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Universal prevention of anxiety and depression in school children

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Abstract
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Anxiety and depression are common in children and adolescents, and involve individual suffering, risk of future psychiatric problems, and high costs to society. However, only a limited number of children experiencing debilitating anxiety and depression are identified and receive professional help. One approach that could possibly reduce the prevalence of these conditions is universal school-based prevention aimed at reducing the impact of risk factors and strengthening protective factors involved in the development of anxiety and depression. The current thesis aimed to contribute to the literature on universal prevention of anxiety and depression in children. Study I involved a meta-analysis of earlier randomized, and cluster-randomized trials of universal prevention of anxiety and depression. Overall, the meta-analysis showed small but significant effects of universal preventive interventions, meaning that lower levels of anxiety and depression were evident after intervention completion and partially evident at follow-up assessments. No variables were found to significantly enhance the effects, however, there was a tendency for larger effects to be associated with mental health professionals delivering the interventions. In Study II, a widely adopted prevention program called Friends for Life was evaluated in a large school-based cluster-randomized effectiveness trial. The results showed no evidence of an intervention effect for the whole sample. However, children with elevated depressive symptoms at baseline and children with teachers who highly participated in supervision, seemed to benefit from the intervention in the short term. Study III involved a 3-year follow-up of Study II and an examination of the effects of sample attrition. The results showed no long-term effects for the whole sample and no maintenance of the short-term subgroup effects observed in Study II. Finally, to increase our understanding of the development of anxiety in children and to assist future improvements of universal prevention, Study IV evaluated different trajectories of overall anxiety together with related patterns of disorder-specific symptoms in a school-based sample over 39 months. Evidence favored a model of three different developmental trajectories across age. One trajectory was characterized by increasing levels of overall anxiety, but fluctuating disorder-specific symptoms arguably related to the normal challenges of children's developmental level, which warrants an increased focus on age-relevant challenges in universal prevention. The four studies provide further understanding of the overall effectiveness of universal prevention of anxiety and depression in children, the short- and long-term effects of universal prevention in a Swedish context, and ideas for further development of preventive interventions.

Keywords: universal prevention; anxiety; depression; school children; cluster-randomization; long-term effects; developmental trajectories

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List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

I Ahlen, J., Lenhard, F., & Ghaderi, A. (2015). Universal Prevention for Anxiety and Depressive Symptoms in Children: A Meta-analysis of Randomized and Cluster-Randomized Trials. *The Journal of Primary Prevention*, *36*, 387-403.

II Ahlen, J., Hursti, T., Tanner, L., Tokay, Z., & Ghaderi, A. (2017). Prevention of Anxiety and Depression in Swedish School Children: a Cluster-Randomized Effectiveness Study. *Prevention Science.* Advance online publication.

III Ahlen, J., Lenhard, F., & Ghaderi, A. (submitted manuscript). Long-term Outcome of a Cluster-Randomized Universal Preventive Intervention targeting Anxiety and Depression in School Children.

IV Ahlen, J., & Ghaderi, A. (submitted manuscript). Disorder-specific symptom patterns in trajectories of general anxiety: A longitudinal prospective study in school aged children.

Contents

Abbreviations

ACME	Average Causal Mediation Effect
ANOVA	Analysis of Variance
AP	Academic Performance
BI	Behavioral Inhibition
CDI-S	Children's Depression Inventory – Short version
C-RCT	Cluster-Randomized Controlled Trial
DSM	Diagnostic and Statistical Manual of Mental Disorders
EC	Effortful Control
FFL	Friends for life
ICC	Intra Cluster Correlation
LCGMM	Latent Class Growth Mixture Model
LIX	Läsbarhetsindex
LMM	Linear Mixed Model
MHP	Mental Health Professional
MINI-kid	Mini International Neuropsychiatric Interview for Children
NA	Negative Affectivity
NNT	Numbers Needed to Treat
PA	Positive Affectivity
PH	Physiological Hyperarousal
PRP	Penn Resiliency Program
RAP	Resourceful Adolescent Program
RCI	Reliable Change Index
RCT	Randomized Controlled Trials
SCAS	Spence Children's Anxiety Scale
SCAS-P	Spence Children's Anxiety Scale – Parent version
SCAS-12	Spence Children's Anxiety Scale – 12 item version
SDQ	Strength and Difficulties Questionnaire

Introduction

Mental illness is the leading cause of disability in children and adolescents globally (Erskine et al., 2015). A recent report from the Swedish National Board of Health and Welfare (2013) concluded that mental illness has increased in young people during the last two decades, and the latest information at hand indicates a continued increase. Young people particularly reported increased anxiety, which may be a precursor of future mental illness and suicide attempts. A growing fraction of mentally ill children and youths constitute a major public health problem, which is why early interventions have received specific attention in the Swedish government's mental health strategy for the years ahead (National Board of Health and Welfare, 2017).

The evidence base for prevention of mental illness in Sweden is scarce. In a review by the Swedish Council on Technology Assessment (2010), it was concluded that no prevention program targeting mental illness in children was adequately evaluated to be considered as evidence-based in a Swedish context. Consequently, an important aim for prevention research in Sweden is that programs are proven to be effective in a Swedish context, as preventive programs often yield mixed results between countries (Sundell, Ferrer-Wreder, & Fraser, 2014; Swedish Council on Technology Assessment, 2010). One program of interest, and highlighted in the Swedish Council on Technology Assessment review (2010) is Friends for Life (FFL), a prevention program developed in Australia aimed at reducing anxiety and depression in children. The efficacy and effectiveness of FFL has been evaluated in several countries. A pilot study of FFL was also performed in Sweden (Ahlen, Breitholtz, Barrett, & Gallegos, 2012) where it showed preliminary evidence of reducing depressive symptoms, and improving general mental health.

The empirical studies in the current thesis all aimed to contribute to the existing literature on the effectiveness, and further development of preventive interventions of anxiety and depression in children. More specifically, these four studies embraced the overall effectiveness of universal prevention of anxiety and depression, the short and long-term effectiveness of a universal preventive intervention in a Swedish context, possible mechanisms of the effects, important methodological aspects of the design, and developmental issues that are important for the further development of preventive intervention. To introduce the reader to the field, a summary of recent research on anxiety and depression in children, alongside related prevention research, is provided before the empirical studies are presented.

Anxiety in children

Fear is a basic human emotion, which serves as an adaptive response when facing a threat (Gullone, 2000). The words 'fear' and 'anxiety' are frequently used interchangeably, but fear is more commonly chosen when describing a response to an objective or real threat, while anxiety concerns a subjective, or perceived threat (Huberty, 2012). Fears and anxiety are common early in life and are a normal part of a child's development. However, for a considerably large number of children, fears and anxiety become disruptive (Hale, Raaijmakers, Muris, & Meeus, 2008; Muris, Merckelbach, Mayer, & Prins, 2000). Up-to-date models delineating the etiology of maladaptive anxiety in children suggest a complex interaction between biological, psychological, social, and environmental components (Ollendick & Grills, 2016). In the following sections, clinical features of maladaptive anxiety, the onset, prevalence and consequences of anxiety disorders, alongside biological, psychological, social, and environmental risk factors associated with the development of maladaptive anxiety are presented.

Clinical features

Clinical fears, termed anxiety disorders in the literature, are in general distinguished from normal fears based on the frequency and intensity of symptoms, persistence over time, and to what extent it affects the child's life and function (Gullone, 2000). There are several anxiety disorders defined in the Diagnostic and Statistical Manual of Mental Disorders (5th ed.; DSM–5; American Psychiatric Association, 2013). The most common are separation anxiety disorder, specific phobia, social anxiety disorder, panic disorder, agoraphobia, and generalized anxiety disorder. In the earlier version of the Diagnostic and Statistical Manual of Mental Disorders (4th ed., text rev.; DSM–IV–TR; American Psychiatric Association, 2000), obsessive-compulsive disorder was also classified as an anxiety disorder. However, in the DSM-5 it has been relocated to the new chapter called Obsessive-Compulsive and Related Disorders.

Separation anxiety disorder is characterized by an excessive and developmentally deviant level of anxiety in separations or anticipated separations from an attachment figure. Separation anxiety disorder is most common in children, but also rather prevalent in adults (Bögels, Knappe, & Clark, 2013).

Specific phobia is defined as an evident and exaggerated fear when confronting or anticipating a specific object or situation. Specific phobias in children mainly surround fear of animals (e.g., spiders, dogs) and fear of natural environments (e.g., storms, darkness), but also blood-injection-injury fear (Essau, Conradt, & Petermann, 2000; LeBeau et al., 2010)

Social anxiety disorder is characterized by disproportional fear and anxiety in social situations where the individual feels noticed, observed or scrutinized. For children, these features have to be observed in situations with peers and

not solely in interactions with adults. The recent update in DSM-5 more carefully stresses that social anxiety disorder typically includes multiple social fears and consequences rather than just a specific fear of speaking or performing in front of others (Heimberg et al., 2014).

Panic disorder is characterized by unexpected and repeated panic attacks together with a persistent worry of future panic attacks and their consequences. Agoraphobia is defined by an exaggerated fear and engagement in avoidant behavior when confronting or expecting public situations like crowds and public transportation. Contrary to the former version of DSM, panic disorder and agoraphobia are now separated as two specific disorders (Asmundson, Taylor, & Smits, 2014).

Generalized anxiety disorder includes excessive and persistent worry regarding several day-to day situations or activities, together with difficulties controlling worry. School, family, significant others' health, and things going on in the world have been found to be the most common domains of worry in children with generalized anxiety (Jarrett, Black, Rapport, Grills-Taquechel, & Ollendick, 2015).

Obsessive-compulsive disorder is characterized by time-consuming obsessions (i.e., annoying and intrusive thoughts or impulses), compulsions (i.e., repetitive compulsive behaviors or mental rituals) or both. A majority of experts around the world agreed that obsessive-compulsive disorder should be moved from the construct of anxiety to a separate construct in DSM-5, as intrusive thoughts and repetitive behaviors rather than anxiety are the primary features of the disorder (Mataix-Cols, Pertusa, & Leckman, 2007).

Course and onset

The overall course of anxiety symptoms across childhood and adolescent years has been described in several studies (e.g., Hale et al., 2008; Olatunji & Cole, 2009). These studies have typically reported a general decrease in anxiety symptoms from childhood through adolescence, except for a relatively stable course of social anxiety symptoms (Hale et al., 2008). A comprehensive model of the continuity and change of anxiety symptoms has been presented by Weems (2008). The model suggests that there are core features of anxiety such as worry, avoidance, and somatic symptoms, and, that there are secondary features (e.g., fear of separation from parents, fears of bodily symptoms) which discriminate between the anxiety disorders as defined in the DSM-5 (American Psychiatric Association, 2013). Weems (2008) suggested that the core features are rather stable over time, whereas the secondary features might vary across age. In part, the variations in secondary features are thought to be due to normative challenges, meaning typical challenges in childhood development tied to certain ages, for example, separation from caregivers in early school years, or interpersonal interactions in adolescent years. Further, the

model suggests that subgroups of children primarily follow four different trajectories, characterized by (1) low and stable, (2) high and stable, (3) low and increasing, and (4), high and decreasing anxiety levels across age. Numerous recent studies have examined the evidence of different trajectories of anxiety in children (e.g., Allan et al., 2014; Duchesne, Larose, Vitaro, & Tremblay, 2010; Feng, Shaw, and Silk, 2008; Weeks et al., 2014). A couple of these studies have found support for the proposed trajectories as presented by Weems (2008) (e.g., Duchesne et al., 2010; Feng et al., 2008). However, other studies have found another pattern, characterized by rather homogeneous levels of anxiety at the early ages and diverging trajectories over time (e.g., Allan et al., 2014; Crocetti, Klimstra, Keijsers, Hale, & Meeus, 2009; Letcher, Sanson, Smart, & Toumbourou, 2012). Evidence that supports the association between anxiety and normative challenges comes from studies of disorder onset, and studies showing that symptoms of social anxiety typically increase over time in school-aged samples, whereas symptoms of separation anxiety typically decrease (Weems & Costa, 2005; Westenberg, Gullone, Bokhorst, Heyne, & King, 2007).

Anxiety disorders often have their onset early in life. In a large American nationally representative adult sample, retrospective reports yielded a median age of 11 years regarding the overall onset of anxiety disorders (Kessler et al., 2005). Kessler and colleagues (2005), however, found substantial differences between anxiety disorders, where specific phobia and separation anxiety disorder had their median onset at age seven, social phobia at age 13, obsessive-compulsive disorder at age 19, panic disorder at age 24, agoraphobia at age 20, and generalized anxiety disorder at age 31. In a longitudinal study, including a large sample of children and adolescents up to the age of 21, a mean onset before age ten was found for separation anxiety disorder, specific phobia, generalized anxiety disorder, and social phobia. However, a later onset was found for agoraphobia and panic disorder (Costello, Egger, Copeland, Erkanli, & Angold, 2011).

The continuity and change of anxiety disorders (rather than anxiety symptoms) have also been examined in several studies (Costello et al., 2011). In a longitudinal study, Last, Perrin, Hersen, & Kazdin (1996) found that children were typically free from their baseline anxiety disorder after three years, but commonly met criteria for another anxiety disorder (so called heterotypic continuity). Further evidence of heterotypic continuity was found in a recent study by Lieb et al. (2016), who found that specific phobia in childhood largely predicted panic disorder, generalized anxiety disorder, and obsessive-compulsive disorder in young adults. Finally, some support for homotypic continuity have also been found especially regarding separation anxiety disorder, and social anxiety disorder (Bittner et al., 2007).

Prevalence and consequences

Anxiety disorders are the most prevalent psychiatric disorders in children worldwide (Polanczyk, Salum, Sugaya, Caye, & Rohde, 2015). Prevalence rates differ substantially between studies, with point-prevalence studies using strict criteria (including structured questions of distress and impact of symptoms) showing lower prevalence rates (e.g., 3.7%; Ford, Goodman, & Meltzer, 2003). Lifetime-prevalence and retrospective cross-sectional studies typically provide significantly higher prevalence rates (e.g., 31.9%; Merikangas et al., 2010a). A good estimation based on a longitudinal prevalence study following three large cohorts of children between the ages of 9 and 16 showed a cumulative prevalence of 9.9% before the age of 16 (Costello, Mustillo, Erkanli, Keeler, & Angold, 2003). The prevalence seems to differ between age-groups. Copeland, Angold, Shanahan, and Costello (2014) found a relatively high prevalence of anxiety disorders in children aged 9-10 years, but a much lower prevalence in children aged 11-12 years, but thereafter, an increasing prevalence through adolescence. The high prevalence at younger ages was due to a large number of separation anxiety disorders, and the increased prevalence in adolescence was due to an increased number of generalized anxiety, panic, and agoraphobia disorders.

