A Multimodal Approach to Investigating the Importance of Emotional Functioning in Childhood and Adolescence

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by

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To my father.

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Declaration of Independence

The studies submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy were written in collaboration with the mentioned co-authors. Not the author, co-authors, nor any other person has published these studies elsewhere. All citations are indicated and only the cited tools were used.

For the purpose of the dissertation, the following studies have been accepted for publication in peer-reviewed journals. Copies of the studies can be found in the Appendix:

Study I:

Koechlin, H., Coakley, R., Schechter, N., Werner, C., & Kossowsky, J. (2018). The role of emotion regulation in chronic pain: A systematic literature review. *Journal of Psychosomatic Research, 107,* 38–45. doi: 10.1016/j.jpsychores.2018.02.002

Study II:

Koechlin, H., Donado, C., Berde, C. B., & Kossowksy, J. (2018). Effects of childhood life events on adjustment problems in adolescence: A longitudinal study. Manuscript accepted for publication in the *Journal of Developmental and Behavioral Pediatrics*.

Study III:

Locher, C., Koechlin, H., Zion, S. R., Werner, C., Pine, D. S., Kirsch, I., Kessler, R. C., & Kossowsky, J. (2017). Efficacy and safety of selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, and placebo for common psychiatric disorders among children and adolescents: A systematic review and meta-analysis. *JAMA Psychiatry, 74*(10), 1011–1020. doi: 10.1001/jamapsychiatry.2017.2432

With my signature, I testify that all statements are true and complete.

Basel, June 18th 2018

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Abstract

Emotional functioning is a key component of both healthy and abnormal development in children and adolescents. It entails the experience, expression and regulation of emotions as well as emotional disorders. Although both the experience and the regulation of emotions change across the lifespan, they do so at an especially intense and rapid rate throughout childhood and adolescence. It is therefore crucial to investigate the role of different aspects of emotional functioning in various domains in these populations. Moreover, the onset of most emotional disorders occurs in adolescence, and prevalence rates of anxiety and depressive disorders are especially high during this period of life.

For the purpose of this thesis, three components of emotional functioning were studied, using various methods across several domains. The first aim was to examine the role of emotion regulation in chronic pain (Koechlin, Coakley, Schechter, Werner, & Kossowsky, 2018, Study I). For this purpose, a systematic literature search was conducted and studies meeting specific criteria were then synthesized to investigate whether emotion regulation might enhance existing frameworks of chronic pain. In addition, associations between two broad categories of emotion regulation (namely antecedent- and response-focused emotion regulation) and chronic pain were explored. Emotion regulation depends to a great extent on emotional reactivity, i.e. the individual threshold required for emotional reactions – experiencing more and more intense emotions can complicate adequate emotion regulation. Hence, the second aim of this study was to analyze how emotional reactivity influences the occurrence of adjustment problems in adolescents who experience stressful life events in their childhood years (Koechlin, Donado, Berde, & Kossowsky, 2018, Study II). In order to achieve this second aim, a large longitudinal dataset was used and several covariates, among them emotional reactivity, were analyzed with the aim of predicting adjustment problems in 956 children who had experienced some or many stressful life events. Finally, as the prevalence rates of emotional disorders are high in adolescence, the third aim was to examine

the efficacy and safety of a common intervention, namely two classes of antidepressants, selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs). In order to address this aim, a meta-analytic approach was chosen, and all randomized, double-blind, placebo-controlled trials of SSRIs and SNRIs in children and adolescents younger than 18 years who had been diagnosed with an emotional disorder were included (Locher, Koechlin et al., 2017).

Study I showed that in the included reports, emotion regulation was rarely directly associated with pain intensity or pain-related disability. Rather, the relationship between both groups of emotion regulation strategies (antecedent- and response-focused) and chronic pain seemed to be mediated by psychological factors such as high emotionality, anxiety, or negative mood. This raises questions for future research, such as whether interventions that target emotion regulation specifically have the potential to relieve symptoms of chronic pain and emotional disorders simultaneously. Study II found that adjustment problems were best predicted by high emotional reactivity and many stressful life events. The results of this study point to the potential that emotional reactivity holds for the prevention and treatment of adjustment problems in adolescence. Study III revealed that even though antidepressants were more effective than a placebo in treating common emotional disorders in children and adolescents, these effects were small and disorder-specific. The results of this analysis present multiple avenues for further research, such as the underlying differences and similarities in emotional disorders that might help explain the difference in response to antidepressants and placebo.

Patterns of emotional functioning develop in childhood, but may persist into adulthood, which highlights the importance of adaptive emotional functioning. This thesis sheds light on how emotional functioning influences chronic pain and the occurrence of adjustment problems in the face of stressful life events, and examines a common treatment for emotional disorders. Future research should focus on age-specific changes in emotional

functioning and how these influence chronic pain, emotional disorders and other domains. This approach would allow researchers to tailor interventions and prevention to age-specific needs and abilities.

Theoretical Background

Emotional Functioning

Emotions are basic features of human functioning (Shonkoff & Phillips, 2000). As such, they play a key role in both mental health and illness throughout the entire lifespan: maladaptive emotional functioning is thought to be a critical feature in nearly all mental disorders (Sloan, 2006) and hence emotional work is central to a range of psychotherapeutic approaches (e.g., Harned, Banawan, & Lynch, 2006; Mennin, 2006; Suveg, Kendall, Comer, & Robin, 2006). Definitions of emotional functioning vary, but all note that emotional functioning entails the experience, expression and regulation of positive and negative emotions as well as symptoms of emotional problems such as anxiety, depression and aggressive behavior (Gross & John, 2003; Kessler, Turner, & House, 1989; Vriend et al., 2013). Emotional functioning can thus be understood as an umbrella term that includes more specific concepts such as emotion regulation (Vriend et al., 2013), awareness and expression of emotions (Tolstikova, 2010), and psychological symptoms such as depression and anxiety symptoms (Jackson, Misiti, Bridge, Daniels, & Vannatta, 2015). Emerging patterns of emotional functioning in childhood are maintained into adulthood, hence childhood emotional functioning may provide an early indicator of long-term health risk in adulthood (DeSteno, Gross, & Kubzansky, 2013; Repetti, Taylor, & Seeman, 2002).

This thesis examines three different aspects of emotional functioning from different perspectives, namely emotion regulation, emotional reactivity, and emotional disorders. Content and methodology across both childhood and adolescence are considered.

When talking about emotional functioning, it is important to clarify what is meant by an emotion. A distillation of major points of convergence across researchers is depicted in Figure 1.

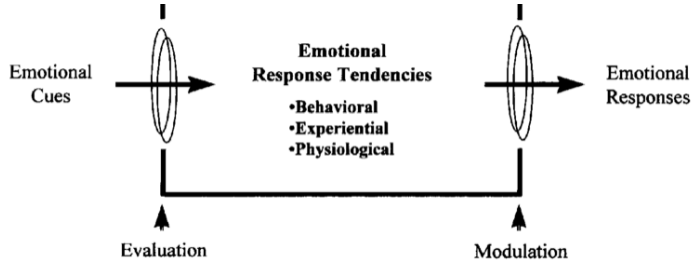

Figure 1. The process model of emotion generation (Gross, 1998b)

Figure 1 shows that an emotional cue (such as a facial expression, bodily posture or a situation that is characteristic of a certain emotion, e.g., a funeral) is always evaluated and the elicited emotional responses are influenced by an individual's goals and by what is meaningful to that individual. As such, emotions are flexible response sequences that arise whenever a situation is evaluated as offering challenges or opportunities to the individual. Emotions are multi-faceted, they involve changes in the behavioral, experiential and physiological domains, and they initiate changes in subjective experience. The modulation of response tendencies determines the final shape of the emotional response (Gross, 1998b). Emotional responses seem to be organized across dimensions such as valence, arousal, and approach-avoidance (Koole, 2009).

Emotion Regulation

Closely linked to the generation and experience of emotions and considered to be an important domain of emotional functioning is the regulation of emotions. Emotion regulation describes how people try to influence which emotions they have, when they have them, and how they experience and express these emotions (Gross, 1998b). A helpful model when describing how emotion regulation can set in at every step of the temporal unfolding of the emotion generation process is the Process Model of Emotion Regulation conceptualized by Gross (2008; Figure 2).

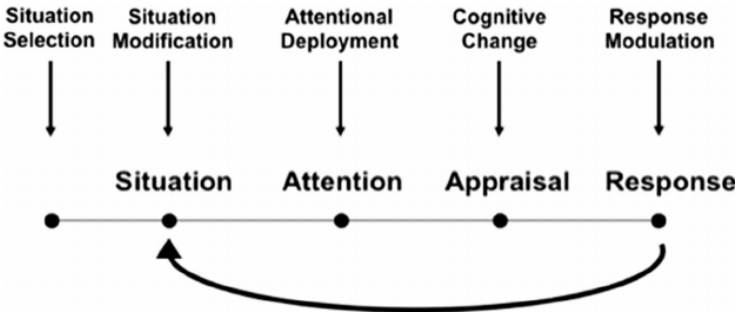

Figure 2. The Process Model of Emotion Regulation

The Process Model of Emotion Regulation broadly distinguishes between antecedent- and response-focused strategies, with the former referring to strategies that occur before the emotion is fully developed (hence their prospect of success is generally greater; Aldao, 2013), and the latter including strategies that appear once an emotion is fully developed and which thus focus mainly on the emotional expression (i.e., the emotional response). Strategies such as selection or modification of a situation, attentional deployment and cognitive change are considered antecedent-focused, while response modulation is regarded as response-focused. Emotion regulation strategies can be behavioral (such as directly selecting or modifying a situation: *situation selection* and *situation modification*), cognitive (such as distracting oneself, ruminating about aspects of the situation, or reappraising the situation altogether: *attentional deployment* and *cognitive change*), or they can focus on the experiential aspects (such as modulating the emotional response: *response modulation*). Emotion regulation may be adaptive or maladaptive; this is largely dependent on both the context and the individual applying the respective strategy. Rather than simply classifying certain strategies as adaptive or maladaptive, newer definitions focus on the flexibility of emotion regulation, i.e., successfully adapting the choice of emotion regulation strategies to contextual and social demands (Aldao, Sheppes, & Gross, 2015).

The ability to regulate one's emotions adaptively develops across childhood and adolescence. The first important step in this process is the growing ability of the young infant

(in the first two years of life) to express different emotional states and to label them verbally accordingly (Compas et al., 2014). This happens in close interaction with adults, especially with the primary caregivers. The importance of an emotional interaction between child and adult is exemplified by the *still face* experiment: in this experiment, the mother (or other primary caregiver), after an episode of emotionally expressive interaction with her child, puts on a still face, i.e., stops her emotional expressions altogether (Tronick et al., 1998). The usual reaction of the infant is an increasing level of distress that only fades once the mother starts interacting emotionally again.

In toddlerhood, the ability to regulate emotions by the use of language (e.g., to talk oneself through a difficult situation or to ask for support) emerges (Petermann & Kullik, 2011). During the preschool and elementary school years, children's ability to regulate their emotions grows and they are increasingly able to manage their emotions according to contextual demands. During this time, children also learn to understand and use display rules, i.e., how intentionally to separate the emotional experience from their facial, vocal and/or behavioral expressions (Zeman, Cassano, Perry-Parrish, & Stegall, 2006). In middle childhood and adolescence, as a consequence of a heightened awareness of changing relationships with peers and parents and an understanding of the consequences of displayed emotions, children and adolescents become warier about which emotions they express in what context. In addition, self-conscious emotions such as pride or shame (that typically emerge for the first time in toddlerhood) might become more prevalent and more intense in adolescent years, as the awareness of being evaluated by the social environment increases (Zeman et al., 2006).

In their development of emotion regulation, children are largely influenced by their familial context. This occurs through several routes: through observation of how parents regulate their emotions, via parenting practices and behaviors (such as how parents react to emotions and whether they are controlling or hostile versus warm and caring towards the

child), and through the emotional climate within the family, which is reflected for example in the quality of parent-child attachment and the parental relationship (Bariola, Gullone, & Hughes, 2011; Morris, Silk, Steinberg, Myers, & Robinson, 2007). However, most studies to date on parental influence on the child's emotion regulation development have focused on early childhood (Bariola et al., 2011; Dorn, Spindler, Kullik, Petermann, & Barnow, 2013), with much less data available for middle childhood and adolescent.

With the increasing recognition of the importance of emotion regulation in adaptive development, its role in mental disorders has also attracted more attention (Mennin, 2006). Maladaptive emotion regulation has been found to play a crucial role in several mental disorders. A large meta-analysis that examined the relationship between six emotion regulation strategies (acceptance, avoidance, problem solving, reappraisal, rumination and suppression) and symptoms of four mental disorders (anxiety, depression, eating disorders, and substance-related disorders) found a large effect size for rumination (r=.49, 95% Confidence Interval (CI) = .45–.52), and medium to large effect sizes for avoidance (r=.38, 95%CI=.33–.44), suppression (r=.34, 95%CI=.28–.39), and problem solving (r=-.31, 95%CI= -.36– -.25; Aldao, Nolen-Hoeksema, & Schweizer, 2009). Surprisingly, in this analysis, reappraisal and acceptance, two strategies that are part of various psychological interventions such as cognitive behavioral therapy (CBT) and acceptance and commitment therapy (ACT) showed only small to medium effect sizes (reappraisal: r=-.14, 95%CI= -.20– -.07; acceptance: r=-.19, 95%CI=-.40 – .05). The other results are in line with previous research that found rumination to be a key symptom of depression (Barnow, Aldinger, Ulrich, & Stopsack, 2013), avoidance to be especially prevalent in many anxiety disorders (Campbell-Sills & Barlow, 2007) and suppression to be associated with behavioral problems in children (Cole, Zahn-Waxler, Fox, Usher, & Welsh, 1996).

Although inappropriate emotion regulation plays a role in a wide range of mental disorders (Gross, 2008), it was not considered a disorder in itself until the new version of the DSM, the DSM-V, was released in 2013, containing the new diagnosis Disruptive Mood Dysregulation Disorder. This disorder is characterized by severe, recurrent, and disproportionate temper outbursts three or more times a week, with a persistent irritable or angry mood between outbursts, and an onset of symptoms before age 10 (American Psychiatric Association, 2013). Disruptive Mood Dysregulation Disorder has emerged in the light of ever-increasing prevalence rates of bipolar disorder (and hence growing prescription rates of antipsychotics) in childhood, which have led some researchers to argue that this non-episodic irritability could be considered a developmental presentation of mania (Leibenluft, 2011; Rao, 2014).

Emotional Reactivity

Intertwined with emotion regulation is emotional reactivity, which refers to individual differences in arousability, i.e., the threshold required for (positive or negative) emotional reactions (Koleva, Krulichova, Bertolini, Caimi, & Garattini, 2005). Recent research has shown that more negatively emotionally reactive children are more susceptible to environmental influences (Belsky & Pluess, 2012) and rearing (Pluess & Belsky, 2010). Experiencing more and more intense emotions might also complicate the emotion regulation process.

The Emotional Security Theory (Davies & Cummings, 1994) suggests that emotional security serves as a mediator between marital functioning and child adjustment. Within this theoretical framework, emotional insecurity may be reflected by high emotional reactivity, which is characterized by heightened fear, distress and vigilance, whereas an emotionally secure child perceives family bonds as positive and stable, even in stressful situations (Davies & Cummings, 1998). In the context of stressful environments, for example marital conflicts,

heightened emotional reactivity might be advantageous, as it elevates vigilance (Cummings, Schermerhorn, Davies, Goeke-Morey, & Cummings, 2006). However, in the long run, emotional insecurity has been shown to increase children's risk of adjustment problems (Thompson, 2000). Emotional security is a result not only of the consistency of quality of care with which children are provided and their early attachment experiences, but is also likely to be influenced by other factors, such as child temperament (Waters, Weinfield, & Hamilton, 2000), and the stability and quality of a child's living conditions (Thompson, 2000). Interestingly, in the differential susceptibility framework, emotional reactivity is considered a plasticity factor, which means that it can render children more susceptible to both supportive and unsupportive environments (Belsky, 2013). Enhanced susceptibility is represented in the nervous system and appears to regulate parts of the brain that are important for fear, reward, and emotional reactivity (Ellis, Boyce, Belsky, Bakermans-Kranenburg, & van IJzendoorn, 2011). Outcomes of such highly reactive phenotypes are bivariate, i.e., whether they increase risk or are protective is dependent on the context, especially on adversity, support and protection (Boyce & Ellis, 2005). For example, children with high emotional reactivity seem to benefit more from supportive rearing environments than less susceptible children (Ellis et al., 2011). What is more, when a group of babies between the ages of seven and 10 months experienced experimentally induced increases in maternal sensitivity, children high in emotional reactivity showed a greater impact on their attachment security than children with lower reactivity (Klein Velderman, Bakermans-Kranenburg, Juffer, & van IJzendoorn, 2006). Consequently, emotional reactivity in itself renders individuals more susceptible to environmental influences – "for better and for worse", as Belsky and colleagues put it (Belsky, Bakermans-Kranenburg, & van IJzendoorn, 2007).

Emotional Disorders

High emotional reactivity and maladaptive emotion regulation are key features of emotional disorders. Anxiety and depressive disorders are very prevalent in adolescence, with lifetime prevalence rates ranging from 11.2% (any mood disorder, i.e., major depressive disorder, dysthymia, and bipolar I or II) to 31.9% (any anxiety disorder, i.e., agoraphobia, generalized anxiety disorder, social phobia, specific phobia, panic disorder, posttraumatic stress disorder, and separation anxiety disorder) and around 10% in both groups experiencing severe impairment (defined as "a lot" or "extreme" impairment in daily activities, or "severe or very severe" distress, Merikangas et al., 2010). Between the ages of 13 and 18 years, the lifetime prevalence rate for any mood disorder increases almost two-fold (Merikangas et al., 2010). Across adolescence, comorbidity rates of anxiety disorders and depressive disorders are significant (Essau, Lewinsohn, Lim, Ho, & Rohde, 2018). Different explanations of why this is the case have been expressed by researchers over the last decades, including theories of a shared underlying factor (i.e., negative affect) that links the two disorders (Tripartite Model; Clark & Watson, 1991), or symptom-related impairment of one disorder as a risk factor for the development of the other (Cummings, Caporino, & Kendall, 2014). Maladaptive emotion regulation has been considered a core component of the development of emotional disorders (Ehrenreich, Goldstein, Wright, & Barlow, 2009). This shared contribution of emotion regulation has led to arguments to include emotion regulation as a sixth domain in the Research Domain Criteria (RDoC; Fernandez, Jazaieri, & Gross, 2016). The RDoC was first introduced by the US National Institute of Mental Health (NIMH) in 2009 and aims to develop a new research classification system for mental disorders, based on the five domains of negative valence (such as fear or threat), positive valence (such as motivation and responsiveness to reward), cognitive systems (such as attention and memory), systems for social processes (such as attachment and perception of self), and arousal/modulatory systems (such as arousal and sleep-wake rhythm; Cuthbert & Insel, 2013). Each domain can be

assessed and measured via several units of analysis, namely genes, molecules, cells, (brain) circuits, physiology, behavior, self-report, and paradigms. The introduction of RDoC was a reaction to the fact that boundaries between mental disorders are often not as rigid as suggested by categorical diagnostic systems such as the DSM or ICD, and underlying mechanisms overlap significantly, which is why the dimensional approach of the RDoC seems more useful (Casey et al., 2013). Fernandez and colleagues now propose to include emotion regulation as a sixth RDoC domain, as it "is the functional consequence of patterns of interaction among the five existing molecular RDoC domains – an emergent construct" (Fernandez et al., 2016, p. 431). Research into the role of emotional functioning across the lifespan is likely to benefit from a possible inclusion of emotion regulation in the RDoC.

A range of interventions exist for emotional disorders, among them psychological interventions such as CBT and ACT, and pharmacotherapy, which show comparable effects on remission, dropouts, and depressive symptoms (Das et al., 2016). However, antidepressants have significant severe side effects, including suicidal thoughts and behaviors, leading in 2004 to the inclusion by the US Food and Drug Administration (FDA) of the "black box" warning on the labels of antidepressants for pediatric use. This remains a controversial issue because of contradictory findings when the data were re-analyzed (Stone, 2014). The scant research on the efficacy of antidepressants for emotional disorders in pediatric populations reveals small to medium effect sizes for depression and medium to large effect sizes for anxiety disorders (Garland, Kutcher, Virani, & Elbe, 2016). In addition, as a result of a lack of evidence on the dosage, safety, and efficacy of medications for children and adolescents, more than half the medication used in hospitalized children is off-label (i.e., prescriptions that differ from the approved labeling with respect to dose, frequency, dosage form, route of administration, or indication for use in children) or unapproved (i.e., not approved at all, not approved or contraindicated for use in children; 't Jong et al., 2000). One

reason for this situation is that enrolling children in clinical trials is more challenging than the enrolment of adults, because the threshold for gaining consent is often higher and more complex and – depending on the disease studied – the pool of eligible children is often small, as prevalence rates for many conditions are lower in children than in adults (Caldwell, Murphy, Butow, & Craig, 2004). Consequently, a recent network meta-analysis that looked at efficacy and tolerability of antidepressants in youth with a major depressive disorder rated the quality of evidence as very low in most comparisons (Cipriani et al., 2016). The authors concluded that all but one of the studied antidepressants did "not seem to be suitable as routine treatment options" (p. 882). Nevertheless, antidepressants are still considered the first-line pharmacological treatment for emotional disorders, that is, for depressive disorders, anxiety disorders, obsessive-compulsive disorder, and posttraumatic stress disorder (Garland et al., 2016).

Emotional Functioning in Chronic Pain

Given the important role that emotional functioning plays in mental disorders, surprisingly little research exists on its role in chronic pain, even though there is a high comorbidity rate between emotional disorders and chronic pain (Bair, Robinson, Katon, & Kroenke, 2003; Goldenberg, 2010; Tegethoff, Belardi, Stalujanis, & Meinlschmidt, 2015; Tsang et al., 2008). The International Association for the Study of Pain (IASP) defines pain as an "unpleasant sensory and *emotional experience* with actual or potential tissue damage, or described in terms of such damage" (Merskey & Bogduk, 1994). This definition points to the important emotional component of pain. Indeed, studies both in healthy volunteers (Godinho, Magnin, Frot, Perchet, & Garcia-Larrea, 2006; Ruiz-Aranda, Salguero, & Fernandez-Berrocal, 2010) and in patients with chronic pain (Tsao et al., 2004) have demonstrated the influence of emotional state on pain perception, indicating that negative emotions tend to increase pain perception.

Pain is considered chronic if it persists or recurs for more than three months or when it persists past normal healing time (Treede et al., 2015). An estimated 20% of people worldwide are affected by chronic pain syndromes such as headache, chronic low back pain, and fibromyalgia (Goldberg & McGee, 2011). Chronic pain ranks amongst the disorders that cause the largest financial, medical and psychosocial burden for individuals and societies (Vos et al., 2012), and accounts for 15% to 20% of physician visits (Koleva, Krulichova, Bertolini, Caimi, & Garattini, 2005). Even though the etiology of most chronic pain conditions remains unknown, current hypotheses point to several mechanisms that contribute to its development, including genetic (Diatchenko et al., 2005), neurological (Tracey & Bushnell, 2009), social (Beck, 2008), and psychological factors (Carter & Threlkeld, 2012). One influential notion is that of central sensitization, which has been defined as an "increase in synaptic efficacy in nociceptive pathways in the central nervous system and/or reduced descending inhibition of pain leading to enhanced pain" (Bromberg, Schechter, Nurko, Zempsky, & Schanberg, 2014, p. 213. As a result of genetic susceptibility, repeated trauma, infections and inflammation, the central nervous system might become overly effective in transmitting pain signals and less effective in inhibiting them. For the upcoming ICD-11, the International Association for the Study of Pain Task Force has created a new category, *chronic primary pain*. Chronic primary pain is defined as pain in one or more bodily regions that persists or recurs for longer than three months and is associated with significant emotional distress or functional disability (Treede et al., 2015). Importantly, this new terminology emphasizes the key role of emotions in the context of chronic pain. The term *primary pain* was first introduced by Neil Schechter in a 2014 JAMA Pediatrics Viewpoint and it was aimed at a paradigm shift towards an understanding that "pain itself is the disease" (Schechter, 2014, p. 694).

Even though some current models of chronic pain include psychological factors and comorbidities (e.g., von Baeyer & Champion, 2011), many questions remain with regard to the relationship between emotion regulation and chronic pain.

Aims of the thesis

This thesis aims to shed light on the role of emotional functioning, that is, emotional reactivity, emotion regulation, and emotional disorders, in various domains across childhood and adolescence. Therefore, three different aims were pursued: first, to examine the role of emotion regulation in chronic pain, looking specifically at the difference between antecedent- and response-focused emotion regulation strategies and their respective relationship with pain-related outcomes. As emotion regulation is closely related to (and in a sense dependent on) emotional reactivity, the second goal was to analyze how emotional reactivity influences the occurrence of behavioral adjustment problems in adolescents who have experienced stressful life events in childhood. Finally, the last aim was to test a common intervention for emotional disorders and to examine the safety and efficacy of second-generation antidepressants in pediatric populations.

The three research projects described in this thesis were designed to provide insight into the following leading questions:

(1) What is the role of emotion regulation in chronic pain?

Study I A high comorbidity rate between emotional disorders and chronic pain (Bair et al., 2003) and the fact that emotional state influences pain perception (Berna et al., 2010) point to a potentially important role played by emotion regulation in the development and maintenance of chronic pain. The Process Model of Emotion Regulation (Gross, 1998a, 1998b) suggests that emotion regulation can set in at every step of the temporally unfolding process of emotion generation. The model divides emotion regulation strategies broadly into antecedent- or response-focused strategies, based on their appearance in the process of emotion generation. As antecedent-focused strategies set in before the emotion is fully developed, the prospect of their success is considered greater (Aldao, 2013). To date, only one review has looked at pain and emotion regulation and focused on overlapping neural circuits

between the two (Konietzny, Suchan, Kreddig, Hasenbring, & Chehadi, 2016). Thus, the goal of Study I was to synthesize the existing body of research on the relationship between antecedent- and response-focused emotion regulation strategies and chronic pain, and to investigate whether the construct of emotion regulation might enhance existing theoretical frameworks of chronic pain. As there is only a small number of studies that have investigated pediatric populations (only two were identified that matched the inclusion criteria), the search was expanded to all age groups.

(2) Does emotional reactivity influence the occurrence of adjustment problems in adolescents with few or many stressful life events during childhood?

Study II Emotional reactivity is considered an important vulnerability factor in the differential susceptibility framework (Belsky et al., 2007). Stressful life events such as abuse, neglect, low socioeconomic status, divorce or separation of parents, and exposure to violence are important risk factors for healthy development in children and adolescents (Shonkoff, Boyce, & McEwen, 2009). Stressful life events have been linked to anxiety and depression (Ge, Conger, & Elder, 2001), delinquent behavior (Vaux & Ruggiero, 1983) and rumination and emotional dysregulation (McLaughlin & Hatzenbuehler, 2009). However, family- and individual-level influences, such as a child's attachment to the primary caregiver, the relationship between parents, a child's emotional reactivity and friendship quality might increase or decrease the risk of adverse outcomes despite stressful life events. Hence, the goal of Study II was to look longitudinally at the influences of individual- (such as emotional reactivity) and family-level factors (such as parent-child interaction and parental relationship) on the relationship between exposure to stressful life events in childhood and clinically elevated adjustment problems in adolescence.

(3) How safe and efficacious are antidepressants in the treatment of emotional disorders in children and adolescents?

Study III Even though the use of selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SRNIs) is still debated (Stone, 2014), they are considered first line pharmaceutical treatments for emotional disorders. To date, only one review has compared the efficacy and risk profile of antidepressants across emotional disorders in childhood and adolescence (Bridge et al., 2007); however, since then, 11 new studies on the use of SSRIs or SNRIs in pediatric populations with emotional disorders have been published. Interestingly, Bridge et al.'s (2007) review found disorder-specific effect sizes for SSRIs and second-generation antidepressants (namely nefazodone, venlafaxine and mirtazapine): between antidepressant-placebo effect sizes were largest for non-OCD anxiety disorders (Hedges' $g = 0.69$), and modest for major depressive disorder (Hedges' $g = 0.20$; Bridge et al., 2007). The goal of Study III was to update and extend this review in order to assess the efficacy and safety of SSRIs and SNRIs for the treatment of emotional disorders, alongside between-disorder variation in drug and placebo responses.

Methods

Different methodological approaches were chosen to address the three aims. In the case of the first aim, a systematic literature search was conducted and the identified papers were then summarized narratively (Study I). This had the advantage of allowing researchers to look at all available evidence without being dependent on consistent outcomes and outcome measures. For the second aim, data from a large longitudinal dataset were analyzed (Study II). The variables of interest (especially emotional reactivity and adjustment problems) were individually assessed at multiple time points, which had the advantage of a reduced risk of recall bias. In order to address the third aim, a meta-analytic approach was chosen (Study III). Meta-analyses are well suited to questions concerning the efficacy and safety of a given intervention, as a more reliable result can be obtained by pooling evidence across all included studies (Borenstein, 2009).

The role of emotion regulation in chronic pain: A systematic literature review (Study I)

Search strategy and study selection. In this systematic literature review, we searched PubMed, Embase, PsycInfo, Web of Science, CINAHL and the Cochrane Central Database of Controlled Clinical Trials from inception through November 2016, using the key words "emotion regulation" and "chronic pain". In order to be included, studies had to report an emotion regulation and a chronic pain measure and an association between the two constructs. The screening and selection process was conducted independently by two authors.

Data Extraction. Information on study sample, pain diagnosis, pain measure, emotion regulation measure, and statistical association between pain and emotion regulation measure was extracted. Questionnaire items on each emotion regulation measure in every study were reviewed and measures were categorized as either antecedent- or response-focused emotion regulation.

Effects of childhood life events on adjustment problems in adolescence: A longitudinal study (Study II)

Sample. Data used for this study originated from the Study of Early Child Care and Youth Development (SECCYD), collected by the National Institute of Child Health and Development (NICHD). In this study, participants were recruited from hospitals and university centers across several locations in the United States at the time of the child's birth in 1991 and followed until age 15. During this time, four study phases were conducted.

Outcome Measure, Main Predictor, and Covariates. The primary outcome of our analysis was the clinical elevation of adjustment problems at age 15. For this outcome, we used two broad groups of syndromes, internalizing and externalizing problems, created from subscales of the Child Behavior Checklist (CBCL; Achenbach & Ruffle, 2000) rated by the mother, and the Youth Self Report (YSR; Achenbach, 1991), rated by adolescents. Clinical elevation of adjustment problems, our primary outcome, was defined as the presence of high internalizing and/or externalizing problems (i.e., T-score of >60, which is one standard deviation above the mean). The main predictor used in this study was a measure of stressful life events. The mother of the child in the study completed a survey on stressful life events (Sarason, Johnson, & Siegel, 1978) at three time points during the child's childhood and reported whether any of the 57 events had occurred during the last year. The list of events included routine happenings (e.g., a wedding in the extended family), major events (e.g., separation of parents) and catastrophic events (e.g., death of a family member). We looked at life events from three different perspectives, following the example of previous research using the same dataset (Lumeng et al., 2013). First, we categorized the total number of stressful life events as either "many" (upper quartile of total number of stressful life events) or "few" (lower three quartiles of total number of life events). In addition, we created a timing/chronicity variable to reflect the time points at which the child was in the upper quartile of the number of life events. This resulted in five categories, namely early exposure,

late exposure, single exposure, never, and always exposed. In a last step, we created four categories of stressful life events depending on the area of life that was most affected by them: parent/family physical or mental health and well-being; parental work, school, or financial stability; emotional aspects of relationships; and change in family structure, routine and caregiving.

We included a number of covariates, among them demographic variables (child gender, race/ethnicity, maternal education, total income-to-needs ratio to assess financial stress), individual-level (i.e., mainly concerning the child, namely mother-child attachment, temperament, emotional reactivity, friendship quality) and family-level covariates (i.e., concerning the child and the child's family, namely mother-child attachment, maternal separation anxiety, parent-child interaction, parental intimacy, maternal and paternal depression) that have been shown to modulate the effect of stressful life events on adjustment problems. All these covariates were measured at least twice during the study period.

Statistical Analyses. All analyses were performed using SAS 9.4 (SAS Institute; Cary, NC). Descriptive statistics were calculated for all demographic and study characteristics. Chi-squared and Wilcoxon's test were used to assess unadjusted associations of individual stressful life events, summary stressful life events variables, and all the covariates with adjustment problems in adolescence. For each of the covariates, we created summary variables using the SAS PROC TRAJ procedure. This group-based trajectory modeling assumes a certain number of discrete underlying groups in the population (Jones, Nagin, & Roeder, 2001). In the case of emotional reactivity of the child, the model identified two trajectories, namely high and low emotional reactivity.

Multiple logistic regression analyses were used to evaluate the association of adjustment problems in adolescence (dependent variable) and the total number of stressful life events (independent variable) while controlling for demographics. The models were re-run using all the stressful life events categorical variables and stressful life events

timing/chronicity as independent variables. Finally, models including individual- and family-level covariates were run. Adjusted odds ratios (ORs) and their 95% confidence intervals (95% CIs) were calculated for all models. Significance values of the final model were Bonferroni-adjusted for multiple comparisons, and p-values <0.01 were considered significant. Linear mixed models were used to evaluate differences in CBCL internalizing and externalizing trajectories over time between children with "few" and those with "many" stressful life events.

Efficacy and safety of SSRIs, SNRIs and placebo in common psychiatric disorders: A comprehensive meta-analysis in children and adolescents (Study III)

Search strategy and study selection. For the purposes of this meta-analysis, we searched PubMed, Embase, PsycInfo, Cochrane, Web of Science, clinicaltrials.gov and fda.gov from inception through August 2016 and checked references of included studies as well as of previous reviews. We included randomized, double-blind, placebo-controlled trials of SSRIs and SNRIs in children and adolescents <18 years of age diagnosed with major depressive disorder, an anxiety disorder, obsessive-compulsive disorder, or posttraumatic stress disorder based on DSM-III, DSM-III-R, or DSM-IV-TR criteria.

Outcome measures and data extraction. The primary outcome as defined by authors (of the included studies) was chosen as the sole outcome measure for each study. Pre- and post-intervention data or mean change data had to be available. Outcomes had to be reported on a well-validated, disorder-specific scale (e.g., Children's Depression Rating Scale – Revised, Multidimensional Anxiety Scale for Children, and Children's Yale-Brown Obsessive Compulsive Scale) or on a general severity scale (i.e., Clinical Global Impression – Severity Scale). Only continuous outcome data were included. Extracted data included demographic information, dropout rates, adverse events, safety information, and baseline and end point assessment scores.

Data analysis. Comprehensive Meta-Analysis V3 (Biostat; Englewood, NJ) and R 3.2.1 (R Foundation; Vienna, Austria) were used for calculations and analyses. We calculated three effect sizes (Hedges' *g*; Hedges & Olkin, 1985) for each included study. First, differences in mean change scores between groups were evaluated. Next, within-group pre-post effect sizes for antidepressant and placebo were calculated. We chose to use random-effects models rather than fixed-effect models as the included studies were heterogeneous and the number of studies for the sub-analyses was relatively small. Random-effects models assume that a combination of sampling error and true variance in effect sizes results in variations in effect sizes across studies included in a meta-analysis, while fixed-effect models act on the assumption that there is one true underlying effect size for all studies and any variation is to the result of sampling error (Borenstein, Hedges, Higgins, & Rothstein, 2010). Heterogeneity was assessed by calculating the Q statistic, the τ^2 and the I^2. A statistically significant Q indicates systematic differences between studies, therefore rejecting the null hypothesis that all variation in effect is the result of random error (Huedo-Medina, Sánchez-Meca, Marín-Martínez, & Botella, 2006). The I^2 is a transformation of Q that indicates the proportion of observed variance across studies that is the result of real heterogeneity rather than sampling error (Higgins, Thompson, Deeks, & Altman, 2003). The τ^2 offers an estimate of the variance among true effect sizes (Higgins, 2008). In order to evaluate whether the risk of adverse events differed between antidepressant and placebo groups, risk ratios (RRs) for treatment emergent adverse events (TEAEs) and serious adverse events (SAEs) were calculated. The RRs of SAEs were based on the percentage of patients with SAEs in each included study. With regard to RRs of TEAEs, we compared two commonly used reporting methods: percentage of patients with TEAEs in each group and mean number of TEAEs per patient across all reported symptoms.

Summary of the Results

The role of emotion regulation in chronic pain: A systematic literature review (Study I)

Our search identified 15 studies including a total of 2065 patients. Only two studies included pediatric populations, six studies had a female-only population, and only one study had a majority of male participants. All measures of emotion regulation were classified as either antecedent- (n=4) or response- (n=5) focused emotion regulation. A number of studies (n=5) used both antecedent- and response-focused measures and one study used a measure that could not be classified definitively.

The group of studies of antecedent-focused emotion regulation did not show a direct influence of these strategies on pain. However, these emotion regulation strategies were correlated with high emotionality and negative mood. Hence, it is possible that adaptive use of antecedent-focused strategies may reduce pain vulnerability or pain experience indirectly by reducing high emotionality or negative mood, both known vulnerability factors for the development of chronic pain.

Studies considering response-focused emotion regulation found a direct correlation between these strategies and pain or pain-related functioning in some cases, while in other cases these strategies related to symptoms of depression, a prevalent psychological comorbidity of chronic pain.

Those studies that measured both groups of emotion regulation strategies found no direct relationship of either group of strategies to pain, but found response-focused strategies to be correlated with catastrophizing thoughts around pain, the likelihood of being hospitalized during pain crises, and the impact of the disease on patients' everyday life.

In summary, the studies included in this review rarely found direct associations between emotion regulation and pain. Rather, the relationship between (antecedent- or response-focused) emotion regulation and pain seemed to be mediated by psychological factors such as emotionality, anxiety or negative mood. Those studies looking exclusively at

response-focused emotion regulation strategies appeared to provide the best evidence for a strong relationship between maladaptive emotion regulation, psychological symptoms, and pain.

Effects of childhood life events on adjustment problems in adolescence: A longitudinal study (Study II)

Of the 1364 children and their families enrolled in the study, information from the YSR at age 15 years was available for 956 subjects. A significant difference between mother- and adolescent-reports was found for the internalizing (11.0% vs. 11.3%, $p<0.001$) and externalizing (10.3% vs. 14.3%, $p<0.001$) subscales as well as for the ratings of adjustment problems (26.3% vs. 21.1%, $p<0.001$). All selected covariates, except temperament, showed a significant association with mother-reported adjustment problems in adolescence in the unadjusted analysis. However, for child-reported adjustment problems, only emotional reactivity ($p=0.002$) and maternal ($p=0.004$) and paternal ($p=0.006$) depression were found to be significant.

Overall, children with adjustment problems at age 15 reported a higher total number of stressful life events (median=24, Interquartile Range (IRQ): 15–30 vs. median=19, IRQ: 12–27, $p<0.001$) than children with no adjustment problems. Variables significantly associated with adjustment problems in adolescence were: total number of stressful life events, gender, maternal education level, emotional reactivity, friendship quality, and paternal (but not maternal) depression. There were no significant associations between timing/chronicity of stressful life events and adjustment problems. Stressful life events categorized as emotional aspects of relationships were significantly associated with child-reported adjustment problems, and marginally significantly associated with mother-reported adjustment problems. Of note was the finding that each additional stressful life event increased the odds ratio (OR) for adjustment problems in adolescence. Results from the model that included only children

with “many” life events showed that mother-reported adjustment problems were associated with high child emotional reactivity scores (OR=3.8, p=0.003). Similarly, results from the model that included only children with “few” stressful life events showed that mother-reported adjustment problems were again associated with high child emotional reactivity (OR=2.0, p=0.006), but also with maternal education at child’s birth (high school education versus graduate studies; OR=3.3, p=0.002). Child-reported adjustment problems were associated with paternal (but not maternal) clinically significant versus low depression scores (OR=3.5, p=0.001).

Efficacy and safety of SSRIs, SNRIs and placebo in common psychiatric disorders: A comprehensive meta-analysis in children and adolescents (Study III)

Our search identified one unpublished and 35 published randomized, double-blind trials, including 6778 participants, that compared an SSRI or an SNRI against placebo in patients younger than 18 years with a diagnosis of an anxiety disorder (AD; n=10), a depressive disorder (DD; n=17), obsessive-compulsive disorder (OCD; n=8), or posttraumatic stress disorder (PTSD; n=1). As we only found one study on PTSD, no disorder-specific subgroup analyses were calculated for this disorder.

The combined analysis between groups across all disorders yielded a small drug-placebo difference (g=0.32; 95%CI, 0.25 to 0.40, p<0.001). In the between-group analysis stratified by disorder, anxiety disorders (g=0.56, 95%CI, 0.40 to 0.72, p<0.001) and obsessive-compulsive disorder (g=0.39, 95%CI, 0.25 to 0.54, p<0.001) did not differ significantly from each other (p=0.14), but both yielded significantly higher (AD vs. DD: p<0.001 and OCD vs. DD: p=0.02) drug-placebo differences than the DD group (g=0.20, 95%CI, 0.13 to 0.27, p<0.001). The within-drug group analysis stratified by disorder yielded no significant difference (p=0.06) between studies of anxiety disorders (g=1.58, 95%CI, 1.35 to 1.81, p<0.001) and depressive disorders (g=1.85, 95%CI, 1.7 to 2.0, p<0.001), yet both

yielded significantly larger drug responses ($p<0.001$) than studies of obsessive-compulsive disorder (g=1.01, 95%CI, 0.88 to 1.14, $p<0.001$). The within-placebo group analysis stratified by disorder yielded a large placebo response for studies of depressive disorders (g=1.57, 95% CI, 1.36 to 1.78, $p<0.001$), which was significantly larger ($p<0.001$) than the placebo response in studies of anxiety disorders (g=1.03, 95%CI, 0.84 to 1.21, $p<0.001$).

Side-effect analysis The two reporting methods of TEAEs (reporting method 1: percentage of patients with TEAEs, reporting method 2: mean number of TEAEs per patient across symptoms) differed significantly, indicating higher RRs for reporting method 2. Patients taking an antidepressant reported significantly more TEAEs (reporting method 1: RR, 1.07, 95%CI, 1.01 to 1.12, $p=0.01$; reporting method 2: RR, 1.49, 95%CI 1.22 to 1.82, $p<0.001$) and SAEs (RR, 1.76, 95%CI, 1.34 to 2.32, $p<0.001$) compared to those taking the placebo.

