Affected by Anxiety

Age-related characteristics and cognitive biases of children and adolescents with anxiety disorders

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Affected by Anxiety

Age-related characteristics and cognitive biases
of anxiety disorders in children and adolescents

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van angststoornissen bij kinderen en adolescenten

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Chapter 1

General introduction

According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5, 2013), anxiety disorders comprise mental disorders characterized by excessive fear and anxiety-related behaviors that impact daily functioning. Anxiety and fear are closely related but also have distinctive features; whereas fear is an emotional response to present or perceived threat in the direct environment, anxiety is anticipation of future threat. Both fear and anxiety may result in endeavors to reduce these feelings and related thoughts by avoidance behaviors. Although every person faces moments of fear and periods of elevated anxiety, the prolongation and exacerbation of fear and worry over time characterize anxiety disorders. Classification criteria differ between the different subtypes of anxiety disorders although they all have an impairment criterion in common which states that the fear, anxiety, or the related behaviors, interfere with daily functioning and result into impairment.

History of Anxiety Disorders

Anxiety disorders have been recognized and diagnosed officially since 1980 (Crocq, 2015). However, the history of anxiety disorders goes back to ancient times as Hippocrates already described pathological cases of anxiety. The term anxiety was reintroduced many centuries later by Robert Burton in 1621. During this interval of centuries, typical cases of anxiety disorders were reported but not classified as a separate illness (Treffers & Silverman, 2001). Most progress in the understanding of anxiety disorders has evolved in the 19th century as more research and knowledge allowed for the rapid growth of medicine, including psychiatry. In the late 19th and early 20th century, anxiety was a key element in diagnostic categories of neurasthenia and neuroses. Also, child and adolescent psychiatry evolved as a separate discipline (Treffers & Silverman, 2001). Freud separated anxiety neurosis from neurasthenia and introduced many categories of anxiety disorders that are still used (Crocq, 2015). Kraepelin introduced more separate constructs of disorders, including phobia's, but did not describe anxiety as a separate diagnosis (Hoff, 2015).

The Diagnostic Statistical Manual of Mental Disorders (DSM-I) was first introduced in 1952 to establish a common language in psychiatry across the globe. In DSM-I anxiety was captured under psychoneurotic disorders, in which anxiety was either directly felt and expressed or a utilization of various psychological defense mechanisms, such as depression or conversion. In DSM-II (1968) anxiety was the main characteristic in the category Neuroses which included anxiety neurosis, phobic neurosis, but also depression neurosis and obsessive-compulsive neurosis. A chapter of anxiety disorders appeared in DSM-III (1980) and was subdivided into

phobic disorders, anxiety states (panic disorder, generalized anxiety disorder (GAD)), and obsessive-compulsive disorder (OCD). The revised version DSM-III-R (1987) eliminated the previous DSM-III hierarchy that prevented the occurrence of an anxiety disorder at the same time as a mood disorder. The introduction of DSM-IV (1994) resulted in diagnostic consistency of anxiety disorders compared to its previous edition, although overanxious disorder was eliminated for childhood disorders.

The main anxiety-related subtypes under DSM-5 (2013) are separation anxiety disorder, social anxiety disorder, specific phobia, panic disorder, agoraphobia, and generalized anxiety disorder. DSM-5 introduced a grouping of the overarching category anxiety disorders of DSM-IV into three spectra: anxiety disorders, obsessive-compulsive disorders (OCD), and trauma- and stressor-related disorders. The new grouping in DSM-5 was based on shared neurobiological, genetic, and psychological features based on improved knowledge in these scientific fields (Crocq, 2015). After the introduction of the DSM-5 in 2014 in the Netherlands, clinical practice and research gradually implemented these new classifications. As the research of this thesis was conducted within this transitional phase, the anxiety disorder subtypes described are those classified by DSM-IV. Before describing the specific aims of this thesis at the end of this chapter in more detail, I will first provide epidemiologic information about anxiety disorders that relate to these aims.

Epidemiology of Anxiety Disorders

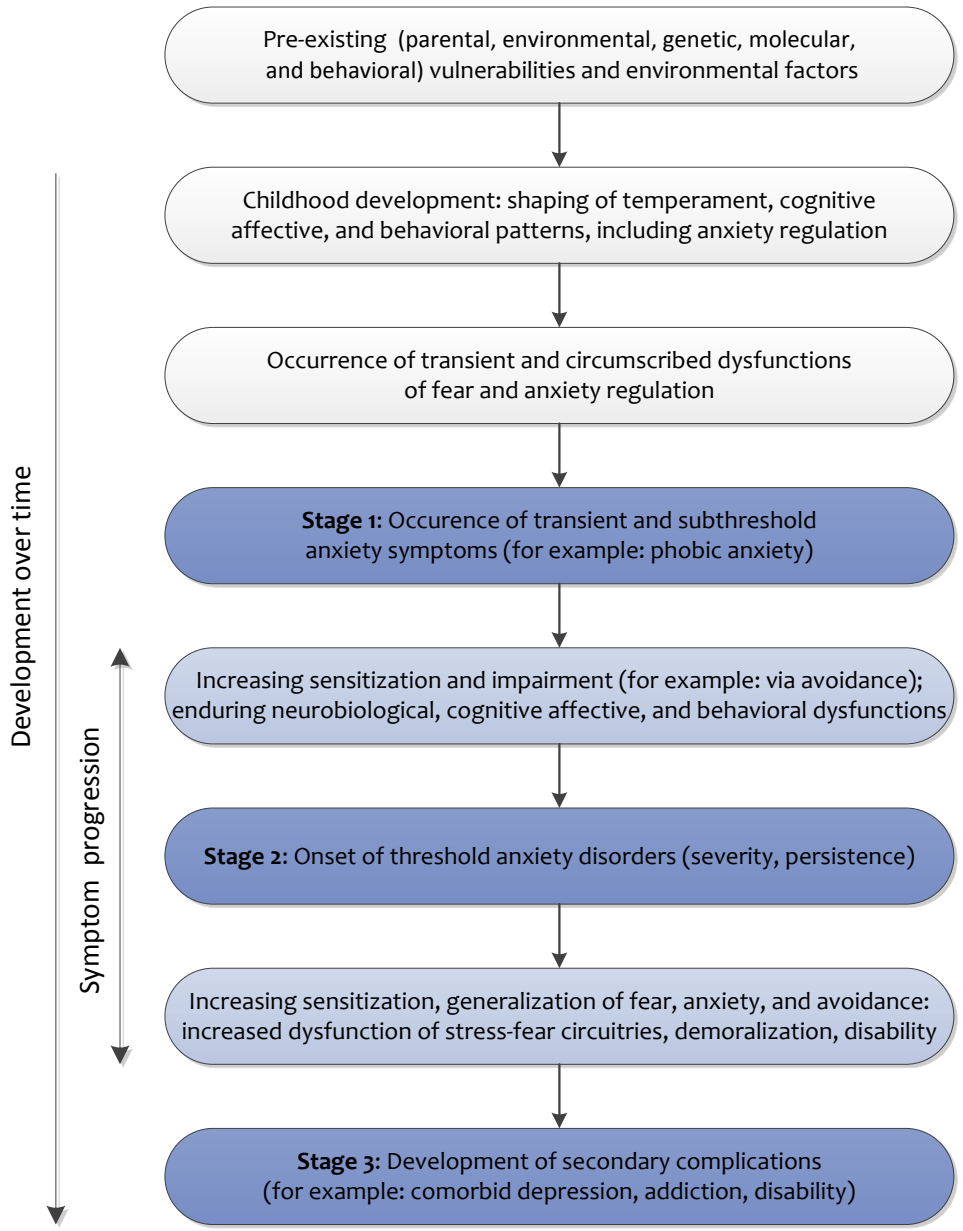
Anxiety disorders are the most prevalent mental disorders worldwide (Bandelow & Michaelis, 2015). Research on the lifetime prevalence rates (i.e. the percentage of people who will develop an anxiety disorder during their life) of anxiety disorders have reported estimates between 3.8% and 33.8% worldwide and between 13.6% and 28.8% in Western countries (Bandelow & Michaelis, 2015; Michael, Zetsche, & Margraf, 2007; Remes, Brayne, Linde, & Lafortune, 2016). Prevalence rates are particularly high in specific subgroups of the general population (Remes et al., 2016), including women (5.2-8.7%), young adults (2.5-9.1%), and individuals from European or Anglo-American cultures (3.8-10.4%). Moreover, prevalence rates for children and adolescents range between 6.5% and 31.9% (Beesdo, Knappe, & Pine, 2009; Merikangas et al., 2010; Polanczyk, Salum, Sugaya, Caye, & Rohde, 2015), making anxiety disorders the most common mental disorders among youth. In addition, comorbid anxiety is the rule rather than the exception with up to three comorbid anxiety disorders being common (Wittchen, Lecrubier, Beesdo, & Nocon, 2007).

As anxiety disorders interfere with daily functioning, they pose a large burden on the personal life of those affected across all ages and bring along high costs for society. Costs for adult anxiety disorders are estimated around US$42 billion annually in the United States (Greenberg et al., 1999) and have risen in the past decades from €41 to €74 billion in Europe (Andlin-Sobocki, Jonsson, Wittchen, & Olesen, 2005; Gustavsson et al., 2011). Anxiety disorders in youth have been related to early termination of secondary education (Bowman, McKinstry, & McGorry, 2017; Breslau, Lane, Sampson, & Kessler, 2008; Lee et al., 2009) and in adults to suicidal ideation, suicidal attempts (Bentley et al., 2016; Thibodeau, Welch, Sareen, & Asmundson, 2013), and substance abuse (Goodwin & Stein, 2013).

Staging

Symptom progression models are an example of how clinical staging is applied to mental disorders by delineating pathways to the onset and further symptom progression. For anxiety disorders, the application of clinical staging is dependent on the differentiation of boundaries between normal and subclinical experiences of anxiety and the characterization of the different stages of the anxiety disorder process (Vazquez-Bourgon, Herran, & Vazquez-Barquero, 2013). Therefore, both general development over time and symptom progression together make up the clinical staging picture (see Figure 1). When applying the symptom progression model to identify and treat anxiety disorders, it is worthwhile to study developmental phenomena of anxiety in children and adolescents as well as how different levels of anxiety affect daily functioning. Hence, the first part of this thesis will focus on age-related characteristics of developmental trajectories of anxiety and depression symptoms (stage 1) and age-related factors of anxiety disorders (stage 2). The second part of this thesis will describe the transmission and treatment of anxiety disorders (stage 2) in children and adolescents via specific cognitive patterns and dysfunction.

Figure 1. Development over time and possible symptom progression of anxiety disorders through clinical stages. *Adapted from Craske et al., 2017 with permission*



Part I Age-related characteristics

There are systematic differences in the expressions of normative anxiety and fears across childhood and adolescence. A range of fears constitute as normal phenomena in typically developing children. These associations between anxiety and age have been explained by the cognitive development of children and developmentally related fears (Broeren & Muris, 2009). As displayed in Table 1, developmentally conditioned periods of fear and anxiety due to cognitive and socioemotional maturation can also be associated with psychopathological relevant symptoms and corresponding anxiety disorders (Beesdo et al., 2009).

Early and Middle Childhood

Developmental tasks for children between the ages of 4 and 10 concern school adjustment (e.g. appropriate conduct), first academic achievements (e.g. learning to read), getting along with peers, and rule-governed conduct (Mash & Wolfe, 2010). Fears of specific objects or real dangers in life such as a burglar in the house are common in this period (Muris, Merckelbach, Gadet, & Moulaert, 2000). Also, children may have periods in which they are scared of contracting a serious illness (Boyer & Bergstrom, 2011). The first obligations and expectations at primary school can cause school or performance anxiety (Wigfield & Eccles, 1989). Also, children's social environment becomes richer as they grow into puberty and become more self-aware. Hence, social fears can arise and worries about fitting in their social group (Weems & Costa, 2005).

Symptoms of anxiety and depression in early childhood have been linked to a range of negative outcomes including emotional disorders at a later age (Goodwin, Fergusson, & Horwood, 2004). These symptoms mark the earliest point at which preventive interventions could be implemented in order to prevent worsening or transition to a clinical disorder. Previous studies have shown that it is likely that the development of these symptoms differs among children in the general population (Broeren, Muris, Diamantopoulou, & Baker, 2013). One of the aims of **chapter 2** is to describe these different developmental patterns of anxiety and depression symptoms during infancy and the preschool period in a sample from the general population. In addition, this chapter aims to identify early risk factors that can be identified before birth and predict elevated anxiety and depression courses. Previous research has shown that symptoms of anxiety and depression in childhood are related to lower performance at elementary school (Ialongo, Edelsohn, Werthamer-Larsson, Crockett, & Kellam, 1995). Chapter 2 also describes how different trajectories are associated with differences in interpersonal, social (i.e. psychosocial), and school outcomes in middle childhood.

Table 1. Normative anxiety and fears across childhood and adolescence. *Adapted from Beesdo et al. (2009) with permission*

Age		Developmentally Conditioned Periods of Fear and Anxiety	Psychopathological Relevant Symptoms	Corresponding DSM-IV Anxiety Disorder
Early infancy	First weeks	Fear of loss, e.g., physical contact to caregivers	–	–
	0–6 months	Salient sensoric stimuli	–	–
Late infancy	6–8 months	Shyness/anxiety with stranger	Separation anxiety disorder	
Toddlerhood	12–18 months	Separation anxiety	Sleep disturbances, nocturnal panic attacks, oppositional deviant behavior	Separation anxiety disorder, panic attacks
	2–3 years	Fears of thunder and lightning, fire, water, darkness, nightmares	Crying, clinging, withdrawal, freezing, eloping, seek for security and physical contact, avoidance of salient stimuli (e.g., turning the light on), pavor nocturnus, enuresis	Specific phobias (environmental subtype), panic disorder
		Fears of animals	–	Specific phobias (animal subtype)
Early childhood	4–5 years	Fear of death or dead people	–	Generalized anxiety disorder, panic attacks
Primary/elementary school age	5–7 years	Fear of specific objects (animals, monsters, ghosts)	–	Specific phobias
		Fear of germs or getting a serious illness	–	Obsessive-compulsive disorder
		Fear of natural disasters, fear of traumatic events (e.g., getting burned, being hit by a car or truck)	–	Specific phobias (environmental subtype), acute stress disorder, post-traumatic stress disorder, generalized anxiety disorder
		School anxiety, performance anxiety	Withdrawal, timidity, extreme shyness to unfamiliar people and peers, feelings of shame	Social anxiety disorder
Adolescence	12–18 years	Rejection from peers	Fear of negative evaluation	Social anxiety disorder

Adolescence

In adolescence, developmental tasks concern the successful transition to secondary schooling, further academic achievement, forming close friendships within and across gender, and forming a cohesive sense of self-identity (Mash & Wolfe, 2010; Roisman, Masten, Coatsworth, & Tellegen, 2004). Also, parent-child relationships change during adolescence as adolescents become more independent (Collins, 1990). Adolescence has been described as a challenging developmental phase and is associated with the clinical manifestation of a broad scope of mental health problems (Merikangas et al., 2010). Among these, symptoms of anxiety are common and up to 20% of youngsters experience an anxiety disorder. In adolescence, normative patterns of separation anxiety disorder and specific phobias decrease, whereas levels of generalized anxiety disorder, social anxiety disorder and panic disorder typically emerge in adolescence (Beesdo et al., 2009; Nelemans et al., 2014). The occurrence of anxiety disorders in adolescence may interfere with the developmental tasks of adolescents. The long-term effects of negative social interactions and academic problems for adolescents are well known (De Ridder et al., 2013; Lev-Wiesel, Nuttman-Shwartz, & Sternberg, 2006). Less is known about the exact impact of anxiety disorders for adolescents who experience these disorders in this transition period from childhood to adult life. **Chapter 3** aims to provide an overview of the social and academic functioning of adolescents with anxiety disorders. Previous studies have focused on specific areas of functioning that are of importance for adolescents, such as social competence and friendships, but also romantic relationships and academic functioning. The synthesis of previous results by a systemic review allows for an overview of the social and academic problems adolescents with anxiety disorders face and hence, guide their opportunities for diagnosis and treatment.

Age of Onset of Anxiety Disorders

The age at which the first episode of an anxiety disorder is experienced, the *age of onset* (AOO), serves as an important statistic in the formulation of mental health policy (de Girolamo, Dagani, Purcell, Cocchi, & McGorry, 2012). AOO enables the prediction of specific lifetime risks of anxiety disorders and helps to understand the etiology and pathogenesis of these disorders (de Girolamo et al., 2018). Intervention in the early stages of mental disorders could help to enhance outcomes and prevent secondary disorders (McGorry, Purcell, Hickie, Pantelis, & Jackson, 2007; Patten, 2017). Early onset of mental disorders has been linked to severe clinical expression of the disease (McGorry, Purcell, Goldstone, & Amminger, 2011). The AOO of anxiety disorders has often been

reported by retrospectively asking when someone experienced the symptoms for the very first time. As has also been described for the different trajectories of anxiety disorder subtypes, different AOO across anxiety disorders can be expected from a developmental perspective. Previous reviews reported on the AOO of anxiety disorders in the general population and found that in particular phobias have their onset in childhood, whereas other anxiety subtypes begin later, usually in adult life (Kessler et al., 2007; McGorry et al., 2011). However, previous reviews did not use a systematic approach and meta-analysis to estimate the average AOO. In addition, study factors have not been taken into account that may have affected the reported AOO. **Chapter 4** of this thesis aims to estimate the AOO of all anxiety disorders and subtypes of anxiety disorders by conducting a systematic review and meta-analysis.

Part II Cognitive biases, familial aggregation and modification

Lize (10 years) has been a shy girl from an early age. She preferred to stay inside and play alone, with her parents or siblings. Although she experienced regular childhood fears for animals, monsters, and burglars, her anxiety of being separated from her parents has increased in the past years. While Lize used to play at the house of a friend, this is no longer possible. Lize often has stomach aches and complaints about feeling sick when she has to go to school. Also, she keeps asking for reassurance from her parents when being separated. If Lize's parents are not back from work when she expects them to be, she experiences high levels of anxiety. Lize's parents seek help at an outpatient clinic for their daughter's separation anxiety.

During the interview with Lize's parents, her mother notes that she has experienced emotional problems herself in adolescence. She finds it difficult to see the intense emotions of anxiety in her daughter and asks for advice on how to cope with these feelings. Lize is diagnosed with a separation anxiety disorder and follows ten sessions of cognitive behavioral therapy (CBT). Lize's parents join each session at the end and support Lize as much as they can. After CBT, Lize experiences less anxiety when being separated from her parents and she can sleep over at a friend's house. Nevertheless, she remains hyper-vigilant for cues of danger in her environment that may cause her or her parents harm.

Etiology of Anxiety Disorders

The etiology of anxiety disorders has been studied from genetic, epigenetic, and environmental perspectives. There is strong evidence for the familiarity of anxiety disorders (Beidel & Turner, 1997; Telman, van Steensel, Maric, & Bögels, 2018) with a 4- to 6-fold higher risk for offspring of parents affected by anxiety disorders (Hettema, Neale, & Kendler, 2001). Both the contribution of genetic factors and the environmental influences from anxious parents, such as giving children threatening information, are of importance in the familial aggregation of anxiety disorders (Eley et al., 2015; Murray, Creswell, & Cooper, 2009; Pahl, Barrett, & Gullo, 2012). Environmental risk factors in early childhood for anxiety disorders include emotional or physical traumas (Blanco et al., 2014; Fernandes & Osorio, 2015; Klauke, Deckert, Reif, Pauli, & Domschke, 2010), and parental factors such as negative affect, parenting stress, and parental control (Moller, Nikolic, Majdandzic, & Bögels, 2016; van der Bruggen, Stams, & Bögels, 2008). In addition, models of cognitive vulnerability for anxiety associate individual differences in the processing of threat-relevant material with the etiology of anxiety disorders (for a review see Ouimet, Gawronski, & Dozois, 2009). As there is usually more information than there are cognitive resources available to process this information, selective processing can create a vicious cycle in which threat is

reinforced. Research has accumulated over the past decade that has identified a promising role for information processing biases or cognitive biases in the transmission, maintenance, and treatment of anxiety disorders in children in adolescents (Hadwin & Field, 2010; Hadwin, Garner, & Perez-Olivas, 2006).

Cognitive biases can be described as predetermined selectivity in cognitive processing. This research originated in the field of experimental psychopathology that uses laboratory-based methods to investigate cognitive processes. Information processing models of anxiety disorders were originally focused on adults. Accumulating evidence shows that cognitive biases occur in children and adolescents as well. Daleiden and Vasey (1997) proposed an extended information-processing model of anxiety in which anxious children experience biases at different stages of information processing (see Figure 2). Although there are different variations of cognitive biases in children, most studies have focused on *attention bias* (AB), also described as attentional bias (Dudeney, Sharpe, & Hunt, 2015; Puliafico & Kendall, 2006), or *interpretation bias* (IB) (White, Suway, Pine, Bar-Haim, & Fox, 2011).

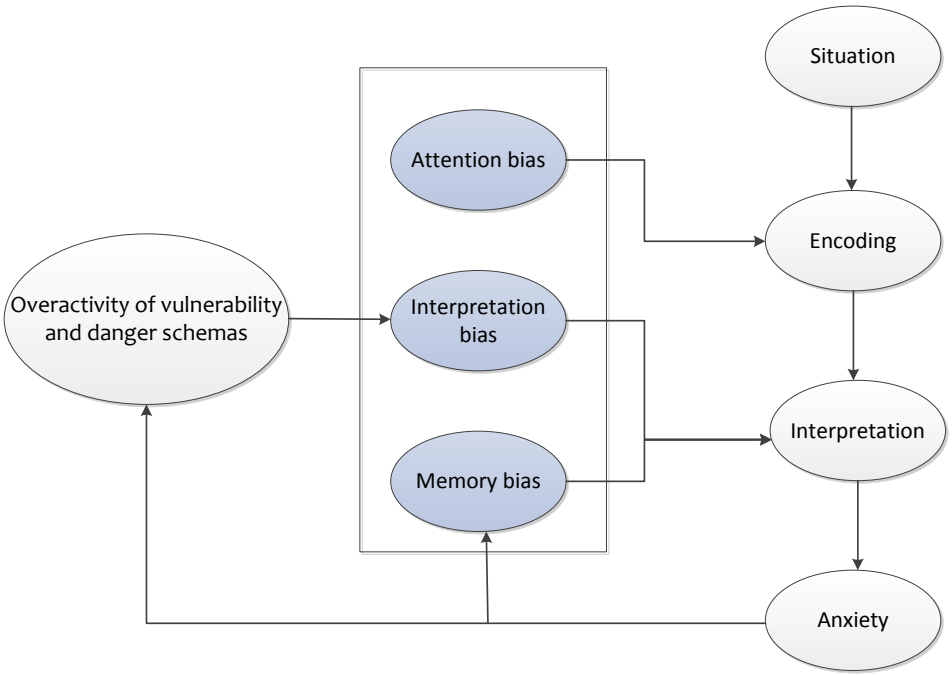


Figure 2. Theoretical model showing the influence of cognitive distortions on the processing of threat-related information. *Adapted from Muris et al. 2008 with permission*

The Dot-Probe Detection Task (MacLeod, Mathews, & Tata, 1986) is the most frequently used task in the assessment of AB in clinical populations (Price et al., 2015). The sequence of presented stimuli for each trial in this computer task is displayed in Figure 3. First, a cross appears in the middle of the screen for 500 ms followed by two pictures shown simultaneously (left and right) for 500 ms for each trial. Picture pairs are either threatening-neutral or neutral-neutral and followed by a probe in the spatial location previously occupied by one of the pictures. Probes consist (for example) of two dots that are either placed next to each other or above each other and are shown until one of the corresponding labeled keys are pressed. Participants are instructed to respond as accurately and quickly as possible. AB is calculated by subtracting reaction times (RT) for trials after which the probe replaced the threatening picture (threat congruent trial) from RT for trials in which the probe replaced the neutral picture (threat incongruent trial). Larger, positive, scores reflect the tendency of participants to direct their attention towards the threatening stimulus, which resulted in longer RT to identify the type of probe on threat congruent trials compared to threat incongruent trials.

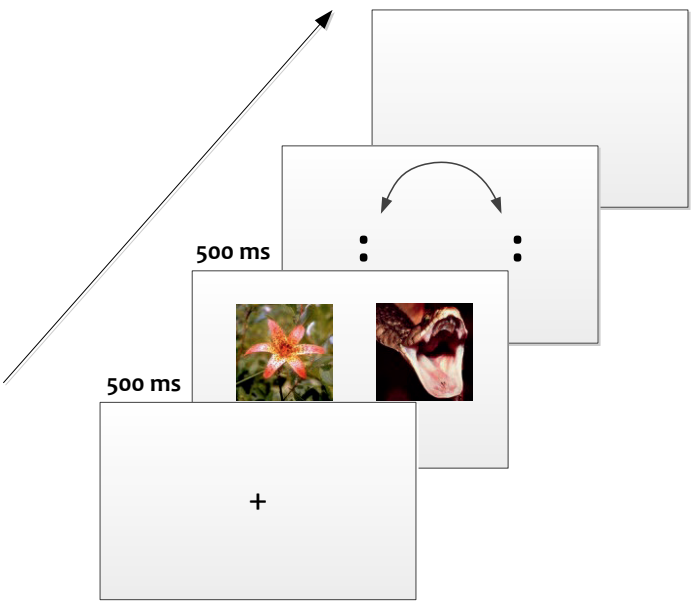


Figure 3. The Dot-Probe Detection Task

Interpretation Bias

Interpretation bias occurs at a later stage in information processing and concerns biased or negative interpretation of neutral or ambiguous situations. This bias is often measured by presenting ambiguous stories or scenarios to children that may have a positive or negative ending. Other tasks concern ambiguous words or the recognition of different facial expressions. Children with an interpretation bias will interpret ambiguous scenarios as threatening or report more feelings of anxiety and worry when imagining they would experience this situation, for instance when listening to stories. Several studies have examined interpretation bias in children and studies assessing the evaluation of ambiguous scenarios generally show that children with anxiety show an interpretation bias of hypothetical situations compared to their non-anxious peers (for an overview see Lau et al., 2012).

Familial Aggregation of Cognitive Biases

A number of theories have been proposed for the development of cognitive biases (Field & Lester, 2010). For example, moderation and acquisition models describe how development moderates innate information processing biases or later acquisition of cognitive biases. As described earlier, anxiety disorders run in families and different factors have been proposed to account for this familial aggregation. Environmental factors such as the exchange of behaviors of parents and children may contribute as well to this understanding. Based on cognitive-behavioral models of the intergenerational transmission of anxiety disorders, studies have therefore started to investigate whether the transmission of cognitive biases from parents to children can explain this familial aggregation (Creswell, Cooper, & Murray, 2010; Ooi, Dodd, Fliek, & Muris, 2016).

As reviewed by Creswell and colleagues (2010), there is evidence supporting the general hypothesis that parents and children show similarities in how they process information regarding threat and coping. Also, how parents process information has been related to parental behavior and this behavior may subsequently influence how children process threating information or interpret ambiguous situations. Moreover, community studies have shown that mothers with higher levels of anxiety are more likely to give children threatening information which results into larger threat information biases in children (Muris, van Zwol, Huijding, & Mayer, 2010; Remmerswaal, Muris, & Huijding, 2016). Although previous studies have related cognitive biases in children to parents' cognitive biases, the mechanism through which parental biases influence children's biases is not fully understood. Also, other dyadic influences such as specific parenting styles and the presence of lifetime emotional disorders may be at play when relating information

processing between parents and children with an anxiety disorder. **Chapter 5** focuses on the familial aggregation of cognitive bias in children with anxiety disorders and their parents.

Attention Bias Modification

Currently, the most effective treatments for children and adolescents with anxiety disorders fall under the umbrella of Cognitive Behavioral Treatment (CBT) (Higa-McMillan, Francis, Rith-Najarian, & Chorpita, 2016; Rapee, Schniering, & Hudson, 2009). CBT focuses on the interplay between emotions, cognitions, and behaviors and learns children to recognize their maladaptive thoughts and how to challenge these in order to control their emotions and change their behavior. However, previous studies have shown that the majority of children with anxiety disorders do not enter treatment (Briggs-Gowan, Horwitz, Schwab-Stone, Leventhal, & Leaf, 2000; Chavira, Stein, Bailey, & Stein, 2004). Besides availability, treatment barriers for youth concern among other things perceived stigma and discomfort discussing mental health problems (Gulliver, Griffiths, & Christensen, 2010). In addition, 40% of children and adolescent are not anxiety disorder-free after completion of these programs (James, James, Cowdrey, Soler, & Choke, 2015; Weisz et al., 2017). Given the high prevalence and burden of anxiety disorders, new treatments that are easily accessible and effective are of the utmost importance.

Several studies have investigated the association between AB and treatment response for children and adolescents with anxiety disorders. As CBT focuses on the restructuring of cognitions, these strategies may be less effective if children have strong, automatic tendencies of information processing, such as AB. Some previous studies showed that children with stronger AB are less likely to benefit from CBT (Legerstee et al., 2010; Waters, Mogg, & Bradley, 2012). Because of the central role of AB in the development and maintenance of anxiety disorders, modification of this bias has been the focus of a possible new treatment of anxiety disorders: Attention Bias Modification (ABM) (Bar-Haim, 2010).

In line with common methods to measure AB in anxious individuals, the most common applied task for ABM is the Dot-Probe Detection Task (see Figure 2). In contrast to the original task in which probes appear with equal frequency after the threatening and neutral stimulus, participants who perform ABM learn to direct their attention away from threat (and towards neutral stimuli instead) because all (or the large majority) probes are displayed after neutral stimuli. The first meta-analysis by Hakamata and colleagues (2010) including studies that examined ABM for adults with anxiety disorders showed a medium effect size. However, the

effectiveness of ABM for adults with anxiety disorders has also been questioned (Cristea, Kok, & Cuijpers, 2015). The effect of ABM has been linked to treatment settings (i.e. laboratory controlled settings or home training) and may depend on whether ABM actually resulted in reduced AB in participants (MacLeod & Grafton, 2016).

Attention Bias Modification has also been suggested to be suitable for children with anxiety disorders (Bar-Haim, 2010). The causal relation between AB and anxiety has been shown by the finding that children who were trained to attend their attention towards threat reported subsequent elevations of anxiety (Eldar, Ricon, & Bar-Haim, 2008). A randomized controlled trial (RCT) study showed that AB of high anxious children could be effectively trained to disengage from threat and resulted in reduced stress vulnerability (Bar-Haim, Morag, & Glickman, 2011). In addition, the first open trial studies showed promising results in children with anxiety disorders seeking treatment (Cowart & Ollendick, 2011; Rozenman, Weersing, & Amir, 2011) and children who did not respond to CBT (Bechor et al., 2014). The first RCT by Eldar and colleagues (2012) reported significant positive effects in alleviating anxiety with large effect sizes. Although the first systematic review of ABM for anxiety in children described overall positive results (Lowther & Newman, 2014), subsequent meta-analyses and review studies have not been conclusive about the effects of ABM compared to sham training for children and adolescents with anxiety disorders (Cristea, Mogoase, David, & Cuijpers, 2015; Mogg, Waters, & Bradley, 2017; Pennant et al., 2015).

As described earlier, standard CBT for anxiety disorders has several concerns such as availability and accessibility. ABM has the potential of reducing these treatment barriers, including cost-effectivity, because of its computerized format. Nevertheless, only one study has examined partial delivery of online ABM for children with anxiety disorders (Chang et al., 2019). Also, despite the promising combination of automatic, bottom-up processes of ABM with controlled top-down processes of CBT, relatively few studies have examined the efficacy of ABM as an add-on treatment (Bennett et al., 2016). Because of the contrasting findings between previous RCT studies, methodological factors may explain differences between previous studies. **Chapter 6** of this thesis examines the efficacy of ABM combined with CBT in an RCT for children and adolescents with anxiety disorders to contribute to the growing body of research about ABM as a possible new treatment.

Study Design ATTENTIO

The second part of this thesis was embedded in the ATTENTIO study, a multicenter RCT study of children and adolescents with anxiety disorders. The main aim of the study was to examine the efficacy of Attention Bias Modification combined with CBT as compared to Attention Control Condition (ACC) combined with CBT on clinician, parent, and child reported anxiety symptomatology. Children who were referred to four different mental health centers in the Rotterdam area (the Netherlands) for psychiatric assessment and treatment of anxiety disorders were screened between October 2013 and October 2016. In total, 54 children and their parents participated in the study. After baseline assessment (T1), children were randomized to the ABM or ACC condition and completed the online training at home in nine sessions over a period of three weeks. In the ABM condition, children were trained towards neutral stimuli, whereas children in the ACC condition were not trained in a particular direction (neutral or threat stimuli). Follow-up assessments included interviews, questionnaires, and cognitive tasks and took place after online training (T2), after receiving individual CBT during ten weekly sessions (T3), and at 6-months follow-up (T4). Please see chapter 5 and chapter 6 for a more detailed description of the study and flow chart.

Chapter 7 will further elaborate upon the most recent developments within the field of anxiety related AB and ABM that has accumulated during the years in which the ATTENTIO study was carried out.

Aims and Outline of this Thesis

The first aim of this thesis is to provide more insight into age-related characteristics of anxiety disorders. In particular, we aim to investigate how symptoms of anxiety develop across age, how they are associated with social and school functioning, and at what age anxiety disorders have their onset. In Part I of this thesis, the following studies are discussed that address this aim. In **chapter 2**, we investigated the developmental course of anxiety and depression symptoms from early to middle childhood in a large population-based sample (Generation R). Also, predictors and outcomes of differences in the developmental course of these symptoms were examined. **Chapter 3** provides a systematic review of studies that have reported on the social or academic functioning of adolescents with anxiety disorders. In **chapter 4**, we performed meta-analyses on previous epidemiologic studies that reported the AOO of different types of anxiety disorders and investigated how characteristics of these studies influenced this specific parameter.

The second aim of this thesis is to gain more knowledge about the role of cognitive biases in both the familial aggregation and treatment of anxiety disorders in children and adolescents. This part of the thesis is based on the results of the ATTENTIO study, a multicenter RCT in which children and adolescents with an anxiety disorder participated with their parent(s). **Chapter 5** concerns the baseline measurement of ATTENTIO and aims to investigate the familial aggregation of cognitive biases in children and adolescents with an anxiety disorder and their parents, along with possible moderators and mediators to further explain this familial aggregation. In **chapter 6**, we describe the results of the multicenter RCT by examining the efficacy of online ABM in combination with CBT as a treatment for children and adolescents with anxiety disorders.

Finally, in **chapter 7**, the main findings and conclusions of these studies are discussed in the context of recent literature while taking methodological considerations into account. In addition, implications for both prevention and clinical practice are discussed, as well as recommendations for future research.