In recent years, anxiety disorders have been identified as the sixth leading cause of disability worldwide (Baxter, Vos, Scott, Ferrari, & Whiteford, 2014), and have been found to be as disabling as depression and oppositional defiant disorder in children and adolescents (Ezpeleta, Keeler, Erkanli, Costello, & Angold, 2001) including adverse effects on several life domains like school functioning (i.e., Weeks, Coplan, & Kingsbury, 2009) peer relationships (i.e., Danzig et al., 2013) and family life (i.e., Ezpeleta et al., 2001). Furthermore, anxiety disorders in children have been found to predict future anxiety disorders and depression (i.e., Bittner et al., 2007), alcohol and drug abuse and suicidal behavior in adolescence (Marmorstein, White, Loeber, & Stouthamer-Loeber, 2010; Woodward, & Fergusson, 2001) and health, financial, and interpersonal problems in young adulthood (Copeland et al., 2014). Finally, anxiety disorder in children also involves significant costs to society (Bodden, Dirksen, & Bögels, 2008; Snell et al., 2013).

Biological perspectives

Not surprisingly, research indicates that childhood anxiety is influenced by both genes and the environment (Gregory & Eley, 2011). Twin studies have typically found evidence of a genetic influence on anxiety, but the effect differs between sources of reporting (e.g., parent ratings vs. self-reports), and the child's gender and age (Ask, Torgersen, Seglem, & Waaktaar, 2014; Gregory & Eley, 2007). For example, studies using parent reports of the child's anxiety

have found that the genetic influence is more central than environmental factors, while studies using children's self-reports have suggested the opposite (Ask et al., 2014; Thapar & McGuffin, 1995). A general suggestion is that about one-third to one-half of the variation in etiology is influenced by genes (Fisak & Grills-Taquechel, 2007; Spatola et al., 2007). The genetic influence on anxiety is complex to study, because, there are probably plentiful genes involved which interact with each other, and the environment (Smoller, Block, & Young, 2009). Although recent research has found a strong association between anxiety and specific gene regions (e.g., Otowa et al., 2016), replicating studies, and especially those involving children, have found very mixed results (Gregory & Eley, 2011).

The neural foundation of childhood anxiety is not comprehensively explored, and the understanding of the fear circuitry in humans is largely based on functional neuroimaging studies in adults (Blackford & Pine, 2012). In summary, adult studies suggest that anxiety disorder may be characterized by a hyperactive amygdala, and a hypoactive prefrontal cortex (Diekhof, Geier, Falkai, & Gruber, 2011; Etkin & Wager, 2007). Neuroimaging studies in children have shown similar locations of abnormalities in the brain compared to studies on adults (Mana, Martinot, & Martinot, 2010). However, contrary to adults, an increased (rather than decreased) activity has been found in the prefrontal cortex in children with anxiety disorders (Blackford & Pine, 2012).

Temperament

Temperament is defined as a heritable, biologically based alteration that affects the character and behavior of an individual (Lonigan, Phillips, Wilson, & Allan, 2011). Although the distinction between temperament, personality, and psychopathology is not completely clear (Lonigan et al., 2011; Muris & Ollendick, 2005), temperament is assumed to (partially) underlie and predispose anxiety disorders. Two models of temperament relevant to the development of anxiety disorder are briefly described in this section; (1) affective reactivity and effortful control and (2), behavioral inhibition. According to Rothbart and Rueda (2005), temperament refers to affective reactivity and self-regulation processes which alter this reactivity. In short, affective reactivity is divided into two higher-order dimensions labeled negative affectivity (NA) and positive affectivity (PA). NA includes feelings of sadness, anger and fear, and these feelings activate, for example, avoidant behaviors. PA includes feelings of happiness and activeness, which activates approaching behaviors (Rothbart & Rueda, 2005). Additionally, a third higher-order dimension labeled Effortful Control (EC) includes attention shifting and inhibitory control, which alter negative emotions and activate coping strategies to reach long-term goals (Lonigan et al., 2011; Rothbart & Rueda, 2005). In a longitudinal study, Lonigan, Phillips and Hooe (2003) found evidence supporting the notion that NA predicted change in anxiety symptoms in children. Further,

Meesters, Muris, and van Rooijen (2007) showed that NA was positively associated, and EC negatively associated with anxiety symptoms, and, additionally, that NA and EC had an interactive effect on anxiety symptoms in children. More recent research has showed that the strength of the association with NA varies between different anxiety disorders and that the association between NA and EC is valid only for generalized anxiety disorder, separation anxiety disorder, panic disorder, and agoraphobia (Lonigan et al., 2011). Recent research has also found that in children displaying high NA, EC only work as a regulator at low, but not at high, stress levels (Gulley, Hankin, & Young, 2016).

Behavioral inhibition is characterized by high levels of physiological arousal and behavioral avoidance to novel or unfamiliar situations, persons, or objects (Degnan, Almas, & Fox, 2010; Fox & Pine, 2012). The expression of BI is considered to vary between age groups, from motor reactivity and negative emotions in babies, crying and clinginess in toddlers, quietness and shyness in preschoolers, to avoidant behavior in social contexts in childhood and adolescents, and to cautiousness and restraint in conversations in adulthood (Hirshfeld-Becker et al., 2008). About 15% of all children are thought to display BI, and these children have been found to be at increased risk of anxiety disorders, especially social anxiety disorder (Muris, van Brakel, Arntz, & Schouten, 2011). Referring to studies of the neurobiology of anxiety, Pérez-Edgar and Fox (2005) and Fox and Pine (2012) have suggested that the temperament of BI involves reacting immediately to threats (i.e., a hyperactive amygdala).

Information processing

A considerable amount of research has been conducted on the relationship between anxiety and information processes (Field, Hadwin, & Lester, 2011). Two forms of information processing biases commonly addressed in the anxiety literature are: (1) attentional bias and (2) interpretation bias. Attention bias is characterized by a hyper-attention towards threatening or fearful stimuli in the environment (Muris & Fields, 2008). A recent meta-analysis showed that an attention bias towards threat is found in all children, but significantly greater in anxious children compared to non-anxious children (Dudeney, Sharpe, & Hunt, 2015). Field and Lester (2010) have proposed a model delineating the development of attention bias, which suggests that children generally display attention bias to threats early in life, but over time, children develop in different ways. This model has been supported by Dudeney and colleagues (2015) who found that the difference in attention bias between anxious and non-anxious children increased with age.

Interpretation bias concerns the tendency to imagine overly threatening interpretations of ambiguous stimuli (Field et al., 2011). Several studies have found that children with an anxiety disorder interpret ambiguous stories more

threatening than normal controls (Bögels & Zigterman, 2000; Creswell & O'Connor, 2011). However, this difference was only found in children aged 9-18 years, and not in younger children (Ooi, Dodd, & Walsh, 2015). Unlike the model proposed for the development of attention bias over time, interpretation bias does not seem to be displayed by all children at young ages and are probably learned during childhood (Field & Lester, 2010).

Attention bias towards threat and interpretation bias in ambiguous situations have been proposed to be vulnerability factors for future anxiety disorders (Beck & Clark, 1997). However, recent longitudinal research has rather found evidence supporting anxiety symptoms predicting changes in information processing biases (Creswell & O'Connor, 2011), or that these biases possibly maintain anxiety symptoms over time (Dodd, Hudson, Morris, & Wise, 2012). Furthermore, some evidence suggests that the development of information processing bias is explained by anxious parenting, typically directing the child's interpretation towards threat (Field et al., 2011).

Emotion regulation

The awareness of one's one emotions, and the ability to evaluate and alter the emotional experience has been progressively studied within the concept of emotion regulation (Jacob, Thomassin, Morelen, & Suveg, 2011). Emotion dysregulation is not exclusively linked to anxiety disorders, but there are distinct features of emotion regulation strategies typically associated with anxiety disorders (Amstadter, 2008). Recent research suggests that different emotion regulation strategies affect the amplitude of the anxiety response (Cisler, Olatunji, Feldner, & Forsyth, 2010). Correspondingly, and closely related to the temperament of NA and EC addressed above, children with anxiety disorders have been found to display more dysregulated expressions of emotions and less adaptive coping (Suveg & Zeman, 2004). The foundations of emotion dysregulation associated with anxiety are thought to be biological, cognitive, and environmental (Jacob et al., 2011). Regarding biology, neuroimaging studies have found that reappraisal strategies (i.e., cognitively try to reinterpret negative stimuli into not evoking negative emotion) are associated with less activity in amygdala, and increased activity in the pre-frontal cortex (Banks, Eddy, Angstadt, Nathan, & Phan, 2007; Ochsner et al., 2004; Phan et al., 2005). Regarding cognitions, attention to positive stimuli have been found to be associated with better emotion regulation and less frustration (Cisler & Koster, 2010). Finally, regarding environmental factors, anxious parents have been found to model dysfunctional emotion regulation strategies like avoidance behaviors, and, parents of anxious children have been found to be less encouraging in emotional discussions with them (Hannesdottir & Ollendick, 2007; Suveg, Zeman, Flannery-Schroeder, & Cassano, 2005).

Parental influences

Research suggests that a significant part of the etiology of anxiety disorder is explained by environmental factors (Fisak & Grills-Taquechel, 2007). Most commonly studied are parental factors, thus, parents' influence on childhood anxiety (Francis & Chorpita, 2011). There is growing evidence that parenting style influences the risk of childhood anxiety (Wood, McLeod, Sigman, Hwang, & Chu, 2003). The literature suggests that children with a vulnerability to anxiety may be extra sensitive to a dysfunctional parenting style in comparison to children without this vulnerability (Cartwright-Hatton, McNicol, & Doubleday, 2006; Pereira, Barros, Mendonça, & Muris, 2014). Several studies have found an association between anxiety in children and a parental style characterized by rejection, criticism, and low warmth (Breinholst, Esbjørn, Reinholdt-Dunne, & Stallard 2012). These parental behaviors are thought to impede the child's learning of emotional regulation, and how to cope with negative emotions (Wood et al., 2003). Controlling and over-protective behaviors have also been found to play a central part in the maintenance of anxiety disorders (Van Der Bruggen, Stams, & Bögels, 2008; Clarke, Cooper, & Creswell, 2013; Wood, Piancentini, South-Gerow Chu, & Sigman, 2006). Controlling and overprotective behaviors are characterized by helping the child do things that the child would be able to manage him/herself, or by stopping the child from participating in age-appropriate activities (Breinholst et al., 2013). Finally, anxious parents might pass on dysfunctional ways to cope with anxiety through model learning (Fisak & Grills Taquechel, 2007).

Depression in children

Depression is varyingly operationalized between studies. While sometimes referring to merely depressed mood (i.e., symptoms of dysphoria), most often, depression concerns depressive disorders, a group of disorders including symptoms of dysphoria combined with related cognitive and behavioral changes (Cicchetti & Toth, 1998; Friedman & Anderson, 2014; Kessler, Avenevoli, & Merikangas, 2001). Not too long ago, children were thought to be too immature to experience depressive disorders and moreover, changes in depressed mood were supposed to be self-regulated at that time in their development (Maughan, Collishaw, & Stringaris, 2013; Kessler et al., 2001). Today, most researchers and clinicians believe that children can be depressed and that it is not uncommon (Kessler et al., 2001; Weiss & Garber, 2003). In the following sections, clinical features of depression, the onset, prevalence and consequences of depressive disorders, together with biological, psychological, social, and environmental risk factors associated with the development of depression are presented.

Clinical features

There are two main depressive disorders, major depressive disorder and persistent major disorder (the latter formerly labeled as dysthymic disorder). Both these disorders include sad, depressive, or irritable mood, together with loss of interest in activities previously enjoyed. Depressive disorders involve undesirable changes in different domains (e.g., changed appetite, problems sleeping, less energy, etc.), which negatively affect the individuals' ability to function (American Psychiatric Association, 2013). Symptoms of depression can vary from mild to severe, and different subtypes of depression can be specified in a diagnostic process (e.g., with anxious distress, with melancholic features) to guide treatment choices (Beauchaine & Hayden, 2016).

Course and onset

The development of childhood and adolescent depression has been examined and described in several studies (e.g., Cicchetti & Toth, 1998; Dekker et al., 2007; Hankin, 2015; Hankin et al., 1998; Weiss & Garber, 2003). Studies examining the trajectories of depressive symptoms in community samples have typically found increasing symptoms in girls and stable symptoms in boys from childhood through adolescence (e.g., Hankin et al., 1998). Studies examining the presence of possible subgroup-specific trajectories have found evidence of several different paths (e.g., Castelao & Kröner-Herwig, 2013; Dekker et al., 2007). In summary, these studies have generally found that most boys follow trajectories labeled *low-stable*, or *low-decreasing*, while most

girls follow trajectories labeled as *low-stable*, or *low-increasing*. Studies examining the homotypic and heterotypic continuity of depressive disorders have found that a depressive disorder in childhood predicts future depression and/or anxiety disorders in adolescence (e.g., Costello et al., 2003). However, the continuity of depression from childhood into adulthood has generally not been supported (e.g., Copeland, Shanahan, Costello, & Angold, 2009).

Contrary to anxiety disorders, which often have their onset in childhood, the median onset of a depressive disorder is at the age of 30 years (Kessler et al., 2005). However, depression is still frequent in adolescence, with a sharp increase in depressive disorders during the age range of 13-15 years (Hankin et al., 1998; Merikangas et al., 2010a).

Prevalence and consequences

Although depression is not as common in childhood as in late adolescence and adulthood, depression is nevertheless quite prevalent in early adolescence (12-month prevalence of 4%), and in children, (12-month prevalence of 2%) (Merikangas et al., 2010b). The cumulative prevalence between the ages 9 and 16 has been estimated at 9.5%, comparable to the cumulative prevalence of an anxiety disorder (Costello et al., 2003).

Depression is a very serious disorder, as it is strongly associated with suicidal behaviors. Children and adolescents with a depressive disorder have a 12-fold increased risk of suicide attempts (Nock et al., 2013). Moreover, depressive disorders, especially at young ages, often involve a comorbidity to other psychiatric disorders. In school samples, the majority of children with a depressive disorder also meet criteria for another emotional or disruptive disorder (Maughan et al., 2013).

Depression has been found to be the second leading cause of years lived with disability (Ferrari et al., 2013). Depressive symptoms in childhood predict poor social well-being in adolescence (Verboom, Sijtsema, Verhulst, Penninx, & Ormel, 2014), unfavorable health profiles (e.g., obesity, smoking, low physical activity), increased risk of cardiovascular diseases in adulthood (Rottenberg et al., 2014), increased risk of substance abuse (Birmaher, Ryan, Williamson, Brent, & Kaufman, 1996), and lower academic achievements (Dekker et al., 2007).

Biological perspectives

Studies have rather consistently provided evidence that depression in children and adolescents are to some extent heritable (Rice, Harold, & Thapar, 2002). However, estimates of the effect vary between study-methods, which makes it difficult to draw any firm conclusions. For example, studies using parent-ratings of children's depressive symptoms have showed a median heritability of 60%, whereas studies using children's self-reports have found a median

heritability of 30% (Rice et al., 2002). Moreover, findings from twin studies have found evidence that it is mainly early onset depression that is heritable (Lau & Eley, 2008).