Discussion

This thesis pursued the main goal of improving our current understanding of the role of emotional functioning across different domains in childhood and adolescence. Emotional reactivity, emotion regulation and emotional disorders are part of emotional functioning. Therefore, the thesis had three different aims: to examine the role of emotion regulation in chronic pain; to analyze the role of emotional reactivity in the context of stressful life events; and to test a common intervention for emotional disorders in children and adolescents. Emotional (mal)functioning can be considered a shared underlying process of emotional disorders, and patterns of emotional functioning that emerge in childhood persist into adulthood, presenting as an early indicator of or risk factor for long-term health and adjustment (Repetti et al., 2002). Overall, emotional functioning has been found to be a key process of healthy development in children and adolescents, across several important domains. Emotional disorders show high prevalence rates, are a major public health concern, and predict long-term risk for various adverse outcomes. Therefore, the recognition of the importance of emotional functioning in childhood and adolescence as well as the proper treatment of emotional disorders is crucial.

The role of emotion regulation in chronic pain: A systematic literature review (Study I)

At first sight, the finding that emotion regulation is rarely directly correlated with pain intensity or pain-related might seem surprising. However, when examining it from a more integrated perspective, it seems plausible that emotion regulation serves as a key moderator that influences the overall wellbeing of patients with chronic pain via several psychological factors (such as negative emotionality and depressed mood). Current models of chronic pain development and maintenance point to several aspects that are potentially influenced by maladaptive emotion regulation, namely psychological vulnerability, comorbid psychological conditions and impaired pain regulatory systems (von Baeyer & Champion, 2011).

Furthermore, a recent study found some shared genetic components of emotion regulation and chronic widespread pain (Burri, Ogata, Vehof, & Williams, 2015). Having a comorbid emotional disorder might present as an additional stressor to patients with chronic pain and may increase their disability, but may also serve as a target well suited for interventions that aim to improve emotional functioning. Indeed, preliminary case and pilot studies on both adults and adolescents that have targeted emotional functioning report positive results (e.g., Allen, Tsao, Seidman, Ehrenreich-May, & Zeltzer, 2012; Gottschalk, Bleichhardt, Kleinstauber, Berking, & Rief, 2015). One of these studies, a case report of two adolescent patients with chronic pain and comorbid emotional disorders, used modules such as psychoeducation about emotions and pain, modification of emotion-driven behaviors, and flexibility in thinking during the course of treatment (Allen et al., 2012). Both patients showed improvements over at least some of the various domains of interest, such as pain, functional disability, emotion regulation, anxiety and depression. Another study extended CBT for adult patients with somatoform disorders (including pain) with emotion regulation training modules. The researchers focused on the impact of emotions on pain and psychological symptoms, explored how emotion regulation can help to change this impact, and found greater effect sizes for CBT with emotion regulation than for CBT alone for almost all treatment objectives. The group differences were not significant, however, possibly the result of small group sizes (Gottschalk et al., 2015). These promising first results argue for the inclusion of emotion regulation (and more broadly, emotional functioning) in current theoretical frameworks of chronic pain, which may help to further clarify why some people are more vulnerable to chronic pain (and comorbid emotional disorders) and how this knowledge can be implemented in new interventions.

The new category of chronic primary pain, as suggested for the upcoming ICD-11 (Treede et al., 2015), takes the importance of emotional functioning (which includes emotion regulation) in patients with chronic pain into account: the diagnostic criteria for chronic primary pain

state that it is “characterized by significant emotional distress (anxiety, anger/frustration or depressed mood)” or functional disability (ICD-11 – Mortality and Morbidity Statistics, 2018).

Effects of childhood life events on adjustment problems in adolescence: A longitudinal study (Study II)

Study II found a further aspect of emotional functioning, namely emotional reactivity, to have an important influence on the relationship between stressful life events in childhood and adjustment problems in adolescence. Interestingly, we found a significant difference between mother- and self-reported adjustment problems in adolescence, with adolescents rating themselves higher on the Youth Self Report than their mothers did on the Child Behavior Checklist. This is in line with previous research that found self-rated emotional disorders to be consistently higher compared to ratings of other informants (such as parents or teachers; van der Ende, Verhulst, & Tiemeier, 2012). When the emotional development across childhood and adolescence is taken into account, this finding makes sense: it is in middle childhood and during adolescence that children become warier with regard to which emotions they display in what context, and self-conscious emotions (such as pride or shame) become more intense and more prevalent (Zeman et al., 2006). Hence, adolescents might want to hide symptoms of emotional disorders from their parents. With regard to the development of adjustment problems in adolescence, Study II found emotional reactivity to be among the most important predictors. In the differential susceptibility framework (Belsky, 2013), emotional reactivity is thus considered a vulnerability factor that, depending on positive or negative influences from the environment, may lead to either adaptive or maladaptive outcomes. Indeed, when we closely examined possible protective factors against adjustment problems for children in the group with “many” stressful life events, low emotional reactivity

was one of them. In a very stressful environment, it might be advantageous to have a higher threshold for emotional reactions, in order to avoid constant emotional distress.

Efficacy and safety of SSRIs, SNRIs, and placebo in common psychiatric disorders: A comprehensive meta-analysis in children and adolescents (Study III)

In the treatment of emotional disorders, SSRIs and SNRIs are considered first- and second-line pharmacological treatment choices. Interestingly, Study III found effect sizes of antidepressants to be larger for anxiety disorders than for depressive disorders. This disorder-specific difference in drug-placebo response might be attributable to the large placebo response in depressive disorders, which in turn might be explained by the greater demoralization and hence greater sensitivity to change in patients with depressive disorders when compared to patients with anxiety disorders (Cohen et al., 2008). It might also be because of the heterogeneous phenotype of depressive disorders that makes prediction of treatment effect challenging (Kessler et al., 2016). This was apparent in the DSM-5 field trials on major depressive disorder, which found a low test-retest reliability (kappa=0.28) for children, adolescents and adults (Regier et al., 2013). Furthermore, there is high comorbidity between anxiety and depression. As a consequence, the DSM-V Field trials tested a new diagnosis, namely “mixed anxiety and depression disorder” (Regier et al., 2013). When this disorder was tested in the DSM-5 Field Trials, it turned out to have an unacceptable rate of test-retest reliability (kappa: -0.04; Regier et al., 2013). In the case of these findings, new ways of looking at mental disorders are needed, as the current categorical perspective does not seem to capture the complexity of emotional disorders adequately. Hence, the US-National Institute of Mental Health (NIMH) proposed the Research Domain Criteria (RDoC), a dimensional framework to describe mental disorders along several domains (Insel et al., 2010). As has been proposed previously, emotional functioning, especially emotion regulation (Fernandez et al., 2016), could be included as a new domain in RDoC. This would facilitate

research into similarities and differences between emotional disorders on several units of analysis (Dillon et al., 2014). In addition, as a result of the high comorbidity of emotional disorders and chronic pain (Study I), inclusion of emotional functioning in RDoC would allow researchers to study shared underlying mechanisms. Studying processes instead of diagnoses could lead to the development of interventions that target these processes specifically and hence affect symptoms of emotional disorders and chronic pain simultaneously.

As pharmacotherapy shows comparable effects on remission, dropouts, and depressive symptoms to psychological interventions such as CBT or ACT (Das et al., 2016), and taking into consideration the increased risk of serious adverse events in a course of treatment with antidepressants, a cautious and individual cost-benefit analysis is important before the start of treatment for emotional disorders.

Limitations

The results reported in this thesis have some limitations. Study I reflected the difficulties caused by a highly heterogeneous use of the term emotion regulation, which made the study search and selection process challenging. The same applied in the case of the chronic pain conditions included in the systematic review. The greatest limitation, however, was the small number of studies on pediatric samples: we found only two studies that included children and adolescents. With this research gap identified by our study, we decided to broaden the search to all age groups. Given that emotion regulation involves higher order cognitive processing, no generalization to broader pediatric samples can be made, especially not with regard to possible age-specific relationships between emotion regulation and chronic pain. An additional limitation of the included studies was the bias of female only studies (six of 15 studies).

In Study II, the analyses were conducted using a community (not a clinical) sample. Hence, our outcome, adjustment problems in adolescence, represented differences within the norm that only in rare cases exceeded a clinical threshold. The same assumptions should therefore be tested on a clinical sample. Other than that, all information in our study relied on self-report by participating children and their mothers. Previous research has shown that depressed or anxious mothers tend to report more cases of child behavior problems than their healthy counterparts or the children themselves (Najman et al., 2000). This might have influenced our results, as a considerable number of mothers reported either depressive symptoms or symptoms of separation anxiety at some point during the study period.

The limitations of Study III include the fact that none of the RCTs included in our analysis directly compared the effectiveness of SSRIs and SNRIs across disorders. Thus, we could only make indirect conclusions with regard to disorder specificity. Mean age and age distribution of participants varied among studies, which might have had an effect on the results, as the response to SSRIs and SNRIs has been shown to be lower in children than in adolescents (Bridge et al., 2007).

Conclusions and Implications for Future Research

Despite these limitations, the results of this thesis emphasize the importance of emotional functioning across various domains in childhood and adolescence. As emotional functioning develops across age, future research should focus on the age-specific influences of emotional functioning on chronic pain and emotional disorders. This would allow medical practitioners to tailor intervention and prevention to age-specific needs and abilities. The heterogeneous phenotype of emotional disorders, especially of depressive disorders, calls for new ways of studying these phenomena. Investigating within-comparisons might offer a new and interesting perspective, shedding light at how depressive symptoms change over time within a person and how these processes manifest. Examining emotional functioning using various

methods across different levels of analysis might also be a promising method (Dorn et al., 2013; Fernandez et al., 2016). If a large number of people were to be studied in this fashion, conclusions could be drawn at the population level (Kendler & Aggen, 2017).

Furthermore, individual patient-level analyses could help to explore the influence of individual characteristics on treatment effects, as they are – other than in meta-analyses – not based on aggregated data (Zhou et al., 2018). Here, the inclusion of more psychological factors, such as emotional functioning in RCTs would help to increase our knowledge of how these factors influence treatment outcomes.

In the field of chronic pain, the new category of chronic primary pain (Schechter, 2014; Treede et al., 2015) should be examined for its validity. Here, the focus should be on the role of emotional distress, which is now defined as a symptom of anxiety, anger/frustration and depression, but might be of better use if defined more broadly. In this way, other emotional symptoms that might interfere with patients' wellbeing despite pain would not be missed.

Children are not small adults (Foster & Lyall, 2015). Results from research in adult populations cannot and should not be transferred directly to pediatric populations. Hence, despite challenges posed by the enrollment of children in clinical trials (Caldwell et al., 2004), future researchers should make an effort to include children in order to do justice to developmental features that are specific to this age group.

References

Achenbach, T. M. (1991). *Manual for the Youth Self-Report and 1991 Profile.* Burlington, VT: University of Vermont, Department of Psychiatry.

Achenbach, T. M., & Ruffle, T. M. (2000). The Child Behavior Checklist and related forms for assessing behavioral/emotional problems and competencies. *Pediatrics in Review/American Academy of Pediatrics*, *21*(8), 265–271. https://doi.org/10.1542/pir.21-8-265

Aldao, A. (2013). The future of emotion regulation research: Capturing context. *Perspectives on Psychological Science: A Journal of the Association for Psychological Science*, *8*(2), 155–172. https://doi.org/10.1177/1745691612459518

Aldao, A., Nolen-Hoeksema, S., & Schweizer, S. (2009). Emotion-regulation strategies across psychopathology: A meta-analytic review. *Clinical Psychology Review*, *30*(2), 217–237. https://doi.org/10.1016/j.cpr.2009.11.004

Aldao, A., Sheppes, G., & Gross, J. J. (2015). Emotion regulation flexibility. *Cognitive Therapy and Research*, 1–16. https://doi.org/10.1007/s10608-014-9662-4

Allen, L. B., Tsao, J. C. I., Seidman, L. C., Ehrenreich-May, J., & Zeltzer, L. K. (2012). A unified, transdiagnostic treatment for adolescents with chronic pain and comorbid anxiety and depression. *Cognitive and Behavioral Practice*, *19*(1), 56–67. https://doi.org/10.1016/j.cbpra.2011.04.007

American Psychiatric Association (2013). *Diagnostic and Statistical Manual of Mental Disorders (DSM-5®)*. Washington, DC, US: APA Press.

Bair, M. J., Robinson, R. L., Katon, W., & Kroenke, K. (2003). Depression and pain comorbidity: A literature review. *Archives of Internal Medicine*, *163*(20), 2433–2445. https://doi.org/10.1001/archinte.163.20.2433

Bariola, E., Gullone, E., & Hughes, E. K. (2011). Child and adolescent emotion regulation: the role of parental emotion regulation and expression. *Clinical Child and Family*

Psychology Review, *14*(2), 198–212. https://doi.org/10.1007/s10567-011-0092-5

Barnow, S., Aldinger, M., Ulrich, I., & Stopsack, M. (2013). Emotionsregulation bei Depression. *Psychologische Rundschau*, *64*(4), 235–243. https://doi.org/10.1026/0033-3042/a000172

Beck, J. E. (2008). A developmental perspective on functional somatic symptoms. *Journal of Pediatric Psychology*, *33*(5), 547–562. https://doi.org/10.1093/jpepsy/jsm113

Belsky, J. (2013). Differential susceptibility to environmental influences. *International Journal of Child Care and Education Policy*, *7*(2), 15–31. https://doi.org/10.1007/2288-6729-7-2-15

Belsky, J., Bakermans-Kranenburg, M. J., & van IJzendoorn, M. H. (2007). For better and for worse: differential susceptibility to environmental influences. *Current Directions in Psychological Science*, *16*(6), 300–304. https://doi.org/10.1111/j.1467-8721.2007.00525.x

Belsky, J., & Pluess, M. (2012). Differential susceptibility to long-term effects of quality of child care on externalizing behavior in adolescence? *International Journal of Behavioral Development*, *36*(1), 2–10. https://doi.org/10.1177/0165025411406855

Berna, C., Leknes, S., Holmes, E. A., Edwards, R. R., Goodwin, G. M., & Tracey, I. (2010). Induction of depressed mood disrupts emotion regulation neurocircuitry and enhances pain unpleasantness. *Biological Psychiatry*, *67*(11), 1083–1090. https://doi.org/10.1016/j.biopsych.2010.01.014

Borenstein, M. (Ed.). (2009). *Introduction to meta-analysis*. Chichester, U.K: John Wiley & Sons.

Borenstein, M., Hedges, L. V., Higgins, J. P. T., & Rothstein, H. R. (2010). A basic introduction to fixed-effect and random-effects models for meta-analysis. *Research Synthesis Methods*, *1*(2), 97–111. https://doi.org/10.1002/jrsm.12

Boyce, W. T., & Ellis, B. J. (2005). Biological sensitivity to context: I. An evolutionary-

developmental theory of the origins and functions of stress reactivity. *Development and Psychopathology*, *17*(2), 271–301. https://doi.org/10.1017/S0954579405050145

Bridge, J. A., Iyengar, S., Salary, C. B., Barbe, R. P., Birmaher, B., Pincus, H. A., Ren, L., & Brent, D. A. (2007). Clinical response and risk for reported suicidal ideation and suicide attempts in pediatric antidepressant treatment: A meta-analysis of randomized controlled trials. *JAMA*, *297*(15), 1683–1696. https://doi.org/10.1001/jama.297.15.1683

Bromberg, M. H., Schechter, N. L., Nurko, S., Zempsky, W. T., & Schanberg, L. E. (2014). Persistent pain in chronically ill children without detectable disease activity. *Pain Management*, *4*(3), 211–219. https://doi.org/10.2217/pmt.14.6

Burri, A., Ogata, S., Vehof, J., & Williams, F. (2015). Chronic widespread pain: Clinical comorbidities and psychological correlates. *PAIN*, *156*(8), 1458–1464. https://doi.org/10.1097/j.pain.0000000000000182

Caldwell, P. H., Murphy, S. B., Butow, P. N., & Craig, J. C. (2004). Clinical trials in children. *The Lancet*, *364*(9436), 803–811. https://doi.org/10.1016/S0140-6736(04)16942-0

Campbell-Sills, L., & Barlow, D. (2007). Incorporating emotion regulation into conceptualizations and treatments of anxiety and mood disorders. In J. J. Gross (Ed.), *Handbook of Emotion Regulation* (pp. 542–559). New York, NY, US: Guilford Press.

Carter, B. D., & Threlkeld, B. M. (2012). Psychosocial perspectives in the treatment of pediatric chronic pain. *Pediatric Rheumatology*, *10*, 15. https://doi.org/10.1186/1546-0096-10-15

Casey, B. J., Craddock, N., Cuthbert, B. N., Hyman, S. E., Lee, F. S., & Ressler, K. J. (2013). DSM-5 and RDoC: Progress in psychiatry research? *Nature Reviews. Neuroscience*, *14*(11), 810–814. https://doi.org/10.1038/nrn3621

Cipriani, A., Zhou, X., Giovane, C. D., Hetrick, S. E., Qin, B., Whittington, C., et al. (2016). Comparative efficacy and tolerability of antidepressants for major depressive disorder in children and adolescents: A network meta-analysis. *The Lancet*, *388*(10047), 881–890.

https://doi.org/10.1016/S0140-6736(16)30385-3

Clark, L. A., & Watson, D. (1991). Tripartite Model of Anxiety and Depression: Psychometric evidence and taxonomic implications. *Journal of Abnormal Psychology, 100*(3), 316–336. https://doi.org/10.1037/0021-843X.100.3.316

Cohen, D., Deniau, E., Maturana, A., Tanguy, M.-L., Bodeau, N., Labelle, R., et al. (2008). Are child and adolescent responses to placebo higher in major depression than in anxiety disorders? A systematic review of placebo-controlled trials. *PLoS ONE*, *3*(7), e2632. https://doi.org/10.1371/journal.pone.0002632

Cole, P. M., Zahn-Waxler, C., Fox, N. A., Usher, B. A., & Welsh, J. D. (1996). Individual differences in emotion regulation and behavior problems in preschool children. *Journal of Abnormal Psychology*, *105*(4), 518–529. https://doi.org/10.1037/0021-843X.105.4.518

Compas, B. E., Jaser, S. S., Dunbar, J. P., Watson, K. H., Bettis, A. H., Gruhn, M. A., & Williams, E. K. (2014). Coping and emotion regulation from childhood to early adulthood: Points of convergence and divergence. *Australian Journal of Psychology*, *66*(2), 71–81. https://doi.org/10.1111/ajpy.12043

Cummings, C. M., Caporino, N. E., & Kendall, P. C. (2014). Comorbidity of anxiety and depression in children and adolescents: 20 years after. *Psychological Bulletin*, *140*(3), 816–845. https://doi.org/10.1037/a0034733

Cummings, E. M., Schermerhorn, A. C., Davies, P. T., Goeke-Morey, M. C., & Cummings, J. S. (2006). Interparental discord and child adjustment: Prospective investigations of emotional security as an explanatory mechanism. *Child Development*, *77*(1), 132–152. https://doi.org/10.1111/j.1467-8624.2006.00861.x

Cuthbert, B. N., & Insel, T. R. (2013). Toward the future of psychiatric diagnosis: The seven pillars of RDoC. *BMC Medicine*, *11*, 126. https://doi.org/10.1186/1741-7015-11-126

Das, J. K., Salam, R. A., Lassi, Z. S., Khan, M. N., Mahmood, W., Patel, V., & Bhutta, Z. A. (2016). Interventions for adolescent mental health: An overview of systematic reviews.

The Journal of Adolescent Health, *59*(4 Suppl), S49–S60. https://doi.org/10.1016/j.jadohealth.2016.06.020

Davies, P. T., & Cummings, E. M. (1994). Marital conflict and child adjustment: An emotional security hypothesis. *Psychological Bulletin*, *116*(3), 387–411. https://doi.org/10.1037/0033-2909.116.3.387

Davies, P. T., & Cummings, E. M. (1998). Exploring children's emotional security as a mediator of the link between marital relations and child adjustment. *Child Development*, *69*(1), 124–139. https://doi.org/10.1111/j.1467-8624.1998.tb06138.x

DeSteno, D., Gross, J. J., & Kubzansky, L. (2013). Affective science and health: The importance of emotion and emotion regulation. *Health Psychology: Official Journal of the Division of Health Psychology, American Psychological Association*, *32*(5), 474–486. https://doi.org/10.1037/a0030259

Diatchenko, L., Slade, G. D., Nackley, A. G., Bhalang, K., Sigurdsson, A., Belfer, I., et al. (2005). Genetic basis for individual variations in pain perception and the development of a chronic pain condition. *Human Molecular Genetics*, *14*(1), 135–143. https://doi.org/10.1093/hmg/ddi013

Dillon, D. G., Rosso, I. M., Pechtel, P., Killgore, W. D. S., Rauch, S. L., & Pizzagalli, D. A. (2014). Peril and pleasure: An RDoC-inspired examination of threat responses and reward processing in anxiety and depression. *Depression and Anxiety*, *31*(3), 233–249. https://doi.org/10.1002/da.22202

Dorn, C., Spindler, G., Kullik, A., Petermann, F., & Barnow, S. (2013). Erfassung von Emotionsregulationsstrategien–eine Übersicht. *Psychologische Rundschau*, *64*(4), 217–227. https://doi.org/10.1026/0033-3042/a000176

Ehrenreich, J. T., Goldstein, C. M., Wright, L. R., & Barlow, D. H. (2009). Development of a unified protocol for the treatment of emotional disorders in youth. *Child & Family Behavior Therapy*, *31*(1), 20–37. https://doi.org/10.1080/07317100802701228

Ellis, B. J., Boyce, W. T., Belsky, J., Bakermans-Kranenburg, M. J., & van IJzendoorn, M. H. (2011). Differential susceptibility to the environment: An evolutionary-neurodevelopmental theory. *Development and Psychopathology*, *23*(01), 7–28. https://doi.org/10.1017/S0954579410000611

Essau, C. A., Lewinsohn, P. M., Lim, J. X., Ho, M. R., & Rohde, P. (2018). Incidence, recurrence and comorbidity of anxiety disorders in four major developmental stages. *Journal of Affective Disorders*, *228*, 248–253. https://doi.org/10.1016/j.jad.2017.12.014

Fernandez, K. C., Jazaieri, H., & Gross, J. J. (2016). Emotion regulation: A transdiagnostic perspective on a new RDoC domain. *Cognitive Therapy and Research*, *40*(3), 426–440. https://doi.org/10.1007/s10608-016-9772-2

Foster, C., & Lyall, H. (2015). Children are not small adults. *Journal of Virus Eradication*, *1*(3), 133.

Garland, E. J., Kutcher, S., Virani, A., & Elbe, D. (2016). Update on the use of SSRIs and SNRIs with children and adolescents in clinical practice. *Journal of the Canadian Academy of Child and Adolescent Psychiatry*, *25*(1), 4–10.

Ge, X., Conger, R. D., & Elder, G. H. J. (2001). Pubertal transition, stressful life events, and the emergence of gender differences in adolescent depressive symptoms. *Developmental Psychology*, *37*(3), 404–417. https://doi.org/10.1037/0012-1649.37.3.404

Godinho, F., Magnin, M., Frot, M., Perchet, C., & Garcia-Larrea, L. (2006). Emotional modulation of pain: Is it the sensation or what we recall? *Journal of Neuroscience*, *26*(44), 11454–11461. https://doi.org/10.1523/jneurosci.2260-06.2006

Goldberg, D. S., & McGee, S. J. (2011). Pain as a global public health priority. *BMC Public Health*, *11*, 770. https://doi.org/10.1186/1471-2458-11-770

Goldenberg, D. L. (2010). Pain/depression dyad: A key to a better understanding and treatment of functional somatic syndromes. *The American Journal of Medicine*, *123*(8), 675–682. https://doi.org/10.1016/j.amjmed.2010.01.014

Gottschalk, J. M., Bleichhardt, G., Kleinstauber, M., Berking, M., & Rief, W. (2015). Extension of CBT by emotion regulation training in patients with multiple somatoform symptoms. *Verhaltenstherapie*, *25*(1), 13–21. https://doi.org/10.1159/000371526

Gross, J. J. (1998a). Antecedent- and response-focused emotion regulation: Divergent consequences for experience, expression, and physiology. *Journal of Personality and Social Psychology*, *74*(1), 224–237.

Gross, J. J. (1998b). The emerging field of emotion regulation: An integrative review. *Review of General Psychology*, *2*(3), 271–299. https://doi.org/10.1037/1089-2680.2.3.271

Gross, J. J. (2008). Emotion regulation. In M. Lewis, J. M. Haviland-Jones & L. Feldman Barrett (Eds.), *Handbook of emotions* (3rd ed.). New York, NY, US: The Guilford Press.

Gross, J. J., & John, O. P. (2003). Individual differences in two emotion regulation processes: Implications for affect, relationships, and well-being. *Journal of Personality and Social Psychology*, *85*(2), 348–362. https://doi.org/10.1037/0022-3514.85.2.348

Harned, M. S., Banawan, S. F., & Lynch, T. R. (2006). Dialectical behavior therapy: An emotion-focused treatment for borderline personality disorder. *Journal of Contemporary Psychotherapy, 36*(2), 67–75. https://doi.org/10.1007/s10879-006-9009-x

Hedges, L. V., & Olkin, I. (1985). *Statistical methods for meta-analysis*. New York, NY, US: Academic Press.

Higgins, J. P. T. (2008). Commentary: Heterogeneity in meta-analysis should be expected and appropriately quantified. *International Journal of Epidemiology, 37*(5), 1158–1160. https://doi.org/10.1093/ije/dyn204

Higgins, J. P. T., Thompson, S. G., Deeks, J. J., & Altman, D. G. (2003). Measuring inconsistency in meta-analyses. *British Medical Journal, 327*(7414), 557–560. https://doi.org/10.1136/bmj.327.7414.557

Huedo-Medina, T. B., Sánchez-Meca, J., Marín-Martínez, F., & Botella, J. (2006). Assessing heterogeneity in meta-analysis: Q statistic or I2 index? *Psychological Methods, 11*(2),

193–206. https://doi.org/10.1037/1082-989X.11.2.193

ICD-11 – Mortality and Morbidity Statistics. Retrieved May 18, 2018, from https://icd.who.int/dev11/l-m/en#/http://id.who.int/icd/entity/1326332835

Insel, T., Cuthbert, B., Garvey, M., Heinssen, R., Pine, D. S., Quinn, K., et al. (2010). Research Domain Criteria (RDoC): Toward a new classification framework for research on mental disorders. *American Journal of Psychiatry, 167*(7), 748–751. https://doi.org/10.1176/appi.ajp.2010.09091379

Jackson, J. L., Misiti, B., Bridge, J. A., Daniels, C. J., & Vannatta, K. (2015). Emotional functioning of adolescents and adults with congenital heart disease: A meta-analysis. *Congenital Heart Disease, 10*(1), 2–12. https://doi.org/10.1111/chd.12178

Jones, B. L., Nagin, D. S., & Roeder, K. (2001). A SAS procedure based on mixture models for estimating developmental trajectories. *Sociological Methods & Research, 29*(3), 374–393. https://doi.org/10.1177/0049124101029003005

Kendler, K. S., & Aggen, S. H. (2017). Symptoms of major depression: Their stability, familiality, and prediction by genetic, temperamental, and childhood environmental risk factors. *Depression and Anxiety, 34*(2), 171–177. https://doi.org/10.1002/da.22591

Kessler, R. C., van Loo, H. M., Wardenaar, K. J., Bossarte, R. M., Brenner, L. A., Ebert, D. D., et al. (2016). Using patient self-reports to study heterogeneity of treatment effects in major depressive disorder. *Epidemiology and Psychiatric Sciences*, *26*(1), 22-36. https://doi.org/10.1017/S2045796016000020

Kessler, Ronald C., Turner, J. B., & House, J. S. (1989). Unemployment, reemployment, and emotional functioning in a community sample. *American Sociological Review, 54*(4), 648–657. https://doi.org/10.2307/2095885

Klein Velderman, M., Bakermans-Kranenburg, M. J., Juffer, F., & van IJzendoorn, M. H. (2006). Effects of attachment-based interventions on maternal sensitivity and infant attachment: Differential susceptibility of highly reactive infants. *Journal of Family*

Psychology, 20(2), 266–274. https://doi.org/10.1037/0893-3200.20.2.266

Koleva, D., Krulichova, I., Bertolini, G., Caimi, V., & Garattini, L. (2005). Pain in primary care: An Italian survey. *European Journal of Public Health*, *15*(5), 475–479. https://doi.org/10.1093/eurpub/cki033

Konietzny, K., Suchan, B., Kreddig, N., Hasenbring, M. I., & Chehadi, O. (2016). Emotion regulation and pain: Behavioral and neuronal correlates: A transdiagnostic approach. *Schmerz*, *30*(5), 412–420. https://doi.org/10.1007/s00482-016-0162-1

Koole, S. L. (2009). The psychology of emotion regulation: An integrative review. *Cognition and Emotion, 23*(1), 4–41. https://doi.org/10.1080/02699930802619031

Leibenluft, E. (2011). Severe mood dysregulation, irritability, and the diagnostic boundaries of bipolar disorder in youths. *The American Journal of Psychiatry, 168*(2), 129–142. https://doi.org/10.1176/appi.ajp.2010.10050766

Lumeng, J. C., Wendorf, K., Pesch, M. H., Appugliese, D. P., Kaciroti, N., Corwyn, R. F., & Bradley, R. H. (2013). Overweight adolescents and life events in childhood. *Pediatrics, 132*(6), e1506-1512. https://doi.org/10.1542/peds.2013-1111

McLaughlin, K. A., & Hatzenbuehler, M. L. (2009). Mechanisms linking stressful life events and mental health problems in a prospective, community-based sample of adolescents. *The Journal of Adolescent Health*: *Official Publication of the Society for Adolescent Medicine, 44*(2), 153–160. https://doi.org/10.1016/j.jadohealth.2008.06.019

Mennin, D. S. (2006). Emotion regulation therapy: An integrative approach to treatment-resistant anxiety disorders. *Journal of Contemporary Psychotherapy, 36*(2), 95–105. https://doi.org/10.1007/s10879-006-9012-2

Merikangas, K. R., He, J., Burstein, M., Swanson, S. A., Avenevoli, S., Cui, L., et al. (2010). Lifetime prevalence of mental disorders in US adolescents: Results from the National Comorbidity Study – Adolescent Supplement (NCS-A). *Journal of the American Academy of Child and Adolescent Psychiatry, 49*(10), 980–989.

https://doi.org/10.1016/j.jaac.2010.05.017

Merskey, H. D., & Bogduk, N. (Eds.). (1994). *Classification of chronic pain – descriptions of chronic pain syndromes and definition of pain terms* (2nd ed.). Washington, DC, US: IASP Press.

Morris, A. S., Silk, J. S., Steinberg, L., Myers, S. S., & Robinson, L. R. (2007). The role of the family context in the development of emotion regulation. *Social Development, 16*(2), 361–388. https://doi.org/10.1111/j.1467-9507.2007.00389.x

Najman, J. M., Williams, G. M., Nikles, J., Spence, S., Bor, W., O'Callaghan, M., et al. (2000). Mothers' mental illness and child behavior problems: Cause-effect association or observation bias? *Journal of the American Academy of Child & Adolescent Psychiatry, 39*(5), 592–602. https://doi.org/10.1097/00004583-200005000-00013

Petermann, F., & Kullik, A. (2011). Frühe Emotionsdysregulation: Ein Indikator für psychische Störungen im Kindesalter? *Kindheit und Entwicklung, 20*(3), 186–196. https://doi.org/10.1026/0942-5403/a000055

Pluess, M., & Belsky, J. (2010). Differential susceptibility to parenting and quality child care. *Developmental Psychology, 46*(2), 379–390. https://doi.org/10.1037/a0015203

Rao, U. (2014). DSM-5: Disruptive mood dysregulation disorder. *Asian Journal of Psychiatry, 11*, 119–123. https://doi.org/10.1016/j.ajp.2014.03.002

Regier, D. A., Narrow, W. E., Clarke, D. E., Kraemer, H. C., Kuramoto, S. J., Kuhl, E. A., & Kupfer, D. J. (2013). DSM-5 field trials in the United States and Canada, Part II: Test-retest reliability of selected categorical diagnoses. *American Journal of Psychiatry*, *170*(1), 59–70. https://doi.org/10.1176/appi.ajp.2012.12070999

Repetti, R. L., Taylor, S. E., & Seeman, T. E. (2002). Risky families: Family social environments and the mental and physical health of offspring. *Psychological Bulletin*, *128*(2), 330–366.

Ruiz-Aranda, D., Salguero, J. M., & Fernandez-Berrocal, P. (2010). Emotional regulation and

acute pain perception in women. *Journal of Pain*, *11*(6), 564–569. https://doi.org/10.1016/j.jpain.2009.09.011

Sarason, I. G., Johnson, J. H., & Siegel, J. M. (1978). Assessing the impact of life changes: Development of the Life Experiences Survey. *Journal of Consulting and Clinical Psychology*, *46*(5), 932–946.

Schechter, N. L. (2014). Functional pain: Time for a new name. *JAMA Pediatrics*, *168*(8), 693–694. https://doi.org/10.1001/jamapediatrics.2014.530

Shonkoff, J. P., Boyce, W. T., & McEwen, B. S. (2009). Neuroscience, molecular biology, and the childhood roots of health disparities: Building a new framework for health promotion and disease prevention. *JAMA*, *301*(21), 2252–2259. https://doi.org/10.1001/jama.2009.754

Shokoff, J., & Phillips, D. (Eds). (2000). *From neurons to neighborhoods: The science of early childhood development.* Washington, DC, US: National Academy Press.

Skinner, E. A., & Zimmer-Gembeck, M. J. (2007). The development of coping. *Annual Review of Psychology*, *58*(1), 119–144. https://doi.org/10.1146/annurev.psych.58.110405.085705

Sloan, D. M. (2006). The importance of emotion in psychotherapy approaches. *Journal of Contemporary Psychotherapy*, *36*(2), 59–60. https://doi.org/10.1007/s10879-006-9007-z

Stone, M. B. (2014). The FDA warning on antidepressants and suicidality – why the controversy? *The New England Journal of Medicine*, *371*(18), 1668–1671. https://doi.org/10.1056/NEJMp1411138

Suveg, C., Kendall, P. C., Comer, J. S., & Robin, J. (2006). Emotion-focused cognitive-behavioral therapy for anxious youth: A multiple-baseline evaluation. *Journal of Contemporary Psychotherapy*, *36*(2), 77–85. https://doi.org/10.1007/s10879-006-9010-4

't Jong, G. W., Vulto, A. G., de Hoog, M., Schimmel, K. J., Tibboel, D., & van den Anker, J. N. (2000). Unapproved and off-label use of drugs in a children's hospital. *The New*

England Journal of Medicine, *343*(15), 1125. https://doi.org/10.1056/NEJM200010123431515

Tegethoff, M., Belardi, A., Stalujanis, E., & Meinlschmidt, G. (2015). Comorbidity of mental disorders and chronic pain: Chronology of onset in adolescents of a national representative cohort. *The Journal of Pain*, *16*(10), 1054–1064. https://doi.org/10.1016/j.jpain.2015.06.009

Thompson, R. A. (2000). The legacy of early attachments. *Child Development*, *71*(1), 145–152. https://doi.org/10.1111/1467-8624.00128

Tolstikova, K. (2010). *Emotional functioning and meaning making in grief.* Unpublished dissertation, University of Saskatchewan, Canada.

Tracey, I., & Bushnell, M. C. (2009). How neuroimaging studies have challenged us to rethink: Is chronic pain a disease? *The Journal of Pain: Official Journal of the American Pain Society*, *10*(11), 1113–1120. https://doi.org/10.1016/j.jpain.2009.09.001

Treede, R.-D., Rief, W., Barke, A., Aziz, Q., Bennett, M. I., Benoliel, R., et al. (2015). A classification of chronic pain for ICD-11. *Pain*, *156*(6), 1003–1007. https://doi.org/10.1097/j.pain.0000000000000160

Tronick, E. Z., Bruschweiler-Stern, N., Harrison, A. M., Lyons-Ruth, K., Morgan, A. C., Nahum, J. P., et al. (1998). Dyadically expanded states of consciousness and the process of therapeutic change. *Infant Mental Health Journal*, *19*(3), 290–299. https://doi.org/10.1002/(SICI)1097-0355(199823)19:3<290::AID-IMHJ4>3.0.CO;2-Q

Tsang, A., Von Korff, M., Lee, S., Alonso, J., Karam, E., Angermeyer, M. C., et al. (2008). Common chronic pain conditions in developed and developing countries: Gender and age differences and comorbidity with depression-anxiety disorders. *The Journal of Pain*, *9*(10), 883–891. https://doi.org/10.1016/j.jpain.2008.05.005

Tsao, J. C. I., Myers, C. D., Craske, M. G., Bursch, B., Kim, S. C., & Zeltzer, L. K. (2004). Role of anticipatory anxiety and anxiety sensitivity in children's and adolescents'

laboratory pain responses. *Journal of Pediatric Psychology, 29*(5), 379–388. https://doi.org/10.1093/jpepsy/jsh041

van der Ende, J., Verhulst, F. C., & Tiemeier, H. (2012). Agreement of informants on emotional and behavioral problems from childhood to adulthood. *Psychological Assessment*, *24*(2), 293–300. https://doi.org/10.1037/a0025500

Vaux, A., & Ruggiero, M. (1983). Stressful life change and delinquent behavior. *American Journal of Community Psychology*, *11*(2), 169–183. https://doi.org/10.1007/BF00894365

von Baeyer, C. L., & Champion, G. D. (2011). Commentary: Multiple pains as functional pain syndromes. *Journal of Pediatric Psychology*, *36*(4), 433–437. https://doi.org/10.1093/jpepsy/jsq123

Vos, T., Flaxman, A. D., Naghavi, M., Lozano, R., Michaud, C., Ezzati, M., et al. (2012). Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: A systematic analysis for the Global Burden of Disease Study 2010. *Lancet, 380*(9859), 2163–2196. https://doi.org/10.1016/S0140-6736(12)61729-2

Vriend, J. L., Davidson, F. D., Corkum, P. V., Rusak, B., Chambers, C. T., & McLaughlin, E. N. (2013). Manipulating sleep duration alters emotional functioning and cognitive performance in children. *Journal of Pediatric Psychology, 38*(10), 1058–1069. https://doi.org/10.1093/jpepsy/jst033

Waters, E., Weinfield, N. S., & Hamilton, C. E. (2000). The stability of attachment security from infancy to adolescence and early adulthood: General discussion. *Child Development, 71*(3), 703–706. https://doi.org/10.1111/1467-8624.00179

Zeman, J., Cassano, M., Perry-Parrish, C., & Stegall, S. (2006). Emotion regulation in children and adolescents. *Developmental and Behavioral Pediatrics*, *27*(2), 155–170.

Zhou, X., Cipriani, A., Furukawa, T. A., Cuijpers, P., Zhang, Y., Hetrick, S. E., et al. (2018). Comparative efficacy and tolerability of new-generation antidepressants for major depressive disorder in children and adolescents: Protocol of an individual patient data

meta-analysis. *British Medical Journal Open*, *8*(1). https://doi.org/10.1136/bmjopen-2017-018357

Appendix A

Study I

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Review article

The role of emotion regulation in chronic pain: A systematic literature review

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ABSTRACT

Objective: Emotion regulation (ER) includes a set of cognitive and attentional processes used to change or maintain emotional state. A small but growing body of research suggests that maladaptive ER might be a risk factor for the development of chronic pain. This review aims to summarize existing literature on the association between ER and chronic pain, and to determine whether the construct of ER may further enhance our understanding of the risk and protective factors that may contribute to the onset and maintenance of chronic pain.
Methods: A systematic search was conducted using the search terms "chronic pain" and "emotion regulation." Studies that measured both constructs across all age groups were included.
Results: We found 15 studies that met our inclusion criteria. Nine studies were completed within the last five years, suggesting that the evaluation of ER as it relates to pain is a new line of research. Studies that measured "response-focused" ER found associations between maladaptive ER and pain. Studies that measured "antecedent-focused" ER strategies were less likely to show a direct association with pain.
Conclusion: Maladaptive response-focused ER may be an important risk factor in the development and maintenance of chronic pain, as it is associated with pain and psychological comorbidities. Adding ER to chronic pain investigations may help to further explain individual differences in the risk and protective mechanisms that are known to influence chronic pain. Importantly, this line of research has potential to directly inform future interventions for patients with chronic pain.

1. Introduction

Chronic pain is defined as any pain condition that exists for more than three months, either continuously or recurrently [14,48]. Chronic pain is estimated to effect 20% of the population and causes an enormous burden to both individuals and the healthcare system [25]. Current models of chronic pain illustrate the complex interplay of sensory, environmental, psychological, and pain regulatory risk factors that shape the pain vulnerability of an individual ([55]; see Fig. 1). Research on chronic pain seeks to disentangle the various risk and protective influences of biological, psychological, and environmental factors that are known to contribute to chronic pain disorders. Understanding these factors is critical to the development and implementation of targeted intervention.

Pain has long been defined as an "unpleasant sensory and emotional experience" ([40]). The recognition of the sensory and psychological components of pain have recently been strengthened by controlled laboratory studies that illustrate the link between emotional state and pain perception, both in healthy volunteers (e.g. [24,43]) and in patients with chronic pain (e.g. [50]). Additionally, research using fMRI has supported the notion that inducing negative mood can influence subsequent pain ratings [11]. Beyond the research linking the sensory and emotional experience of pain, patients with chronic pain have three times the risk of being diagnosed with anxiety and depression as compared to the general population [7,26,49]. Despite the multiple links between pain and negative emotions, surprisingly little is known about how emotion regulation styles may influence pain, pain-related disability, and psychological comorbidities in chronic pain populations.