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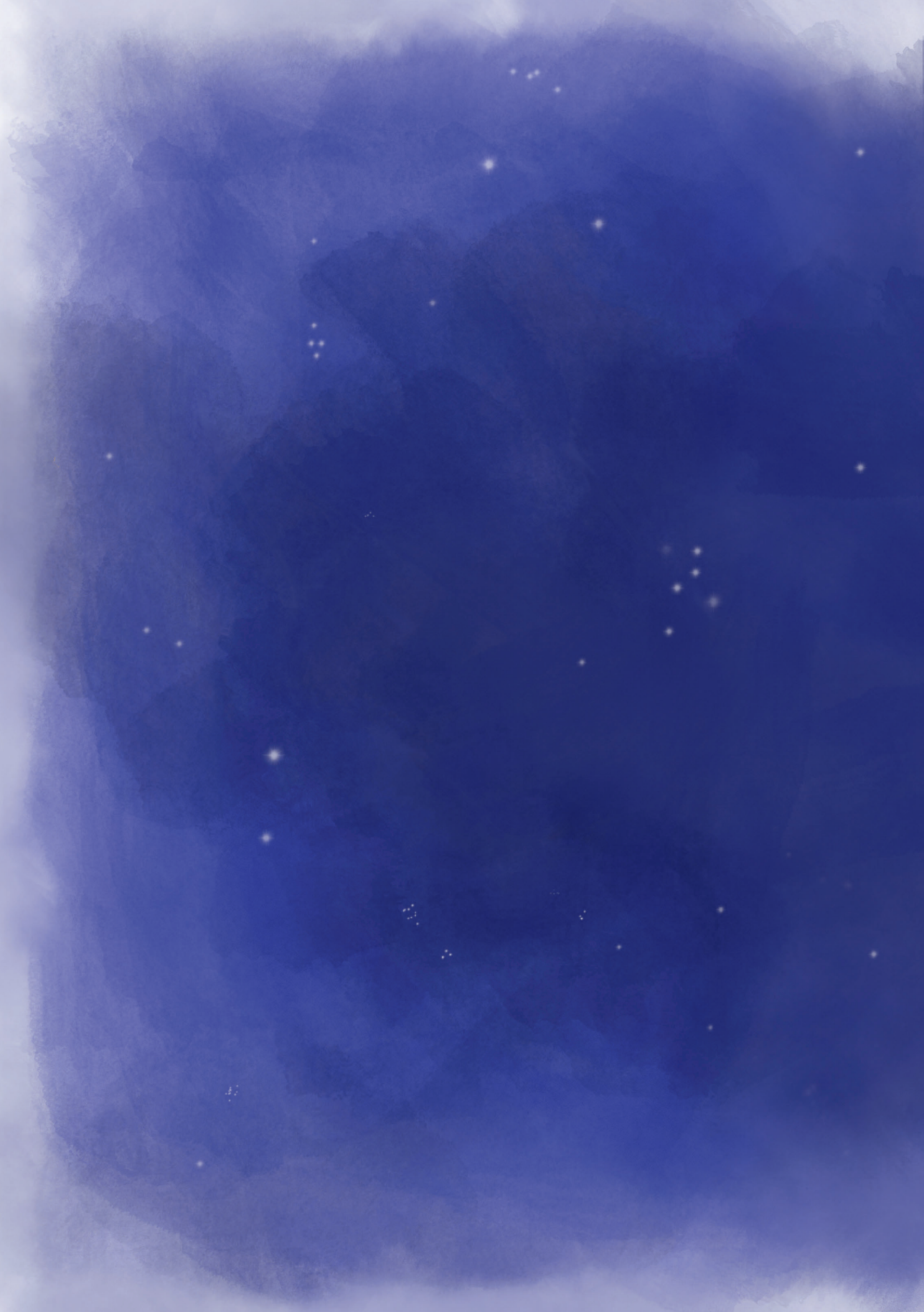
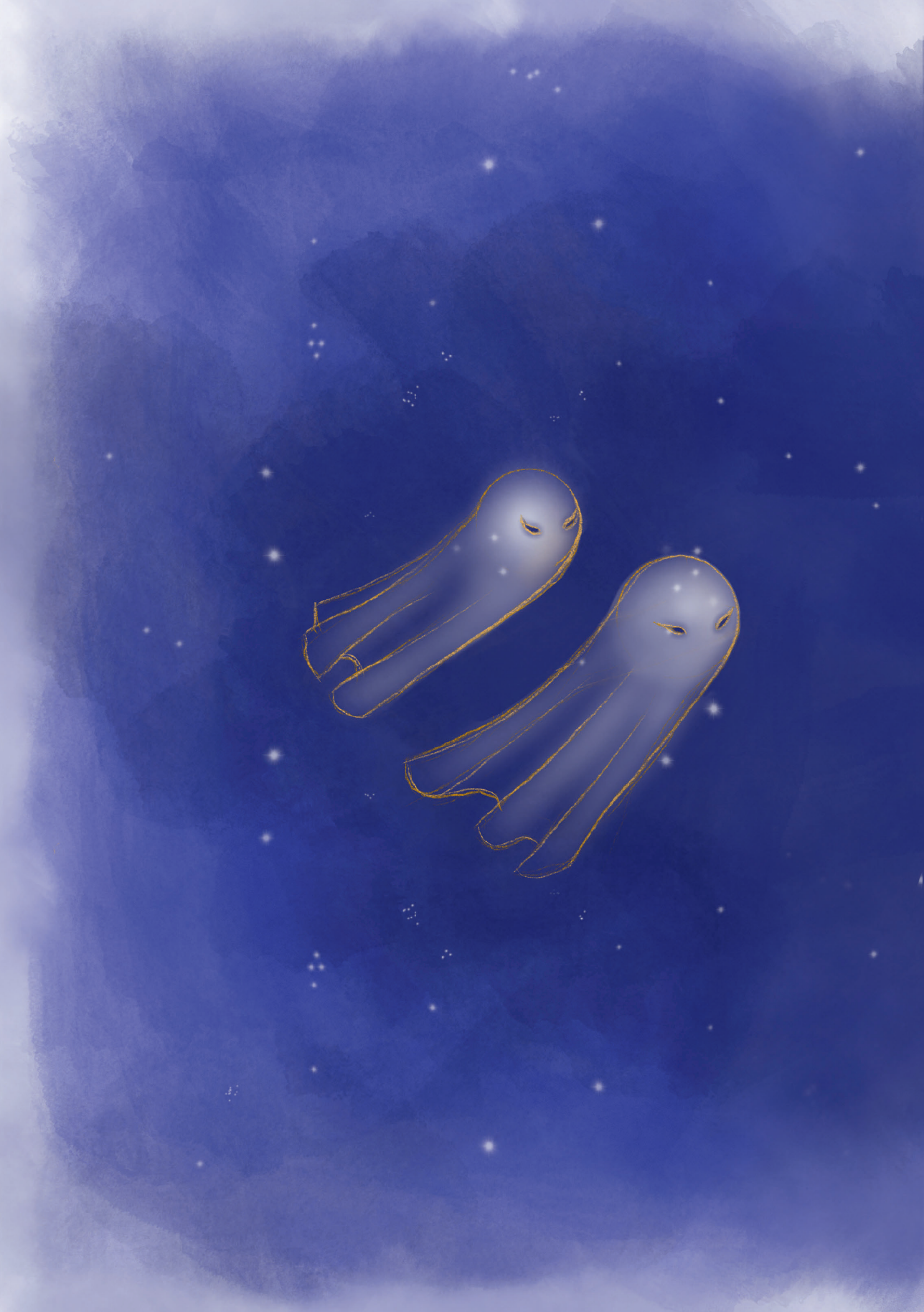


Part I

Age-related characteristics of anxiety disorders



Chapter 2

Developmental trajectories of anxiety and depression symptoms from early to middle childhood: A population-based cohort study in the Netherlands

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ABSTRACT

Developmental patterns of anxiety and depression symptoms in early childhood have previously been related to anxiety and mood disorders in middle childhood. In the current study, trajectories of anxiety and depression symptoms (1.5 – 10 years) were related to children's broader psychosocial and school-related functioning at 10 years. We included a population-based sample of 7,499 children, for whom primary caregivers reported anxiety and depression symptoms on the Child Behavior Checklist, at children's ages of 1.5, 3, 6, and 10. Growth Mixture Modeling identified four distinct, gender-invariant, trajectories of anxiety and depression symptoms: low (82.4%), increasing (7.4%), decreasing (6.0%), and increasing symptoms up to age 6 followed by a decrease to age 10 (preschool-limited, 4.2%). Children with a non-Dutch ethnicity had lower odds to be in the increasing trajectory and higher odds to be in the decreasing and pre-school limited trajectory. Also, low maternal education predicted the decreasing and pre-school limited trajectory. Higher levels of psychopathology during pregnancy for both mothers and fathers predicted the increasing, decreasing, and preschool-limited trajectory, compared to the low trajectory. At age 10, children in the increasing and preschool-limited trajectory had diminished psychosocial outcomes (friendship-quality and self-esteem) and worse school-related outcomes (school performance and school problems). This study adds to current knowledge by demonstrating that developmental patterns of anxiety and depression symptoms in early childhood are related to broader negative outcomes in middle childhood. Child and family factors could guide monitoring of anxiety and depression symptoms in the general population and provide targets for prevention programs.

INTRODUCTION

During early childhood, anxiety and depression symptoms are common. Studies have shown that up to 14 percent of preschool-aged children have clinical levels of anxiety and depression (Bayer, Hastings, Sanson, Ukoumunne, & Robin, 2008; Egger & Angold, 2006). Anxiety and depression during childhood are linked to a broad range of negative outcomes, including emotional disorders at a later age (Goodwin, Fergusson, & Horwood, 2004; Roza, Hofstra, van der Ende, & Verhulst, 2003). In addition, symptoms of anxiety and depression have been related to social problems and diminished school functioning. More specifically, anxiety and depression symptoms have been negatively associated with children's daily functioning; such as lower performance at elementary school (Ialongo, Edelsohn, Werthamer-Larsson, Crockett, &Kellam, 1994; Ialongo, Edelsohn, Werthamer-Larsson, Crockett, & Kellam, 1995; Kovacs & Goldston, 1991; Muris & Meesters, 2002) and a diminished social competence, peer acceptance, and friendship quality (Kingery, Erdley, Marshall, Whitaker, & Reuter, 2010; Rudolph, Hammen, & Burge, 1994).

Children with high levels of anxiety and depression symptoms in early childhood are more likely to experience these symptoms in middle childhood (Bayer, Hastings, Sanson, Ukoumunne, & Rubin, 2010; Mesman, Bongers, & Koot, 2001; Mian, Mainwright, Briggs-Gowan, & Carter, 2011). However, the developmental course of anxiety and depression symptoms in children from the general population is likely to follow different patterns (Broeren, Muris, Diamantopoulou, & Baker, 2013; Cote, Tremblay, Nagin, Zoccolillo, & Vitarol, 2002). Mapping differences in developmental trajectories of anxiety and depression symptoms might help to identify children who are at risk of developing psychosocial problems before clinical anxiety and depression manifest. Group-based trajectory modeling is a valuable statistical approach to identify different courses of anxiety and depression in early childhood (Curran, Obeidat, & Losardo, 2010). This approach is able to identify sub-groups with shared common patterns of change in anxiety and depression over time (Fanti &, Henrich 2010; Jung & Wickrama, 2008).

Several previous population-based studies have indeed identified trajectories of anxiety and depression symptoms across early childhood and related these to adverse outcomes. Feng, Shaw, and Silk (2008) identified four trajectories between the ages of 2 and 10 of anxiety symptoms in a small sample of boys from low-income families. Decreasing as well as increasing trajectories of anxiety were associated with an anxiety or mood disorder at the age of 10 years. Sterba, Prinstein, and Cox (2007) and Fanti and Henrich (2010) identified three trajectories from

early to middle childhood: a low, a moderate, and a high anxiety and depression trajectory. Most of the children were assigned to the low trajectory. Both studies showed that the trajectories of high anxiety and depression symptoms were associated with problem behavior, such as self-reported depression by the age of 11 years (Sterba et al., 2007) and parent-reported peer problems at the age of 12 years (Fanti & Henrich, 2010). However, in the general population, the relation between developmental trajectories of anxiety and depression symptoms with broader psychosocial and school functioning in childhood has, to our knowledge, not been investigated. Studying associations between anxiety and depression trajectories and psychosocial and school functioning is valuable because these domains are important indicators of children's quality of life and psychological well-being (Almquist, 2012; Masselink, van Roekel, & Oldehinkel, 2018).

More insight into predictors of trajectories could further help to understand which children are at risk of developing anxiety and depression symptoms from early to middle childhood. Several child and family characteristics have been related to trajectories of anxiety and depression symptoms in early childhood. For instance, gender has been identified as a risk factor for the longitudinal course of anxiety and depression symptoms (Cote et al., 2002; Cote et al., 2009; Sterba et al., 2007). In addition, developmental trajectories of anxiety and depression symptoms have been consistently associated with maternal psychopathology in previous studies (Cote et al., 2009; Feng et al., 2008; Sterba et al., 2007). Although the role of paternal psychopathology in the development of anxiety and depression symptoms has been acknowledged (Bögels & Phares, 2008), this effect has not been taken into account when predicting trajectories. Economic disadvantage has been associated with children's internalizing symptoms in early childhood (Bradley & Corwyn, 2002; Rijlaarsdam et al., 2013). However, inconsistent results have been found for socioeconomic disadvantage as a risk factor for increasing levels of anxiety and depression symptoms (Cote et al., 2009; Fanti et al., 2010). As socioeconomic disadvantage is associated with parental psychopathology (Lancaster et al., 2010), both parental characteristics should be taken into account to estimate their relative contribution in predicting children's trajectories of anxiety and depression symptoms.

The present study examined predictors of developmental trajectories of anxiety and depression from early to middle childhood as well as the effect of these trajectories on psychosocial (friendship quality and self-esteem) and school-related outcomes (school performance and school problems). Previous studies have examined parent-ratings of children's psychosocial functioning as outcomes of trajectories. Although parent-ratings can approximate children's

experiences, these measures are not well suited to replace self-reports (Jonsson et al., 2017). We used data from the Generation R Study; a large, population-based cohort including repeated measures across childhood and detailed information regarding outcomes in middle childhood from both the child and parents perspective. Aims of this study were: (1) to examine developmental trajectories of anxiety and depression symptoms from early to middle childhood, (2) to identify predictors associated with these trajectories, and (3) to examine associations between anxiety and depression symptom trajectories and psychosocial and school-related outcomes. Based on previous studies, we hypothesized to identify up to four different trajectories of anxiety and depression symptoms with most children having constant low symptoms. We further hypothesized low socioeconomic status and parental psychopathology to be associated with increasing trajectories of anxiety and depression. In addition, we hypothesized worse psychosocial and school-related outcomes for children whose symptoms increase from early to middle childhood.

METHOD

Participants

This study was embedded in the Generation R Study, an ongoing multi-ethnic population-based prospective cohort from fetal life onward in Rotterdam, the Netherlands. The Generation R Study is designed to identify early causes of normal and abnormal growth, development, and health. Its design has been previously described in detail (Kooijman et al., 2016). In short, all pregnant women living in Rotterdam, with an expected delivery date between April 2002 and January 2006, were invited to participate and contacted via obstetrician practices. The study was approved by the Medical Ethics Committee of the Erasmus Medical Center. Anonymity was guaranteed and written informed consent was obtained from children's primary caregivers at each study phase.

In total, 9778 mothers enrolled in the study gave birth to 9749 live-born children. During the preschool period (0-4 years), parents of the 1,166 children living outside the definite study area at birth were not approached as the logistics of postnatal follow-up were embedded in the municipal routine child care system. When all parents were contacted again when children were 5 years, consent for their children to participate was 85% of the original sample (Jaddoe et al., 2012). Data on children's anxiety and depression symptoms were available at ages 1.5 years (n =

5,223), 3 years (n = 4,939), 5 to 7 years (n = 6,210; hereafter referred to as 'age 6') and 10 years (n = 4,938). In total, the study sample comprised of 7,499 children with anxiety and depression data available for one or more research assessment(s) (76.2% response rate). For psychosocial and school-related outcomes, the study sample varied across outcomes (n = 4,336 friendship quality, n = 4,355 self-esteem, n = 3,669 school performance, and n = 3,857 school problems).

Measures

Child anxiety and depression symptoms

Child anxiety and depression symptoms were assessed with the Child Behavior Checklist (CBCL). The CBCL/1½-5 was sent to all primary caregivers to be completed at home around the time of the research assessments at the ages 1.5, 3, and 6 years. For the assessment at 5 to 7 years, both versions of the CBCL could have been used. As it was anticipated that the majority of children were younger than 6 years at the time of assessment, the CBCL/1½-5 was used for all children to assure a uniform assessment at this age. The CBCL/6-18 was used at the assessment of 10 years (Achenbach & Rescorla, 2001). Good reliability and validity have been reported for both versions of the CBCL across different populations (Achenbach & Rescorla, 2000; 2001). At all ages, the CBCL was completed by primary caregivers, which were generally mothers. For this study, we used the empirically derived Anxious/Depressed subscale. The Anxious/Depressed scale comprises eight items in the CBCL/1½-5 and 13 items in the CBCL/6-18. Correlations of the Anxious/Depressed subscale over time followed an autoregressive pattern with values between $r = 0.16$, $p < 0.001$ (1.5 years and 10 years) and $r = 0.44$, $p < 0.001$ (1.5 and 3 years).

Internal consistency (reliability) was measured with categorical omega's (ωc) because of the categorical-ordered items in all questionnaires in this study (Kelley & Pornprasertmanit, 2016). In addition, we report 95% CIs to illustrate the uncertainty of these estimates. For the CBCL Anxious/Depressed scale, internal consistency in the current study was 0.62, 95% CI [0.61, 0.64] at age 1.5 years, 0.70, 95% CI [0.68, 0.71] at age 3 years, 0.75, 95% CI [0.73, 0.76] at age 6 years and 0.82, 95% CI [0.81, 0.82] at age 10 years, which is comparable to normative samples (Achenbach & Rescorla, 2000; 2001).

Predictors of anxiety and depression symptom trajectories

Socioeconomic status was measured by children's ethnicity and mother's highest completed educational level at study enrollment. Children were classified as non-Dutch if one of the parents was born abroad. Ethnicity was defined into three categories: Dutch, other Western, and non-

Western. Mothers educational level was classified into three categories: low (primary school or lower vocational education), intermediate (intermediate vocational education), and high (higher vocational education or university). Further, at study enrollment, parental psychopathology symptoms were assessed with the use of the Brief Symptom Inventory (BSI; Derogatis, 1993; De Beurs, 2004). The BSI is a widely used screening tool for general psychopathology with excellent reliability and validity (Boulet & Boss, 1991; De Beurs & Zitman, 2006). Levels of parental psychopathology in the Generation R sample are in correspondence with data from the manual by de Beurs (2009) and other population-based studies found the same percentages of mothers (6-7%) and fathers (2-3%) scoring above the cut off of general psychopathology during pregnancy (Kjeldgaard, Eberhard-Gran, Benth, Nordeng, & Vikanes, 2017; Kvalegvaag et al., 2013). To determine the level of psychopathology, we used the Global Severity Index (GSI) based on the total 53 items of the BSI. Scores on the GSI were standardized into z-scores to facilitate the interpretation of these predictor variables. Internal consistency (ωc) was 0.97, 95% CI [0.97, 0.97] for fathers and 0.99, 95% CI [0.99, 0.99] for mothers.

Psychosocial functioning (Age 10)

Friendship quality

We used an adapted version of the Friendship Quality Questionnaire (FQQ; Parker & Asher, 1993). The FQQ has been validated using socio-metric rating methods and is predictive of both peer acceptance and feelings of loneliness (Parker & Asher, 1993). This first questionnaire for children in Generation R comprised multiple domains and was completed at home. Therefore, 10 items of the original 40-item FQQ were selected based on expert opinion and relevance to the Dutch elementary school setting. Items represented subscales 'validation and caring' (i.e. *we give each other compliments*), 'companionship' (i.e. *we are always together during our break at school*), 'conflict resolution' (i.e. *if we are angry at each other, we always talk it out*), 'intimate exchange' (i.e. *we tell each other secrets*), and 'help and guidance' (*if we need to get something done, we will help each other*). Children rated how true each statement was about their best friend (1 = not true, 2 = somewhat true, 3 = very true, total range 10 – 30). Missing values were replaced by the mean score of the remaining items (weighted total score). If there were more than 20 percent of the answers missing, this was coded as a missing value. Internal consistency (ωc) of the adapted FQQ in this study was 0.70, 95% CI [0.68, 0.71].

Self-esteem

Children's self-esteem was measured with an adapted question format of the Harter's Self Perception Profile for Children (SPPC) corresponding to Wichstrom (1995) containing 18 items of the original SPPC (CBSK in Dutch; Veerman, Straathof, & Treffers, 1997). Answers were given on an adapted scale (1 = not true, 2 = somewhat true, 3 = very true, total range 18 – 54). A weighted total score was created for statistical analysis when at least 14 items were completed. The CBSK has acceptable reliability and validity (Dongen-Melman, Koot, & Verhulst, 1993) and has been shown to be gender-invariant (Van den Bergh & Van Ranst, 1998). In this study, internal consistency (ωc) of the modified version of the CBSK was 0.81, 95% CI [0.80, 0.82].

School functioning (Age 10)

School performance

We used the school performance scores from the CBCL/6-18 at age ten years. The child's performance was rated across four major academic subjects: 'reading or language', 'history', 'arithmetic or math', and 'geography' (1 = failing, 2 = below average, 3 = average, 4 = above average, and not applicable, total range 4 – 20). A weighted total score was created for statistical analysis when at least three items were completed. When a subject was not applicable to a child, we treated that score as a missing value. Internal consistency (ωc) of the child's school performance score was 0.74, 95% CI [0.73, 0.74].

School problems

School problems were measured through three items from the CBCL/6-18 mother report at age 10, which describe possible difficulties that a child might experience during school. These were the following three questions: 1 'Does your child receive special or remedial services or attend a special class or special school?', 2 'Has your child repeated any grade?', and 3 'Has your child had any academic or other problems in school?'. The total school problems score was dichotomized to no school problems versus ≥1 school problems.

Statistical Methods

Categorical omega's for internal consistency were computed with the MBESS R package version 4.4.3 (Kelley, 2018). Descriptive analyses were conducted with SPSS version 24.0 (IBM Corp. 2016). All other analyses were performed with Mplus version 8 (Muthén & Muthén, 2017). We used growth mixture modeling (GMM) to determine trajectories of anxiety and depression symptoms in early childhood (1.5 – 10 years). To be able to model these trajectories, average

scores on the Anxious/Depressed scale of the CBCL/1½-5 and CBCL/6-8 from the four assessments were used when at least 75% of the items were completed. GMM is a statistical technique that can be used to find subgroups of change in individuals over time while allowing for within-class or trajectory variability (Fanti & Henrich, 2010; Jung & Wickrama, 2008).

To identify the best model fit, we compared models with different trajectory solutions with the use of both the Bayesian information criterion (BIC) and the Lo-Mendell-Rubin test (LMRT). A lower BIC score indicates a model with a better fit and the LMRT tests indicates whether a given model has a significantly better fit than a solution with one trajectory less. In addition, a plot of trajectories for each model was produced to see whether these solutions were distinctive in capturing the development of anxiety and depression symptoms. Each model was fitted with a linear slope and with a quadratic slope in addition. Classification accuracy was determined by both mean assignment probabilities for each trajectory and overall model entropy. Entropy with values approaching one indicate a clear delineation of trajectories (Celeux & Soromenho, 1996). Because of the low internal consistency of the CBCL Anxious/Depressed subscale at age 1.5 years, we compared trajectories with four assessments from 1,5 to 10 years with trajectories based on the sample of children from the three assessments 3, 6, and 10 years (n = 7,130).

We then examined gender invariance by determining whether the best fitting model in the total group was valid for both boys and girls. Invariance was examined by testing whether trajectories had the same growth parameters (mean, variance and covariance of the intercept, linear slope, and quadratic slope) across gender (Sterba et al., 2007). This was done by simultaneously estimating the models for both boys and girls and using Wald tests to examine differences in growth parameters between boys and girls.

After determining the final model, we examined the association between possible predictors of anxiety and depression symptom trajectories by entering the predictors as auxiliary variables in the growth mixture model. We simultaneously fitted the trajectories and the associations of predictors in a multinomial logistic regression model. As maternal age has been related to increased levels of psychological stress during pregnancy (Aasheim et al., 2012), maternal age was included as a predictor of anxiety and depression symptom trajectories as well.

Then, we examined the associations of anxiety and depression symptom trajectories with psychosocial and school-related outcomes using the three-step approach with an auxiliary model (Asparouhov & Muthén, 2013). This approach uses classification probabilities together with the

most likely trajectory to correct for classification errors when examining the association of the trajectories with outcomes. For continuous outcomes, differences in the mean and for dichotomous outcomes, the thresholds were compared across trajectories while adjusting for the predictors of these anxiety and depression symptom trajectories. A threshold model was used to test differences for dichotomous outcomes; thresholds are expected values that have to be exceeded for a person to be in a particular category (Muthén & Muthén, 2017). Because of the high comorbidity between internalizing and externalizing problems (Thomas & Guskin, 2001), all outcomes analyses were repeated while adjusting for externalizing problems at age 10 years. We used global Wald model tests for differences in outcomes across trajectories. When significant, subsequent follow-up Wald model tests were performed to determine which trajectories contributed to the overall difference in outcomes. This hierarchical approach reduces the number of independent tests.

Missing data

GMM is able to account for missing values within the growth trajectories using Full Information Maximum Likelihood (FIML) with all data that is available. Thus, missing values on anxiety and depression symptoms were taken into account by FIML for the model decision and gender invariance analyses. In addition, missing data on possible predictors of anxiety and depression symptom trajectories were imputed with the use of multiple imputation. Percentages of missing data were 1.7% for child ethnicity, 8.0% for maternal education, 25.8% for maternal and 41.4% for paternal psychopathology symptoms. For this, 20 imputed datasets were generated by using a fully conditional specified model.

RESULTS

Sample Characteristics

Table 1 gives an overview of the descriptive characteristics of the children and their parents in the study sample and the original Generation R sample. Children from the study sample most often had a Dutch or non-Western ethnicity and the majority of the mothers had an intermediate or higher educational level. Most mothers and fathers reported low levels of parental psychopathology. Mean levels of anxiety and depression symptoms for children in the study sample were 0.15 (*SD* = 0.18) at 1.5 years, 0.13 (*SD* = 0.19) at 3 years, 0.18 (*SD* = 0.23) at 6 years, and 0.17 (*SD* = 0.20) at 10 years.

Table 1. Sample characteristics of the study sample (*n* = 7,499) and original Generation R sample (*N* = 9,749)

Characteristics	Study sample *n* = 7,499	Original sample *N* = 9,749
Child gender, %		
Boys	49.5	49.3
Girls	50.5	50.7
Child ethnicity, %		
Dutch	58.7[a]	53.8
Other Western	9.0	8.9
Non-Western	32.3	37.3
Maternal education, %		
High	48.8[a]	42.9
Intermediate	30.1	30.6
Low	21.0	26.4
Maternal age, mean (SD)	30.7 (5.04)[a]	29.9 (5.37)
Maternal psychopathology symptoms, mean (SD)	0.27 (0.35)[a]	0.30 (0.38)
Paternal psychopathology symptoms, mean (SD)	0.14 (0.22)[a]	0.15 (0.24)

[a] Characteristic significantly different in study sample

Non-response Analyses

The sample characteristics of the study sample (*n* = 7,499) were compared with the characteristics of children and their parents from the original sample who did not participate (n = 2,250). Children in the study sample were more likely to be Dutch (χ^2 = 426.96, $p < 0.001$) than those not participating. Mothers of children from the study sample were more likely to have a high level of education ($\chi 2$ = 689.50, $p < 0.001$) and be older (t = 25.20, $p < 0.001$). Psychopathology during pregnancy of participating mothers (t = -11.02, $p < 0.001$) and fathers (t = -5.99, $p < 0.001$) in the study, was lower compared to parents who were not participating.

Model Selection and Model Fit

Fit indices for models with 2 to 5 number of latent classes are presented in Table 2. The 4 class trajectory model solution with a quadratic slope had the best fit. Although the BIC for the model with 5 classes showed a slightly better fit, the 5 class solution did not lead to another distinct trajectory. Additionally, the LMRT value indicated that the more parsimonious model with 4 trajectory classes provided a better fit than the 5 class model. For the model with 4 latent classes, a model with a quadratic slope showed a better fit (BIC = -14196.50) compared to a 4 class model with only a linear slope (BIC = -13797.95). Classification accuracy of the 4 class model was good with an entropy value of 0.85 and average latent class probabilities ranging from 0.74 to 0.95. The same 4 class solution came forward for the sample that included measurements at 3, 6, and 10 years (n = 7,130), supporting the inclusion of the measurement of anxiety and depression symptoms at 1.5 years despite lower internal consistency. As a 4 class model with a random linear slope and/or random quadratic slope did not converge for the gender-invariance analyses, a model with a random intercept only was chosen as a final model for subsequent analyses.

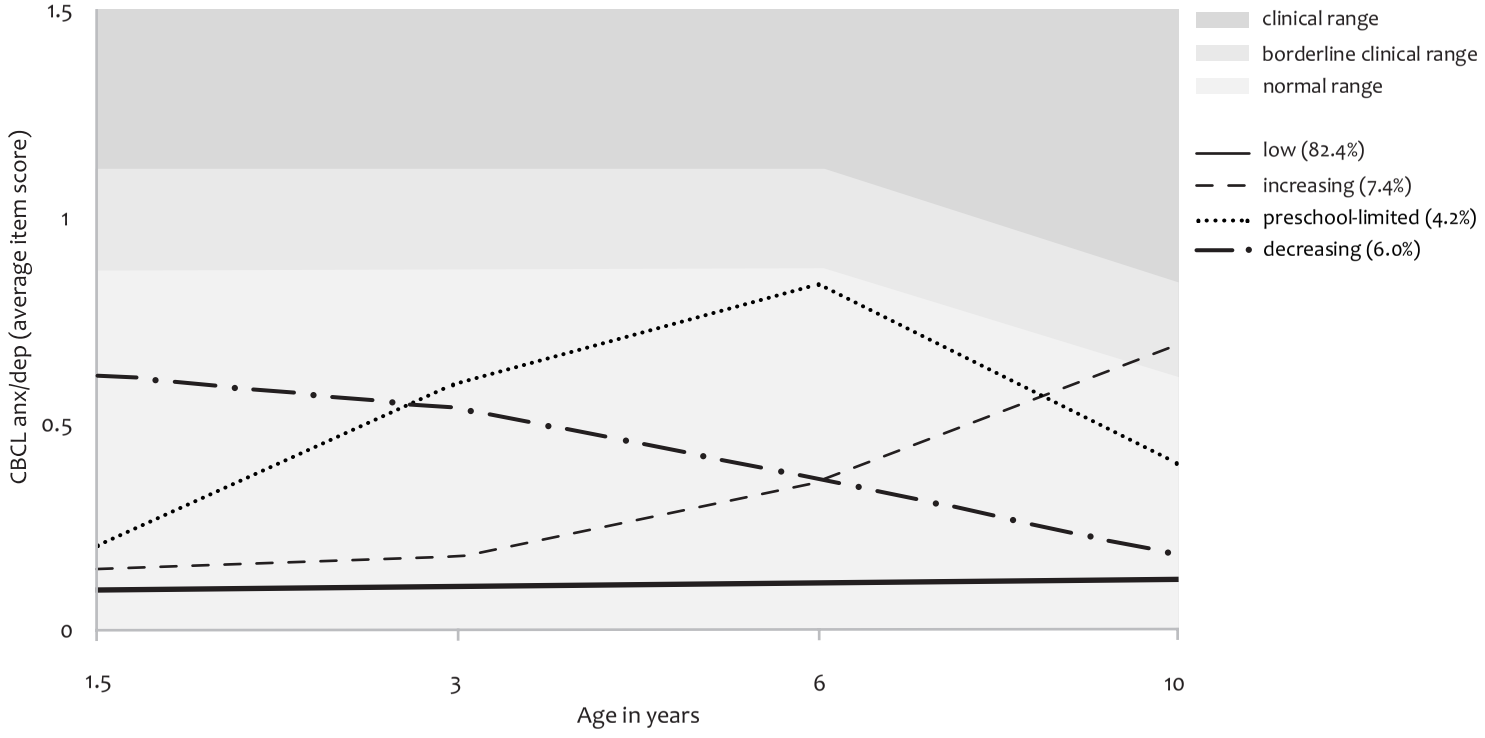
Developmental Trajectories of Anxiety and Depression Symptoms

Figure 1 gives a graphical presentation of the four anxiety and depression symptom trajectories. We defined the steady low anxiety and depression slope over time (solid line) as the *low trajectory*. Most children were within this trajectory (82.4%). The decreasing anxiety and depression slope over time (dashed-dotted line) comprised 6.0% of the children (*decreasing trajectory*). The slope that shows increasing anxiety and depression symptoms up to 6 years and a decreasing slope from 6 to 10 years (dotted line), was defined as the *preschool-limited trajectory* and comprised 4.2% of the children. The increasing anxiety and depression slope over time (dashed line) comprised 7.4% of the children (*increasing trajectory*). Anxiety and depression symptoms for children in this trajectory increased to borderline clinical levels at age 10. To examine whether differences between the trajectories were driven by certain items of the CBCL Anxious/Depressed scale, we conducted in-depth analyses of discrepancies in anxiety and depression items between the trajectories. Eight overlapping items that were assessed in both versions of the CBCL showed the same pattern of trajectories as presented in Figure 1. Thus, differences between trajectories were driven by age and the number of symptoms, instead of specific items.

Table 2. Comparison of model fit for different latent class trajectories of anxiety and depressive symptoms (*n*=7,499)

Model	#	%	Trajectories	BIC	LMRT *p*-value	Entropy	Average latent class probability
2	1	0.910	Low	-12,049.08	0.001	0.90	0.88
	2	0.090	Increasing to decreasing				0.98
3	1	0.851	Low	-13,439.29	< 0.001	0.86	0.95
	2	0.077	Increasing				0.87
	3	0.072	Decreasing				0.85
4	1	0.824	Low	-14,196.50	0.064	0.85	0.82
	2	0.074	Increasing				0.95
	3	0.060	Decreasing				0.74
	4	0.042	Pre-school limited				0.86
5	1	0.746	Low	-14,718.07	0.125	0.81	0.75
	2	0.131	Increasing to medium				0.90
	3	0.057	Decreasing				0.87
	4	0.038	Pre-school limited				0.73
	5	0.028	Increasing to high				0.84

Figure 1. Developmental trajectories of anxiety and depression symptoms (*n* = 7,499)



Note. CBCL Anxious/Depressed average item scores range from 0 to 2. Norm scores for the normal, borderline clinical and clinical range were based on the midgroup multicultural norms for the total scores of the Anxious/Depressed subscales of the CBCL 1 ½-5 years (Achenbach & Rescorla, 2000) and CBCL 6-18 years (6-11 years) (Achenbach & Rescorla, 2001)

Gender Invariance

With regard to differences in trajectories across gender, invariance held for the 4 class model solution. The 4 class model elicited the same type of trajectories for both boys (n = 3,785) and girls (n = 3,714). The means of the intercepts, linear slopes, quadratic slopes and variance of the intercept of the 4 trajectories were equal across gender (all $p > 0.16$). We, therefore, concluded that the anxiety and depression symptom trajectories were gender invariant. Small gender differences in the distribution of proportions across categories were observed within the trajectories. The percentage of boys was higher in the low trajectory (82.6%) and pre-school limited trajectory (3.9%) than the percentage of girls (77.3% and 2.9%, respectively). In contrast, the percentage of boys was lower in the increasing (7.3% boys vs. 8.4% girls) and decreasing (6.1% boys vs. 11.4% girls) trajectory compared to girls.