In the recent decade, numerous studies have explored gene* environment interactions, rather than assuming that genetic and environmental effects are independent of each other (Lau & Eley, 2008). For example, studies have found that children with a genetic variation (regarding genes involved in the regulation of serotonin) were at risk of developing depression, however, only when this genetic variation was combined with previous maltreatment or stressful life events, and, most severe also in combination with a lack of social support (Kaufman et al., 2004).

Recent neuroimaging studies in depressed children and adolescents have found alterations in the striatum regarding the anticipation and outcome of rewards (Forbes et al., 2009), especially, in situations with loss of rewards (Luking, Pagliaccio, Luby, & Barch, 2016). In summary, neuroimaging studies imply that depressed children display a different pattern of brain responses in experiences of rewards.

Temperament

The temperament model most relevant to the development of depression is the model of affective reactivity and effortful control. Similar to anxiety, depression has typically been associated with high levels of NA. However, in addition, depression has also been found to be associated with low levels of PA (Compas, Connor-Smith, & Jaser, 2004). For example, low PA and high NA in three-year-old children have been found to be associated with increased depressive symptoms at age ten (Dougherty, Klein, Durbin, Hayden and Olino, 2010). Furthermore, high NA low PA and low EC in adolescence have been found to be associated with high levels of depressive symptoms at a 1-year follow-up assessment. (Verstraeten, Vasey, Raes, & Bijttebier, 2009). However, contrary to the recent findings that effortful control may buffer the association between negative affect and anxiety, no such buffering effect has been found for depression (Gulley et al., 2016). Finally, the association between high NA and depression have been suggested to be driven by amplified stress, and that the association between low PA and depression by reduced social support (Wetter & Hankin, 2009).

Cognitive vulnerabilities

There is a huge literature on cognitive perspectives of depression (Abela & Hankin, 2008). In this section, we will briefly summarize some of these perspectives relevant for the development of depression in children and adolescents. Cognitive vulnerabilities are defined as stable cognitive attributes, which (in the interaction with environmental factors) puts an individual at risk

of developing depression (Abela & Hankin, 2008). Contrary to temperament (which is supposed to be an antecedent vulnerability to depression), cognitive vulnerabilities are thought to be stabilized in early adolescence (Hankin et al., 2009).

Most research on cognitive vulnerabilities has been conducted within the theorizing of attributional style. According to this perspective, individuals with depression are likely to interpret negative life events and life stress in a negative manner (regarding the consequences of the event, and their own ability to manage such consequences; Jacobs, Reinecke, Gollan, & Kane, 2008). However, studies examining the association between attributional style and depression in children have found mixed results. For example, while some researchers have found that negative attributional style predicts depressive symptoms in children (Steca et al., 2014), others have found that this association is only valid as children become adolescents (Cole et al., 2008). Furthermore, some researchers suggest that depression predicts a negative attributional style and not vice versa (i.e., LaGrange et al., 2011).

Moreover, taken from the perspective called the response style theory, which posits that individuals have different cognitive responses to depressive symptoms, a ruminating style has been found to be associated with future episodes of depression and to greater length of depressive episodes in children and adolescents (Abela & Hankin, 2011).

Parental depression

The association between maternal depression and an increased prevalence of childhood mood disorders (as well as other psychopathologies) is well recognized (Goodman et al., 2011; Hammen & Brennan, 2003). The effects of paternal depression are not equally studied, however, studies including depressed parents (i.e., both mothers and fathers) have found similar results (e.g., Weissman et al., 2006b). Moreover, those few existing studies of paternal depression have found similar negative effects on family functioning and child functioning compared to studies of maternal depression (Cummings, Kelly, & Davis, 2005; Wilson & Durbin, 2010). The increased risk of depression in offspring of depressed parents is suggested to be mainly caused by environmental factors (Singh et al., 2011). Accordingly, marital conflicts have been found to mediate the relationship between parental and child depression (Cummings et al., 2005), and high child-parent relationship quality has been found to weaken the association between stress and adolescent depression (Hazel, Oppenheimer, Technow, Young, & Hankin, 2014). Additional evidence that supports an environmental causal link between parental and offspring depression comes from studies showing that remission in maternal depression is associated with improvements (or less impairment) in offspring depression (e.g., Weissman et al., 2006a). Finally, different styles of positive parenting (i.e., low control, low over-involvement, and high warmth) have

been found to weaken the link between parental and offspring depression (Brennan, Le Brocque, & Hammen 2003).

Negative life events and childhood adversities

Negative life events and early childhood adversities have been found to be strongly associated with depression (Hankin et al., 2015). Two different models have been proposed, either that depression increases the probability of negative life events (i.e., the stress-generation model), or, that negative life events increase the probability of depression (i.e., the stress-exposure model). Evidence that supports both models has been found (Cole, Nolen-Hoeksema, Girgus, & Paul, 2006). Furthermore, an extension of these models is the stress-sensitization model, which postulates that an episode of depression scars the individual, who then becomes more sensitive to future negative stress (Shapero et al., 2014). Studies indicate that childhood adversities (especially emotional neglect) may be most strongly associated with lifelong depression (Spinhoven et al., 2010).

Although undoubtedly a risk factor in the development of depression, some individuals react more negatively than others to stressful life events and childhood adversities, which is why many studies have evaluated possible moderators of this association (Shapero et al., 2014). For example, dysfunctional attitudes and low self-esteem have been found to enhance the association between stress and depression in children (Abela & Skitch, 2007). Furthermore, female gender has been suggested to increase the association between age-related life stress in adolescence (e.g., pubertal transition) and depression (Ge, Conger, & Elder, 2001). Finally, positive life experiences such as parental support during adolescence have been found to decrease the risk (Stice, Ragan, & Randall, 2004), and children with high self-efficacy (i.e., children with beliefs in their own skills), have been found to be less susceptible to increased levels of stress (Steca et al., 2014).

Overlap between anxiety and depression

The literature has consistently reported high comorbidity between anxiety and depression in children (Cummings, Caporino, & Kendall, 2014). This has been found both regarding clinical comorbidity (i.e., the co-occurrence of the disorders) and epidemiological comorbidity (i.e., the overall association between symptoms; Cummings et al., 2014). Generally, high levels of anxiety have been found in depressed children, whereas high levels of depression in anxious children are not as commonly found (Costello et al., 2003; Ferdinand, de Nijs, van Lier, & Verhulst, 2005).

Several possible yet non-exclusive explanations have been suggested to elucidate the high degree of comorbidity. First, genetic studies have found evidence of a shared genetic background to anxiety and depression (e.g., Franić, Middeldorp, Dolan, Ligthart, & Boomsma 2010). Second, several studies have found a large overlap in symptoms questionnaires (sometimes even identical items) thought to evaluate the distinct constructs of anxiety and depression (Garber & Weersing, 2010). Third, shared risk factors have been suggested. For example, the tripartite model (Clark & Watson, 1991) postulates that high NA is a risk factor for both of these disorders, but that low PA is a specific risk factor for depression, and that high physiological hyperarousal (PH) is a specific risk factor for anxiety. According to this model, NA is the explanation for the high degree of comorbidity. However, some researchers have emphasized limitations to the tripartite model as PA and PH have not been found to adequately discriminate between anxiety and depression in empirical studies, and NA has been found to be variously associated with different specific anxiety disorders (Anderson & Hope, 2008). A variation of the tripartite model suggests two latent factors underlying anxiety and depression (i.e., fear and distress; Watson, 2005). In this model, depression and generalized anxiety are to a larger extent constituted by distress, whereas, for example, panic attacks and specific phobia are primarily constituted by fears (Garber & Weersing, 2010). Additionally, regarding shared risk factors, research has found that many cognitive features (e.g., information-processing biases, rumination, catastrophizing, and worrying) characterize both anxiety and depression (Garber & Weersing, 2010). Finally, in light of research showing that anxiety to a larger degree precedes depression, anxiety could serve as a risk factor for developing depression, which consequently may be an additional explanation to the high co-occurrence of disorders (Bittner et al., 2004).

The comorbidity between anxiety and depression has implications for the prevention of these disorders. First, given that anxiety and depression in part share the same risk factors, preventive interventions that target these risk factors may prevent both anxiety and depression (Garber & Weersing, 2010). Furthermore, some prevention studies have found effects on both outcomes (e.g., Essau, Conradt, Sasagawa, & Ollendick 2012) or an effect only on the construct not serving as the primary outcome (e.g., Roberts, Kane, Thomson,

Bishop, & Hart, 2003) regardless of primary target of the intervention (i.e., anxiety or depression). Finally, given that anxiety to a larger extent predicts depression, researchers have proposed that treating or preventing anxiety could be a way of preventing subsequent depression (Garber & Weersing, 2010).

Gender differences

Consistently in research, women show an increased risk of anxiety or depression (Craske, 2003). These differences are small in childhood (e.g., Muris, Merckelbach, Gadet, & Moulaert, 2000) but increase with age (Beesdo, Knappe, & Pine 2009; Nolen-Hoeksema, 2001). Several explanations for the emerging differences observed in adolescence have been presented. One hypothesis is that girls experience higher levels of negative affect, which results in increased anxiety and subsequent depression (Hankin & Abramson, 2001). Specifically regarding anxiety, research indicates that girls show increased anxious responses in contexts associated with fears and memories of fears, and furthermore, that girls are more prone to avoid fearful situations compared to boys (Craske, 2003). Specifically regarding depression, girls have been found to face more trauma (e.g., sexual abuse), more negative interpersonal events, harassments, and constrained choices compared to boys (Nolen-Hoeksema, 2001). Additionally, there may also be gender differences in the responses to stressful events. For example, elevated cortisol levels and elevated rumination in response to stress have been said to be involved in the increased risk of depression for girls (Nolen-Hoeksema, 2001).

Why prevention of anxiety and depression

Prevention of mental disorders, in comparison to treatment, aims to prevent or limit the occurrence of future negative outcomes, by reducing important risk factors and increasing important protective factors linked to the disorder of interest (Coie et al., 1993). The number of studies evaluating preventive interventions of anxiety and depression in children have increased in the last two decades, but the clinical utility of such interventions has not been fully established (Werner-Seidler, Perry, Calear, Newby, & Christensen, 2017).

There are several reasons why further evaluation and development of prevention of anxiety and depression is needed. First, only a few children and adolescents with life-interfering anxiety and/or depression use mental health services, which implies that many children and adolescents who suffer from these conditions are unidentified. For example, in Germany, Essau (2005) found that only 18% of adolescents with anxiety and 23% of adolescents with depression used mental health services. Further, in USA, Chavira, Stein, Bailey, and Stein (2004) found that only 30% of children with an anxiety disorder, and 40% of children with a depressive disorder had received either psychological or pharmacological treatment during their lives. Second, in cases when treatment has been initiated, the child has typically suffered from the condition for several years (Andrews, 2006). Finally, although there is evidence of effective treatments for anxiety and depression in children and adolescents (e.g., Hofmann, Asnaani, Vonk, Sawyer, & Fang, 2012), treatment dropout is not uncommon, and some researchers argue for the benefit of early prevention before negative cognitive and behavioral patterns have been solidly established (Werner-Seidler et al., 2017).

Prevention of mental disorders is commonly classified into three different levels depending on what selection of individuals the intervention is targeted to (Mrazek & Haggerty, 1994). In universal prevention, no selection of individuals is made, which mean that the intervention is directed to all individuals in the specific context (e.g., whole school classes; Lock & Barrett, 2003). In selective prevention, individuals are selected based on their being exposed to one or several risk factors (e.g., children with a depressed parent; Clarke et al., 2001; or behaviorally inhibited children, Morgan et al., 2017). Finally, in indicated prevention, individuals are selected based on their exhibiting early signs or symptoms of psychiatric problems (e.g., children with anxiety symptom scores over a certain cut-off; Rohde, Stice, Shaw, & Brière, 2014).

Indicated and selective interventions have generally involved stronger intervention effects in prevention of anxiety and depression (Fisak, Richard, & Mann, 2011; Horowitz & Garber, 2006; Stice, Shaw, Bohon, Marti, & Rohde, 2009; Teubert & Pinquart, 2011). Although displaying smaller intervention effects, some researchers argue for using universal intervention for a number of reasons. First, the larger effect-sizes found in selected and indicated prevention may not infer larger benefits to society (Nehmy & Wade, 2014). Small

effect-sizes in regard to the whole population can be of practical significance (Wilson & Lipsey, 2007), and, the larger effect-sizes in selective and indicated prevention might in part be an artifact due to evaluating more homogenous populations[1], or possibly due to floor-effects in universal prevention studies evaluating children where the majority are not symptomatic (Nehmy & Wade, 2014). Second, researchers have emphasized the universal prevention's possibility to reach all children in a certain context and, not be affected by screening problems. For example, Simon and Bögels (2009) found that although higher levels of self-rated anxiety predicted an anxiety disorder, many children who reported high anxiety did not meet the criteria for a disorder (i.e., a high degree of false positives), and, quite many children who reported low anxiety actually met criteria for a disorder (i.e., a high degree of false negatives). Furthermore, the use of depressive symptom questionnaires to screen for depression in children have showed similar problems (Swedish Council on Technology Assessment in Health Care, 2012). Finally, researchers suggest that universal interventions are more easily integrated into the school curriculum, associated with low dropout rates, and may be a way to avoid stigma associated with selective or indicated interventions (Fazel, Hoagwood, Stephan, & Ford, 2014; Fisak et al., 2011; Horowitz & Garber, 2006). On the other hand, some researchers have also highlighted the possible limitations with universal prevention underlining that these interventions might not be cost-effective as the intervention is given to a large number of children with very low risk of developing anxiety or depression (Fisak et al., 2011). Furthermore, Spence and Shortt (2007) have also emphasized the problem that a universal intervention might be too non-specific and low-intensity for children experiencing increased levels of anxiety or depression.

Universal prevention of anxiety and depression

Previous universal preventive interventions have most typically primarily targeted either anxiety or depression (e.g., Barrett & Turner, 2001; Chaplin et al., 2006; respectively), but sometimes both disorders jointly (e.g., Calear, Christensen, Mackinnon, Griffiths, & O'Kearney, 2009). However, when examining the content of these programs, many components are the same regardless of the primary target. For example, the most evaluated programs targeting anxiety (Friends for Life; Barrett, 2010) and depression (Penn Resiliency Program; Gillham, Brunwasser, & Freres, 2008), both contain the link between thoughts and feelings, negative and positive thoughts, breathing and relaxing exercises, support from others, breaking a challenging situation into smaller

[1] Homogenous populations involve smaller standard deviations of the outcome. This is associated with larger effect-sizes as the standard deviation serves as the denominator in the effect-size statistic commonly presented, i.e., Cohen's *d*.

steps, and problem-solving techniques (Briesch, Sanetti, & Briesch, 2010; Brunwasser, Gillham, & Kim, 2009).