Emotion regulation (ER) describes a person's ability to modulate his or her emotional state and expression, that includes influencing which emotions people have, when they have these emotions, and how emotions are experienced and expressed [1,31]. Assessment of ER thus encompasses measurement of cognitive, behavioral, and psychophysiological responses to an event or stressor [18,56]. The regulation of emotions has been the focus of various studies, among them studies in the field of stress and coping research [31]. However, ER is different

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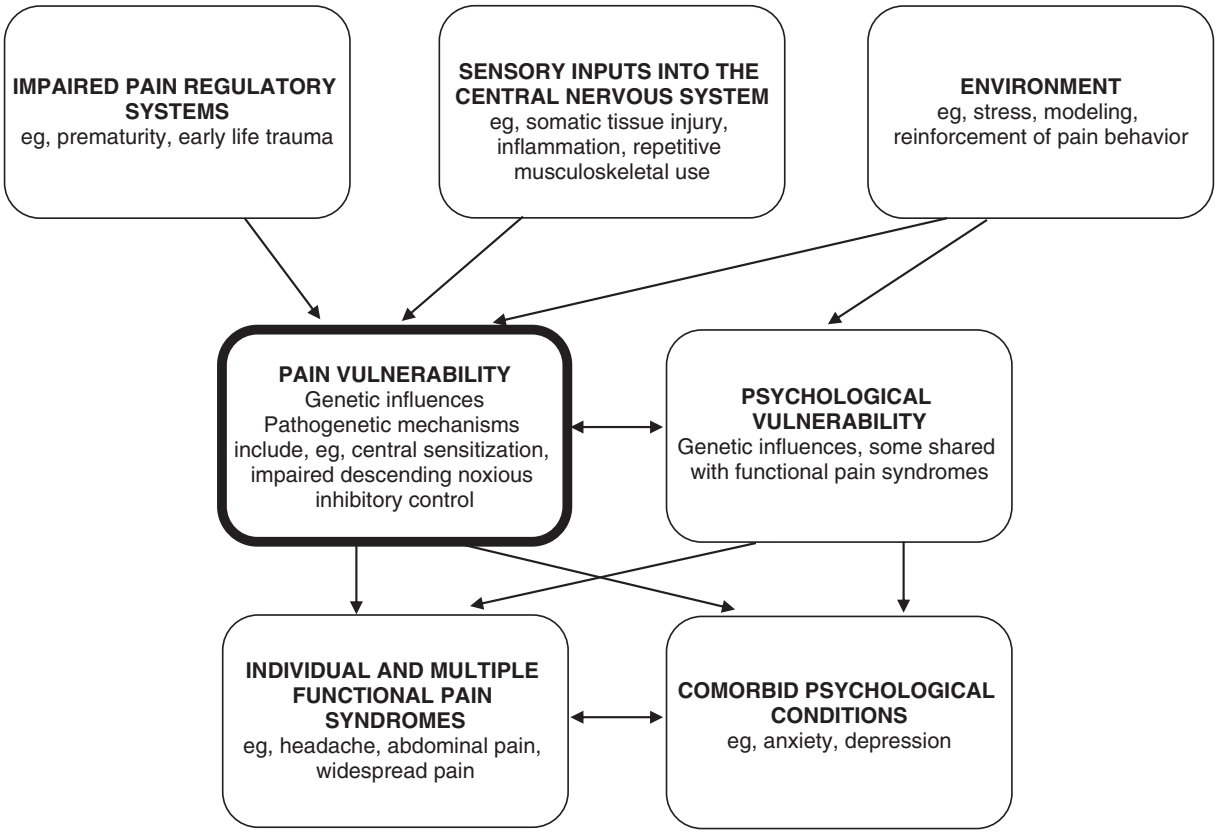

Fig. 1. Antecedents and consequences of pain vulnerability [55].
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from coping on the one hand in that coping includes non-emotional actions; ER on the other hand includes processes not traditionally considered in the coping literature, such as maintaining or up-regulating positive emotions [15].

A helpful model of organizing the diverse cognitive and behavioral strategies people use to regulate their emotions is the Process Model of ER [30,34]. The Process Model of ER is based on the modal model of emotion, which presents the core features of emotions and specifies that ER can set in at every step of the emotion generation process: Emotion arises in a *situation* that is meaningful to the individual and demands *attention*, has a particular *meaning* and gives rise to a multifaceted, embodied *response* (see Fig. 2). The Process Model broadly divides ER into antecedent- and response-focused strategies. Antecedent-focused strategies include situation selection, situation modification, attentional deployment, and cognitive change, that set in before the emotion is fully developed – hence their prospect of success is generally greater [3]. Strategies such as avoiding a situation that potentially elicits negative emotions or shifting one's attention to thoughts of an upcoming vacation to prevent boredom in a long work meeting are considered antecedent-focused. In contrast, response-focused strategies emphasize

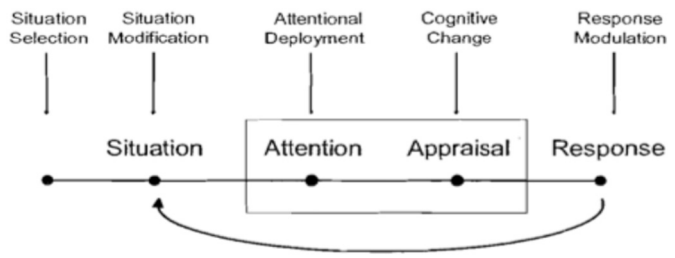

Fig. 2. The Process Model of Emotion Regulation [34].
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regulating the emotional response, especially its physiological and behavioral aspects, once the event has already onset [29,38]; holding back one's tears in public is one example.

ER is considered maladaptive if it shows a negative short- and/or long-term outcome, antagonizes personal goals or shows a lack of ER flexibility (i.e., is inappropriate to contextual or social demands [5]). Research on ER has studied how ER affects the individuals as well as the people around them. This has yielded results linking maladaptive ER to psychopathology (for a review see [4]), negative affect [9], learning difficulties [17], memory deficits [19,42], and physiological stress reactions [13]. Importantly, research has demonstrated that training in adaptive ER is effective for treating a range of psychological and psychosocial difficulties. As a result, these skills and strategies are often incorporated as a component part of cognitive behavioral therapy treatment [10,27].

This systematic review synthesizes the existing body of research that explores the relationship between ER and chronic pain. To our knowledge, this is the first review to examine the ER – chronic pain relationship. Our goal is to investigate whether the construct of ER may enhance the existing theoretical frameworks of chronic pain, to increase our understanding of individual-level risk and protective influences that contribute to development and maintenance of chronic pain conditions. Further, we seek to explore the associations between the two categories of ER, antecedent- and response-focused strategies, and chronic pain. Based on our understanding of the process model of ER, we hypothesize that response-focused ER is more likely to have negative associations with chronic pain as compared to antecedent-focused ER.

2. Methods

For this systematic review, we searched PubMed, Embase, PsychInfo, Web of Science, CINAHL, and the Cochrane Central Database

Table 1
Search terms.

PubMed	(emotion regulat*[tiab] OR emotional regulat*[tiab] OR emotion dysregulat*[tiab] OR emotional dysregulat*[tiab] OR emotional modulat*[tiab] OR emotion modulat*[tiab] OR emotion management[tiab] OR emotional management[tiab] OR emotional competenc*[tiab] OR emotion comptetenc*[tiab] OR emotional expression[tiab] OR emotion expression[tiab] OR emotional control[tiab] OR emotion control[tiab] OR emotional self-efficacy[tiab] OR emotional suppression[tiab] OR emotion suppression[tiab] OR affect regulat*[tiab] OR affect dysreg*[tiab] OR effortful control[tiab] OR situation selection[tiab] OR situation modification[tiab] OR attentional deployment[tiab] OR cognitive change[tiab] OR response modulation[tiab]) AND ("pain"[mesh] OR "Pain Measurement"[mesh] OR pain[tiab])
Embase	((emotion* NEXT/1 (regulat* OR dysregulat* OR modulat* OR management OR competenc* OR expression OR control OR 'self efficacy' OR suppression)):ab,ti OR (affect* NEXT/1 (regulat* OR dysregulat*)):ab,ti OR 'effortful control':ab,ti OR 'situation selection':ti,ab OR 'situation modification':ti,ab OR 'attentional deployment':ti,ab OR 'cognitive change':ti,ab OR 'response modulation':ti,ab) AND ('pain'/exp. OR 'pain measurement'/exp. OR pain:ab,ti) AND [embase]/lim
PsycINFO	DE ("Emotional Regulation" OR DE "Emotional Control") OR TI ((emotion* W1 (regulat* OR dysregulat* OR modulat* OR management OR competenc* OR expression OR control OR "self efficacy" OR suppression)) OR (affect* W1 (regulat* OR dysregulat*)) OR "effortful control" OR "situation selection" OR "situation modification" OR "attentional deployment" OR "cognitive change" OR "response modulation") OR AB ((emotion* W1 (regulat* OR dysregulat* OR modulat* OR management OR competenc* OR expression OR control OR 'self efficacy' OR suppression)) OR (affect* W1 (regulat* OR dysregulat*)) OR 'effortful control' OR 'situation selection' OR 'situation modification' OR 'attentional deployment' OR 'cognitive change' OR 'response modulation') AND DE ('Pain Measurement' OR 'Pain' OR "Back Pain" OR 'Chronic Pain' OR "Headache" OR "Myofascial Pain" OR "Neuralgia" OR "Neuropathic Pain" OR "Pain Perception" OR "Pain Thresholds") OR TI pain OR AB pain
CINAHL	TI ((emotion* W1 (regulat* OR dysregulat* OR modulat* OR management OR competenc* OR expression OR control OR 'self efficacy' OR suppression)) OR (affect* W1 (regulat* OR dysregulat*)) OR 'effortful control' OR 'situation selection' OR 'situation modification' OR 'attentional deployment' OR 'cognitive change' OR 'response modulation') OR AB ((emotion* W1 (regulat* OR dysregulat* OR modulat* OR management OR competenc* OR expression OR control OR 'self efficacy' OR suppression)) OR (affect* W1 (regulat* OR dysregulat*)) OR 'effortful control' OR 'situation selection' OR 'situation modification' OR 'attentional deployment' OR 'cognitive change' OR 'response modulation') AND MH ("Pain+" OR 'Pain Measurement') OR TI pain OR AB pain
Web of Science	TS = ("emotion regulat*" OR "emotional regulat*" OR "emotion dysregulat*" OR "emotional dysregulat*" OR "emotional modulat*" OR "emotion modulat*" OR "emotion management" OR "emotional management" OR "emotional competenc*" OR "emotion comptetenc*" OR "emotional expression" OR "emotion expression" OR 'emotional control' OR "emotion control" OR "emotional self-efficacy" OR "emotional suppression" OR "emotion suppression" OR "affect regulat*" OR "affect dysreg*" OR 'effortful control' OR 'situation selection' OR 'situation modification' OR 'attentional deployment' OR 'cognitive change' OR 'response modulation') AND TS = pain
Cochrane Central Database of Controlled Clinical Trials	('emotion regulat*' OR 'emotional regulat*' OR 'emotion dysregulat*' OR 'emotional dysregulat*' OR 'emotional modulat*' OR 'emotion modulat*' OR 'emotion management' OR 'emotional management' OR 'emotional competenc*' OR 'emotion comptetenc*' OR 'emotional expression' OR 'emotion expression' OR 'emotional control' OR 'emotion control' OR 'emotional self-efficacy' OR 'emotional suppression' OR 'emotion suppression' OR 'affect regulat*' OR 'affect dysreg*' OR 'effortful control' OR 'situation selection' OR 'situation modification' OR 'attentional deployment' OR 'cognitive change' OR 'response modulation') AND pain

of Controlled Clinical Trials using the key words "emotion regulation" and 'chronic pain'. For additional information on search terms, see Table 1. In total, our search returned 2893 articles, of which 1041 duplicates were removed. The screening and selection process was conducted by two authors independently (HK and CW). We included studies that measured both ER and chronic pain using a cross-sectional, observational, longitudinal, or interventional design across all age groups and pain conditions, published from the earliest available record from 1923 through November 2016. We excluded studies of acute and/or experimentally induced pain, studies that did not report on the associations between ER and pain measures, and studies that assessed coping or alexithymia instead of ER. Reviews, meta-analyses, dissertations, posters, and conference abstracts were also excluded. Based on abstract and title search, 48 papers were included in full text review (see Fig. 3). We extracted information on study sample, pain diagnosis, pain measure, ER measure, and statistical associations between pain and ER measures. Further, we reviewed questionnaire items on each measure of every study and categorized measures into antecedent- or response-focused ER.

3. Results

The study selection procedure is summarized in Fig. 3. Our search identified fifteen studies including a total of 2065 patients who met our criteria. Two studies included pediatric populations, six studies had a female-only population, and only one study had a majority of male participants. The studies included in this review assessed patients with one or more of the following pain conditions: fibromyalgia (n = 5), rheumatoid arthritis (n = 4), back pain (n = 4), multiple pain sites (n = 3), juvenile idiopathic arthritis (n = 1), pelvic pain (n = 1), and sickle cell disease (n = 1). Characteristics of the included studies are shown in Table 2. All measures of ER were classified as either antecedent (n = 4)- or response (n = 5)-focused ER. Several studies (N = 5) used both antecedent- and response-focused measures and one study used a measure that could not clearly be classified. The statistics and the multivariate and bivariate associations for the studies are reported in the supplement (Table S1).

3.1. Antecedent-focused emotion regulation

Four studies measured ER strategies that were classified as antecedent-focused (see Table 2). This included cognitive ER strategies such as thought suppression or cognitive reappraisal.

This group of studies sought to determine how pain intensity or pain-related functioning was influenced by cognitive ER strategies that are typically employed prior to the full-blown emotional response. For example, one study that was interested in participants' tendency to employ cognitive change strategies, asked them to rate statements such

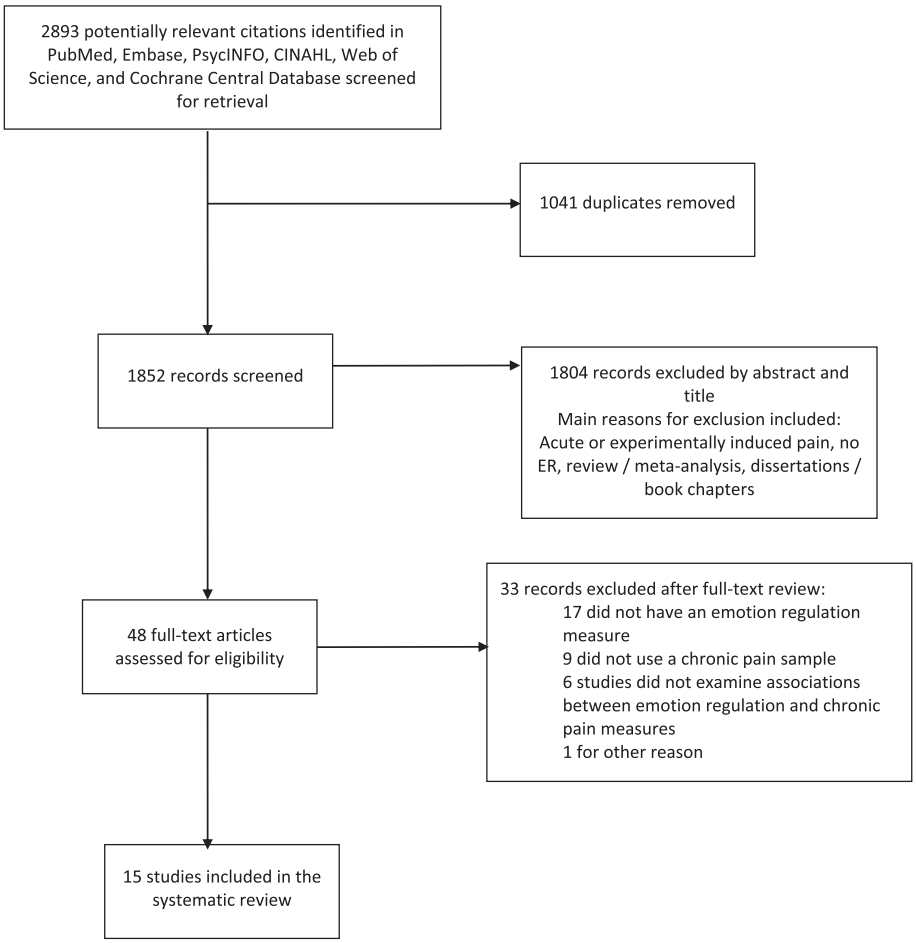

Fig. 3. Flow chart.

as: "No matter how badly I feel, I try to think about pleasant things" [36]. Findings from this group of studies suggest that while there might not be direct associations between antecedent-focused ER and pain, there was a link between antecedent-focused ER and depression, in that thought suppression was positively correlated with more depressive mood and major depressive disorder [22]. Additionally, there was an association between high emotionality and reduced use of adaptive antecedent-focused ER such as cognitive reappraisal [37]. In other words, when patients had more negative emotions, they were less likely to use cognitive reappraisal and thus experienced more pain. Similarly, in the same group of patients, high pain was linked to lower mood [36]. Further, women with chronic pelvic pain reported to suppress their thoughts and emotions more often compared to controls [46]. This study also found that the tendency to suppress unwanted thoughts or emotion was associated to more pain.

Thus, while antecedent-focused ER may not directly influence pain, it is possible that adaptive use of these strategies may reduce pain vulnerability or pain experience indirectly by reducing high emotionality or negative mood, both known vulnerability factors for the development of chronic pain.

3.2. Response-focused emotion regulation

Five studies measured response-focused ER. This included strategies such as response modulation (i.e., influencing physiological, experiential, or behavioral responding) and expression of emotions.

This group of studies sought to determine how pain intensity or pain-related functioning was influenced by behavioral or experiential ER that is typically employed after response tendencies have been initiated. For example, one study investigated whether anger inhibition or expression was related to concurrent pain and pain three hours after anger inhibition or expression [12]. They found that both expression of anger (such as slamming doors or shouting) and inhibition of anger (such as hiding anger or keeping it to oneself) were correlated with pain intensity, in that those participants who strongly expressed or inhibited their anger experienced more pain. Similarly, in patients with more problems controlling their emotional expression, for example, those who had emotional outbursts or sudden and/or frequent mood changes, pain interfered more with their physical activity, mood, relationships, and sleep [8].

With regard to psychological comorbidities, a study that measured participants' self-perceived ability to regulate emotions found that those with low self-perceived ability to do so often also showed depressive symptoms [35]. Interestingly, however, this self-perception was not correlated with pain, but those patients who reported depression symptoms also reported significantly more pain. Similarly, two studies looked at the same sample of patients with rheumatoid arthritis, distinguished different styles of ER and tested if these different styles would relate to dimensions of perceived health such as social and physical functioning and disease activity. They found that none of the ER styles was significantly related to physical functioning or disease activity. However, ER styles were related to social functioning and positive and negative affect [52]. Additionally, they tested if men and women differ with regard to ER styles and perceived health and found that indeed, women had higher scores than men on an ER style that is best described in terms of attending to and intensely experiencing emotions, and valuing emotions in daily life and decision making [53]. For women, the styles of ER found in this study explained 3% of the

Table 2
Demographics and study characteristics.

First Author, Publication Year	Study type	Sample size (N) [+]	Age, M (SD)	% Female	Pain diagnosis	Pain measure	Pain duration M (SD), in Years	Emotion regulation measure	Type of ER	Main finding ER - Pain
Agar-Wilson [2]	Cross-sectional	128	52.9 (16.8)	66%	Back pain, multiple pain sites	Oswestry Disability Questionnaire (ODQ)	8.3 (9.0)	Assessing Emotions Scale (AES)	N/A	Efficacy in ER not related to pain-related disability
Baker [8]	Cross-sectional	63	46.8	60%	Back pain, multiple pain sites, fibromyalgia	Brief Pain Inventory (BPI)	9.0	Behavior Rating Inventory of Executive Function, Adult version (BRIEF-A)	R	Clinically elevated emotional control values positively related to worse pain-related functioning
Burns [12]	Observation	105	46.3 (12.1)	49%	Chronic low back pain	Numerical (0–8)	9.0 (7.8)	State-Trait Anger Expression Inventory (STAXI) items	R	Anger expression and inhibition positively correlated with pain intensity
Connelly [16]	Observation	43	13.2 (2.7)	86%	Juvenile Idiopathic Arthritis[°]	Visual Analogue Scale (VAS)	N/A	Children's Emotion Management Scale (CEMS)	A, R	ER self- and parent-report not correlated with pain or functional limitations
Garland [22]	Cross-sectional	115	48.3	68%	Low back pain, fibromyalgia, arthritis, other	Brief Pain Inventory – Short Form (BPI-SF)	N/A At least 90 days	White Bear Suppression Inventory (WBSI)	A	Thought suppression not correlated with pain severity
Geenen [23]	Cross-sectional	403	46.5 (12.3)	100%	Fibromyalgia	Fibromyalgia Impact Questionnaire (FIQ)	10.9 (8.6)	Emotion Regulation Questionnaire (ERQ) Emotion Approach Coping Scales (EACS)	A, R	Cognitive reappraisal not correlated with disease impact, expressive suppression positively correlated with disease impact
Hamilton [37][*]	Longitudinal	81	62.2 (7.3)	100%	Rheumatoid arthritis[°]	Numerical (0 − 100)	N/A	Trait Meta-Mood Scale (TMMS)	A	ER not correlated with pain
Hamilton [36][*]	Longitudinal	81	62.2 (7.3)	100%	Rheumatoid arthritis[°]	Numerical (0–100)	N/A	Trait Meta-Mood Scale (TMMS)	A	ER not correlated with pain
Hamilton [35]	Cross-sectional	35	47.0 (10.5)	100%	Fibromyalgia[°]	McGill Pain Questionnaire – Short Form (MPQ – S)	13.0 (9.2)	The Emotion Amplification and Reduction Scales (TEARS)	R	ER not correlated with sensory dimension of pain experience
Thomas [46]	Cross-sectional	61	31.8 (7.8)	100%	Pelvic pain with and without endometriosis	Visual Analogue Scale (VAS) National Women's Sexual Pain Scale (NWSPS)	7.3 (5.7)	Marlowe-Crowne Social Desirability Scale (MC-SDS) Bending short-form of the Taylor Manifest Anxiety Scale (TMAS Bending SF) State-Trait Anger Expression Inventory (STAXI)	A	Patients with chronic pelvic pain use significantly more thought suppression compared to controls
Tsao et al. [50]	Cross-sectional	69	13.4 (2.0)	55%	Sickle-cell disease	No. Hosp.[1]	N/A	Emotion Regulation Questionnaire for Children and Adolescents (ERQ-CA)	A, R	Cognitive reappraisal and expressive suppression not correlated with pain
Van Middendorp [52][*] Van Middendorp [53][*]	Cross-sectional	335	57.8 (13.3)	73%	Rheumatoid Arthritis[°]	Impact of Rheumatic Diseases on General Health and Lifestyle (IRGL)	12.1 (11.0)	Five Expressivity Facet Scale (FEFS) Self-Assessment Questionnaire Nijmegen (SAQ-N) Ambivalence over Emotional Expressiveness Questionnaire (AEQ)	R	ER style explains 0% of variance of physical functioning and disease activity
Van Middendorp [54]	Cross-sectional	403	46.5 (12.3)	100%	Fibromyalgia[°]	Fibromyalgia Impact Questionnaire (FIQ)	10.9 (8.6)	Emotion Approach Coping Scales (EACS) Emotion Regulation Questionnaire (ERQ) Self-Expression and Control Scale (SECS)	A, R	Cognitive reappraisal and expressive suppression not correlated with pain
Wong [57]	Cross-sectional	224	45.66 (9.87)	55%	Chronic pain[2]	Chronic Pain Grade(CPG)	4.35 (6.05)	Emotion Regulation Questionnaire (ERQ)	A, R	Cognitive reappraisal and expressive suppression not correlated with pain

A: antecedent-focused ER.
R: response-focused ER.
[*] These studies used the same sample.
[1] The number of pain crises in the previous year that did not require hospitalization served as a measure for pain during the study period (comparison between frequent and infrequent hospitalization group).
[+] Number indicates sample size of patients with chronic pain.
[°] These patients had a physician-certified diagnosis of a pain syndrome and are therefore considered to be patients with chronic pain.
[2] Pain sites: head, neck, shoulder, hand, chest, upper back, lower back, pelvis, knee, leg, joint or muscle.

variance of disease activity, which means that a small part of difference between individuals with regard to disease activity is explained by their different styles of ER. This was not true for men, in turn, men reported better physical functioning than women.

Thus, in some cases, response-focused ER was directly correlated with pain and pain-related functioning, while in other cases these strategies related to symptoms of depression, a prevalent psychological comorbidity of chronic pain.

3.3. Antecedent- and response-focused emotion regulation

Five studies measured both antecedent- and response-focused ER. This group of studies sought to determine how antecedent- and response-focused ER strategies differ with regard to their relationship to pain, pain-related disability, and disease impact. For example, one of the few studies that examined a pediatric population asked their participants and participants' parents to complete a baseline ER measure prior to a one-month electronic diary study that assessed emotions and pain thrice daily. The baseline ER measures asked for both antecedent- and response-focused ER to deal with negative emotions, but no correlation with pain intensity was found [16]. However, children that reported more emotional ups and downs in the electronic diary also reported more pain compared to those children with less emotional variability.

Three studies that all measured both cognitive reappraisal and expressive suppression did not find significant correlations of pain with either one of the ER strategies [51,54,57]. However, findings of these studies suggest that while cognitive reappraisal and expressive suppression do not directly influence pain, expressive suppression seems to have a negative impact on patients' experience of their pain. For example, one study found that participants who used more suppression of their emotional expression also reported significantly more symptoms of anxiety and depression [54]. In the same study, a significant positive correlation between negative emotions, such as feeling upset or scared, and pain was reported. Another study found that patients who employed more expressive suppression also had more catastrophic thoughts around pain such as “When I'm in pain, I worry all the time about whether the pain will end” (item from the Pain Catastrophizing Scale PCS; [45]). These catastrophic thoughts were significantly positively correlated with pain intensity and pain-related disability [57]. Additionally, children with sickle cell disease who used expressive suppression were more likely to be hospitalized due to pain crises compared to those who employed less expressive suppression [51]. In line with these findings, patients who reported often expressing their feelings freely also reported less consequences of their pain such as number days of work missed, physical impairment, and morning tiredness [23].

Thus, most studies that measured both antecedent- and response-focused ER found no direct relationship of either strategy to pain, but found response-focused ER to be correlated with catastrophizing thoughts around pain, likelihood of being hospitalized during pain crises, and the impact the disease has in patients' everyday life.

One study measured ER that could not be classified as either antecedent- or response-focused. Questions such as “When I experience a positive emotion, I know how to make it last” or “I have control over my emotions” were asked to determine participants' efficacy in ER [2]. Participants who rated themselves as being effective in regulating their emotions also reported less negative affect and better quality of life. ER efficacy was not correlated with pain-related disability, but positively with self-efficacy in managing pain [2].

In sum, the studies included in this review rarely found direct associations between emotion regulation and pain intensity or pain-related disability. Rather, the relationship between ER (antecedent or response-focused) and pain seemed to be mediated by psychological factors such as emotionality, anxiety, or negative mood. The studies that more closely explored response-focused ER seemed to provide the best evidence for a strong relationship between maladaptive ER, psychological symptoms, and pain.

4. Discussion

This systematic review examined the relationship between antecedent- and response-focused ER and chronic pain. We found that ER is a relatively new construct in the chronic pain literature and the direct and indirect influences of ER and pain are not yet clearly defined. Most studies in this review found indirect associations between ER and pain, via other psychological factors. However, there were several studies that found direct associations between maladaptive response-focused ER and chronic pain, pain-related disability, and depressive symptoms. This is in line with previous research that differentiated between adaptive and maladaptive ER based on their relationship with psychological symptoms and found antecedent-focused strategies (such as cognitive reappraisal) to be more adaptive compared to response-focused strategies (such as expressive suppression; [4]). However, the differentiation between adaptive and maladaptive ER is more precise when it incorporates the idea of ER flexibility, i.e. the ability of an individual to implement an ER strategy that matches the contextual demands [5]. Maladaptive ER can thus be thought of as a limited range of strategies inappropriately matched to changing social and contextual demands. Suffering from chronic pain may present as a constant stressor that increases the amount of negative affect one experiences (due to missing days at work or school or not being able to actively participate in social activities; Vos et al. [58]) and thus it might become increasingly difficult to employ adaptive ER.

Even in cases where ER is not directly associated with pain intensity or disability, it plays an important role in patients' overall well-being and functioning, as it can be associated with symptoms of depression, anxiety, stress [8,35,54], or quality of life [2]. All these factors might then further worsen pain or limit functioning in this population. It is therefore suggested to include ER in current models of chronic pain, such as the one proposed by von Baeyer and Champion ([55]; see Fig. 1). Based on Mayer and Bushnell's work [39], von Baeyer and Champion differentiate between primary risk factors for chronic pain, such as central sensitization, or autonomic nervous system activity, and secondary risk factors, such as catastrophizing, and symptom-related worries. While early gene-environment interactions may shape primary risk factors, secondary risk factors may be more responsive to the cultural, social, and medical environment and are thus commonly targets of chronic pain interventions. The results of our systematic review suggest that ER may be an important secondary risk factor that cuts across different chronic pain syndromes.

Further, as a secondary risk factor, ER is a good target for training modules within the treatment of chronic pain, as adaptive use of ER strategies can be trained (e.g. [17,20,27]). Preliminary studies that included ER in current treatment options for chronic pain report positive results, both in adolescents (e.g. [6]) and adults (e.g. [27]). In a study of two case examples of patients with chronic pain and comorbid anxiety or depression, the training of ER lead to improvements in at least some of the domains of interest (pain, functional limitations, anxiety, ER, and others more; [6]). In a study that extended cognitive behavioral therapy (CBT) with ER training and compared it to CBT alone, CBT with ER training showed greater effect sizes for almost all treatment objectives [27]. Hence, adding ER to current theoretical frameworks of chronic pain may help to further clarify why some people are more vulnerable to chronic pain than others and how this knowledge can be implemented in new interventions.

Several limitations have to be considered when interpreting the results of this review. We only found a small number of studies that examined ER and chronic pain, and one major obstacle in conducting this systematic review was that even in this small sample of literature the term ER was used very heterogeneously. Besides the Process Model of ER [30], there is significant variability in regards to how the term ER

is operationalized. Some working definitions include (or do not clearly exclude) alexithymia, coping style, emotional awareness, and emotional intelligence. The variability in conceptualization of this term is also evident in the wide range of measures developed to systematically assess ER [18,56]. The studies included in this review used a range of different questionnaires. However, in an attempt to clarify the subject, only studies that explicitly measured ER were included. Similar challenges present themselves in the field of chronic pain. First, there are a variety of pain sites and syndromes assessed within this review. Second, study participants suffered from chronic pain conditions for time periods that ranged between several months and more than a decade. Living with chronic pain for such an extended period of time might lead to more accentuated problems in the areas of social life, job, and functioning in general [41]. Further, although we included all age groups, only two of the 15 studies looked at pediatric populations. Given that ER involves higher order cognitive processing, we certainly cannot assume that our findings would generalize more broadly to pediatric samples. Moreover, no statement can be made regarding age-specific relationships between ER and chronic pain. Other significant limitations include the bias of female only studies (6/15) in this review and the cross-sectional design of most of the studies.

The results of this review are also limited in part by the standard questionnaire format of all measures used for studies within this review. In general, as ER is a phenomenon that includes cognitive, behavioral, and physiological aspects, it is advisable to measure it using several methods, such as psychophysiological and observational methods and questionnaires [28,33,47]. Future studies should employ newer ambulatory assessment methods, such as ecological momentary assessment [44]. Electronic diaries are one example for electronic momentary assessment [18]. Fernandez and colleagues [21] proposed to include ER as a new Research Domain Criteria (RDoC) domain. This would support future research in the field of ER and chronic pain, as it would allow to further understand not just the cognitive and behavioral, but also the neural, genetic, and physiological systems that underlie the ER - chronic pain relationship.

To our knowledge, this is the first review to systematically examine the role of both antecedent- and response-focused ER in chronic pain. Our results suggest that ER may be an important and understudied risk factor that can have direct or indirect influences on pain, pain-related disability, and psychological comorbidities in patients with chronic pain. Further investigation is needed to more directly explore the role of ER in chronic pain and importantly to ascertain if training in adaptive ER strategies could provide direct symptom relief or even potentially serve as a protective factor, reducing pain vulnerability in patients who may have other identified risk factors for the development of chronic pain.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychores.2018.02.002.

Conflicts of interest

The authors have no competing interests to report.

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References*

[1] M. Adrian, J. Zeman, G. Veits, Methodological implications of the affect revolution: a 35-year review of emotion regulation assessment in children, J. Exp. Child Psychol. 110 (2) (2011) 171–197, http://dx.doi.org/10.1016/j.jecp.2011.03.009.
[2] *M. Agar-Wilson, T. Jackson, Are emotion regulation skills related to adjustment among people with chronic pain, independent of pain coping? Eur. J. Pain 16 (1) (2012) 105–114, http://dx.doi.org/10.1016/j.ejpain.2011.05.011.
[3] A. Aldao, The future of emotion regulation research: capturing context, Perspect. Psychol. Sci. 8 (2) (2013) 155–172, http://dx.doi.org/10.1177/1745691612459518.
[4] A. Aldao, S. Nolen-Hoeksema, S. Schweizer, Emotion-regulation strategies across psychopathology: a meta-analytic review, Clin. Psychol. Rev. 30 (2) (2009) 217–237, http://dx.doi.org/10.1016/j.cpr.2009.11.004.
[5] A. Aldao, G. Sheppes, J.J. Gross, Emotion regulation flexibility, Cogn. Ther. Res. (2015) 1–16, http://dx.doi.org/10.1007/s10608-014-9662-4.
[6] L.B. Allen, J.C.I. Tsao, L.C. Seidman, J. Ehrenreich-May, L.K. Zeltzer, A unified, transdiagnostic treatment for adolescents with chronic pain and comorbid anxiety and depression, Cogn. Behav. Pract. 19 (1) (2012) 56–67, http://dx.doi.org/10.1016/j.cbpra.2011.04.007.
[7] M.J. Bair, R.L. Robinson, W. Katon, K. Kroenke, Depression and pain comorbidity: a literature review, Arch. Intern. Med. 163 (20) (2003) 2433–2445, http://dx.doi.org/10.1001/archinte.163.20.2433.
[8] *K.S. Baker, S. Gibson, N. Georgiou-Karistianis, R.M. Roth, M.J. Giummarra, Everyday executive functioning in chronic pain: specific deficits in working memory and emotion control, predicted by mood, medications, and pain interference, Clin. J. Pain 32 (8) (2016) 673–680, http://dx.doi.org/10.1097/AJP.0000000000000313.
[9] A.C. Belden, J.L. Luby, D. Pagliaccio, D.M. Barch, Neural activation associated with the cognitive emotion regulation of sadness in healthy children, Dev. Cogn. Neurosci. 9 (2014) 136–147, http://dx.doi.org/10.1016/j.dcn.2014.02.003.
[10] M. Berking, P. Wupperman, A. Reichardt, T. Pejic, A. Dippel, H. Znoj, Emotion-regulation skills as a treatment target in psychotherapy, Behav. Res. Ther. 46 (11) (2008) 1230–1237, http://dx.doi.org/10.1016/j.brat.2008.08.005.
[11] C. Berna, S. Leknes, E.A. Holmes, R.R. Edwards, G.M. Goodwin, I. Tracey, Induction of depressed mood disrupts emotion regulation neurocircuitry and enhances pain unpleasantness, Biol. Psychiatry 67 (11) (2010) 1083–1090, http://dx.doi.org/10.1016/j.biopsych.2010.01.014.
[12] *J.W. Burns, J.I. Gerhart, S. Bruehl, K.M. Peterson, D.A. Smith, L.S. Porter, E. Schuster, E. Kinner, A. Buvanendran, A.M. Fras, F.J. Keefe, Anger arousal and behavioral anger regulation in everyday life among patients with chronic low back pain: relationships to patient pain and function, Health Psychol. 34 (5) (2015) 547–555, http://dx.doi.org/10.1037/hea0000091.
[13] L. Campbell-Sills, D.H. Barlow, T.A. Brown, S.G. Hofmann, Effects of suppression and acceptance on emotional responses of individuals with anxiety and mood disorders, Behav. Res. Ther. 44 (9) (2006) 1251–1263, http://dx.doi.org/10.1016/j.brat.2005.10.001.
[14] M. Cohen, J. Quintner, D. Buchanan, Is chronic pain a disease? Pain Med. 14 (2013) 1284–1288, http://dx.doi.org/10.1111/pme.12025.
[15] B.E. Compas, S.S. Jaser, J.P. Dunbar, K.H. Watson, A.H. Bettis, M.A. Gruhn, E.K. Williams, Coping and emotion regulation from childhood to early adulthood: points of convergence and divergence, Aust. J. Psychol. 66 (2) (2014) 71–81, http://dx.doi.org/10.1111/ajpy.12043.
[16] *M. Connelly, K.K. Anthony, M.H. Bromberg, L. Franks, K.M. Gil, L.E. Schanberg, Emotion regulation predicts pain and functioning in children with juvenile idiopathic arthritis, Pediatr. Rheumatol. 10 (2012), http://dx.doi.org/10.1093/jpepsy/jsr088.
[17] E.L. Davis, L.J. Levine, Emotion regulation strategies that promote learning: reappraisal enhances children's memory for educational information, Child Dev. 84 (1) (2013) 361–374, http://dx.doi.org/10.1111/j.1467-8624.2012.01836.x.
[18] C. Dorn, G. Spindler, A. Kullik, F. Petermann, S. Barnow, Erfassung von Emotionsregulationsstrategien–eine Übersicht, Psychol. Rundsch. 64 (4) (2013) 217–227, http://dx.doi.org/10.1026/0033-3042/a000176.
[19] B.D. Dunn, D. Billotti, V. Murphy, T. Dalgleish, The consequences of effortful emotion regulation when processing distressing material: a comparison of suppression and acceptance, Behav. Res. Ther. 47 (9) (2009) 761–773, http://dx.doi.org/10.1016/j.brat.2009.05.007.
[20] J.T. Ehrenreich, C.M. Goldstein, L.R. Wright, D.H. Barlow, Development of a unified protocol for the treatment of emotional disorders in youth, Child Family Behav. Ther. 31 (1) (2009) 20–37, http://dx.doi.org/10.1080/07317100802701228.
[21] K.C. Fernandez, H. Jazaieri, J.J. Gross, Emotion regulation: a transdiagnostic perspective on a new RDoC domain, Cogn. Ther. Res. 40 (3) (2016) 426–440, http://dx.doi.org/10.1007/s10608-016-9772-2.
[22] *E.L. Garland, S.M. Brown, M.O. Howard, Thought suppression as a mediator of the association between depressed mood and prescription opioid craving among chronic pain patients, J. Behav. Med. 39 (1) (2016) 128–138, http://dx.doi.org/10.1007/s10865-015-9675-9.
[23] *R. Geenen, L. van Ooijen-van der Linden, M.A. Lumley, J.W.J. Bijlsma, H. van Middendorp, The match-mismatch model of emotion processing styles and emotion regulation strategies in fibromyalgia, J. Psychosom. Res. 72 (1) (2012) 45–50, http://dx.doi.org/10.1016/j.jpsychores.2011.09.004.
[24] F. Godinho, M. Magnin, M. Frot, C. Perchet, L. Garcia-Larrea, Emotional modulation of pain: is it the sensation or what we recall? J. Neurosci. 26 (44) (2006) 11454–11461, http://dx.doi.org/10.1523/jneurosci.2260-06.2006.
[25] D.S. Goldberg, S.J. McGee, Pain as a global public health priority, BMC Public Health 11 (770) (2011), http://dx.doi.org/10.1186/1471-2458-11-770.
[26] D.L. Goldenberg, Pain/depression dyad: a key to a better understanding and treatment of functional somatic syndromes, Am. J. Med. 123 (8) (2010) 675–682, http://dx.doi.org/10.1016/j.amjmed.2010.01.014.

* Studies included in systematic review.

[27] J.M. Gottschalk, G. Bleichhardt, M. Kleinstauber, M. Berking, W. Rief, Extension of CBT by emotion regulation training in patients with multiple somatoform symptoms, Verhaltenstherapie 25 (1) (2015) 13–21, http://dx.doi.org/10.1159/000371526.
[28] K.L. Gratz, L. Roemer, Multidimensional assessment of emotion regulation and dysregulation: development, factor structure, and initial validation of the difficulties in emotion regulation scale, J. Psychopathol. Behav. Assess. 26 (1) (2004) 41–54, http://dx.doi.org/10.1007/s10862-008-9102-4.
[29] J.J. Gross, Antecedent- and response-focused emotion regulation: divergent consequences for experience, expression, and physiology, J. Pers. Soc. Psychol. 74 (1) (1998) 224–237 http://psycnet.apa.org/doi/10.1037/0022-3514.74.1.224.
[30] J.J. Gross, The emerging field of emotion regulation: an integrative review, Rev. Gen. Psychol. 2 (3) (1998) 271–299, http://dx.doi.org/10.1037/1089-2680.2.3.271.
[31] J.J. Gross, Emotion Regulation, Handbook of Emotions, 3rd ed., The Guilford Press, New York, 2008.
[33] J.J. Gross, R.W. Levenson, Emotional suppression: physiology, self-report, and expressive behavior, J. Pers. Soc. Psychol. 64 (6) (1993) 970–986 http://psycnet.apa.org/doi/10.1037/0022-3514.64.6.970.
[34] J.J. Gross, R.A. Thompson, Emotion regulation: conceptual foundations, Handbook of Emotion Regulation, Guilford Press, New York, NY, US, 2007, pp. 3–24.
[35] *N.A. Hamilton, M. Pressman, T. Lillis, R. Atchley, C. Karlson, N. Stevens, Evaluating evidence for the role of sleep in fibromyalgia: a test of the sleep and pain diathesis model, Cogn. Ther. Res. 36 (6) (2012) 806–814, http://dx.doi.org/10.1007/s10608-011-9421-8.
[36] *N.A. Hamilton, A.J. Zautra, J. Reich, Individual differences in emotional processing and reactivity to pain among older women with rheumatoid arthritis, Clin. J. Pain 23 (2) (2007) 165–172, http://dx.doi.org/10.1097/AJP.0b013e31802b4f58.
[37] *N.A. Hamilton, A.J. Zautra, J.W. Reich, Affect and pain in rheumatoid arthritis: do individual differences in affective regulation and affective intensity predict emotional recovery from pain? Ann. Behav. Med. 29 (3) (2005) 216–224, http://dx.doi.org/10.1207/s15324796abm2903_8.
[38] S.L. Koole, The psychology of emotion regulation: an integrative review, Cognit. Emot. 23 (1) (2009) 4–41, http://dx.doi.org/10.1080/02699930802619031.
[39] E.A. Mayer, M.C.B. Bushnell (Eds.), Functional Pain Syndromes: Presentation and Pathophysiology, 1st ed., IASP, Seattle, 2009.
[40] H.D. Merskey, N. Bogduk (Eds.), Classification of Chronic Pain - Descriptions of Chronic Pain Syndromes and Definition of Pain Terms (Second), IASP Press, 1994.
[41] D. Rajapakse, C. Liossi, R.F. Howard, Presentation and management of chronic pain, Arch. Dis. Child. 99 (2014) 474–480, http://dx.doi.org/10.1136/archdischild-2013-304207.
[42] J.M. Richards, J.J. Gross, Emotion regulation and memory: the cognitive costs of keeping one's cool, J. Pers. Soc. Psychol. 79 (3) (2000) 410–424 http://psycnet.apa.org/doi/10.1037/0022-3514.79.3.410.
[43] D. Ruiz-Aranda, J.M. Salguero, P. Fernández-Berrocal, Emotional regulation and acute pain perception in women, J. Pain 11 (6) (2010) 564–569, http://dx.doi.org/10.1016/j.jpain.2009.09.011.
[44] S. Shiffman, A.A. Stone, M.R. Hufford, Ecological momentary assessment, Annu. Rev. Clin. Psychol. 4 (1) (2008) 1–32, http://dx.doi.org/10.1146/annurev.clinpsy.3.022806.091415.
[45] M.J. Sullivan, S.R. Bishop, J. Pivik, The pain catastrophizing scale: development and validation, Psychol. Assess. 7 (4) (1995) 524–532, http://dx.doi.org/10.1037/1040-3590.7.4.524.
[46] *E. Thomas, R. Moss-Morris, C. Faquhar, Coping with emotions and abuse history in women with chronic pelvic pain, J. Psychosom. Res. 60 (1) (2006) 109–112, http://dx.doi.org/10.1016/j.jpsychores.2005.04.011.
[47] N. Tottenham, T.A. Hare, B.J. Casey, Behavioral assessment of emotion discrimination, emotion regulation, and cognitive control in childhood, adolescence, and adulthood, Front. Psychol. 2 (39) (2011) 1–9, http://dx.doi.org/10.3389/fpsyg.2011.00039.
[48] R.-D. Treede, W. Rief, A. Barke, Q. Aziz, M.I. Bennett, R. Benoliel, ... S.-J. Wang, A classification of chronic pain for ICD-11, Pain 156 (6) (2015) 1003–1007, http://dx.doi.org/10.1097/j.pain.0000000000000160.
[49] A. Tsang, M. Von Korff, S. Lee, J. Alonso, E. Karam, M.C. Angermeyer, ... M. Watanabe, Common chronic pain conditions in developed and developing countries: gender and age differences and comorbidity with depression-anxiety disorders, J. Pain 9 (10) (2008) 883–891, http://dx.doi.org/10.1016/j.jpain.2008.05.005.
[50] J.C.I. Tsao, C.D. Myers, M.G. Craske, B. Bursch, S.C. Kim, L.K. Zeltzer, Role of anticipatory anxiety and anxiety sensitivity in children's and adolescents' laboratory pain responses, J. Pediatr. Psychol. 29 (5) (2004) 379–388, http://dx.doi.org/10.1093/jpepsy/jsh041.
[51] *J. Tsao, E. Jacob, L. Seidman, M. Lewis, L. Zeltzer, Frequent hospitalization for pain crises among children with sickle cell disease: associations with pain, somatization, catastrophization, and emotion regulation, J. Pain 13((4) (2012) S104, http://dx.doi.org/10.1016/j.jpain.2012.01.431.
[52] *H. van Middendorp, R. Geenen, M.J. Sorbi, J.J. Hox, A. Vingerhoets, L.J.P. van Doornen, J.W.J. Bijlsma, Gender differences in emotion regulation and relationships with perceived health in patients with rheumatoid arthritis, Women Health 42 (1) (2005) 75–97, http://dx.doi.org/10.1300/J013v42n01_05.
[53] *H. van Middendorp, R. Geenen, M.J. Sorbi, J.J. Hox, A. Vingerhoets, L.J.P. van Doornen, J.W.J. Bijlsma, Styles of emotion regulation and their associations with perceived health in patients with rheumatoid arthritis, Ann. Behav. Med. 30 (1) (2005) 44–53, http://dx.doi.org/10.1207/s15324796abm3001_6.
[54] H. van Middendorp, M.A. Lumley, J.W. Jacobs, L.J. van Doornen, J.W. Bijlsma, R. Geenen, Emotions and emotional approach and avoidance strategies in fibromyalgia, J. Psychosom. Res. 64 (2) (2008) 159–167, http://dx.doi.org/10.1016/j.jpsychores.2007.08.009.
[55] C.L. von Baeyer, G.D. Champion, Commentary: multiple pains as functional pain syndromes, J. Pediatr. Psychol. 36 (4) (2011) 433–437, http://dx.doi.org/10.1093/jpepsy/jsq123.
[56] J.A. Weiss, K. Thomson, L. Chan, A systematic literature review of emotion regulation measurement in individuals with autism Spectrum disorder, Autism Res. 7 (6) (2014) 629–648, http://dx.doi.org/10.1002/aur.1426.
[57] *W.-S. Wong, R. Fielding, Suppression of emotion expression mediates the effects of negative affect on pain catastrophizing: a cross-sectional analysis, Clin. J. Pain 29 (10) (2013) 865–872, http://dx.doi.org/10.1097/AJP.0b013e31827da3b5.
[58] T. Vos, A.D. Flaxman, M. Naghavi, R. Lozano, C. Michaud, M. Ezzati, ... Z.A. Memish, Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010, Lancet 380 (9859) (2012) 2163–2196, http://dx.doi.org/10.1016/S0140-6736(12)61729-2.