Predictors of Anxiety and Depression Symptom Trajectories

An overview of the associations between predictors and anxiety and depression symptom trajectories is presented in Table 3. Most strongly, children with a Western ethnicity or non-Western ethnicity had higher odds to be in the decreasing trajectory relative to the low trajectory, OR = 4.41, 95% CI [2.21, 8.82], OR = 8.79, 95% CI [5.10, 15.16], than Dutch children. Also, children with a non-Western ethnicity had higher odds to be in the pre-school limited trajectory, OR = 1.64, 95% CI [1.14, 2.34]. In contrast, children with a Western or non-Western ethnicity had lower odds to be in the increasing trajectory relative to the low trajectory, OR = 0.57, 95% CI [0.33, 1.00], OR = 0.68, 95% CI [0.48, 0.97]. Children of mothers with low educational level had higher odds to be in the decreasing, OR = 2.02, 95% CI [1.28, 3.16] as well as in the preschool-limited trajectory, OR = 1.57, 95% CI [1.02, 2.41], compared to children of mothers with high educational level. Maternal psychopathology was positively associated with the increasing trajectory, OR = 1.77, 95% CI [1.50, 2.10], the decreasing trajectory, OR = 1.62, 95% CI [1.36, 1.93], and the preschool-limited trajectory, OR = 1.80, 95% CI [1.55, 2.09]. A similar pattern was found for paternal psychopathology being positively associated with the increasing trajectory, OR = 1.24, 95% CI [1.05, 1.46], decreasing, OR = 1.24, 95% CI [1.07, 1.45], and preschool-limited trajectory, OR = 1.29, 95% CI [1.12, 1.49].

Table 3. Adjusted associations between predictors and anxiety and depression symptoms trajectories (n = 7,499): the increasing, decreasing, preschool-limited trajectory compared with the low trajectory

	Anxiety and depression symptoms trajectories									
Predictors	**Low (ref)**	**Increasing**			**Decreasing**			**Preschool-limited**		
	OR	**OR**	**95% CI**	***p*-value**	**OR**	**95% CI**	***p*-value**	**OR**	**95% CI**	***p*-value**
Child gender										
Boys	ref	1.00			1.00			1.00		
Girls		1.18	0.90 – 1.54	0.352	0.91	0.67 – 1.22	0.511	1.03	0.77 – 1.39	0.841
Child ethnicity										
Dutch	ref	1.00			1.00			1.00		
Western		**0.57**	**0.33 – 1.00**	**0.049**	**4.41**	**2.21 – 8.82**	**< 0.001**	1.00	0.55 – 1.83	0.990
Non-Western		**0.68**	**0.48 – 0.97**	**0.032**	**8.79**	**5.10 – 15.16**	**< 0.001**	**1.64**	**1.14 – 2.34**	**0.007**
Maternal education										
High	ref	1.00			1.00			1.00		
Intermediate		0.75	0.52 – 1.07	0.109	1.07	0.66 – 1.75	0.774	0.92	0.60 – 1.40	0.690
Low		0.84	0.56 – 1.25	0.398	**2.02**	**1.28 – 3.16**	**0.002**	**1.57**	**1.02 – 2.41**	**0.042**
Age mother		0.99	0.96 – 1.02	0.653	0.99	0.96 – 1.01	0.323	1.00	0.97 – 1.03	0.925
Maternal psychopathology		**1.77**	**1.50 – 2.10**	**< 0.001**	**1.62**	**1.36 – 1.93**	**< 0.001**	**1.80**	**1.55 – 2.09**	**< 0.001**
Paternal psychopathology		**1.24**	**1.05 – 1.46**	**0.011**	**1.24**	**1.07 – 1.45**	**0.005**	**1.29**	**1.12 – 1.49**	**< 0.001**

Note. Maternal and paternal psychopathology represent z-scores. Significant predictors ($p < 0.05$) are printed in bold

Psychosocial Functioning

The associations of anxiety and depression symptom trajectories with friendship quality and self-esteem are presented in Table 4a. Friendship quality varied between the four trajectories (Wald = 15.63, p = 0.001). Children in the increasing and preschool-limited trajectory had lower friendship quality compared to children in the low trajectory (d = -0.15). After adjusting for externalizing problems at 10 years, self-reported friendship quality did no longer differ across the four trajectories (Wald = 6.52, p = 0.089).

Further, different levels of self-esteem were observed between the trajectories (Wald = 181.51, p < 0.001). Children in the increasing trajectory had a lower self-esteem than children in the other three trajectories (d = -0.80 to -0.94). For self-esteem, the same results were found after adjusting for externalizing problems (Wald = 96.54, p < 0.001).

School Functioning

Table 4b presents the results of the associations of anxiety and depression symptom trajectories with school performance and school problems. School performance of the children varied across trajectories (Wald = 14.05, p = 0.003). Children with a decreasing trajectory of anxiety and depression symptoms had a higher school performance (d = 0.17) compared to children in the low trajectory. Children within the increasing trajectory and the preschool-limited trajectory had worse school performance compared to children in the decreasing trajectory (d = -0.25, d = -0.26). Although the model test for school performance remained significant after adjusting for externalizing problems (Wald = 12.56, p = 0.006), school performance between children in the pre-school limited trajectory and decreasing trajectory no longer differed (Wald = 2.98, p = 0.084).

School problems of the children varied across trajectories (Wald = 57.15, p <0.001). Children within the increasing trajectory had a lower threshold for school problems compared to children in the low and decreasing trajectory (d = -0.30, d = -0.36). Children within the preschool-limited trajectory had a lower threshold for school problems compared to children in the low class (d = -0.24). School problems varied across trajectories after adjusting for externalizing problems (Wald = 15.56, p < 0.001). However, the same thresholds for school problems were found for children in the increasing and decreasing trajectory (Wald = 3.76, p = 0.052).

Table 4a. Differences in adjusted means of psychosocial outcomes per trajectory at the age of ten years

	Psychosocial outcomes							
	Friendship quality[b,f]				Self-esteem[c]			
Trajectory	**Mean[a]**	***Wald***	***d***	***p*-value**	**Mean[a]**	***Wald***	***d***	***p*-value**
Low (ref)	23.43	-	-	-	46.72	-	-	-
Increasing	22.57	**7.71**	**- 0.15**	**0.006**	39.05	**173.33**	**- 0.83**	**< 0.001**
Decreasing	22.75	2.40	- 0.12	0.121	46.99	0.67	0.05	0.413
Preschool-limited	22.67	**4.23**	**- 0.15**	**0.040**	46.05	1.87	- 0.10	0.171
Low	23.43	2.40	0.12	0.121	46.72	0.67	- 0.05	0.413
Increasing	22.57	0.12	- 0.03	0.733	39.05	**156.22**	**- 0.94**	**< 0.001**
Decreasing (ref)	22.75	-	-	-	46.99	-	-	-
Preschool-limited	22.67	0.89	- 0.02	0.895	46.05	2.44	- 0.18	0.119
Low	23.43	**4.23**	**0.15**	**0.040**	46.72	1.87	0.10	0.171
Increasing	22.57	0.05	- 0.02	0.830	39.05	**83.80**	**- 0.80**	**< 0.001**
Decreasing	22.75	0.89	0.02	0.895	46.99	2.44	0.18	0.119
Preschool-limited (ref)	22.67	-	-	-	46.05	-	-	-

Note. Significant differences ($p < 0.05$) between mean values are printed in bold

[a] Means and thresholds were adjusted for child's gender, ethnicity, maternal age, education and maternal and paternal psychopathology

[b] $n = 4{,}336$, [c] $n = 4{,}355$, [d] $n = 3{,}669$, [e] $n = 3{,}857$

[f] No longer significant after adjusting for children's externalizing problems at 10 years of age

Table 4b. Differences in adjusted means of school-related outcomes per trajectory at the age of ten years

	School-related outcomes							
	School performance[d]				School problems[e]			
Trajectory	**Mean[a]**	***Wald***	***d***	***p*-value**	**Threshold[a]**	***Wald***	***d***	***p*-value**
Low (ref)	14.31	-	-	-	0.74	-	-	-
Increasing	13.46	3.55	- 0.15	0.060	- 0.55	**44.39**	**- 0.36**	**< 0.001**
Decreasing	14.84	**9.00**	**0.17**	**0.003**	0.42	1.51	- 0.09	0.220
Preschool-limited	14.17	0.24	- 0.04	0.626	- 0.06	**12.50**	**- 0.24**	**< 0.001**
Low	14.31	**9.00**	**- 0.17**	**0.003**	0.74	1.51	0.09	0.220
Increasing	13.46	**8.39**	**- 0.26**	**0.004**	- 0.55	**9.37**	**- 0.30**	**0.002**[f]
Decreasing (ref)	14.84	-	-	-	0.42	-	-	-
Preschool-limited	14.17	**3.87**	**- 0.25**	**0.049**[f]	- 0.06	1.96	- 0.16	0.161
Low	14.31	0.24	0.04	0.626	0.74	**12.50**	**0.24**	**< 0.001**
Increasing	13.46	1.40	- 0.13	0.237	- 0.55	2.77	- 0.17	0.096
Decreasing	14.84	**3.87**	**0.25**	**0.049**[f]	0.42	1.96	0.16	0.161
Preschool-limited (ref)	14.17	-	-	-	- 0.06	-	-	-

Note. Significant differences ($p < 0.05$) between mean values are printed in bold

[a] Means and thresholds were adjusted for child's gender, ethnicity, maternal age, education and maternal and paternal psychopathology

[b] $n = 4,336$, [c] $n = 4,355$, [d] $n = 3,669$, [e] $n = 3,857$

[f] No longer significant after adjusting for children's externalizing problems at 10 years of age

DISCUSSION

This study examined developmental trajectories of anxiety and depression symptoms from early to middle childhood in a large population-based cohort. For children between the ages of 1.5 and 10 years old, four distinct trajectories of anxiety and depression symptoms were found. These increasing, preschool-limited, decreasing, and low trajectories were predicted by child and family characteristics that were identifiable before anxiety and depression symptoms developed. Both the increasing and preschool-limited trajectories were associated with lower self-esteem and poorer school-related outcomes at 10 years old when externalizing symptoms were taken into account. This study, therefore, shows that developmental patterns of anxiety and depression symptoms in early childhood are related to negative psychosocial and school outcomes in middle childhood.

The four trajectories identified in the current study are partly in line with the results of previous studies from early to middle childhood. As expected within a population-based cohort, most children (82.4%) experienced low levels of anxiety and depression symptoms. Previous studies also found similar patterns of increasing and decreasing symptoms in this age group (Fanti & Henrich, 2010; Feng et al., 2008). However, our study also shows a unique trajectory, which is not established before. This trajectory was apparent for a small proportion (4.2%) of children who experienced an increase in anxiety and depression symptoms up to the age of 6, followed by a decrease of these symptoms by the age of 10 years. Both moderate and steep trajectories of increasing symptoms have previously been reported for children between the ages of 1.5 and 5 years (Cote et al., 2009). The results of our study indicate that increasing symptoms show two patterns after the age of 5, namely a preschool-limited trajectory and a persistent increasing trajectory. An explanation for the preschool-limited trajectory could be that these symptoms represent fears that are specific and developmentally related (Broeren et al., 2013). Also, this trajectory could be explained by comorbid externalizing symptoms after the age of 6 that may become more visible and result in underreporting of internalizing symptoms (Thomas & Guskin, 2001). Studies on internalizing and externalizing problems have shown that a subsample of children shows persistent comorbidity between these symptoms between the ages of 2 and 12 (Fanti & Henrich, 2010). However, as children in the pre-school limited trajectory remained to have more school problems than children in the low trajectory after adjusting for externalizing problems, other factors than comorbidity may explain this trajectory.

Identifying which children are more likely to follow a certain trajectory of anxiety and depression symptoms may help predict their further course of symptoms in middle childhood. Previous studies defined gender as a risk factor of increasing anxiety and depression symptom trajectories (Cote et al., 2009) or specified trajectories for boys and girls separately (Cote et al., 2002; Sterba et al., 2007). In contrast to previous studies, gender did not explain differential trajectories when adjusting for other child and family characteristics. In addition, our gender invariance analyses showed that the trajectories for boys and girls were comparable. An explanation for the discrepancy between our gender-invariance results and those found by Sterba et al. (2007), could be the small difference in the children's maximum age of the samples. Children in the study by Sterba and colleagues were followed up from 2 years until the age of 11 and gender differences for the increasing trajectories in their study became greater with increasing age. In the current study, these differences were not found between boys and girls up to the age of 10. Most probably, differences in the developmental course of anxiety and depression might become more apparent during puberty (Legerstee et al., 2013).

Both child and family characteristics in this study predicted differential trajectories of anxiety and depression symptoms. Consistent with previous research, maternal psychopathology was a risk factor for the increasing, decreasing, and preschool-limited trajectory (Cote et al., 2009; Feng et al., 2008; Sterba et al., 2007). The advantage of the current study is that we included symptoms of psychopathology of both parents, assessed at the time when they were expecting a child. While adjusting for symptoms of psychopathology of the mother, paternal psychopathology independently predicted increasing, decreasing and preschool-limited trajectories of anxiety and depression symptoms as well. Whereas maternal psychopathology can influence both the fetus and the further development of the child, paternal psychopathology can act as a stressor in the direct environment of the child (O'Donnell, Glover, Barker, & O'Conner, 2014; Stein et al., 2014).

The development of children's anxiety and depression symptoms was associated with lower self-esteem and poorer school-related outcomes at the age of 10. In line with previous studies (Fanti & Henrich, 2010; Sterba et al., 2007), children in the low group had more self-esteem, better school performance, and fewer school problems. More favorable outcomes were also found for children in the decreasing group, although the study by Feng and colleagues (2008) showed that boys with high declining symptoms of anxiety were more likely to be diagnosed with an anxiety disorder. As the decreasing trajectory was predicted by low maternal education and non-Dutch ethnicity of the child, a part of these children in this trajectory may grow up in a high-risk

environment. Instead of persistent vulnerability, this group might be able to show resilience instead of persistent vulnerability when their environment becomes more enriched (Zolkoski & Bullock, 2012). These results could also be explained by acculturation of these families over time (Sam & Berry, 2010). Additional explorative analyses showed that for families with a non-Dutch ethnicity in the decreasing trajectory, a positive association was found between time in the Netherlands for mothers and self-esteem reported by children.

Both increasing and preschool-limited symptoms were associated with lower self-esteem and poorer school-related outcomes. Specifically, children who experienced consistent increasing symptoms reported the lowest levels of self-esteem with large effect sizes. As symptoms in the increasing trajectory reached borderline clinical levels at age 10, increasing anxiety and depression symptoms together with poorer functioning indicate that these children may be at risk of developing clinical problems. Both anxiety and depression during childhood and adolescence have been associated with diminished social skills and victimization (de Lijster et al., 2018; Kingery et al., 2010; Maughan, Collishaw, & Stringaris, 2013). Internalizing and externalizing problems have previously been related to diminished social competence in middle childhood (Bornstein, Hahn, & Haynes, 2010), which could explain why experienced friendship quality no longer differed between the trajectories after adjusting for external problems. It should also be mentioned that apart from the outcome self-esteem, effect sizes were low, which is fairly common in a sample that is representative of the general population.

Strengths and Limitations

One strength of the current study is that we identified predictors of anxiety and depression symptom trajectories that were measured when parents were expecting a child. Also, this is the first study that relates anxiety and depression symptom trajectories to broader psychosocial and school functioning. Moreover, we related these trajectories to the children's own reports of their experienced friendship and feelings of self-worth. However, the use of shorter versions of these questionnaire resulted in a lower internal consistency of these outcomes. Therefore, replication of associations between the trajectories and outcomes is warranted in studies that use more extensive measures of children's psychosocial and school functioning. A final strength is that most previous studies failed to take the uncertainty of trajectory membership into account when the most likely assigned trajectory for each individual is exported to other statistical software outside the growth mixture model. By conducting all analyses within the growth mixture model, our results are not hampered by possible misclassifications of class membership.

One limitation of the current study, and in line with previous studies, is that we only relied on reports of the primary caregiver for measuring child anxiety and depression symptoms. In addition, average scores of the Anxious/Depressed subscale 1.5-5 years and 6-18 years consisted of a different number of items which may hamper the comparability of the average scores across time. As already mentioned, internal consistency of the Anxious/Depressed subscale was low at 1.5 years old. Comparable reliability coefficients less than 0.70 have been found for most narrow-band scales of the CBCL in preschool children world-wide (Rescorla et al., 2011). Moreover, the factor structure of the CBCL provides culture-general taxonomic constructs (Ivanova et al., 2010) and the Anxious/Depressed subscale has criterion-related validity in preschool children, despite low internal consistency (Achenbach & Rescorla, 2000). In our study, the same trajectory solution appeared when performing the analyses without this first measurement. Future studies may consider using a Factor Mixture Model with item-response information to identify item-level latent variables of the CBCL. Another limitation is the number of children for whom no outcomes measures were available. We should be cautious when generalizing the trajectories as children with a non-Western ethnicity, mothers with a low level of education, and parents who reported on levels of psychopathology during pregnancy were underrepresented in the outcome samples because of drop-out. In particular, missing data on paternal psychopathology was high which weakens our confidence in the results of this predictor. As previous research has shown that study drop-out does not result into different associations between predictors and outcomes in population-based longitudinal follow-up studies (Wolke et al., 2009), we are hesitant to speculate whether these findings would have been different for the whole cohort.

Implications for Prevention Policies

The current study has implications for prevention policies that aim to ward off problems with internalizing, psychosocial, and school functioning for young children in the general population. Our results showed that 7.4% of the children developed anxiety and depression symptoms within the borderline clinical range at age 10 and had lower self-esteem and poorer school-related outcomes. Our findings suggest that selective (i.e. asymptomatic population at higher risk) and indicated (i.e. high risk children with detectable symptoms foreshadowing clinical anxiety or depression) prevention programs are needed instead of universal prevention programs (Stockings et al., 2016; Vázquez-Bourgon, Herrán, & Vázquez-Barquero, 2013; Werner-Seidler, Perry, Calear, Newby, & Christensen, 2017). In this study, parental psychopathology served as a risk factor for the development of children's anxiety and depression symptoms. Although the risk

to develop internalizing problems for children of parents with a mood or anxiety disorder is well known (Maciejewski, Hillegers, & Penninx., 2018; Weissman et al., 2016), general psychopathology should not be overlooked. Moreover, information about psychopathology experienced by the father should be taken into consideration as well. Prevention programs often target factors that are related to the maintenance of anxiety and depression symptoms instead of modification of risk factors (Lawrence, Rooke, & Creswell, 2017). Selective and indicated prevention programs could benefit from addressing risk factors that predict the development of anxiety and depression symptoms, such as parental psychopathology or indicators of socioeconomic status.

Conclusion

There are distinct courses of anxiety and depression symptoms in early childhood that are related to differences in self-esteem and school-related outcomes by the age of ten. These trajectories were predicted by child and family factors that are identifiable before anxiety and depression symptoms developed, and could, therefore, guide monitoring these symptoms in the general population and provide targets for prevention programs.

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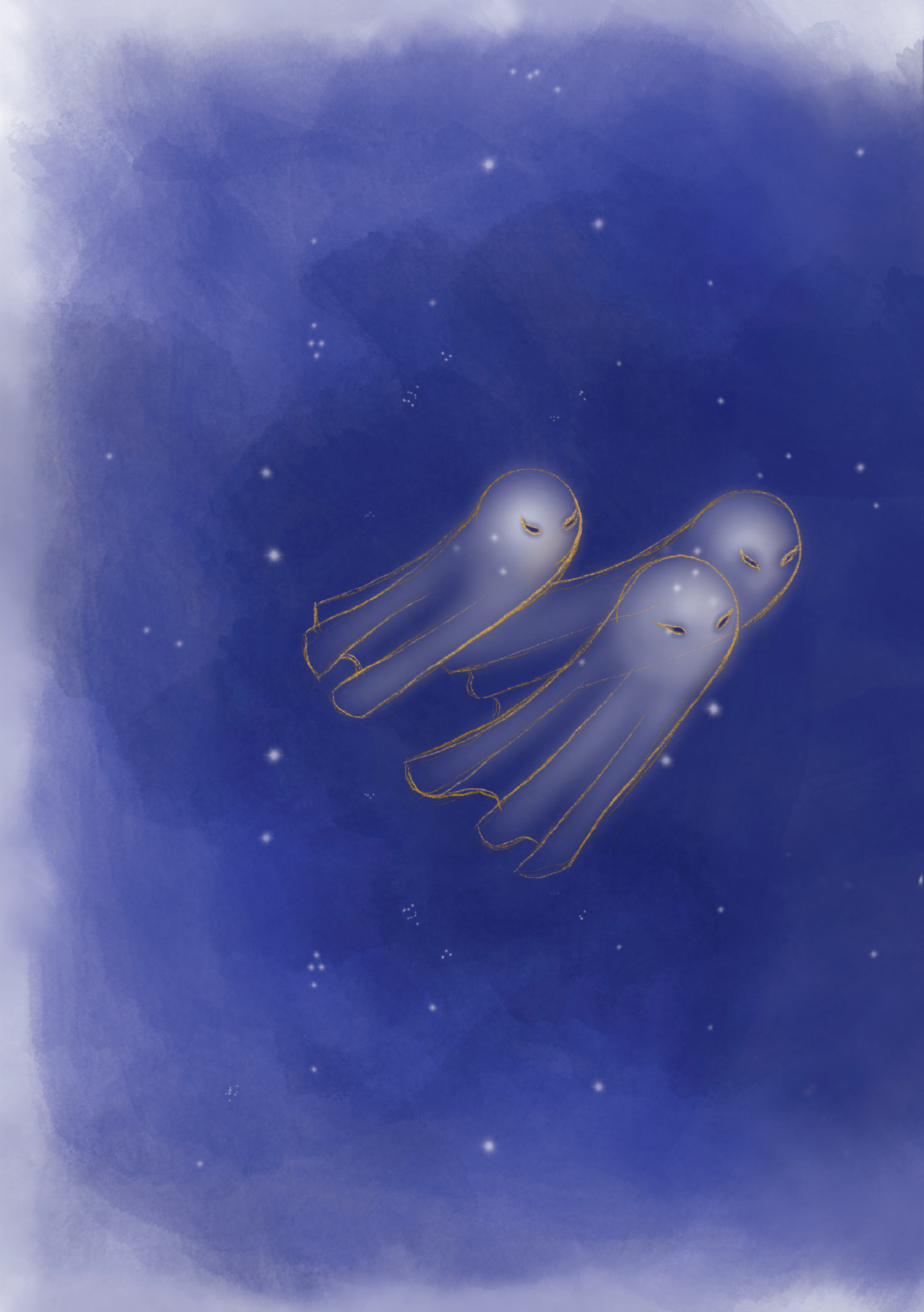

Chapter 3

Social and academic functioning in adolescents with anxiety disorders: A systematic review

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ABSTRACT

Background: Anxiety disorders are highly prevalent during adolescence. Although literature points out that anxiety symptoms are related to problems in social and academic functioning, the extent of these problems among adolescents with clinical anxiety disorders has not been systematically reviewed before.

Methods: Electronic databases were searched up to October 2017, with keywords representing anxiety disorders, adolescents, and social or academic functioning. The inclusion criteria were studies with a sample of adolescents (10-19 years) with anxiety disorders that provided data regarding their social or academic functioning. 3431 studies were examined, of which 19 met the inclusion criteria.

Results: Adolescents with anxiety disorders had a lower social competence relative to their healthy peers. They reported more negativity within interpersonal relationships, higher levels of loneliness, and victimization. Most adolescents with anxiety disorders felt impaired at school, however, findings of their average school results, compared to peers, were mixed. In addition, they had a higher risk for school refusal and entered higher education less often. Impairments in social and academic functioning differed across type and the number of anxiety disorders. Limitations: Most studies examined social phobia or anxiety disorders in general and methodological approaches varied widely between studies.

Conclusions: This systematic review indicates that adolescents with anxiety disorders experience a range of significant problems in both social and academic functioning. These findings suggest that the assessment and treatment of anxiety disorders in adolescence should focus on improving functioning across domains.

INTRODUCTION

Adolescence is a period of critical transition youngsters go through growing up from child- into adulthood (WHO, 2016). During this transition, adolescents cope with a number of developmental challenges. Their social interactions become more complex and adolescents spend an increasing amount of time with peers (Lerner & Steinberg, 2004). Academic achievement becomes more important, while adolescents typically show a decline in motivation to study (Corpus, McClintic-Gilbert, & Hayenga, 2009). The long-term effects of negative social interactions and academic problems for adolescents are well known (De Ridder et al., 2013; Lev-Wiesel, Nuttman-Shwartz, & Sternberg, 2006; Maynard, Salas-Wright, & Vaughn, 2015; Wolke & Lereya, 2015). Moreover, adolescence is considered as a risk period for the onset of mental health problems (Kessler et al., 2007). In particular, anxiety disorders are highly prevalent during this developmental period (Beesdo, Knappe, & Pine, 2009; de Lijster et al., 2016; Merikangas et al., 2010), with 12 month prevalence rates up to 8% for social phobia (SOP) and 16% for specific phobia (Merikangas et al., 2010). The extent to which anxiety disorders are related to problems in social and academic functioning during adolescence is, however, relatively unknown.

Social functioning is an important aspect of adolescence and anxiety may have a negative influence on social interactions. In general community samples, high levels of social anxiety in adolescence were found to be associated with decreased peer acceptance, peer victimization and lower friendship quantity and quality (Erath, Flanagan, & Bierman, 2007; Flanagan, Erath, & Bierman, 2008; Kingery, Erdley, Marshall, Whitaker, & Reuter, 2010; Ladd, Kochenderfer-Ladd, Eggum, Kochel, & McConnell, 2011; Ranta, Kaltiala-Heino, Fröjd, & Marttunen, 2013; Ranta, Kaltjala-Heino, Pelkonen, & Marttunen, 2009a; Tillfors, Persson, Willén, & Burk, 2012). Moreover, peer rejection and social anxiety seem to mutually affect each other (Crawford & Manassis, 2011; Ranta et al., 2013) and social skills partially explained the relation between anxiety symptoms and the experience of negative and positive peer interactions in a cross-sectional study by Motoca, Williams and Silverman (2012). Following the social skill deficits theory (Levitan & Nardi, 2009), previous clinical studies in adolescents predominantly focused on SOP, utilized different methodological approaches, and examined distinct aspects of social functioning (Gren-Landell, Aho, Anderssen, & Svedin, 2011; Inderbitzen-Nolan, Anderson, & Johnson, 2007). Given the results from previous studies, problems in social functioning for adolescents with anxiety disorders could be categorized in social competence, interpersonal relations, and victimization.

Across numerous studies, adolescents with anxiety symptoms perform poorer at school (Seipp, 1991). Anxious adolescents are less engaged at school and test anxiety directly impacts performance and grade point averages (Caraway, Tucker, Reinke, & Hall, 2003; McDonald, 2001). In a community study, the overall prevalence of anxiety-based school refusal and truancy among adolescents was estimated around 8.2% (Egger, Costello, & Angold, 2003). In addition, this study showed that school-related fears, worries, and somatic complaints predict school refusal in the general population. Nevertheless, the different domains of school functioning in adolescents with anxiety disorders haven't been systematically examined before.

As individual studies with various methodological approaches hamper definite conclusions, the current review aims to systematically examine the extent of problems in social and academic functioning in adolescents with anxiety disorders. More insight into social and academic difficulties specifically for adolescents with anxiety disorders is important in order to identify impediments during this developmental period as well as to design intervention strategies directed at this specific age group.

METHODS

Data Sources and Selection Criteria

The following databases were searched from inception on 3 October 2017: Excerpta Medica dataBASE (EMBASE), PsycINFO (OvidSP), PubMed (as supplied by publisher), and Education Resource Information Center (ERIC). Titles and abstracts were searched with a combination of keywords: "anxiety disorder" AND "adolescents" AND "social functioning" OR "academic functioning". See Table 1 for an overview of all search terms used.

Studies were included if they reported on the social or academic functioning of adolescents aged 10-19 years (WHO, 2016) with an anxiety disorder classification or diagnosis according to DSM-III-R, DSM-IV, DSM-5, or ICD-10 criteria and were published in an English, peer-reviewed, and indexed scientific journal. We excluded studies: which did not discriminate between adolescents and younger children and/or adults, studies that examined sub-clinical anxiety, studies with a specific sample of anxiety-disordered youth (e.g. with a comorbid somatic disease), and studies that examined the prevalence of anxiety disorders among adolescents in a school refusal sample. Obsessive-compulsive and trauma- and stressor-related disorders are no longer classified as

anxiety disorders in DSM-5 and studies that included these disorders were therefore excluded. Reviews, meta-analyses, doctoral theses, single case studies, and conference papers or abstracts were excluded as well.

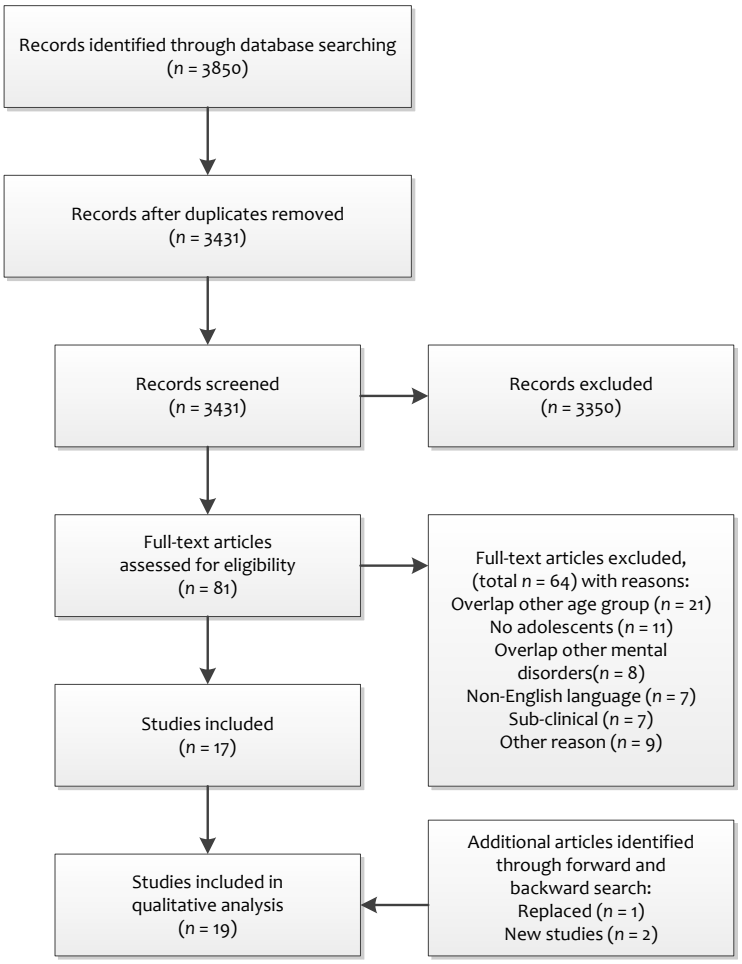
Table 1. Literature search terms used for keywords

#	Keywords	Included
1	Anxiety disorder	anxiety disorder, generalized anxiety disorder, agoraphobia, (specific/isolated) phobia, social phobia, separation anxiety disorder, panic disorder
2	Adolescents	adolescence, adolescent, prepubescent, prepuberty, puberty, pubescent, juvenile underage, teenagers, youth, youngsters
3	Social functioning	(social/interpersonal/peer) adaptation, acceptance, behavior, bullying, compatibility, competence, conflict, distance, friend, functioning, friendship, interaction, participation, peer group, performance, pressure, problem, relation, rejection, skills, stress, victimization
4	Academic functioning	(academic/grade/school/student) achievement, behavior, dropout, failure, functioning, overachievement, performance, problem, refusal, retention, stress, underachievement
	#1 AND #2 AND #3 OR #4	

A detailed overview of the study selection process is displayed in Figure 1. In line with the PRISMA guidelines (Moher et al., 2009), two of the authors independently reviewed the identified articles in two steps. Disagreement among the two reviewers was discussed until consensus was reached. In step one, 81 of the 3431 identified studies were included (97% reviewer consensus) based on title and abstract. Second, 17 of the 81 studies were included based on full texts (91% reviewer consensus). Overlap with child or adult samples (i.e. other age groups, (n = 21)), samples without adolescents (n = 11), and overlap with other mental disorders (n = 8) were the most often applied exclusion criteria in the full-text assessment. A backward search for the included studies by the first author resulted in one additional study that fulfilled the inclusion criteria. Although this study (Essau et al., 2000a) reported on the same sample as one selected

study (Essau et al., 2000b), it was selected because it provided outcome data for more anxiety disorders. In addition to the backward search, a forward search was performed by examining studies that cited the included studies. This resulted in two additional studies that fulfilled the inclusion criteria. In total, 19 studies were included in the qualitative synthesis.

Figure 1. PRISMA flowchart of study selection



Assessment of Study Quality

All included studies were assessed on study quality with a scale measuring seven different topics, for which each statement within a topic received one point. The scale was based on the STROBE criteria (von Elm et al., 2007) for observational studies and on a review published by Sanderson, Tatt and Higgins (2007). It was adapted in order to assess the specific criteria for the data of interest. Criteria included study design, sample characteristics, psychometric properties of instruments, statistical analyses, and presentation of results. A full description of the rating system is displayed in Table 2. Each article was independently assessed by two authors and discrepancies (12%) were solved by consensus decision.

RESULTS

Study Characteristics

Characteristics and results of the included studies are presented in Table 3a-c and 4a-b. Of the 19 studies, 16 reported data regarding social functioning, eight provided data on academic functioning, and five reported data on both social and academic functioning. Most studies had a cross-sectional design (63%) and 15 studies used a control group (79%). Sample sizes ranged from 4 to 2967 adolescents, and girls were the small majority (*M* = 60.0%, range 43-100%). The age range of the participants varied between 11 and 19 years. Nine studies included adolescents with primary SOP (47%). Comorbidity with another anxiety disorders was high (around 60%) for all studies. All included studies are indicated with an asterisk in the reference list.

Study Quality

Table 3a-c and 4a-b also show the quality of the selected studies. The average quality of the 19 included studies was 12.5 (*SD* = 2.5, range 7-16) out of 17 points. All studies described their recruitment procedure and reported adequate participant characteristics; half had drawn a sample from the general population (53%), the remaining studies were either ongoing treatment (26%) or referred samples (21%). Inclusion and exclusion criteria of participants were often not reported (42%) and multi-informant outcome assessment was used in nine studies (53%).

Table 2. Quality check for included studies

Method	
Design	□ Adequate study design for addressing research questions and hypotheses
Clinical sample	□ The sampling method is described (e.g. clinical, community)
	□ The sample is from the general population □ Post-hoc power is at least .8 based on reported effect size
	□ Inclusion and exclusion criteria are stated
Control group	□ Control group is included □ The source of the controls is explained and is appropriate
Anxiety disorder assessment	□ Valid instrument used □ Interrater-reliability assessed and sufficient □ Comorbidity is assessed and described
Outcome assessment	□ Instrument covers concept (validity) □ Psychometric properties of instruments known and sufficient □ Outcome assessment is multi-informant
Results	
Attrition	□ Numbers of individuals at each stage of the study are given, number of participants with missing data are reported for each variable of interest
Reporting	□ Adequate characteristics of study participants (e.g. demographic, clinical, social) are reported □ Adequate statistical analyses for addressing hypotheses □ Possible confounders are examined and taken into account in the reporting of the results

Max. total score 17 points.

Social Functioning

Social competence

All five studies that reported on social competence were focused on adolescents with SOP (Table 3a). These studies used a laboratory setting to expose participants to social anxiety-provoking situations. Based on role plays, four studies found that adolescents with SOP received lower observer ratings regarding social performance (Alfano, Beidel, & Turner, 2008; Beidel et al., 2007), assertiveness, and friendliness (Inderbitzen-Nolan et al., 2007) compared to same-aged peers. Adolescents with SOP also judged themselves as performing worse than their same-aged peers (Alfano et al., 2008; Inderbitzen-Nolan et al., 2007). One study found that adolescents with SOP needed more help with initiating and continuing contact than healthy peers, but they did not differ on other measures of social performance (Mesa, Beidel, & Bunnell, 2014).