The bulk of research on universal prevention of anxiety in children are evaluations of the FFL program. The first cluster-randomized controlled study of FFL (*N*=489) compared teacher-administered, and psychologist-administered FFL to a control group (Barrett & Turner, 2001). The results showed that children in both FFL groups had significantly larger decreases in anxiety symptoms between baseline and post intervention compared to controls. Furthermore, in a second cluster-randomized trial evaluating teacher-administered FFL (*N*=594), a similar result was found. Children in the intervention group showed decreased anxiety symptoms after the intervention compared to controls (Lowry-Webster et al., 2001). Finally, in a third cluster-randomized trial, comparing psychologist-administered FFL to a control group (*N*=977), the results showed that children in the intervention group had lower levels of anxiety post intervention and at follow-up assessments up to 36 months (Lock & Barrett, 2003; Barrett, Farrell, Ollendick, & Dadds, 2006). However, it is worth noting that the results of the third cluster-randomized trial are difficult to interpret as the analyses did not consider possible baseline differences in the analyses. More precisely, the intervention group had seemingly lower anxiety scores at baseline assessment, but unfortunately, statistical tests examining differences in baseline symptoms were not reported. To demonstrate the problem, the between-group effect-size (Cohen's *d*) at the 3-year follow-up was 0.19, but when controlling for pre-differences it was -0.01.

Four cluster-randomized trials of FFL have been performed outside of Australia, two in Canada (*N*=595 and *N*=293), one in Germany (*N*=638), and one in Great Britain (*N*=1448). These studies have found mixed results. In the Canadian trials (Miller et al., 2011a; Miller et al., 2011b), teachers and school counselors administered FFL and the results did not show any significant difference in anxiety between the intervention group and controls, neither at post nor at follow-up. In the German trial (Essau, et al., 2012), psychologists administered FFL. The results showed significantly lower anxiety and depressive symptoms for the intervention group at the one-year follow-up but not at post. Finally, the Great Britain trial (Stallard et al., 2014) which compared FFL administered by teachers to FFL administered by mental health professionals (MHPs), and to controls. In this trial, significantly lower anxiety and depressive symptoms were found in the MHP-administered FFL at the 1-year follow-up compared to the teacher-administered FFL and controls.

Regarding universal prevention of depression in children, several different programs have been evaluated. For example, Spence, Sheffield, and Donovan (2003) compared a teacher-administered intervention (Problem solving for life) to a control group in a large cluster-randomized trial (*N*=1500). The study found an intervention effect on depressive symptoms post intervention, but no significant effects were found at any of the annual follow-up assessments over

a 4-year period (Spence, Sheffield, & Donovan, 2005). In a randomized controlled trial (*N*=392), Merry, McDowell, Wild, Bir and Cunliffe (2004) compared a teacher-administered intervention (Resourceful Adolescent Program; RAP) to a placebo condition.[2] The results indicated a significantly larger decrease in depressive symptoms for children in the RAP condition post intervention compared to placebo. At the 18-month follow-up, differences in depressive symptoms were maintained for one of the two measures of depression. Finally, most studies of universal prevention of depression have involved evaluations of the Penn Resiliency Program (PRP). The largest evaluation of the PRP (*N*=697) was conducted by Gillham and colleagues (2007). The study was a randomized controlled trial with follow-up assessments over a 3-year period. No overall intervention effect was found on depressive symptoms either post intervention or at any follow-up assessment.

Gaps in evidence and research needed

Although there has been an increase in trials evaluating the effect of universal prevention on anxiety and depression since the millennium, there are still unanswered questions regarding the efficacy and effectiveness, and, possible factors associated with efficacy and effectiveness of such interventions. Beyond the need to examine the evidence base for preventive interventions in a Swedish context, there are a number of other issues to also consider.

First, almost all studies of universal prevention of anxiety and depression have exclusively used self-reports as outcome. Although some studies have aimed to include parent ratings of the child's symptomatology (e.g., Barrett & Turner, 2001; Lowry-Webster, Lock & Barrett, 2003), these studies have not managed to retain the number of parent reports needed to do statistical analyses, and, these outcomes have consequently been dropped from the results. Only one previous study has included teacher ratings (i.e., Stallard et al., 2014). There are reasons why a multi-informant approach is important to consider to fully understand the effects of preventive interventions for children. Most importantly, different informants might reveal information about distinctive contexts in which the child expresses anxiety or depressive symptoms (De Los Reys et al., 2015). Further, the lack of effects typically found in the literature on universal prevention of anxiety and depression might be an effect of only examining self-reports. For example, in one meta-analysis evaluating treatments of childhood anxiety, effect-sizes from self-reports were smaller than those from parent reports (Ishikawa, Okajima, Matsuoka, & Sakano, 2007). In the current thesis, a multi-informant approach using children, parents, teachers, and clinicians was used to address this issue.

[2] The placebo condition used similar workbooks, but only with focus on having fun, and not including any components thought to be active in preventing depression.

Second, although there exist a growing number of studies evaluating universal prevention of anxiety and depression (see, for example, Werner-Seidler et al., 2017), very few long-term evaluations have been conducted. For example, only four studies have included longer follow-ups than two years (Barrett et al., 2006; Gillham et al., 2007; Johnstone, Rooney, Hassan, & Kane, 2014; Spence et al., 2005). The possibility to draw valid conclusions based on the results from these studies have also been limited as these studies have suffered from high attrition rates. To really understand the preventive impact of universal interventions, long-term evaluations are needed. In the current thesis, a 3-year follow-up with a thorough examination of possible attrition-effects were performed to address this issue.

Third, one of the main arguments for the use of universal prevention, in favor of selective or indicated prevention, is the possibility to implement the intervention within the school-curriculum by school staff. However, meta-analyses have consistently showed that interventions administered by teachers show smaller effects. The causes have not been thoroughly examined, but researchers have suggested that it may partly be explained by a lack of broad and frequent support to teachers, which may decrease the fidelity of the implementation (Atkins, Cappella, Shernoff, Mehta, & Gustafson, 2017; Stice et al., 2009). To address this issue in the current thesis, supervision was offered to teachers during the delivery of the intervention.

Fourth, several meta-analyses of prevention on anxiety and/or depression have been conducted, and have generally showed small but significant mean effects sizes. However, as the results of individual trials have been mixed (i.e., some studies have showed small-to-medium effect-sizes; e.g., Essau et al., 2012; and some studies have showed null-effects or even tendencies of negative effects, e.g., Miller et al., 2011b), there is a great need to further evaluate possible factors that might explain the differences in results between studies (Collins, & Dozois, 2008). Although recent meta-analyses have provided some clues of possible moderators, these meta-analyses have suffered from two limitations regarding specific moderators of universal prevention. When conducting these moderator analyses, recent meta-analyses have combined intervention from different levels (i.e., universal, selective, and indicated), which is problematic as the level of prevention is likely to be correlated to some of the moderators. Also, previous meta-analyses have mixed randomized controlled trials (RCTs) with Cluster-randomized controlled trials (C-RCTs) without correcting for the clustering effects (Hedges, 2007). In the current thesis, level of supervision, gender, age, and baseline symptomatology were evaluated as possible moderators of the effect.

Finally, universal preventive interventions targeting anxiety and depression in children have most commonly been adapted from cognitive-behavioral treatments or interpersonal treatments for the corresponding disorders, rather than developed specifically from research on risk and protective factors (Donovan & Spence, 2000; Gladstone & Beardslee, 2009). As most children do

not experience problems with depression and anxiety, this format may not serve as the best option when targeting a whole population. Although the adaption process has been attentive to research on risk and protective factors associated with the development of anxiety and depression, there is much room for improvement and reconsiderations regarding the design of preventive interventions. The current thesis involves an examination of a prominent theory regarding the detrimental development of anxiety in children (Weems, 2008) to increase understanding of how to further develop preventive interventions.

Friends for Life

One program of special interest is the widely evaluated Australian program FFL. In a review by the Swedish Council on Technology Assessment (2010), the FFL program was identified to be one of a handful of programs worth evaluating in a Swedish context according to the preliminary positive results found in Australia. The FFL program has also been proposed to be potentially more effective than average (Fisak et al., 2011).

The FFL program was originally an adaption of a cognitive-behavioral treatment for anxiety in children called the Coping Cat (Kendall, 1994). In the past 15 years or so, FFL has been developed into a program with a broader aim. In the FFL-manual, it is highlighted that FFL today is a prevention program mainly developed to be implemented within the school (Barrett, 2010). The main objectives of the FFL program are to (1) normalize the anxious emotion, (2) build resilience and problem-solving skills, (3) build supportive social-networks, and (4) increase self-competence and the ability to cope with challenging situations.

The word "friends" is an acronym, meaning that each letter (F-R-I-E-N-D-S) represents a skill (or concept) learned in the program. The skills are supposed to build on each other, which is why the program is recommended to be implemented according to the structure of the FFL-manual. The educational material includes workbooks for children including exercises to work with during the sessions, and at home (i.e., in homework assignments). The material also includes a group leader manual containing detailed instructions for all sessions.

The first letter, F, represents "Feelings, yours and others" and is linked to the objectives of normalizing the anxious emotion and coping with challenging situations. The anxious feeling is not specifically the target, rather, children learn about different emotions such as happiness, sadness, nervousness, and anger. For example, children learn how to recognize their own feelings by understanding their own bodily signals of different emotions, and, others' feelings by looking at facial expressions and body language. The main learning outcome regarding the first letter in FFL is to learn how to early identify one's

own feelings to have a better chance of regulating the feeling before it becomes excessively intense. Consequently, the first letter could be thought to mainly address a dysfunctional emotion regulation, described above to be associated with the development of anxiety.

The second letter, R, represents "Remember to relax." The skills learned in this part of the program is mainly linked to the objective of building resilience. As the acronym reveals, some of the exercises involve learning how to relax. However, the second letter also includes identifying and exploring what activities make you feel good. The main learning outcome of the second letter in FFL is that calm and fun activities can make you feel better. The work under the second letter in the FFL program could be thought to address the hyperarousal in children at risk of anxiety (e.g., hyperactive amygdala response), but also possibly addressing the risk factors of stress and negative life events relevant to the development of depression.

The third letter, I, represents "Inner helpful thoughts" and is linked to the objective of building resilience and self-competence. Most of the exercises involve different variations of how to differentiate between helpful thoughts (i.e., green thoughts) and unhelpful thoughts (i.e., red thoughts). The colors of red and green originates from the metaphor of a traffic light, where some thoughts (red) make us uncertain and makes us stop, whereas some thoughts (green) make us more confident and brave and help us try new or challenging things. Furthermore, some exercises more specifically address what we pay our attention to in our environment and how we can direct our attention to positive things in our lives. The main learning outcome is that children learn the concept of self-talk and how they can increase the amount of green thoughts, or even how to change red thoughts into green thoughts. The work in this part of the FFL program addresses the cognitive aspects and vulnerabilities associated with the development of anxiety and depression (e.g., attention, interpretation, and attributional biases, and rumination).

The fourth letter, E, "Explore solutions" constitutes the largest part of FFL and is linked to the objectives of building problem-solving skills and supportive social networks, and to the objectives of increasing self-competence and the ability to cope with challenging situations. First, children learn the idea of, and are encouraged to work with, a coping step plan (breaking challenging things into small steps), which is basically an alteration of the exposure hierarchy typically found in CBT manuals of childhood anxiety. Contrary to the exposure hierarchy, the coping step plan does not need to address a fear, instead the child could do a coping step plan for learning a new activity. Second, children also learn how to solve problems using a structured method, and third, children work with identifying their supportive social network. The fourth letter could be thought to mainly address the risk factors of behavioral inhibition and negative affectivity associated with the development of anxiety and depression.

The fifth letter, N, “Now rewards yourself” is linked to the objective of building self-competence. In this part of the FFL program, children learn to reward themselves for trying. The primary learning outcome is to identify rewards that are easily accessed, and, to reward themselves not for success but rather for trying their best. The idea of the rewards is mainly to increase the motivation to work with the coping step plan previously introduced.

The sixth and seventh letter, D, (Don’t forget to practice) and, S, (Stay calm for life) do not include any new strategies but rather involve exercises that aim to maintain all the strategies learned previously in the program.

The empirical studies

Aims

The overall aim of studies I-IV was to increase the knowledge on prevention of anxiety and depression in children generally, and in a Swedish context specifically. Previous meta-analyses of prevention on anxiety and depression have partly suffered from conceptual, methodological and statistical limitations. Consequently, the aim of Study I was to conduct a meta-analysis strictly of universal prevention, by evaluating anxiety and depression jointly, with adequate statistical corrections given the methodological differences between studies. The aim of Study II was to evaluate FFL in a large Swedish school-based cluster-randomized trial, using a multi-informant approach, and including a 1-year follow-up. Study II also aimed to evaluate possible moderators and mediators of the effect. Study III aimed to evaluate the long-term outcomes of Study II and to examine the effects of long-term sample attrition. Finally, the aim of Study IV was to prospectively evaluate developmental trajectories of general anxiety, and, possible differences in patterns of disorder-specific symptoms to provide insights for the future development of screening procedures and preventive intervention.

Method

Participants

Study I

The first paper concerned a meta-analysis of universal preventive trials targeting anxiety and/or depression. To identify relevant trials, we performed a comprehensive electronic literature search. Following the literature search, we scrutinized titles and abstracts (when needed) for 4,117 studies. A total of 59 studies were retained for further full-text evaluation according to the inclusion and exclusion criteria of the meta-analysis. Finally, a total of 30 trials which comprised a total of 21,439 children (52% girls) constituted the study sample. The estimated mean age was 12.3 (*SD*=1.6).

Study II-IV

The second, third and fourth papers were based on a school-based sample of children in Stockholm county. A power analysis revealed that a sample of 35 children from 18 schools (N=635) would be required to find an effect size of Cohen's d=0.30 given a two-tailed significance level of .05, a power of .80 and an intra-cluster correlation (ICC) of .02, in a cluster-randomized trial with two arms (i.e., intervention vs. control; Hemming, Girling, Sitch, Marsh, & Lilford, 2011). The ICC was chosen based on ICCs in previous studies using similar measures and studying similar populations (e.g., Calear et al., 2009; Spence et al., 2003).

A total of 41 schools from six different districts in Stockholm county were invited to participate in the trial. Schools were invited by telephone and e-mail and repeated attempts were made to reach all eligible schools. The author of the current thesis visited the management officials of all of the schools that were interested to participate. A total of 18 schools ultimately accepted the invitation, whereas nine schools declined and 14 schools did not respond to the invitation. Unfortunately, one school dropped out after randomization. Children in third and fourth grade were eligible for participation. Consequently, information regarding the study and informed consent forms were sent to the parents of these children. In addition to Swedish, information and informed consent forms were translated into the most common native languages at the schools in the study - Arabic, Spanish, Kurmanji, Sorani, Turkish, English, and Polish. Out of 1,021 children, 695 (68%) agreed to participate, 91 (9%) declined, and 235 (23%) did not respond to the invitation. The sample comprised 337 girls (48%) and 358 boys (52%). The mean age of the total sample was 9.6 years (SD=0.6). Studies II and III were based on the whole sample, whereas Study IV was based solely on the control condition.