Supplementary Material

sTable 1. Data Analysis and Results of Included Studies

sTable I. Data Analysis and Results of Included Studies

	First Author (Year)	Data Analysis	Result	*p*-Value
Antecedent-focused emotion regulation strategies	Hamilton (2005)	Zero order correlation between pain and mood repair Hierarchical linear modeling to predict the prospective relationship between pain and negative affect using mood repair	r=-.01 B=-.005 for mood repair	n.s. <.05
	Hamilton (2007)	Zero order correlation between pain and mood repair Hierarchical linear modeling to predict differences in negative affect in response to pain using mood repair and the interaction of affect intensity and mood repair	r=-0.01 B=-0.001 for mood repair B=-0.023 for the interaction of affect intensity and mood repair	n.s. n.s. <0.01
	Garland (2016)	Zero order correlations between comorbid depression diagnosis and use of suppression as well as between pain severity and depressive mood and major depressive disorder	Major depressive disorder and use of suppression: r=.24 Pain severity: r=.44 for depressive mood r=.24 for major depressive disorder	<.05
	Thomas (2006)	Chi square to compare frequency of emotion suppression between patients with chronic pelvic pain and controls ANOVA to compare pain M and SD between those who suppressed emotions and the other groups (repressors, high anxious, low anxious)	34.3% vs. 8.2%, χ^2=24.68 M=16.81, SD=5.8 (suppressors) M=9.96, SD=6.63 (repressors) M=9.56, SD=8.44 (high anxious) M=6.03, SD=4.88 (low anxious) *F*(3,87)=10.41	<.001 <.005
Response-focused emotion regulation strategies	Baker (2016)	MANOVA to determine differences between participants in the normal range and those with clinically elevated emotional control values with regard to pain interference, pain self-efficacy, anxiety, depression and stress	Pain interference: M=7.9, SD=1.6 for elevated values, M=6.2, SD=1.8 for normal values Pain self-efficacy: M=18.2, SD=10.7 for elevated values, M=24.9, SD=11.8 for normal values Anxiety, depression, stress: M=67.0, SD=27.7 for elevated values, M=40.1, SD=26.4 for normal values	<.001 <.05 <.001

Response-focused emotion regulation strategies (cont.)	Burns (2015)	Zero order correlations between anger inhibition, anger expression and pain intensity Hierarchical linear modeling to test concurrent and lagged relationships between anger expression, anger inhibition and pain and pain interference	r=0.26 for anger expression and pain intensity r=0.3 for anger inhibition and pain intensity Anger expression: B=.02, SE=.02 for concurrent pain intensity B=.04, SE=.01 for pain intensity 3h after anger expression B=.02, SE=.02 for concurrent pain interference Anger inhibition: B=.02, SE=.01 for concurrent pain intensity B=.01, SE=.01 for pain intensity 3h after anger inhibition B=.05, SE=.01 for concurrent pain interference	<.05 <.01 n.s. <.01 n.s. n.s. n.s. <.01
	Connelly (2012)	Hierarchical linear modeling to predict overall pain and functional limitations using greater variability in negative emotion levels and child self-report baseline emotion regulation	B=55.68 ± 22.94 for pain using negative emotion variability B=12.93 ± 5.06 for functional limitations using negative emotion variability B=10.40 ± 11.42 for pain using child self-report B=2.32 ± 2.75 for functional limitations using child self-report	 .02 n.s. n.s.
	Hamilton (2012)	Zero order correlations between self-perceived ability to amplify or reduce of emotions and the sensory dimension of pain experience or depression	Amplification of emotions: r=-0.21 for the sensory dimension of pain experience r=-0.30 for depressive symptoms Reduction of emotions: r=-0.08 for the sensory dimension of pain experience r=-0.48 for depressive symptoms	 n.s. <.10 n.s. <.01
	Van Middendorp (2005a)	Structural equation model to determine percentage of variance accounted for by emotion regulation styles	16% of variance of negative affect 7% of variance of positive affect 20% of variance of social functioning 0% of variance of physical functioning and disease activity	

	Van Middendorp (2005b)	Effect sizes of gender differences regarding emotion regulation styles (ambiguity, control, orientation, expression) and physical functioning	Ambiguity: d=.24 Women: M=-.06, SD=.78 Men: M=.16, SD=.76 Control: d=0.10 Women: M=-.03, SD=.78 Men: M=.08, SD=.67 Orientation: d=0.69 Women: M=.14, SD=.75 Men: M=-.39, SD=.64 Expression: d=0.13 Women: M=.04, SD=.80 Men: M=-.12, SD=.80 Physical functioning: d=0.59 Women: M=-.10, SD=.92 Men: M=.28, SD=.83	 .07 .51 .00 .33 .00
Antecedent- and response-focused emotion regulation strategies	Van Middendorp (2008)	Zero order correlations between cognitive reappraisal, expressive suppression and mental distress, pain, and fatigue	Cognitive reappraisal: r=-.09 for mental distress r=.06 for pain r=.06 for fatigue Expressive suppression: r=.21 for mental distress r=.08 for pain r=.05 for fatigue	 n.s. n.s. n.s. <.001 n.s. n.s.
	Wong (2013)	Zero order correlations between expressive suppression, cognitive reappraisal and pain intensity, pain-related disability and pain catastrophizing	Expressive suppression: Pain intensity° Pain-related disability° Cognitive reappraisal: Pain intensity° Pain-related disability* Pain catastrophizing: r=-0.14 for cognitive reappraisal r=0.37 for expressive suppression r=0.39 for pain intensity r=0.34 for pain-related disability	 n.s. n.s. n.s. n.s. <.05 <.01 <.01 <.01

Antecedent- and response-focused emotion regulation strategies (cont.)	Tsao (2014)	Zero order correlations between cognitive reappraisal, expressive suppression and pain Sequential logistic regression with blood type and pain as step 1 variables and emotional suppression and somatization as step 2 variables.	r=-.06 for cognitive reappraisal and pain r=-.07 for expressive suppression and pain B=.22, OR=1.25 for emotional suppression	n.s. n.s. .04
	Geenen (2012)	Zero order correlations of cognitive reappraisal, expressive suppression, emotion expression and disease impact	Disease impact: Cognitive reappraisal° Expressive suppression: r=.18 Emotion expression: r=-.18	 n.s. <.001 <.001
	Agar-Wilson (2012)	Zero order correlation between efficacy in emotion regulation and pain-related disability Hierarchical multiple regression analyses to predict negative affect and quality of life using efficacy in emotion regulation.	r=-.14 Negative affect: β=-.21, sr^2=-18, t=-2.40 Quality of life: β=.26, sr^2=.20, t=2.89	n.s. .018 <.005

* No results of other MPI subscales or other pain measures were given.

° No further information was provided for not significant results in these papers.

Abbreviations

n.s.: not significant; B= unstandardized Beta-values; β=standardized Beta-values

Appendix B

Study II

Koechlin, H., Donado, C., Berde, C. B., & Kossowksy, J. (2018). Effects of childhood life events on adjustment problems in adolescence: A longitudinal study. Manuscript accepted for publication in the *Journal of Developmental and Behavioral Pediatrics*.

Effects of Childhood Life Events on Adjustment Problems in Adolescence: A Longitudinal Study

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Abstract

Objectives

Stressful life events have been associated with adjustment problems in adolescence in cross-sectional studies. Using a longitudinal cohort, we examined the influence of these events and predefined covariates on adjustment problems in adolescence, and compared internalizing and externalizing trajectories among children with many vs. few stressful life events.

Methods

Data were obtained from the Study of Early Child Care and Youth Development. 1,364 children and their families were followed from child's birth until age 15. Adjustment problems at age 15 were defined as high (>60 T-score) internalizing and/or externalizing problems on the Youth Self-Report and Child Behavior Checklist. Stressful life events were evaluated at 54 months, in 3rd and 5th grade. Categories created by mixture model analyses for covariates were used in logistic regressions to predict adolescent-reported adjustment problems.

Results

Mothers reported higher rates of adjustment problems than adolescents (21.1% vs. 16.3%; $p<0.0001$). Adjustment problems were associated with more stressful life events (OR=1.7, p=0.0042), male gender (OR=1.9, p=0.001), and child's high emotional reactivity (OR=1.6, p=0.01). Analysis using mother report of adjustment problems showed the same predictors, as well as lower maternal education level (OR=3.5, p=0.0003), child's friendship quality (OR=0.4, p=0.005), and paternal depression (OR=2.1, p=0.0165). Higher internalizing and externalizing T-scores were apparent in children with more stressful life events from the age of 2 onwards (*P*s<0.0001).

Conclusions

After adjusting for multiple covariates, stressful life events during childhood predicted adjustment problems at age 15. Our results suggest that emotional reactivity and paternal depression play a significant role in the development of adjustment problems in adolescence.

Introduction

Stressful life events, such as physical, sexual, or emotional abuse, neglect, exposure to violence, mental illness, incarceration, substance abuse in the family, parental absence due to divorce or separation, and low socioeconomic status[1] present a risk factor to healthy development in children and adolescents. Previous research on the impact of stressful life events in childhood has linked them to depression and anxiety,[2] delinquent behavior,[3] and somatic health.[4] In addition, stressful life events have been found to be associated with rumination and emotional dysregulation.[5] Early stressful life events pose a risk for maladaptive development when they accumulate over time or if they occur during sensitive developmental periods.[6] However, most previous studies have used cross-sectional designs, often focused solely on one type of life event, and examined few mediators or moderators that might increase or decrease the risk of adverse outcomes following life events. One of the few longitudinal studies that looked at the impact of social support on the relationship between stressful life events and internalizing and externalizing behavior within a year found a main effect for stressful life events as a predictor for problematic behaviors in adolescent girls only.[7] Another longitudinal study looked at gender differences within the relationship between stressful life events and depressive symptoms and again found this relationship to be significant for girls only.[8] A review paper found stressful life events to predict both internalizing and externalizing symptoms, with a stronger association for internalizing symptoms.[9] However, further elucidation of the exact mechanisms leading to these associations is warranted.

In our study, several potential risk and protective factors are taken into consideration. The choice of these factors is based on research on resilience[10] and differential susceptibility,[11] and includes individual-level and family-level risk factors, namely mother-child attachment, child

temperament, child emotional reactivity, child peer relationship, maternal separation anxiety, father-child and mother-child relationship, parental relationship, and maternal and paternal depression.

Past research has introduced the concepts of resilience and differential susceptibility. The idea of resilience states that among those children growing up under adverse circumstances, some grow up to be healthy, while others show an impaired functioning, i.e., symptoms of psychopathology, and/or low levels of academic or social achievements.[10] In a pioneering longitudinal study, a birth cohort from the island of Kauai, Hawaii, was followed from the prenatal period to young adulthood.[12] This study found that some children developed into competent adults despite growing up in adverse circumstances. The research that followed this initial study found some factors that resilient children seemed to share, such as average or better IQ, social and academic competences, at least one stable attachment figure, sensitive parenting, and good regulation of behavior and emotion.[13] However, resilience has also been defined as arising from "ordinary human adaptive processes,"[10] highlighting that it is neither a hereditary trait, nor some extraordinary set of skills, but rather a series of adaptive processes.

While the concept of resilience is part of the diathesis-stress framework that describes protective processes and individual differences in response to adversity, the model of differential susceptibility is not restricted to such negative effects of contextual adversity.[14] Rather, differential susceptibility states that some individuals are more susceptible to both negative and positive exposures, as well as developmental experiences[11]. Additionally, people differ fundamentally in how they perceive and process their environment: some are generally more sensitive, while others are generally less sensitive.[15] For example, increased sensitivity is associated with difficult infant temperament, negative emotionality, candidate genes (e.g. 5-

HTTLPR, MAOA), and high physiological stress reactivity, but will only develop into vulnerability when combined with an adverse environment.[11] If combined with a supportive environment, the presence of sensitivity features is likely to lead to positive outcomes.[14]

Using a prospective, longitudinal dataset, and taking the findings from research on resilience and differential susceptibility into account, we were interested in early determinants of child behavior, and influences of individual (such as child temperament and child emotional reactivity) and family factors (such as parent-child interaction, parental depression, and parental intimacy) on the relationship between early exposure to stressful life events and clinical elevation for adjustment problems in adolescence.

One variable that can be classified both on the individual- (with regard to the child) and family-level (with regard to the mother-child relationship) is attachment. Early attachment quality is known to be an important influence on many aspects of child development.[16] Attachment is conceptualized through the mother-child interaction and can be classified into three main groups[17]: Securely attached children use their mother as a secure base from which they explore and where they return. Insecurely attached children show either dominantly ambivalent or anxious-avoidant behavior.[18] Results from a longitudinal study that classified children into attachment groups at 1 year of age and assessed them again to test for the presence of psychopathology at 17.5 years of age found that belonging to one of the insecure groups was the main significant predictor of anxiety disorders in adolescence.[19] Previous studies in children have found that possessing at least one stable and dependable attachment figure, low emotional reactivity, a flexible temperament, and having good peer relationships can be protective against adverse consequences of early insecure attachment experiences.[20]

Insecure attachment is related and may contribute to high maternal separation anxiety, a family-level variable which is defined as a mother's increased concern and apprehension when separated from their children.[21] Maternal separation anxiety is an important psychological construct that shapes maternal behavior, and has implications for both the child's emotional development and the mother's mental health.[22] Higher levels of maternal separation anxiety are specifically related to increased levels of depressive symptoms and feelings of being a less effective mother.[23] Perceived difficult child temperament can increase maternal separation anxiety.[24] Other risk factors for maternal separation anxiety include low socioeconomic status,[25] which is also considered a risk factor for children's mental health problems.[26]

Several family-level variables have been shown to be potentially protective against adverse child outcomes and might mitigate the negative effect of stressful life events. One of them is the father-child relationship. The role of the father-child relationship is often overlooked, even though a positive father-child relationship is considered a protective factor against risky behavior in adolescence.[27] In contrast, paternal depression is significantly related to child's internalizing and externalizing symptomatology.[28] A father's involvement in a child's life has shown to decrease a child's conduct problems, hyperactivity, emotional problems, and peer problems.[29] However, families with high levels of inter-parental conflict often show a decrease in fathers' involvement.[30] Moreover, high levels of inter-parental conflict can disrupt the child's feeling of emotional security, which can contribute to difficulties in regulating emotional arousal and impact psychological adjustment.[31] Continuous marital conflict,[32] as well as both maternal and paternal psychopathology,[29] hence can increase the risk for adjustment problems in children and adolescents.

Past research has shown that both the number and the timing of stressful life events can have an impact on child development.[33] For the purpose of this study, we decided to look at the impact of stressful life events in three different ways: (I) to categorize the number of stressful life events a child experienced as either "many" or "few", (II) to create a timing variable to reflect the time points at which the child experienced stressful life events, and (III) to create different categories of stressful life events, with regard to the domain they were related to, namely to parent/family physical or mental health and well-being; to parental work, school, or financial stability; to emotional aspects of relationships; or to change in family structure, routine, and caregiving. As an outcome measure, we use adjustment problems in adolescence. This was defined as either high internalizing and/or high externalizing symptoms on the Youth Self Report. High, in this case, means more than one standard deviation above the mean, a classification typically used in clinics.[34] As internalizing and externalizing symptoms are often comorbid in childhood and adolescence,[35] we decided to take them together to define the presence of adjustment problems.

Our study prospectively evaluates the influence of stressful life events in childhood on the presence of clinical elevation of adjustment problems at age 15. We tested a number of family- and individual-level covariates that possibly influence this association, relying on previous research in the field of resilience and differential susceptibility, and analyzed the impact of stressful life events from various perspectives. This study adds to the literature on the detrimental health effects of early stressful life events in children and adolescents. We simultaneously evaluate how multiple individual- and family-level factors can influence the presence of adverse outcomes, such as clinical elevation of adjustment problems following stressful life events in a prospective cohort of children. The aims of our study are threefold: (1)

to test the influence of stressful life events (total number, type, and timing of stressful life events) on clinical elevation of adjustment problems in adolescence, (2) to examine the effect of predefined family- and individual-level covariates on the found associations, and (3) to compare internalizing and externalizing behavior trajectories throughout childhood and adolescence between children with “many” and “few” stressful life events.

Methods

Sample

We used data the Eunice Kennedy Shriver *National Institute of Child Health and Development* (NICHD) collected for the Study of Early Child Care and Youth Development (SECCYD). Participants were recruited from different hospitals and university centers across 10 locations in the United States at the time of child's birth in 1991 and followed until age 15 (https://secc.rti.org). The NICHD catchment population was defined as all babies (and their families) born in the hospitals participating in the study during the period of recruitment. The sample was selected by a conditional random sampling plan, designated to ensure that the recruited families included (i) mothers who planned to go to work or school full-time, part-time or stay at home during the child the first year, and (ii) reflected the demographic diversity of the sites. The major exclusion criteria were: (a) mothers younger than 18 years at the time of childbirth, (b) families that did not anticipate remaining in the catchment area for at least 3 years, (c) Children with obvious disabilities at birth or who remained in the hospital more than 7 days postpartum, and (d) mothers not sufficiently conversant in English.

The final sample of this longitudinal study included 1.364 children and their families. Throughout the course of the study, the main study investigators invested considerable time and substantial effort in creating procedures that allow them to argue that whatever site effects are found are actually present due to real differences (e.g., due to demography, economy, or any of a vast number of unmeasured factors) and not by site procedural differences (NICHD technical note #9 in data report sheet).

The institutional review boards of all participating institutions approved this study. Data were provided to us pre-processed as totals or summary values for different measurement scores; all

analyses were done in a de-identified manner. Figure 1 shows all measures and data points used in the study.

Outcome: Adjustment Problems

Our primary outcome was clinical elevation of adjustment problems at age 15 years. We used the well-validated subscales of the Child Behavior Checklist[36] (CBCL), rated by the mother, and the Youth Self Report[37] (YSR), a self-report for adolescents derived from the CBCL. The CBCL is a standardized form parents complete to describe their child's behavioral and emotional problems. A series of descriptions of behaviors (around 100 items, depending on the age-group) are rated on a 3-point scale from 0 (not true of the child) to 2 (very true of the child or often true) for the past six months. Reported test-retest reliability in all subscales is good ($r=0.71$-0.93; $p<0.0001$). For this study, we focused on two broad groups of syndromes provided by the YSR and the CBCL: *internalizing problems*, which combines social withdrawal, somatic complaints, and anxiety/depression scales; and *externalizing problems*, which combines delinquent and aggressive behavior scales.[36] The presence of high internalizing or externalizing problems was defined as having a T-score >60 (one standard deviation above the mean) for each scale.[37] The primary outcome variable, clinical elevation of adjustment problems, was defined as the presence of high internalizing *and/or* externalizing problems at age 15 years, as rated by adolescents' self report on the YSR.

Main predictor: Stressful Life Events

The study child's mother completed an adapted version of the Life Experience Survey[38] at three time points during childhood: 54 months, in 3rd grade, and 5th grade. At each time point, mothers reported if each of 57 evaluated stressful life events had occurred during the last year, reported

test-retest reliability is moderated (r=0.56-0.8). The list of events included routine happenings (such as a wedding in the extended family), major events (such as separation of parents), and catastrophic events (such as the death of a family member). This questionnaire aimed to provide an overview of events that the child's family may have experienced, and that could have had an impact on the child and family well-being as well as on the quality of parenting.

Similar to previous research,[39] we first categorized the total number of stressful life events as either "many" (upper quartile of a total number of stressful life events), or "few" (lower three quartiles of the total number of stressful life events) at each time point. Next, we created a timing/chronicity variable to reflect the time points at which the child was in the upper quartile: (i) early: at 54 months and in 3rd grade (n =38); (ii) late: in 3rd and 5th grade (n = 65); (iii) single exposure (n=314); (iv) never (n = 513); and (v) always (n=51). We then created four categories of stressful life events: (i) parent/family physical or mental health and well-being (21 questions); (ii) parental work, school, or financial stability (16 questions); (iii) emotional aspects of relationships (16 questions); and (iv) change in family structure, routine, and caregiving (15 questions). We averaged the number of stressful life events in each category across time points and defined "many" scores as belonging to the top quartile for each category.

Covariates

We included child gender (male or female), race/ethnicity (white or non-white [American Indian, Eskimo, Aleut; Asian or Pacific Islander; Black or Afro-American]; other), maternal education (years of education; categorized as (i) No high school degree (<12y); (ii) High school degree (12y); (iii) Bachelor's degree (13 to 16 y); (iv) Post graduate studies (>16y)), and total income-to-needs ratio (3 items that assess financial stress, 1 item asking how many people are supported;

and 2 items to assess sources of income, and the amount of income from these sources) at first month after birth as the primary demographic covariates. Additionally, we included individual- (i.e., concerning the child only) and family-level (i.e., concerning the child and the child's family) covariates that have been shown to modulate the effect of stressful life events on adjustment problems.

The following measures were collected on ≥2 time points during the study. We created summary variables (compound or trajectory variables, see *Statistical analysis*) as follows:

Mother-child attachment (individual and family level; 2 time points): The Strange Situation[18] measure has been validated by several studies in the first year of life, it measures the organization of child attachment. The videotapes of 3 episodes of separation and reunion of mother and child are reviewed and coded by trained personnel. The organization of the child attachment and exploratory behaviors, especially in the reunion episodes, is analyzed and the mother-child attachment is then classified into one of the three major classifications: secure, insecure-avoidant, and insecure-ambivalent. For our analyses, children were classified as (i) always secure, (ii) always insecure, (iii) increasingly secure, and (iv) increasingly insecure.

Child temperament (individual level; 2 time points): The Early Infant Temperament Questionnaire[40] is a 39-item questionnaire that evaluates mother's perception of the activity, adaptability, approach, mood, and intensity of the child. Reported test-retest reliability range from 0.48 to 0.80 across questionnaire subscales. Items are rated on a 1- to 6-point scale from "almost never" to "almost always." Mean (3.3) and SD (0.7) at one month and six months were used to calculate changes in child temperament as (i) increasingly (six months value > one month value +0.7), or (ii) decreasingly difficult temperament (six months value < one month value -0.7), and (iii) no change.

Child emotional reactivity (individual level; 4 time points): Mothers completed a composite measure for emotional reactivity[41] that evaluates their perception of how their child expresses emotions in response to events. Reported test-retest reliability range from 0.74 to 0.78 across timepoints. Respondents were asked to rate their child's frequency of display of emotions on a 5-point scale from 1 ("never") to 5 ("always"). Our model identified two trajectories (i) high vs. (ii) low emotional reactivity.

Child friendship quality (individual level; 5 time points): The Friendship Quality Questionnaire/My Best Friend & Me[42] evaluates the child's perceptions of the previously identified best friendship he/she has. Reported test-retest reliability range from 0.63 to 0.93 across timepoints. The 21-item questionnaire utilizes a 5-point response scale ranging from 1 ("not at all true") to 5 ("really true") to measure six qualitative aspects of the friendship: validation and caring, conflict resolution, conflict and betrayal, help and guidance, companionship and recreation, and intimate exchange. Our model identified four trajectories: (i) Stable high, (ii) medium and decreasing, (iii) medium and increasing, and (iv) low but increasing friendship quality.

Maternal separation anxiety (family level; 4 time points): The Maternal Separation Anxiety Scale[43] is a 21-item questionnaire that evaluates mother's level of worry, sadness, and guilt when separated from the infant. Reported internal consistency reliability ranged from 0.91 to 0.93. Each item is rated on a 5-point Likert scale ranging from 1 ("strongly disagree") to 5 ("strongly agree"). Our model identified two trajectories: (i) low and (ii) high maternal separation anxiety.

Parent-child interaction (family level; 5 time points): The Parent-Child Interaction Task[44] is rated from 15-min videotapes of free play between parent and child. Our model identified four trajectories for the maternal sensitivity subscale: (i) increasing, (ii) stable-low, (iii) stable-middle,

and (iv) stable-high maternal sensitivity; and two trajectories for paternal sensitivity: (i) high vs. (ii) low.

Parental intimacy (family level; 9 time points): The Personal Assessment of Intimacy in Relationships[45] is a 36-item questionnaire that evaluates the degree of five areas of intimacy that an individual perceives he/she has with his/her partner. Internal consistency reliability ranged from 0.91 to 0.93 across samples We used the emotional intimacy subscale. Our model identified two trajectories for mother's and father's perception of intimacy in their relationship. We categorized the agreement between parents as (i) high and (ii) low intimacy agreement, and (iii) intimacy disagreement.

Maternal depression (family level; 11 time points) and paternal depression (family level; 6 time points): The Center for Epidemiologic Studies Depression Scale[46] evaluates depressive symptomatology for non-clinical samples. Reported test-retest reliability is 0.57. Respondents rate the frequency of 20 symptoms of depression during the past week. Response categories are "rarely or none of the time (less than one day)", "some or a little of the time (1-2 days)", "occasionally or a moderate amount of time (3-4 days) 11, and "most or all of the time (5-7 days)". Our model identified three trajectories (i) low, (ii) borderline significant, and (iii) clinically significant maternal and paternal depression.

Statistical analysis

All analyses were performed using SAS 9.4 (SAS Institute, Cary, NC), hypotheses were two-tailed. Descriptive statistics were calculated for all demographics and study characteristics; we assumed no normality and used non-parametric tests for continuous variables. Chi-squares and Wilcoxon's test were used to assess unadjusted associations of individual stressful life events,

summary stressful life events variables, and all the covariates with adjustment problems in adolescence.

For the covariates assessed at ≥2 time points (see *Covariates*), we used the SAS PROC TRAJ procedure. This procedure is a group-based trajectory modeling that assumes there is a certain number of discrete underlying groups in the population[47] (Supplemental Material S1 provides more detailed information).

Multiple logistic regressions analyses were used to evaluate the association of adjustment problems in adolescence (dependent variable) and the total number of stressful life events (independent variable) while controlling for sociodemographic variables. The models were re-run using all the stressful life events categorical variables and stressful life events timing/chronicity as independent variables. Finally, models including individual- and family-level covariates were run. The final models presented in the manuscript included only variables that showed significance in the individual or family-level models. Adjusted odds ratios (ORs) and their 95% confidence intervals (CIs) were calculated for all models. Final model's significance values were Bonferroni-adjusted for multiple comparisons and p-values <0.01 were considered significant.

Linear mixed models were used to evaluate differences in CBCL internalizing and externalizing trajectories over time between children with "many" and "few" stressful life events. This model intrinsically consists of two components: subject-specific and population-specific models, while accounting for correlation at each level [48]. Missing data can be handled readily by this technique.

Results

Table 1 shows the sociodemographic characteristic of the population, covariates, and bivariate associations with adjustment problems as rated by adolescent self-report (information about adjustment problems rated by the mother is presented in the Supplemental Materials Table 1). Of the 1.364 children and families enrolled in the study, information from the YSR at age 15 years was available for 956 subjects. Some differences between those with complete data at age 15 years compared to those not included in the analysis were found. Those with complete data on adjustment problems had a higher income-to-needs ratio (median=2.5, IQR: 1.4-3.9 vs. median=1.8, IQR: 0.8-3.2, $p<0.001$) and the percentage of females was higher (50.1% vs. 44.1%, $p=0.043$). There was no difference in ethnicity (81.4% vs. 78.2%, $p=0.17$).

A significant difference between mother- and adolescent-reports were found for the internalizing (11.0% vs. 11.3%, $p<0.001$) and externalizing (10.3% vs. 14.3%, $p<0.001$) subscales. This difference was also found in the ratings of adjustment problems (26.3% vs. 21.1%, $p<0.001$). All selected covariates, except change in temperament, showed a significant association with mother-reported adjustment problems in adolescence in the unadjusted analysis (Supplemental Material S2). However, for child-reported adjustment problems, only emotional reactivity ($p=0.002$), and maternal ($p=0.004$) and paternal depression ($p=0.006$) were found to be significant (Table 1).

Detailed information about individual stressful life events at each evaluated time point and their association with adjustment problems separated by mother- and child-report are provided in the Supplemental Material (S3). Common stressful life events significantly associated with adjustment problems at all three time points were: Arguments/conflicts with husband/partner,

major changes in the emotional closeness (increasing or decreasing) of family members, and problems with child (e.g., school, discipline, etc.). Table 2 shows the prevalence and unadjusted association of all stressful life events with adjustment problems. Overall, children with adjustment problems at age 15 reported a higher total number of stressful life events (median=24, IQR:15-30 vs. median=19, IQR:12-27, $p<0.001$).

Families of children with "few" total number of stressful life events differed from those with "many" with regard to some key sociodemographic variables, such as maternal education level (13% vs. 8% didn't have a high school degree and 11% vs. 17% completed graduate studies; $p=0.015$), lower median income-to-needs ratio (median=1.84, IQR: 0.9-3.1 vs. median=2.52, IQR: 1.4-4.0 $p<0.001$), more arguments and conflicts with husband/partner (at 54m: 57.5% vs. 28.0%, $p<0.001$; 3rd grade: 53.6% vs. 23.6%, $p<0.001$; 5th grade: 47.7 vs. 23.0%, $p<0.001$), more family violence (at 54m: 5% vs. 1.1%, $p<0.001$; 3rd grade: 5.6% vs. 0.7%, $p<0.001$; 5th grade: 2.6% vs. 0.81, $p=0.023$) and living in violent neighborhoods (at 54m: 11.5% vs. 3.9%, $p<0.001$; 3rd-grade: 9.4% vs. 2.1%, $p<0.001$; 5th-grade: 5.3% vs. 0.9%, $p<0.001$).

Variables significantly associated with adjustment problems in adolescence were: total number of stressful life events, gender, maternal education level, emotional reactivity, friendship quality, and paternal depression (Table 3, Model 1). There were no significant associations between stressful life events timing/chronicity and adjustment problems (Table 3, Model 2). Stressful life events categorized as parent/family physical or mental health and well-being were associated with mother-report of adjustment problems, but not with child-report. Stressful life events categorized as emotional aspects of relationships were significantly associated with child-reported adjustment problems, and marginally significant with mother-reported adjustment problems (Table 3, Model 3). Of note, each additional stressful life event increased the odds ratio

(OR) for adjustment problems in adolescence. Children with "many" versus those with "few" stressful life events had significantly higher odds of adjustment problems in adolescence (OR=1.7, p=0.004). All information on the models analyzed using mother-report can be found in the Supplemental Material (S4).

Results from the model that included only children with "many" stressful life events showed that mother-rated adjustment problems were associated only with high child emotional reactivity scores (OR=3.8, p=0.003); and child-rated adjustment problems were marginally associated with child's father or mother's husband/partner living in the same household at child's birth (OR=2.5, p=0.015).

On the other hand, results from the model including only children with "few" stressful life events showed that mother-rated adjustment problems were associated with maternal education at child's birth (high school education vs. graduate studies; OR=3.3, p=0.002), high child emotional reactivity (OR=2.0, p=0.006), and child's report of low and increasing vs. medium and increasing friendship quality (OR=2.9, p=0.014). Child-rated adjustment problems were associated with paternal clinically significant versus low depression scores (OR=3.5, p=0.001).

Finally, Figure 1 depicts the mixed regression trajectories for internalizing and externalizing scores over time with significant differences between children with "many" and "few" stressful life events (ps<0.001 for both trajectories).

Discussion

This study evaluated the influence of stressful life events in childhood on clinical elevation of adjustment problems at age 15 as well as the role of individual- and family-level covariates. We tested the influence of a number of covariates derived from research on resilience and differential susceptibility and examined the influence of stressful life events on adjustment problems in adolescence from numerous perspectives: the effect of individual stressful life events, total number of stressful life events across childhood, stressful life event type (by life domain), and timing/chronicity of stressful life event exposure. Additionally, we compared internalizing and externalizing trajectories of children with "few" and "many" stressful life events.

Our study resulted in several main findings. First, we found that mother- and child-report of adjustment problems in adolescence differ. This is in line with findings from a previous study showing that parents and children generally agree on the presence of symptoms, but not necessarily on the level/intensity of symptoms.[49] Achenbach et al. reported an average correlation between self- and parent-report on behavioral and emotional problems across childhood and adolescence to be as low as r=0.22.[50] In our study, adolescents rated themselves higher on the YSR than their mothers did on the CBCL. Previous research has shown that self-ratings of internalizing problems are consistently higher than ratings by other informants (such as parents or teachers) and this agreement decreases when subjects get older. The opposite was found for externalizing problems, where the agreement is larger and increases with age.[51]

Next, we found experiencing "many" stressful life events to be the single most important predictor of adjustment problems, even after controlling for sociodemographic variables and multiple individual- and family-level covariates. The increased risk associated with every

additional stressful life event was significant. This result supports the cumulative risk model [52] that highlights the importance of the number of adverse childhood experiences (which includes stressful life events and other factors, such as socioeconomic status) in the development of adjustment problems, especially externalizing problems.[53] Interestingly, we found that the timing of stressful life events was much less important than the total number of stressful life events across childhood. Another study that looked at stressful life events and obesity in the same study sample also came to this conclusion.[39] Of note, the assessment of stressful life events started at 4.5 years, so we could not examine their influence on earlier sensitive periods of development.[6] Stressful life events related to emotional aspects of relationships, such as conflicts within the (extended) family, divorce, and major change in the emotional closeness of family members were more important compared to other types of stressful life events. Although a change of attachment classification (i.e., increasingly secure after first being classified as insecurely attached and vice versa) showed significant univariate associations with adjustment problems, this association - contrary to our expectations - was not maintained as a predictive factor of adjustment problems after adjusting for other covariates (even though it showed a trend towards significance). This is surprising, given that mother-child attachment is considered a key component of early child development.[16] Our results suggest that other factors such as stressful life events and child emotional reactivity may be more important in the development of adjustment problems. This is in line with the idea of differential susceptibility, in that more susceptible individuals are more affected by both positive and negative (i.e., stressful life events) environmental exposures[11], and the more recently proposed idea of vantage sensitivity[14]. The model of vantage sensitivity describes individual differences in response to positive experiences. Responses to negative experiences are not captured in the model of vantage sensitivity – this is

in contrast to differential susceptibility, where individual differences to both positive and negative experiences are addressed. Interestingly, Pluess and Belsky identified negative emotionality as one behavioral endogenous susceptibility and vantage sensitivity factor.[14]

For children with "few" stressful life events, paternal, but not maternal depression was the most significant risk factor for adjustment problems in adolescence. This is partly in line with Compas et al.,[54] one of few studies that reported on both maternal and paternal depression and child outcomes over a nine-month period and found that both parents' psychological symptoms are associated with an increase in adjustment problems in adolescence. Paternal depression is rarely assessed, although a meta-analysis has shown that when assessed, paternal depression is significantly related to child's adjustment problems.[28] Interestingly, in the analyses of individual CBCL subscales, paternal depression was significantly associated only with child's self-reported anxiety/depression, an association that was not found for mother-report. Future studies should examine the specific influence of paternal depression on different areas of child adjustment problems. Finally, low and medium but increasing friendship quality served as a protective factor against adjustment problems for children with "few" stressful life events. This is in line with previous research suggesting that peer environment can present both a risk and a protective factor.[55]

In the subsample of children with "many" stressful life events, we found only two protective factors: Child's low emotional reactivity and absence of father (or mother's husband/partner) living in the same household at child's birth. The positive and large effect (OR=2.5) of not having a father or father-figure living in the same household at birth appears counter-intuitive. We found no assessed moderator or mediator that could explain this result. The fact that this was only assessed at childbirth makes its contribution difficult to understand. After

correcting for multiple comparisons, the result remains only borderline significant for the child-report model (p=0.0152).

The other protective factor we found was low emotional reactivity. The Emotional Security Theory[32] proposes that in a conflict-laden environment, high emotional reactivity can serve as a sensible short-term coping strategy, as heightened emotional arousal helps to facilitate access to physical and psychological resources. Following the differential susceptibility model, high emotionality is considered a "plasticity marker" that can increase sensitivity to both positive and negative environmental exposures.[14] In our sample, low emotional reactivity was a protective factor against adjustment problems for children with "many" stressful life events.

Further, we looked at differences in internalizing and externalizing behavior trajectories among children with "many" and "few" stressful life events. Children with "many" stressful life events showed higher trajectories of internalizing and externalizing behaviors even before the first occurrence of stressful life events was assessed. Children with "many" stressful life events later on in life were born into significantly more stressful environments compared to those with "few" stressful life events, including lower maternal education, lower income, more arguments and conflicts within the family, more family violence, and living in dangerous neighborhoods. These results emphasize the need for targeted interventions for high-risk children in toxic stress environments. Children born in families and communities with low education and income levels are especially vulnerable to early stressful exposures, and in some cases, the cumulative burden of multiple risk factors in life may limit the benefit of protective factors and the effectiveness of intervention programs.[1]

Although internalizing and externalizing behaviors decreased for both groups over the course of the study, the group of children with "many" stressful life events decreased slower, and the difference at the final assessment was almost one standard deviation higher than those with "few" stressful life events. The steady decrease of both internalizing and externalizing behaviors conflicts with previous research that showed a decrease of externalizing, but an increase of internalizing behaviors in school-aged children over time.[56] However, as data were collected until the age of 15, we might have missed a future reoccurring increase of internalizing behavior.[2]

Our study has several strengths. First, we were able to use a prospective, longitudinal data set that followed children and their families over 15 years. Our main predictor, stressful life events, and our outcome measure, clinical elevation of adjustment problems, were both individually assessed at multiple time points, which reduces the risk of recall bias. Our methodology has several advantages, as the trajectory analysis not only deals well with missing data but also allows for a reduction of data without the loss of important information. We analyzed stressful life events by taking multiple factors into account (individual stressful life event, the total number of stressful life events across childhood, type and timing of stressful life event exposure). Further, thanks to the extensive amount of information collected in this dataset, we were able to assess the influence of multiple individual- and family-level covariates that we deemed important, based on previous research on resilience and differential susceptibility.

Limitations of our study include that we had no child report of stressful life events, which means we could not determine if children and mothers agreed on their ratings of what they considered stressful. Moreover, all the information used in our study relied on self-report of participating mothers and children. Also, there was a considerable amount of missing data and

changes regarding the father figure over time (due to separation and divorce). As we used a community and not a clinical sample, our outcome, adjustment problems, represented differences within the norm and did only in rare cases exceed a clinical threshold. It is, therefore, uncertain whether our findings can be generalized to a clinical sample.

Despite these limitations, our study indicates that early intervention for children in high-risk environments addressing the emotional reactivity of the children, the appropriate establishment of friendships, and the assessment and treatment of paternal depression in preventing future psychopathology are of crucial importance. We highlight the need for early screening and detection of families and children in vulnerable situations or high-risk toxic environments. Further, specific interventions are warranted in order to reduce the number of stressful life events and to mitigate the impact that these events can have on children's health, both in the short and long run. Future studies should gather longitudinal data into adulthood to observe the development of trajectories during the transition to adulthood.

References

1. Shonkoff JP, Boyce WT, McEwen BS. Neuroscience, molecular biology, and the childhood roots of health disparities: building a new framework for health promotion and disease prevention. *JAMA*. 2009;301(21):2252-2259. doi:10.1001/jama.2009.754.

