 2001	Cases: Offspring of Nazi Holocaust survivor (i.e. having been born to at least one biological parent who survived being kept in a labour- or concentration camp, or had to hide during the Nazi Holocaust); Controls: Jewish individuals in the same age range (24–60 years) who did not have a parent who was a Holocaust survivor	Current alcohol or substance abuse problems, an active major medical condition (e.g., cancer, diabetes, non-stabilized endocrinopathies, chronic fatigue syndrome), or had taken beta-blockers, lithium, or other psychotropic medications within 2 months of the study	US	Participants were solicited from lists obtained from the Jewish community or responded to community group announcements and newspaper advertisements, others volunteered after taking part in short-term group psychotherapy at the Mount Sinai Specialized Treatment Program for Holocaust Survivors and their Families	92	53.3	< 15	CTQ	PTSD	SCID and the Parental PTSD Scale	39.6±8.2	Lower cortisol levels (ANOVA)
Zaidi et al. 1994	None	None	US	NR	22	0	NR	The Assessing Environments III questionnaire	PTSD	M-PTSD and the PTSD subscale of the MMPI	42.6±1.8	Combat exposure (correlation)
Zeugmann et al. 2013	Previous MDE as assessed with the DSM IV or ICD 10	Patients with acute respiratory infections <two weeks, any active medical illnesses that could etiologically be related to the ongoing depression, immune and autoimmune diseases, anti-inflammatory medication, a history of drug or alcohol abuse within 1 year prior to admission, a schizophrenic or schizoaffective disorder	Ger	Patients were recruited when referred to the Clinic for Psychiatry and Psychotherapy at the University Hospital Berlin – Charité, Campus Benjamin Franklin between 2005 - 2007	22	77.3	< 15	CTQ	Depressive symptoms	HDRS-17	47.8±15	Fibrinogen levels (multiple regression)
Zhao et al. 2015	ICD-10 MDE with score > 25 on HAMD, aged 18–75 years, without taking any antipsychotics, antidepressants and anticonvulsants before and after admission, education of at least at the level of elementary school	History of neurological diseases or other severe physical (such as heart, liver and kidney) diseases or endocrine diseases, a history of other mental diseases, a history of alcohol and morphine-like substance abuse, failed to cooperate the examination of neurological soft signs and other psychology evaluations	China	Recruited from the Changzhou No.2 People's Hospital, The Affiliated Hospital of Nanjing Medical University, Changzhou, China from February to October, 2010	103	88.4	< 15	CTQ	MDE	ICD-10 HAM-D24 and BHS	42.5±14.8	Structural changes in frontal and temporal brain areas (t-tests and correlations)

Note. US = United States ; Can = Canada ; NL = The Netherlands ; Ger = Germany ; IRE = Ireland ; CTQ = Childhood trauma questionnaire ; CPSAQ = Childhood physical and sexual abuse questionnaire ; CTS = Childhood trauma scale ; CDTHI = Columbia demographic and treatment history inventory ; M-CTQ = Modified-Childhood trauma questionnaire ; ETI = Early trauma inventory ; CMIS = Childhood maltreatment interview schedule ; SAAIVS = Sexual assault and additional interpersonal violence schedule ; CTS = Conflict tactics scales ; SI-SSC = Structured interview for social support as a child ; FCVQ = Vinkelhor childhood victimization questionnaire ; MOPS = Measure of parental style ; SAEQ = Sexual abuse exposure questionnaire ; TEC = Traumatic experience checklist ; LSC = Life stressor checklist ; ACE = Adverse childhood experiences questionnaire ; TAQ = Traumatic antecedents questionnaire ; CTI = Childhood trauma inventory ; TLEQ = Traumatic life events questionnaire ; LEQ = Life events questionnaire ; SCID = Structured clinical interview for DSM disorders ; HAM-D = Hamilton depression scale ; PHQ = Physical health questionnaire ; CIDI = Composite international diagnostic interview ; DSM = Diagnostic and statistical manual of mental disorders ; BDI = Beck depression inventory ; PCL = PTSD checklist ; M-PSS = Modified PTSD symptoms scale ; SRIP = Self-rating inventory for PTSD ; DAPS = Detailed assessment of adult posttraumatic stress ; SCL = Symptom checklist ; PCL = PTSD checklist ; LASC = Los Angeles symptom checklist ; MINI = Mini international neuropsychiatric interview ; ICD = International classification of diseases ; CAPS = Clinician-administered PTSD scale ; MPTSD = Mississippi Scale for PTSD ; QIDS = Quick inventory of depressive symptomatology ; EPDS = Edinburgh postnatal depression scale ; GDS-SF = The geriatric depression scale - short form ; CES-D = Centre of epidemiological studies depression scale ; ZSDS = Zung self-rating depression scale ; BSI = Brief symptom inventory ; HDRS = Hamilton depression rating scale ; ASI = Anxiety sensitivity index ; PDS = PTSD diagnostic scale ; BAI = Beck anxiety inventory ; IES = Impact of events scale ; MASQ = Mood and anxiety symptoms questionnaire ; DTS = Davidson trauma scale ; PSS = PTSD symptom scale ; BSI = Brief symptom inventory ; TSC = Traumatic symptom checklist ; MMPI = Minnesota multiphasic personality inventory ; BHS = Beck hopelessness scale