The intervention

The intervention evaluated in Study II and Study III was the FFL program described in detail above. The material (workbook and manual) was tested in a pilot trial of FFL in three Swedish school classes in 2010 (Ahlen et al., 2012). Due to mixed opinions from parents and teachers regarding the quality and comprehensibility of the material, both workbook and manuals were re-translated and culturally adapted by the author of the current thesis and a colleague, both of whom are clinical psychologists. After the re-translation, a focus-group of four teachers working with children of the relevant ages carefully examined and provided feedback on the workbook and group leader manual, which were revised accordingly. Instructions and exercises in the new workbook showed an adequate readability index for children in grades three and four (i.e., LIX generally between 25 and 30; Björnsson, 1968).

Teachers in the intervention group attended to a one-day standardized training session, and then, these teachers administered the intervention in their classes one hour per week for the ten subsequent weeks. In the standardized training, teachers were informed about early signs of anxiety and depression, the risk and protective factors associated with the development of anxiety and depression, and group leadership skills. The training also included a rationale for prevention together with a thorough walkthrough of the FFL group leader manual (Barrett, 2010). Finally, the training also included a discussion regarding the ethical concerns of implementing mental health intervention in schools. Teachers in the intervention group were offered supervision on three occasions during the time FFL was running. The supervision sessions were primarily intended to help teachers plan for future sessions and discuss possible obstacles in the administration of the program. Teachers in the control group were instructed to run classes as usual.

Measures

Spence Children's Anxiety Scale

The Spence Children's Anxiety Scale (SCAS; Spence, 1998) is a widely used, 44-item self-reported measure of anxiety. The SCAS was developed to facilitate screening in large populations based on the DSM-IV classification system. Six items are filler items meant to reduce negative response bias, and, the remaining 38 items aim to assess six dimensions of anxiety; separation anxiety, social anxiety, obsessive-compulsive disorder, panic-attacks/agoraphobia, physical injury fears, and generalized anxiety. Children are asked to rate how often they experience each symptom (e.g., "I worry about things") according to a four-point Likert-scale (never, sometimes, often, or always). An advantageous feature of the SCAS is that it was originally developed for children and not an adaption of an adult questionnaire as has often been the case (Spence, 1998). The internal consistency of total scale scores was found to be excellent and the internal consistency of subscale scores were found to be acceptable in a Swedish sample (Essau, Sasagawa, Anastassiou-Hadjicharalambous, Guzmán, & Ollendick, 2011). Furthermore, in the same Swedish sample, a significantly stronger correlation was found between the SCAS and internalizing, compared to externalizing symptoms as measured by the Strength and Difficulties Questionnaire (SDQ; Goodman, 1997) which provides preliminary support to its convergent and discriminant validity. The SCAS has also showed high correlations to other anxiety symptom rating scales (Essau, Muris, & Ederer, 2002).

Spence Children's Anxiety Scale – Parent version

The Spence Children's Anxiety Scale-Parent Version (SCAS-P, Spence, 1999) is a 38-item parent report of child anxiety (the filler items have been

removed). The items mirror the items of the SCAS, however, formulated from the parent's perspective (e.g., "My child worries about things"). Psychometric evaluations of the SCAS-P are currently missing in Sweden, however, in a Dutch sample, good internal consistency of total scale scores and acceptable internal consistencies of subscale scores were found (Nauta et al., 2004). Similar to the SCAS, the SCAS-P has showed a stronger correlation with internalizing, compared to externalizing symptoms as measured by the Child Behavior Checklist (CBCL; Achenbach, 1991) which gives preliminary support of convergent and discriminant validity.

Spence Children's Anxiety Scale – 12 item version

The Spence Children's Anxiety Scale – 12-item version (SCAS-12; Unpublished manuscript) is a brief version of the SCAS that was developed specifically for the current thesis to assess changes in levels of anxiety during the intervention. In previous factor-analytic evaluations of the SCAS, a six correlated factors model (based on the six subscales of SCAS) has generally shown the best fit (e.g., Essau et al. 2011; Spence 1998; Zhao, Xing, & Wang, 2012). Consequently, the SCAS-12 was developed by choosing the two highest loading items from each of the six subscales according to a confirmatory factor analysis. The SCAS-12 showed good internal consistency of scale scores in a large school-based sample, and a very strong correlation to the original SCAS (r=.95). Furthermore, it showed a strong correlation to parent ratings of anxiety measured by the SCAS-P, and a smaller correlation to externalized behavior as measured by parent-ratings of the SDQ, which offers preliminary evidence of convergent and discriminant validity.

Children' Depression Inventory – Short Version

The Children's Depression Inventory - Short Version (CDI-S; Kovacs, 2003) is an abbreviated version of the original Children's Depression Inventory (CDI) and aims to assess depressive symptoms in children. The ten items in the CDI-S cover sadness, pessimism, self-deprecation, self-hate, crying, distress, negative body image, loneliness, lack of friends, and feeling unloved. For each symptom, children are asked to choose one of three statements that most accurately describe how they feel. Good internal consistency of total scores and evidence of convergent validity (i.e., stronger correlation to another depression questionnaire vs. an anxiety questionnaire) was found in a large Swedish school-based sample (Ahlen & Ghaderi, 2017). Regarding predictive validity, Allgaier et al. (2012) found that the CDI-S performed as good as the original CDI regarding diagnostic accuracy in a pediatric sample.

The Strength and Difficulties Questionnaire

The Strength and Difficulties Questionnaire (SDQ; Goodman, 1997) is a 25-item screening instrument developed to assess general mental health in chil-

dren. The SDQ covers four problem areas: conduct problems, emotional problems, peer problems, and hyperactivity-inattention, which could be merged into a measure of total difficulties. In addition, the SDQ also contains one subscale assessing pro-social behavior (i.e., strengths). In the SDQ, informants are asked to choose how well different items describe the child's behavior according to a three-point Likert scale (not true, somewhat true, certainly true). Acceptable internal consistency has been found for the total difficulties scores and for the scores of all subscales except for the subscale of conduct problems (Malmberg, Rydell, & Smedje, 2003). Convergent validity has been supported according to strong associations with related constructs of the Child Behavior Checklist (Goodman & Scott, 1999) and predictive validity has been supported according to a satisfactory ability to discriminate between community and clinical samples (Malmberg et al., 2003).

Mini International Neuropsychiatric Interview

The Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-kid; Sheehan et al., 1998) is a structured diagnostic interview developed to be a short and user-friendly diagnostic interview for children and adolescents covering several psychiatric disorders (e.g., major depressive disorder, social anxiety, separation anxiety, conduct disorder, etc.). The MINI-kid is an adaption of the adult version of the interview, and, similarly to the adult version, it includes screening questions for every disorder. Additional questions are given for those disorders where the screening questions are confirmed by the child. The MINI-kid has shown good-to-excellent concordance to another diagnostic interview and acceptable-to-excellent inter-rater and test-retest reliability (Sheehan et al., 2010).

Academic performance

To evaluate the child's academic performance in Study II, we also included three questions covering reading, writing and math skills. Teachers were supposed to rate the child's ability within these domains according to a five-point Likert-scale (ranging from much lower than average to much higher than average). The three questions were merged into a single measure of academic performance, and we found good internal consistency of the total score.

Social Acceptability of the FFL Program

To assess the social acceptability of the intervention in Study II, we also included a questionnaire evaluating to what degree the children enjoyed FFL and what they learned from the program. The questionnaire additionally included a question of the degree of homework assignments they received during the intervention. The questionnaire of social acceptability was adapted from a questionnaire used in previous research of the FFL program (Barrett, 2005).

Procedure

An important methodological aspect of studies I-III is the cluster randomization procedure and its implications. Further, an analytic method to handle hierarchically structured data, the linear mixed model (LMM), formed the basis for the analyses in studies II-IV. Therefore, an introduction to cluster-randomization and the LMM is presented below. Study-specific procedures are presented in the study summaries later in the thesis.

Cluster randomization

Cluster randomization generally means that clusters of individuals (e.g., schools, classes, municipalities) are randomized to different conditions rather than randomizing individuals separately (Eldridge, & Kerry, 2012). This randomization procedure has been widely adopted in prevention trials due to the advantageous features of facilitated implementation and reduced risk of contamination (i.e., classification bias; Donner & Klar, 2004). However, if a cluster-randomization is performed by, for example, schools (as in the current thesis), but the effect of interest is to compare individuals, the possible dependencies between individuals within schools must be taken into consideration (Donner & Klar, 2004).

To understand why this dependency matters, one can imagine a study where researchers are interested in estimating the mean height of adult women in Sweden. Imagine that the researchers involved in the study have measured the height of ten women randomly drawn from the population. The sample is of course very small which means that the certainty of the mean height is low (i.e., the standard error/confidence intervals are relatively large). Thus, the research group needs more participants to make a better estimate of the mean height of women. The best choice here would be to measure the height of new women randomly drawn from the population. However, due to time constraints, the researchers choose to contact the ten women already assessed and ask for the height of their mothers. The problem here is obviously that there are similarities in heights between mothers and daughters which reduce the variability in responses. Basically, the women are nested within families. The similarities within clusters is expressed by the intra-cluster correlation (ICC), which is calculated by dividing the variance between clusters by the total variance (Eldridge, Ukoumunne, & Carlin, 2009). Thus, the ICC is a statistic that ranges between zero and one. If the ICC is close to one, the responses within the clusters are very similar, and contrary, when the ICC is close to zero, there is a lot of variation between individuals within clusters. The only situation when ICC is zero is when individuals are independent from each other, thus, individuals within clusters are not more similar compared to others.

In our example, the information from these now 20 women (10 daughters and their mothers) are intrinsically not as good for estimating the mean height in Swedish women compared to 20 independent women. More specifically,

the standard errors/confidence intervals are inflated by the clustering, and consequently, the precision of the estimate is reduced. When the ICC is known, the number of individuals that need to be included ($N_{cluster}$) to get equally good precision as when using independent subjects (labeled the effective sample size; ESS) could be calculated by the following formula[3] (Hemming et al., 2011):

$$N_{cluster} = ESS(1 + (n - 1)\rho)$$

Or conversely:

$$ESS = \frac{N_{Cluster}}{(1 + (n - 1)\rho)}$$

n represents the cluster size, and ρ the ICC. Based on a convenience sample (i.e., personal friends), the ICC turned out to be 0.61 between mothers and daughters regarding height. The relatively high ICC is expected in this example due to a high level of heritability in height. If we want to know the effective sample size that the researchers actually obtained by including the mothers, this is calculated as the following:

$$ESS = \frac{20}{(1 + (2 - 1)0.61)} \approx 12.4$$

It is not uncommon that researchers do not consider the clustering effect in the analyses when the ICC is low (e.g., below .05). However, when using very few clusters, even a low ICC could infer a huge impact on the precision. For example, in a study by Aune and Stiles (2009), only two clusters with approximately 1,000 children in each cluster were randomized to either the intervention or the control. Even at very low ICCs, for example, .01, the effective sample size would be severely reduced:

$$ESS = \frac{2000}{(1 + (1000 - 1)0.01)} \approx 182$$

To improve precision, it is generally more efficient to increase the number of clusters rather than increase cluster size (Killip, Mahfoud, & Pearce, 2004).

Previous trials of FFL have most commonly not considered the clustering effects in their analyses of the intervention effects (i.e., Barrett et al., 2006;

[3] The formula below is a special version for fixed cluster sizes. This is almost never the case in reality, but this simpler formula is presented for educational reasons.

Barrett & Turner, 2001; Lock & Barrett, 2003, Lowry-Webster et al., 2001; Lowry-Webster et al., 2003; Essau et al., 2012). Consequently, the results of the inferential statistics from these studies suffer from an increased risk of a type-I error compared to what is implicitly assumed (i.e., risk = 5%).

Linear Mixed Models

One way to handle the dependent structure of clustered data in the inferential statistical analyses is to use the linear mixed model (LMM; Verbeke & Molenberghs, 2000). Similar versions of the LMM have been presented with other names, for example, hierarchical linear models (HLM; Bryk & Raudenbush, 1987), random effects models (Laird & Ware, 1982), or multilevel modeling (Heck, Thomas, & Tabata, 2013). Accordingly, the LMM considers the hierarchical levels of the data (e.g., observations across time [level one] are nested within subjects [level two], which are nested within schools [level three]). Specifically, the LMM handles the hierarchical structure by including random effects. The name "mixed" simply refers to including both fixed effects to estimate the parameters of interest, and random effects to handle the similarity within clusters (by modeling the variability between clusters).

A fixed effect has a single estimated value (Hayes, 2006). Further, a fixed effect is considered to be repeatable and to involve known levels of the variable. For example, a categorical variable such as intervention/control, or a continuous variable such as age are both repeatable in that their levels are possible to evaluate in future studies (Bates, 2005). Other variables are not usually considered to be repeatable, for example, the variable identifying subjects in designs with repeated observations of the same subjects. Thus, the subject effect is regarded as random as subjects are considered to be a random sample of the population (Bates, 2005).

In a standard linear regression model, the observed values will more or less differ from the predicted values. These differences vary in magnitude between observations and this variability is defined as ϵ, which is assumed to be normally distributed around a mean of zero. In the regression model, this is denoted as:

$$Y = \beta_0 + \beta_1 X + \epsilon$$

where β_0 represents the intercept of the regression line (i.e., the value of Y when X equals zero), and β_1 represent the slope of the predicted regression line (i.e., the strength of the effect of X on Y). The β_1 is considered a fixed effect. The ϵ is actually a random effect and estimated as a variance component rather than a fixed value as the difference between a particular observed value and the corresponding predicted value will vary between observations.

In the LMM, the variability in responses is portioned to different sources. For example, we can imagine a prevention trial comparing an intervention aimed at reducing depression to a control condition where schools rather than

individuals have been randomly assigned to the two conditions. When evaluating the dependent variable (i.e., depression), some of the response variability could be due to conditions (i.e., a fixed effect of the intervention). However, given that there are similarities between children of the same school (i.e., ICC>0), some response variability may also be due to the similarity within clusters. Basically, in the LMM, the fixed effect is in that way controlled for the clustering.

In this example, schools are considered a random effect, thus similar to ϵ, a variance component. Without getting to specific, a random effect of schools (here denoted as ζ) could be assumed to be associated with overall levels of depression (i.e., a random intercept model), which would imply different intercepts for different schools, but similar slope:

$$Y = \beta_0 + \zeta_1 + \beta_1 X + \epsilon$$

The random effect could also be associated with the slope (i.e., a random slope model), which also implies that the magnitude of the intervention effect could differ between schools:

$$Y = \beta_0 + \zeta_1 + (\beta_1 + \zeta_2)X + \epsilon$$

The formulas above represent a two-level model. An LMM could also include additional levels. For example, the model above could be extended by including a higher order random factor such as municipalities. This would be considered a three-level LMM comprising children nested within schools and schools nested within municipalities.

Beyond the possibility to adequately handle the dependent structure of clustered data, the LMM also comprises an additional important advantage compared to the standard repeated measures ANOVA. Studies including repeated observations often report a different number of completed assessments from subjects. In LMMs, all observations are included in the analysis, which means that it is possible to analyze subjects with incomplete data (Verbeke & Molenberghs, 2000). Basically, in LMMs, subjects with partly missing observations are still included in the analysis compared to the standard repeated measures ANOVA, where participants are deleted list-wise (Heck et al., 2014).