2. Ge X, Conger RD, Elder GHJ. Pubertal transition, stressful life events, and the emergence of gender differences in adolescent depressive symptoms. *Dev Psychol*. 2001;37(3):404-417. doi:10.1037/0012-1649.37.3.404.

3. Vaux A, Ruggiero M. Stressful life change and delinquent behavior. *Am J Community Psychol*. 1983;11(2):169-183.

4. Johnson SB, Riley AW, Granger DA, Riis J. The science of early life toxic stress for pediatric practice and advocacy. *Pediatrics*. 2013;131(2):319-327. doi:10.1542/peds.2012-0469.

5. McLaughlin KA, Hatzenbuehler ML. Mechanisms Linking Stressful Life Events and Mental Health Problems in a Prospective, Community-Based Sample of Adolescents. *J Adolesc Health Off Publ Soc Adolesc Med*. 2009;44(2):153-160. doi:10.1016/j.jadohealth.2008.06.019.

6. Fox SE, Levitt P, Nelson CA. How the Timing and Quality of Early Experiences Influence the Development of Brain Architecture. *Child Dev*. 2010;81(1):28-40. doi:10.1111/j.1467-8624.2009.01380.x.

7. Windle M. A longitudinal study of stress buffering for adolescent problem behaviors. *Dev Psychol*. 1992;28(3):522-530. doi:10.1037/0012-1649.28.3.522.

8. Ge X, Lorenz FO, Conger RD, Elder GH, Simons RL. Trajectories of stressful life events and depressive symptoms during adolescence. *Dev Psychol*. 1994;30(4):467-483. doi:10.1037/0012-1649.30.4.467.

9. Grant KE, Compas BE, Thurm AE, McMahon SD, Gipson PY. Stressors and Child and Adolescent Psychopathology: Measurement Issues and Prospective Effects. *J Clin Child Adolesc Psychol*. 2004;33(2):412-425. doi:10.1207/s15374424jccp3302_23.

10. Masten AS. Ordinary magic: Resilience processes in development. *Am Psychol*. 2001;56(3):227-238. doi:10.1037/0003-066X.56.3.227.

11. Belsky J, Pluess M. Beyond diathesis stress: differential susceptibility to environmental influences. *Psychol Bull*. 2009;135(6):885-908. doi:10.1037/a0017376.

12. Werner EE, Smith RS. *Vulnerable, but Invincible : A Longitudinal Study of Resilient Children and Youth*. New York : McGraw-Hill; 1982. https://trove.nla.gov.au/version/30175146. Accessed January 9, 2018.

13. Masten AS, Hubbard JJ, Gest SD, Tellegen A, Garmezy N, Ramirez M. Competence in the context of adversity: Pathways to resilience and maladaptation from childhood to late adolescence. *Dev Psychopathol*. March 1999. /core/journals/development-and-psychopathology/article/div-classtitlecompetence-in-the-context-of-adversity-pathways-to-resilience-and-maladaptation-from-

childhood-to-late-adolescencediv/B1E79A19BE8017ADAC44B66199D9B401. Accessed December 12, 2016.

14. Pluess M, Belsky J. Vantage sensitivity: individual differences in response to positive experiences. *Psychol Bull*. 2013;139(4):901-916. doi:10.1037/a0030196.

15. Pluess M. Individual Differences in Environmental Sensitivity. *Child Dev Perspect*. 2015;9(3):138-143. doi:10.1111/cdep.12120.

16. Berlin LJ, Cassidy J. Mothers' Self-Reported Control of Their Preschool Children's Emotional Expressiveness: A Longitudinal Study of Associations with Infant–Mother Attachment and Children's Emotion Regulation. *Soc Dev*. 2003;12(4):477-495. doi:10.1111/1467-9507.00244.

17. Ainsworth MS. Infant–mother attachment. *Am Psychol*. 1979;34(10):932-937. doi:10.1037/0003-066X.34.10.932.

18. Ainsworth MDS, Blehar MC, Waters E, Wall SN. *Patterns of Attachment: A Psychological Study of the Strange Situation*. S.l.: Psychology Press; 1978.

19. Warren SL, Huston L, Egeland B, Sroufe LA. Child and Adolescent Anxiety Disorders and Early Attachment. *J Am Acad Child Adolesc Psychiatry*. 1997;36(5):637-644. doi:10.1097/00004583-199705000-00014.

20. Wustmann C. Die Erkenntnisse der Resilienzforschung – Beziehungserfahrungen und Ressourcenaufbau. *Psychother Forum*. 2009;17(2):71-78. doi:10.1007/s00729-009-0285-2.

21. Cooklin AR, Lucas N, Strazdins L, et al. Heightened Maternal Separation Anxiety in the Postpartum The Role of Socioeconomic Disadvantage. *J Fam Issues*. 2014;35(11):1497-1519. doi:10.1177/0192513X13481776.

22. Hock E, Schirtzinger M b. Maternal separation anxiety: Its developmental course and relation to maternal mental health. *Child Dev*. 1992;63(1):93. doi:10.1111/1467-8624.ep9203091728.

23. McBride S, Belsky J. Characteristics, determinants, and consequences of maternal separation anxiety. *Dev Psychol*. 1988;24(3):407-414. doi:10.1037/0012-1649.24.3.407.

24. Mayseless O, Scher A. Mother's attachment concerns regarding spouse and infant's temperament as modulators of maternal separation anxiety. *J Child Psychol Psychiatry*. 2000;41(7):917-925.

25. Lupien SJ, King S, Meaney MJ, McEwen BS. Child's stress hormone levels correlate with mother's socioeconomic status and depressive state. *Biol Psychiatry*. 2000;48(10):976-980. doi:10.1016/S0006-3223(00)00965-3.

26. Essex MJ, Kraemer HC, Armstrong JM, et al. Exploring Risk Factors for the Emergence of Children's Mental Health Problems. *Arch Gen Psychiatry*. 2006;63(11):1246-1256. doi:10.1001/archpsyc.63.11.1246.

27. Bronte-Tinkew J, Moore KA, Carrano J. The Father-Child Relationship, Parenting Styles, and Adolescent Risk Behaviors in Intact Families. *J Fam Issues*. 2006;27(6):850-881. doi:10.1177/0192513X05285296.

28. Kane P, Garber J. The relations among depression in fathers, children's psychopathology, and father–child conflict: A meta-analysis. *Clin Psychol Rev*. 2004;24(3):339-360. doi:10.1016/j.cpr.2004.03.004.

29. Flouri E. Fathering and adolescents' psychological adjustment: the role of fathers' involvement, residence and biology status. *Child Care Health Dev*. 2008;34(2):152-161. doi:10.1111/j.1365-2214.2007.00752.x.

30. Buehler C, Benson MJ, Gerard JM. Interparental hostility and early adolescent problem behavior: The mediating role of specific asepcts of parenting. *J Res Adolesc*. 2006;16(2):265-292.

31. Davies PT, Cummings EM. Exploring Children's Emotional Security as a Mediator of the Link between Marital Relations and Child Adjustment. *Child Dev*. 1998;69(1):124-139. doi:10.1111/j.1467-8624.1998.tb06138.x.

32. Cummings EM, Schermerhorn AC, Davies PT, Goeke-Morey MC, Cummings JS. Interparental Discord and Child Adjustment: Prospective Investigations of Emotional Security as an Explanatory Mechanism. *Child Dev*. 2006;77(1):132-152. doi:10.1111/j.1467-8624.2006.00861.x.

33. Bethell CD, Newacheck P, Hawes E, Halfon N. Adverse childhood experiences: assessing the impact on health and school engagement and the mitigating role of resilience. *Health Aff Proj Hope*. 2014;33(12):2106-2115. doi:10.1377/hlthaff.2014.0914.

34. Achenbach TM. *Manual for the Child Behavior Checklist/4-18 and 1991 Profile*. Department of Psychiatry, University of Vermont Burlington, VT; 1991. http://scholar.google.com/scholar?cluster=13886491576511918212&hl=en&oi=scholarr. Accessed December 12, 2016.

35. Rutter M, Kim-Cohen J, Maughan B. Continuities and discontinuities in psychopathology between childhood and adult life. *J Child Psychol Psychiatry*. 2006;47(3-4):276-295. doi:10.1111/j.1469-7610.2006.01614.x.

36. Achenbach TM, Ruffle TM. The Child Behavior Checklist and related forms for assessing behavioral/emotional problems and competencies. *Pediatr Rev Am Acad Pediatr*. 2000;21(8):265-271.

37. Achenbach TM. *Manual for the Youth Self-Report and 1991 Profile.* Burlington, VT: University of Vermont, Department of Psychiatry; 1991.

38. Sarason IG, Johnson JH, Siegel JM. Assessing the impact of life changes: development of the Life Experiences Survey. *J Consult Clin Psychol*. 1978;46(5):932-946.

39. Lumeng JC, Wendorf K, Pesch MH, et al. Overweight adolescents and life events in childhood. *Pediatrics*. 2013;132(6):e1506-1512. doi:10.1542/peds.2013-1111.

40. Medoff-Cooper B, Carey WB, McDevitt SC. The Early Infancy Temperament Questionnaire. *J Dev Behav Pediatr JDBP*. 1993;14(4):230-235.

41. Shields A, Cicchetti D. Emotion regulation among school-age children: the development and validation of a new criterion Q-sort scale. *Dev Psychol*. 1997;33(6):906-916.

42. Baker JR, Hudson JL. Friendship quality predicts treatment outcome in children with anxiety disorders. *Behav Res Ther*. 2013;51(1):31-36. doi:10.1016/j.brat.2012.10.005.

43. Hock E, McBride S, Gnezda MT. Maternal Separation Anxiety: Mother-Infant Separation from the Maternal Perspective. *Child Dev*. 1989;60(4):793. doi:10.1111/1467-8624.ep9676077.

44. Egeland B, Hiester M. *Teaching Task Rating Scales*. Institute of Child Development, University of Virginia; 1993.

45. Schaefer MT, Olson DH. Assessing Intimacy: The Pair Inventory*. *J Marital Fam Ther*. 1981;7(1):47-60. doi:10.1111/j.1752-0606.1981.tb01351.x.

46. Lewinsohn PM, Seeley JR, Roberts RE, Allen NB. Center for Epidemiologic Studies Depression Scale (CES-D) as a screening instrument for depression among community-residing older adults. *Psychol Aging*. 1997;12(2):277-287.

47. Jones BL, Nagin DS, Roeder K. A SAS Procedure Based on Mixture Models for Estimating Developmental Trajectories. *Sociol Methods Res*. 2001;29(3):374-393. doi:10.1177/0049124101029003005.

48. Cnaan A, Laird NM, Slasor P. Using the general linear mixed model to analyse unbalanced repeated measures and longitudinal data. *Stat Med*. 1997;16(20):2349-2380.

49. Cole DA, Tram JM, Martin JM, et al. Individual differences in the emergence of depressive symptoms in children and adolescents: A longitudinal investigation of parent and child reports. *J Abnorm Psychol*. 2002;111(1):156-165. doi:10.1037/0021-843X.111.1.156.

50. Achenbach TM, McConaughy SH, Howell CT. Child/Adolescent Behavioral and Emotional Problems: Implications of Cross-Informant Correlations for Situational Specificity. [Review]. *Psychol Bull*. 1987;101(2):213-232.

51. van der Ende J, Verhulst FC, Tiemeier H. Agreement of informants on emotional and behavioral problems from childhood to adulthood. *Psychol Assess*. 2012;24(2):293-300. doi:10.1037/a0025500.

52. Yoshikawa H. Prevention as cumulative protection: effects of early family support and education on chronic delinquency and its risks. *Psychol Bull*. 1994;115(1):28-54.

53. Deater-Deckard K, Dodge KA, Bates JE, Pettit GS. Multiple risk factors in the development of externalizing behavior problems: Group and individual differences. *Dev Psychopathol*. 1998;10(3):469-493.

54. Compas BE, Howell DC, Phares V, Williams RA, Giunta CT. Risk factors for emotional/behavioral problems in young adolescents: A prospective analysis of adolescent and parental stress and symptoms. *J Consult Clin Psychol*. 1989;57(6):732-740. doi:10.1037/0022-006X.57.6.732.

55. Grant KE, Compas BE, Stuhlmacher AF, Thurm AE, McMahon SD, Halpert JA. Stressors and child and adolescent psychopathology: Moving from markers to mechanisms of risk. *Psychol Bull*. 2003;129(3):447-466. doi:10.1037/0033-2909.129.3.447.

56. Crijnen AA, Achenbach TM, Verhulst FC. Comparisons of problems reported by parents of children in 12 cultures: total problems, externalizing, and internalizing. *J Am Acad Child Adolesc Psychiatry*. 1997;36(9):1269-1277. doi:10.1097/00004583-199709000-00020.

Figure Legends:

Figure 1. Outcome measures and data points used in the study.

Figure 2. Mixed regression models of internalizing and externalizing scores by upper quartile vs. lower three quartiles for the number of stressful life events. Bold lines represent the fix values and soft lines represent 95% confidence intervals. “Many” stressful life events: upper quartile of number of stressful life events; “Few” stressful life events: lower three quartiles of number of stressful life events.

Table 1. Demographics and bivariate associations with clinical elevation for adjustment problems rated by self-report.

Variable	Clinical elevation for adjustment Problems (n=203) %	No clinical elevation for adjustment problems (n=753) %	*p-value*
Study Child: Female	55.67	48.61	0.0742
White ethnicity	75.86	82.87	0.1343
Maternal education			
No high school degree	9.36	7.57	
High school degree	24.14	18.86	0.2622
Bachelor's degree	51.72	57.5	
Post-graduate studies	14.78	16.07	
Father/mother's husband or partner living in the same household	80.3	88.71	**0.0016**
Income-to-needs ratio	2.0 (0.9-3.4)	2.5 (1.5-4.0)	**0.0002**
Mother-child attachment			
Always secure	49.72	51.03	
Increasingly secure	19.89	19.21	0.7933
Increasingly insecure	20.99	18.48	
Always insecure	9.39	11.29	
Temperament changes			
Increasingly difficult temperament	10.66	8.24	
Decreasingly difficult temperament	15.74	18.78	0.3979
No change	73.6	72.97	
Maternal separation anxiety			
Low	56.16	62.15	0.1204
High	43.84	37.85	
Maternal sensitivity			
Increasing	3.94	3.05	
Stable low	6.4	4.52	0.0531
Stable middle	33	25.37	
Stable high	56.65	67.07	
Paternal sensitivity			
Low	15.27	15.01	0.9256
High	84.73	84.99	
Relationship Intimacy			
Agree high	51.23	52.19	
Agree low	22.17	19.52	0.6879
Disagree	26.6	28.29	
Emotional reactivity			

Low	36.45	51	**0.0002**
High	63.55	49	
Friendship quality			
High	41.38	43.29	0.1469
Middle decreasing	11.33	8.23	
Middle increasing	28.57	34.13	
Low but increasing	41.38	14.34	
Maternal depression			
Low	42.86	53.12	**0.0035**
Borderline	42.36	38.78	
Clinically significant	14.78	8.1	
Paternal depression			
Low	49.75	59.23	**0.0058**
Borderline	37.44	34	
Clinically significant	12.81	6.77	

Significant p-values are marked in bold ($p<0.05$).

"Clinical elevation for adjustment problems" is defined as the presence of high (>1 standard deviation above the mean) internalizing and/or externalizing problems measured by the Youth Self-Report scale at age 15.

Table 2. Stressful life event variables and bivariate associations with clinical elevation for adjustment problems rated by adolescent self-report.

Variable	Clinical elevation for adjustment Problems %	No clinical elevation for adjustment problems %	*p-value*
Total number of stressful life events, median (IQR)	24 (15-30)	19 (12-27)	**<0.0001**
"Many" stressful life events			
54 months (n=1077)	24.73	18.5	0.0578
3rd grade (n=1028)	38.38	21.21	**<0.0001**
5th grade (n=1012)	31.12	19.81	**0.0007**
Timing/chronicity of stressful life events			
Never (n=513)	41.27	58.47	**<0.0001**
Always (n=51)	10.05	4.05	**0.0011**
Early (n=38)	4.76	3.76	0.5323
Late (n=65)	11.11	5.21	**0.0035**
Single time point (n=314)	32.8	28.15	0.2506
Stressful life events, Categories			
Health and wellbeing	33	29.61	0.3511
Work/school/finances	33	25.5	0.0327
Emotional aspects	39.9	24.04	**<0.0001**
Change in family structure	38.42	29.88	0.0202

Significant p-values are marked in bold ($p<0.01$).

"Clinical elevation for Adjustment problems" is defined as the presence of high (>1 standard deviation above the mean) internalizing and/or externalizing problems measured by the Youth Self-Report scale at age 15.

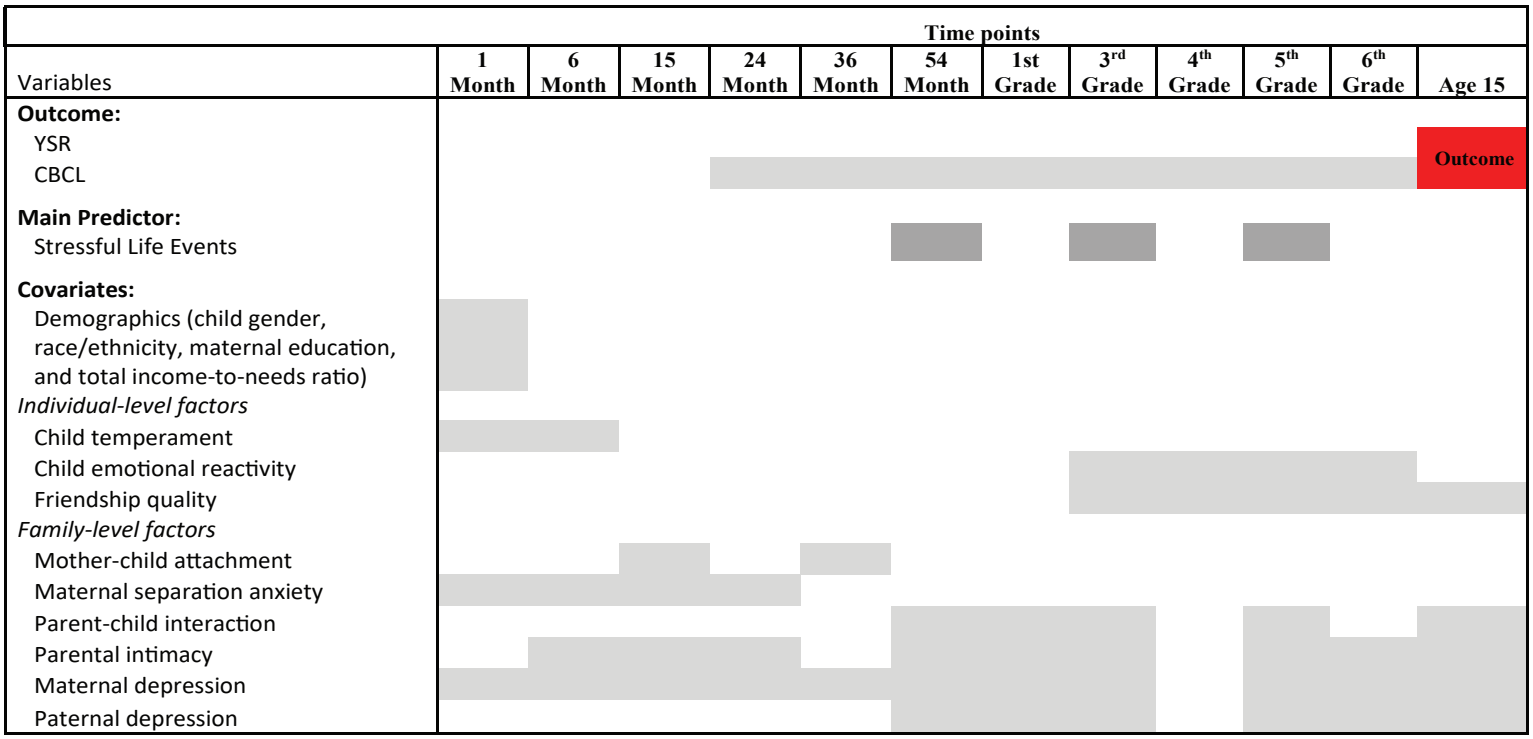
Table 3. Variables associated with clinical elevation for adjustment problems at age 15, rated by adolescent self-report.

		Adolescent report	
Variable	**OR**	**95% CI**	***p-value***
Model 1.			
Total number of stressful life events (continuous variable, odds per additional stressful life event)	1.03	(1.02-1.04)	**<.0001**
Gender: Male vs. female	1.89	(1.29-2.76)	**0.001**
Maternal education level			
High school vs. graduate studies	1.29	(0.75-2.2)	0.0963
Bachelor's vs. graduate studies	0.83	(0.51-1.36)	0.0885
Individual-level factors			
Emotional Reactivity: High vs. low	1.59	(1.12-2.26)	**0.0103**
Friendship quality			
High vs. low but increasing	0.53	(0.32-0.9)	**0.0212**
Middle decreasing vs. low but increasing	1.05	(0.55-2)	0.1074
Middle increasing vs. low but increasing	0.56	(0.33-0.95)	0.0537
Family-level factors			
Attachment			
Always insecure vs always secure	0.74	(0.41-1.35)	0.1811
Became insecure vs. always secure	1.15	(0.73-1.8)	0.4241
Became secure vs. always secure	1.18	(0.75-1.86)	0.3468
Paternal depression			
Clinically significant vs. low	2.10	(1.2-3.66)	**0.0165**
Borderline vs. low	1.19	(0.82-1.73)	0.3344
Model 2.			
Stressful life events timing/chronicity			
Once vs. never	1.51	(1.01-2.27)	0.1217
Always vs. never	3.20	(1.66-6.2)	0.0798
Early vs. never	1.59	(0.67-3.78)	0.5243
Late vs. never	4.04	(2.02-8.06)	**0.0124**
Gender: Male vs. female	1.86	(1.26-2.76)	**0.0019**
Maternal education level			
High school vs. graduate studies	1.40	(0.8-2.46)	0.0599
Bachelor's vs. graduate studies	0.88	(0.53-1.47)	0.1125
Individual-level factors			
Temperament change			
Increasingly difficult vs. no change	0.87	(0.53-1.43)	0.2625
Decreasingly difficult vs. no change	1.40	(0.77-2.53)	0.1911
Emotional Reactivity: High vs. low	1.51	(1.04-2.17)	**0.0293**
Friendship quality			
High vs. low but increasing	0.51	(0.29-0.87)	**0.0167**
Middle decreasing vs. low but increasing	0.96	(0.49-1.89)	0.2151

Middle increasing vs. low but increasing	0.59	(0.34-1.01)	0.1595
Family-level factors			
Attachment			
Always insecure vs. always secure	0.82	(0.44-1.53)	0.3199
Became insecure vs. always secure	1.04	(0.64-1.69)	0.9789
Became secure vs. always secure	1.34	(0.84-2.15)	0.1507
Paternal depression			
Clinically significant vs. low	2.24	(1.24-4.03)	**0.0118**
Borderline vs. low	1.19	(0.8-1.76)	0.2718
Model 3.			
Stressful life events categories (high total scores)			
Health and wellbeing	0.89	(0.6-1.31)	0.5432
Work/school/finances	1.00	(0.66-1.52)	0.9961
Emotional aspects	2.19	(1.46-3.29)	**0.0002**
Change in family structure	1.28	(0.86-1.9)	0.2295
Gender: Male vs. female	1.90	(1.29-2.79)	0.0011
Maternal education level			
High school vs. graduate studies	1.16	(0.67-2.01)	0.2085
Bachelor's vs. graduate studies	0.80	(0.49-1.3)	0.0973
Individual-level factors			
Emotional reactivity: High vs. low	1.58	(1.1-2.26)	0.0123
Friendship quality			
High vs. low but increasing	0.51	(0.3-0.87)	0.0257
Middle decreasing vs. low but increasing	0.98	(0.5-1.91)	0.1454
Middle increasing vs. low but increasing	0.52	(0.31-0.89)	0.04
Family-level factors			
Attachment			
Always insecure vs. always secure	0.77	(0.42-1.41)	0.2365
Became insecure vs. always secure	1.08	(0.68-1.71)	0.6822
Became secure vs. always secure	1.22	(0.77-1.94)	0.2591
Paternal depression			
Clinically significant vs. low	2.15	(1.23-3.76)	0.0164
Borderline vs. low	1.24	(0.85-1.81)	0.4113

Significant p-values are marked in bold (p<0.01).

"Clinical elevation for Adjustment problems" is defined as the presence of high (>1 standard deviation above the mean) internalizing and/or externalizing problems measured by the Youth Self-Report scale at age 15.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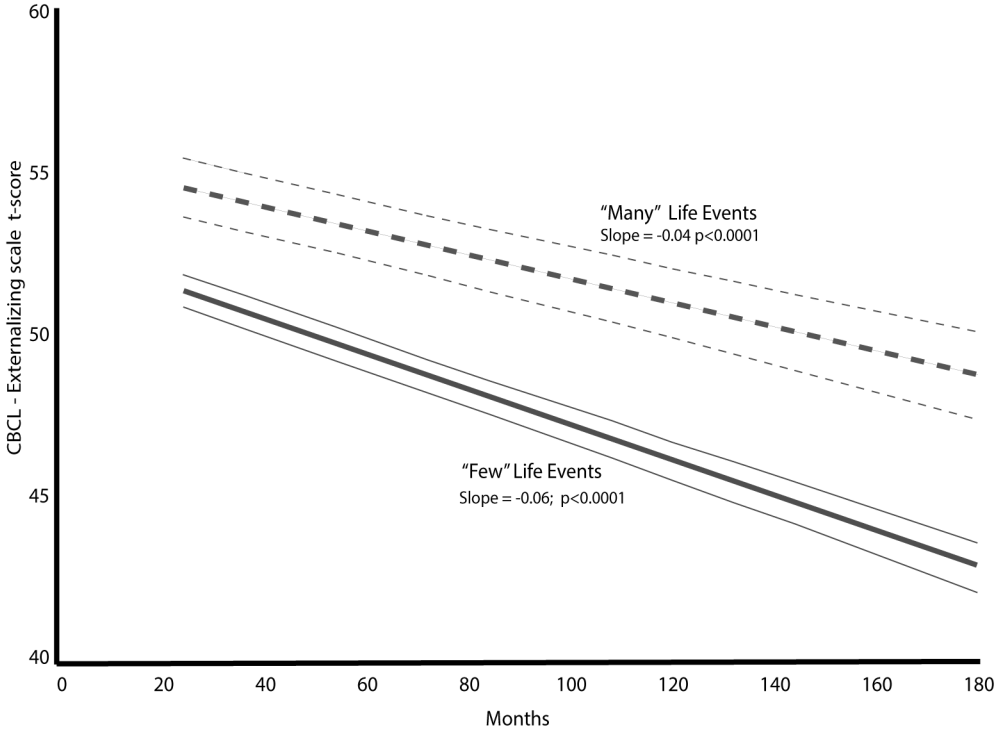
6 Month
15 Month
24 Month
36 Month
54 Month
1st Grade
3rd Grade
4th Grade
5th Grade
6th Grade
Age 15
Outcome:
YSR
CBCL
Outcome
Main Predictor:
Stressful Life Events
Covariates:
Demographics (child gender, race/ethnicity, maternal education, and total income-to-needs ratio)
Individual-level factors
Child temperament
Child emotional reactivity
Friendship quality
Family-level factors
Mother-child attachment
Maternal separation anxiety
Parent-child interaction
Parental intimacy
Maternal depression
Paternal depression

A. Externalizing



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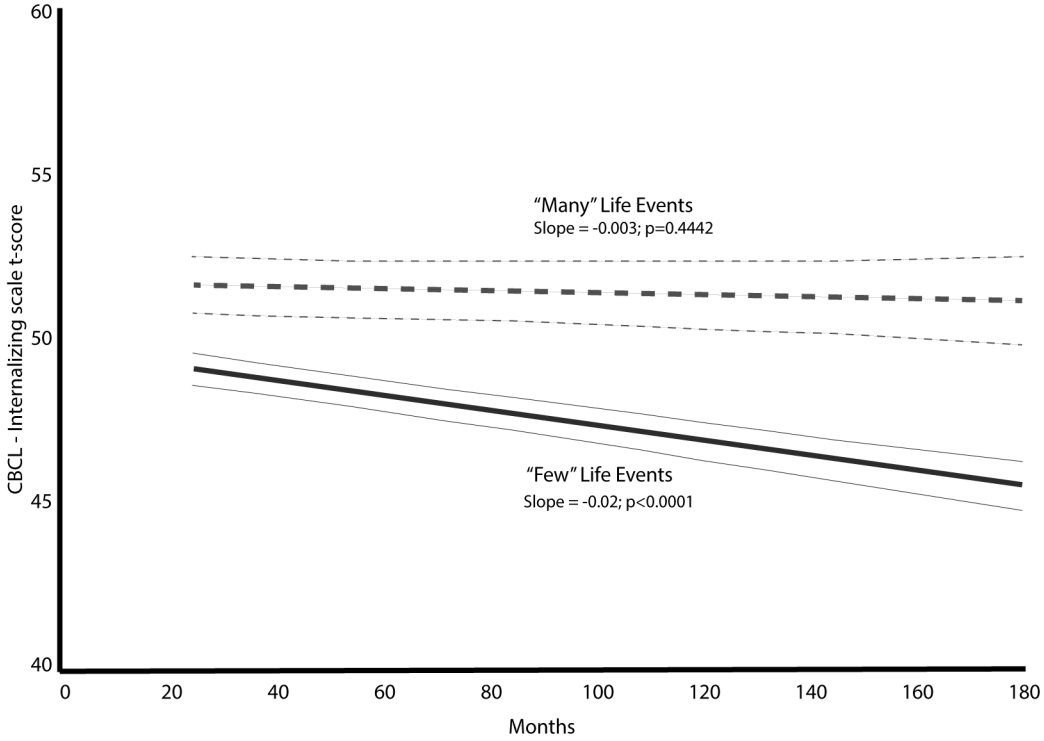

SUPPLEMENTAL MATERIAL

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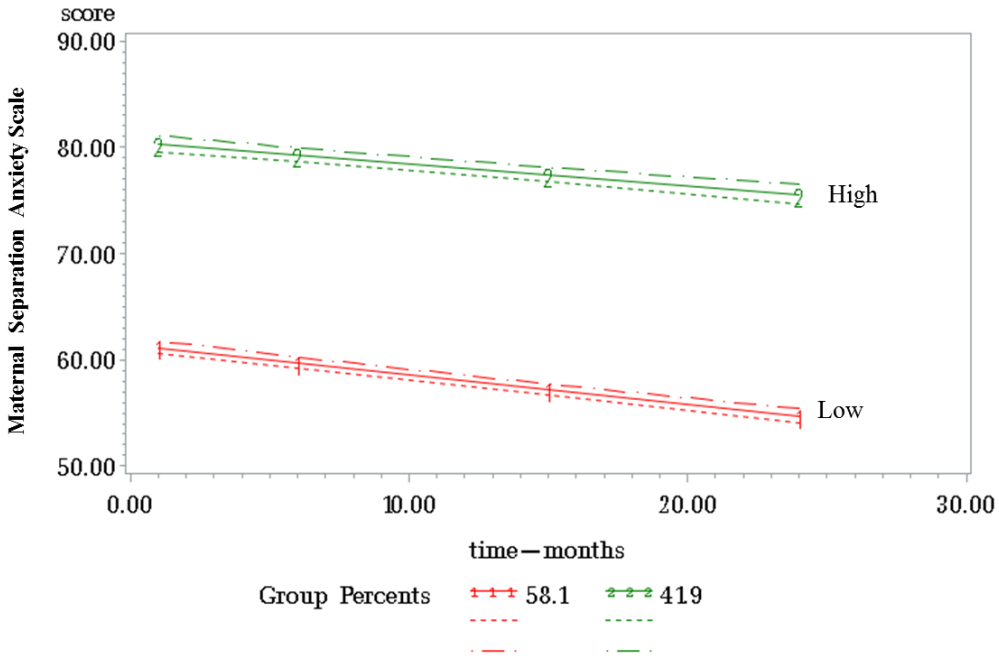
1. Trajectory analysis

The Eunice Kennedy Shriver National Institute of Child Health and Development (NICHD) Study of Early Child Care and Youth Development (SECCYD) collected a wide range of variables at multiple time-points during four study phases over 15 years. In order to include the time factor of the follow-ups without increasing the complexity of our models, and with the aim of providing clear results in mind, we decided to use growth mixture modeling as a first step to create summary variables that could be included in posterior analyses. One advantage of these models is that they address the problem of varying time-points by clustering similar trajectories together and creating categorical indicators of each trajectory.

Two variables were only assessed twice: Mother-child attachment (at 15 and 36 months of age) and child temperament (at one and six months of age). For variables assessed at more than 2 time-points we used the SAS PROC TRAJ procedure. This procedure is a group-based trajectory modeling that assumes there is a certain number of discrete underlying groups in the population and that each group has its own prevalence, intercept, and slope (trajectory shape or change in BMI Z-score). Based on a calculated probability of belonging to a group, the model assigns the individual to the group to which the individual has the highest probability of belonging.[1] This model is robust and allows missing data in the analysis, using all available data from each case to estimate the individual's timeline. For all variables assessed at more than 2 time-points we started with models for four groups, then decreasing number of groups down to two groups. Polynomials were selected for each model, and we used Bayesian information criterion (BIC) scores and authors' criteria to determinate the best fit of the model.[2] Authors' criteria means that we were especially interested in those groups that changed over time (i.e. from high to low or the opposite way), as we thought of trajectory change as a potential risk or protective mechanism across development.

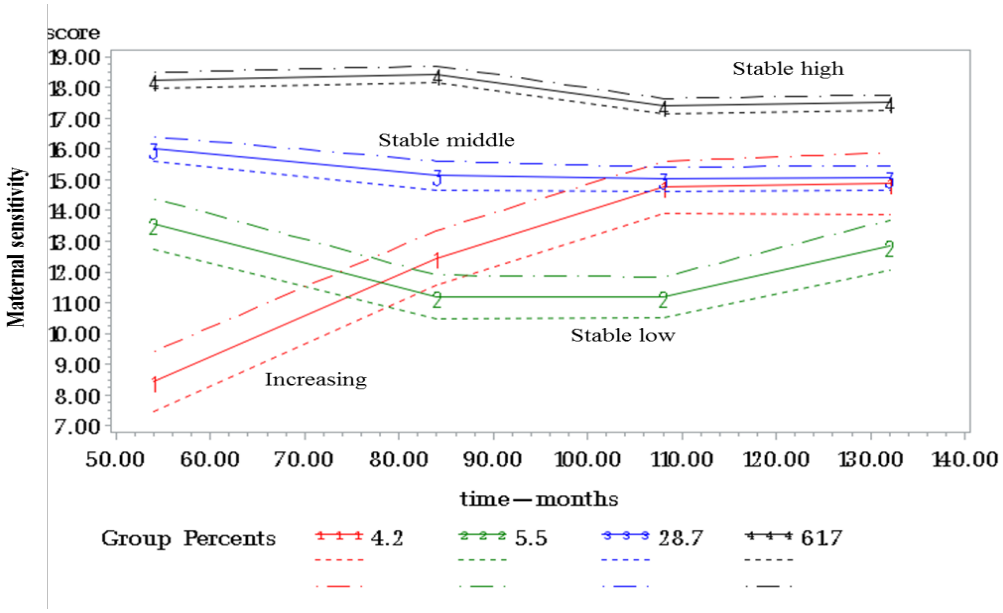
<u>Maternal Separation Anxiety (assessed at one, six, 15 and 24 months):</u>

The Maternal Separation Anxiety Scale[3] (MSAS) was completed by the study child's mother at 4 time-points during phase I of the study. The selected model resulted in two linear trajectories: (i) high vs. (ii) low maternal separation. BIC=-19072.


score
90.00
80.00
70.00
60.00
50.00
Maternal Separation Anxiety Scale
0.00
10.00
20.00
30.00
time—months
High
Low
Group Percents
1 1 1 58.1
2 2 2 419

Parent-child interaction (assessed at 54 months, 1st-, 3rd- and 5th-grade, and at age 15 years):

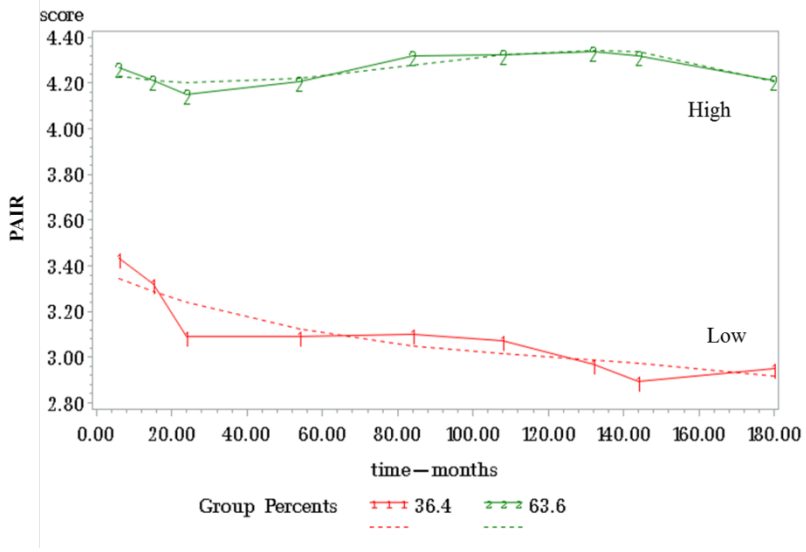
The Parent-Child Interaction Task[4] was observed at five time-points during the study. We used the maternal and paternal sensitivity composite measure, which includes parental supportive presence, respect for child's autonomy, and parental reversed hostility. The selected model for maternal sensitivity resulted in four trajectories (one quadratic and three cubic trajectories): (i) increasing, (ii) stable low, (iii) stable middle, (iv) stable high (BIC=-9065).



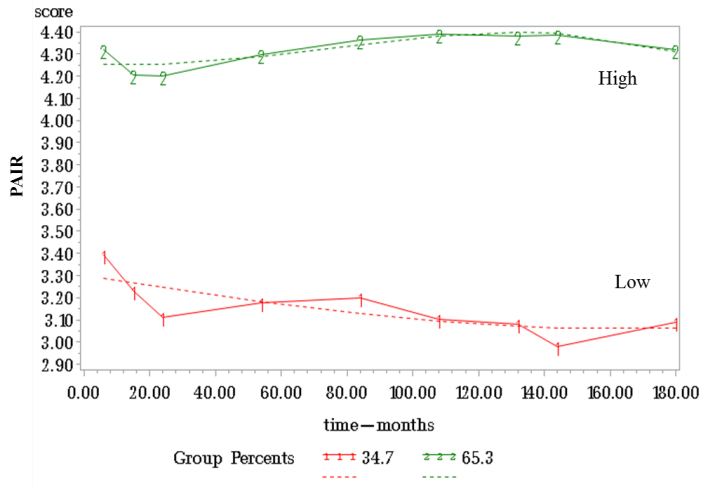
The selected model for paternal sensitivity resulted in two cubic trajectories: (i) high vs. (ii) low. (BIC=-6652).

Parental intimacy (assessed at six, 15, 24, 54 months, 1st-, 3rd-, 5th-, and 6th grade, and at age 15 years):

The "Love and Relationships" subscale of the Personal Assessment of Intimacy in Relationships[5] was evaluated at nine time-points throughout the study. The selected model for pair agreement on shared intimacy resulted in two cubic trajectories: (i) high vs. (ii) low intimacy agreement for mother ratings (BIC=-7354).

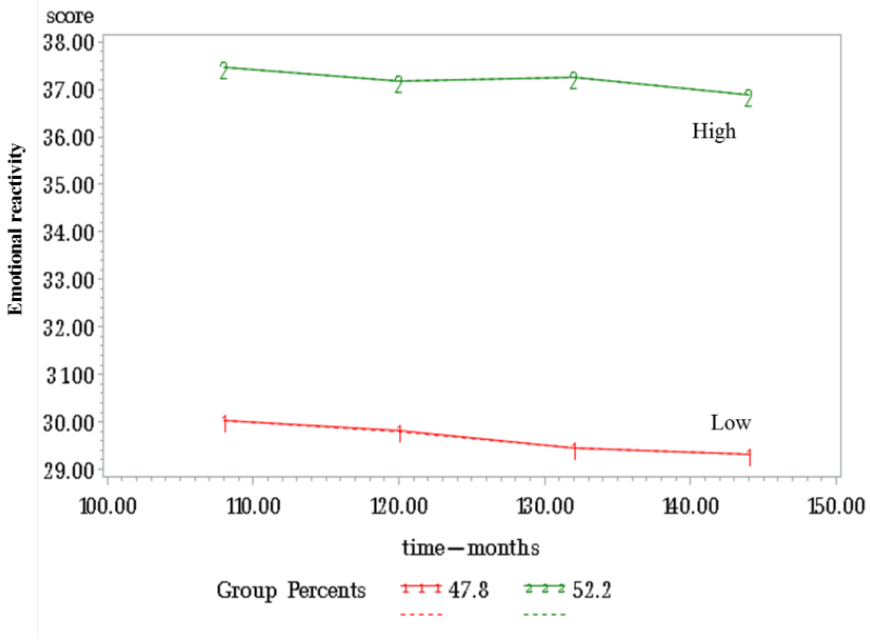


The selected model for intimacy resulted in two cubic trajectories (i) high vs. (ii) low intimacy agreement for father ratings (BIC=-6278).



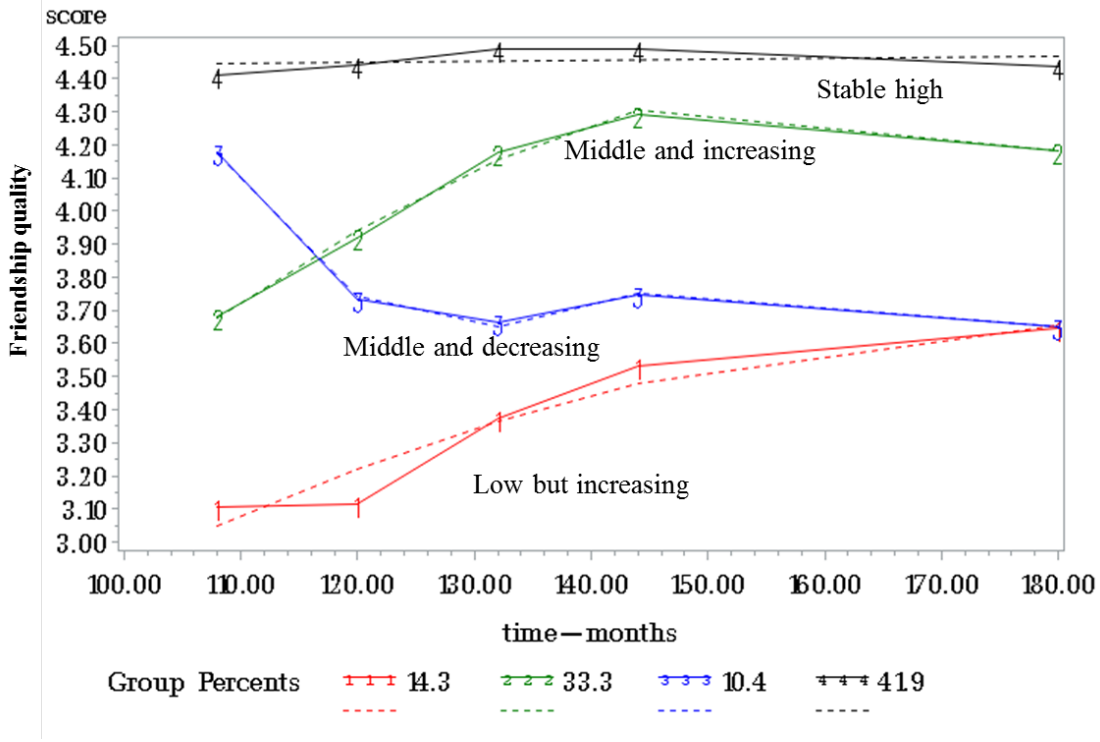
Child emotional reactivity (assessed in 3rd-, 4th-, 5th-, and 6th- grade):

Two measures[6,7] were completed by the study child's mother at four time-points during the study to create a composite measure of child's emotional reactivity. The selected model for emotional reactivity resulted in two cubic trajectories: (i) high vs. (ii) low emotional reactivity (BIC=-12221).