For more structured social tasks (i.e. reading aloud, speech task), three studies highlighted poorer social performance for adolescents with SOP (Beidel et al., 2007; Inderbitzen-Nolan et al., 2007; Mesa et al., 2014). One study did not find any differences in social competence between adolescents with SOP and healthy peers, both for self- and observer-reports during a speech task (Alfano et al., 2008). However, the total sample size was relatively small and they included a third, intermediate group in their statistical analyses. Whereas feelings of social self-efficacy were related to self-rated social performance in one study, efficacy was independent of how adolescents with SOP were observed by others during role plays and giving a speech (Gaudiano & Herbert, 2007).

Differences between observer- and self-rated social performance were examined by three studies. Self-ratings of social performance of adolescents with SOP were consistently found to approximate observer-ratings (Alfano et al., 2008; Beidel et al., 2007; Gaudiano & Herbert, 2007). Moreover, Inderbitzen-Nolan and colleagues (2007) showed an interaction effect between gender and differences between observer- and self-ratings of performance during role play. Self-ratings of boys with SOP were lower than observer ratings, whereas no difference was apparent for girls with SOP.

Table 3a. Social functioning: characteristics and results of included studies that report on social competence (*n* = 5)

Authors (year)	Study design	Anxiety diagnosis[a]	Age in years	% Female	Anxiety disorder group[b, c, d, e]		Comparison group[b, e]		Measure[f]	Results[e, g]	Study quality[h]
					N	disorder	*N*	controls			
Alfano et al. (2008)	Cross-sectional (laboratory)	ADIS-C	12-16	43	21[c]	SOP	42[b]	healthy	Observer and self-ratings of social performance	○ Lower observer- and self-rated social performance during role play[g] ○ No difference between observer and self-rated social performance during speech task[g]	13
Beidel et al. (2007)	Cross-sectional (laboratory)	ADIS-C	13-16	52	63[d]	SOP	43[b]	healthy	Observer ratings of social performance	○ Lower observer-rated social performance during role-play[g] ○ Lower observer-rated social performance during speech task[g]	15
Inderbitzen-Nolan et al. (2007)	Cross-sectional (laboratory)	ADIS-C	13-17	46.7	53[b]	SOP	202[b]	nANX	Observer and self-ratings of social performance	○ Lower observer- and self-rated friendliness, social skillfulness and assertiveness during role play[g] ○ Lower observer- and self-rated friendliness, social skillfulness and assertiveness during speech task[g] ○ Gender interaction effect for differences between observer and self-rated social performance during role play[g]	16

Table 3a continued

Gaudiano & Herbert (2007)	Descriptive (laboratory)	ADIS-C	12-18	60	50 [d]	SOP	-	-	Observer and self-ratings of social performance, SESS score	○ No difference between observer and self-rated performance across tasks (role play interactions and a speech task) ○ Social self-efficacy associated with self-rated performance, not with observer-rated performance	11
Mesa et al. (2014)	Cross-sectional (laboratory)	ADIS-C	13-17	Na	16 [b]	SOP	14 [b]	Healthy	Observer ratings of elements of social performance	○ More prompts needed during role play [g] ○ Same performance for speaking latency, number of questions asked, and number of spontaneous comments made during role play [g] ○ Shorter duration of speech task [g]	14

Note. [a] ADIS-C= Anxiety Disorders Interview Schedule for Children, [b] represents a community sample, [c] clinical referred sample, [d] clinical sample in an ongoing treatment study, [e] social phobia (SOP), [f] SESS= Self-Efficacy for Social Situations Scale, [g] significant difference compared to control group, [h] total score (max. 17 points) based on "Quality checklist for studies reporting on social and academic functioning for adolescents with anxiety disorders" (Table 2)

Table 3b. Social functioning: characteristics and results of included studies that report on interpersonal relationships (*n* = 9)

Authors (year)	Study design	Anxiety diagnosis[a]	Age in years	% Female	Anxiety disorder group[b, c, d, e]		Comparison group[b, e]		Measure[f]	Results[e, g]	Study quality[h]
					N	disorder	*N*	controls			
Beidel et al. (2007)	Cross-sectional	ADIS-C	13-16	52.4	21[d]	SOP	43[b]	healthy	LS scale	o Higher levels of social isolation [g] o LS total scores within clinical range	15
Brumariu et al. (2013)	Combined cohort	SCID-I	19-23	60.6	44[b]	ANX	65[b]	healthy, other Axis I disorders	ADAPFA interview	o Higher levels of dysfunction in friendships, romantic relationships and school relationships [g] o Comparable levels to adolescents with other Axis I disorders of dysfunction in friendships, romantic relationships, and school relationships	15
Essau et al. (2000a)	Descriptive	CIDI	12-17	59.3	192[b]	ANX	-	-	CAPI-DSM-IV impairment: leisure activities and social contacts	o Impairment of social contacts from 16% for those diagnosed with SP 58% for SOP, 80% PA and 100% of adolescents with GAD in the past 4 weeks	7
Fernandez-Castelo et al. (2015)	Cross-sectional	Expert opinion, K-DIPS, CIDI	12-19	63.8	31[c]	SOP	115	nSOP	SASKO-J	o Higher scores on subscale LONELY [g]	12
Gaudiano & Herbert (2007)	Descriptive	ADIS-C	12-18	60	50[d]	SOP	-	-	SDS	o SOP symptoms disrupted social functioning on average moderately	11

Table 3b continued

McClure-Tone et al. (2011)	Cross-sectional	K-SADS-PL	*M* = 13.4 *SD* = 2.2	n/a	12[d]	ANX	17	healthy	PD game	o More likely to cooperate following co-player defection [g] o More negative feelings towards co-player at end of the game [g]	13
Reinherz et al. (1993)	Cross-sectional	Diagnostic interview DSM-III-R	17-18	49.5	88[b]	ANX	298[b]	healthy	Interpersonal Problems Scale	o More interpersonal problems [g]	14
Soohinda & Sampath (2016)	Cross-sectional	SPIN with added ICD-10 criteria	13-17	75.3	33[b]	SOP	595[b]	nSOP	Question yes/no for perceived impairment	o No difference in satisfaction with number of friends [g] o Less satisfied with the quality of their friendships [g]	13
Waters et al. (2008)	Time-series	ADIS-C	14-16	100	4[d]	GAD	-	-	IIP-C	o Interpersonal difficulties within clinical range for three out of four patients	7

Note. [a] ADIS-C= Anxiety Disorders Interview Schedule for Children, CIDI= Composite International Diagnostic Interview, K-DIPS= Structured Diagnostic Interview for Mental Disorders in Children, K-SADS-PL=Schedule for Affective Disorders and Schizophrenia for School-Age Children, SCID-I= Structured Clinical Interview for DSM-IV Axis I Disorders, SPIN=Social Phobia Inventory, [b] community sample, [c] clinical referred sample, [d] clinical sample in an ongoing treatment study, [e] anxiety disorders (ANX), generalized anxiety disorder (GAD), social phobia (SOP), [f] ADAPFA = Adolescence to Adult Personality Functioning, CAPI-DSM-IV = Computer-Assisted Personal Interview DSM-IV, IIP-C= Inventory of Interpersonal problems – circumplex scales, JVQ= Juvenile Victimization Questionnaire, LS= Loneliness Scale, PD=Prisoner's Dilemma, SASKO-J = The Questionnaire for Social Anxiety and Social Competence Deficits for Adolescents, SDS= Sheehan Disability Scale, [g] significant difference compared to control group, [h] total score (max. 17 points) based on "Quality checklist for studies reporting on social and academic functioning for adolescents with anxiety disorders" (Table 2)

Table 3c. Social functioning: characteristics and results of included studies that report on victimization and social acceptance (*n* = 4)

Authors (year)	Study design	Anxiety diagnosis[a]	Age in years	% Female	Anxiety disorder group[b, c, d, e]		Comparison group[b, e]		Measure[f]	Results[e, g]	Study quality[h]
					N	disorder	*N*	controls			
Early et al. (2017)	Cross-sectional	MINI-KID	12-14	54.8	59[c], 95[c]	SOP, other ANX	116[b]	healthy	VS, peer acceptance questions	○ Lower self- and parent-reported social acceptance for SOP and ANX, lowest for SOP[g] ○ No higher mean of relational of overt victimization in past 3 months[g]	15
Gren-Landell et al. (2011)	Cross-sectional	SPSQ-C with added DSM-IV questions	14-17	51	340[b]	SOP	2871[b]	nSOP	JVQ (total, peer or siblings victimization, sexual victimization in prior year)	○ Higher mean values of peer or siblings victimization[g]	12
Thomas et al. (2017)	Cross-sectional	DISC-IV	11-17	48.4	213[b]	ANX	2751[b]	nANX	Bully-Victim Questionnaire	○ Among adolescents who reported victimization, the odds for ANX was 2.62	13
Ranta et al. (2009)	Cross-sectional	K-SADS	12-17	50	22[b]	SOP	301[b]	SSP, healthy	Question: being bullied by peers in a way that caused harm or suffering	○ Previous bullying experiences were reported by 68% of adolescents with SP, 45% of adolescents with SSP (8% without anxiety disorder)	14

Note. [a] DISC = The Diagnostic Interview Schedule for Children, K-SADS-PL = Schedule for Affective Disorders and Schizophrenia for School-Age Children, MINI-KID = Mini International Neuropsychiatric Interview for Children and Adolescents, SPSQ-C = Social Phobia Screening Questionnaire for Children, [b] community sample, [c] clinical referred sample, [d] clinical sample in an ongoing treatment study, [e] anxiety disorders (ANX), social phobia (SOP), [f] JVQ = Juvenile Victimization Questionnaire, VS =Victimization of Self scale of the Peer Experiences Questionnaire, [g] significant difference compared to control group, [h] total score (max. 17 points) based on "Quality checklist for studies reporting on social and academic functioning for adolescents with anxiety disorders" (Table 2)

Interpersonal relationships

All nine studies on interpersonal relationships had several methodological differences and used different outcome measures. Five studies compared self-reports of adolescents with anxiety disorders to healthy peers with regard to their experience of interpersonal relationships (Table 3b). These studies documented significantly more interpersonal problems in adolescents with anxiety disorders (Beidel et al., 2007; Brumariu, Obsuth, & Lyons-Ruth, 2013; Reinherz, Giaconia, Lefkowitz, Pakiz, & Frost, 1993). Across anxiety disorders, adolescents reported more difficulties with various interpersonal relationships (i.e. friendships, romantic relations, school relationships) compared to their non-anxious peers (Brumariu et al., 2013; Reinherz et al., 1993; Soohinda & Sampath, 2016). For example, they more frequently had no people to depend on, experienced problems when communicating with others (Reinherz et al., 1993), or were less satisfied with the quality of their friendships (Soohinda & Sampath, 2016). In addition, adolescents with SOP also experienced higher levels of loneliness (Beidel et al., 2007; Fernandez Castelao, Naber, Alstadt, Kroner-Herwig, & Ruhl, 2015).

Another study showed that during a fictitious peer-interaction, adolescents with anxiety disorders experienced more negative feelings toward these peers afterward, compared to healthy controls (McClure-Tone et al., 2011). More negative feelings were regardless of the outcome of the interaction (i.e. cooperating or being let down) and these feelings were not higher compared to healthy peers in advance. In addition, this study showed that adolescents with anxiety disorders were more likely to continue to cooperate after they were let down at the end of the interaction.

The results of three descriptive studies on adolescents with anxiety disorders without a comparison group show corresponding impairments in relationships with peers (Essau et al., 2000a; Gaudiano & Herbert, 2007; Waters, Donaldson, & Zimmer-Gembeck, 2008). Adolescents with SOP in the study by Gaudiano and Herbert (2007) reported moderate social impairment. Likewise, two studies with a lower study quality highlighted perceived social impairment for anxiety disorder subtypes. In a study by Essau and colleagues (2000a), impairment in social contacts was reported most often for adolescents with SOP, PA and GAD. In a time series study by Waters et al. (2008), females with GAD reported interpersonal problems within the clinical range.

Victimization and social acceptance

Four large, cross-sectional community studies examined victimization of adolescents with anxiety disorders (Table 3c). Compared to their non-anxious peers, adolescents with SOP in the study by (Ranta, Kaltiala-Heino, Rantanen, & Marttunen, 2009b) were over eight times more likely to have been bullied. Similarly, adolescents in the study by Thomas et al. (2017) who reported victimization, were more likely to have an anxiety disorder. More victimization by a peer or sibling for adolescents with SOP compared to peers without SOP was also reported in the study by Gren-Landell et al. (2011). The study by Early et al. (2017) examined victimization in the past three months, besides parent and self-reported social acceptance. Adolescents with anxiety disorders, and especially SOP, were less socially accepted but did not report more recent experiences of victimization.

Conclusion

In summary, adolescents with SOP have lower observed and self-reported social performance than healthy peers. Adolescents with anxiety disorders report more interpersonal problems and experience more negative feelings about interpersonal relationships. In addition, adolescents with anxiety disorders are socially less accepted and experience more victimization.

Academic Functioning

School attendance

In one study (see Table 4a) which examined school refusal in adolescents and children with an anxiety disorder, school refusal was apparent for one out of five adolescents with anxiety disorders (Waite & Creswell, 2014). In this study, school refusal was almost three times more likely in adolescents compared to children.

Perceived school impairment

Four studies reported on perceived school impairment of adolescents with anxiety disorders (Table 4a). Compared to healthy peers, adolescents with SOP reported more impairment in academics in the study by Soohinda and Sampath (2016). Another study showed that within a sample of anxiety-disordered adolescents, nearly half were perceived by their parents as impaired while concentrating on school work, when giving oral reports, or taking an exam (Nail et al., 2014). Gaudiano and Herbert (2007) showed a mild level of self-reported school impairment for adolescents with SOP. In addition, feelings of social self-efficacy were found to mediate the

Table 4a. Academic functioning: characteristics and results of included studies that report on school impairment and school refusal (*n* = 5)

Authors (year)	Study design	Anxiety diagnosis [a]	Age in years	% Female	Anxiety disorder group [b, c, d, e]		Comparison group [b, c, e]		Measure [f]	Results [e, g]	Study quality [h]
					N	disorder	N	controls			
Essau et al. (2000a)	Descriptive	CIDI	12-17	59.3	192 [b]	ANX	-	-	CAPI-DSM-IV impairment: school	○ Impairment at school for 28% diagnosed with SP, 40% for PA, 50% GAD and 67% for adolescents with SOP, in the past 4 weeks	7
Gaudiano & Herbert (2007)	Descriptive	ADIS-C	12-18	60	50 [d]	SOP	-	-	SDS	○ SOP symptoms disrupted school functioning on average mildly ○ Lower social self-efficacy was (moderately r = -.40) associated with higher perceived impairment in school domain	11
Nail et al. (2015)	Descriptive	ADIS-C	12-17	n/a	169 [d]	ANX	-	-	CAIS-P	○ Impaired at school when concentrating on work (49.7%), giving oral reports (45.6%), taking tests/exams (43.8%), completing assignments (40.8%), getting good grades (39.6%), doing homework (37.3%) and writing in class (22.5%)	10
Soohinda & Sampath (2016)	Cross-sectional	SPIN, ICD-10 criteria	13-17	75.3	33 [b]	SOP	595 [b]	nSOP	Question yes/no for perceived impairment	○ More perceived difficulties in academics [g]	13
Waite & Creswell (2014)	Cross-sectional	ADIS-C	13-18	67	81 [c]	ANX	100 [c]	ANX children	ADIS-C diagnosis school refusal	○ 18% school refusal (21% male, 17% female) ○ 2.8 times more likely to not regularly attend school [g]	9

Note. [a] ADIS-C = Anxiety Disorders Interview Schedule for Children, CIDI = Composite International Diagnostic Interview, SPIN = Social Phobia Inventory, [b] represents a community sample, [c] clinical referred sample, [d] clinical sample in an ongoing treatment study, [e] anxiety disorders (ANX), social phobia (SOP) , [f] ADIS-C = Anxiety Disorders Interview Schedule for Children, CAIS-P=Child Anxiety Impact Scale for Parents, CAPI-DSM-IV = Computer-Assisted Personal Interview DSM-IV, SDS= Sheehan Disability Scale, [g] significant difference compared to control group, [h] total score (max. 17 points) based on "Quality checklist for studies reporting on social and academic functioning for adolescents with anxiety disorders" (Table 2)

association between anxiety symptoms and impairment. Lower social self-efficacy was moderately related to higher perceived impairment in the school domain. In a smaller study, the percentage of adolescents who reported school impairment differed across anxiety diagnoses (Essau et al., 2000a) and adolescents with SOP reported school impairments most often.

School results

Three studies reported on school results and compared adolescents with anxiety disorders to healthy peers (Table 4b). In two studies, adolescents with anxiety disorders had comparable histories of failing a grade and similar grade point averages at the end of high-school (Ranta et al., 2009b; Reinherz et al., 1993). One study found lower half-year exam scores for adolescents with SOP compared to healthy peers (Soohinda & Sampath, 2016).

School transition

Another study focused on the transition from high school to tertiary educational involvement in a prospective cohort of adolescents with and without anxiety disorders (Table 4b). Woodward and Fergusson (2001) showed that by the age of 21, adolescents with more anxiety disorders were less likely to enter university compared to non-anxious peers in a prospective cohort. This relation was not shown for entering lower tertiary education or training, after controlling for confounding variables.

Conclusion

In summary, there is tentative evidence that school refusal is more common among adolescents with anxiety disorders compared to clinically anxious children. It has not been examined whether adolescents with anxiety disorders refuse school more often than their healthy counterparts. Most adolescents with anxiety disorders are impaired at school, however; findings of their average school results compared with healthy peers, are mixed. In addition, adolescents with anxiety disorders enter university less frequently.

Table 4b. Academic functioning: characteristics and results of included studies that report on school results and school transition (*n* = 4)

Authors (year)	Study design	Anxiety diagnosis[a]	Age in years	% Female	Anxiety disorder group[b, c, d, e]		Comparison group[b, c, e]		Measure	Results[e, f]	Study quality[g]
					N	disorder	*N*	controls			
Ranta et al. (2009)	Cross-sectional	K-SADS	12-17	50	22[b]	SOP	301[b]	SSP, healthy	History of failing a grade	○ Comparable history of failing a grade	12
Reinherz et al. (1993)	Cross-sectional	Diagnostic interview DSM-III-R	17-18	49.5	88[b]	ANX	298[b]	healthy	Grade 12 grade-point average	○ Comparable school results	14
Soohinda & Sampath (2016)	Cross-sectional	SPIN, ICD-10 criteria	13-17	75.3	33[b]	SOP	595[b]	nSOP	Half yearly exam scores	○ Lower half year exam scores[f]	13
Woodward & Fergusson (2001)	Prospective cohort	DISC, CIDI	14-21	49.8	288[b]	ANX	676[b]	nANX	Entering university and/or entering tertiary education/ training before the age of 21	○ Number of anxiety disorders associated with decreased percentage school transition ○ Decreased percentage of entering university after controlling for several associated confounding variables, not for tertiary education/training[f]	13

Note.[a] ADIS-C= Anxiety Disorders Interview Schedule for Children, CIDI= Composite International Diagnostic Interview, DISC= The Diagnostic Interview Schedule for Children, K-SADS-PL=Schedule for Affective Disorders and Schizophrenia for School-Age Children, [b] represents a community sample, [c] clinical referred sample, [d] clinical sample in an ongoing treatment study, [e] anxiety disorders (ANX), social phobia (SOP), subclinical social phobia (SSP), [f] significant difference compared to, control group, [g] total score (max. 17 points) based on "Quality checklist for studies reporting on social and academic functioning for adolescents with anxiety disorders" (Table 2)

DISCUSSION

In this systematic review, the results of 19 studies were presented, providing an overview of social and academic functioning in adolescents with anxiety disorders. Overall, studies highlighted that anxiety-disordered adolescents face numerous difficulties in social and academic performance. They have a lower social competence compared to healthy peers, experience negativity in interpersonal relationships, loneliness, and victimization. Although findings of differences in school results of adolescents with anxiety disorders compared to peers are mixed, perceived impairment at secondary school and into higher education give reasons for concern. Moreover, there is some evidence that social and academic problems are not limited to adolescents with SOP but apparent across different anxiety disorder subtypes. Clinical characteristics and feelings of self-efficacy provide further insight into the extent of social and academic difficulties in adolescents with anxiety disorders.

A lower social performance, both on self- and observer ratings, was found in adolescents with SOP compared to healthy peers. These results are in line with the social skill deficit theory and with research in subclinical anxious adolescents (i.e. Kingery et al., 2010). Besides social skills, one study in this review found that behavior shown by adolescents with SOP during social tasks is observed and self-reported as less friendly. This is in line with behavior from socially anxious young adults being interpreted as awkward and weak (Gee, Antony, Koerner, & Aiken, 2012). In addition, this review shows that adolescents with SOP are aware of their limited social skills. In contrast to highly anxious adolescents who perform socially competent but rate themselves as performing badly (Miers, Blöte, Bokhorst, & Westenberg, 2009), low self-rated social competence by adolescents with SOP is comprehensible. The social performance of anxiety-disordered adolescents is also appraised as poor by observers. Opposed to findings in subclinical anxious adolescents and clinically anxious adults (Levitan & Nardi, 2009; Thompson & Rapee, 2002), the present review shows that social competence of youth with SOP is irrespective of the amount of structure in a social situation. Thus, adolescents with SOP are less socially competent than healthy peers in both structured (i.e. reading aloud, giving a presentation) and unstructured tasks (social interactions). As the studies for social competence only included adolescents with SOP, the results cannot be generalized to other anxiety disorders.

For interpersonal relationships, adolescents with anxiety disorders were found to have problems in their interactions with others and experienced negative feelings after these interactions.

Although the included studies used different outcome measures, they consistently showed that adolescents with anxiety disorders experience problems with interpersonal relationships. Difficulties with friends and in relationships across anxiety disorders are in line with findings from studies in adults with anxiety disorders and in children with SOP (Hoffman, Dukes, & Wittchen, 2008; Kingery et al., 2010; Mendlowicz & Stein, 2000; Wittchen, Fuetsch, Sonntag, Müller, & Liebowitz, 2000). For non-SOP anxiety disorders in childhood, contrasting findings regarding peer difficulties have been reported in previous studies (Hoff et al., 2017; Scharfstein, Alfano, Beidel, & Wong, 2011; Strauss, Lahey, Frick, Frame, & Hynd, 1988; Verduin & Kendall, 2008). Therefore, anxiety disorders during adolescence may come along with more difficulties in interpersonal relationships than during childhood.

In addition, four studies in this systematic review examined victimization, and in three studies, adolescents with SOP were more often victimized by peers or siblings compared to their non-anxious peers. In one study, two out of three adolescents with SOP reported being bullied by peers in a way that caused harm or suffering. In addition, especially adolescents with SOP are less socially accepted. Few studies reported on experiences of victimization for adolescents with other anxiety disorder subtypes, whereas the predictive effect of victimization on anxiety has been studied broadly (Hawker & Boulton, 2000; Kingery et al., 2010). Overt and relational victimization have been associated with more social anxiety, generalized anxiety, and lower self-concept (Hawker & Boulton, 2000). The diminished social performance, extensive peers problems, and high rate of victimization illustrate the amount and severity of social problems that adolescents with anxiety disorders face.

With regard to academic functioning, this review shows mixed evidence regarding the difference in school results of adolescents with anxiety disorders compared to those of their non-anxious peers. The two studies that showed no difference, correspond to other studies showing symptoms of SOP are merely related to slow perceived academic progression but not performance (Ranta et al., 2016; Strahan, 2003). Nevertheless, adolescents with anxiety disorders, particularly those with SOP, feel impaired at school. They experience problems concentrating on their work, getting good grades, doing homework, and when performing tests. One out of five adolescents with anxiety disorders even refused to go to school. A previous, retrospective study showed that leaving school prematurely is common for young adolescents with SOP and leaving or not enjoying school is related to feelings of social anxiety independent of SOP (Van Ameringen, Mancini, & Farvolden, 2003). In addition, this review provides some

evidence that adolescents with more anxiety disorders have a lower chance to enter university. Anxiety disorders have been reported to account for more failure to enter and complete college compared to mood, substance and conduct disorders, even after controlling for sociodemographic differences (Kessler, Foster, Saunders, & Stang, 1995).

This review pinpoints factors that are associated with social and academic functioning in adolescents with anxiety disorders. First, lower feelings of self-efficacy were related to lower self-rated social performance and perceived impairment at school for adolescents with SOP. Self-efficacy is defined as people's beliefs about their capabilities to produce designated levels of performance that exercise influence over events that affect their lives (Bandura, 1994). Self-efficacy could be a specific target of treatment for adolescents with SOP. Second, the number of diagnoses and type of anxiety disorder in three studies were related to the level of reported social and academic impairment. Nevertheless, clinical levels of interpersonal problems were not merely described for SOP in this review. In line with this finding, overall anxiety symptomatology has been suggested to be more important than diagnostic categories in assessing peer problems for anxiety treatment-seeking adolescents (Cohen & Kendall, 2014).

Limitations

The following limitations should be taken into account when interpreting the results of the current review. First, although the average quality of the studies was moderate to good, some studies were given a lower quality mostly because they lacked a control group and statistical analyses. The results of these predominantly, observational studies are, therefore, more difficult to interpret as they were not contrasted to adolescents without anxiety disorders. Second, many studies could not be included in the synthesis of the results as the age of the sample overlapped with a younger age group (i.e., children between the ages 6 and 12). Third, as only some studies examined factors that may explain differences in reported impairment, the identified factors in this review are not explanatory robust. In line with this, the overrepresentation of SOP in the included studies hampers the generalizability of our findings to other anxiety disorders. Future studies should, therefore, also focus on other types of anxiety disorders than SOP.

Despite our elaborate literature search, we did not find studies that provided information about the direction of effects between anxiety disorders and experienced problems in the social and school domain. As we selected studies that reported on functioning in adolescents with current anxiety disorders, we cannot distinguish if problems in social and academic functioning preceded

or were a consequence of the disorder. Previous studies have shown that subclinical social anxiety, peer friendships, and victimization have a mutual influence during adolescence (Crawford & Manassis, 2011; La Greca & Harrison, 2005; Ranta et al., 2013). This illustrates that more research is needed that focuses on the temporal sequence of anxiety disorders and social and academic functioning to provide more insight in the direction of this effect.

Implications

The amount and severity of social problems and academic impairment for adolescents with anxiety disorders highlights the need for clinicians to take social and academic functioning into account in their assessment and treatment. Recently, efforts have been made to integrate adolescents' perception and cognition of social competence in the diagnostic process of SOP symptoms (Fernandez Castelao et al., 2015). In addition, the implementation of a cognitive-behavioral school-based intervention for adolescent SOP was shown to improve students' overall functioning, besides reducing SOP (Masia-Warner et al., 2005). Future studies should focus on the prognostic value of impairment ratings, which has been shown to predict treatment success in anxiety disordered children (Goodyer, Germany, Gowrusankur, & Altham, 1991; Settipani & Kendall, 2013). Describing the effect of treatment for social and academic problems was beyond the scope of this review, however; three included studies with different treatments, reported enhanced social or academic functioning at post-treatment for adolescents with anxiety disorders (Gaudiano & Herbert, 2007; Nail et al., 2014; Waters et al., 2008). Future treatment studies may specifically address social and academic functioning, besides alleviating anxiety.

Conclusion

This systematic review indicates that adolescents with anxiety disorders experience various and significant problems in both social and academic functioning. Although most studies included a sample with SOP, we found indications that problems in social and academic functioning are also apparent for other anxiety disorders. These results underline the importance of assessment and treatment of social and academic problems adolescents with anxiety disorders face, as well as a step-wise approach to improve functioning across role domains.

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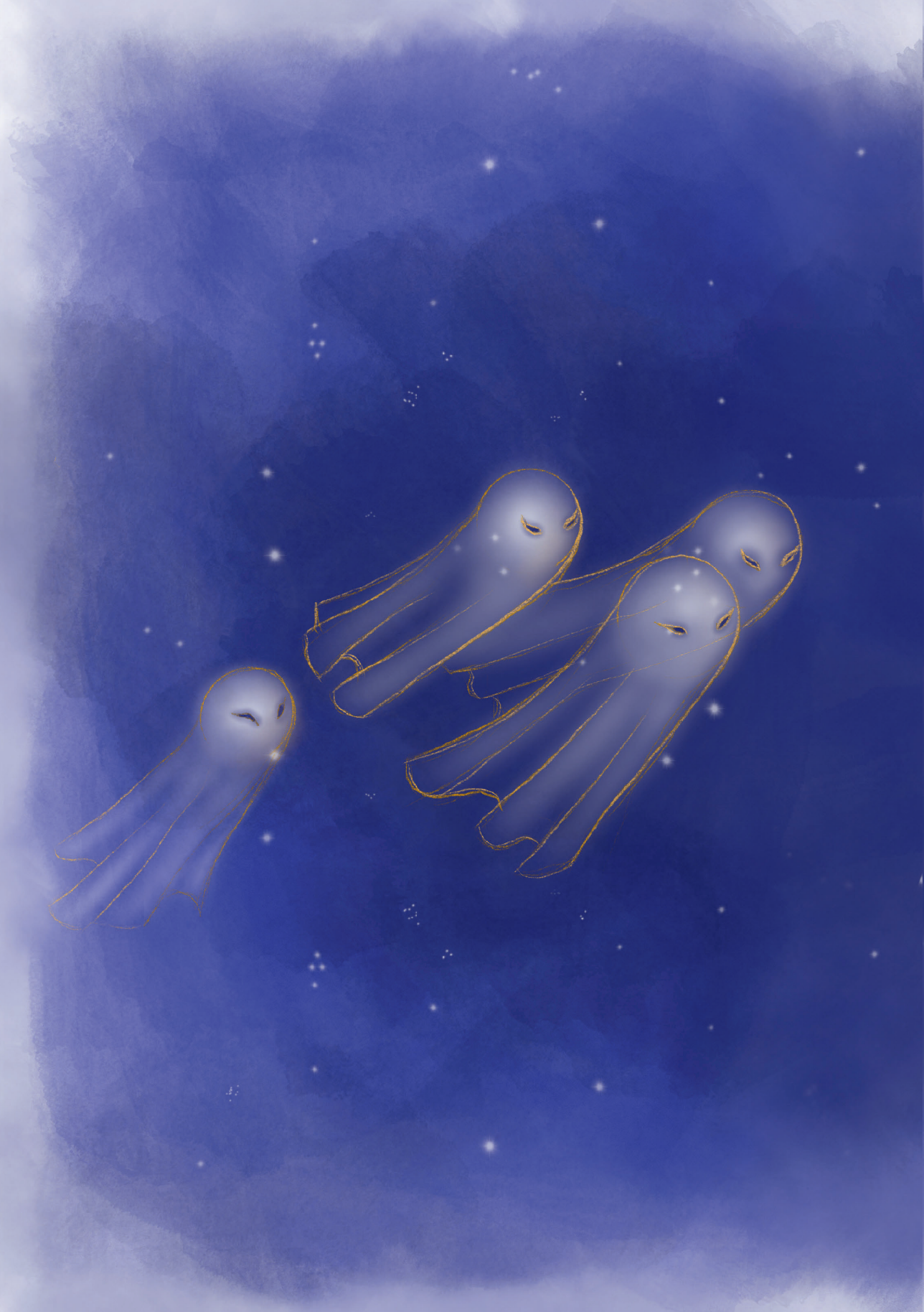

Chapter 4

The age of onset of anxiety disorders: A meta-analysis

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ABSTRACT

Objective: The objective was to estimate the age of onset (AOO) for all anxiety disorders and for specific subtypes. Gender differences in the AOO of anxiety disorders were examined, as were the influence of study characteristics on reported AOOs.

Method: Seven electronic databases were searched up to October 2014, with keywords representing anxiety disorder subtypes, AOO, and study design. The inclusion criteria were studies using a general population sample that provided data on the AOO for all anxiety disorders, or specific anxiety disorders, according to DSM-III-R, DSM-IV or ICD-10 criteria.

Results: There were 1028 titles examined, which yielded 24 studies meeting the inclusion criteria. Eight studies reported the AOO and gender. Meta-analysis found a mean AOO of all anxiety disorders of 21.3 years (95% CI 17.46 to 25.07). Separation anxiety disorder, specific phobia, and social phobia had their mean onset before the age of 15 years, whereas the AOO of agoraphobia, obsessive-compulsive disorder, post-traumatic stress disorder, panic disorder, and generalized anxiety disorder began, on average, between 21.1 and 34.9 years. Meta-analysis revealed no difference in AOO between genders. A prospective study design and higher developmental level of the study country were associated with earlier AOO.

Conclusions: Results from this meta-analysis indicate that anxiety disorder subtypes differ in the mean AOO, with onsets ranging from early adolescence to young adulthood. These findings suggest that prevention strategies of anxiety disorders should be directed towards factors associated with the development of anxiety disorder subtypes in the age groups with the greatest vulnerability for developing those disorders.

INTRODUCTION

Numerous community surveys have shown that anxiety disorders are the most common mental disorders worldwide (Kessler et al., 2007a). Anxiety disorders are debilitating and often cause impairment in social and occupational functioning (Medlowicz & Stein, 2000; Stein et al., 2005). Anxiety disorders cause more disability than all other mental health disorders (Baxter, Vos, Scott, Ferrari, & Whiteford, 2014). Economic losses arising from anxiety disorders have been estimated at around US$42 billion annually in the United States and €41 billion in Europe (Andlin-Sobocki, Jonsson, Wittchen, & Olesen, 2005; Greenberg et al., 1999). Childhood anxiety symptoms often persist into adulthood and early identification as well as treatment of children at risk for anxiety disorders may prevent the development of more severe disorders (Barrett, Farrell, Ollendick, & Dadds, 2006; Benjamin, Harrison, Settipani, Brodman, & Kendall et al., 2013; Christensen, Pallister, Smale, Hickie, & Calear., 2010; Kendall, Safford, Flannery-Schroeder, & Webb, 2004; Saavedra, Silverman, Morgan-Lopez, & Kurtines, 2010).

The age of onset (AOO) of mental disorders is a vital statistic in the formulation of mental health policy (de Girolamo, Dagani, Purcell, Cocchi, & McGorry, 2012). Several studies have compared the outcomes of early versus late onset of anxiety disorders. Early (childhood) onset has been associated with more severe psychopathology and comorbidity (Anholt et al., 2014; Ramsawh, Weisberg, Dyck, Stout, & Keller, 2011; Rosellini, Rutter, Bourgeois, Emmert-Aronson, & Brown, 2013), more avoidance behavior (Lim, Ha, Shin, Bae, & Oh, 2013), and even with higher rates of suicide (Tibi et al., 2013). Although outcomes of early anxiety disorder onset demonstrate the need for accurate information about the AOO, there is wide variation in the reported mean AOO between studies and for anxiety disorder subtypes.

Two previous reviews (Kessler et al., 2007b; McGorry, Purcell, Goldstone, & Amminger, 2011) have reported on the AOO of a range of mental health disorders in the general population, including anxiety disorders. They found that some anxiety disorders, particularly phobias, have their onset in childhood, whereas other anxiety disorder subtypes begin later, usually in early adult life. However, these review studies did not systematically estimate the AOO of different anxiety disorders, and did not examine factors that might have influenced reported AOOs. First, the reliability of retrospective recollection of AOOs, may be affected by recall bias, and prospective studies may provide more reliable information on AOOs (Wittchen et al., 1989). Second, as prevalence rates vary between countries and individual studies reports differences in

AOO for males and females, both country of origin and gender may be influence AOO (Tibi et al., 2013; WHO, 2000). To our knowledge, there are no studies to have used meta-analyses to estimate the AOO of all anxiety disorders and the AOO of specific anxiety disorders. Meta-analysis has the advantage of combining data from a number of studies, improving the accuracy of the final estimate of the AOO. Meta-regression can examine factors that influence the AOO, reducing the probability of type I error.