Study I - Universal prevention for anxiety and depressive symptoms in children: A meta-analysis of randomized and cluster-randomized trials

Background

To examine the potential effect of preventive interventions aimed at reducing anxiety and depressive symptoms, several recent meta-analyses have been performed (Fisak et al., 2011; Horowitz & Garber, 2006; Stice et al., 2009; Teubert & Pinquart, 2011). However, these recent meta-analyses all suffer from at least three possible limitations when it comes to delineating the potential effect specifically in universal preventive interventions. First, a methodological issue is that all levels of prevention (i.e., universal, selective, and indicated) have been included in previous meta-analyses. This involves a limitation as the different levels of prevention are fundamentally dissimilar (e.g., what concerns population and implementation; Horowitz & Garber, 2006). Especially troublesome is the analyses of moderators, which have not previously been separated by prevention level. Second, a conceptual issue is that previous meta-analyses typically have examined prevention of anxiety or prevention of depression separately. However, it does make plenty of sense to investigate the overall effect of such prevention programs on both anxiety and depression. Especially regarding universal prevention, program content has been very similar regardless of primary target (Briesch et al., 2010; Brunwasser et al., 2009), both outcomes are commonly included in studies (e.g., Barrett et al., 2006; Ruini et al., 2009; Sheffield et al., 2006), and interventions aimed at preventing depression have also been found to affect anxiety and vice versa (Garber & Weersing, 2010). Thus, only evaluating the preventive effect on one of these constructs might not provide a comprehensive understanding of the effects of these programs. Finally, a statistical issue is that previous meta-analyses have not considered the problem of comparing randomized and cluster-randomized studies without correcting for the inflated standard errors of the effect-sizes estimated from cluster-randomized trials (Hedges, 2007). Consequently, the aim of Study I was to estimate the weighted mean effect size of universal preventive interventions regarding anxiety and depressive symptoms, and, to examine possible moderators of the effect solely for universal prevention.

Method

Studies were included in the meta-analysis if they were randomized controlled trials (RCTs) or cluster-randomized controlled trials (C-RCTs), peer-reviewed, examined a universal intervention primarily targeting anxiety or de-

pression, and comprising children 6-18 years. A total of 30 studies were included. These 30 studies were additionally coded on the following variables; age, gender distribution, primary target (anxiety, depression or both), number of sessions and total length, administrator (teachers or MHPs), blinding, intention to treat analyses, adherence, attrition-rate, and follow-up duration. Effect-sizes for all RCTs were calculated by standard procedures (Cohen, 1987), whereas effect-sizes for C-RCTs were corrected according to a procedure suggested by Hedges (2007). If studies comprised several measures of the same construct, these were merged into a single effect-size according to recommendation by Borenstein, Hedges, and Higgins (2007).

Mean effect-sizes were calculated using a random effect model and heterogeneity was assessed using the I^2 statistic, representing the percent of variability in effect-sizes that are not due to sampling error (Higgins, 2008). In the moderator analyses, dichotomous variables were examined using a Q-test based on analysis of variance (Borenstein et al., 2007) and continuous variables were examined using meta-regression (Wallace, Schmid, Lau, & Trikalinos, 2009).

Results

We were able to calculate 18 and 25 post-intervention effect-sizes for anxiety and depression respectively. The weighted mean post-intervention effect-size (i.e., standardized mean difference) was 0.13 for anxiety and 0.11 for depression, both significantly larger than zero. There was evidence of substantial heterogeneity in effect-sizes between studies (I^2=68% and 62% respectively). Further, based on 12 follow-up effect-sizes of anxiety, the weighted mean effect-size was 0.14 (not significantly different from zero). Based on 20 follow-up effect-sizes of depression, the weighted mean effect-size was 0.10 (significantly different from zero). There was evidence of large heterogeneity regarding anxiety (79%), and moderate heterogeneity regarding depression (58%) at follow-up.

We found no significant moderators of the effects regarding anxiety, however, a tendency that MHP were more effective as administrators with a post-intervention mean effect-size of 0.28 compared to 0.04 for teachers. Similarly, we found no significant moderators of the effects regarding depression, but, a tendency that MHPs were associated with larger follow-up effect-sizes (g=0.22) compared to teachers (g=0.03).

Discussion

Study I showed that universal interventions targeting anxiety and depression were associated with significant but small effect-sizes. Follow-up effect-sizes were similarly small, but only significantly differed from zero regarding de-

pression. Effect-sizes below 0.20 are commonly regarded as trivial (e.g., Cohen, 1992), however, evaluating effect-sizes according to rules of thumb is often not very helpful. Instead, effect-sizes must be exemplified to be clinically interpretable. An effect-size of 0.13 regarding anxiety could be translated to about a 20% risk-reduction in scoring above a cut-off suggested by several researchers to be of clinical interest (i.e., one standard deviation above the mean; Reynolds & Richmond, 1978; Simon & Bögels, 2009).

Regarding the methodological issue addressed above, the current study evaluated several possible moderators (i.e., age, gender, primary target of intervention, administrator, using FFL or PRP, length of intervention) in universal preventive trials only. According to our results, there was no clear evidence that any of these variables moderated the effect. However, there was a tendency both regarding anxiety and depression that MHPs as administrators might be associated with larger effects. Unfortunately, our study suffered from relatively few studies, and given the small effect-sizes found, this resulted in a low power of identifying any moderator of the effect. For a better understanding of what factors may enhance the effect in universal prevention, future RCTs and C-RCTs (as well as future meta-analyses) should more thoroughly evaluate possible moderators and mediators.

Furthermore, concerning the conceptual issue addressed above, the current study showed that the overall effects of these programs were similarly small regarding both evaluated constructs (i.e., anxiety and depression), and moreover, that the effect-sizes did not differ between constructs when comparing studies with different primary aims (i.e., aiming primarily at anxiety or depression). Finally, regarding the statistical issue addressed above, the current study showed that there were, at least, significant short-term effects of universal prevention of anxiety and depression even when controlling for the cluster effects within studies.

Study II - Prevention of anxiety and depression in Swedish school children: A cluster-randomized effectiveness study

Background

Given the high prevalence, early onset, and severe negative consequences of anxiety and depression (Birmaher, Ryan, Williamson, Brent, & Kaufman, 1996; Bittner et al., 2007; Costello et al., 2003), there is a great need to further evaluate the efficacy and effectiveness of preventive interventions targeting these conditions. When a preventive intervention is given to a whole school class or a whole school, it is defined as universal prevention. Beyond the opportunity to reach a large number of individuals, universal prevention has also been recommended because it may involve lower costs and reduced risk of stigmatization compared to targeted interventions (Fazel et al., 2014).

No previous randomized or cluster-randomized trial of universal prevention of anxiety and depression has been conducted in Sweden. One intervention of interest, and possibly more effective than similar interventions (Fisak et al., 2011) is the Friends for Life (FFL; Barrett, 2010), an intervention developed in Australia aimed at preventing anxiety and depression in children. Recent research of FFL has yielded mixed results. Whereas some studies support the evidence of FFL as an effective universal preventive intervention (i.e., Barrett & Turner, 2001; Barrett et al., 2006; Lock & Barrett, 2003; Essau et al., 2012), other studies have not been able to replicate these results (Miller et al., 2011a; Miller et al., 2011b). Previous trials of FFL have typically only included measures of anxiety, or anxiety and depression (e.g., Barrett, 2006; Lock & Barrett, 2003; Miller et al., 2011a; Miller et al., 2011b). However, the author of the FFL program (Paula Barrett) has encouraged the inclusion of a wider range of measures to better understand the complete benefits of universal prevention (Farrell & Barrett, 2007).

The aim of Study II was to evaluate the effectiveness of a teacher-administered FFL in Sweden. More specifically, the trial examined whether participation in FFL reduced levels of anxiety, depression, and general mental health as rated by children, parents, and teachers. The current study additionally evaluated whether elevated baseline symptoms, child's age or gender, or teacher's use of supervision enhanced the effect of FFL.

Method

The trial was reviewed and approved by the Uppsala Regional Ethical Review Board. Schools in the trial were randomly allocated to FFL or to a control condition. Three main measurement points were included, at baseline (children, parents, and teachers), one week after the last session of FFL (children,

parents, and teachers), and 12 months after the last session of FFL (children, parents, teachers). In addition to the main assessments, we included two intermediate measurement points (for children only) after the 5th and the 7th session. Children completed the SCAS and the CDI-S in their classroom during regular school hours. Parents completed the SCAS-P and the SDQ via Internet, and teachers completed the subscales of emotional problems and pro-social behavior in the SDQ together with the measure of academic performance (AP) during working hours. To measure the fidelity of the implementation, teachers were asked to record all sessions using a USB recorder.

We used a four-level LMM with observations nested within subjects, subjects nested within classes, and classes nested within schools. To statistically evaluate the intervention effects, beta-coefficients of the time* condition interaction effects inclusive of the corresponding bootstrap confidence intervals were examined. Effect-sizes of the intervention effects were estimated by transforming t-values into the commonly used statistic Cohen's *d*. Mediation analyses were performed under the causal inference approach (Valeri and VanderWeele, 2013). In the causal inference approach, the effect is apportioned into a direct effect and an indirect effect (i.e., the mediation effect), labeled the average causal mediation effect (ACME). All statistical analyses were performed in the R software program (R Core Team, 2015).

Results

In a series of LMMs, we found no short-term (pre- to post-) or long-term (pre- to follow-up) intervention effects regarding the child-rated SCAS, *B*=-0.38, 95% CI [-2.48, 1.37], *d*=0.02; *B*=-0.07, 95% CI [-1.10, 0.98], *d*=0.01; respectively, or the CDI, *B*=-0.32, 95% CI [-0.71, 0.07], *d*=0.11; *B*=-0.09, 95% CI [-0.31, 0.13], *d*=0.07; respectively.

Further, we found no short or long-term effects regarding parent-rated SCAS-P, *B*=0.87, 95% CI [-0.46, 2.31], *d*=-0.03; *B*=-0.21, 95% CI [-0.98, 0.55], *d*=0.04; respectively, or SDQ, *B*=-0.04, 95% CI [-0.72, 0.65], *d*=0.01; *B*=0.00, 95% CI [-0.38, 0.37], *d*=0.00; respectively.

Finally, we found no short or long-term effects regarding the teacher-rated measurements of emotional problems, *B*=-0.16, 95% CI [-0.79, 0.49], *d*=0.04; *B*=-0.32, 95% CI [-1.38, 0.82], *d*=0.05; respectively, pro-social behaviors, *B*=-0.27, 95% CI [-0.79, 0.30], *d*=-0.06; *B*=-0.32, 95% CI [-0.35, 0.20], *d*=-0.04; respectively, or AP, *B*=0.05, 95% CI [-0.09, 0.19], *d*=0.12; *B*=0.07, 95% CI [0.00, 0.13], *d*=0.15; respectively.

In the first moderation analysis, controlled for baseline differences in anxiety and age, we found a significantly larger short-term reduction of self-rated anxiety for children whose teacher attended a larger number of supervision sessions compared to controls, *B*=-2.93, 95% CI [-5.47, 0.11], *d*=0.21, and compared to children whose teachers attended a lower degree of supervision sessions, *B*=-3.27, 95% CI [-6.15, 0.27], *d*=0.22. A mediation analysis showed

that the short-term difference in anxiety reductions between levels of supervision was primarily driven by late intervention reductions (i.e., reductions within sessions 7-10), ACME=0.95, 95% CI [0.05, 2.00], p=.04.

We also found a significantly larger short-term reduction of self-rated depressive symptoms in the intervention condition compared to the controls, for children with elevated depressive symptoms at baseline, B=-2.71, 95% CI [-5.12, -0.55], d=0.67. None of these effects were sustained at the 1-year follow-up.

Discussion

Although consistent with recent trials from Europe and Canada, our results differ from the results of previous trials in Australia. In these earlier trials (i.e., Barrett & Turner, 2001; Barrett et al., 2006; Lowry-Webster et al., 2003), significant intervention effects have been found both when teachers and MHPs have administered the FFL program. A few explanations are possible. First, teachers in Sweden may have more experience in working with social and emotional health due to previous experiences of similar program, which therefore may have reduced the magnitude of the intervention's effect on the outcome. Second, the author of the FFL program may have secured a better and more sustainable training for teachers in Australia. Our results partly support this explanation as we found preliminary evidence that the level of supervision enhanced the effect. The mediation effect also showed that the difference in anxiety reduction between levels of supervision was driven by reductions in the final phase of the intervention. Consequently, it is possible that teachers who regularly attended supervision administered FFL with more fidelity.

One major limitation of the study was that the fidelity assessment did not work out as planned. Although technically easy to implement, most teachers did not record their sessions. Consequently, regarding the implementation of FFL, we could only provide quantitative measures like child-attendance, teacher attendance at supervision sessions, and level of homework-assignments. Other aspects of adherence or fidelity of the implementation was not possible to evaluate. Future effectiveness trials would benefit from incorporating knowledge generated from implementation research, or even combining effectiveness and implementation research as proposed by some (e.g., Curran, Bauer, Mittman, Pyne, & Stetler, 2012). In future trials of similar interventions, much effort should also be made to ensure that teachers get continual support in the implementation process.

Study III - Long-term outcome of a cluster-randomized universal preventive intervention targeting anxiety and depression in school children

Background

Long-term evaluations of universal prevention aimed at reducing the prevalence of anxiety and depression are rare. Only four randomized or cluster-randomized trials have included follow-up beyond two years (i.e., Barrett et al., 2006; Gillham et al., 2007; Johnstone et al., 2014; Spence et al., 2005). These previous long-term evaluations have generally not found evidence of any long-term effects regarding anxiety or depressive symptoms even though some of them initially found short-term effects. Beyond the possibility that these interventions are actually ineffective in the long-term, a possible explanation for the lack of significant results could also be low power, resulting from high attrition rates and the small effect-sizes generally found in non-risk samples (e.g., Stice et al., 2009; Teubert & Pinquart, 2011). Previous long-term evaluations have all suffered from high attrition, ranging from 39% - 80% between studies. In addition to reduced power, attrition may also include threats to the external and internal validity (Foster & Fang, 2004). Previous long-term evaluations have generally not examined how attrition affects the outcome, which has dampened the possibility of drawing valid conclusions.

Although Study II in the current thesis did not show any overall effects post-intervention or at the 1-year follow-up, it may still be theoretically possible that intervention effects appear over time when children face future challenges and get use of the skills learned in the program (Rapee, 2013). Empirically, there are examples of these so-called sleeper effects both regarding interventions targeting disruptive behavior (van Aar, Leijten, de Castro, & Overbeek, 2017) and interventions targeting anxiety and depression (e.g., Essau et al., 2012).

Study III concerned a 3-year follow-up of Study II and aimed to evaluate the long-term effects of FFL on anxiety, depression, and general mental health. Further, the study aimed to examine whether the short-term effects in relation to elevated depressive symptoms and level of supervision were sustained at the 3-year follow-up. Finally, the study aimed to evaluate attrition and its effect on the outcome.