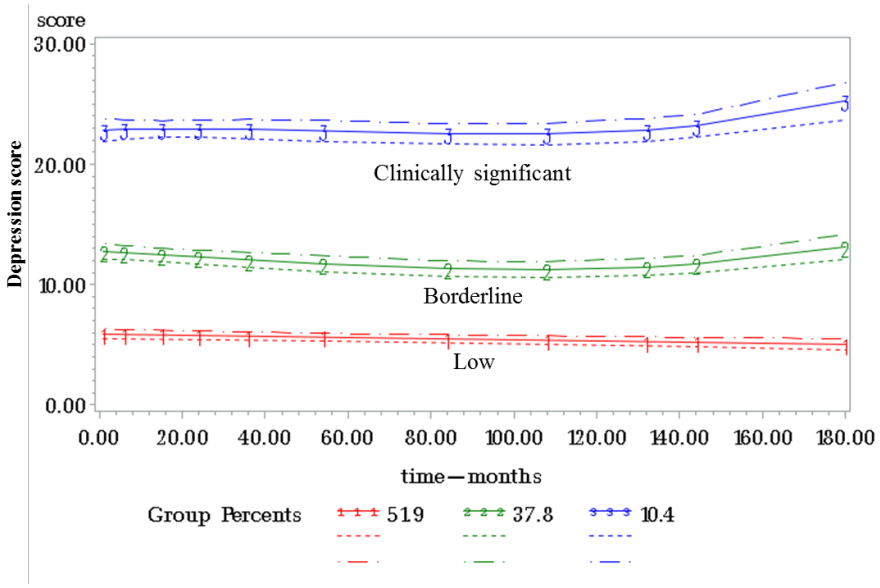
Friendship quality (assessed in 3rd-, 4th-, 5th-, and 6th- grade and at age 15 years):

The Friendship Quality Questionnaire/My Best Friend & Me[8] was completed by the study child at five time-points. The selected model for child friendship quality resulted in four trajectories (one linear, one quadrantic and 2 cubic): (i) stable high friendship quality, (ii) middle and decreasing friendship quality, (iii) middle and increasing friendship quality, and (iv) low but increasing friendship quality (BIC=-4113).

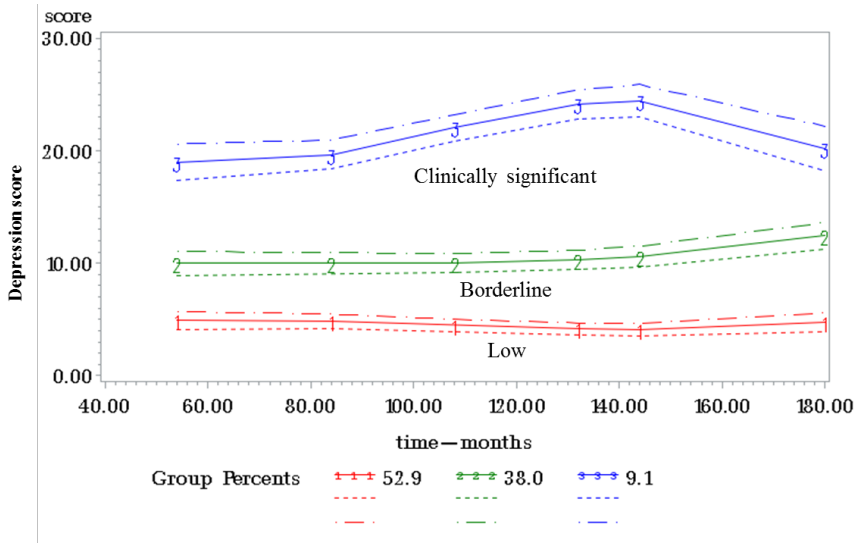


Maternal (assessed at one, six, 15, 24, 36, 54 months, 1st-, 3rd-, 5th-, 6th-grade and at age 15 years) and paternal depression (assessed at 54 months, 1st-, 3rd-, 5th-, 6th-grade and at age 15 years):

The Center for Epidemiologic Studies Depression Scale[9] was completed at eleven time-points by the study child's mother and at six time-points by the study child's father. The selected model for maternal depression resulted in three cubic trajectories: (i) low, (ii) borderline, and (iii) clinically significant depression (BIC=-40507).



The selected model paternal depression resulted in three cubic trajectories: (i) low, (ii) borderline, and (iii) clinically significant paternal depression. (BIC=-14010)



sTable 1. Demographics and bivariate associations with clinical elevation for adjustment problems rated by mother (n=973).

Variable	Total (n=1364) %	Clinical elevation for adjustment problems (n=161) %	No clinical elevation for adjustment problems (n=812) %	*p-value*
Study Child: Female	48.31	54.66	49.14	0.2006
White ethnicity	80.43	79.5	82.02	0.1813
Maternal education				
No high school degree	10.2	12.42	7.14	
High school degree	21.06	27.33	18.84	**0.0004**
Bachelor's degree	54.22	52.8	56.4	
Post-graduate studies	14.53	7.45	17.61	
Father/mother's husband or partner living in the same household	85.48	80.75	88.55	**0.0067**
Income-to-needs ratio	2.3 (1.1-3.7)	2.0 (1.1-3.1)	2.5 (1.5-4.0)	**<0.0001**
Mother-child attachment				
Always secure	49.41	50.34	50.75	
Increasingly secure	19.78	13.61	21.12	0.0807
Increasingly insecure	19.78	24.49	17.56	
Always insecure	11.03	11.56	10.56	
Temperament changes				
Increasingly difficult temperament	8.91	6.88	8.84	
Decreasingly difficult temperament	17.98	21.25	17.55	0.436
No change	73.1	71.88	73.61	
Maternal separation anxiety				
Low	58.14	48.45	63.42	**0.0004**
High	41.86	51.55	36.58	
Maternal sensitivity				
Increasing	3.23	3.73	3.2	
Stable low	4.33	7.45	4.19	**0.0141**
Stable middle	22.51	34.78	25.74	
Stable high	69.94	54.05	66.87	
Paternal sensitivity				
Low	12.24	21.12	13.79	**0.0174**
High	87.76	78.88	86.21	
Relationship Intimacy				
Agree high	58.36	40.99	54.8	**0.0029**
Agree low	16.86	27.33	18.1	

Disagree	24.78	31.68	27.09	
Emotional reactivity				
Low	37.98	27.33	51.72	**<0.0001**
High	62.02	72.67	48.28	
Friendship quality				
High	54.4	44.72	42.49	
Middle decreasing	6.89	11.8	8.5	**0.0143**
Middle increasing	26.98	22.98	34.61	
Low but increasing	11.73	20.5	14.41	
Maternal depression				
Low	52.2	29.19	55.91	
Borderline	37.54	48.45	37.07	**<0.0001**
Clinically significant	10.26	22.36	7.02	
Paternal depression				
Low	65.69	46.56	59.98	
Borderline	27.71	38.51	33.5	**0.0002**
Clinically significant	6.6	14.91	6.53	

Significant p-values are marked in bold ($p<0.05$).

"Clinical elevation for Adjustment problems" is defined as the presence of high (>1 standard deviation above the mean) internalizing and/or externalizing problems measured by the Youth Self-Report scale at age 15.

sTable 2: Correlations between individual life events and clinical elevation for adjustment problems at age 15

	Variable	Study Phase 2 at 54 Months n=1075		Study Phase 3 at 3rd Grade n=1024		Study Phase 3 at 5th Grade n=1011	
		Yes (%)	No (%)	Yes (%)	No (%)	Yes (%)	No (%)
Emotional Aspects of Relationships							
1	Argument or Conflict with Husband /Partner	35.16*I	64.84	31.38*I	68.62	29.5*	70.5
2	Major Change of Emotional Closeness Between Family Members (Increased or Decreased)	23.63*I	76.37	23.88*I	76.12	17.61*	82.39
3	Arguments or Conflicts with In-laws or Other Family Members (Not Including Husband)	19.24	80.76	17.22*I	82.78	14.13*I	85.87
4	Separated from Husband/Partner (Due To Work, Travel, Etc.)	12.09	87.91	8.41I	91.59	6.33	93.67
5	Trouble with In-Laws	11.8	88.2	10.25I	89.75	6.45	93.55
6	Change of Family Situation of Close Relative (e.g., Sister's Divorce or Marriage)	9.94	90.06	9.92*	90.08	6.63	93.37
7	Arguments or Conflicts with Close Friend	8.65*	91.35	7.88*	92.12	7.12*	92.88
8	Broke Up with Boyfriend/Partner	6.41*I	93.59	5.74*	94.26	5.93*	94.07
9	Marital Separation (Due to Conflict)	5.86	94.14	6.26*	93.74	4.45	95.55
10	Gunshots or Violence in Neighborhood	5.76*I	94.24	3.99*I	96.01	2.08	97.92
11	Aftermath of Divorce (e.g., Change in Visiting, Continued Conflict)	5.20	94.8	6.54	93.46	4.85	95.15
12	Marriage	4.09	95.91	3.99	96.01	3.95	96.05
13	Divorce	3.07	96.93	4.00I	96.00	3.56	96.44
14	Marital Reconciliation	2.97*	97.03	1.95	98.05	2.19	97.81
15	Reconciliation with Boyfriend/Partner	2.51*I	97.49	2.24*	97.76	1.98*	98.02
16	Family Violence or Abuse	2.04I	97.96	1.95I	98.05	1.29	98.71
Parent or Family Physical or Mental Health and Well-Being							
17	Had Psychological Counseling or Therapy For Self	11.98	88.02	11.41*I	88.59	12.69*	87.31
18	Took Prescription Drugs for at Least One Month to Help with Mental Problems	6.41*	93.59	11.59*I	88.41	13.55*	86.45
19	Took Non-Prescription Drugs for at Least One Month to Help with Mental Problems	0.56	99.44	2.34	97.66	1.78*	98.22
20	Had Family Psychological Counseling or Therapy For Marital or Family or Child Problems			11.21*	88.79	11.77*	88.23
21	Had Psychological Counseling or Therapy for Study Child			8.19*I	91.81	7.53*I	92.47
22	Study Child Took Prescription Drugs Regularly to Help with Mental Problem(s)			2.91*I	97.09	3.17*	96.83
23	Major Personal Injury or Illness	6.41	93.59	6.68	93.32	9.41*	90.59
	Serious Illness of Grandparent	12.61	87.39	9.56	90.44	8.13	91.87
24	Serious Illness of Mother	8.40*	91.60	8.86	91.14	6.36	93.64
	Serious Illness of Father	7.17	92.83	9.24*	90.76	7.55	92.45

	Serious Illness of Child	6.20	93.80	5.90*	94.10	5.07	94.93
	Serious Illness of Spouse	4.51	95.49	5.30*	94.70	4.66	95.34
	Serious Illness of Sister/Brother	4.41	95.59	4.63	95.37	4.07	95.93
25	Serious Illness or Injury of a Close Friend	5.67	94.33	6.15	93.85	5.84*	94.16
26	Death of Husband/Partner	0.09	99.91	0.39	99.61	0.6	99.4
	Death of Grandparent	10.62	89.38	10.30Ɨ	89.70	6.45	93.55
	Death of Father	2.63	97.37	3.77	96.23	2.78	97.22
	Death of Mother	1.38	98.62	3.16	96.84	1.49	98.51
	Death of Sister/Brother	0.88	99.12	0.99	99.01	1.19	98.81
	Death of Child	0.50	99.50	-	-	0.40	99.60
27	Death of Close Friend	6.41	93.59	6.82*	93.18	5.34	94.66
Family Structure, Routine and Caregiving Change							
28	Child Started School	42.55	57.45	20.96	79.04	12.75	87.25
29	Problem with Child(ren) (e.g., School, Discipline, Etc.)	31.10*	68.9	38.42*Ɨ	61.58	32.74*Ɨ	67.26
30	Major Change in Social Activities, e.g., Parties, Movies, Visiting (Increasing or Decreasing)	25.33*Ɨ	74.67	19.57*	80.43	15.71*	84.29
31	Major Change in Church Activities (Increased or Decreased Attendance)	22.30	77.70	18.19	81.81	14.84*	85.16
32	Change of Residence	22.10*Ɨ	77.90	19.32*	80.68	12.21	87.79
33	Major Change in Usual Type and/or Amount of Recreation	20.52*	79.48	18.99*	81.01	14.94*	85.06
34	Pregnancy	18.14	81.86	10.6	89.4	6.23Ɨ	93.77
35	Gained a New Member of Household (i.e. Family Member or Friend Moved In, Etc.)	17.50	82.50	13.04	86.96	12.27*	87.73
36	Major Change in Living Conditions (Building New Home, Remodeled, Etc.)	16.73	83.27	19.16	80.84	15.91	84.09
37	Birth or Adoption of A Child	11.57	88.43	7.68	92.32	4.15	95.85
38	Change in Mode of Daily Transportation (e.g., Bus Route, Car, Carpool, Etc.)	8.45	91.55	8.66	91.34	6.20	93.80
39	Change in Child Custody Arrangements/Visitations	6.04*Ɨ	93.96	5.93*	94.07	4.35Ɨ	95.65
40	Needed to Care for Aging Family Member	5.58Ɨ	94.42	10.51	89.49	9.50	90.50
41	Had a Miscarriage	3.92	96.08	2.82	97.18	1.19	98.81
42	Had an Abortion	1.30	98.70	1.27	98.73	0.59	99.41
Parental Work, School or Financial Stability							
43	Outstanding Personal Achievement	44.09	55.91	40.23	59.77	32.15	67.85
44	Change in Work Situation (Different Work Responsibility, Working Conditions, Working Hours, Etc.) or New Job	43.77	56.23	39.57	60.43	38.83	61.17
45	Major Change in Financial Status (A Lot Better or A Lot Worse)	35.04*	64.96	35.12	64.88	31.09	68.91
46	Change in Husband's/Partner's Work (Loss Of Job, Beginning New Job, Increased Responsibility, Longer Hours, Etc.)	32.34	67.66	28.85	71.15	25.62	74.38
47	Borrowed Less Than $10,000 (For Car, T.V., School Loan, Etc.)	18.31	81.69	19.49	80.51	16.30	83.70
48	Borrowed More Than $10,000 (For Home, Business, Etc.)	17.49	82.51	22.47	77.53	21.80Ɨ	78.20
49	Return to Work	15.26	84.74	12.45Ɨ	87.55	10.54	89.46

50	Future of Husband's/Partner's Job is Insecure	13.02	86.98	11.61	88.39	14.03	85.97
51	Minor Law Violation (e.g., Traffic Tickets)	11.44	88.56	13.72	86.28	12.25	87.75
52	Returned/Began College, Graduate School Or Professional Training	11.27*	88.73	8.09	91.91	7.82	92.18
53	Stopped Working Outside the Home	9.85	90.15	7.78	92.22	6.62Ɨ	93.38
54	Trouble With Employer (In Danger of Losing Job, Being Suspended, Demoted, Etc.)	5.67	94.33	5.06Ɨ	94.94	5.83*	94.17
55	Fired or Laid Off From Job	4.74	95.26	5.06Ɨ	94.94	5.34Ɨ	94.66
56	Completed Formal Schooling	4.18	95.82	3.99	96.01	2.96	97.04
57	Husband/Partner Detained In Jail For Law Violation	1.95	98.05	2.33*	97.67	1.88*	98.12
58	Foreclosure on Mortgage Loan	0.56	99.44	1.07*	98.93	1.28	98.72

Significantly associated with clinical elevation for adjustment problems rated by Mother* and/or self-report Ɨ on a bi-variate analysis ($p<0.05$)

"Clinical elevation for Adjustment problems" is defined as the presence of high (>1 standard deviation above the mean) internalizing and/or externalizing problems measured by the Youth Self-Report scale at age 15.

sTable 3. Variables associated with clinical elevation for clinical elevation for adjustment problems at age 15, rated by mother.

		Mother report	
Variable	**OR**	**95% CI**	***p-value***
Model 1.			
Total number of stressful life events (continuous variable, odds per additional stressful life event)	1.05	(1.03-1.06)	**<.0001**
Gender: Male vs. female	1.57	(1.03-2.39)	0.0375
Maternal education level			
High school vs. graduate studies	3.49	(1.7-7.17)	**0.0003**
Bachelor's vs. graduate studies	2.09	(1.05-4.16)	0.6122
Individual-level factors			
Emotional Reactivity: High vs. low	2.41	(1.59-3.64)	**<.0001**
Friendship quality			
High vs. low but increasing	0.56	(0.32-0.98)	0.3166
Middle decreasing vs. low but increasing	0.83	(0.41-1.68)	0.3021
Middle increasing vs. low but increasing	0.40	(0.22-0.73)	**0.0054**
Family-level factors			
Attachment			
Always insecure vs always secure	0.92	(0.49-1.73)	0.8974
Became insecure vs. always secure	1.37	(0.84-2.22)	0.049
Became secure vs. always secure	0.65	(0.37-1.14)	0.073
Paternal depression			
Clinically significant vs. low	2.00	(1.09-3.68)	0.0313
Borderline vs. low	1.12	(0.74-1.7)	0.2925
Model 2.			
Stressful life events timing/chronicity			
Once vs. never	2.41	(1.52-3.8)	0.3055
Always vs. never	3.69	(1.79-7.62)	0.4126
Early vs. never	4.74	(1.98-11.32)	0.1606
Late vs. never	4.95	(2.34-10.48)	0.0744
Gender: Male vs. female	1.68	(1.08-2.6)	**0.0203**
Maternal education level			
High school vs. graduate studies	4.01	(1.89-8.54)	**0.0002**
Bachelor's vs. graduate studies	2.32	(1.13-4.78)	0.5380
Individual-level factors			
Temperament change			
Increasingly difficult vs. no change	1.50	(0.9-2.48)	0.0087
Decreasingly difficult vs. no change	0.43	(0.18-1)	**0.0159**
Emotional Reactivity: High vs. low	2.50	(1.63-3.83)	**<.0001**
Friendship quality			
High vs. low but increasing	0.65	(0.36-1.17)	0.4895
Middle decreasing vs. low but increasing	0.93	(0.44-1.96)	0.2904

Middle increasing vs. low but increasing	0.46	(0.24-0.86)	**0.0119**
Family-level factors			
Attachment			
Always insecure vs. always secure	1.07	(0.56-2.03)	0.7807
Became insecure vs. always secure	1.53	(0.92-2.55)	0.0264
Became secure vs. always secure	0.61	(0.33-1.1)	0.0265
Paternal depression			
Clinically significant vs. low	1.84	(0.96-3.51)	0.0689
Borderline vs. low	1.08	(0.7-1.67)	0.3277
Model 3.			
Stressful life events categories (high total scores)			
Health and wellbeing	1.91	(1.27-2.88)	**0.0019**
Work/school/finances	1.02	(0.65-1.6)	0.9285
Emotional aspects	1.73	(1.11-2.7)	0.0157
Change in family structure	1.41	(0.91-2.16)	0.1232
Gender: Male vs. female	1.64	(1.07-2.5)	0.0235
Maternal education level			
High school vs. graduate studies	3.72	(1.8-7.68)	**0.0002**
Bachelor's vs. graduate studies	2.11	(1.06-4.2)	0.6937
Individual-level factors			
Emotional reactivity: High vs. low	2.41	(1.59-3.65)	**<.0001**
Friendship quality			
High vs. low but increasing	0.62	(0.35-1.09)	0.5977
Middle decreasing vs. low but increasing	0.85	(0.41-1.76)	0.3287
Middle increasing vs. low but increasing	0.39	(0.21-0.72)	**0.0027**
Family-level factors			
Attachment			
Always insecure vs. always secure	1.03	(0.55-1.94)	0.8844
Became insecure vs. always secure	1.43	(0.87-2.33)	0.0562
Became secure vs. always secure	0.68	(0.38-1.19)	0.0686
Paternal depression			
Clinically significant vs. low	2.11	(1.14-3.89)	0.021
Borderline vs. low	1.12	(0.73-1.71)	0.2475

4. References

1. Jones BL, Nagin DS, Roeder K. A SAS Procedure Based on Mixture Models for Estimating Developmental Trajectories. *Sociol Methods Res*. 2001;29(3):374-393. doi:10.1177/0049124101029003005.

2. Nagin DS. Analyzing developmental trajectories: A semiparametric, group-based approach. *Psychol Methods*. 1999;4(2):139-157. doi:10.1037/1082-989X.4.2.139.

3. Hock E, Schirtzinger M b. Maternal separation anxiety: Its developmental course and relation to maternal mental health. *Child Dev*. 1992;63(1):93. doi:10.1111/1467-8624.ep9203091728.

4. Egeland B, Hiester M. *Teaching Task Rating Scales*. Institute of Child Development, University of Virginia; 1993.

5. Schaefer MT, Olson DH. Assessing Intimacy: The Pair Inventory*. *J Marital Fam Ther*. 1981;7(1):47-60. doi:10.1111/j.1752-0606.1981.tb01351.x.

6. Eisenberg N, Fabes RA, Bernzweig J, Karbon M, Poulin R, Hanish L. The Relations of Emotionality and Regulation to Preschoolers' Social Skills and Sociometric Status. *Child Dev*. 1993;64(5):1418-1438. doi:10.1111/j.1467-8624.1993.tb02961.x.

7. Shields A, Cicchetti D. Emotion regulation among school-age children: the development and validation of a new criterion Q-sort scale. *Dev Psychol*. 1997;33(6):906-916.

8. Baker JR, Hudson JL. Friendship quality predicts treatment outcome in children with anxiety disorders. *Behav Res Ther*. 2013;51(1):31-36. doi:10.1016/j.brat.2012.10.005.

9. Lewinsohn PM, Seeley JR, Roberts RE, Allen NB. Center for Epidemiologic Studies Depression Scale (CES-D) as a screening instrument for depression among community-residing older adults. *Psychol Aging*. 1997;12(2):277-287.

Appendix C

Study III

Locher, C., Koechlin, H., Zion, S. R., Werner, C., Pine, D. S., Kirsch, I., Kessler, R. C., & Kossowsky, J. (2017). Efficacy and safety of selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, and placebo for common psychiatric disorders among children and adolescents: A systematic review and meta-analysis. *JAMA Psychiatry, 74*(10), 1011–1020. doi: 10.1001/jamapsychiatry.2017.2432

JAMA Psychiatry | Original Investigation

Efficacy and Safety of Selective Serotonin Reuptake Inhibitors, Serotonin-Norepinephrine Reuptake Inhibitors, and Placebo for Common Psychiatric Disorders Among Children and Adolescents

A Systematic Review and Meta-analysis

Cosima Locher, PhD; Helen Koechlin, MSc; Sean R. Zion, MA; Christoph Werner, BSc; Daniel S. Pine, MD; Irving Kirsch, PhD; Ronald C. Kessler, PhD; Joe Kossowsky, PhD, MMSc

IMPORTANCE Depressive disorders (DDs), anxiety disorders (ADs), obsessive-compulsive disorder (OCD), and posttraumatic stress disorder (PTSD) are common mental disorders in children and adolescents.

OBJECTIVE To examine the relative efficacy and safety of selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and placebo for the treatment of DD, AD, OCD, and PTSD in children and adolescents.

DATA SOURCES PubMed, EMBASE, PsycINFO, Web of Science, and Cochrane Database from inception through August 7, 2016.

STUDY SELECTION Published and unpublished randomized clinical trials of SSRIs or SNRIs in youths with DD, AD, OCD, or PTSD were included. Trials using other antidepressants (eg, tricyclic antidepressants, monoamine oxidase inhibitors) were excluded.

DATA EXTRACTION AND SYNTHESIS Effect sizes, calculated as standardized mean differences (Hedges *g*) and risk ratios (RRs) for adverse events, were assessed in a random-effects model.

MAIN OUTCOMES AND MEASURES Primary outcomes, as defined by authors on preintervention and postintervention data, mean change data, and adverse event data, were extracted independently by multiple observers following PRISMA guidelines.

RESULTS Thirty-six trials were eligible, including 6778 participants (3484 [51.4%] female; mean [SD] age, 12.9 [5.1] years); 17 studies for DD, 10 for AD, 8 for OCD, and 1 for PTSD. Analysis showed that SSRIs and SNRIs were significantly more beneficial compared with placebo, yielding a small effect size (g = 0.32; 95% CI, 0.25-0.40; P < .001). Anxiety disorder (g = 0.56; 95% CI, 0.40-0.72; P < .001) showed significantly larger between-group effect sizes than DD (g = 0.20; 95% CI, 0.13-0.27; P < .001). This difference was driven primarily by the placebo response: patients with DD exhibited significantly larger placebo responses (g = 1.57; 95% CI, 1.36-1.78; P < .001) compared with those with AD (g = 1.03; 95% CI, 0.84-1.21; P < .001). The SSRIs produced a relatively large effect size for ADs (g = 0.71; 95% CI, 0.45-0.97; P < .001). Compared with participants receiving placebo, patients receiving an antidepressant reported significantly more treatment-emergent adverse events (RR, 1.07; 95% CI, 1.01-1.12; P = .01 or RR, 1.49; 95% CI, 1.22-1.82; P < .001, depending on the reporting method), severe adverse events (RR, 1.76; 95% CI, 1.34-2.32; P < .001), and study discontinuation due to adverse events (RR, 1.79; 95% CI, 1.38-2.32; P < .001).

CONCLUSIONS AND RELEVANCE Compared with placebo, SSRIs and SNRIs are more beneficial than placebo in children and adolescents; however, the benefit is small and disorder specific, yielding a larger drug-placebo difference for AD than for other conditions. Response to placebo is large, especially in DD. Severe adverse events are significantly more common with SSRIs and SNRIs than placebo.

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Editorial
Supplemental content

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Depressive disorders (DDs), anxiety disorders (ADs), obsessive-compulsive disorder (OCD), and posttraumatic stress disorder (PTSD) are among the most common mental disorders in children and adolescents.[1] They are major public health concerns and predict long-term risk for various adverse outcomes.[2] Thus, early diagnosis and proper treatment is of critical importance. Selective serotonin reuptake inhibitors (SSRIs) are first-line pharmaceutical treatments for these disorders, whereas serotonin-norepinephrine reuptake inhibitors (SNRIs) are considered second- or third-line treatments, given the limited available trial data to support their use.[3] This meta-analysis compares the differential efficacy of these drugs across the disorders for which they are primarily prescribed in a pediatric population and also assesses differences in response to placebo and in adverse events.

Since the release of fluoxetine hydrochloride in the mid-1980s, the number of SSRIs and SNRIs has grown substantially. However, their use in children and adolescents is still debated, thus indicating a need for more research into their safety and efficacy and the comparative efficacy of the newer SNRIs vs SSRIs.[4] Recent meta-analyses generate many questions about the overall benefits vs costs of using SSRIs to treat major depression in children and adolescents.[5] The small amount of research on SNRIs for pediatric DD has had mixed results.[3] One meta-analysis on pediatric depression found that, although SSRIs differed significantly from placebo, SNRIs and tricyclic antidepressants did not.[6]

Although most prior reviews and meta-analyses of the effects of SSRIs and SNRIs focused on pediatric DD, considerable data also exist on pediatric AD and OCD. The latter studies suggest that most SSRIs have a favorable risk-benefit ratio, whereas there are insufficient data for the remaining SSRIs.[3] There have been relatively few studies on SNRIs for pediatric AD, despite the fact that the only US Food and Drug Administration (FDA)–approved agent for pediatric AD, duloxetine hydrochloride, is an SNRI. To our knowledge, no double-blind, randomized clinical trials of SNRIs for pediatric OCD had been conducted as of 2016, and limited data have been reported for SSRIs and SNRIs in pediatric PTSD.[7]

Research on safety and tolerability indicates a high risk of developing treatment-emergent adverse events (TEAEs)—most prominently headache and nausea—during treatment with an antidepressant in pediatric DD.[6] Severe adverse events (SAEs), such as an increased risk of suicidal thoughts and behavior, in adults and youth receiving antidepressants have also been reported,[8] leading to the implementation of a boxed warning on the labels of all antidepressants for pediatric use by the FDA in 2004, although adoption of the warning remains controversial.[9] In addition, to date no recent meta-analyses have focused on how pediatric adverse effect profiles of SSRIs, SNRIs, and placebo might differ across disorders.

Finally, there is a growing body of literature concerning the role of placebo effects in studies of SSRIs and SNRIs, based on large placebo responses in studies of antidepressants in both adult and pediatric samples.[10] Factors such as contact with research staff may lead to large placebo response rates in pediatric DD[11] and may explain much of the variability in pediatric antidepressant trials.[12] For adults with DD, a genuine placebo effect has been demonstrated, as the combination of placebo and supportive care has been shown to be more beneficial than supportive care alone.[13] Conversely, patients in the placebo group also demonstrate TEAEs.[6] However, how response to placebo differs across disorders or other study design features in pediatrics remains understudied.

To our knowledge, only 1 other review or meta-analysis has examined the use of SSRIs and SNRIs across pediatric DD, AD, OCD, and PTSD.[14] However, that earlier study is now a decade old and predates 11 primary studies (n = 2068) that fulfill our inclusion criteria. The earlier review also did not include any studies on duloxetine, which is currently the only medication approved for pediatric AD. We therefore conducted an updated and extended review to assess the efficacy and safety of these drugs for treatment of DD, AD, OCD, and PTSD, along with between-disorder variation in drug and placebo responses. Psychological therapies are not part of this meta-analysis. However, a more recent review has compared psychological therapies alone and in combination with antidepressant medication for depression in children and adolescents.[15]

Key Points

Question Is there a scientific justification to prescribe selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors for children and adolescents, based on what is known about their efficacy and safety?

Findings In a systematic review and meta-analysis including 36 trials (6778 participants), selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors were significantly more beneficial compared with placebo in treating common pediatric psychiatric disorders, yet also led to significantly more treatment-emergent and severe adverse events, such as suicide ideation and suicide attempts, as well as study discontinuation due to adverse events. The magnitude of the effect and adverse event profiles were disorder dependent.

Meaning There is some evidence for the benefit of selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors in children and adolescents, but owing to the higher risk for severe adverse events, a cautious and individual cost-benefit analysis is of importance.

Methods

Search Strategy and Study Selection

The study was conducted in accordance with the PRISMA statement.[16,17] We searched PubMed, EMBASE, PsycInfo, Cochrane, and Web of Science from inception until August 7, 2016; clinicaltrials.gov; and fda.gov and checked references of the included studies as well as previous reviews. Additional information on search terms is presented in the eAppendix 1 in the Supplement. In total, this search returned 4899 articles (eFigure 1 in the Supplement). The screening and selection process was conducted independently by 3 of us (C.L., H.K., and S.R.Z.). We included randomized, double-blind, placebo-controlled trials of SSRIs and SNRIs in children and adolescents younger than 18 years, including studies that examined

drug vs placebo, both in the context of a psychosocial intervention, in which case the combination group was extracted only if no comparison of drug and placebo alone was given. Participants were required to have a diagnosis of a DD, AD, OCD, or PTSD, based on *DSM-III*, *DSM-III-R*, or *DSM-IV-TR* criteria. Comorbidity was allowed, and information about comorbid disorders was extracted.

Case reports, comments, letters, gray literature, and reviews were excluded. Non-second-generation antidepressants (eg, monoamine oxidase inhibitors, tricyclic antidepressants) were also excluded.[18] Boston Children's Hospital provided approval for the study.

Methodologic Quality Assessment

Two of us (C.L. and S.R.Z.) independently rated the quality of included studies based on the Cochrane Risk of Bias Assessment Tool,[19] with final quality ratings based on consensus. Risk of bias was assessed in individual studies (eTable 1 in the Supplement) and across studies (eFigure 2 in the Supplement).

Outcome Measures and Data Extraction

The primary outcome as defined by authors was chosen as the sole outcome measure for each study. Preintervention and postintervention data or mean change data had to be available. Outcomes had to be reported on a well-validated, disorder-specific scale (eg, Children's Depression Rating Scale-Revised, Multidimensional Anxiety Scale for Children, and Children's Yale-Brown Obsessive Compulsive Scale) or on a general severity scale (ie, Clinical Global Impression-Severity Scale). We included only continuous outcome data, since dichotomizing continuous scores into categorical outcome data leads to a loss of information, reduces power, and creates an artificial boundary.[20,21] We did not extract data from improvement scales, such as the Clinical Global Impression-Global Improvement Scale. Repeated attempts were made to contact the authors of studies with incomplete or insufficient data. Two studies[22,23] did not include SDs or SEs, and they were imputed by way of the leaving-1-out method.[24]

Data were extracted independently by 3 of us (C.L., H.K., and S.R.Z.). Discrepancies were resolved by consensus. Extracted data included demographic information, dropout rates, adverse events, safety information, and baseline and end point assessment points. Data from open-label extensions or follow-up after the predesignated end point were not extracted.

Statistical Analysis

Three effect sizes were calculated for each included study. First, drug-placebo difference response was assessed as the difference in mean change scores between the antidepressants and placebo. The drug and placebo responses were assessed as the mean change scores of preanalyses vs postanalyses in the drug and placebo groups, respectively. Effect sizes were calculated as Hedges *g*.[25] We chose to use random-effects models rather than fixed-effects models because the studies that we included were heterogeneous and the number of studies for the subanalyses were relatively small.[26] Heterogeneity was assessed by calculating the *Q* statistic,[27] the τ^2, and the I^2, a transformation of *Q* that indicates the proportion of observed variance that can be attributed to heterogeneity rather than sampling error.[28] The τ^2 offers an estimate of the variance among true effect sizes.[29] Effect size differences between subgroups were analyzed using a mixed-effects model.[30] Publication bias was assessed visually by means of funnel plots[31] and formally by means of the fail-safe N[32] and the Begg adjusted-rank correlation test.[33] We estimated the sensitivity of publication bias, using the trim-and-fill method.[34]

Moderator analyses were conducted for 6 continuous moderators (treatment duration, publication year, illness duration, age of onset, number of sites, and baseline severity) and 4 categorical moderators (placebo lead-in, comorbidity, region, and primary funding source). Details of the applied statistical approaches are provided in eAppendix 2 in the Supplement.

To evaluate the risk of adverse events in the antidepressant and placebo groups, risk ratios (RRs) for TEAEs, SAEs, and study discontinuation due to adverse events across trials were calculated in a random-effects model. The RRs of SAEs were based on the percentage of patients with SAEs. Regarding RRs of TEAEs, 2 commonly used reporting methods were compared: percentage of patients with TEAEs in each group and mean number of TEAEs per patient across all reported symptoms. Comprehensive Meta-Analysis, version 3 (Biostat) and R, version 3.2.1 (R Foundation) were used for calculations and analyses.

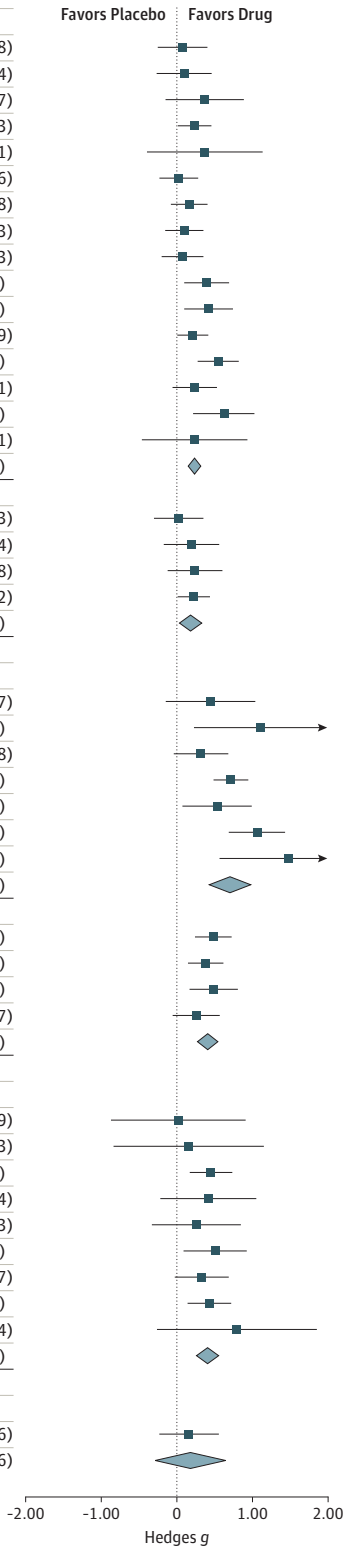
Results

Our search identified 35 published and 1 unpublished randomized, double-blind trials[7,22,23,35-67] including 6778 participants (3484 [51.4%] female; mean [SD] age, 12.9 [5.1] years) that compared an SSRI or an SNRI against placebo in patients younger than 18 years with a diagnosis of AD (n = 10), DD (n = 17), OCD (n = 8), or PTSD (n = 1) (eFigure 1 in the Supplement). One study reported 2 trials that were treated independently for analyses[55] and another compared a drug plus psychosocial intervention group vs a placebo plus psychosocial intervention group and was therefore excluded from the drug and placebo response analyses.[59] Characteristics of the 36 included trials are presented in eTable 1 in the Supplement, and details regarding heterogeneity and publication bias can be found in the eTable 2, eAppendix 3, eFigure 2, and eFigure 3 in the Supplement.

The combined analysis between groups across all disorders yielded a small drug-placebo difference ($g = 0.32$; 95% CI, 0.25 to 0.40; $P < .001$). In the between-group analysis stratified by disorder, AD ($g = 0.56$; 95% CI, 0.40 to 0.72; $P < .001$) and OCD ($g = 0.39$; 95% CI, 0.25 to 0.54; $P < .001$) did not differ significantly from each other ($P = .14$), but both yielded significantly higher (AD vs DD: $P < .001$ and OCD vs DD: $P = .02$) drug-placebo differences than the DD group ($g = 0.20$; 95% CI, 0.13 to 0.27; $P < .001$) (**Figure 1**). Excluding the unpublished study in the DD group[47] led to a negligible change in effect size. Between-drug analysis yielded the smallest effect sizes for citalopram ($g = 0.18$; 95% CI, −0.18 to 0.54; $P = .33$) and escitalopram ($g = 0.18$; 95% CI, 0.01 to 0.34; $P = .03$) and the largest effect size for fluvoxamine ($g = 0.68$; 95% CI, −0.05 to 1.41; $P = .07$). However, owing to the

Figure 1. Between-Group Analyses Stratified by Disorder

Source	Hedges *g*	SE (95% CI)
Depressive disorders		
SSRI		
Atkinson et al,[48] 2014	0.05	0.17 (−0.27 to 0.38)
Emslie et al,[49] 2014	0.07	0.19 (−0.29 to 0.44)
PIR112487,[47] 2011	0.34	0.27 (−0.18 to 0.87)
Emslie et al,[45] 2009	0.21	0.11 (−0.01 to 0.43)
Findling et al,[46] 2009	0.35	0.39 (−0.42 to 1.11)
von Knorring et al,[43] 2006	0.00	0.13 (−0.25 to 0.26)
Wagner et al,[23] 2006	0.14	0.12 (−0.10 to 0.38)
Berard et al,[41] 2006	0.08	0.13 (−0.18 to 0.33)
Emslie et al,[42] 2006	0.05	0.14 (−0.22 to 0.33)
Wagner et al,[22] 2004	0.37	0.15 (0.07 to 0.67)
March et al,[40] 2004	0.40	0.17 (0.07 to 0.72)
Wagner et al,[39] 2003	0.19	0.11 (−0.02 to 0.39)
Emslie et al,[38] 2002	0.52	0.14 (0.25 to 0.80)
Keller et al,[37] 2001	0.21	0.15 (−0.08 to 0.51)
Emslie et al,[36] 1997	0.60	0.21 (0.19 to 1.00)
Simeon et al,[35] 1990	0.21	0.36 (−0.49 to 0.91)
Subtotal	0.21	0.04 (0.13 to 0.29)
SNRI		
Atkinson et al,[48] 2014	0.00	0.17 (−0.33 to 0.33)
Emslie et al,[49] 2014[a]	0.17	0.19 (−0.20 to 0.54)
Emslie et al,[49] 2014[a]	0.22	0.19 (−0.15 to 0.58)
Emslie et al,[44] 2007	0.20	0.11 (−0.02 to 0.42)
Subtotal	0.16	0.08 (0.01 to 0.31)
Anxiety disorders		
SSRI		
Melvin et al,[59] 2017	0.47	0.31 (−0.14 to 1.07)
da Costa et al,[57] 2013	1.11	0.45 (0.23 to 2.00)
Walkup et al,[56] 2008	0.32	0.18 (−0.04 to 0.68)
Wagner et al,[53] 2004	0.72	0.18 (0.49 to 0.95)
Birmaher et al,[52] 2003	0.53	0.23 (0.08 to 0.99)
RUPP,[50] 2001	1.06	0.19 (0.69 to 1.43)
Rynn et al,[51] 2001	1.48	0.47 (0.56 to 2.39)
Subtotal	0.71	0.13 (0.45 to 0.97)
SNRI		
Strawn et al,[58] 2015	0.48	0.12 (0.24 to 0.73)
March et al,[54] 2007	0.38	0.12 (0.15 to 0.62)
Rynn et al,[55] 2007[b]	0.49	0.16 (0.17 to 0.81)
Rynn et al,[55] 2007[b]	0.26	0.16 (−0.05 to 0.57)
Subtotal	0.41	0.07 (0.27 to 0.54)
Obsessive-compulsive disorder		
SSRI		
Storch et al,[67] 2013[c]	0.00	0.45 (−0.89 to 0.89)
Storch et al,[67] 2013[c]	0.14	0.51 (−0.85 to 1.13)
Geller et al,[66] 2004	0.44	0.14 (0.15 to 0.72)
POTS,[65] 2004	0.40	0.32 (−0.24 to 1.04)
Liebowitz et al,[64] 2002	0.24	0.30 (−0.35 to 0.83)
Geller et al,[62] 2001	0.49	0.21 (0.07 to 0.91)
Riddle et al,[63] 2001	0.31	0.18 (−0.04 to 0.67)
March et al,[61] 1998	0.42	0.15 (0.13 to 0.70)
Riddle et al,[60] 1992	0.78	0.54 (−0.28 to 1.84)
Subtotal	0.39	0.08 (0.25 to 0.54)
Posttraumatic stress disorder		
SSRI		
Robb et al,[7] 2010	0.16	0.20 (−0.23 to 0.56)
Subtotal	0.16	0.20 (−0.23 to 0.56)



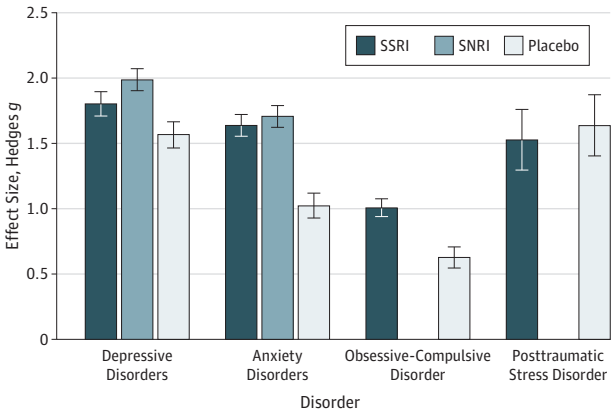
Because there was only 1 study, posttraumatic stress disorder was not included in the overall analysis. POTS indicates Pediatric OCD Treatment Study; RUPP, Research Unit on Pediatric Psychopharmacology Anxiety Study Group; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

[a] One study reported 2 different dosages of duloxetine.