The present study aimed to conduct a systematic review and meta-analysis of published studies to estimate the AOO of all anxiety disorders and subtypes of anxiety disorder. In addition, we aimed to examine the influence of gender differences and study characteristics on the AOO of anxiety disorders.

METHODS

Data sources

The following databases were searched from inception on October 17, 2014: Excerpta Medica dataBASE (EMBASE), MEDLINE (OvidSP), Web of Science, PsycINFO (OvidSP), Cochrane, PubMed (as supplied by publisher), and Google Scholar. Titles and abstracts were searched with a combination of the following keywords (adjusted for the specific database): "Anxiety disorder" (i.e. anxiety disorder, acute stress disorder, generalized anxiety disorder, agoraphobia, (specific/isolated) phobia, social phobia, obsessive-compulsive disorder, post-traumatic stress disorder, adjustment disorder, separation anxiety disorder, stress disorder, panic disorder),"Age of Onset" (i.e. onset age, age of onset, age at onset) and "Study design" (i.e. cohort, longitudinal, prospective, retrospective). Searches were limited to studies published in English.

Study selection

First, 2 master psychologists (J.d.L. and C.Z.) independently reviewed the title and abstract of the articles for relevance. We included studies using a complete sample from the general population that reported on AOO, prevalence, incidence, lifetime occurrence, or epidemiology of anxiety, psychiatric, or mental disorders and that were published in a peer-reviewed, indexed scientific journal. We excluded studies that did not examine a representative sample of the general population, reviews of other studies, and studies that reported on subclinical anxiety (i.e., no diagnosis).

Second, the full texts of articles found eligible in the first step were screened by the 2 psychologists independently for both the inclusion and exclusion criteria mentioned above and for the following additional criteria: 1) anxiety disorders were classified by either DSM-III-R, DSM-IV or ICD-10; 2) AOO was defined as age at which the first symptoms of an anxiety disorder were experienced; and 3) there was an availability of summary statistics or projections (i.e. Kaplan-Meier) of the location (i.e. mean or median) and/or spread (i.e., SD or interquartile range (IQR)) for the AOO of anxiety disorders.

Data extraction process

Author contact

All corresponding authors of the articles that were included after the second step of study selection were contacted by e-mail and asked to send means and SDs (or medians and IQRs) and corresponding sample sizes for the AOO of anxiety disorders in general and subtypes. In addition, all authors were asked to send these results for males and females separately.

Sample overlap

When studies were based on an identical sample, only one study was included based on the following hierarchical rules: 1) the statistical, most usable AOO characteristics; 2) for prospective studies, the study conducted over the longest duration; and 3) the study with most information about AOO (i.e., subtypes, gender differences).

Data extraction

The study design (retrospective or prospective) and sample characteristics (total sample size, % males, age range at time of the study and the classification system used (DSM-III-R, DSM-IV or ICD-10)) were extracted. The Human Developmental Index (HDI) was used to quantify the level of development of a country and represents a summary measure of average life expectancy, education, and income (UN, 2014). The following AOO characteristics were extracted: number of participants with a lifetime history of an anxiety disorder, summary statistics (differentiated by gender if available), AOO assessment instrument, number of subtypes covered by the assessment instrument, and definition of AOO defined by the assessment instrument. When the number of participants with a lifetime history of an anxiety disorder was not reported, sample size was calculated based on the prevalence rates of anxiety disorders as reported by the study. For AOO characteristics, preference was given to data that were provided by e-mail by authors if

the data either qualitatively or quantitatively (i.e., subtypes) outperformed data from the original article.

Statistical analysis

The statistical program Comprehensive Meta-Analysis was used for the meta-analysis (Bornstein et al., 2005). A random-effects model was employed because of the high likelihood of between-study heterogeneity. The method of moments was chosen for meta-regression. Medians of the AOO were transformed to means and SDs as described by Wan et al. (2014) in which both the IQR (25th and 75th percentiles) and sample size related to the median are taken into account. First, the mean AOO was estimated for anxiety disorders in general (ANX) and for the following subtypes: separation anxiety disorder (SAD), specific phobia (SP), social phobia (SOP), agoraphobia without panic disorder (AwP), obsessive-compulsive disorder (OCD), post-traumatic stress disorder (PTSD), panic disorder (PD), and generalized anxiety disorder (GAD). Second, meta-analyses were performed to test for gender differences in the AOO. Third, meta-regressions were performed to examine the impact of moderator variables on the reported AOO measures. Study design, number of anxiety disorders covered, and HDI were entered as moderators.

RESULTS

Study selection

A detailed overview of the study selection process is displayed in Figure 1. In the first step of screening for study inclusion based on title and abstract, 189 of the 1028 identified studies were eligible (95.9% reviewer consensus). In the second step based on full texts, 41 of the 189 studies were included (92.1% reviewer consensus). The corresponding authors of 8 studies provided additional data by e-mail. After considering priorities of quality and quantity regarding sample overlap, 30 articles were selected for data extraction. Six studies were excluded because they did not report, and we were unable to locate by correspondence with the authors the sample size, prevalence rates, or spread measures of the AOO. Twenty-four studies were included in the meta-analysis (for an overview, see Table 1), of which 8 presented gender-specific AOO data. Included studies are indicated with an asterisk in the reference list.

Figure 1. Flowchart of study selection process

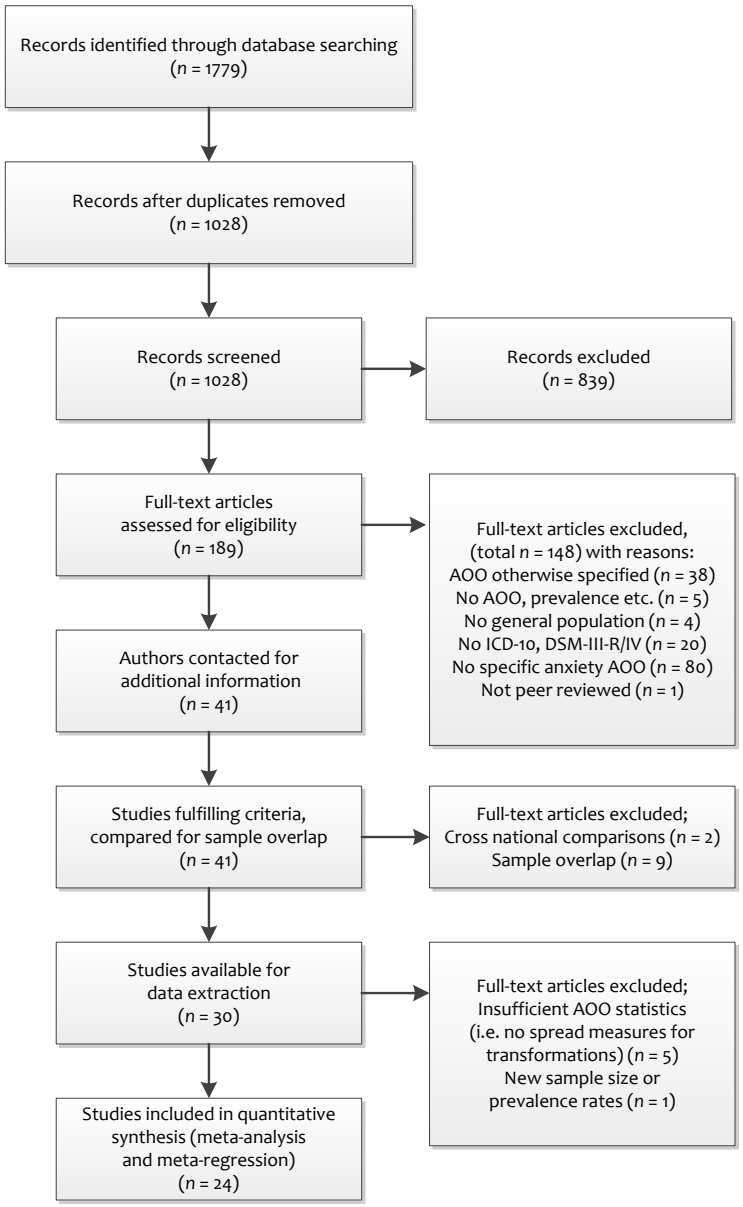


Table 1. Characteristics of included studies that reported on the Age of Onset (AOO) of anxiety disorders in the general population (n = 24)

Study (1st-named author)	**Total sample** N, % male	**Country, region**	**Age**	**Instrument**[a]	**Classification system**[b]	**AOO details**[c] Anxiety disorder subtypes Gender differences Estimates used in analyses	**Number of subtypes covered**[d]	**Study design**[e]	**HDI**[f]
Alhasnawi 2009	World Mental Health survey 4332, †	Iraq	18 +	WHO CIDI 3.0	DSM-IV	SP, SOP, OCD, PD, PTSD, GAD, ANX - Transformed median/IQR	7	0	0.64
Angst 2004	Zurich community 591, 49.4%	Switzerland, Zürich	20 – 41	SPIKE	DSM-IV	OCD OCD Mean, SD, N by e-mail	n/a	1	0.92
Becker 2007	Dresden Study of Mental Health 5204, 0%	Germany, Dresden	18 – 24	F-DIPS	DSM-IV	SAD, SP, SOP, AwP, OCD, PA, PwA, PTSD GAD, ANX - Mean, SD, N by e-mail	7	1	0.91
Bienvenu 2006	Epidemiologic Catchment Area 816, †	USA, Baltimore	18 – 86	DIS / SCAN	DSM-III-R	AwP - Mean, SD, N original	n/a	1	0.91
Bonnewyn 2007	European Study on the Epidemiology of Mental Disorders 2419, 48.3%	Belgium	18+	WHO CIDI 3.0	DSM-IV	ANX - Transformed median/IQR	6	0	0.88
Caraveo-Anduaga 2004	Mexican household survey 1932, 50%	Mexico, Mexico-city	18 – 65	WHO CIDI 1.1	ICD-10	SP, SOP, PwA, OCD, GAD SP, SOP, PwA, OCD, GAD Mean, SD, N by e-mail	n/a	0	0.76
Chap-man 2012	Australian National Survey of Mental Health 8841, -	Australia	16 – 85	WHO CIDI	DSM-IV	PTSD PTSD Transformed median/IQR	n/a	0	0.93
Chartier 2003	Ontario Health Survey 8116, 48.6%	Canada	15 – 64	WHO CIDI	DSM-III-R	SOP - Transformed median/IQR	n/a	0	0.90

Table 1 continued

Cho 2012	Korean Epidemiologic Catchment Area Study Replication (KECA-R) 7972, †	South Korea	18 – 64	Korean CIDI 2.1	DSM-IV	ANX, SP, SOP, OCD, PTSD, GAD - Transformed median/IQR	7	0	0.89
Falk 2008	National Epidemiologic Survey on Alcohol and Related Conditions 19504, 50%,	USA	18+	AUDADIS-IV	DSM-IV	SP, PA, PwA, GAD SP, PA, PwA, GAD Mean, SD, N by e-mail	n/a	0	0.91
Gau 2007	Randomly selected high school sample 428, 50.2%	Taiwan	12.5 – 15.5	K–SADS–E	DSM-IV	ANX - Mean, SD, N original	8	1	0.88
Giaconia 1994	Follow-up of public kindergarten sample 386, 50.5%	USA, North-East	M = 17.9	DIS-III-R	DSM-III-R	SP, SOP, PTSD - Mean, SD, N original	n/a	1	0.91
Goncal-ves 2012	Australian National Survey of Mental Health 8841, 50%	Australia	16 – 85	WHO CIDI 3.0	DSM-IV	GAD - Transformed median/IQR	n/a	0	0.93
Gureje 2008	Nigerian Survey of Mental Health and Wellbeing 6752, 49.4%	Nigeria	18+	WHO CIDI 3.0	DSM-IV	ANX - Transformed median/IQR	7	0	0.50
Kessler 2005	National Comorbidity Survey Replication 1808 - 9282, 44.6%	USA	18 +	WMO CIDI	DSM-IV	SAD, SP, SOP, AwP, PwA, OCD, PTSD, GAD, ANX - Transformed median/IQR	8	0	0.91
Knappe 2011	Early Developmental Stages of Psychopathology Study 3021, 50.7%	Germany	14 – 34	DIA-X/M-CIDI	DSM-IV	SAD, SP, SOP, AwP, PA, PwA, OCD, PTSD, GAD SAD, SP, SOP, AwP, PA, PwA, OCD, PTSD, GAD, ANX Mean, SD, N by e-mail	n/a	1	0.91

Table 1 continued

Study (1st-named author)	**Total sample** N, % male	**Country, region**	**Age**	**Instrument**[a]	**Classification system**[b]	**AOO details**[c] Anxiety disorder subtypes Gender differences Estimates used in analyses	**Number of subtypes covered**[d]	**Study design**[e]	**HDI**[f]
Lee 2007	World Mental Health household survey 5201, 52.6%	China, Beijing and Shanghai	18 – 70	WHO CIDI	DSM-IV	SP, GAD, ANX - Transformed median/IQR	7	0	0.72
Levinson 2007	Israel National Health Survey 4589, 49%	Israel	21+	WHO CIDI	DSM-IV	PwA, PTSD, GAD, ANX - Transformed median/IQR	4	0	0.89
Lewin-sohn 1998	Oregon Adolescent Depression Project 816, 48%	USA, Oregon	*M* = 16.6 *SD* = 1.2	K-SADS-E	DSM-III-R	SAD, SP, SOP, AwP, PD, OCD, PTSD, GAD, ANX SAD, SP, SOP, PD, OCD, PTSD, GAD, ANX Mean, SD, N by e-mail	8	1	0.91
Marque-nie 2007	The Netherlands Mental Health Survey and Incidence Study 1 7076, 46.6%	Netherlands	*M* = 41.3 *SD* = 11.8	WHO CIDI 1.1	DSM-III-R	ANX - Mean, SD, N original	5	0	0.92
Ritchie 2004	Random selection from the 15 electoral rolls 1873, 41.5%	France, Mont-pellier	65+	MINI, French 5.00	DSM-IV	SOP, AwP, PD, OCD, PTSD, GAD, ANX SOP, AwP, PD, OCD, PTSD, GAD, ANX Mean, SD, N by e-mail	7	0	0.88
Stein 2008	South African Stress and Health Study 4351, -	South Africa	18+	WHO CIDI	DSM-IV	SOP, AwP, PD, PTSD, GAD, ANX - Transformed median/IQR	5	0	0.66

Table 1 continued

Viana 2012	The São Paulo Megacity Mental Health Survey 5037, 47%	Brazil, São Paulo	18+	WHO CIDI	DSM-IV	SAD, SP, SOP, AwP, PD, OCD, PTSD, GAD, ANX - Transformed median/IQR	8	0	0.74
Vain-gankar 2013	The Singapore mental health study 6616, 48.5%	Singapore	*M* = 42.0 *SD* = 14.5	WHO CIDI 3.0	DSM-IV	OCD, GAD OCD, GAD Mean, SD, N by e-mail	n/a	0	0.90

Note.

† No reports on gender distribution for the total sample

[a] WHO CIDI = The World Health Organization World Mental Health Composite International Diagnostic Interview; SPIKE = Structured Psychopathological Interview and Rating of the Social Consequences for Epidemiology; F-DIPS=Diagnostisches Interview psychischer Störungen (Forschungversion); DIS/SCAN = Diagnostic Interview Schedule/ Schedules for Clinical Assessment in Neuropsychiatry; AUDADIS-IV = The Alcohol Use Disorder and Associated Disabilities Interview Schedule-IV; K–SADS–E=Schedule for Affective Disorders and Schizophrenia for School-Age Children; DIS-III-R = Diagnostic Interview Schedule, version three – revised; DIA-X/M-CID I= The computer-assisted Munich-Composite International Diagnostic Interview; MINI = The Mini-International Neuropsychiatric Interview

[b] DSM-III-R = Diagnostic and Statistical Manual of Mental Disorders – 3rd Edition Revised, DSM-IV = Diagnostic and Statistical Manual of Mental Disorders – 4th Edition, ICD-10=10th Edition of the International Classification of Diseases

[c] SAD = separation anxiety disorder; SP = specific phobia; SOP = social phobia; AwP = agoraphobia without panic disorder; OCD = obsessive-compulsive disorder; PTSD = post-traumatic stress disorder; PD = panic disorder; PA = panic disorder with agoraphobia, PwA = panic disorder without agoraphobia, GAD = generalized anxiety disorder; ANX = anxiety disorders in general

- No reports on age of onset for gender differences

[d] Number of subtypes covered by the instrument used by the study to diagnose anxiety disorder subtypes, n/a = study did not define "ANX" age of onset

[e] Study design 0=retrospective, 1=prospective

[f] HDI = Human Developmental Index, report United Nations 2014

Study Characteristics

Most studies had a retrospective design (70.8%) and used the DSM-III-R or DSM-IV classification (95.8%). The age range of the participants in the studies varied from narrow to broad, and samples ranged from early adolescence until late adulthood. Twelve AOO medians with IQRs were transformed to means and SDs. When studies reported the AOO for both PD with (PA) and PD without agoraphobia (PwA), these separate estimates were combined in the meta-analysis, together representing PD.

Meta-analyses

Age of onset

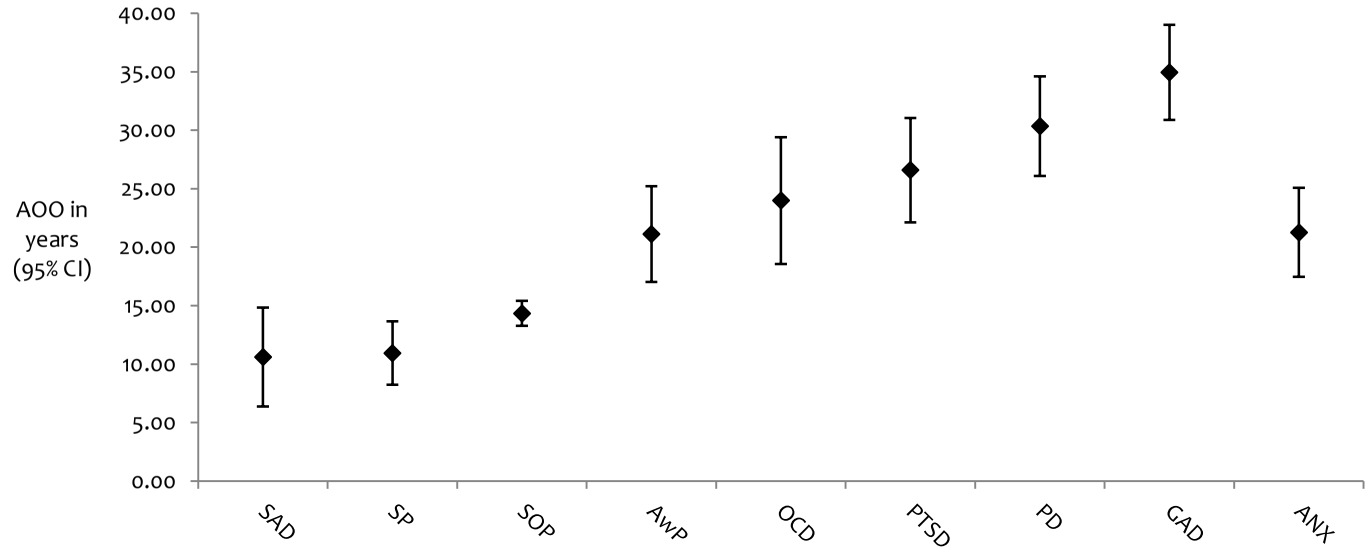
Figure 2 gives an overview of the estimated mean AOO and number of estimates of each anxiety disorder. The meta-analysis for ANX included estimates from 14 non-overlapping studies with a total sample of 7443 individuals. The estimated mean AOO was 21.3 years (95% CI 17.46 to 25.07). The estimated AOO was lowest for SAD (10.6 years; 95% CI: 6.38 to 14.84), followed by SP (11.0 years; 95% CI: 8.25 to 13.65) and SOP (14.3 years; 95% CI: 13.27 to 15.41). Higher AOOs were estimated for AwP (21.1 years; 95% CI: 17.02 to 25.23), OCD (24.0 years; 95% CI: 18.57 to 29.41), PTSD (26.6 years; 95% CI: 22.13 to 31.06), PD (30.3 years; 95% CI: 26.09 to 34.59), and GAD (34.9 years; 95% CI: 30.88 to 39.01). As evidenced by the non-overlapping confidence intervals of their estimates, SAD, SP, and SOP have a significantly earlier AOO than other anxiety disorders, and GAD has a significantly later AOO than SAD, SP, SOP, AwP, and OCD.

Gender differences

Because only 2 studies reported gender-specific estimates for SAD, AwP, and ANX, these AOO outcomes could not be analyzed. A total of 31 estimates of 8 separate studies were included in this meta-analysis with a total sample size of 3256 males and 7766 females.

Publication bias could not be assessed because there were not enough estimates for each anxiety disorder subtype. Moreover, combining al different anxiety disorder subtypes in one funnel plot could result in a non-informative conclusion of publication bias.

Figure 2. Mean age of onset (AOO) estimates for anxiety disorders



Note. SAD = Separation anxiety disorder, 4 studies, *n* = 388; SP = specific phobia, 11 studies, *n* = 7207; SOP = social phobia, 12 studies, *n* =3407; AwP = agoraphobia without panic disorder, 8 studies, *n* = 1209; OCD = obsessive-compulsive disorder, 11 studies, *n* = 866; PTSD = post-traumatic stress disorder, 12 studies, *n* = 1459; PD = panic disorder, 11 studies, *n* = 3240; GAD = generalized anxiety disorder, 15 studies, *n* = 4422; ANX = anxiety disorders in general, 14 studies, *n* = 7443) I^2 = 93.6% – 99.7% (all $p < 0.0001$)

Figure 3. Combined forest plot for gender difference in age of onset (years) for anxiety disorders

	Number of studies	Sample size females (*n*)	Sample size males (*n*)
Specific Phobia (SP)	4	3213	1289
Social Phobia (SOP)	4	265	125
Obsessive-Compulsive Disorder (OCD)	6	209	157
Post-traumatic Stress Disorder (PTSD)	4	651	286
Panic Disorder (PD)	5	7603	3118
Generalized Anxiety Disorder (GAD)	6	1640	693

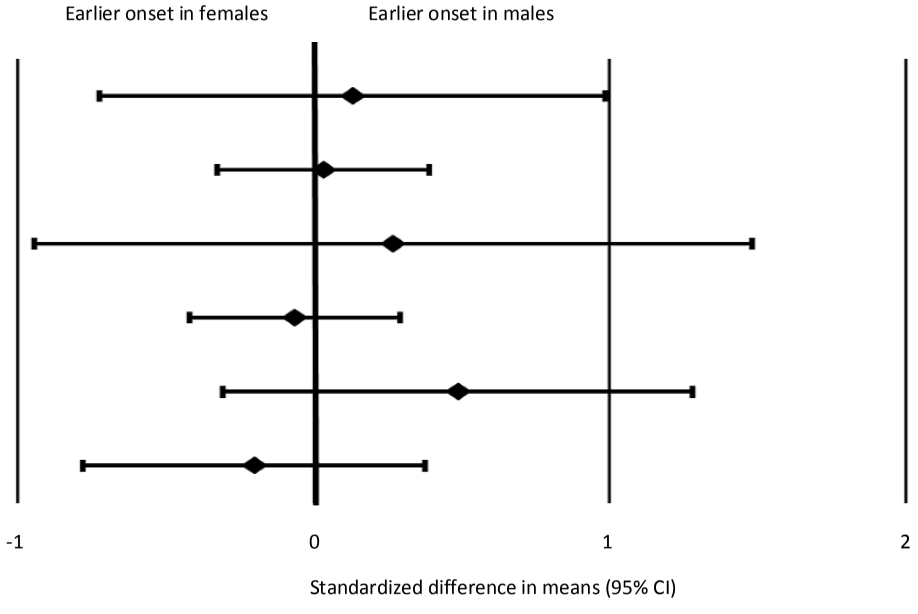


Figure 3 shows the combined, abbreviated forest plot with weighted effect size and 95% CI for 6 anxiety disorder subtypes. No significant difference in AOO of anxiety disorders was found between males and females. The weighted mean difference (WMD) between genders in the AOO varied between -0.20 (95% CI -0.78 to 0.38; I^2 = 82.2%, p < 0.001) for SOP to 0.49 (95% CI -0.31 to 1.28; I^2= 97.7%, p < 0.001) for SP. Both I^2 measures indicate that there is significant amount of heterogeneity between studies, which supports our choice of a random effects model. A nonsignificant trend was found for an earlier onset of OCD in males (WMD = 0.21, 95% CI -0.03 to 0.45, p = 0.08, I^2= 6.4%, p = 0.376).

Meta-regressions

Meta-regression outcomes of the impact of study design, number of anxiety disorders covered by ANX, and HDI on the AOO of anxiety disorders are shown in Table 2.

First we investigated the impact of a prospective design versus a retrospective design on the AOO. Ninety-eight estimates were included in 9 separate meta-regressions. The results showed an earlier AOO of AwP, OCD, PTSD, PD, and GAD, for studies with a prospective design, explaining 30.93% to 75.57% of the variance in AOO between studies.

Second, we determined whether the AOO of ANX was associated with the number of anxiety disorder subtypes covered by ANX in the different studies. Fourteen estimates were included in this analysis. The results showed that an earlier AOO of ANX was found when ANX was covered by more anxiety disorder subtypes (β = -6.34 [1.31], 95% CI -8.90 to 3.78, R^2 = 0.32, p < 0.001).

Third, we related the HDI of the study country to the AOO of anxiety disorders. A total of 98 estimates were included in this analysis. Differences in AOO between different levels of HDI were found. An earlier onset of SAD, SOP, OCD, and GAD was reported for countries with a higher HDI. Explained variances varied between anxiety disorder subtypes with 4.46% for GAD up to 94.45% for SAD.

Table 2. Meta-regression on the effect of study characteristics on AOO of anxiety disorders

Anxiety disorder subtype		Slope (standard error)	95% CI	R^2 value
SAD	Study design	n.s.		
	HDI	-90.45 (9.10)[a]	-108.29 to -72.61	0.94
SP	Study design	n.s.		
	HDI	n.s.		
SOP	Study design	-3.12 (1.21)[b]	-5.49 to -0.74	[c]
	HDI	-17.38 (4.20)[a]	-25.61 to -9.14	0.44
AwP	Study design	-8.25 (2.64)[b]	-13.43 to -3.08	0.65
	HDI	n.s.		
OCD	Study design	-13.16 (4.78)[a]	-22.54 to -3.79	0.31
	HDI	-88.21 (19.42)[a]	-126.27 to -50.15	0.62
PTSD	Study design	-16.60 (3.33)[a]	-23.12 to -10.07	0.51
	HDI	n.s.		
PD	Study design	-15.21 (2.76)[a]	-20.62 to -9.80	0.69
	HDI	n.s.		
GAD	Study design	-18.19 (3.62)[a]	-25.29 to -11.09	0.51
	HDI	-83.75 (20.55)[a]	-124.03 to -43.47	0.45
ANX	Study design	-12.36 (4.87)[b]	-21.91 to -2.81	[c]
	Number of subtypes covered	-6.34 (1.31)[a]	-8.90 to -3.78	0.32
	HDI	n.s.		

Note. SAD = separation anxiety disorder; SP = specific phobia; SOP = social phobia; AwP = agoraphobia without panic disorder; OCD = obsessive-compulsive disorder; PTSD = post-traumatic stress disorder; PD = panic disorder; PA = panic disorder with agoraphobia, PwA = panic disorder without agoraphobia, GAD = generalized anxiety disorder; ANX = anxiety disorders in general. Study design represents a dummy variable (0 = retrospective, 1 = prospective). AOO = age of onset; HDI = Human Developmental Index; n.s. = not significant, [a] $p < 0.001$, [b] $p < 0.01$, [c] Explained variance could not be calculated because the between-study variance was higher after entering the covariate

DISCUSSION

This meta-analysis aimed to estimate the AOO of anxiety disorders, examine gender differences in AOO and the effect of study characteristics on the AOO. Twenty-four studies with a general population sample were included in the present study. ANX had an estimated mean AOO of 21.3 years. Significant differences in the AOO were found between anxiety disorder subtypes. SAD, SP, and SOP had their onset in childhood and early adolescence, whereas AwP, OCD, PTSD, PD, and GAD had their onset in young adulthood. Gender was not related to the AOO of anxiety disorders. An earlier AOO was found for ANX when it comprised more anxiety disorder subtypes. For certain specific anxiety disorder subtypes, study design and developmental level of the study were associated with AOO.

A strength of the current meta-analysis is that we were able to use previous empirical studies in the general population to estimate the AOO for each anxiety disorder subtype. The 2 previous reviews of Kessler et al. (2007b) and McGorry et al. (2011) did not specify AOOs for each anxiety disorder. Moreover, the AOO reported by McGorry et al. was younger, probably because their review was limited to studies of adolescents.

The current meta-analysis shows differences in the onset of anxiety disorder subtypes, ranging from early adolescence to young adulthood. This sequence validates the current taxonomy of anxiety disorders (Beesdo, Knappe, & Pine, 2009), as social and cognitive development has been shown to affect the timing of anxiety disorder subtypes (Broeren & Muris, 2009; Muris, Merckelbach, & Luijten, 2002), in addition to environmental and genetic risk factors (Martin, Ressler, Binder, & Nemeroff, 2009). The later onset of AwP, PD and GAD, for instance, is in line with research that separates these disorders from SP based on genetic predisposition (Hettema, Prescott, Myers, Naele, & Kendler, 2005; Kendler, Presscott, Myers, & Naele, 2003). SOP, which was found to emerge in adolescence, has a shared genetic susceptibility with AwP, PD, and GAD.

We found that GAD had the latest AOO at around 35 years. This high estimation of the AOO of GAD might be biased due to the large diagnostic overlap with major depressive disorders (Gorwood, 2004; Zbozinek et al., 2012) in combination with the relatively later onset of mood disorders (Kessler et al., 2007b). SAD was found to have the earliest AOO. This early onset is probably due to the requirement in ICD-10, DSM-III-R and DSM-IV that the onset of SAD is before the age of eighteen. As DSM-5 allows for the onset of SAD in adulthood (APA, 2013), AOO estimates for SAD will probably be higher in future studies.

Although it is well known that anxiety disorders are more common among women (for an overview, see Somers, Goldner, Waraich, & Hsu, 2006), and that women comprised two-thirds of the individuals in our study, we did not find gender differences in the AOO of anxiety disorders. No gender difference in AOO was found in a large study by McLean, Asnaani and Litz (2011). This finding suggests that the period of greatest vulnerability for developing an anxiety disorder is the same for men and women.

An earlier AOO was estimated for SAD, SOP, GAD, and OCD in countries with a higher HDI. This suggests that some anxiety disorder subtypes have an earlier onset in countries that provide better life expectancy, education, and income. However, other factors can explain these findings as well. First, most studies had a retrospective design. Retrospective studies on AOO rely heavily on the recall of first onset of symptoms. More public awareness of and less prejudice against mental health problems in developed countries than in developing countries might result in earlier recognition and recall of anxiety problems in people from developed countries (Lauber & Rössler, 2007). Additionally, families in developing countries might have more pressing concerns, which could result in delayed recall of the onset of anxiety disorders when asked retrospectively. Second, most of the prospective studies were carried out in developed countries. Prospective studies likely have a more accurate estimate of the AOO of mental disorders compared to retrospective studies. This could be an explanation why earlier AOO was found for developed countries. Third, half of the studies in countries with a low HDI did not cover SAD and OCD. Therefore, AOO estimates of SAD and OCD for developing countries are not very robust.

Limitations

Because of the large diversity in study characteristics and statistics reported by the studies included in this meta-analysis, the following limitations should be taken into account. First, many studies could not be included in the present meta-analysis because they did not report sufficient statistical summary measures. Second, we were not able to control for the age of the samples as no study provided mean age statistics. Presumably, an older sample will be associated with later AOO due to recall bias and a longer period of being at risk of developing the disorder. Third, we found that prospective studies reported lower AOOs of anxiety disorders. As most studies that were included in this meta-analysis had a retrospective design, this could have led to higher estimates of AOO due to recall bias. Fourth, we had to transform reported medians to means, while skewness of the data favors using median instead of mean scores. This may also have led to a later estimated AOO. Using prevalence rates to determine the sample size of individuals who

reported on the AOO of anxiety disorders probably overestimated the weight of these studies in the meta-analysis, as not all individuals are able to report on their AOO.

Implications

There are several important implications from the results of this meta-analysis. The estimated AOOs identified risk periods for the development of different anxiety disorders. This information could guide prevention programs to target factors contributing to the emergence of anxiety disorders in key vulnerability periods. Because primary prevention programs have generally been provided at schools, the later onset of AwP, OCD, PTSD, PD, and GAD highlights the need for prevention beyond the education system. As to future research, when studying AOOs in either general community or clinical samples, more uniform reporting would help in the interpretation of study results. Based on the diversity found in reporting of AOO and the results of the current study, we propose reporting both the mean or median and the variation of this measure. In addition, more prospective studies with frequent screening would further guide our understanding of the AOO of anxiety disorder.

Conclusion

The current meta-analysis indicates that ANX have an onset around 21 years, and that anxiety disorder subtypes differ in the mean AOO. No gender differences in AOO of anxiety disorders were found. Moreover, a prospective study design and higher development status of a country were associated with an earlier onset of anxiety disorders. The identified age intervals of onset for different anxiety disorders indicate windows of risk in which to implement tailored preventive strategies.