Method

Study II included three assessment points, baseline, post-intervention, and 1-year follow-up, and Study III additionally included a 3-year follow up completed by children and parents. Schools in the control condition were given access to training for teachers and implementation of the FFL program after

the 1-year follow-up. Unfortunately, only four schools proceeded with the training, and no school ultimately implemented FFL in classes. To be included in the 3-year follow-up, we required a new active informed consent from the child and a passive consent from parents. A total of 499 children (72%) and 336 parents (48%) completed the 3-year follow-up.

We undertook a similar analytic procedure as in Study II to evaluate any long-term intervention effects and possible maintenance of the short-term moderator effects found in Study II. To evaluate the clinical relevance of significant effects, we also calculated the reliable change index (RCI; Jacobson & Truax, 1991), an approach to evaluate the number of children who have made statistically reliable changes rather than a change in scores being due to measurement error. To analyze attrition, we coded two variables of missingness (1) separating children not completing the 3-year assessment from those who did and (2) separating children with missing parent-ratings at the 3-year follow-up. We examined missingness at baseline and the variables of missingness were also entered in the LMMs' examination of the intervention effect. As parent and child attrition was not completely overlapping (i.e., we received quite many child ratings even though their parents did not complete the last follow-up, and vice versa), we were able to model the long-term outcome for children with attrition.

Results

In a series of LMMs, we found no significant long-term effects of FFL regarding SCAS, *B*=0.004, 95% CI [-0.05, 0.06], *d*=-0.01, CDI, *B*=-0.003, 95% CI [-0.02, 0.01], *d*=0.04, or the SDQ, *B*=-0.01, 95% CI [-0.03, 0.01], *d*=0.15. However, regarding the SCAS-P, we found a significant time* condition interaction effect, *B*=-0.04, 95% CI [-0.08, -0.01], *d*=0.23, meaning that the intervention showed a decrease in anxiety symptoms over time compared to controls. However, when examining the significant time* condition interaction effect according to reliable change, a Fisher's exact test showed no significant difference between conditions, *p*=.727.

The short-term effect in Study II showing reduced depressive symptoms in the intervention group for children with elevated depressive symptoms at baseline was not maintained in the follow-up analysis, *B*=0.04, 95% CI [-0.25, 0.34], *d*=-0.03. Further, the short-term effect in Study II of reduced anxiety symptoms for children whose teachers attended a high degree of supervision was similarly not maintained compared to the control condition, *B*=0.01, 95% CI [-0.06, 0.08], *d*=-0.02, or the low-supervision group, *B*=0.01, 95% CI [-0.06, 0.08], *d*=-0.04.

When adding the variable of child attrition to the LMMs, we found that child attrition was associated with overall higher child-rated depression, *B*=0.72, 95% CI [0.12, 1.31], *d*=0.19, and parent-rated total difficulties, *B*=2.18, 95% CI [0.78, 3.38], *d*=0.25. Further, child attrition was associated

with an increase in total difficulties over time (i.e., parent ratings of these children increased more over the four assessment points compared to children retained at the last follow-up), *B*=0.03, 95% CI [0.01, 0.07], *d*=0.15, and child attrition in the control condition specifically had a significantly larger increase, *B*=0.06, 95% CI [-0.11, -0.01], *d*=0.17.

When adding the variable of parent attrition to the LMMs, we found that parent attrition was associated with overall higher total difficulties, *B*=1.43, 95% CI [0.05, 2.77], *d*=0.16. Further, we found that parent attrition was associated with an increase in depressive symptoms over time (i.e., child ratings for children with missing parent reports at last follow-up increased more over the four assessment points compared to children with parents retained at the last follow-up), *B*=0.03, 95% CI [0.01, 0.05], *d*=0.23, and that parent attrition in the control condition showed a significantly larger increase, *B*=-0.03, 95% CI [-0.01, -0.05], *d*=0.16.

Discussion

The current study failed to find a clinically meaningful long-term effect of a universal preventive intervention targeting anxiety and depression. Although we found a significant decrease in parent rated child anxiety, this effect was not found to be of much clinical relevance when looking more closely at the data. The results of our study are similar to other recent studies which also failed to find support for any long-term effects (Gillham et al., 2007; Johnstone et al., 2014; Spence et al., 2005). Moreover, similar to a study by Spence et al. (2005), we found no evidence for the long-term maintenance of the short-term intervention effect for children with elevated depressive symptoms at baseline. Although brief universal interventions might be effective in the short term for a subsample of children, future studies should consider stretching programs or using frequent booster-sessions. Furthermore, the unsustained long-term effect regarding supervision levels indicates the need for a better long-term support-system for teachers, as suggested by, for example, Atkins et al. (2017).

Finally, during the attrition analyses, we found an indication of a possible intervention effect for children with missing data. As these children are assigned lower weights in the LMMs, our overall results of the long-term effectiveness might have been biased towards the null-hypothesis. We suggest that future studies make large efforts to reduce the rate of attrition.

Study IV - Disorder-specific symptom patterns in trajectories of general anxiety: A longitudinal prospective study in school-aged children

Background

Experiencing and regulating emotions of fear and anxiety is a natural part of a child's life, but, for some children, fear and anxiety reach the point of interfering with their lives (Muris et al., 2000). In Weems' (2008) theory regarding the development of maladaptive anxiety in children, it is postulated that subgroups of children follow different developmental trajectories of anxiety across age. Building on previous research (e.g., Watson, 2005), the theory suggests that there are both core and secondary features of anxiety. Core anxiety features represent the overall tendency to worry, avoid challenging situations, and be bothered by somatic symptoms, whereas the secondary features concerns disorder-specific symptoms found in the DSM (5th ed.; DSM–5; American Psychiatric Association, 2013). Weems (2008) further suggested that children with high levels of overall anxiety may show fluctuating levels of secondary features of anxiety, partly due to age- or developmentally related challenges (Weems & Costa, 2005; Westenberg et al., 2007).

Universal preventive interventions targeting anxiety have typically been adapted from treatment protocols (Donovan & Spence, 2000). As these interventions have showed limited effects over time (see Study III), there is room for further development of such interventions, preferably, by considering to a larger extent what we know about the development of anxiety rather than the treatment of anxiety. To increase our understanding of the development of debilitating anxiety in children, Study IV aimed to evaluate trajectories of general anxiety across age, and, to examine possibly different patterns of disorder-specific symptoms in subgroups of children following different trajectories of general anxiety. Study IV involved a four-wave prospective longitudinal design over 39 months.

Method

In Study IV, we only included the control group of the school-based sample. To adequately model the long-term trajectories of anxiety, children who completed only one assessment point (n=8) or only the pre- and post-assessments were excluded (n=34). A total of 150 girls and 150 boys aged 8.5 to 10.8 years at baseline constituted the study sample. Trajectories of anxiety across age were generated according to two different methods, first, the latent class growth mixture modeling (LCGMM), which is an extension of the LMM that handles the sample heterogeneity by subdividing children into different groups (Jung & Wickrama, 2008), and, second, the clinical change framework

(Jacobson & Truax, 1991) in which children are classified based on whether they have made statistically reliable changes, and whether such changes have moved them from a dysfunctional to a functional population (or vice versa). Cut-off values from a large school-based Dutch sample of children between the ages of 7 and 12 were used to define a functional and a dysfunctional population (Muris, Schmidt, & Merckelbach, 2000). Furthermore, continuity and change for different dimensions of anxiety was estimated within the subgroups of children following different trajectories of general anxiety in a series of LMMs. Finally, we evaluated the overlap between the two methods (i.e., LCGMM and clinical change).

Results

According to the LCGMM, the preferred model involved three latent classes. Most children (83%) followed a trajectory characterized by low and stable anxiety symptoms across age. One subgroup of the sample (14%) followed a trajectory characterized by moderate and increasing anxiety symptoms across age and one subgroup (3%) followed a trajectory characterized by high and decreasing anxiety symptoms across age. As this last subgroup was very small, we also experimented with running the LCGMM without these children. The result showed that the two larger classes were very robust and remained essentially the same. Within the framework of clinical change, we classified children into six categories. Most children (75%) were classified as healthy, 12% were classified as recovered, 7% as deteriorated, 2% as chronic, 2% as temporarily improved, and finally, 2% as temporarily impaired.

The analyses of disorder-specific patterns produced quite similar results between the two methods, which is why in the present summary, we will focus on the results from the analyses of the latent classes generated in the LCGMM. In the statistical reporting below, the effect of the low-stable class equals the main age effects, whereas the effect of the other two classes are calculated by summing the effect of the low-stable class to their specific effect, which equals an age*-class interaction effect.

Even when controlling for the effect of general anxiety, we found different patterns of disorder-specific symptoms between the latent classes. In summary, most evidently, symptoms of separation anxiety decreased across age in the low-stable latent class, B=-0.05, 95% CI [-0.07, -0.04], whereas symptoms of social anxiety increased, B=0.05, 95% CI [0.04, 0.07]. Further, in the low-stable class, a small increase in generalized anxiety, B=0.02, 95% CI [0.01, 0.03], and small decreases were also found in symptoms of obsessive-compulsive disorder, B=-0.02, 95% CI [-0.01, -0.04], and panic attack/agoraphobia symptoms, B=-0.03, 95% CI [-0.04, -0.02]. The moderate-increasing class typically showed amplified changes compared to the low-stable class, for example, double the decrease in separation anxiety across age, =-0.05, 95% CI [-0.09, -0.01], a more than double-size increase in social phobia,

B=0.07, 95% CI [0.03, 0.12], and triple the increase in generalized anxiety, *B*=0.05, 95% CI [0.01, 0.09]. The high-decreasing class did not show any different patterns to the low-stable class regarding separation anxiety, social anxiety, or generalized anxiety, but instead significantly larger decreases in symptoms of obsessive-compulsive disorder, *B*=-0.12, 95% CI [-0.21, -0.02], and panic attacks/agoraphobia, *B*=-0.16, 95% CI [-0.22, -0.09].

Discussion

Overall, our study found support for the different trajectories suggested in the literature. We found much congruence between the two methods used where the low-stable class generated from the LCGMM to a large extent overlapped the healthy category in the clinical change framework.

An important finding is the amplified disorder-specific changes in the moderate-increasing class (and the corresponding deteriorated category) compared to the low-stable class. Based on the developmental theory by Weems (2008), this subgroup of children might suffer from problems in the regulation of fears and anxiety when facing challenges typical for their age, and thus, are less successful in coping with these.

There are a few interesting implications of the study results related to the screening and prevention of anxiety in children. First, given the findings that the subgroup with increasing levels of anxiety over time might be due to normative challenges, one suggestion is that future preventive interventions might benefit from being more tailored to the child's age and its related challenges. Accordingly, preventive interventions could specifically target the challenge of separations from caregivers in the early school years (i.e., ages six to eight), and generalized anxiety in middle school years (i.e., ages nine to eleven) by addressing worry over different things like war, the environment, health, etc. Finally, interventions in older children (i.e., ages 12-14) could more specifically address the challenges of social evaluation in adolescence. Previous universal preventive trials have typically not specifically targeted normative challenges, with one exception where social anxiety was addressed specifically in children between the ages of 10 and 15 (Aune & Stiles, 2009). Second, when screening for children at risk for a maladaptive anxiety development, our study suggests that repeated assessments are crucial to identify children with increasing levels of anxiety across age.

A limitation of Study IV was that we did not have enough power to perform gender-specific analyses of the trajectories. Also, some of our subgroup analyses suffered from a severe power problem, due to only being comprised of very few children. Much larger samples will be necessary to validly evaluate specific disorder-specific patterns in smaller classes/categories.

General discussion

Is there justification for universal prevention?

Previous research of universal prevention on anxiety and depression shows mixed results between studies, but according to Study I, these interventions involve at least a significant effect in the short-term compared to passive controls. The effects are small but not necessarily clinically unimportant, and moreover, may not be straightforwardly compared to effect-sizes in indicated prevention (Nehmy & Wade, 2014). However, whether such small effects warrant a widespread dissemination of these programs remains unclear and is dependent on, but not limited to, three empirical questions that have not been sufficiently examined in research. These empirical questions correspond to the appealing features of universal prevention which are often emphasized in the literature.

First, universal interventions could be justified if they are found to be cost-effective compared to targeted interventions. However, such analyses are basically lacking (Spence et al., 2014). Following the reasoning from Study I, (i.e., that a proxy for a healthy child is a score below one standard deviation above the mean), an effect-size of 0.13 could be translated to the number needed to treat (NNT) of 36. Basically, this means that the intervention must be delivered to 36 children in order for one more child to be classified as healthy.

Second, universal interventions could be justified if they involve reduced stigmatization compared to targeted interventions or treatment. However, Martinsen, Kendall, Stark and Neumer (2016) recently found very low levels of such concerns in an indicated intervention targeting anxiety and depression implemented in Norway. Furthermore, although slightly more concerns of stigma were found in an indicated intervention compared to universal intervention in Australia (Rapee et al., 2006), the indicated intervention was valued as much more positive as rated by both children and program leaders.

Third, an argument for the implementation of universal interventions in favor of selective and targeted intervention is that the uncertainty involved in the selection of children is avoided. This is probably the strongest argument as the procedure most commonly employed (i.e., risk-status is based on a single-point symptom questionnaire result) suffers from several limitations. For example, symptom questionnaires have only shown a moderate ability to actually identify disordered children (e.g., Skarphedinsson, Villabø, & Lauth,

2015), and studies reporting both parent and child ratings of anxiety symptoms, have in general found a very low agreement between ratings which results in an uncertainty of which report to use in such a screening (Cosi, Canals, Hernández-Martinez, & Vigil-Colet, 2010). However, in recent years, some researchers have successfully implemented selective preventive interventions where children have been selected more sophisticatedly (i.e., Ginsburg, Drake, Tein, Teetsel, & Riddle, 2015; Morgan et al., 2017). Conclusively, to decide whether there is a justification for universal prevention, more research regarding the issues addressed above are needed.

Friends for Life in Sweden

Although the overall evidence for universal prevention of anxiety and depression may be limited, it is still possible that specific programs could be more effective than others. FFL stands out in research as it is the most frequently evaluated program and has probably shown the most promising results (e.g., Briesch et al., 2010; Fisak et al., 2011). However, while a success in Australia, involving short and long-term effects both as administered by MHPs (Lock & Barrett, 2003; Barrett et al., 2006) and teachers (Lowry-Webster et al., 2001; Lowry-Webster et al., 2003), most evaluations outside of Australia have had trouble to replicating these results (i.e., Miller et al., 2011a; Miller et al., 2011b; Stallard et al., 2014). Study II-III in the current thesis joins these recent studies.

In a review of family-based interventions, Sundell et al. (2014) suggested four reasonable explanations for why effects of an intervention developed in a certain context fails to be replicated when the intervention is implemented in a new context. These four plausible explanations were divided by methodological differences between studies, ambiguities in cultural adaption, non-sufficient implementation, and unanticipated contextual influences. So, what are the explanations of the failure to find any effect of FFL in Sweden? A few clues are available, and discussed below.