[b] One study reported 2 trials that were treated independently for analyses.

[c] One study examined 2 forms of dosing. One treatment arm was sertraline at standard dosing and the second treatment arm was sertraline titrated slowly.

Figure 2. Drug and Placebo Effect Size by Disorder Category



Because there was only 1 study, posttraumatic stress disorder (PTSD) was not included in subgroup analyses. Responses to selective serotonin reuptake inhibitors (SSRIs) were significantly larger in depressive disorders (DDs) and anxiety disorders (ADs) compared with obsessive-compulsive disorder (OCD) (both $P < .001$). The placebo response was significantly larger in DDs compared with ADs ($P < .001$) and OCD ($P < .001$) and significantly larger in ADs compared with OCD ($P < .002$). SNRI indicates serotonin-norepinephrine reuptake inhibitor.

small number of studies and large 95% CI, the effect size for fluvoxamine was not significant.

In the between-group analysis stratified by drug category, SSRIs and SNRIs did not differ significantly in the DD group ($Q = 0.43_1$; $P = .51$), but SSRIs were significantly better than SNRIs in the AD group ($Q = 4.16_1$; $P = .04$). No studies investigated the use of SNRIs in OCD.

The within-drug group analysis stratified by disorder yielded no significant difference ($P = .07$) between studies of AD ($g = 1.68$; CI, 1.56-1.79; $P < .001$) and DD ($g = 1.85$; 95% CI, 1.7-2.0; $P < .001$), yet both yielded significantly larger drug responses ($P < .001$) than studies of OCD ($g = 1.01$; 95% CI, 0.88-1.14; $P < .001$). When stratified by drug, duloxetine yielded the largest response ($g = 1.95$; 95% CI, 1.73-2.18; $P < .001$) and fluvoxamine the smallest response ($g = 1.22$; 95% CI, 0.41-2.02; $P = .003$); however, the difference between those 2 drugs was not significant ($Q = 3.02_1$; $P = .08$). The combined analysis across all disorders for the within-group analysis yielded a drug response of $g = 1.65$ (95% CI, 1.52-1.78; $P < .001$). The SSRIs and SNRIs did not differ significantly in both the DD group ($Q = 2.35_1$; $P = .13$) and the AD group ($Q = 0.34_1$; $P = .56$).

The within-placebo group analysis stratified by disorder yielded a large placebo response for studies of DD ($g = 1.57$; 95% CI, 1.36-1.78; $P < .001$), which was significantly larger ($P < .001$) than the placebo response in studies of AD ($g = 1.03$; 95% CI, 0.84-1.21; $P < .001$). The moderate placebo response in the OCD group ($g = 0.63$; 95% CI, 0.47-0.79; $P < .001$) was significantly lower than in both the DD ($P < .001$) and AD ($P = .002$) groups (**Figure 2**). The combined analysis across all disorders for the within-group analysis yielded a placebo response size of $g = 1.23$ (95% CI, 1.06-1.39; $P < .001$).

Adverse Event Analysis

Twenty-six trials reported the percentage of patients with TEAEs (reporting method 1), 26 trials reported the mean number of TEAEs per patient across symptoms (reporting method 2), and 15 trials reported both reporting methods. The 2 reporting methods differed significantly (across all 52 trials: $P = .002$; within the 15 studies reporting both reporting methods: $P = .045$), indicating higher RRs with reporting method 2. Patients taking an antidepressant reported significantly more TEAEs (reporting method 1: RR, 1.07; 95% CI, 1.01-1.12; $P = .01$; reporting method 2: RR, 1.49; 95% CI, 1.22-1.82; $P < .001$) and SAEs (RR, 1.76; 95% CI, 1.34-2.32; $P < .001$) compared with placebo. No significant differences in TEAEs or SAEs were found between SSRIs and SNRIs. The RRs for TEAEs stratified by drug and disorder are displayed in **Table 1**. Discontinuation of treatment due to adverse events was significantly more common in the antidepressant group compared with the placebo group (RR, 1.79; 95% CI, 1.38-2.32; $P < .001$). The RRs for study discontinuation and SAEs stratified by drug and disorder are summarized in **Table 2**. Mean rates of TEAEs, SAEs, and study discontinuation can be found in eTable 3 in the Supplement.

Moderator Analysis

Univariate analyses indicated larger effect sizes as a function for earlier trials, fewer sites, longer illness duration, and nonindustry funding. However, none of the moderators was found to be significant in a multivariate meta-regression (eAppendix 3 and eTables 4-6 in the Supplement).

Discussion

Our meta-analysis addresses the response and safety profile of SNRIs, SSRIs, and placebo in pediatric DD, AD, OCD, and PTSD. Results indicate that SSRIs and SNRIs are more beneficial than placebo in treating these commonly diagnosed conditions in children and adolescents. However, the overall drug-placebo difference is small and varies significantly by disorder, with a larger response in AD than DD, especially for SSRIs ($g = 0.71$; 95% CI, 0.45-0.97; $P < .001$). This difference in drug-placebo difference response is mainly due to a higher placebo response in pediatric DD. Furthermore, patients with OCD exhibit a significantly smaller response to both drug treatment and placebo treatment compared with AD and DD.

The small effect size between SSRIs and SNRIs vs placebo in pediatric DD might be owing to the lack of a clear depression phenotype. This was apparent in *DSM-5* field trials on major depressive disorder (MDD), which found a low test-retest reliability ($\kappa = 0.28$) for children, adolescents, and adults.[68] Furthermore, there is high comorbidity between pediatric DD and other disorders, especially AD. A recent review on the use of SSRIs and SNRIs in pediatric populations reported that approximately 25% of patients with MDD had a comorbid AD.[3] In our meta-analysis, although not all included studies reported comorbidity rates, those doing so reported comorbidity rates in AD ranging between 6% and 56% in patients with DD. Yet, attempts by the *DSM-5* work group to create a "mixed anxiety and depression disorder" resulted in an unaccept-

Table 1. Risk Ratios of TEAEs[a]

Disorder and Intervention	Reporting Method 1[b] No. of Trials	RR (95% CI)	*P* Value	Reporting Method 2[c] No. of Trials	RR (95% CI)	*P* Value
Overall						
SSRI vs placebo	19	1.07 (1.02-1.13)	.006	24	1.52 (1.22-1.88)	<.001
SNRI vs placebo	7	1.07 (0.94-1.22)	.33	2	1.56 (0.48-5.04)	.46
Stratified by Disorder						
DDs						
SSRI vs placebo	11	1.06 (0.98-1.14)	.13	11	1.46 (1.03-2.07)	.03
SNRI vs placebo	4	1.12 (0.84-1.50)	.44			
Combined vs placebo	15	1.06 (0.98-1.15)	.13			
ADs						
SSRI vs placebo	3	1.23 (0.86-1.76)	.25	4	1.39 (0.85-2.26)	.19
SNRI vs placebo	3	1.06 (0.90-1.24)	.49	2	1.56 (0.48-5.04)	.46
Combined vs placebo	6	1.08 (0.97-1.21)	.16	6	1.40 (0.93-2.12)	.11
OCD						
SSRI vs placebo	4	1.08 (0.96-1.21)	.19	8	1.89 (1.23-2.88)	.003
SNRI vs placebo						
PTSD						
SSRI vs placebo	1	1.00 (0.83-1.22)	.97	1	1.28 (0.42-3.88)	.67
SNRI vs placebos						

Abbreviations: ADs, anxiety disorders; DDs, depressive disorders; OCD, obsessive-compulsive disorder; PTSD, posttraumatic stress disorder; RR, risk ratio; SNRI, serotonin-norepinephrine reuptake inhibitors SSRI, selective serotonin reuptake inhibitor; TEAEs, treatment-emergent adverse events.

[a] Empty cells indicate that no data were available to compute any scores.

[b] Percentage of patients reporting TEAEs.

[c] Mean number of TEAEs per patient across all reported symptoms.

Table 2. Risk Ratios of Study Discontinuation Due to Adverse Effects and SAEs[a]

Disorder and Intervention	Discontinuation[b] No. of Trials	RR (95% CI)	*P* Value	SAE[c] No. of Trials	RR (95% CI)	*P* Value
Overall						
SSRI vs placebo	27	1.84 (1.38-2.44)	<.001	17	1.71 (1.22-2.40)	.002
SNRI vs placebo	6	1.56 (0.83-2.94)	.17	7	2.10 (1.19-3.69)	.01
Stratified by Disorder						
DDs						
SSRI vs placebo	14	1.40 (0.99-1.98)	.06	11	1.72 (1.12-2.63)	.01
SNRI vs placebo	3	2.95 (1.61-5.40)	<.001	3	4.43 (1.73-11.32)	.002
Combined vs placebo	17	1.66 (1.20-2.28)	.002	14	1.99 (1.33-2.97)	.001
ADs						
SSRI vs placebo	5	3.45 (1.34-8.86)	.01	2	2.22 (0.45-10.87)	.33
SNRI vs placebo	3	0.78 (0.39-1.56)	.48	4	1.37 (0.67-2.78)	.39
Combined vs placebo	8	1.38 (0.73-2.60)	.33	6	1.48 (0.77-2.83)	.24
OCD						
SSRI vs placebo	7	3.59 (1.89-6.84)	<.001	3	1.35 (0.47-3.92)	.58
SNRI vs placebo						
PTSD						
SSRI vs placebo	1	2.31 (0.47-11.49)	.31	1	13.90 (0.81-238.36)	.07
SNRI vs placebo						

Abbreviations: ADs, anxiety disorders; DDs, depressive disorders; OCD, obsessive-compulsive disorder; PTSD, posttraumatic stress disorder; RR, risk ratio; SAEs, severe adverse events; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

[a] Empty cells indicate that no data were available to compute any scores.

[b] Percentage of patients who discontinued the study owing to adverse events.

[c] Percentage of patients reporting SAEs.

able rate of test-retest reliability (κ = −0.004) when tested in the *DSM-5* field trials.[68]

Although it appears that the response to placebo is robust in pediatric DD, children and adolescents with ADs, who

respond to pharmacologic treatment to the same degree as those with DD, do not appear to exhibit such a robust placebo response. While in line with older reviews in children,[69] this finding is in contrast to adult studies that found no significant differences in placebo effect size between depression and anxiety.[70] This contrast is not unique: placebo responses between children and adults differ significantly for binary outcomes across a wide variety of diseases.[71] One explanation might be that children and adolescents with major DD may be more demoralized than patients with AD and are therefore more sensitive to changes in hope and favorable meanings.[69] However, because no pediatric trial included a no-treatment arm that could serve as a control for the natural course of the disorders, the difference in placebo response may also reflect differences in the probability of spontaneous improvement between the 2 pediatric disorders rather than differences in the placebo effect. Owing to the small number of studies in children, we could not estimate the drug and placebo response for the individual ADs, yet a recent adult study found drug and placebo effect sizes to be roughly equivalent across ADs.[72] In pediatric patients, however, those with panic disorder seem to experience a greater placebo response compared with patients with generalized AD or social phobia.[73]

Our results are very similar to those of a recent meta-analysis of 5 decades of research on youth psychological therapy,[74] which found that mean effect sizes at posttreatment were strongest for AD (g = 0.61), weakest for DD (g = 0.29), and nonsignificant for multiproblem treatment (g = 0.15), indicating a general difficulty in establishing a clinically relevant benefit in the treatment of pediatric depression. The substantial placebo response in MDD indicates that depressed children and adolescents might benefit from innovative treatment modalities that harness the power of the placebo effect in an ethical fashion, including clinician contact[11] and other common factors, such as the patients' expectations of improvement, their desire for relief, and the exposure to treatment rituals. Placebo response also offers several implications for research design in antidepressant trials. Alternative designs, such as a discontinuation design[75] or n-of-1 trials,[76,77] might be recommended when establishing efficacy,[78] yet also have their individual shortcomings.[79] Differences between 2 medication groups could provide information about the magnitude of expectancy effects. In this regard, response and remission rates to antidepressants have been shown to be significantly higher in comparator trials compared with placebo-controlled trials.[80] Future instructive studies could incorporate designs in which people who respond to placebo continue to receive placebo.

With regard to adverse events, our finding that patients receiving any antidepressant reported more TEAEs, SAEs, and study discontinuation compared with those receiving placebo is in line with other meta-analyses reporting increased suicidality (odds ratio, 2.39; 95% CI, 1.31- 4.33),[81] suicidal ideation, and suicide attempts (risk difference: antidepressant vs placebo, 0.7%; 95% CI, 0.1%-1.3%)[14] in children and adolescents receiving SSRIs and SNRIs compared with placebo. This finding is mainly due to the large amount of significant SSRI studies, although patients receiving SNRIs reported significantly more SAEs than did those receiving placebo. Thus, our results support concerns about the safety of antidepressants in children and adolescents. Evaluating the mean number of adverse events provides a more sensitive measure than the percentage of patients exhibiting at least 1 adverse event and might be recommended as the primary reporting method in future clinical trials.

Limitations

Our study has some limitations. First, none of the randomized clinical trials included directly compared effectiveness across disorders. Accordingly, we could only make indirect conclusions with regard to disorder specificity. Second, although our meta-analysis included unpublished trials, reporting bias could lead to an overly positive representation of findings in the literature.[82] In this regard, many concerns have been raised about the accuracy of the data of 1 study in particular: Paxil Study 329. A reanalysis of the original data found that paroxetine did not show efficacy for MDD in adolescents and that the initial study underplayed the drug's potential to increase suicidal thoughts among adolescents.[83] Third, there was variability in the mean age and age distribution between studies, which may have had an effect on results. Response to SSRIs and SNRIs has been shown to be lower in children than in adolescents, in part related to a higher placebo response in children.[14] Fourth, the Begg and Eggers tests[31,33] used to assess publication bias are valid only when there are 10 or more studies being evaluated, and our OCD group consisted of only 8 trials. However, no evidence of publication bias was found in the respective funnel plot. The different reporting methods of adverse events led to subgroup analyses based on only a few studies and should therefore be considered preliminary, requiring further investigation. Furthermore, restrictive inclusion criteria of clinical trials, such as noninclusion of comorbidity and a higher symptom severity threshold, make it difficult to generalize results to real-world populations.[84] Finally, because only 1 study met our inclusion criteria for PTSD,[7] no categorical analysis of SSRIs and SNRIs for the treatment of pediatric PTSD was possible.

Conclusions

The main findings of this meta-analysis present multiple avenues for further analyses. First, the nearly identical response rate for pediatric DD and AD deserves further investigation and perhaps the revision of federal prescribing guidelines for these 2 conditions. Although several SSRIs and SNRIs have been approved for the treatment of pediatric DD and OCD, only 1—duloxetine—has recently received FDA approval for treatment of pediatric ADs.[85] Second, the substantial differential response to both drug treatment and placebo treatment in OCD compared with AD and DD highlights underlying differences in the etiologies and pathogeneses of the disorders that may require additional interventions for pediatric patients with OCD.[86] It is our hope that a research domain criteria approach[87] will help to elucidate the above-mentioned points and could lead to better treatment outcomes.

Third, additional research into the factors that moderate the efficacy of SSRIs and SNRIs in children is warranted, as is the need for more comprehensive reporting of population and illness details (eg, age at onset, duration of illness) in clinical and pragmatic trials. Finally, the significant variability in the assessment and reporting of adverse events highlights the need for a standardized method of reporting TEAEs and SAEs. Given the potential for life-threatening events in young children and adolescents, understanding the extent to which these medications pose a genuine risk to youth is urgent. This need would allow future research to deviate from the current line of studies estimating the magnitude and differences between drug and placebo effects and focus more on precision medicine-driven questions, such as which treatment or combination thereof may be most advantageous for certain patient subgroups in certain clinical settings.

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REFERENCES

1. Merikangas KR, He JP, Burstein M, et al. Lifetime prevalence of mental disorders in US adolescents: results from the National Comorbidity Survey Replication–Adolescent Supplement (NCS-A). *J Am Acad Child Adolesc Psychiatry*. 2010;49(10):980-989.

2. Rutter M, Kim-Cohen J, Maughan B. Continuities and discontinuities in psychopathology between childhood and adult life. *J Child Psychol Psychiatry*. 2006;47(3-4):276-295.

3. Jane Garland E, Kutcher S, Virani A, Elbe D. Update on the use of SSRIs and SNRIs with children and adolescents in clinical practice. *J Can Acad Child Adolesc Psychiatry*. 2016;25(1):4-10.

4. Machado M, Einarson TR. Comparison of SSRIs and SNRIs in major depressive disorder: a meta-analysis of head-to-head randomized clinical trials. *J Clin Pharm Ther*. 2010;35(2):177-188.

5. Cipriani A, Zhou X, Del Giovane C, et al. Comparative efficacy and tolerability of antidepressants for major depressive disorder in children and adolescents: a network meta-analysis. *Lancet*. 2016;388(10047):881-890.

6. Rojas-Mirquez JC, Rodriguez-Zuñiga MJ, Bonilla-Escobar FJ, et al. Nocebo effect in randomized clinical trials of antidepressants in children and adolescents: systematic review and meta-analysis. *Front Behav Neurosci*. 2014;8:375.

7. Robb AS, Cueva JE, Sporn J, Yang R, Vanderburg DG. Sertraline treatment of children and adolescents with posttraumatic stress disorder: a double-blind, placebo-controlled trial. *J Child Adolesc Psychopharmacol*. 2010;20(6):463-471.

8. Mann JJ, Emslie G, Baldessarini RJ, et al. ACNP Task Force report on SSRIs and suicidal behavior in youth. *Neuropsychopharmacology*. 2006;31(3):473-492.

9. Stone MB. The FDA warning on antidepressants and suicidality—why the controversy? *N Engl J Med*. 2014;371(18):1668-1671.

10. Walsh BT, Seidman SN, Sysko R, Gould M. Placebo response in studies of major depression: variable, substantial, and growing. *JAMA*. 2002;287(14):1840-1847.

11. Rutherford BR, Sneed JR, Tandler JM, Rindskopf D, Peterson BS, Roose SP. Deconstructing pediatric depression trials: an analysis of the effects of expectancy and therapeutic contact. *J Am Acad Child Adolesc Psychiatry*. 2011;50(8):782-795.

12. Bridge JA, Birmaher B, Iyengar S, Barbe RP, Brent DA. Placebo response in randomized controlled trials of antidepressants for pediatric major depressive disorder. *Am J Psychiatry*. 2009;166(1):42-49.

13. Leuchter AF, Hunter AM, Tartter M, Cook IA. Role of pill-taking, expectation and therapeutic alliance in the placebo response in clinical trials for major depression. *Br J Psychiatry*. 2014;205(6):443-449.

14. Bridge JA, Iyengar S, Salary CB, et al. Clinical response and risk for reported suicidal ideation and suicide attempts in pediatric antidepressant treatment: a meta-analysis of randomized controlled trials. *JAMA*. 2007;297(15):1683-1696.

15. Cox GR, Callahan P, Churchill R, et al. Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents. *Cochrane Database Syst Rev*. 2012;11:CD008324.

16. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Ann Intern Med*. 2009;151(4):W65-94.

17. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. 2009;6(7):e1000097.

18. Birmaher B, Brent D, Bernet W, et al; AACAP Work Group on Quality Issues. Practice parameter for the assessment and treatment of children and adolescents with depressive disorders. *J Am Acad Child Adolesc Psychiatry*. 2007;46(11):1503-1526.

19. Higgins JP, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions*. The Cochrane Collaboration. Chichester, England: John Wiley & Sons; 2011.

20. Altman DG, Royston P. The cost of dichotomising continuous variables. *BMJ*. 2006;332(7549):1080.

21. Moncrieff J, Kirsch I. Efficacy of antidepressants in adults. *BMJ*. 2005;331(7509):155-157.

22. Wagner KD, Robb AS, Findling RL, Jin J, Gutierrez MM, Heydorn WE. A randomized, placebo-controlled trial of citalopram for the treatment of major depression in children and adolescents. *Am J Psychiatry*. 2004;161(6):1079-1083.

23. Wagner KD, Jonas J, Findling RL, Ventura D, Saikali K. A double-blind, randomized, placebo-controlled trial of escitalopram in the

treatment of pediatric depression. *J Am Acad Child Adolesc Psychiatry*. 2006;45(3):280-288.

24. Furukawa TA, Barbui C, Cipriani A, Brambilla P, Watanabe N. Imputing missing standard deviations in meta-analyses can provide accurate results. *J Clin Epidemiol*. 2006;59(1):7-10.

25. Hedges LV, Olkin I. *Statistical Methods for Meta-analysis*. Cambridge, Massachusetts: Academic Press;2014.

26. Cooper GL. The safety of fluoxetine—an update. *Br J Psychiatry Suppl*. 1988;(3):77-86.

27. Cochran WG. The comparison of percentages in matched samples. *Biometrika*. 1950;37(3-4):256-266.

28. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327(7414):557-560.

29. Higgins JP. Commentary: heterogeneity in meta-analysis should be expected and appropriately quantified. *Int J Epidemiol*. 2008;37(5):1158-1160.

30. Borenstein M, Hedges LV, Higgins JP, Rothstein HR. A basic introduction to fixed-effect and random-effects models for meta-analysis. *Res Synth Methods*. 2010;1(2):97-111.

31. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315(7109):629-634.

32. Rosenthal R. Meta-analytic Procedures for Social Research. Thousand Oaks, California: Sage Publications; 1991.

33. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics*. 1994;50(4):1088-1101.

34. Duval S, Tweedie R. Trim and fill: a simple funnel-plot–based method of testing and adjusting for publication bias in meta-analysis. *Biometrics*. 2000;56(2):455-463.

35. Simeon JG, Dinicola VF, Ferguson HB, Copping W. Adolescent depression: a placebo-controlled fluoxetine treatment study and follow-up. *Prog Neuropsychopharmacol Biol Psychiatry*. 1990;14(5):791-795.

36. Emslie GJ, Rush AJ, Weinberg WA, et al. A double-blind, randomized, placebo-controlled trial of fluoxetine in children and adolescents with depression. *Arch Gen Psychiatry*. 1997;54(11):1031-1037.

37. Keller MB, Ryan ND, Strober M, et al. Efficacy of paroxetine in the treatment of adolescent major depression: a randomized, controlled trial. *J Am Acad Child Adolesc Psychiatry*. 2001;40(7):762-772.

38. Emslie GJ, Heiligenstein JH, Wagner KD, et al. Fluoxetine for acute treatment of depression in children and adolescents: a placebo-controlled, randomized clinical trial. *J Am Acad Child Adolesc Psychiatry*. 2002;41(10):1205-1215.

39. Wagner KD, Ambrosini P, Rynn M, et al; Sertraline Pediatric Depression Study Group. Efficacy of sertraline in the treatment of children and adolescents with major depressive disorder: two randomized controlled trials. *JAMA*. 2003;290(8):1033-1041.

40. March J, Silva S, Petrycki S, et al; Treatment for Adolescents With Depression Study (TADS) Team. Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression: Treatment for Adolescents With Depression Study (TADS) randomized controlled trial. *JAMA*. 2004;292(7):807-820.

41. Berard R, Fong R, Carpenter DJ, Thomason C, Wilkinson C. An international, multicenter, placebo-controlled trial of paroxetine in adolescents with major depressive disorder. *J Child Adolesc Psychopharmacol*. 2006;16(1-2):59-75.

42. Emslie GJ, Wagner KD, Kutcher S, et al. Paroxetine treatment in children and adolescents with major depressive disorder: a randomized, multicenter, double-blind, placebo-controlled trial. *J Am Acad Child Adolesc Psychiatry*. 2006;45(6):709-719.

43. von Knorring AL, Olsson GI, Thomsen PH, Lemming OM, Hultén A. A randomized, double-blind, placebo-controlled study of citalopram in adolescents with major depressive disorder. *J Clin Psychopharmacol*. 2006;26(3):311-315.

44. Emslie GJ, Findling RL, Yeung PP, Kunz NR, Li Y. Venlafaxine ER for the treatment of pediatric subjects with depression: results of two placebo-controlled trials. *J Am Acad Child Adolesc Psychiatry*. 2007;46(4):479-488.

45. Emslie GJ, Ventura D, Korotzer A, Tourkodimitris S. Escitalopram in the treatment of adolescent depression: a randomized placebo-controlled multisite trial. *J Am Acad Child Adolesc Psychiatry*. 2009;48(7):721-729.

46. Findling RL, Pagano ME, McNamara NK, et al. The short-term safety and efficacy of fluoxetine in depressed adolescents with alcohol and cannabis use disorders: a pilot randomized placebo-controlled trial. *Child Adolesc Psychiatry Ment Health*. 2009;3(1):11.

47. GlaxoSmithKline Clinical Study Register. Study ID: 112487; clinical study ID: PIR112487. A randomised, double-blind, placebo controlled, parallel group, flexible dose study to evaluate the efficacy and safety of Paxil tablets in children and adolescents with major depressive disorder; post-marketing clinical study. https://www.gsk-clinicalstudyregister.com/study/112487#rs. Updated August 29, 2013. Accessed August 21, 2016.

48. Atkinson SD, Prakash A, Zhang Q, et al. A double-blind efficacy and safety study of duloxetine flexible dosing in children and adolescents with major depressive disorder. *J Child Adolesc Psychopharmacol*. 2014;24(4):180-189.

49. Emslie GJ, Prakash A, Zhang Q, Pangallo BA, Bangs ME, March JS. A double-blind efficacy and safety study of duloxetine fixed doses in children and adolescents with major depressive disorder. *J Child Adolesc Psychopharmacol*. 2014;24(4):170-179.

50. The Research Unit on Pediatric Psychopharmacology Anxiety Study Group. Fluvoxamine for the treatment of anxiety disorders in children and adolescents. *N Engl J Med*. 2001;344(17):1279-1285.

51. Rynn MA, Siqueland L, Rickels K. Placebo-controlled trial of sertraline in the treatment of children with generalized anxiety disorder. *Am J Psychiatry*. 2001;158(12):2008-2014.

52. Birmaher B, Axelson DA, Monk K, et al. Fluoxetine for the treatment of childhood anxiety disorders. *J Am Acad Child Adolesc Psychiatry*. 2003;42(4):415-423.

53. Wagner KD, Berard R, Stein MB, et al. A multicenter, randomized, double-blind, placebo-controlled trial of paroxetine in children and adolescents with social anxiety disorder. *Arch Gen Psychiatry*. 2004;61(11):1153-1162.

54. March JS, Entusah AR, Rynn M, Albano AM, Tourian KA. A Randomized controlled trial of venlafaxine ER versus placebo in pediatric social anxiety disorder. *Biol Psychiatry*. 2007;62(10):1149-1154.

55. Rynn MA, Riddle MA, Yeung PP, Kunz NR. Efficacy and safety of extended-release venlafaxine in the treatment of generalized anxiety disorder in children and adolescents: two placebo-controlled trials. *Am J Psychiatry*. 2007;164(2):290-300.

56. Walkup JT, Albano AM, Piacentini J, et al. Cognitive behavioral therapy, sertraline, or a combination in childhood anxiety. *N Engl J Med*. 2008;359(26):2753-2766.

57. da Costa CZ, de Morais RM, Zanetta DM, et al. Comparison among clomipramine, fluoxetine, and placebo for the treatment of anxiety disorders in children and adolescents. *J Child Adolesc Psychopharmacol*. 2013;23(10):687-692.

58. Strawn JR, Prakash A, Zhang Q, et al. A randomized, placebo-controlled study of duloxetine for the treatment of children and adolescents with generalized anxiety disorder. *J Am Acad Child Adolesc Psychiatry*. 2015;54(4):283-293.

59. Melvin GA, Dudley AL, Gordon MS, et al. Augmenting cognitive behavior therapy for school refusal with fluoxetine: a randomized controlled trial. *Child Psychiatry Hum Dev*. 2017;48(3):485-497.

60. Riddle MA, Scahill L, King RA, et al. Double-blind, crossover trial of fluoxetine and placebo in children and adolescents with obsessive-compulsive disorder. *J Am Acad Child Adolesc Psychiatry*. 1992;31(6):1062-1069.

61. March JS, Biederman J, Wolkow R, et al. Sertraline in children and adolescents with obsessive-compulsive disorder: a multicenter randomized controlled trial. *JAMA*. 1998;280(20):1752-1756.

62. Geller DA, Hoog SL, Heiligenstein JH, et al; Fluoxetine Pediatric OCD Study Team. Fluoxetine treatment for obsessive-compulsive disorder in children and adolescents: a placebo-controlled clinical trial. *J Am Acad Child Adolesc Psychiatry*. 2001;40(7):773-779.

63. Riddle MA, Reeve EA, Yaryura-Tobias JA, et al. Fluvoxamine for children and adolescents with obsessive-compulsive disorder: a randomized, controlled, multicenter trial. *J Am Acad Child Adolesc Psychiatry*. 2001;40(2):222-229.

64. Liebowitz MR, Turner SM, Piacentini J, et al. Fluoxetine in children and adolescents with OCD: a placebo-controlled trial. *J Am Acad Child Adolesc Psychiatry*. 2002;41(12):1431-1438.

65. Pediatric OCD Treatment Study (POTS) Team. Cognitive-behavior therapy, sertraline, and their combination for children and adolescents with obsessive-compulsive disorder: the Pediatric OCD Treatment Study (POTS) randomized controlled trial. *JAMA*. 2004;292(16):1969-1976.

66. Geller DA, Wagner KD, Emslie G, et al. Paroxetine treatment in children and adolescents with obsessive-compulsive disorder: a randomized,

multicenter, double-blind, placebo-controlled trial. *J Am Acad Child Adolesc Psychiatry*. 2004;43(11):1387-1396.

67. Storch EA, Bussing R, Small BJ, et al. Randomized, placebo-controlled trial of cognitive-behavioral therapy alone or combined with sertraline in the treatment of pediatric obsessive-compulsive disorder. *Behav Res Ther*. 2013;51(12):823-829.

68. Regier DA, Narrow WE, Clarke DE, et al. *DSM-5* field trials in the United States and Canada, part II: test-retest reliability of selected categorical diagnoses. *Am J Psychiatry*. 2013;170(1):59-70.

69. Cohen D, Deniau E, Maturana A, et al. Are child and adolescent responses to placebo higher in major depression than in anxiety disorders? a systematic review of placebo-controlled trials. *PLoS One*. 2008;3(7):e2632.

70. Sugarman MA, Loree AM, Baltes BB, Grekin ER, Kirsch I. The efficacy of paroxetine and placebo in treating anxiety and depression: a meta-analysis of change on the Hamilton Rating Scales. *PLoS One*. 2014;9(8):e106337.

71. Janiaud P, Cornu C, Lajoinie A, Djemli A, Cucherat M, Kassai B. Is the perceived placebo effect comparable between adults and children? a meta-regression analysis. Pediatr Res. 2017;81(1-1)11-17. Medline:27648807

72. Sugarman MA, Kirsch I, Huppert JD. Obsessive-compulsive disorder has a reduced placebo (and antidepressant) response compared to other anxiety disorders: a meta-analysis. *J Affect Disord*. 2017;218:217-226.

73. Dobson ET, Strawn JR. Placebo response in pediatric anxiety disorders: implications for clinical trial design and interpretation. *J Child Adolesc Psychopharmacol*. 2016;26(8):686-693.

74. Weisz JR, Kuppens S, Ng MY, et al. What five decades of research tells us about the effects of youth psychological therapy: a multilevel meta-analysis and implications for science and practice. *Am Psychol*. 2017;72(2):79-117.

75. Emslie GJ, Kennard BD, Mayes TL, et al. Fluoxetine versus placebo in preventing relapse of major depression in children and adolescents. *Am J Psychiatry*. 2008;165(4):459-467.

76. Scuffham PA, Nikles J, Mitchell GK, et al. Using N-of-1 trials to improve patient management and save costs. *J Gen Intern Med*. 2010;25(9):906-913.

77. Kent MA, Camfield CS, Camfield PR. Double-blind methylphenidate trials: practical, useful, and highly endorsed by families. *Arch Pediatr Adolesc Med*. 1999;153(12):1292-1296.

78. Temple R, Ellenberg SS. Placebo-controlled trials and active-control trials in the evaluation of new treatments, part 1: ethical and scientific issues. *Ann Intern Med*. 2000;133(6):455-463.

79. Deshauer D, Grimshaw J. Can discontinuation trials inform the use of antidepressants in depressed children? *Am J Psychiatry*. 2008;165(9):1205.

80. Rutherford BR, Sneed JR, Roose SP. Does study design influence outcome? The effects of placebo control and treatment duration in antidepressant trials. *Psychother Psychosom*. 2009;78(3):172-181.

81. Sharma T, Guski LS, Freund N, Gøtzsche PC. Suicidality and aggression during antidepressant treatment: systematic review and meta-analyses based on clinical study reports. *BMJ*. 2016;352:i65.

82. Roest AM, de Jonge P, Williams CD, de Vries YA, Schoevers RA, Turner EH. Reporting bias in clinical trials investigating the efficacy of second-generation antidepressants in the treatment of anxiety disorders: a report of 2 meta-analyses. *JAMA Psychiatry*. 2015;72(5):500-510.

83. Le Noury J, Nardo JM, Healy D, et al. Restoring Study 329: efficacy and harms of paroxetine and imipramine in treatment of major depression in adolescence. *BMJ*. 2015;351:h4320.

84. Zimmerman M, Clark HL, Multach MD, Walsh E, Rosenstein LK, Gazarian D. Have treatment studies of depression become even less generalizable? a review of the inclusion and exclusion criteria used in placebo-controlled antidepressant efficacy trials published during the past 20 years. *Mayo Clin Proc*. 2015;90(9):1180-1186.

85. Strawn JR, Welge JA, Wehry AM, Keeshin B, Rynn MA. Efficacy and tolerability of antidepressants in pediatric anxiety disorders: a systematic review and meta-analysis. *Depress Anxiety*. 2015;32(3):149-157.

86. Weinberg A, Kotov R, Proudfit GH. Neural indicators of error processing in generalized anxiety disorder, obsessive-compulsive disorder, and major depressive disorder. *J Abnorm Psychol*. 2015;124(1):172-185.

87. Insel T, Cuthbert B, Garvey M, et al. Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. *Am J Psychiatry*. 2010;167(7):748-751.

SUPPLEMENTARY MATERIALS

Table of Contents

1. Search Terms

1.1. PubMed

"Depressive Disorder"[mesh] OR depression*[tiab] OR depressive[tiab] OR dysthymic[tiab] OR dysthymia*[tiab] OR "Anxiety Disorders"[Mesh] OR "Anxiety"[Mesh:noexp] OR anxiety[tiab] OR obsessive-compulsive[tiab] OR ocd[tiab] OR anankastic[tiab] OR phobic[tiab] OR phobia*[tiab] OR panic[tiab] OR stress disorder*[tiab] OR post traumatic stress[tiab] OR posttraumatic stress[tiab] OR post traumatic symptom*[tiab] OR posttraumatic symptom*[tiab] OR ptsd[tiab]

"Serotonin Uptake Inhibitors"[Mesh] OR "Serotonin Uptake Inhibitors"[pa] OR serotonin reuptake inhibitor*[tiab] OR serotonin uptake inhibitor*[tiab] OR SSRI*[tiab] OR SRI*[tiab] OR serotonin norepinephrine reuptake inhibitor*[tiab] OR serotonin norepinephrine uptake inhibitor*[tiab] OR SNRI* OR venlafaxin*[tiab] OR desvenlafaxin*[tiab] OR effexor[tiab] OR pristiq[tiab] OR milnacipran[tiab] OR levomilnacipran[tiab] OR fetzima[tiab] OR savella[tiab] OR duloxetin*[tiab] OR cymbalta[tiab] OR sibutramine[tiab] OR citalopram[tiab] OR celexa[tiab] OR escitalopram[tiab] OR lexapro[tiab] OR fluoxetin*[tiab] OR prozac[tiab] OR sarafem[tiab] OR symbyax[tiab] OR fluvoxamin*[tiab] OR luvox[tiab] OR paroxetin*[tiab] OR paxil[tiab] OR brisdelle[tiab] OR sertralin*[tiab] OR zoloft[tiab]

Child[MeSH Terms] OR Pediatrics[MeSH] OR child*[tiab] OR adolescen*[tiab] OR toddler*[tiab] OR teen*[tiab] OR boy[tiab] OR boys[tiab] OR girl*[tiab] OR pediatric[tiab] OR paediatric[tiab] OR puber*[tiab] OR pubescen*[tiab] OR prepubescen*[tiab] OR prepuberty*[tiab] OR schoolchild*[tiab] OR school age*[tiab] OR preschool*[tiab] OR kindergar*[tiab] OR primary school*[tiab] OR secondary school*[tiab] OR elementary school*[tiab] OR high school*[tiab] OR highschool*[tiab] OR youth*[tiab]

random*[tw] OR blind*[tiab] OR placebo*[tiab] OR trial[tiab] OR untreated[tiab] OR "not treated"[tiab] OR sham[tiab]

1.2. Embase

'depression'/exp OR depression*:ab,ti OR depressive:ab,ti OR dysthymic:ab,ti OR dysthymia*:ab,ti OR 'anxiety disorder'/exp OR 'anxiety'/de OR anxiety:ab,ti OR obsessive-compulsive:ab,ti OR ocd:ab,ti OR anankastic:ab,ti OR phobic:ab,ti OR phobia*:ab,ti OR panic:ab,ti OR (stress NEXT/1 disorder*):ab,ti OR (('post traumatic' OR posttraumatic) NEXT/1 (stress OR symptom*)):ab,ti OR ptsd:ab,ti

'serotonin uptake inhibitor'/exp OR 'serotonin noradrenalin reuptake inhibitor'/exp OR (('serotonin reuptake' OR 'serotonin uptake' OR 'serotonin norepinephrine reuptake' OR 'serotonin norepinephrine uptake') NEXT/1 inhibitor*):ab,ti OR ssri*:ab,ti OR snri*:ab,ti OR venlafaxin*:ab,ti OR desvenlafaxin*:ab,ti OR effexor:ab,ti OR pristiq:ab,ti OR milnacipran:ab,ti OR levomilnacipran:ab,ti OR fetzima:ab,ti OR savella:ab,ti OR duloxetin*:ab,ti OR cymbalta:ab,ti OR sibutramine:ab,ti OR citalopram:ab,ti OR celexa:ab,ti OR escitalopram:ab,ti OR lexapro:ab,ti OR fluoxetin*:ab,ti OR prozac:ab,ti OR sarafem:ab,ti OR symbyax:ab,ti OR fluvoxamin*:ab,ti OR luvox:ab,ti OR paroxetin*:ab,ti OR paxil:ab,ti OR brisdelle:ab,ti OR sertralin*:ab,ti OR zoloft:ab,ti

'child'/exp AND 'pediatrics'/exp OR child*:ab,ti OR adolescen*:ab,ti OR toddler*:ab,ti OR teen*:ab,ti OR boy:ab,ti OR boys:ab,ti OR girl*:ab,ti OR pediatric:ab,ti OR paediatric:ab,ti OR puber*:ab,ti OR pubescen*:ab,ti OR prepubescen*:ab,ti OR prepuberty*:ab,ti OR schoolchild*:ab,ti OR (school NEXT/1 age*):ab,ti OR preschool*:ab,ti OR kindergar*:ab,ti OR ((primary OR secondary OR elementary OR high) NEXT/1 school*):ab,ti OR highschool*:ab,ti OR youth*:ab,ti

random*:ab,de,ti OR blind*:ab,ti OR placebo*:ab,ti OR trial:ab,ti OR untreated:ab,ti OR 'not treated':ab,ti OR sham:ab,ti

1.3. PsycInfo

DE ("Major Depression" OR "Dysthymic Disorder" OR "Endogenous Depression" OR "Reactive Depression" OR "Recurrent Depression" OR "Treatment Resistant Depression" OR "Anxiety" OR "Acute Stress Disorder" OR "Generalized Anxiety Disorder" OR "Obsessive Compulsive Disorder" OR "Panic Disorder" OR "Phobias" OR "Posttraumatic Stress Disorder" OR "Panic Disorder" OR "Panic" OR "Panic Attack") OR TI (depression* OR depressive OR dysthymic OR dysthymia* OR anxiety OR

"obsessive-compulsive" OR ocd OR anankastic OR phobic OR phobia* OR panic OR "stress disorder*" OR "post traumatic stress" OR "posttraumatic stress" OR "post traumatic symptom*" OR "posttraumatic symptom*" OR ptsd) OR AB (depression* OR depressive OR dysthymic OR dysthymia* OR anxiety OR "obsessive-compulsive" OR ocd OR anankastic OR phobic OR phobia* OR panic OR "stress disorder*" OR "post traumatic stress" OR "posttraumatic stress" OR "post traumatic symptom*" OR "posttraumatic symptom*" OR ptsd)

DE ("Serotonin Reuptake Inhibitors" OR "Chlorimipramine" OR "Citalopram" OR "Fluoxetine" OR "Fluvoxamine" OR "Paroxetine" OR "Zimeldine" OR "Serotonin Norepinephrine Reuptake Inhibitors" OR "Venlafaxine") OR TI ("serotonin reuptake inhibitor*" OR "serotonin uptake inhibitor*" OR SSRI* OR SRI* OR "serotonin norepinephrine reuptake inhibitor*" OR "serotonin norepinephrine uptake inhibitor*" OR SNRI* OR venlafaxin* OR desvenlafaxin* OR effexor OR pristiq OR milnacipran OR levomilnacipran OR fetzima OR savella OR duloxetin* OR cymbalta OR sibutramine OR citalopram OR celexa OR escitalopram OR lexapro OR fluoxetin* OR prozac OR sarafem OR symbyax OR fluvoxamin* OR luvox OR paroxetin* OR paxil OR brisdelle OR sertralin* OR zoloft) OR AB ("serotonin reuptake inhibitor*" OR "serotonin uptake inhibitor*" OR SSRI* OR SRI* OR "serotonin norepinephrine reuptake inhibitor*" OR "serotonin norepinephrine uptake inhibitor*" OR SNRI* OR venlafaxin* OR desvenlafaxin* OR effexor OR pristiq OR milnacipran OR levomilnacipran OR fetzima OR savella OR duloxetin* OR cymbalta OR sibutramine OR citalopram OR celexa OR escitalopram OR lexapro OR fluoxetin* OR prozac OR sarafem OR symbyax OR fluvoxamin* OR luvox OR paroxetin* OR paxil OR brisdelle OR sertralin* OR zoloft)

AG ("Childhood (birth-12 yrs)") OR TI (child* OR adolescen* OR toddler* OR teen* OR boy OR boys OR girl* OR pediatric OR paediatric OR puber* OR pubescen* OR prepubescen* OR prepuberty* OR schoolchild* OR "school age*" OR preschool* OR kindergar* OR "primary school*" OR "secondary school*" OR "elementary school*" OR "high school*" OR highschool* OR youth*) OR AB (child* OR adolescen* OR toddler* OR teen* OR boy OR boys OR girl* OR pediatric OR paediatric OR puber* OR pubescen* OR prepubescen* OR prepuberty* OR schoolchild* OR "school age*" OR preschool* OR kindergar* OR "primary school*" OR "secondary school*" OR "elementary school*" OR "high school*" OR highschool* OR youth*)

DE (random*) OR TI (random* OR placebo* OR trial OR untreated OR sham) OR AB (random* OR placebo* OR trial OR untreated OR sham)
Note: "not treated" is handled as a stop word so all records with treated are retrieved.