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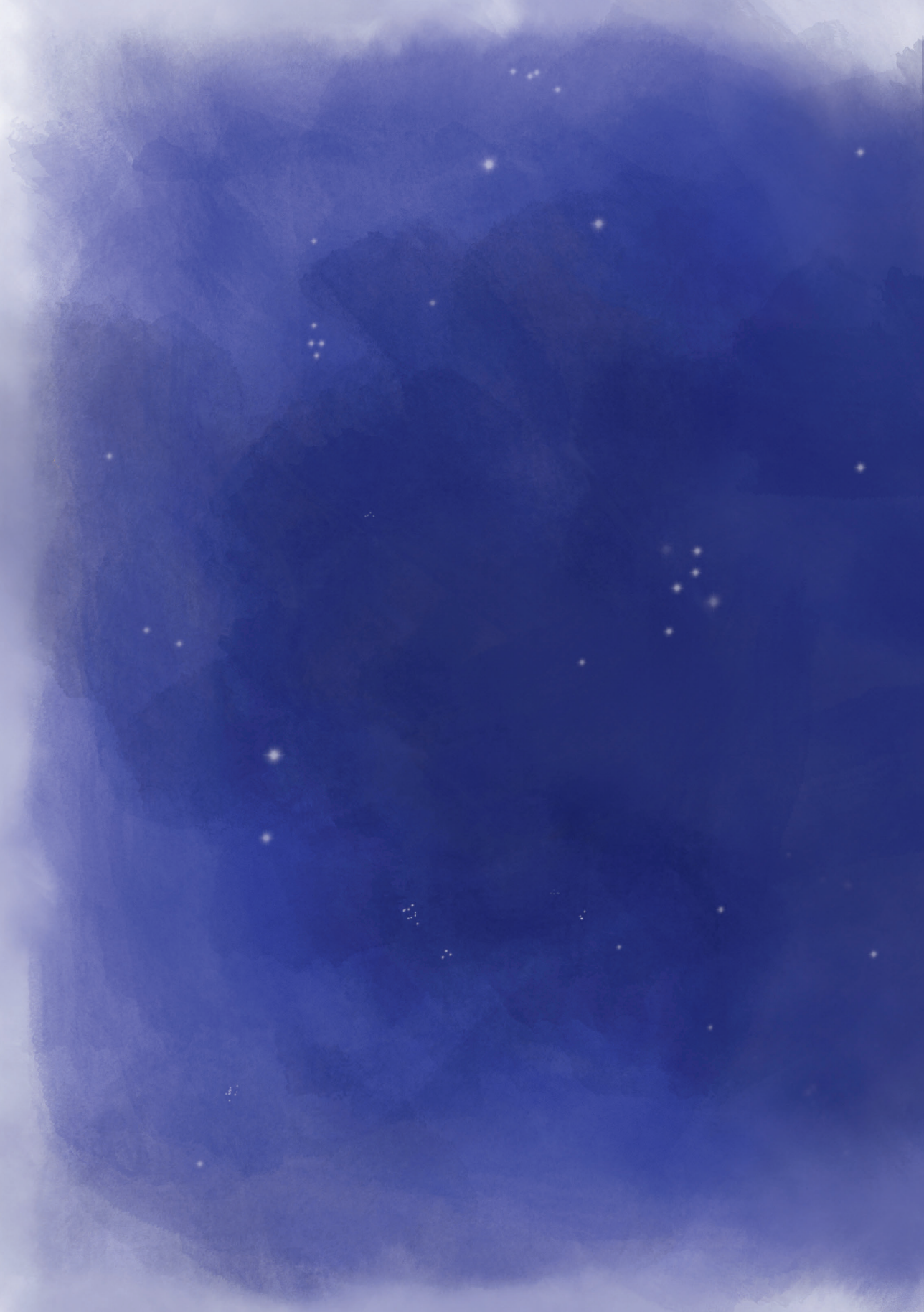
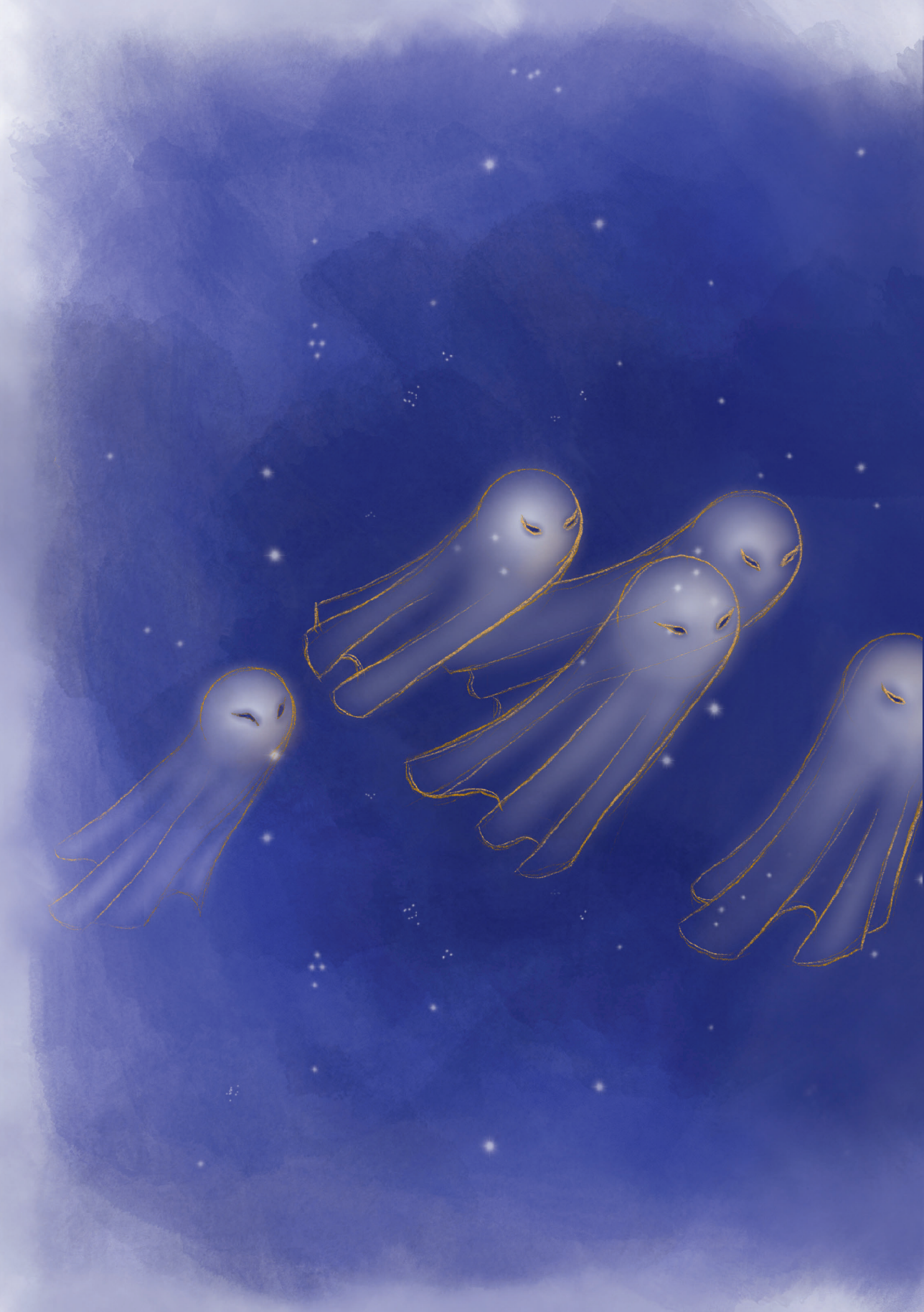


Part II

Cognitive biases: familial aggregation and modification



Chapter 5

Familial aggregation of cognitive biases for children with anxiety disorders

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ABSTRACT

Previous studies described a relation between anxiety-related cognitive biases in normally developing children and parents. The current study examined the familial aggregation of cognitive biases in children with anxiety disorders (N = 55) and their parents, with possible moderators and mediators as mechanisms underlying this aggregation. Cognitive biases for children were measured by the dot-probe task for attention bias and by ambiguous stories for interpretation bias. Mothers' (n = 50) and fathers' (n = 30) lifetime mood and anxiety disorders were assessed, along with their attention bias (dot-probe task) and self-reported rearing styles. Results showed an association between maternal attention bias and interpretation bias of children (r = 0.31, p = 0.032). However, this association was neither moderated by maternal lifetime mood or anxiety disorders nor mediated by maternal rearing styles. The familial aggregation of maternal attention bias and children's interpretation bias is presumably influenced by other factors than maternal mood or anxiety disorders or rearing styles.

INTRODUCTION

Accumulating evidence shows that children with anxiety disorders have cognitive biases that are involved in both the development, maintenance, and treatment response of anxiety (Dodd, Hudson, Morris, & Wise, 2012; Dudeney, Sharp, & Hunt, 2015; Pérez-Edgar et al., 2011; Waters & Craske, 2016; Legerstee et al., 2009; Waters, Mogg, & Bradley, 2012). In particular, information processing in children with anxiety disorders is biased towards threat-related information in the environment (Lonigan, Vasey, Phillips, & Hazen, 2004). Several cognitive biases have been related to anxiety disorders that occur at different stages of information processing, such as attentional biases, interpretation biases, and confirmation biases. As these cognitive biases have a central role in childhood anxiety disorders (Dudeney et al., 2015; Pine, Helfinstein, Bar-Haim, Nelson, & Fox, 2009), studies have also examined the familial aggregation of anxiety-related biases.

Several studies have focused on the familial aggregation or co-occurrence of cognitive biases in parents and children within community samples and found associations between mothers' and children's anticipation of distress (Creswell, Shildrick, & Field, 2011; Creswell, O'Conner, & Brewin, 2006), threat interpretations (Creswell, Schniering, & Rapee, 2005; Creswell & O'Connor, 2006) and information search bias (Remmerswaal, Muris, & Huijding, 2016). Moreover, Lester, Field, Oliver and Cartwright-Hatton (2009) showed that parents exhibit the same interpretation biases in threatening situations that involved themselves as compared to threatening situations that involved their children. Thus, parents' threat interpretations within their own environment are likely to be related to threat anticipated for their child. However, Gifford, Reynolds, Bell and Wilson (2008) showed in a clinical sample that threat interpretations made by anxiety-disordered children and their mothers were not related, but mother's threat interpretation was related to anxiety reported by the child. The contradictory results between community and clinical studies highlight that other dyadic influences could be at play when relating information processing between parents and children within clinical samples.

Although previous studies have related cognitive biases in children to parents' cognitive biases, the mechanism through which parental biases influence children's biases is not fully understood. Parents may contribute to the transmission of cognitive biases through several mechanisms, such as parental modeling, parental reinforcement of anxious or avoidant behavior, and information transfer (Chorpita & Barlow, 1998; Hadwin, Garner, & Perez-Olivas, 2006; Fisak &

Grills-Taquechel, 2007; Ooi, Dodd, Fliek, & Muris, 2016). For example, parental psychopathology has been related to both symptoms of anxiety and cognitive biases in children (Kujawa et al., 2011; Muris et al., 2010; Montagner et al., 2016). In the study of Waters, Forrest, Peters, Bradley, & Mogg (2015) attention bias in children was related to the attention bias of mothers with a lifetime mood or anxiety disorder only. This suggests a moderating role for parental psychopathology, assuming that the relation between biases in children and parents is influenced by whether anxiety in the family is clinically expressed (Legerstee & Utens, 2018). In addition, parents' cognitive biases may exert influence on their children by parental rearing practices (Finegood, Raver, DeJoseph, & Blair, 2017). As parenting behaviors have also been associated with anxiety-related cognitive biases in children (Gulley, Oppenheimer, & Hankin, 2014; Gibb et al., 2011), parenting could operate as a mediating variable in this familial aggregation.

Previous studies into the relation between parental and child cognitive biases have mostly been carried out in community samples (Creswell et al., 2006; Creswell & O'Connor, 2006; Creswell et al., 2005; Creswell et al., 2011; Remmerswaal et al., 2016). Although these studies provide valuable insights into the role parents may play in the development of cognitive biases, the familial aggregation of cognitive biases in clinical samples can contribute to our understanding of the intergenerational transmission of anxiety disorders. Even though fathers have been shown to play an important role in childhood anxiety (Bögels & Phares, 2008), fathers have been rarely involved when studying parental and child cognitive biases.

The current study aims to fill this gap in the literature of familial aggregation of cognitive biases in clinical samples by examining the aggregation of attention and interpretation biases in children with anxiety disorders and both mothers' and fathers' attention bias. We hypothesized that cognitive biases between children and their parents would be related, without specific expectations for differences between mothers and fathers. The second aim of this study was to examine the influence of both maternal and paternal psychopathology and rearing styles as respectively, moderators and mediators in the familial aggregation of these cognitive biases. Based on the literature, we hypothesized that the familial aggregation of cognitive biases would be especially apparent for parents with past or current psychopathology. Also, we hypothesized that this aggregation would be mediated by parental rearing styles that have previously been associated with anxiety-related cognitive biases in children. Whereas in the literature also the

term familial transfer or transmission is used, we here refer to aggregation, considering the bottom-up approach of our study.

METHODS

Participants

The sample consisted of 55 children (*M* age = 11.15, *SD* = 2.27, range = 8.04 – 16.91), of whom their mothers and fathers were also asked to participate. In total, 50 mothers (91% of all mothers, *n* = 55) and 30 fathers (61% of all fathers, *n* = 49) agreed to participate themselves. Descriptive characteristics of children and participating parents are displayed subsequently in Table 1 and Table 2. Children with participating parents did not differ on severity score of primary anxiety diagnosis compared to children with non-participating parents (t (53) = 1.02, p = 0.312). Also, participating parents did not differ on demographic characteristics from non-participating parents ($t < 1.78$, $ps > 0.081$).

Eligible for participation were children consecutively referred to the outpatient clinic of the Erasmus Medical Center, Sophia's Children's Hospital or the Lucertis Center for Child and Adolescent Psychiatry in the Rotterdam area, The Netherlands, between September 2013 and July 2016. This study is part of a larger research project to investigate the role of cognitive biases in the treatment of childhood anxiety disorders by examining the effectiveness of attention bias modification (ABM) in combination with cognitive behavioral therapy (CBT) (de Lijster et al., 2019). This study was approved by the Medical Ethics Committee of the Erasmus Medical Center in Rotterdam, The Netherlands (MEC-2013-375) and the randomized controlled trial was registered with ClinicalTrials.gov, number NCT03764644.

Inclusion criteria were based on children's eligibility for CBT: age between 8 and 16 years along with a primary diagnosis of separation anxiety disorder (SAD), social phobia (SOP), specific phobia (SP), or generalized anxiety disorder (GAD), according to the Anxiety Disorders Interview Schedule for children and parents (ADIS-C). Exclusion criteria were a total IQ of 85 or less, poor command of the Dutch language, serious physical disease, psychosis, substance abuse, autism spectrum disorders, obsessive-compulsive disorder (OCD), post-traumatic stress disorder (PTSD), acute stress disorder, panic disorder (PD), agoraphobia (AGO), major depressive disorder (MDD), and current pharmacological anxiety treatment or psychological treatment in the past six

months. Children who fulfilled the study criteria but declined to participate (*n* = 11) did not differ regarding gender, age, Socioeconomic status (SES), or anxiety disorder severity compared to eligible children who participated ($t < 1.64$, $ps > 0.105$).

Table 1. Descriptive characteristics for children (*N* = 55)

	Children (*N* = 55)
Age (*M*, *SD*)	11.15 (2.27)
Gender ratio (M:F)	27:28
Ethnicity (n, %)	
Dutch	34 (61.8)
Non-Dutch	4 (7.3)
Missing	17 (30.9)
ADIS-C/P EBC ≥ 4 (*n*, %)	
Separation anxiety disorder	15 (27.3)
Social phobia	19 (34.5)
Specific phobia	25 (45.5)
Generalized anxiety disorder	29 (52.7)
SES (*M*, *SD*)	0.22 (1.29)
IQ (*M*, *SD*)	104.45 (12.42)

Note. Socioeconomic status (SES) represents a continuous (status) z-score

Measures

Demographics

IQ was measured as full scale IQ by the Weschler Intelligence Scale for Children-III (WISC-III) and part of the regular clinical assessment. When IQ was not part of clinical assessment (*n* = 6), tasks verbal fluency and block patterns of the WISC-III were used for inclusion into the study. SES was based on the residential area of the children and their families, for which SES status z-scores were derived based on the average household income, level of education, and employment rates of the area (Knol, Boelhouwer, & Veldheer, 2012). Higher status z-scores indicate higher SES.

Table 2. Descriptive characteristics for mothers (*n* = 50) and fathers (*n* = 30)

	Mothers (*n* = 50)	**Fathers (*n* = 30)**
Lifetime child mood or anxiety disorder (*n*, %)		
No	29 (58)	23 (76.7)
Yes	21 (42)	7 (23.3)
Panic disorder	1 (2)	-
Agoraphobia	-	-
Social phobia	1 (2)	-
Specific phobia	12 (24)	6 (20)
Generalized anxiety disorder	-	-
Obsessive-compulsive disorder	-	-
Post-traumatic stress disorder	2(4)	-
Dysthymic disorder	1 (2)	-
Major depressive disorder	14 (28)	3 (10)
EMBU-P (*M*, *SD*)		
Emotional Warmth	67.72 (6.05)	65.79 (7.04)
Rejection	24.12 (3.23)	24.24 (3.58)
Overprotection	17.48 (3.86)	15.79 (2.60)
Age (*M*, *SD*)	43.06 (4.36)	45.01 (6.03)

Compositional Interview Diagnostic Schedule (CIDI) for parental psychopathology

The CIDI 2.1 (WHO, 1997) is a fully structured and computerized diagnostic interview and was used to assess parental lifetime and current anxiety and mood disorders according to criteria of the DSM-IV. Based on the CIDI 2.1, the following anxiety disorders were classified: namely SP, PA, AGP, SOP, GAD, OCD, and PTSD. In addition: MDD, depression NAO, dysthymia, bipolar disorder, and cyclothymic disorder were diagnosed as lifetime or current mood disorders. Master level students were trained for the assessment of the computerized CIDI. As the computerized CIDI provides classifications, the interview can be administered with minimal training as clinical

judgment is not required (Cooper, Peters, & Andrews, 1998). The reliability of the CIDI 2.1 has been demonstrated to be excellent, and the validity has been demonstrated to be adequate (Andrews & Peters, 1998; Wittchen, 1994). Parental psychopathology was defined as the presence or absence of a current or lifetime anxiety or mood disorder. Lifetime disorders which duration ended before the child was born, were considered as no parental psychopathology for analyses.

Egna Minnen Beträffande Uppfostran, parent report (EMBU-P)

The EMBU-P (Swedish acronym for My Memories of Upbringing) assessed parental rearing styles from the parents' perspective. Conceptually, the parent report version is very similar to the child report questionnaire EMBU-C (Markus, Lindhout, Boer, Hoogendijk, & Arrindell, 2003) and the items reflect parents' current thoughts on their own parenting practices and experiences of parenting behavior. For the current study, the subscales emotional warmth (19 items), rejection (18 items), and overprotection (10 items) were assessed on a 4-point scale (1 = no, never, 2 = yes, sometimes, 3 = yes, often, 4 = yes, most of the time). In this study, subscale internal consistency for mothers was 0.85, 0.73 and 0.74 and for fathers 0.89, 0.76, 0.57, which is generally in line with the psychometric properties reported for the EMBU-C (Markus et al., 2003). For the overprotection scale, the item "If your child has a secret, you want to know them" was removed due to insufficient item-total correlations.

Attention bias children and parents

Attention bias in children and parents was measured with the dot-probe detection task. This task was programmed using E-prime v2.0 (Psychology Software Tools, Inc.) and presented on a Fujitsu Lifebook computer in a quiet room with minimal visual and auditory distractions. In this task, a cross appeared in the middle of the screen for 500 ms followed by two stimuli shown simultaneously (left and right) for 500 ms for each trial. Stimuli and total number of trials were the same for parents and children and followed by a probe in the spatial location previously occupied by one of the pictures. Probes consisted of two dots that were either placed next to each other or above each other and were shown until one of the corresponding labeled keys were pressed. Participants were instructed to respond as accurately and quickly as possible. Because of a software defect, attention bias could not be assessed for one mother. For two fathers, attention bias was missing because they could not physically attend the research assessment.

Ten practice trials with neutral stimuli were performed which allowed a maximum of four errors. Practice trials were repeated if children made more than four errors. After the practice trials, four blocks consisting of 40 trials each (180 trials in total) were performed and participants were allowed to take short breaks in between. Picture pairs were either threatening-neutral (128 trials) or neutral-neutral (32 trials). For threatening-neutral pairs, probes occurred in half of the trials at the same spatial location as the threatening picture (congruent trials) and in half of the trials at the opposite location of the threatening picture (incongruent trials).

Because of the high rate of homotypic comorbidity of anxiety disorders (Wittchen, Lecrubier, Beesdo, & Nocon, 2007), stimuli reflected all included anxiety disorders (SAD, SP, SOP, and GAD). For SAD, pictures that showed either separation (threatening) or reuniting (neutral) scenarios of adults and children were used (In-Albon, Dubi, Rapee, & Schneider, 2009). Pictures of faces expressing anger or disgust (threatening) or neutral faces from a set of Japanese and Caucasian Facial Expressions of Emotions (JACFEE; Biehl et al., 1997; Matsumoto & Ekman, 1988) were used to reflect SOP. For SP, pictures were selected from the International Affective Picture System (IAPS; Lang, Bradley, Cuthbert, 1997) of animals (e.g. a barking dog), blood, and threatening phenomena in nature, along with neutral pictures of objects or nature. Four additional pictures of a tunnel and elevator were taken to ensure full coverage of different phobias. The first three blocks comprised the SAD, SOP, and SP stimuli per participant in a randomized order. In the final block, threat-related and neutral words were selected to comprise GAD from the Dutch Affective Words List (Moors et al., 2013) because of the difficulty to visualize words like "dead" or "pain". Both the location of the probes, number of (in)congruent trials and type of stimuli (for the first three blocks) were counterbalanced across trials. In this study, we calculated the average attention bias for children, mothers, and fathers across anxiety disorder stimuli subtype.

Data preparation was conducted in line with previous studies with excluding Reaction Times (RTs) from trials with errors, if RTs were <200 ms, >1500 ms, and when >2.5 SD above the participant's mean RT (Montagner et al., 2016; Schechner et al., 2014). The average amount of excluded trials was 15.2% for children, 5.9% for mothers, and 6.8% for fathers. In line with previous studies, attention bias scores were calculated by subtracting the average RT on congruent trials from the average RT on incongruent trials (Roy et al., 2008). Positive values represent greater attention towards threatening compared to neutral stimuli, whereas negative values reflect attention away from the threatening relative to neutral stimuli.

Interpretation bias child

We used ambiguous stories to measure children's interpretation bias (Muris et al., 2000). Nine audiotaped, hypothetical stories consisting of five sentences each were used, with three types of stories: separation anxiety stories (e.g. your parents go on holiday and you have to stay with your aunt), social anxiety stories (e.g. first day at a hockey training), and generalized anxiety stories (e.g. you have to make a very difficult test at school). After listening to the stories, the child was asked to tell the researcher how he or she thinks that the story will end. The researcher wrote what the child said verbatim. Two raters who were blind to the other collected measures judged whether the child interpreted the story as scary (1) or non-scary (0). An interrater reliability analysis using the Kappa statistic was performed to determine consistency among the two raters (McHugh 2012). For the category separation anxiety the interrater reliability was Kappa = 0.73 ($p < 0.001$), for social anxiety Kappa = 0.83 ($p < 0.001$) and for generalized anxiety Kappa = 0.71 ($p < 0.001$). For total interpretation bias score in statistical analyses, a total score (max. 9) was created by summing up the scores of all stories. Two children could not complete the interpretation bias task because of time concerns. In addition, a weighted total score was created when one score of the three story types was missing ($n = 2$).

Procedure

The ADIS-C was completed before participation in the study as part of the regular clinical assessment. After the clinical assessment was completed, parents and children were informed about the study verbally and with patient information letters in which the concept of attention bias was explained in layman's language. At the day of the research assessment, children and their parent(s) were invited to the outpatient clinic for which parents received a compensation of their travel costs but no participation fee. Informed consent was obtained from both parents and children aged 12 years and older and from parents regarding their own participation. After signing informed consent, both children and parents were given instructions about the dot-probe task. Participants were told they would see different images and their task was not to pay attention to the images but to respond to the appearing dots. Children first performed the dot-probe task and subsequently the interpretation bias task which was explained as listening to stories that were either "scary" or "non-scary" and it was their task to guess how each story would end. In the meanwhile, parents alternately completed the CIDI, dot-probe task and digital questionnaires in a separate room. No debriefing was given regarding the tasks.

Statistical Analyses

All analyses were performed with SPSS version 24 (IBM, 2017). To describe the familial aggregation between parents' and children's attention biases, paired sample t-tests for attention bias were used. In addition, bivariate associations were computed with Pearson correlation coefficients between parents' attention bias and children's attention bias and interpretation bias. Follow-up moderation and mediation analyses were performed for significant associations between parents' attention bias and children's attention bias and interpretation bias. Models of moderation were analyzed separately for mothers and fathers in which parental psychopathology was hypothesized to moderate the familial aggregation of parental attention bias and children's cognitive biases. Models of mediation were analyzed separately for mothers and fathers with parental rearing styles as mediating variables. Formal moderation and mediation analyses were performed using the 'PROCESS' macro for SPSS, version 3.3 (http://www.afhayes.com/) with bias-corrected bootstrapping using 1000 replications for mediation analyses (Preacher & Hayes, 2008). Because of the explorative character of the study, $\alpha = 0.05$ was used for all statistical analyses without correcting for multiple testing.

RESULTS

Descriptive Analyses

Child and parental disorders

Table 1 shows the descriptive and clinical characteristics of children and parents. Children most often had an ADIS-C severity rating of ≥ 4 for GAD (52.7%) and SP (45.5%) and comorbidity was high (49.1%). Table 2 shows that less than half of the mothers (42%) fulfilled the criteria of a mood or anxiety disorder during the lifetime of the child and SP (24%) and MDD (28%) were the most common disorders. In total, seven fathers (23.3%) fulfilled the criteria for a mood or anxiety disorder during the lifetime of their child. For fathers, SP and MDD were the only classified disorders (20% and 10%, respectively).

Cognitive biases for children and parents

On average, the direction of the attention bias of anxiety-disordered children was towards threat ($M = 11.31$, $SD = 44.89$) for which the one sample t-test of statistical difference from zero showed a trend towards significance ($t\ (54) = 1.87$, $p = 0.067$, $d = 0.25$). The direction of the attention bias of mothers was also towards positive ($M = 4.45$, $SD = 29.73$) but not significant different from

zero (t (48) = 1.05, p = 0.300, d = 0.15). Fathers' attention bias was away from threat (M = -7.76, SD = 17.42), and significantly differed from zero (t (27) = -2.36, p = 0.026, d = 0.45). Paired samples t-tests indicated a statistical difference between the attention bias scores of children and fathers (t (27) = 2.57, p = 0.016, d = 0.76), but not between children and mothers (t (48) = 1.32, p = 0.192, d = 0.36). Children's threatening interpretations ranged from zero to seven out of the nine stories (M = 1.82, SD = 1.79). When relating demographic characteristics in relation to children's cognitive biases, no variable (gender, age, SES, IQ) was either related to attention bias or threat interpretation scores (all r < .23, p > 0.116). Also, parents' age and SES was not related to their attention bias scores (all r < 0.18, p > 0.375).

Familial Aggregation of Cognitive Biases

A correlation matrix is presented in Table 3 with the strength of the relations between parental and children's cognitive biases. Attention bias scores of mothers and fathers were not related to attention bias scores of children (r = -0.23, p = 0.109, r = -0.29, p = 0.138). For children's interpretation bias, a significant small positive correlation was found with maternal attention bias (r = 0.31, p = 0.032). Thus, attention bias towards threat for mothers was associated with more threat interpretation biases in children. Fathers' attention bias score was not related to threat interpretations made by children (r = -0.10, p = 0.632).

Table 3. Familial aggregation of cognitive biases for children and parents

	1 Maternal Attention Bias	**2 Paternal Attention Bias**	**3 Child Attention Bias**	**4 Child Interpretation Bias**
1	1	-	-	-
2	-0.10	1	-	-
3	-0.23	-0.29	1	-
4	0.31*	-0.10	-0.04	1

Note. * p-value < 0.05

Effects of Parental Psychopathology and Rearing Styles

Follow-up analyses were performed for the association between maternal attention bias and children's interpretation bias (Figure 1a). The moderation effect of maternal psychopathology and the mediating effect of rearing styles were examined (as displayed in Figure 1b-e).

Moderation effect of maternal psychopathology

A moderation analysis was performed to assess whether the association between maternal attention bias and children's attention bias was influenced by maternal psychopathology. The moderation analysis showed no interaction between maternal attention bias and maternal psychopathology (*B* = 0.00, *t* (47) = 0.19, *p* = 0.852, 95% CI = -0.03; 0.04). Also, there were no main effects of maternal attention bias (*B* = 0.02, *t* (47) = 1.99, *p* = 0.053), or maternal psychopathology (*B* = 0.42, *t* (47) = 0.78, *p* = 0.439) on children's interpretation bias score.

Mediation effect of maternal rearing styles

To assess whether rearing styles were mediators in the association between maternal attention bias and child interpretation bias, three mediation analyses were performed for maternal emotional warmth, maternal rejection, and maternal overprotection separately (as displayed in Figure 1b, c, and d).

The first mediation analysis for maternal emotional warmth showed that the direct effect (c' path) of maternal attention bias on child interpretation bias remained significant after controlling for maternal emotional warmth (*B* = 0.02, *t* (47)= 2.24, *p* = 0.030, 95% CI = 0.00; 0.04). The indirect (a*b path) effect through maternal emotional warmth was small and not significant (*B* = 0.00, 95% CI = -0.01; 0.00). This implies that the total effect (c' path) between maternal attention bias and child interpretation bias was not mediated by maternal emotional warmth.

In the second mediation analysis, adding maternal rejection to the model led to a non-significant direct effect (c' path) of maternal attention bias on child interpretation bias (*B* = 0.02, *t* (47) = 1.92, *p* = 0.061, 95% CI = 0.00; 0.04). The indirect (a*b path) effect through maternal rejection was small and not significant (*B* = 0.00, 95% CI = -0.01; 0.01), indicating no mediating effect of maternal rejection.

For the third mediation analysis, maternal attention bias was significantly related to maternal overprotection (a path), *B* = 0.04, *t* (47) = 2.34, *p* = 0.024, 95% CI = 0.01; 0.07. The direct effect (c' path) of maternal attention bias on child interpretation bias was not significant after controlling

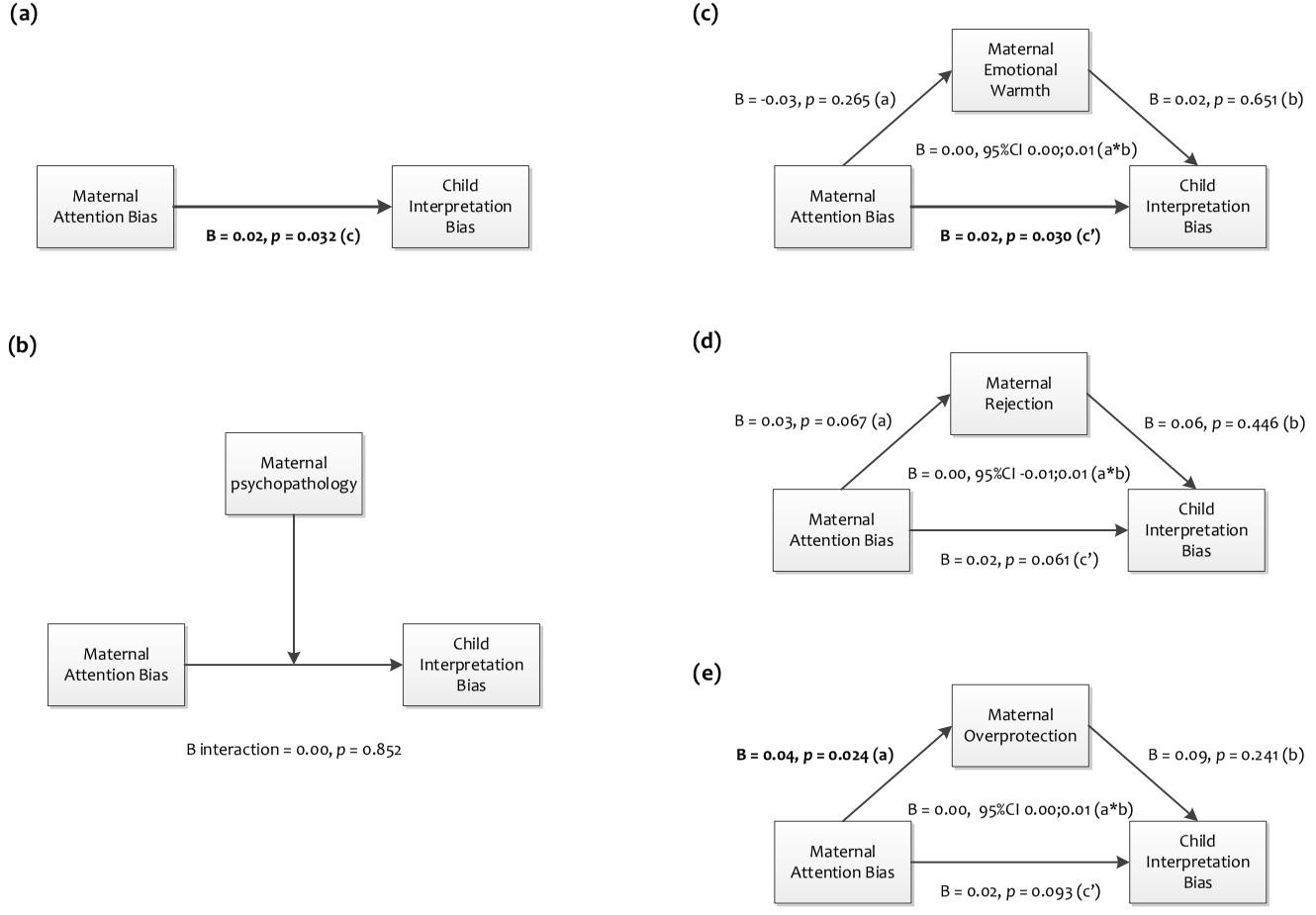
for maternal overprotection (*B* = 0.02, *t* (47) = 1.72, *p* = 0.093, 95% CI = -0.00; 0.03). The indirect (a*b path) effect through maternal overprotection was small and not significant (*B* = 0.00, 95% CI = -0.00; 0.01). Thus, the total effect (c' path) between maternal attention bias and child interpretation bias was not mediated by maternal overprotection.

DISCUSSION

The first aim of this study was to examine the familial aggregation of cognitive biases in children with anxiety disorders and their parents. Results showed that maternal attention bias was related to the interpretation bias of children. In contrast to our hypothesis, children's attention bias was not related to parental attention bias within this study's clinical sample. The second aim of this study was to examine the effect of parental psychopathology and rearing styles as respectively, moderators and mediators in the familial aggregation of cognitive biases. In contrast to our expectations, the association between maternal attention bias and children's interpretation bias was not significantly influenced by maternal psychopathology, neither were maternal rearing styles found to mediate this relation. The current study adds to previous community studies into cognitive biases in children and parents by demonstrating how these biases are interrelated when children are diagnosed with an anxiety disorder.

Although the effect was small, maternal attention bias towards threat was related to more threat interpretations made by children. There are several explanations for this familial aggregation from maternal attention bias to child interpretation bias. First, attention bias of mothers could affect their own information processing at a later stage than attention regulation, which correlates with their child's interpretation bias. However, as the previous study with a clinical sample by Gifford et al., (2008) found no relation between interpretation biases of mothers and children, so far this is not supported by the literature. Second, as attention bias operates at a subliminal level, another explanation could be that children observe their mother's verbal or behavioral response following their attention bias (Waters & Craske, 2016). This explanation is in line with the indirect transmission of maternal attention biases to offspring proposed by Waters et al., (2015) via greater exposure to negative information by mothers. Third, maternal attention bias could be a response to children's interpretation bias. Previous studies in community and at-risk samples have shown a reciprocal relation between children's cognitive

Figure 1. Moderation (b) and mediation analyses (c, d, e) between maternal attention bias and child interpretation bias (a)



bias and maternal attention bias and expectations of their child's anxious cognitions (Creswell et al., 2006; Creswell et al., 2011; Waters, Candy, & Candy, 2018).

In contrast to our expectations, we found no association between parents' attention bias and children's attention bias. In the study by Waters et al., (2015), attention bias towards threat for children was associated with attention bias away from happy faces for mothers with lifetime emotional disorders. As we only measured attention bias towards threat, we could not test whether some mothers had an attention bias away from happy stimuli. A more recent study examined the prospective and concurrent relations between anxiety and attention bias of children and parents in a community sample. This study by Aktar, van Bockstaele, Perez-Edgar, Wiers, & Bögels (2019) showed that instead of attention biases of parents being a predictor for children's attention bias at 7.5 years, parents' anxiety when children were 4.5 years old predicted children's attention bias over time. Because we used a cross-sectional study design, we could not examine the developmental change of cognitive biases for children. It should be mentioned that in line with previous studies (for an overview, see Mogg, Waters, & Bradley, 2017), children in our study did not have a significant attention bias towards threat. In contrast to adults, the relative role of attention bias for children with anxiety seems to be minor (Abend et al., 2018).