Methodological differences

Regarding methodological differences, study II employed similar methodology of trials compared to the original Australian studies, for example, cluster-randomization, comparing intervention to a passive control, and similar outcome measures. Conceptually, however, these studies may differ, and may be one explanation for the differing results. Trials are often labeled as either an efficacy (best possible circumstances) or effectiveness trial (real world circumstances), but in reality, studies are better understood as placed on a continuum between these concepts (Singal, Higgins, & Waljee, 2014). Those prevention trials that are located closer to the efficacy trial on this continuum should presumably show larger effects compared to effectiveness trials as effectiveness trials likely suffer from less involvement of the program developer

and thus less control over the implementation (Sundell et al., 2014). Most likely, the trials where the author of FFL has been involved lie closer to an efficacy trial than those evaluated overseas. Information from the articles also testify to this. For example, in the trial by Lowry-Webster et al. (2001) it is reported that teachers that administered the intervention regularly met the program leader during the 10 weeks of intervention to discuss any issues. Such procedure could arguably not be best considered a "real world circumstance", rather, it fits more with a "best possible circumstance" description. According to this reasoning, it is somewhat expected that larger effects were found in the original studies. One could ask whether it would have made more sense to evaluate the FFL program within an efficacy trial to delineate possible evidence for an effect outside of Australia by independent researchers. However, the C-RCT of the FFL program in Germany (Essau et al., 2012) have already shown that positive results are possible outside of Australia. Furthermore, the aim of Study II was to evaluate the trial administered by teachers under conditions that were reasonable within the Swedish school context. This was motivated by the fact that evidence of efficacy does not justify a widespread dissemination of a program under less favorable circumstances (e.g., see Flay et al., 2005), and meant, for example, that the level of training and supervision was matched to what the schools considered to be possible. Finally, it is important to highlight the performance of FFL program under representative circumstances, as this is how FFL has typically been implemented in reality in, for example, Canada and Finland (e.g., teachers with one-day training deliver the program).

The difference between efficacy and effectiveness trials also have consequences for study power. More specifically, a fallacy in recent trials evaluating FFL (and also in Study II) has been to calculate power for an effect-size similar to the effect-size found in the Australian trials (i.e., d=0.30). With an expected lower effect-size of, for example, 0.20, a sample with 30 children from at least 40 schools (i.e., N>1200) would be needed to compare two experimental conditions. No evaluations of FFL have comprised such study power.

Cultural adaption

Regarding cultural adaption, recent trials of FFL have both evaluated culturally enriched FFL (Miller et al., 2011a), minimally adapted FFL (Essau et al., 2012), or the original FFL (Stallard et al., 2014; Miller et al., 2011b). No conclusions of whether levels of adaption may have affected the results in these studies could be drawn. The material in Study II was somewhat adapted on the surface (i.e., examples were exchanged to better fit a Swedish context). Although a focus group of teachers sanctioned the feasibility of the material, a few teachers involved in Study II expressed that they had difficulties feeling completely relaxed with some of the examples presented in the workbooks.

Thus, there is a possibility that the material was insufficiently adapted and that this affected the motivation and fidelity of the implementation.

Implementation

Insufficient implementation seems to be a reasonable (at least in part) explanation for the lack of result in Study II, and for the different results in other previous trials outside of Australia. A key feature of successful implementation is an adequate support system for the administrators, for example, training, assistance, and supervision (Wandersman et al., 2008). Training in study II was limited to a one-day intense training compared to two-days training of teachers in the trial by Lowry-Webster et al. (2001). Furthermore, three supervision sessions were offered in Study II compared to "regular" supervision in Lowry-Webster et al. (2001). Table 1 displays all controlled trials of FFL including a follow-up assessment, in order of the size of the effect at follow-up together with descriptions of the administrator, initial training, and supervision during intervention.

Table 1. *Information of support for implementation, in those previous controlled trials of FFL, in order of effect-size at longest follow-up regarding anxiety*

Study	**Administrator**	**Effect-size**	**Training**	**Supervision**
Essau	MHP	0.69*	3 days	Weekly (i.e., 10 times)
Lowry-Webster	Teacher	0.56*	2 days	Regularly
Lock & Barrett	MHP	0.26*	1 day	Not reported
Stallard (a)	MHP	0.19*	2 days	5 times
Miller (a)	Teacher	0.18	1 day	Not reported
Åhlén	Teacher	-0.01	1 day	3 times, varied attendance
Stallard (b)	Teacher	-0.08	2 days	5 times, low attendance
Miller (b)	Teacher	-0.16	1 day	Not reported

* Significantly different from zero

Table 1 suggests that several aspects of implementation may be associated with the effect. Specifically, significant effects at least appear to be associated with MHPs as administrators, more initial training, and more frequent and successful supervision. Consequently, one conclusion regarding Study II could be that teachers did not get enough support to administer the intervention effectively, and therefore, this study could arguably suffer from low internal validity with possibly misleading results. On the other hand, one could argue that the procedure in Study II is more coherent to the real-world possibilities for teachers (to be present at training and supervision), and, that on the contrary, trials like Lowry-Webster et al., (2001) suffer from low external validity. One solution to bridge the gap between efficacy and effectiveness (i.e., the science-practice gap), could be to more consistently build support-systems

within schools instead of the support-system being based on program-developers, program-partners, or researchers. This approach has been discussed by, for example, Atkins et al., 2017.

Contextual influences

An expected feature of an intervention developed in a certain context is that it is calibrated to several aspects specific to this context. For example, when developing a parent training intervention, one important task would be to teach strategies simple enough for parents to assimilate in their parenting, but, at the same time these strategies need to contribute to a real change of behavior (i.e., not only teach strategies that the parents already use regularly). Some of the components of the FFL program are rather generic and are generally included in other school-based programs aiming to enhance the child's social and emotional development. In Sweden, about 15 years ago, life competence (in Swedish, "livskunskap") became a popular and rather widespread element implemented in schools during regular school hours (von Brömssen, 2013). A program called SET (i.e., social emotional training) was implemented in many schools and included strategies like learning about different emotions, relaxation, problem solving, and doing more things that make one feel good (Kimber, Sandell, & Bremberg, 2008). The SET has not been rigorously scientifically evaluated (i.e., not in a RCT or C-RCT), but preliminary results from a quasi-experimental trial showed that the SET promoted self-image and wellbeing. In study II, no teacher in the control group used a structured program at least during the first year of the study. However, it is not impossible that exposure to previous programs led teachers to use similar strategies, which aimed at enhancing a child's emotional development, in their day-to-day teaching. Accordingly, previous experiences of programs aimed to promote mental health may differ between countries and may also be one explanation of the observed inconsistencies in results.

Future directions in universal prevention

Three areas of future directions in research on universal prevention of anxiety and depression are suggested. First, as these interventions overall show small short-term effects and lack of effects in long-term follow-ups (see Study III), ways to boost the short-term effect and to sustain these effects in the longer term are essential. Regarding the boosting of short-term effects, existing universal interventions generally involve many different strategies. An important task is to further evaluate which of these strategies are involved in producing changes. This is important as some strategies included it the program might be very effective and others may not. Today, the theoretical model in the FFL program (and other programs) includes targeting a range of risk-factors by providing a smorgasbord of strategies and exercises in the intervention. Whether this current model or a model with fewer strategies is the best model

is an unanswered question. Examples from research on the treatment of depression (e.g., Richards et al., 2016) and anxiety (e.g., Ale, McCarthy, Rothschild, & Whiteside, 2015) have indicated that some components often included in treatments do not necessarily involve any additional effects. Thus, slimming program content may lead to more time available to cultivate skills that are truly effective which may boost the effect. There are several ways to examine active components of a preventive intervention. For example, future meta-analyses could more specifically code intervention strategies, and individual trials could allocate children to different versions of the interventions, comprising different strategies. Regarding the sustenance of long-term effects, Weems's (2008) theory of anxiety development (also supported by the results of Study IV) suggests that high levels of general anxiety over time are to some extent driven by different expressions of anxiety. Perhaps the strategies learned in programs like FFL need to be relearned across new situations related to the child's age. Beyond the fact that long-term evaluations typically have suffered from methodological limitations, one possible explanation of the lack of long-term effects could be due to the children's inability to use strategies across different situations (i.e., age-related normative challenges that the child faces).

Second, the possible effect of implementation factors discussed in the current thesis (e.g., training and supervision of teachers, adherence and fidelity of the delivery, and adaption of program content) is a very relevant target for future evaluations of similar universal prevention programs. For example, regarding training and supervision, Owens et al. (2014) posed four different research questions that were urgent to evaluate further: (1) What dosage of training and supervision is needed to satisfactorily equip different administrators to deliver the program? (2) What training and supervision strategies are most effective? (3) Should training and supervision be conducted by in-school staff or external professionals? (4) In what way do the administrator's cognitions and motivation predict successful implementation? To test such implementation factors, the variable of interest must be manipulated (e.g., dosage, external or internal support). The dependent variable could be both an implementation outcome (e.g., implementation cost, fidelity, adherence) and/or a variable of effectiveness, such as child anxiety or depressive symptoms (Owens et al., 2014; Peters, Adam, Alonge, Agyepong, & Tran, 2013). Additionally, a so-called implementation-effectiveness hybrid design could also be applied where both the effect of the intervention, and the implementation factor of interest could be manipulated (Curran et al., 2012).

The third suggestion is to conduct cost-effectiveness studies of universal prevention compared to controls, or preferably, compared to targeted interventions. Previous studies of the cost-effectiveness of preventive intervention are few and have generally suffered from low quality (Zechmeister, Kilian, & McDaid, 2008). Relatively easily implemented and reliable measures of costs involved in mental illness are available (e.g., TIC-P; Bouwmans et al., 2013)

and future trials should include such measurements to better understand possible cost-benefits of universal prevention compared to targeted interventions.

Thinking outside the box

The strong indication of a small and often insignificant effect in universal preventive interventions when administered by teachers, one could wonder whether the administrator's skills rather than program-content are the active ingredients in these interventions. In an interesting approach by McLeod et al. (2017) a set of core skills (labeled 'practice elements') were extracted from interventions targeting social-emotional difficulties. Many of these practice elements can be expected to be acquired by an MHP during former education, for example, providing reward to an appropriate response, ignoring unfavorable behavior, or establishing behavioral contingencies between child actions or behavior. So far, prevention programs targeting anxiety and depression are typically adapted treatment programs in which a lot of responsibility is placed on the child to integrate these strategies in their behavioral repertoire. Perhaps a conceptually different approach could be beneficial where teachers are trained in core practice elements instead of delivering a manualized program. For example, instead of a one-day training program for teachers, and 10 weekly sessions of a manualized program, all efforts could be directed to the training of teachers.

Turning to targeted interventions?

Although there are (at least theoretically) attractive features of universal prevention, studies with adequate power to validly evaluate the possible clinical significance, cost-effectiveness and moderators and mediators of change in universal prevention of anxiety and depression will most certainly be costly and probably complicated. Is it perhaps more efficient to start turning to targeted interventions? According to the classification of prevention used in the current thesis, a targeted intervention means either selective prevention targeting groups of individuals that are exposed to one or several risk factors, or indicated prevention targeting individuals with early signs or symptoms of the current problem. In indicated prevention, children have typically been selected by choosing individuals with elevated symptoms at a single baseline assessment. However, there are several problems with such selection of individuals as mentioned earlier in the discussion. Fortunately, there are at least two recent interesting selective approaches regarding prevention of anxiety, first, Ginsburg and colleagues (e.g., Ginsburg, 2009; Ginsburg et al., 2015), who examined the possibility to hinder or delay the onset of anxiety disorders in offspring to parents with anxiety, and, studies by Rapee and colleagues (e.g., Morgan et al., 2017; Rapee, Kennedy, Ingram, Edwards, & Sweeney, 2010), who examined the possibility to prevent anxiety disorders in children with

early signs of behaviorally inhibitory temperament. Both of these approaches have shown promising results regarding the prevention of anxiety disorders. Further, they may involve a more adequate selection of individuals compared to the selection commonly performed in indicated interventions as elevated symptoms of anxiety at a single occasion may not be a good proxy for being at risk for an anxiety disorder, or vice versa, low levels at a single occasion is not a good proxy for not being at risk (e.g., in Study IV, subgroups of trajectories were not very stable over time).

One risk factor in the development of anxiety and depression is undoubtedly female gender (e.g., Craske, 2003). Previous prevention studies primarily targeting anxiety or depression have not typically been directed specifically to girls with a few exceptions of studies of depression (Stice et al., 2009; Teubert & Pinquart, 2011). The results in Study IV suggest that a subgroup of children (9-14% between the two methods applied) follows a detrimental trajectory of anxiety. This group predominantly includes girls (71-78% between methods) and implies that about 20% of all girls follow such detrimental trajectory (compared to 6% of all boys). As discussed in Study IV, this group stood out, given that it showed notable decreases in symptoms of separation anxiety and increases in symptoms of social anxiety and generalized anxiety, which were interpreted in terms of possible difficulties in regulations of anxiety related to normal challenges. To increase the gender equality of health, one suggestion is to direct interventions specifically to girls (i.e., selective prevention), and perhaps also by selecting those girls with increasing levels of anxiety in repeated screening assessments (i.e., indicated prevention).

Finally, an interesting idea, however one not yet implemented, but only suggested by some researchers (e.g., Lieb et al, 2016) is to treat specific phobias in young children as a way of preventing a broad range of psychopathology later in life. Lieb et al. (2016) suggest such an approach as they found that specific phobia at young ages were a strong predictor of later psychopathology. Trumpf, Margraf, Vriends, Meyer and Becker (2010) found a similar prediction in a sample of young women. This approach is attractive as it involves early intervention and because specific phobias have been found to be effectively and time efficiently treated in children (Davis, Ollendick, Öst, 2009).

Limitation of the current thesis

As mentioned previously in the discussion, Study II was not adequately powered to find the expected effect-sizes as small as those reported in Study I. Further, the aim to include an objective measure of adherence and fidelity failed, which resulted in a limited possibility to describe the adherence and fidelity of the FFL program. Finally, although FFL was tested in Sweden in a pilot-study and surface-adapted based on parent and child feedback, and a focus group of teachers, no systematic adaption of the material was undertaken.

Given the null-results in Study II, a more systematic adaption of the intervention could be justified (Castro, Barrera, Holleran Steiker, 2010). The relatively low attendance to supervisory sessions of teachers and the low degree of received informed consent in a second wave of Study II insinuate a possible lack of relevance of the intervention for parents and teachers. According to the social acceptability measure (Study II), children, on the other hand, generally enjoyed the program and thought they learned relevant skills.

Final conclusions

The conclusion from the current thesis is that universal prevention of anxiety and depression as performed today, using modified treatment programs in large groups of children, may not be the answer to the increasing number of children and adolescents facing a detrimental development of anxiety and depression. Hopefully, the current thesis' critical point of view could provide incentives to better develop interventions and to take fresh perspectives regarding the prevention of these disorders. There is still much development and improvement to make in the prevention of anxiety and depression.

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