1.4. Cochrane Central

TI ("serotonin reuptake inhibitor*" OR "serotonin uptake inhibitor*" OR SSRI* OR SRI* OR "serotonin norepinephrine reuptake inhibitor*" OR "serotonin norepinephrine uptake inhibitor*" OR SNRI* OR venlafaxin* OR desvenlafaxin* OR effexor OR pristiq OR milnacipran OR levomilnacipran OR fetzima OR savella OR duloxetin* OR cymbalta OR sibutramine OR citalopram OR celexa OR escitalopram OR lexapro OR fluoxetin* OR prozac OR sarafem OR symbyax OR fluvoxamin* OR luvox OR paroxetin* OR paxil OR brisdelle OR sertralin* OR zoloft) OR AB ("serotonin reuptake inhibitor*" OR "serotonin uptake inhibitor*" OR SSRI* OR SRI* OR "serotonin norepinephrine reuptake inhibitor*" OR "serotonin norepinephrine uptake inhibitor*" OR SNRI* OR venlafaxin* OR desvenlafaxin* OR effexor OR pristiq OR milnacipran OR levomilnacipran OR fetzima OR savella OR duloxetin* OR cymbalta OR sibutramine OR citalopram OR celexa OR escitalopram OR lexapro OR fluoxetin* OR prozac OR sarafem OR symbyax OR fluvoxamin* OR luvox OR paroxetin* OR paxil OR brisdelle OR sertralin* OR zoloft)

TI (depression* OR depressive OR dysthymic OR dysthymia* OR anxiety OR "obsessive-compulsive" OR ocd OR anankastic OR phobic OR phobia* OR panic OR "stress disorder*" OR "post traumatic stress" OR "posttraumatic stress" OR "post traumatic symptom*" OR "posttraumatic symptom*" OR ptsd) OR AB (depression* OR depressive OR dysthymic OR dysthymia* OR anxiety OR "obsessive-compulsive" OR ocd OR anankastic OR phobic OR phobia* OR panic OR "stress disorder*" OR "post traumatic stress" OR "posttraumatic stress" OR "post traumatic symptom*" OR "posttraumatic symptom*" OR ptsd)

TI (child* OR adolescen* OR toddler* OR teen* OR boy OR boys OR girl* OR pediatric OR paediatric OR puber* OR pubescen* OR prepubescen* OR prepuberty* OR schoolchild* OR "school age*" OR preschool* OR kindergar* OR "primary school*" OR "secondary school*" OR "elementary

school*" OR "high school*" OR highschool* OR youth*) OR AB (child* OR adolescen* OR toddler* OR teen* OR boy OR boys OR girl* OR pediatric OR paediatric OR puber* OR pubescen* OR prepubescen* OR prepuberty* OR schoolchild* OR "school age*" OR preschool* OR kindergar* OR "primary school*" OR "secondary school*" OR "elementary school*" OR "high school*" OR highschool* OR youth*)

1.5. Web of Science

TS=("serotonin reuptake inhibitor*" OR "serotonin uptake inhibitor*" OR SSRI* OR SRI* OR "serotonin norepinephrine reuptake inhibitor*" OR "serotonin norepinephrine uptake inhibitor*" OR SNRI* OR venlafaxin* OR desvenlafaxin* OR effexor OR pristiq OR milnacipran OR levomilnacipran OR fetzima OR savella OR duloxetin* OR cymbalta OR sibutramine OR citalopram OR celexa OR escitalopram OR lexapro OR fluoxetin* OR prozac OR sarafem OR symbyax OR fluvoxamin* OR luvox OR paroxetin* OR paxil OR brisdelle OR sertralin* OR zoloft)

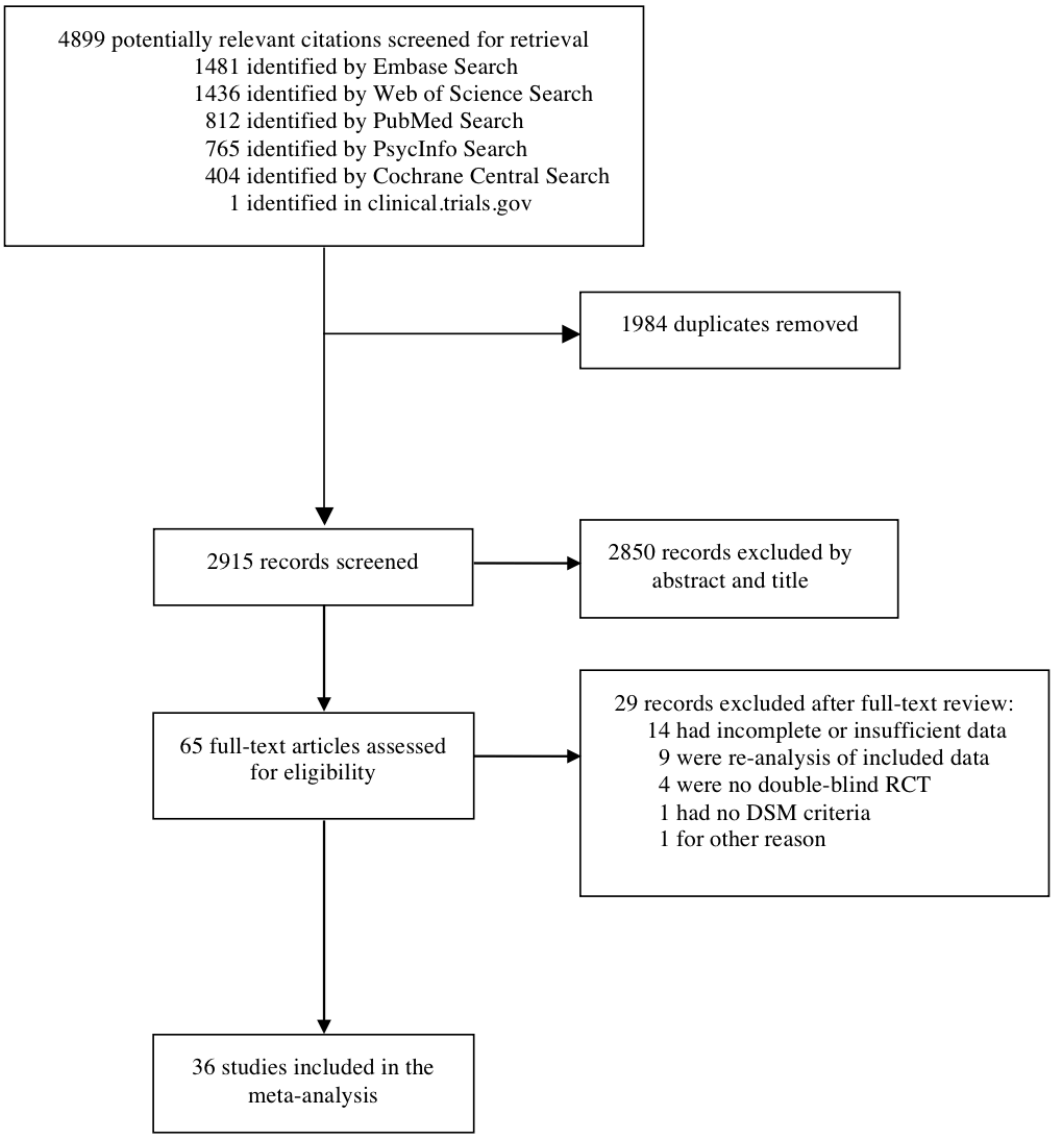
TS=(depression* OR depressive OR dysthymic OR dysthymia* OR anxiety OR "obsessive-compulsive" OR ocd OR anankastic OR phobic OR phobia* OR panic OR "stress disorder*" OR "post traumatic stress" OR "posttraumatic stress" OR "post traumatic symptom*" OR "posttraumatic symptom*" OR ptsd)

TS=(child* OR adolescen* OR toddler* OR teen* OR boy OR boys OR girl* OR pediatric OR paediatric OR puber* OR pubescen* OR prepubescen* OR prepuberty* OR schoolchild* OR "school age*" OR preschool* OR kindergar* OR "primary school*" OR "secondary school*" OR "elementary school*" OR "high school*" OR highschool* OR youth*)

TS=(random* OR placebo* OR trial OR untreated OR sham)

2. Study Selection

sFigure 1. Flow Chart



3. Details on Heterogeneity and Publication Bias

3.1 Overall

sTable 1. Heterogeneity

Drug	Treatment Arms	Hedges g	95% CI	SE	p-Value	Q-value	p-Value	I^2	Tau^2
Stratified Between Drug									
Citalopram	2	0.18	-0.18 - 0.54	0.18	.33	N/A[a]	N/A[a]	N/A[a]	N/A[a]
Escitalopram	2	0.18	0.01 - 0.34	0.08	.03	N/A[a]	N/A[a]	N/A[a]	N/A[a]
Fluoxetine	13	0.38	0.26 - 0.51	0.06	<0.001	13.17	.36	8.90	0.01
Fluvoxamine	2	0.68	-0.05 - 1.41	0.37	.07	N/A[a]	N/A[a]	N/A[a]	N/A[a]
Paroxetine	6	0.31	0.07 - 0.54	0.12	.01	19.83	.001	74.78	0.06
Sertraline	8	0.31	0.15 - 0.47	0.08	<.001	9.38	.23	25.37	0.01
Venlafaxine	4	0.31	0.18 - 0.44	0.07	<.001	2.66	.45	0.00	0.00
Duloxetine	4	0.24	0.06 - 0.46	0.16	.04	5.91	.12	49.20	0.03
Stratified Within Drug									
Citalopram	2	1.78	1.56 - 2.04	0.12	<.001	N/A[a]	N/A[a]	N/A[a]	N/A[a]
Escitalopram	2	1.68	1.48 - 1.87	0.10	<.001	N/A[a]	N/A[a]	N/A[a]	N/A[a]
Fluoxetine	13	1.73	1.32 - 2.13	0.21	<.001	100.36	<.001	88.05	0.45
Fluvoxamine	2	1.22	0.41 - 2.02	0.41	.003	N/A[a]	N/A[a]	N/A[a]	N/A[a]
Paroxetine	6	1.46	1.31 - 1.61	0.08	<.001	7.19	.21	30.45	0.01
Sertraline	8	1.38	1.02-1.73	0.18	<.001	37.54	<.001	81.35	0.18
Venlafaxine	4	1.77	1.59-1.95	0.09	<.001	3.71	.29	19.15	0.01

sTable 1. Heterogeneity (cont.)

Drug	Treatment Arms	Hedges g	95% CI	SE	p-Value	Q-value	p-Value	I^2	Tau^2
Duloxetine	4	1.95	1.73-2.18	0.11	<.001	5.17	.16	41.97	0.02

[a]Heterogeneity was not assessed due to the low number of studies.

3.2 Stratified by Disorder

OCD: The eight studies exhibited no heterogeneity (Q=2.28, p=.07, I^2=0.00 τ^2=0.00). There was no evidence of asymmetry in a funnel plot. Neither the Begg's test nor the Egger's test yielded a significant result. The fail-safe N indicated that 43 unpublished null studies would be needed to remove the significance from the findings. The trim-and-fill method lead to a very slight adjustment of Hedges' g (g=0.41, CI=0.26-0.55).

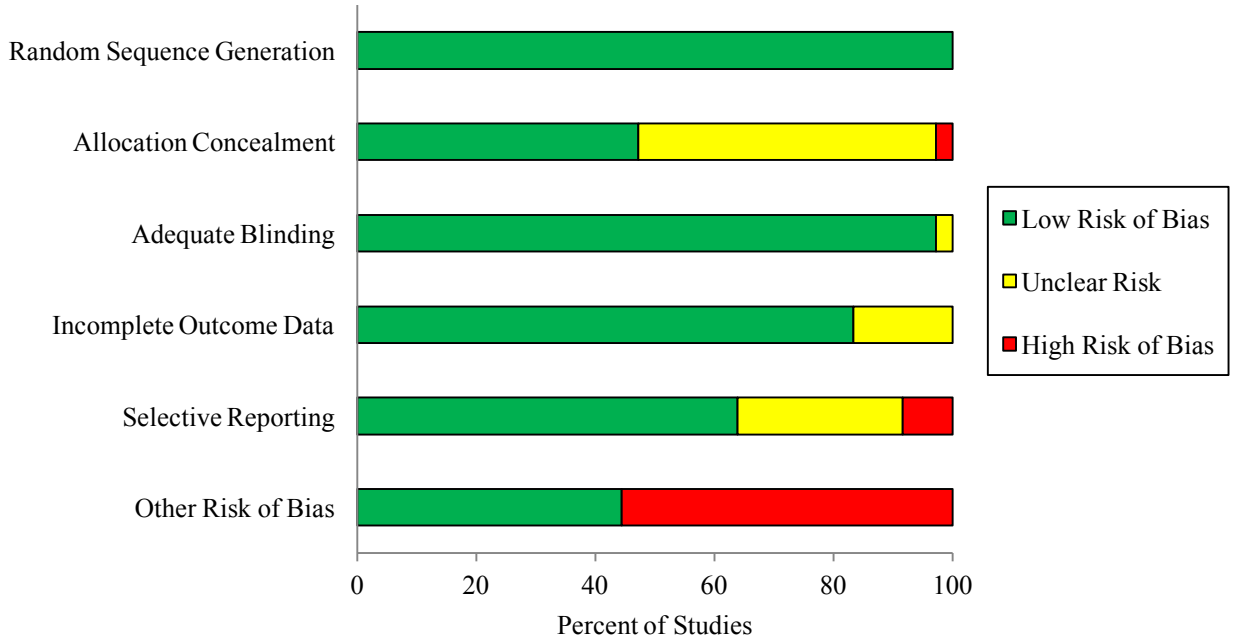
DD: The seventeen studies exhibited moderate heterogeneity (Q=20.28, p=.38, I^2=6.31, τ^2=0.00). There was some evidence of asymmetry in a funnel plot. Neither the Begg's test nor the Egger's test yielded a significant result. The fail-safe N indicated that 165 unpublished null studies would be needed to remove the significance from the findings. The trim-and-fill method did not lead to an adjustment of Hedges' g.

AD: The ten studies exhibited moderate heterogeneity (Q=22.93, p=.01, I^2=56.40, τ^2=0.04). There was evidence of asymmetry in a funnel plot. Both the Begg's test and the Egger's test yielded a non-significant result (2-tailed p > .05). The fail-safe N indicated that 308 unpublished null studies would be needed to remove the significance from the findings. The trim-and-fill method lead to a slight adjustment of the standard mean difference (g=0.53, CI=0.36-0.70).

Across all studies: The combined analysis yielded low to moderate heterogeneity (Q=76.62, p<.001, I^2=47.79, τ^2=0.03).

3.3. Risk of Bias Assessment

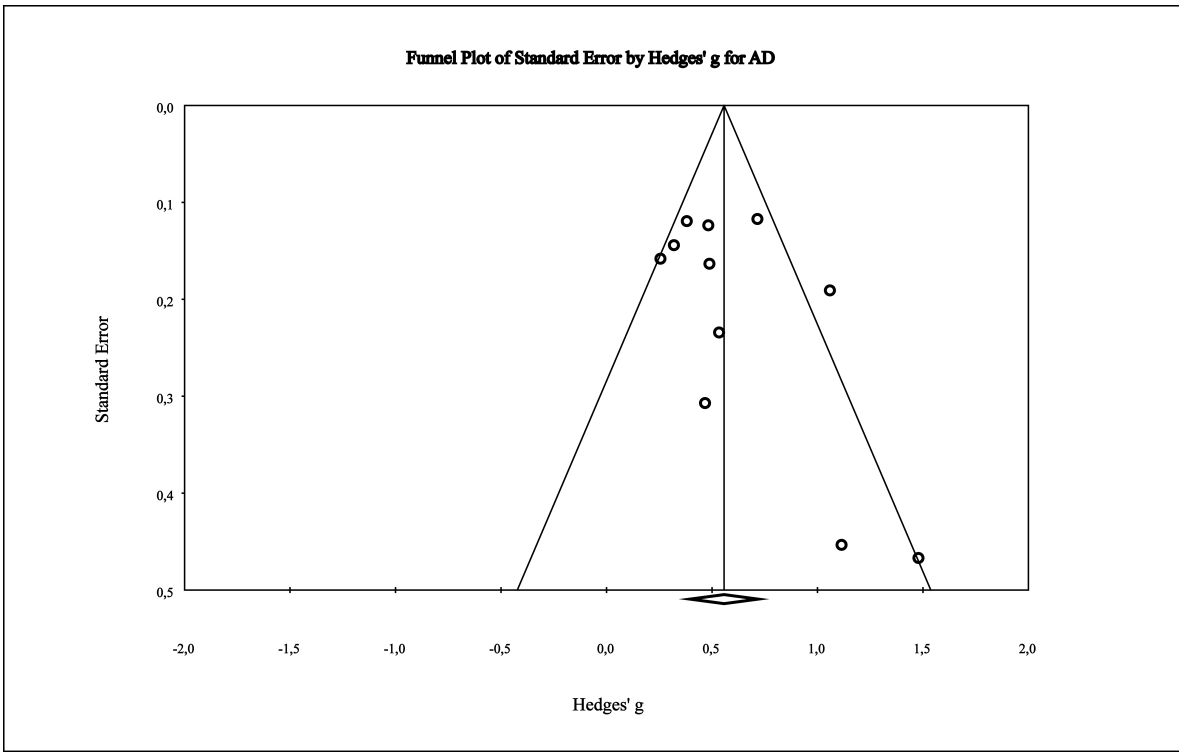
sFigure 2



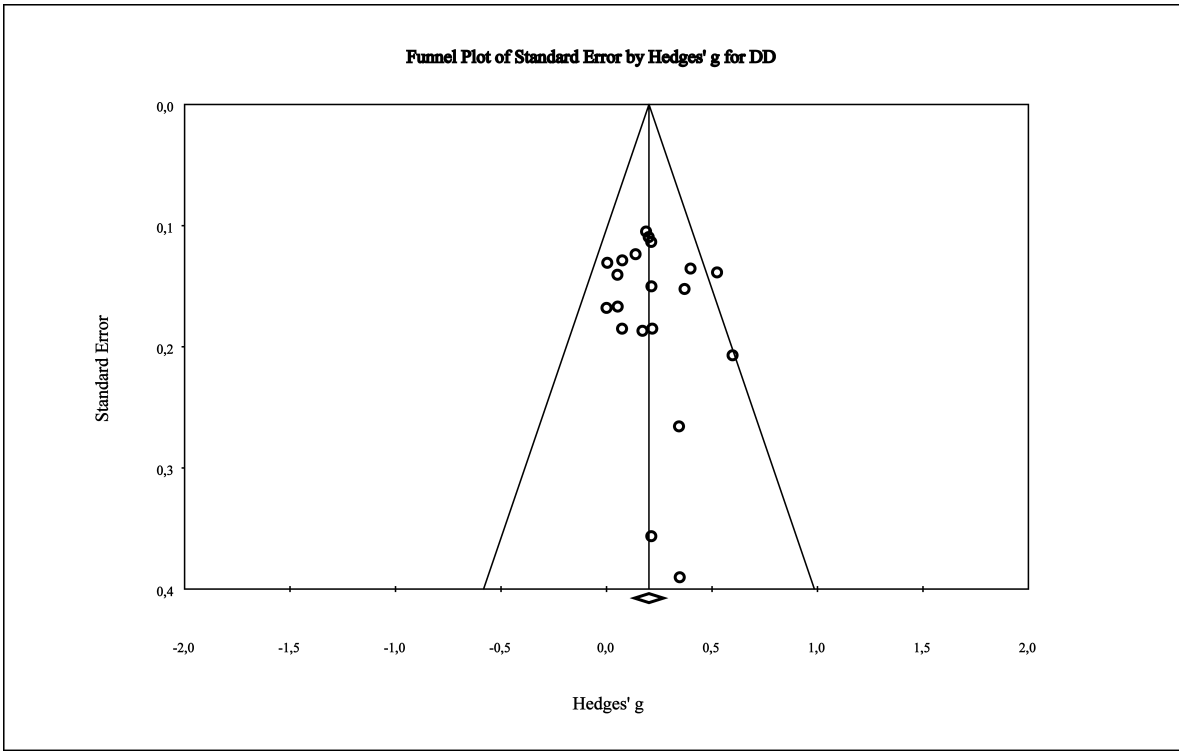
Note: The large amount of high risk in the "other risk of bias" category was mainly due to per protocol analysis rather than intent-to-treat analysis.

3.4. Funnel Plots Stratified by Disorder

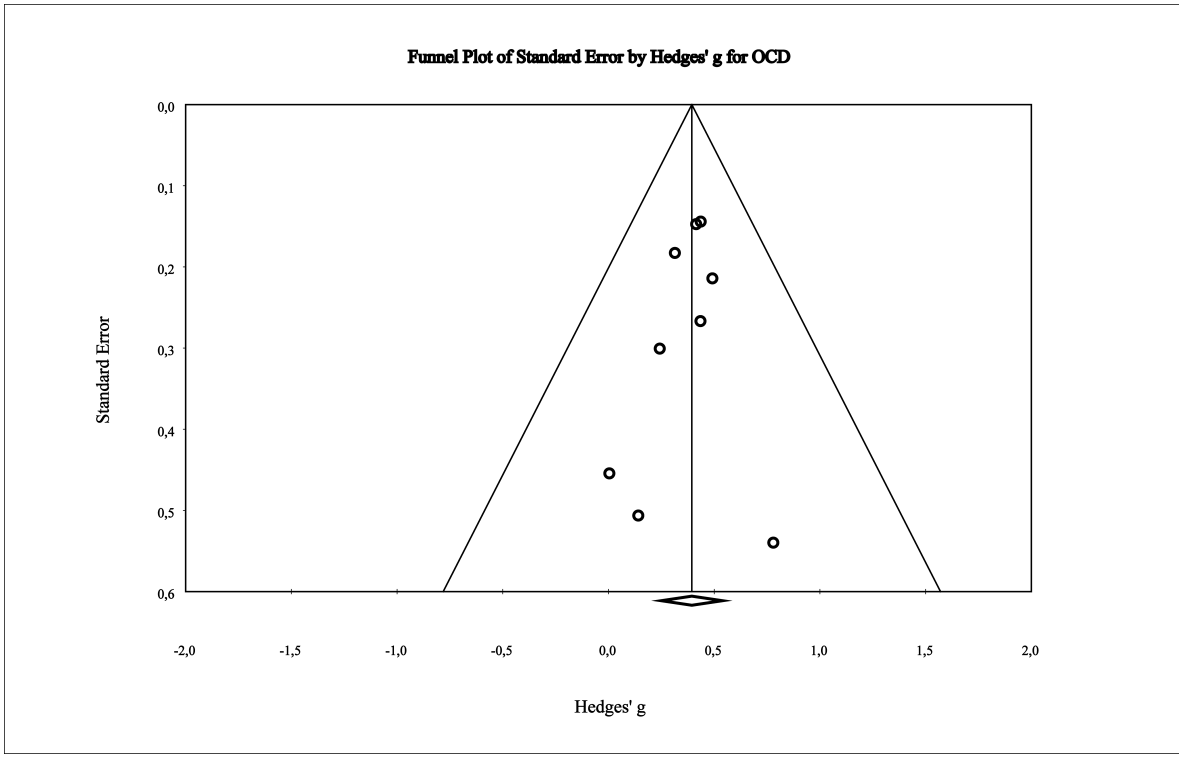
Anxiety Disorders



Depressive Disorder



Obsessive-Compulsive Disorder


Funnel Plot of Standard Error by Hedges' g for OCD
Standard Error
0,0
0,1
0,2
0,3
0,4
0,5
0,6
-2,0
-1,5
-1,0
-0,5
0,0
0,5
1,0
1,5
2,0
Hedges' g

4. Side Effects

4.1 Mean Percentages and Numbers

sTable 2a. Mean Percentages and Numbers of TEAEs

	Reporting Method 1[a]			Reporting Method 2[b]		
Intervention	No. Trials	Mean Percentage Drug	Mean Percentage Placebo	No. Trials	Mean Number Drug	Mean Number Placebo
SSRI vs. Placebo	19	66.89%	56.84%	24	0.14	0.09
SNRI vs. Placebo	7	62.09%	57.99%	2	0.13	0.09

[a]Percent of patients reporting TEAEs.
[b]Mean number of TEAEs per patient across all reported symptoms.

sTable 2b. Mean Percentages of Discontinuation of Study due to TEAEs and SAEs and Mean Percentages of SAEs

	Discontinuation[c]			SAE[d]		
Intervention	No. Trials	Mean Percentage Drug	Mean Percentage Placebo	No. Trials	Mean Percentage Drug	Mean Percentage Placebo
SSRI vs. Placebo	27	6.83%	3.46%	17	6.24%	3.42%
SNRI vs. Placebo	6	6.80%	3.62%	7	4.75%	2.17%

[c]Percent of patients who discontinued the study due to TEAEs and SAEs.
[d]Percent of patients reporting SAEs.

5. Moderator Analyses

5.1. Methods and Results for the Univariate Analyses – Continuous Variables

Methods: Moderator analyses were conducted for six continuous moderators (treatment duration, publication year, illness duration, age of onset, number of sites, and baseline severity) for both the combined disorders group and individual disorders groups. We examined whether specific characteristics of the studies were related to the effect sizes (i.e., drug-placebo differences) in univariate analyses. Continuous variables were analyzed with a meta-regression analysis using method-of-moments analyses in a random-effects model. The Z-statistic was used to test the significance of the slope. As various scales were used to assess baseline severity, we standardized the baseline and outcome values by dividing the mean values by the SD.

Results: The relationship between effect size and publication year was significant in the combined analyses (Z=-2.36, p=.02), as well as in the DD subgroup analyses (Z=-2.26, p=.02), with recently published studies yielding smaller antidepressant-placebo differences. Further, the relationship between effect size and illness duration was significant in the combined analyses (Z=2.89, p=.004), indicating that children with a longer duration of illness exhibit greater response to antidepressants compared to placebo. Finally, number of sites was found to be significantly correlated to effect size in the combined analyses (Z=-2.98, p=.003), as well as in the DD subgroup analyses (Z=-2.16, p<.03), and the OCD subgroup analyses (Z=-2.16, p=.03), with number of study sites negatively associated with magnitude of differences between antidepressants and placebo. See sTable 2 for all calculations.

5.2. Methods and Results for the Univariate Analyses – Categorical Variables

Methods: Moderator analyses were conducted for four categorical moderators (placebo lead-in, comorbidity, region, and primary funding source) for both the combined disorders group and individual disorders groups. Categorical variables were analyzed using a mixed-effects model We examined whether specific characteristics of the studies were related to the effect sizes (i.e., drug-placebo differences) in univariate analyses.

Results: The relationship between effect size and primary funding source was significant in the combined analyses (p = .02), as well as in the DD subgroup analyses (p = .02). In both cases, studies that were funded by industry yielded significantly smaller effect sizes than those that reported public sources of funding only (e.g., NIMH). See sTable 3 for further details.

5.3. Methods and Results for the Multivariate Metaregression Analysis

Methods: Given the relatively large number of moderator analyses, we decided to conduct a multivariate meta-regression. Effect sizes (i.e., dependent variable) were weighted by the sample size divided by s2 (i.e., n/var; (1)). Multivariate regression analyses were conducted in SPSS (Version 21.0.0.2).

This approach is in line with the methods adopted by Cuijpers (2-5). The model indicates the significance of each potential moderator while controlling for the others. To avoid collinearity among the predictors of the regression model, we first tested whether high correlations (i.e., correlations higher than 0.60) were found among the moderators that could be entered into the model. Three variables were found to have correlations higher than 0.60: the funding source correlated high with the number of sites (r = .698), treatment duration correlated high with illness duration (r = 0.62), and comorbidity correlated high with the number of sites (r = -0.75). We decided to use the number of sites (not funding source or comorbidity) and illness duration (not treatment duration) as predictors in the model. All remaining variables (i.e., illness duration, publication year, baseline severity, number of sites, age of onset, placebo lead-in, and study location) were included as predictors in the model.

Results: None of the moderators were found to be significant in the multivariate meta-regression with weighted effect sizes. All results can be found in the sTable 4.

sTable 3. Continuous Univariate Moderator Analyses

Moderator	Z-Value	p-Value
	Overall	
Treatment Duration	0.57	.57
Publication Year	-2.36	.02
Baseline Severity	0.20	.84
Number of Sites	-2.98	.003
Illness Duration	2.89	.004
Age of Onset	-1.11	.27
	Depressive Disorder	
Treatment Duration	-1.12	.26
Publication Year	-2.26	.02
Baseline Severity	1.21	.23
Number of Sites	-2.16	.03
Illness Duration	-0.01	1.00
Age of Onset	-0.31	.76
	Obsessive-Compulsive Disorder	
Treatment Duration	-0.47	.64
Publication Year	-0.88	.38
Baseline Severity	-0.33	.74
Number of Sites	-0.50	.62
Illness Duration	0.45	.65
Age of Onset	*N/A*[a]	
	Anxiety Disorders	
Treatment Duration	-0.55	.58
Publication Year	-1.90	.06
Baseline Severity	-1.18	.24
Number of Sites	-1.84	.07
Illness Duration	1.62	.11
Age of Onset	*N/A*[b]	

[a]Only 1 Study
[b]No Studies

sTable 4. Categorical Univariate Moderator Analyses

Moderator	Number of included studies	Hedges g	95% CI	Q-value	I^2	p-Value
Overall						
Placebo lead-in				0.23		.63
No	28	0.35	0.25 - 0.46		64.30	
Yes	13	0.31	0.17 - 0.45		8.66	
Comorbidity				2.47		.12
No	6	0.24	0.04 - 0.43		29.90	
Yes	28	0.41	0.31 - 0.51		60.61	
Study location				1.94		.16
US only	27	0.38	0.28 - 0.48		50.10	
Not US only	14	0.26	0.13 - 0.39		62.97	
Primary funding source				5.42		.02[a]
Industry only	27	0.26	0.19 - 0.33		37.91	
Public only	11	0.48	0.31 - 0.64		2.97	
Depressive Disorder						
Placebo lead-in				2.71		.10
No	11	0.15	0.06 - 0.24		0.00	
Yes	9	0.26	0.16 - 0.35		23.51	
Comorbidity				1.98		.16
No	3	0.12	-0.04 - 0.28		0.00	
Yes	11	0.25	0.16 - 0.35		27.54	
Study location				2.61		.11
US only	10	0.25	0.16 - 0.35		15.15	
Not US only	10	0.15	0.05 - 0.24		0.00	
Primary funding source				5.64		.02[a]
Industry only	18	0.18	0.11 - 0.25		0.00	
Public only	2	0.46	0.24 - 0.68		0.00	
Obsessive-Compulsive Disorder						
Placebo lead-in				0.05		.83
No	7	0.41	0.22 - 0.60		0.00	
Yes	2	0.38	0.15 - 0.60		0.00	
Comorbidity	*N/A*[b]					
Study location	*N/A*[b]					
Primary funding source				0.07		.79
Industry only	4	0.41	0.25 - 0.58		0.00	
Public only	4	0.36	-0.03 - 0.74		0.00	
Anxiety Disorder						
Placebo lead-in				1.69		.19
No	9	0.69	0.47 - 0.91		71.87	
Yes	2	0.37	-0.06 - 0.80		4.13	
Comorbidity				3.32		0.07
No	3	0.37	0.06 - 0.69		0.00	
Yes	8	0.74	0.51 - 0.97		71.38	
Study location				0.00		0.96
US only	7	0.62	0.37 - 0.88		78.68	
Not US only	4	0.63	0.28 - 0.99		9.85	
Primary funding source				0.31		0.58
Industry only	4	0.47	0.24 - 0.70		55.44	
Public only	5	0.57	0.28 - 0.87		48.85	

[a]Significant at the $p<0.05$ level
[b]Not enough variance

sTable 5. Multivariate Metaregression Analyses		
	B[1]	**p**
Placebo lead-in	-1.02	.90
Study location	0.63	.59
Illness Duration	-1.23	.52
Publication Year	0.47	.73
Age of Onset	-1.07	.50
Number of Sites	-0.58	.70
Baseline Severity	0.14	.85

[1] Standarized Beta

6. PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	p. 1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	p. 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	p.3-4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	p.4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	p.6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	p.5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	p.4 sFig 1
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	S1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	p.4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	p.4-5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	p.5

Section/topic	#	Checklist item	Reported on page #
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	p.5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	p.6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	p.6
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	p.6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	p.6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	p.7 sFigure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Table 1 (Quality)
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Figure 1
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	p.7-8
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	sFigure 2 S3
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	p.8 S4 S5

Section/topic	#	Checklist item	Reported on page #
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	p.8-9
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	p.10-11
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	p.11
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	p.6

References

1. Lipsey MW, Wilson DB. Practical meta-analysis: Sage publications Thousand Oaks, CA; 2001.
2. Cuijpers P, van Straten A, Warmerdam L, Smits N. Characteristics of effective psychological treatment of depression: a metaregression analysis. Psychotherapy Research. 2008;18(2):225-36.
3. Cuijpers P, van Straten A, Bohlmeijer E, Hollon SD, Andersson G. The effects of psychotherapy for adult depression are overestimated: a meta-analysis of study quality and effect size. Psychological Medicine. 2010;40:211-23.
4. Cuijpers P, Huibers M, Ebert DD, Koole SL. How much psychotherapy is needed to treat depression? A metaregression analysis. Journal of Affective Disorders. 2013;149:1-13.
5. Cuijpers P, Sijbrandij M, Koole SL, Andersson G, Beekman AT, Reynolds CFI. The efficacy of psychotherapy and pharmacotherapy in treating depressive and anxiety disorders: a meta-analysis of direct comparisons. World Psychiatry. 2013;12:137-48.

Appendix D

Curriculum Vitae

CURRICULUM VITAE: HELEN KOECHLIN

1. Personal Information

Date of Birth	03.08.1988
Nationality	Swiss
Contact	Salinenstrasse 17 4052 Basel helen.koechlin@unibas.ch +41 (0)79 747 29 88
Marital Status	Married
Children	Theodor, born May 1st 2017
h-index	1
OcrID:	0000-0001-6680-8027
Researchgate ID:	Link
Google Scholar ID:	Link

2. Education

Since July 2016	*Faculty of Psychology, University of Basel, Switzerland* PhD student at the department of Clinical Psychology and Psychotherapy, supervised by Professor Jens Gaab
Sept. 2015 – Dec. 2016	*Boston Children's Hospital, Harvard Medical School* Visiting scholar, supervised by Joe Kossowsky, PhD
Since August 2014	*Dissertation project*, *University of Basel* A Multimodal Approach to Investigating the Importance of Emotional Functioning in Childhood and Adolescence
Sept. 2011 – Dec. 2013	*Master of Science in Psychology, University of Zurich* Specializing in Clinical Psychology for Children/Adolescents and Couples/Families. Master's dissertation: Validating the German version of the 'Inventory of Interpersonal Strengths (IIS-64) and developing a German short version (IIS-32)' (in English, Grade: 5.5)
Sept. 2008 – June 2011	*Bachelor of Science in Psychology, University of Basel* Bachelor's dissertation: 'Using the example of Triple P: Does the promotion of self-regulation have an impact on children's resilience?' (in English, Grade: 6)

3. Employment History

Since July 2016	**PhD candidate** University of Basel Department of Clinical Psychology and Psychotherapy (50%). Advisor: Prof. Jens Gaab
Aug. 2011 – Aug. 2014	**Teacher for Social Sciences,** School for Technical Diploma, Münchenstein, Switzerland (20-50%). Advisor: Sabina Mohler
April 2013 – Feb. 2014	**Research assistant**, University of Zurich, Department of Clinical Psychology for Children/Adolescents and Couples/Families (10%). Advisor: Prof. Guy Bodenmann
April / May 2012	**Research intern** at the University of Oxford, Department of Psychiatry, Section of Child & Adolescent Psychiatry (100%). Advisor: Prof. Alan Stein
Jan. / Feb. 2012	**Research intern** at Saarland University, Department of Clinical Psychology and Psychotherapy (80%). Advisor: Prof. Tanja Michael

Aug. 2010 – Aug. 2011	**Research assistant** University of Basel, Department of Clinical Child and Adolescent Psychology (20%). Advisor: Prof. Silvia Schneider
Jan / Feb 2010	**Clinical intern**, Outpatients' Department of Child and Adolescent Psychiatry, Basel (100%). Advisor: Dr. Joachim Schreiner

4. Institutional Responsibilities

Since 2017	Co-lead of colloquium for master students

5. Approved Research Projects

September 2016	Efficacy and Safety of SSRIs and SNRIs in Children and Adolescents, PROSPERO: CRD42016048552. Main applicant.
July 2015	"The Role of Emotion Regulation in Chronic Pain" – approved by the Freiwillige Akademische Gesellschaft Basel. Main applicant.

6. Supervision of students / junior researchers

2017 - current:	Supervision of one Master's thesis (by Marion Rudaz) Supervision of two Bachelor's theses (by Caroline Gerber and Berfin Celik)

7. Teaching Activities

Spring semester 2017	Seminar for master students "Emotion regulation in childhood and adolescence"
Fall semester 2018	Lecture for bachelor students "Clinical child and adolescent psychology
Since 2017	Colloquium for master students of the Department of Clinical Psychology and Psychotherapy

8. Memberships in Panels, Boards, etc., and Individual Scientific Reviewing Activities

Since 2018	Ad-hoc reviewer for the Journal of Patient experience

9. Active Membership in Scientific Societies, Fellowships in Renowned Academies

Since 2018	Member of the *International Association for the Study of Pain, Special Interest Group on Pain in Childhood*
Since 2017	Member of the *Society of Pediatric Psychology, American Psychological Association Division 54*
Since 2016	Member of the *Society for Interdisciplinary Placebo Studies* (SIPS)
Since 2016	Affiliated with the Department of Anesthesiology, Perioperative, and Pain Medicine, Boston Children's Hospital, Harvard Medical School, Boston, USA
Since 2015	Member of the *Freiwillige Akademische Gesellschaft*, Basel

10. Organization of conferences

Since May 2018	Member of the Local Organizing Committee for the International Symposium on Pediatric Pain 2019 in Basel

11. Prizes, Awards, Fellowships

May 2018	get on track, University of Basel, funding for a research assistant for 6 months (August 2018 – January 2019)
Feb. – Nov. 2018	antelope@university – successful career program, University of Basel
Feb 2018	Travel grants for the first *Pediatric Placebo Meeting* at Boston Children's Hospital, Harvard Medical School, Boston, from the Travel Fund of the University of Basel
Spring 2017	Nominated for the Teaching Excellence Award, Modern Scholarship
July 2015	Grant by the Freiwillige Akademische Gesellschaft Basel, CHF 7000, for research project 'The Role of Emotion Regulation in Chronic Pain'

12. Personal Skills

Languages	German (native), English (fluent), French and Spanish (basic knowledge)
Technical Skills	Microsoft, Mac OS, SPSS, Zotero, EndNote, R

13. Career Breaks

April – Sept. 2017	Maternity leave

Research Output List

Publications

Locher C*, **Koechlin H*,** Zion SR, Werner C, Pine DS, Kirsch I, Kessler RC, Kossowsky J. Efficacy and Safety of Selective Serotonin Reuptake Inhibitors, Serotonin-Norepinephrine Reuptake Inhibitors, and Placebo for Common Psychiatric Disorders Among Children and Adolescents. A Systematic Review and Meta-analysis. *JAMA Psychiatry, 74(10)*, 1011-1020.

Koechlin H, Coakley R, Schechter N, Werner C, Kossowsky J. (2018). The role of emotion regulation in chronic pain: A systematic literature review. *Journal of Psychosomatic Research, 107,* 38-45.

Koechlin H*, Donado C*, Berde C, Kossowsky J. (accepted). Effects of childhood life events on adjustment problems in adolescence: A longitudinal study. *Journal of Developmental and Behavioral Pediatrics.*

Koechlin H, Kossowsky J, Gaab J, Locher C. (2018). How to address the placebo response in the prescription of SSRIs and SNRIs in children and adolescents. *Expert Opinion on Drug Safety,* DOI: 10.1080/14740338.2018.1475558

*Authors contributed equally to the study.

Presentations

International Association for the Study of Pain, World Congress 2018, Boston, September 12th – 16th 2018. Poster: Koechlin, H. & Locher, C. Best pharmacological treatment option(s) for patients with chronic primary pain: A network meta-analytic approach.

Pediatric Pain Conference: State of the Art and Science 2016, Boston Children's Hospital, Harvard Medical School, Boston, USA, September 30 and October 1, 2016. Poster: Koechlin, H., Coakley, R., Schechter, N. L., Berde, C., & Kossowsky, J. The Role of Emotion Regulation in Chronic Pain: A Systematic Literature Review.

1st Official Society for Interdisciplinary Placebo Studies (SIPS), April 2-4, 2017. Abstract selected for oral presentation: Efficacy and Safety of SSRIs, SNRIs, and Placebo in Common Psychiatric Disorders: A Comprehensive Meta-Analysis in Children and Adolescents.