The current study included both mothers and fathers and hence, we were able to contrast findings regarding paternal and maternal influences. Interestingly, children's direction of attention bias was different from the attention bias measured for their fathers. Although not significantly different from zero, children's direction of attention bias was towards threat (Puliafico & Kendall, 2006). In contrast, fathers were found to have an attention bias away from threat. It has been suggested that when faced with threat, fathers are the first person children turn to as they search for clues how to interpret the situation (Bögels & Phares, 2008; Kilic, Ozguven, & Sayil, 2003). In the presence of their fathers, for children with anxiety disorders, reassurance from fathers regarding threat may be no longer sufficient. This could explain why children are hypervigilant for threat as their fathers avoid threat-related cues. However, in the current study, attention bias between fathers and children was not related and cognitive biases in children could also be irrespective of their fathers' bias.

Although maternal self-reported overprotection was associated with an attention bias towards threat for mothers, we found no effect of maternal psychopathology or rearing styles in explaining the familial aggregation of cognitive biases in children and mothers. Several studies

have shown the aggregation of anxiety disorders in families (Low et al., 2012; Connell & Goodman, 2002). However, the familial aggregation of maternal attention bias and children's interpretation bias was not moderated by maternal psychopathology in the current study. Possibly, transmission of anxiety-related cognitive biases is stronger for specific anxiety disorders, which has previously been shown for PD in parents and negative interpretation of panic scenarios for children (Legerstee & Utens, 2018). An alternative explanation for the lack of the moderating effect of maternal psychopathology could be that cognitive biases aggregate in families regardless of mothers' history of emotional disorders. In addition, the direct effect between maternal attention bias and children's interpretation bias disappeared when maternal rejection and overprotection were added to these models. This suggests that these parenting styles may not be distinctive constructs but instead overlap with cognitive biases in parents. Instead of parental psychopathology and overall parenting styles, other, more specific parental practices in threatening or stressful situations may influence the transmission of cognitive biases (Darling & Steinberg, 1993). This is supported by two previous twin-studies showing that up to 70% of the variance in anxiety-related cognitive biases can be explained by the non-shared environment (Eley et al., 2008; Lau et al., 2012). More dysfunctional parent practices such as lack of consistency of expectations, restricted communication, and poor interpersonal relationship may play a role as the study by Blossom et al., (2013) found an association between child reported family dysfunction and children's threat bias.

A strength of the current study is that we examined the association of several parental characteristics with different cognitive biases in children with anxiety disorders. Previous studies examined this association in community samples, although cognitive biases in children with anxiety disorders are different from normally developing children (Waters, Henry, Mogg, Bradley, & Pine, 2010). Also, by examining both attentional and interpretation bias in children, we could further isolate familial aggregation of these cognitive biases with parental characteristics. In addition, fathers have been rarely involved in previous studies and were included next to mothers. Moreover, this is the first study that focused on mechanisms by which parents' and children's cognitive biases are related.

However, the findings of the current study should be placed in the light of the following limitations. First, the small sample size of the current study may have hampered to detect significant associations and moderating or mediating effects. In addition, we did not correct our statistical analyses for multiple testing because of the small sample and explorative character of

the analyses. Second, although we examined parents' attention bias, we did not assess interpretation bias of parents. Third, because of the cross-sectional nature of the current study, we could not differentiate whether children's cognitive bias was amplified by parents cognitive bias or rearing style, or whether parents developed an attention bias as a response to their child's heightened anxiety. For this purpose, future longitudinal studies with larger sample sizes are needed.

If replicated in a larger sample, our findings could have clinical implications that may guide the involvement of parents in the treatment of childhood anxiety disorders. Even though parents are generally involved along the side during CBT, debate remains whether additional sessions for parents increase treatment effectiveness (Breinholst, Esbjorn, Reinholdt-Dunne, & Stallard, 2012). As attention bias of mothers and interpretation bias of anxiety-disordered children are interrelated it may be beneficial to target maternal cognitive biases to improve anxiety recovery rates. First, maternal cognitive biases could be specifically addressed during parental sessions using ABM (Hakamata et al., 2010). Second, in addition to psychoeducation regarding childhood anxiety, parents of children with anxiety disorders may be informed how cognitive biases operate within their daily rearing practices. A previous pre-post treatment study showed that teaching mothers of anxious children child management skills reduced maternal interpretation bias at post-treatment (Creswell et al., 2005). However, it should be noted that the effect we found regarding the familial aggregation of cognitive biases in our study was small. Future studies with larger sample sizes and hence more statistical power are needed to examine other factors that explain the familial aggregation of cognitive biases for anxiety disorders.

Conclusion

The results of the current clinical study add to previous community studies by demonstrating how cognitive biases between parents and children are interrelated in clinical samples. Findings indicate a possible familial aggregation across type of bias between children with anxiety disorders and their mothers. This aggregation was not dependent on maternal psychopathology, nor did we find evidence for a mediating role of maternal rearing styles. Therefore, the mechanism through which cognitive biases operate warrants further research.

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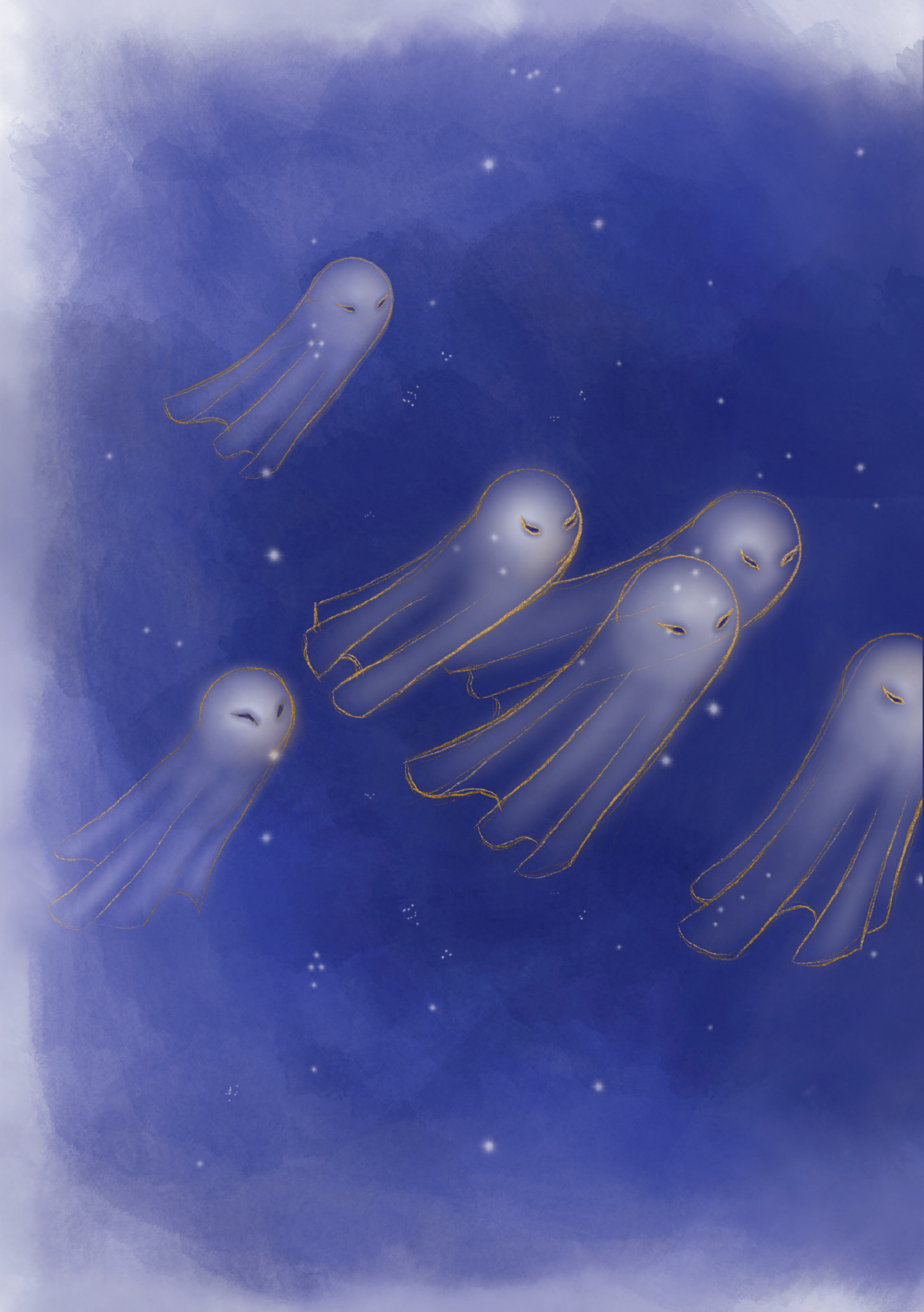

Chapter 6

Online Attention Bias Modification in combination with Cognitive-Behavioral Therapy for children and adolescents with anxiety disorders: A randomized controlled trial

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ABSTRACT

Attention Bias Modification (ABM) targets attention bias (AB) towards threat, which is common in youth with anxiety disorders. Previous clinical trials showed inconsistent results regarding the efficacy of ABM delivered in clinical settings and few studies examined the effect of ABM and, few studies have examined the effect of online ABM and its augmented effect with cognitive behavioral therapy (CBT). The aim of the current study was to examine the efficacy of online ABM combined with CBT for children and adolescents with anxiety disorders in a randomized, double-blind, placebo-controlled trial. Children (aged 8-16 years) completed nine online sessions of ABM (n = 28) or online sessions of the Attention Control Condition (ACC) (n = 27) over a period of three weeks (modified dot-probe task with anxiety disorder-congruent stimuli), followed by CBT. Primary outcomes were clinician-reported anxiety disorder status. Secondary outcomes were patient-reported anxiety and depression symptoms and AB. Results showed a continuous decrease across time in primary and secondary outcomes (ps < 0.001). However, no differences across time between the ABM and ACC group were found (ps > 0.5). Baseline AB and age did not moderate training and treatment effects. Online ABM combined with CBT does not show different efficacy compared with online ACC with CBT for children with anxiety disorders.

INTRODUCTION

Anxiety disorders are among the most common psychiatric disorders in children and adolescents and are associated with social and academic problems, school dropout, suicidal attempts, and other psychiatric illnesses at a later age (de Lijster et al., 2018; Woodward & Fergusson, 2001). Remarkably, many children with anxiety disorders do not receive treatment (Chavira, Stein, Bailey, & Stein, 2004), and 40% of children who receive treatment do not recover (James, James, Cowdrey, Soler, & Choke, 2015; Weisz et al., 2017). Research has shown that children and adolescents with anxiety disorders show an attention bias (AB), that is, differential attention towards threat compared to neutral stimuli (Abend, de Voogd, Salemink, Wiers, & Pérez-Edgar, Dudeney, 2018; Dudeney, Sharpe, & Hunt, 2015). AB has been related to both the onset and maintenance of anxiety symptomatology (Waters & Craske, 2016). A promising new treatment that has received much interest is Attention Bias Modification (ABM) for children and adolescents with anxiety disorders (Bar-Haim, 2010). ABM focuses on directing attention away from threat and towards neutral stimuli instead. For adults with anxiety disorders, ABM has been found to be particularly effective when it exerts a significant change in baseline AB (Hakamata et al., 2010; Macleod & Grafton, 2016; Price et al., 2016). As a result, studies have investigated its effect for children and adolescents with anxiety disorders as well.

Several studies have examined the efficacy of ABM for the treatment of anxiety disorders in children and adolescents. A systematic review by Lowther and Newton (2014) described ABM as a promising novel treatment for child and adolescent anxiety. However, the results of previous studies have been fairly inconsistent. The first randomized controlled trial (RCT) by Eldar and colleagues (2012) showed ABM to be superior compared to its placebo condition (i.e. Attention Control Condition (ACC)) with large effect sizes. In contrast, four successive RCT studies found equal efficacy for ABM and ACC (Britton et al., 2013; Ollendick et al., 2018; Pergamin-Hight, Pine, Fox, & Bar-Haim, 2016; Shechner et al., 2014). Likewise, subsequent meta-analyses and review studies have not been conclusive about the effects of ABM compared to ACC for children and adolescents with anxiety disorders (Cristea, Mogoase, David, & Cuijpers, 2015; Mogg, Waters, & Bradley, 2017; Pennant et al., 2015). Several methodological factors have been reported that may explain contrasting results of ABM in alleviating anxiety in children and adolescents. These factors include the setting in which ABM is delivered (Price, et al., 2016), the type of stimuli used (Pergamin-Hight, Naim, Bakermans-Kranenburg, & Bar-Haim, 2015), and moderators of treatment

efficacy such as the direction and extent of baseline AB and age of the participants (Cristea, Mogoase, David, & Cuijpers, 2015; Van Bockstaele et al., 2014).

The majority of studies have examined the efficacy of ABM for children and adolescents with anxiety disorders in a laboratory setting and have utilized facial stimuli for ABM. First, ABM has the potential to reduce treatment barriers of accessibility and cost-effectiveness for online, at-home training. Second, although negative facial expressions seem particularly ecological valid to represent threat for children with social phobia (SOP), faces have also been used for a range of other anxiety disorder subtypes. AB is more consistently observed when the stimuli used are anxiety disorder congruent (In-Albon, Kossowsky, & Schneider, 2010; Pergamin-Hight et al., 2015; Waters, Lipp, & Spence, 2004). Therefore, adopting stimuli that are congruent with the targeted anxiety disorder subtypes may enhance the efficacy of ABM. Only one study has examined the effect of ABM delivered partly at home and with the use of general threat words instead of face stimuli. This study by Chang and colleagues (2019), found relatively more children who received ABM to be treatment responders compared to ACC. However, for children and adolescents with anxiety disorders, words may have less ecological value compared to pictorial stimuli. Furthermore, given the high rate of comorbidity between anxiety disorder subtypes (Wittchen, Lecrubier, Beesdo, & Nocon, 2007), using different types of stimuli that correspond to the anxiety disorders that are targeted could be promising (Abend et al., 2018).

In addition to these methodological factors, some previous studies have examined characteristics of participants that moderate the efficacy of ABM. First, the direction and extent of baseline AB may be related to the effect of ABM, as it is generally aimed to induce an attention away from threat. However, results have been fairly inconsistent with regard to the effect of baseline AB on ABM success (Eldar et al., 2012; Ollendick et al., 2019; Pergamin-Hight et al., 2016). Furthermore, Mogg et al. (2017) highlight that for most ABM studies, participants often do not show AB towards threat. Another factor that has been reported as a moderator is the age of participants. Larger reductions in anxiety after ABM have been shown for older children (Pergamin-Hight et al., 2016).

ABM has been suggested to improve treatment efficacy rates of CBT for children and adolescents with anxiety disorders (Bar-Haim, 2010). The combination of ABM with CBT has been proposed to be beneficial as CBT involves more 'top-down' processes whereas ABM involves 'bottom-up' processes of information (Cisler & Koster, 2010). However, relatively few studies

have examined the combined effect of ABM with CBT. Three previous studies have examined the efficacy of ABM-enhanced CBT, and one study reported significantly more reductions (White et al., 2017) while two other studies did not find an additive effect of ABM on CBT (Britton et al., 2013; Shechner et al., 2014). Thus, more research is needed to elucidate whether ABM has augmenting effects on CBT (Lowther & Newman, 2014). In these three studies, ABM was delivered in the laboratory before weekly CBT sessions, and stimuli of the ABM procedure consisted of faces.

The aim of the current study is to examine the efficacy of online ABM combined with CBT compared to online ACC with CBT for children and adolescents with anxiety disorders in a randomized, double-blind, placebo-controlled clinical trial. ABM has the potential to become a more accessible treatment when its efficacy can be shown outside the clinic or research center. Therefore, the current study examined online ABM combined with face-to-face CBT for children and adolescents with anxiety disorders. Building further upon previous research, we utilized a combination of anxiety disorder-congruent stimuli for ABM and ACC. Another aim is to examine baseline AB and age as moderators of treatment success. We hypothesized that children with baseline AB towards threat benefit more from ABM with CBT (and less from ACC with CBT) compared to children with a baseline AB away from threat or no bias. Also, we hypothesized that older children benefit more from ABM (and not ACC) than younger children, as larger AB has been found in adolescents with anxiety disorders (Dudeney et al., 2015). Finally, as only two previous studies reported on follow-up effects at 3 months (Ollendick et al., 2019; Pergamin-Hight et al., 2016), we examined long-term effects of treatment at 6-month follow-up.

METHODS

Participants

Eligible for participation in this randomized, double-blind, placebo-controlled, clinical trial were children aged between 8 and 16 years consecutively referred to the outpatient clinic of the Erasmus Medical Center, Sophia's Children's Hospital or Lucertis Center for Child and Adolescent Psychiatry between September 2013 and July 2016, along with a primary diagnosis of separation anxiety disorder (SAD), social phobia (SOP), specific phobia (SP), or generalized anxiety disorder (GAD), according to the Anxiety Disorders Interview Schedule for DSM-IV Child and Parent Version (ADIS-IV-C). In total, 66 children fulfilled criteria for participation, of whom informed

consent was obtained from 55 children and their parents (response rate 83.3%). Children were randomized via a computerized sequence to either online ABM + CBT (*n* = 28; *M* age = 11.62 years, *SD* = 2.52, 53.6% male) or online ACC + CBT (*n* = 27; *M* age = 10.67 years, *SD* = 1.91, 44.4% male). Participating children did not differ regarding gender, age, or severity score of primary anxiety diagnosis compared to eligible children who did not participate (*p*s > 0.10).

Exclusion criteria were a full scale IQ of 85 or less (Wechsler Intelligence Scale for Children-III: Wechsler, 1991), poor command of the Dutch language, serious physical disease, psychosis, substance abuse, autism spectrum disorders, obsessive-compulsive disorder, post-traumatic stress disorder, acute stress disorder, panic disorder, agoraphobia , major depression disorder, current anxiety medication, and psychotherapy in the past 6 months.

For all participating children, socioeconomic status (SES) was based on the residential area of their families by deriving SES-status z scores (Knol, Boelhouwer, & Veldheer, 2012). This study was approved by the Medical Ethics Committee of the Erasmus Medical Center in Rotterdam (MEC-2013-375) and registered with ClinicalTrials.gov, number NCT03764644.

Sample size and interim futility analysis

We aimed to include 128 children to find a medium effect with 90% statistical power for our primary outcomes based on the effect of ABM as monotherapy in adult clinical samples (Hakamata et al., 2010). Because of our unsatisfactory inclusion rate over time, the subsidy partner requested an interim futility analysis by an independent researcher when 48 participants were included. As the futility analysis showed a very low conditional power (*P* = -3.81, *p* < 0.0001) with a futility index above 0.9, the chance of finding different results if we reached our target sample size was futile (Jennison & Turnbull, 1999). Therefore, we independently decided to stop the recruitment of participants before the target sample size was reached. Seven participants who already participated in the study or agreed to participate completed their participation, resulting in a final sample size of 55 children.

Primary Outcomes

Anxiety Disorder status

The Anxiety Disorders Interview Schedule for DSM-IV Child and Parent Version (ADIS-IV-C; Siebelink & Treffers, 2001; Silverman & Albano, 1996) was used to measure anxiety disorder status and the number of anxiety disorders. The ADIS-IV-C is a semi-structured interview and

consists of a separate child and a parent interview. Both parents and children were asked to rate the severity of symptom interference (0 = *not at all*; 8 = *very much*) when a sufficient amount of symptoms were endorsed. Administration of baseline (T1) anxiety disorder status with the ADIS-IV-C by experienced clinicians was part of the regular clinical procedure and hence not videotaped. For the interviews at T2, T3 and T4, administration by the first author (JdL) or a supervised research assistant were video-taped if parents gave their consent (91%). Clinician severity rating (CSR) was based on separate child and parent interviews. For CRS ≥ 4 an anxiety disorder was classified. Training on the ADIS-IV-C consisted of a workshop, practice interview and supervision by the last author (JL), who is a mental health psychologist. Twenty-six percent of the video-taped administrations were also scored by trained research assistants who were blind to randomization and outcomes throughout the study for interrater agreement. Because of the dichotomization of CRS scores for our analyses, interrater agreement was calculated based on anxiety disorder status instead of CRS scores. Interrater agreement across assessments after ABM or ACC (T2), after CBT (T3), and at follow-up (T4) was excellent (K = 0.94). The ADIS-IV-C has a good validity (Wood, Piacentini, Bergman, McCracken, & Barrios, 2002) and good to excellent test-retest reliability for the classification of the DSM-IV diagnoses of SAD, SOP, SP, and GAD (Silverman, Saavedra, & Pina, 2001).

Secondary Outcomes

Anxiety symptoms

The Dutch revised version of the Screen for Child Anxiety Related Emotional Disorders (SCARED-R: Birmaher et al., 1997; Muris, Steerneman, & Brinkman, 2000) child, mother, and father report was used to assess anxiety symptoms. Questionnaires consisted of 69 items and a composite score was created by the sum of total scores of all informants divided by the number of informants. The SCARED-R has good internal consistency and moderate child-parent agreements and excellent convergent validity and good test-retest reliability (Birmaher et al., 1999; Muris et al., 1998). In the current study, internal consistency varied between 0.92 and 0.96 across informants and assessments. Correlations for the total score reports between children, mothers, and fathers ranged between $r = 0.34$ and $r = 0.79$ ($ps < 0.05$).

Depression symptoms

Child depression symptoms were assessed using the Child Depression Inventory (CDI: Kovacs, 1992; Timbremont & Braet, 2002), a 27-item questionnaire with good reliability (Finch, Saylor, Edwards, & McIntosh, 1987) and validity (Timbremont, Braet, & Dreessen, 2004). The CDI total

score is the sum of all items with higher scores representing more depressive symptoms. In the current study, internal consistency varied between 0.75 and 0.85 across assessments.

Attention Bias Measurement and Modification

Dot-probe task

AB in children was measured with the dot-probe detection task. This task was programmed using E-prime v2.0 (Psychology Software Tools, Inc.) and presented on a Fujitsu Lifebook computer in a quiet room with minimal visual and auditory distractions. In this task, a cross appeared in the middle of the screen for 500 ms followed by two pictures shown simultaneously (left and right) for 500 ms for each trial. Picture pairs were either threatening-neutral (128 trials) or neutral-neutral (32 trials) and followed by a probe in the spatial location previously occupied by one of the pictures. Probes consisted of two dots that were either placed next to each other (. .) or above each other (:) and were shown until one of the corresponding labeled keys were pressed. Participants were instructed to respond as accurately and quickly as possible. After ten practice trials, four blocks consisting of 40 trials each (160 trials in total) were performed. For threatening-neutral pairs, probes appeared in half of the trials at the same spatial location as the threatening picture (congruent trials) and in half of the trials at the opposite location of the threatening picture (incongruent trials).

Stimuli reflected all included anxiety disorders with 40 stimuli pairs per subtype (SAD, SOP, SP, and GAD). For SAD, pictures that showed either separation (threatening) or reuniting (neutral) social scenarios of adults and children were used (In-Albon, Dubi, Rapee, & Schneider, 2009). Pictures of faces expressing anger or disgust (threatening), or neutral faces from a set of Japanese and Caucasian facial expressions of emotions (JACFEE; Biehl, et al., 1997; Matsumoto & Ekman, 1988) were used to reflect SOP. For SP, pictures were selected from the International Affective Picture System (IAPS; Lang, Bradley, & Cuthbert, 1997) of animals (e.g. a barking dog), blood, and threatening phenomena in nature, along with neutral pictures. Four additional pictures of a tunnel and elevator were taken to ensure full coverage of different phobias. The first three blocks showed the SAD, SOP, and SP stimuli per participant in a randomized order. In the final block, threat-related and neutral words were selected from the Dutch Affective Words List for GAD (Moors et al., 2013). Both the location and type of the probes, number of (in)congruent trials, and type of stimuli (for the first three blocks) were counterbalanced across

trials. In this study, we calculated both disorder-congruent AB and average AB across anxiety disorder subtypes as all children were presented with the same, mixed stimuli set.

Reaction Times (RTs) were excluded from trials with errors, and if RTs were <200 ms, >1500 ms, and when >2.5 SD above the participant's mean RT. The average amount of missing trials were 15.1% (T1). In line with previous studies, AB scores were calculated by subtracting the average RT on congruent trials from the average RT on incongruent trials (Roy et al., 2008). Positive values represent greater attention towards threatening compared to neutral stimuli, whereas negative values reflect attention away from the threatening relative to neutral stimuli.

Online ABM and ACC

Online ABM or ACC comprised a browser-based (Google Chrome or Firefox), nine-session program children followed in a period of three weeks. Online ABM and ACC consisted of the same stimuli, presentation time, and number of trials as used in the dot-probe task. Probes always appeared in the spatial location of the neutral picture in the ABM, whereas the spatial location was counterbalanced in the ACC. Online ABM or ACC was monitored by the first author (JdL) by verifying the completion of the scheduled sessions in the remote online system. Parents were contacted to reschedule the session if children had not completed the session on a previously agreed day (online ABM and ACC adherence = 99.8%). For one participant, one of the nine sessions could not be rescheduled and was missed. Both groups had similar accuracy rates as the average number of errors did not differ between the ABM (M = 7.14, SD = 4.97) and ACC group (M = 7.42, SD = 3.87, t (53) = -0.24, p >0.8). Also, mean reaction time (RT) was the same for the ABM (M = 1039.21, SD = 359.67) and ACC group (M = 1040.74, SD = 315.83, t (53) = -0.02, p = 1.0).

Cognitive behavioral therapy (CBT)

Children followed individual CBT with the Dutch translation of the FRIENDS for Life program for children and adolescents (Barrett 2014; Utens, de Nijs, & Ferdinand, 2001). This treatment comprises psychoeducation, relaxation and breathing exercises, exposure, problem-solving, social support training, and cognitive restructuring. The individual application of the FRIENDS program for children and adolescents with clinical anxiety includes ten weekly sessions and two booster sessions. CBT was given by licensed mental health psychologists or supervised master-level psychologists in training. CBT adherence analysis was coded via a standardized protocol by trained research assistants, and analysis of a random selection of videotaped sessions showed

that therapist adhered sufficiently (*M* CBT adherence = 2.45, *SD* = 0.48, scale range 0 = *not at all* to 3 = *excellent*) to the CBT protocol.

Procedure

The ADIS-IV-C, SCARED-R, and CDI were completed before participation in the study as part of the regular clinical procedures. At baseline assessment (T1), children completed the AB task and were randomly assigned to the ABM or ACC group. Children, parents, therapists and researchers were blind to the training condition. On the same day, children and parents were instructed about the online training. One week after online ABM or ACC, the second assessment (T2, total *n* = 55) took place. After CBT, children, and parents participated in the T3 assessment. Children and parents who were in the study at T3 were invited to participate 6 months after T3 for follow-up measurement (T4: M follow-up time in months = 5.93, *SD* = 0.62). Information about additional treatment (e.g., separate parent sessions, medication) was gathered at T4.

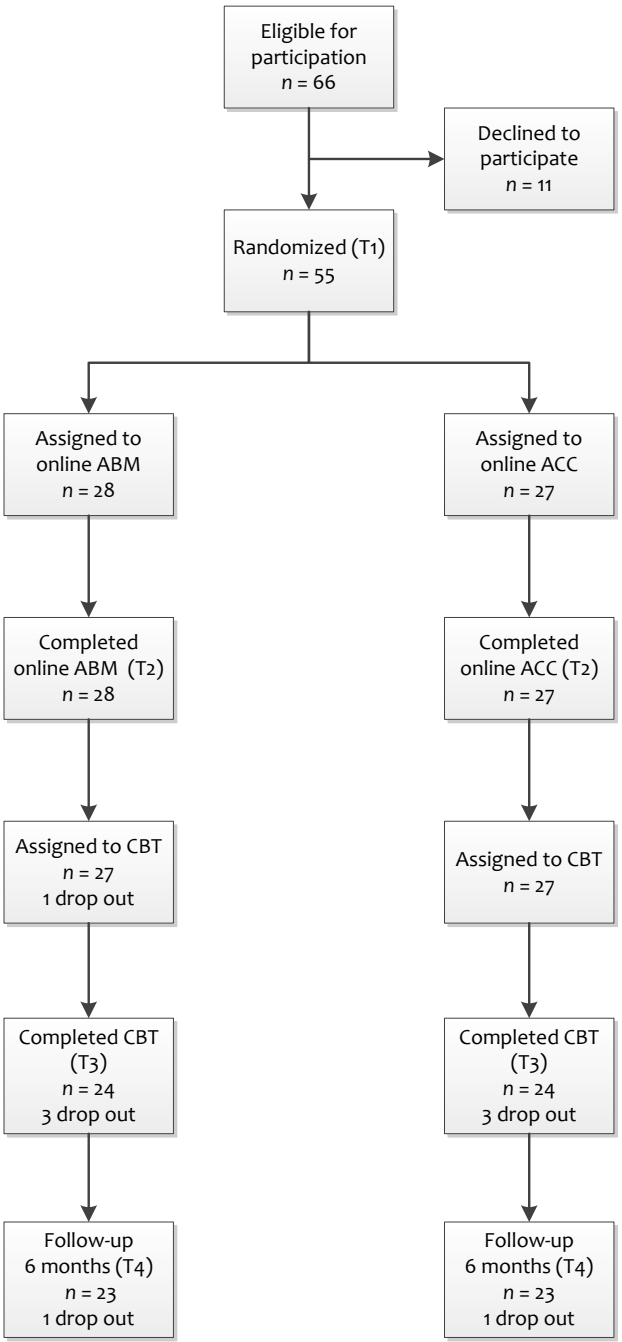
Figure 1 displays the flow of participants throughout the study. One participant from the ABM group needed more intensive treatment because of school-refusal and was not assigned to CBT. During CBT, six participants dropped out of the study equally divided over the ABM and ACC group (T3, total *n* = 48). Reasons for drop-out were unwillingness to continue CBT (*n* = 3) and worsening of symptoms (*n* = 3). At follow-up, 46 children participated with one drop-out (due to the perceived burden of the assessment) in each condition.

Statistical Analyses

To test for group differences in demographic and clinical characteristics at baseline we conducted chi-square tests and *t*-tests. One-sample *t*-tests were used to assess whether threat biases were significantly different from zero at baseline in both groups separately.

All time-related analyses were conducted with Generalized Estimating Equations (GEE; Zeger & Liang, 1986; Zeger, Liang, & Albert, 1988). GEE allows for correlated observations (i.e. repeated measurements), accounts for missing data under the missing-at-random assumption, and accommodates outcomes that are normal, categorical, or count variables. For all analyses, we used un unstructured correlation matrix. Data were included from all participants who were randomized and completed at least one assessment (i.e. intention-to-treat analysis).

Figure 1. Flow of participants



We used GEE for our primary and secondary outcomes. For the dichotomous outcome anxiety disorder status (primary outcome) we selected a binomial distribution and logit link function. For the count outcome number of anxiety disorders, a Poisson distribution with an identity link function was selected. For the continuous outcomes of anxiety symptoms, depression symptoms, and AB score a normal distribution with an identity link function was selected. For each outcome, we conducted two separate analyses. First, we examined the time interval including T1, T2, and T3. Second, we examined the interval from T3 to T4. In each analysis, we investigated the effect of group (ABM + CBT versus ACC + CBT), time, and the interaction between group and time. The group-by-time interaction tested the treatment effect hypothesis of better primary and secondary outcomes over time for the ABM + CBT relative to the ACC + CBT group. Long-term treatment effects from T3 to T4 at follow-up were modeled with separate GEE analyses for all outcome measures because of the possibility that children received additional psychological treatment after CBT. Therefore, additional treatment (yes or no) was added to correct the analyses of long-term treatment effects. In addition, separate analyses for moderators of treatment effects (i.e. three-way interactions with the interaction between group and time and the moderators) from T1 to T3 and from T3 to T4 were conducted with age and baseline AB as continuous, centered variables. Statistical significance was determined using $\alpha = 0.05$. All analyses were performed with SPSS version 24.

RESULTS

Baseline Measures

No differences were found between groups regarding demographic and clinical characteristics (see Table 1). Average baseline AB scores were normally distributed and similar across groups. AB in the ABM group was not significantly different from zero ($t = 0.42$, $p = 0.68$), whereas the ACC group showed a bias towards threat ($t = 2.19$, $p = 0.037$). In the combined ABM and ACC sample, anxiety disorder-congruent AB was not significantly different from zero for children and adolescents with SAD ($n = 15$, $M = 24.42$, $SD = 62.16$, $t = 1.52$, $p = 0.15$), SOP ($n = 19$, $M = -19.09$, $SD = 69.84$, $t = -1.19$, $p = 0.25$), SP ($n = 25$, $M = -19.39$, $SD = 100.99$, $t = -0.84$, $p = 0.41$), and GAD ($n = 29$, $M = 12.42$, $SD = 95.06$, $t = 0.70$, $p = 0.49$). Therefore, further analyses with AB concern average AB and not anxiety disorder-congruent AB. The number of children that received additional treatment after CBT was the same for the ABM ($n = 4$, 17.4%) and ACC ($n = 6$, 26.1%) group, $\chi^2(1) = 0.51$, $p = 0.48$.

Table 1. Descriptive and diagnostic characteristics for children in the Attention Bias Modification (ABM) + cognitive behavioral therapy (CBT) group and Attention Control Condition (ACC) + CBT group at baseline (T1)

	ABM + CBT group (*n* = 28)	ACC + CBT group (*n* = 27)	Between groups statistic
Demographics [a]			
Gender, boys (%)	15 (53.6%)	12 (44.4%)	$\chi^2 = 0.46$, $p = 0.50$
Age (years)	11.62 ± 2.52	10.67 ± 1.91	$t = 0.57$, $p = 0.12$
SES	0.15 ± 1.27	0.28 ± 1.33	$t = -0.37$, $p = 0.72$
Diagnoses [b]			
ADIS-IV-C CRS ≥ 4, n (%)			
Separation anxiety disorder	6 (21.4%)	9 (33.3%)	$\chi^2 = 0.98$, $p = 0.32$
Social phobia	12 (42.9%)	7 (25.9%)	$\chi^2 = 1.74$, $p = 0.19$
Specific phobia	13 (46.4%)	12 (44.4%)	$\chi^2 = 0.02$, $p = 0.88$
Generalized anxiety disorder	17 (60.7%)	12 (44.4%)	$\chi^2 = 1.46$, $p = 0.23$
Primary ADIS-IV-C CRS	5.86 ± 1.18	6.04 ± 0.90	$t = -0.64$, $p = 0.53$
Outcome measures baseline [c]			
Number of anxiety disorders	1.82 ± 1.12	1.89 ± 1.12	$t = -0.22$, $p = 0.83$
Anxiety symptoms (SCARED-R)	48.88 ± 16.60	51.94 ± 18.62	$t = -0.65$, $p = 0.52$
Depression symptoms (CDI)	14.48 ± 8.20	10.85 ± 6.66	$t = 1.78$, $p = 0.09$
Attention bias	3.39 ± 42.89	19.52 ± 46.24	$t = -1.34$, $p = 0.19$

Note. [a] Socioeconomic status represents a continuous (status) z-score, [b] Clinical severity rating (CRS) for the Anxiety Disorders Interview Schedule for DSM-IV Child and Parent Version (ADIS-IV-C), [c] SCARED-R = Screen for Child Anxiety Related Emotional Disorders; CDI = Child Depression Inventory

Treatment Effects

Primary outcomes

Figure 2 and Table 2 show anxiety disorder status of children in the ABM and ACC group at T2, T3, and T4. Analyses indicated a significant change over time from T1 to T3 (Wald = 23.02, *b* = -0.17, *SE* = 0.05, $p < 0.001$) and from T3 to T4 (Wald = 11.04, *b* = -0.08, *SE* = 0.04, *p* = 0.046). However, no significant main effect of group or interaction effect between group and time was found. After 3-week online ABM and online ACC, 18.2% of the children no longer met the criteria for anxiety disorder status. After CBT, this percentage increased to 47.9%. At T4, 76.1% of the children were anxiety-disorder free.

Figure 3a and Table 2 show the change in the number of anxiety disorders across treatment and at follow-up. Although the decrease in the number of anxiety disorders was significant from T1 to T3 (Wald = 17.59, *b* = -0.06, *SE* = 0.02, $p < 0.001$) and from T3 to T4 (Wald = 11.00, *b* = -0.06, *SE* = 0.02, $p < 0.001$), no significant interaction effect between group and time or main effect of group was detected. From T3 to T4 a main effect for additional treatment was found (Wald = 4.11, *b* = 0.83, *SE* = 0.41, *p* = 0.043). Thus, for children who received additional treatment, the further decline in number of anxiety disorders from T3 to T4 was less evident. No significant interaction effect between group and time or main effect of group was found from T3 to T4.

Secondary outcomes

Figure 3b and 3c, and Table 2 show the change in patient-reported anxiety and depression symptoms across treatment and at follow-up. Anxiety symptomatology decreased continuously throughout treatment from T1 to T3 (Wald = 17.96, *b* = -0.52, *SE* = 0.16, *p* = 0.001), but no changes were apparent from T3 to T4 (Wald = 2.38, *b* = -0.20, *SE* = 0.13, *p* = 0.12). No significant main effect of group or interaction effects between group and time were found.

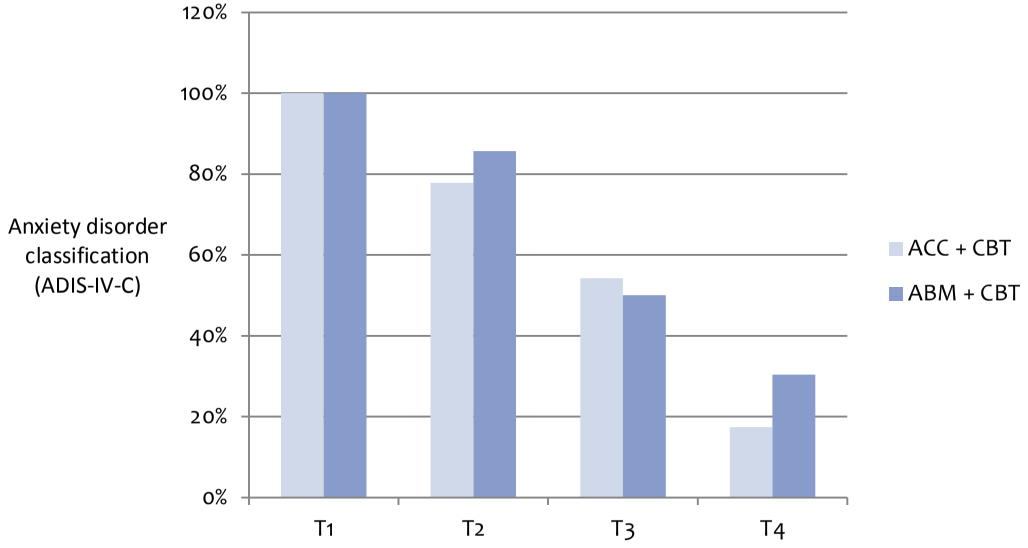
Child-reported depression symptoms decreased from T1 to T3 (Wald = 32.35, *b* = -0.46, *SE* = 0.11, $p < 0.001$), whereas no significant main or interaction effects were found. At T4, a significant interaction effect between group and time was found (Wald = 4.95, *b* = -0.16, *SE* = 0.07, *p* = 0.026), with a larger decrease of depression symptoms for children in the ACC + CBT group compared to the ABM + CBT group. Also, a main effect for additional treatment (Wald = 5.41, *b* = 4.60, *SE* = 1.98, *p* = 0.020) was found, but no main effect of group or time.

Table 2. Descriptive statistics of the outcome measures throughout the study for the ABM + CBT group and ACC + CBT group

	Baseline (T1) (*n* = 55)		Post-ABM or ACC (T2) (*n* = 55)		After CBT (T3) (*n* = 48)		Follow-up (T4) (*n* = 46)	
ADIS-IV-C anxiety disorder								
ABM + CBT	28	(100%)	24	(85.7%)	12	(50.0%)	7	(30.4%)
ACC + CBT	27	(100%)	21	(77.8%)	13	(54.2%)	4	(17.4%)
Number of anxiety disorders								
ABM + CBT	1.82	± 1.12	1.48	± 1.22	0.79	± 1.25	0.43	± 0.79
ACC + CBT	1.89	± 1.12	1.54	± 1.14	0.92	± 1.21	0.35	± 0.93
SCARED-R combined report								
ABM + CBT	48.88	± 16.59	35.57	± 19.93	27.51	± 19.92	24.97	± 17.39
ACC + CBT	51.94	± 18.62	34.27	± 15.23	24.51	± 10.60	21.54	± 14.25
CDI mean score								
ABM + CBT	14.48	± 8.20	8.96	± 4.79	6.04	± 5.00	6.57	± 6.18
ACC + CBT	10.85	± 6.66	7.33	± 4.88	5.29	± 3.64	4.13	± 3.56
Attention bias [a, b]								
ABM + CBT	3.39	± 42.89	11.58[b]	± 38.96	-5.65	± 26.99	8.03	± 29.36
ACC + CBT	19.52[a]	± 46.24	-7.42[b]	± 44.37	10.67	± 28.66	1.51	± 33.81

Note. ADIS-IV-C = Anxiety Disorders Interview Schedule for DSM-IV Child and Parent Version; SCARED-R = Screen for Child Anxiety Related Emotional Disorders; CDI = Child Depression Inventory, ABM = Attention Bias Modification, ACC = Attention Control Condition, CBT = Cognitive-Behavioral Therapy, [a] attention bias score significantly different from zero, [b] cases with too few trials removed at T2 (one participant of the ACC + CBT and one participant of the ABM + CBT)

Figure 2. Changes in anxiety disorder classification (ADIS-IV-C) throughout the study for the ABM + CBT and ACC + CBT groups



Note. ADIS-IV-C = Anxiety Disorders Interview Schedule for Children; ABM = Attention Bias Modification, ACC = Attention Control Condition, CBT = Cognitive-Behavioral Therapy

Changes in AB from T1 to T3 were not significant across time (Wald = 1.06, *b* = -0.77, *SE* = 0.66, *p* = 0.24) and no interaction effect between group and time or main effect of group was found. From T3 to T4, a main effect of group (Wald = 4.62, *b* = 39.58, *SE* = 18.41, *p* = 0.032) and an interaction effect between group and time was found for changes in AB (Wald = 3.87, *b* = -1.76, *SE* = 0.90, *p* = 0.049). Although the direction of AB change from T3 to T4 was different across groups, AB at both assessments for the ABM + CBT group and ACC + CBT group were not significantly different from zero (Table 2).

Moderators of Treatment Effects

For both primary and secondary outcomes, no significant, three-way interactions between group, time, and the moderators' baseline AB and age were found from T1 to T3 and from T3 to T4. Therefore, moderators of treatment effects were examined without the effect of group in the model. Also, for these analyses of primary and secondary outcomes, no significant two-way interactions of time and the moderators were found.

Figure 3. Change in the number of anxiety disorders (a), anxiety symptoms (b), and depression symptoms (c) after Attention Bias Modification (ABM) and Attention Control Condition (ACC; T2), cognitive behavioral therapy (CBT; T3) and at 6-month follow-up (T4)

a.

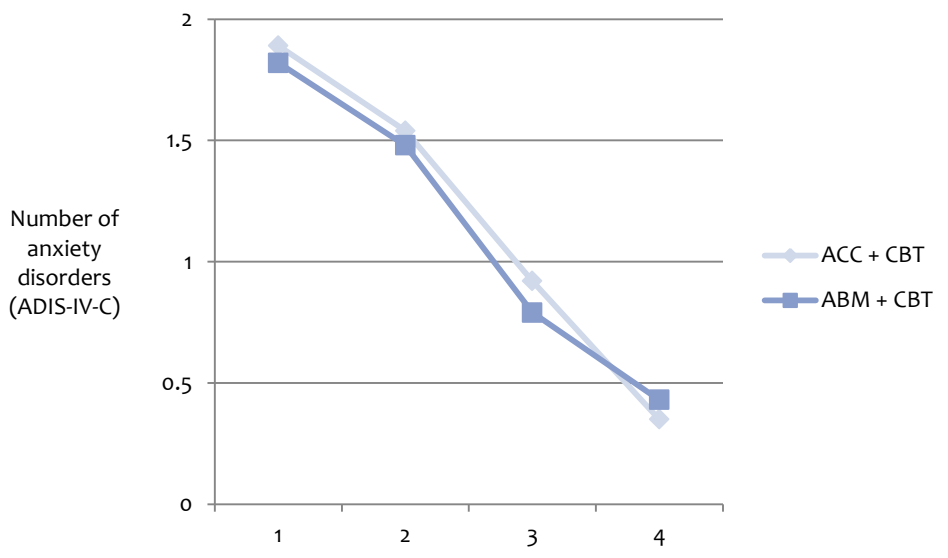
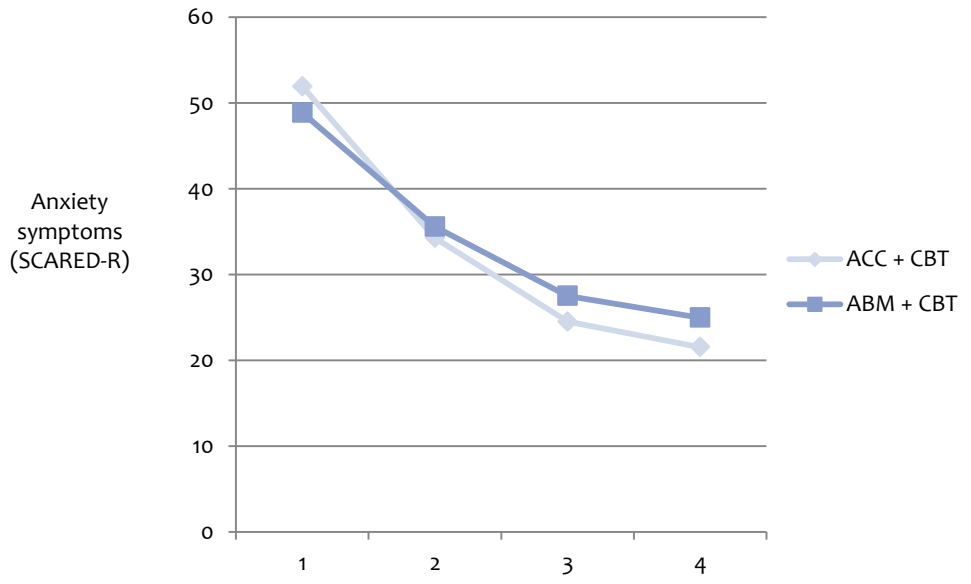
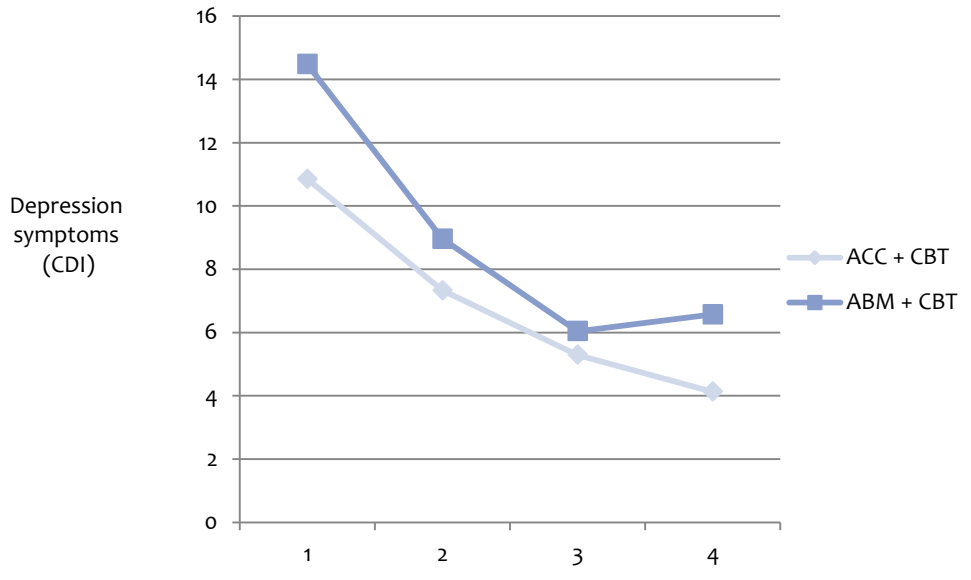


Figure 3 continued

b.



c.



Note. ADIS-IV-C = Anxiety Disorders Interview Schedule for Children; SCARED-R = Screen for Child Anxiety Related Emotional Disorders; CDI = Child Depression Inventory

DISCUSSION

This randomized, double-blind, placebo-controlled clinical trial examined the efficacy of online ABM combined with CBT for children and adolescents with anxiety disorders. Building further upon current knowledge in the field of ABM, we utilized anxiety disorder-congruent stimuli with the four included anxiety disorder subtypes to improve the targeting of AB. Moreover, we examined baseline AB and age and as moderators of ABM efficacy. Finally we conducted a long-term follow-up of all children 6 months after they completed ABM combined with CBT or ACC combined with CBT.

Although online attention training (ABM and ACC) combined with CBT was effective in reducing both clinician-rated anxiety disorders and patient-reported anxiety and depression symptomatology, no differences were found between the ABM and ACC condition. The results indicate that when ABM is delivered online, with stimuli that match all anxiety disorders targeted and in combination with CBT, it is no more effective than ACC. Thus although the current study used a different methodological approach than previous studies, we did not find a superior effect of ABM. This finding is in line with four previous RCTs in children with anxiety disorders (Britton et al., 2013; Ollendick et al., 2019; Pergamin-Hight et al., 2016; Shechner et al., 2014). A significant augmented effect of ABM over ACC has only been reported in one study for clinician-rated symptoms, but not for anxiety disorder status (White et al., 2017). Therefore, results of the current and previous studies show that ABM as an adjunct to CBT does not have a superior effect on anxiety disorder status and that the findings for a beneficial effect of ABM over ACC for patient-reported outcomes are inconsistent and at most modest. Even if there are modest effects of ABM on patient-reported outcomes, these do not outperform the general effectiveness of CBT for anxiety disorders in children and adolescents (James et al. 2015).

Clinician-reported and patient-reported anxiety symptomatology decreased continuously for children in both the ABM and ACC conditions throughout the study. In line with previous studies, decreases in anxiety symptoms were not accompanied by changes in AB (Mogg, Waters, & Bradley, 2017). Possibly other mechanisms are involved in the reduction of anxiety during attention training. Both ABM and ACC have been previously described to increase top-down cognitive control over processing threat stimuli irrelevant to the task performed, that is, attentional control. Top-down cognitive control is the deployment of attention that is based on voluntary goals and expectations (Itti & Koch, 2001). Poor attentional control has previously been

associated with AB in anxious individuals (Derryberry & Reed, 2002). Therefore, an increase in top-down cognitive control might explain the decreases in anxiety symptoms in both training conditions (Cisler & Koster, 2010).

Reductions in anxiety symptoms in both attention training groups may also be due to exposure to threatening stimuli. This explanation is also proposed in the review of Mogg and colleagues (2017). Numerous studies have shown that exposure is a very effective strategy to diminish anxiety problems (Seligman & Ollendick, 2011; Weisz et al., 2017). Future studies are needed to examine the influence of exposure on attention training effects; for example, by comparing ABM and ACC, to an exposure control condition in which patients are only exposed to threatening stimuli. In addition, a placebo control condition with exposure to neutral stimuli should be incorporated to rule out that decreases in anxiety are attributable to retest effects that are commonly observed within clinical samples (Arrindell, 2001).

Our study is the first to examine the effect of ABM and ACC delivered fully online in a clinical sample of children and adolescents with anxiety disorders. In contrast to our findings, relatively more children were found to be treatment responders in the ABM than the ACC group by Chang and colleagues (2019). However, children in the study by Chang et al. also completed an ABM or ACC session at the laboratory, besides performing the training at home for eight sessions. Other studies with full online delivery also did not find a beneficial effect of online ABM compared to ACC for subclinical anxiety symptoms in adolescents (de Voogd et al., 2016; Sportel, de Hullu, de Jong, & Nauta, 2013) and adults with SOP (Boettcher et al., 2003; Enock, Hofmann, & McNally, 2014; Neubauer et al., 2013). Although treatment adherence in our study was almost perfect (99.8%) and children made relatively few errors during attention training, mean RTs were rather large. Children may respond differently to ABM at home than in a research or hospital setting because of several reasons. Performing the training in an uncontrolled setting most likely brings along distractions, which was shown in the current study by relatively large RTs. Also, training in a research center may be related to other non-specific effects such as treatment structure, motivation, and the participants' outcome expectations, also described as a variant of the experimenter effect (Cristea, Kok, & Cuijpers, 2015; Litnetzky, Pergamin-Hight, Pine, & Bar-Haim, 2015). When performed at home, more explicit learning could be achieved by introducing explicit goal-setting, feedback, and variation of training to increase engagement (Mogg & Bradley, 2018). For example, a series of studies by Waters and colleagues (Waters, Pittaway, Mogg, Bradley & Pine, 2013; Waters et al., 2015, 2016) found a novel online attention training, including techniques

to consolidate the positive-search strategies, to be more effective than a control condition or wait-list control group for children with anxiety disorders.

In the current study, baseline AB and age neither moderated the effect of ABM, nor explained differences in symptom reduction throughout the study. A previous study found the efficacy of ABM relative to ACC for children with SOP above the age of 13 (Pergamin-Hight et al., 2016). The median age of our sample was lower (10 years) and this might explain why we did not find a moderating effect of age. Moreover, recent studies found a positive association between treatment gains and baseline AB for adults and not for children or adolescents (Abend et al., 2018; Abend et al., 2019). We also did not find baseline AB to be related to the efficacy of ABM, which is generally in line with previous studies (Ollendick et al., 2019; Pergamin-Hight et al., 2016). It should also be noted that children in the ABM group, whose attention was trained towards neutral, did not show a baseline bias, whereas children in the ACC group showed a bias towards threat. In contrast to our expectations, children and adolescents did not show an anxiety disorder-congruent AB at baseline. This could also explain why in our study ABM was not superior to ACC. Another explanation is low reliability and a paucity of research on the psychometric properties of the dot-probe task (Cisler, Bacon, & Williams, 2009; Roy, Dennis, & Warner, 2015).

The current study has several strengths worth mentioning. By using online ABM and ACC, this is the first study to examine the efficacy of online ABM combined with CBT for children and adolescents with anxiety disorders. In addition, by combining stimuli that matched all included anxiety disorders, content-specificity of the training was attuned. Nevertheless, the current study should also be seen in the light of the following limitations. Our sample size was low which may have hampered detecting significant effects. However, as futility analyses showed a very low chance of finding a significant effect when our target sample size was reached, lack of statistical power was limited to the moderation analyses. Although the training stimuli represented all included anxiety disorders, stimuli were not personalized. Also, the stimuli used to represent SAD consisted of more complex pictures (i.e., scenes of children separating or reuniting with a parent) than the other stimuli. Even though comorbidity in the current study was high and we specifically aimed to target this, the combination of stimuli that required more processing (SAD and GAD), with less complex stimuli (SOP and SP) may have also led to the measurement and training of different stages of AB. Finally, we did not include a CBT-only condition to contrast findings of the ABM and ACC group.

The findings of the current study have several implications for clinical practice and future research. As our study adds to the growing body of research that questions the efficacy of ABM for children and adolescents with anxiety disorders, implementing ABM into clinical practice is not advised. Although we used anxiety disorder-specific stimuli, this did not lead to improved efficacy of ABM. More research is needed that examines which elements of ABM explain decreases in anxiety symptoms, such as increases in top-down cognitive control during exposure of threatening stimuli regardless of bias modification. In addition, combining training attention control with more goal-oriented exercises may be more effective in addressing the complex circuit of cognitive control functions involved in anxiety (Mogg et al., 2017).

Conclusion

We did not find a benefit of online ABM with anxiety disorder-specific stimuli in combination with CBT for the treatment of children and adolescents with anxiety disorders in a randomized, double-blind, placebo-controlled trial. Although anxiety symptomatology decreased throughout the study and improvements remained at the 6-month follow-up, no differences between ABM and ACC were found. More research is needed to identify active elements of attention training for children and adolescents with anxiety disorders.

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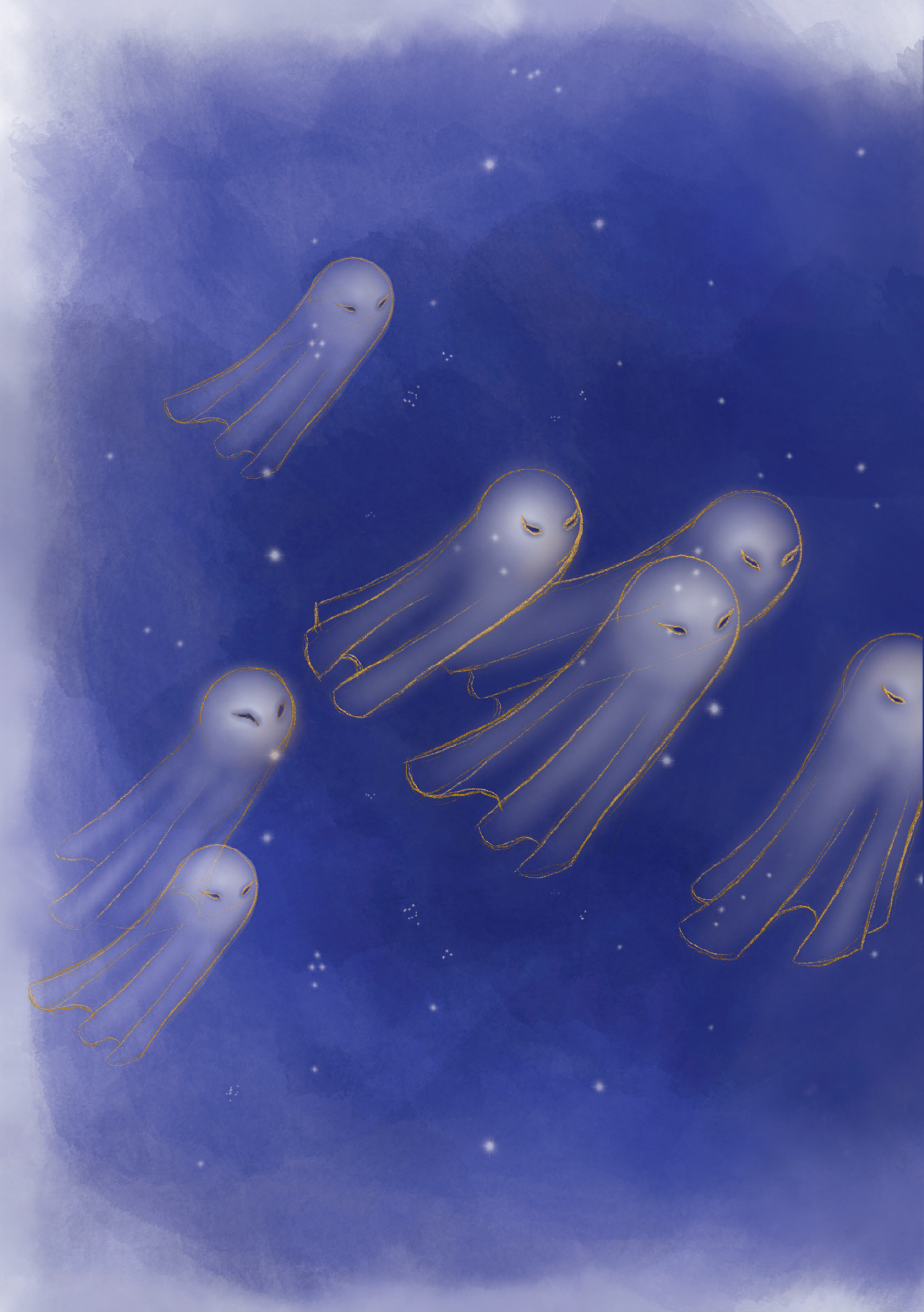

Chapter 7

Discussion

Rationale

Anxiety disorders are the most prevalent mental disorders among children and adolescents (Merikangas et al., 2010). Early onset of the disorder is related to more severe psychopathology (Ramsawh, Weisberg, Dyck, Stout, & Keller, 2011; Rosellini, Rutter, Bourgeois, Emmert-Aronson, & Brown, 2013) and continuation across the lifespan (Bittner et al., 2007; Woodward & Fergusson, 2001). Hence, early identification and treatment of anxiety disorders provide the opportunity to prevent prolongation of the disorder into adulthood and the development of severe mental disorders. The first aim of this thesis is to obtain more insight into age-related characteristics of anxiety disorders. More specifically, we aimed to investigate how symptoms of anxiety develop across age, are associated with daily functioning, and at what age anxiety disorders have their average onset. The second aim of this thesis is to obtain more knowledge into the role of cognitive biases in both the familial aggregation and treatment of anxiety disorders in children and adolescents. Previous research has showed that information processing biases (i.e. cognitive biases) are core characteristics of anxiety disorders as they are involved in the development and maintenance of these disorders (Dudeney, Sharpe, & Hunt, 2015; Hadwin & Field, 2010; Legerstee et al., 2010). This second part of the thesis is based on the results of the ATTENTIO study, a multicenter randomized controlled trial (RCT) that examined the effect of Attention Bias Modification (ABM) for children and adolescents with an anxiety disorder.

In this chapter, I will summarize the main findings of our studies and discuss them in a broader context. Subsequently, I will discuss important methodological considerations that are of importance in the interpretation of our results. Finally, I will address recommendations for future research and implications for clinical practice and options for prevention policies.

Part I Age-related characteristics of anxiety disorders

Part I of this thesis comprises three studies with different methodological approaches that are aimed at age-related characteristics of anxiety disorders. In the first study (chapter 2), I describe how we used a sample from the general population (Generation R) to study different trajectories of anxiety and depression symptoms in children aged between 1.5 and 10 years old. In addition, we studied whether different developmental trajectories of anxiety and depression were related to early child and family predictors and how these trajectories were associated with psychosocial and school functioning when children were 10 years old. In the second study (chapter 3), we conducted a systematic review to describe the social and academic functioning of adolescents with anxiety disorders. In the third study (chapter 4), we used a systematic review, meta-analysis,

and meta-regression to study the age of onset (AOO) of different anxiety disorder subtypes in general population samples.

Main Findings

Across childhood, children experience developmentally appropriate fears that can be associated with psychopathological symptoms. However, it is likely that the manifestation of fears beyond normative anxiety follows different patterns. We found that developmental trajectories of anxiety and depression symptoms in the general population indeed vary between children. In addition to previous research (Fanti & Henrich, 2010; Feng, Shaw, & Silk, 2008), we found a specific trajectory of pre-school limited symptoms (4.2%), besides an increasing (7.4%), decreasing (6.0%), and low stable (82.4%) trajectory. We also found higher levels of maternal and paternal psychopathology, low and high maternal education, and different child ethnicities to predict the less prevalent trajectories. Although previous studies also found gender as a risk factor of increasing levels of anxiety and depression (Cote et al., 2009; Cote, Tremblay, Nagin, Zoccolillo, & Vitaro, 2002; Sterba, Prinstein, & Cox, 2007), the trajectories in chapter 2 were gender-invariant. Thus, our results indicated that trajectories of anxiety and depression symptoms from early to middle childhood are the same for boys and girls.

Another important finding of chapter 2 is that children in the increasing trajectory had borderline clinical anxiety and depression levels in middle school and this trajectory was associated with diminished self-esteem and school functioning (i.e., lower school performance, more school problems). Children in the pre-school limited trajectory remained below the borderline clinical threshold. Nevertheless, these children also had more school problems compared to children in the low trajectory even after controlling for externalizing symptoms. Together, the pre-school limited and increasing trajectories captured almost 12% of the children, which is in line with studies showing that up to 14% of pre-school children experience symptoms at a level that may interfere with daily functioning (Bayer, Hiscock, Ukoumunne, Price, & Wake, 2008).

Chapter 3 described how anxiety disorders are associated with lower social competence, interpersonal problems, and victimization among adolescents. These findings illustrate that besides adolescence being a risk period of developing an anxiety disorder, adolescents with anxiety disorders are also faring badly. This result is in line with studies that showed how anxiety disorders in adults significantly compromise quality of life and psychosocial functioning (Mendlowicz & Stein, 2000). Also, previous studies found adolescents' subclinical levels of

anxiety to negatively impact psychosocial and academic functioning (i.e. Kingery, Erdley, Marshall, Whitaker, & Reuter, 2010; Tillfors, Persson, Willén, & Burk, 2012). We also found that adolescents with anxiety disorders feel impaired at school with respect to concentrating, taking tests and getting good grades. However, we did not find evidence across studies that adolescents with anxiety disorders have lower academic functioning compared to their non-anxious peers. Diminished social competence together with interpersonal problems and victimization could further worsen feelings of self-esteem or self-efficacy, which could explain why adolescents with anxiety disorders feel impaired at school. As a previous systematic review showed that self-esteem is a weak predictor of developing emotional disorders in adolescence (Keane & Loades, 2017), lower self-esteem may instead co-occur with these disorders and moderate (perceived) daily functioning.

In chapter 4, anxiety disorders in general were found to have their average AOO at 21.3 years. In addition, we showed that separation anxiety disorder, specific phobia, and social phobia have their average onset during childhood and adolescence, whereas obsessive-compulsive disorder, panic disorder, agoraphobia, post-traumatic stress disorder, and generalized anxiety disorder start, on average, in early adulthood. Although our findings are fairly in line with two previous reviews regarding the sequence for the different AOO of anxiety disorder subtypes (Kessler et al., 2007; McGorry, Purcell, Goldstone, & Amminger, 2011), we found later estimates of AOO. There are several explanations for this later AOO. The previous review by McGorry et al. only included studies that followed individuals up to the age of 18 years which limited the latest AOO to this age. In addition, we found several study-related factors to be predictive of an earlier AOO, namely a prospective study design, higher social and economic development of the study country, and assessment of more anxiety disorder subtypes. As the majority of the studies in our meta-analysis used a retrospective design with adult populations, this could also explain later estimates of AOO because of recall bias and a longer period of being at risk to develop an anxiety disorder. This also explains why the average AOO we found for anxiety disorders in general was later than may be expected from a child and youth psychiatry perspective. Previous studies have consistently shown that anxiety disorders are more prevalent in women compared to men (Somers, Goldner, Waraich, & Hsu, 2006). However, we did not find that gender was associated with the AOO of anxiety disorders. Thus, periods of vulnerability for developing anxiety disorders seem the same for men and women.

Methodological Considerations

Anxiety and depression symptoms in the general population

We studied the development of anxiety and depression symptoms in the Generation R Study, a large population-based cohort including repeated measures across childhood and detailed information regarding outcomes in middle childhood from both the child and parent perspective. By using a cohort as Generation R, we aimed to examine developmental trajectories that are representative of the general population. This approach comes along with two important methodological considerations in which the findings of chapter 2 should be viewed. First, this study relied on parent reports for the measurement of anxiety and depression symptoms in children. Although this is the most convenient way to assess these symptoms in early childhood, the construct of anxiety and depression at the age of 1.5 years is arguable. Indeed, the internal consistency of anxiety and depression symptom subscale at this age was lower than at older ages. Nevertheless, we found the same trajectories when analyzing the developmental trajectories between 3 and 10 years, without the measurement at 1.5 years. Second, whether symptoms of anxiety and depression serve as precursors of anxiety disorders was not examined in this study. At the same time, the findings underline that also subclinical levels of anxiety and depression are associated with lower self-reported self-esteem and school functioning in middle childhood.

Systematic reviews and meta-analyses

As we used a systematic review approach to study the AOO of anxiety disorders and impairment across domains for adolescents with anxiety disorders, the results of chapter 3 and 4 partly depend on the methodological quality of the included studies. In chapter 3, we used a checklist to describe the quality of the studies on social and academic functioning for adolescents with anxiety disorders. Some studies had a lower quality because, for example, they lacked a control group or statistical analyses. The results of studies without a control group made it more difficult to determine whether the results were specific for adolescents with anxiety disorders or represented general lower life satisfaction in adolescence (Goldbeck, Schmitz, Besier, Herschbach, & Henrich, 2007). Also, the generalizability of some findings was hampered by studies that did not report inclusion and exclusion criteria for participants. We have taken this into account by comparing the results of these studies to those with higher quality and found that they showed approximately the same pattern of results.

For the studies on the AOO of anxiety disorders included in chapter 4, we could not control for the age of participants as most studies did not report the average age of the study sample. An older sample will probably be associated with later AOOs due to recall bias and a longer period of being at risk of developing the disorder. As already noted, the majority of the included studies used a retrospective design. As we found that a retrospective study design was associated with a later AOO, recall bias may have led to higher estimates of AOO in this meta-analysis. However, recall bias can act in both directions, leading to earlier or higher estimates of the true AOO, due to unintentional attempts to explain the disorder onset in relation to specific events of personal significance (De Girolamo, McGorry, & Sartorius, 2019).

When conducting a systematic literature review, one should still be hesitant regarding the possibility of publication bias. Because of the high methodological variabilities of the studies included in chapter 3, we were not able to study publication bias in this chapter. Possibly, studies showing that adolescents with anxiety disorders do not report problems with regard to social or academic functioning are less likely to be published. Nevertheless, some studies in our review showed no differences between adolescents with anxiety disorders and healthy peers which contradicts this line of thought. For our results in chapter 4 on the AOO of anxiety disorders, publication bias is not likely as AOO in the concerning studies was not reported as the main outcome. However, we do not know the AOO of studies that reported on the (lifetime) prevalence of anxiety disorders without assessment and reporting of AOO. We highlight that the methodological approach that is used to examine AOO, can have an effect on the AOO found, and therefore, the study design should be taken into account when interpreting the results.

Part II Cognitive biases: familial aggregation and modification

In Part II of this thesis, two studies were included that focused on the role of cognitive biases in the intergenerational aggregation and treatment of anxiety disorders. Both studies were part of the ATTENTIO study, a multicenter randomized controlled trial (RCT) that examined the effect of Attention Bias Modification (ABM) for children and adolescents with an anxiety disorder. First, we examined whether cognitive biases between children and their parents were related and how this familial aggregation could be further explained by parental lifetime emotional disorders and rearing styles (chapter 5). Second, we examined whether the online delivery of ABM combined with Cognitive Behavioral Treatment (CBT) was effective in treating anxiety disorders in the same sample of children and adolescents (chapter 6).

Main Findings

Cognitive biases are predetermined selectivities in cognitive processing that have been found at different levels of information processing in children and adolescents with anxiety disorders. Previous studies have proposed a role for cognitive biases in the familial transmission of anxiety disorders (Hadwin & Field, 2010; Hadwin, Garner, & Perez-Olivas, 2006). In chapter 5, we found an association between attention bias in mothers and interpretation bias in children. Previous studies focused on the association between the same information processing level of cognitive biases in children and adolescents in clinical (Gifford, Reynolds, Bell, & Wilson, 2008) and community studies (i.e. (Creswell, Schniering, & Rapee, 2005; Remmerswaal, Muris, & Huijding, 2016). We showed that the aggregation of threat related cognitive biases can extend from one information processing level to another. We also found that both maternal lifetime emotional disorders and rearing styles did not explain the association between cognitive biases in mothers and children. Twin-studies have shown that the largest role attributed to the variance of different cognitive biases is the non-shared environment (Eley et al., 2008; Lau et al., 2009; Lau et al., 2012). An example of non-shared environmental effects may be specific parent-child interactions, which can differ between parents and siblings, due to dispositions of anxiety of parents and children. For example, control exerted by anxious children may be followed by an aversive reaction if parents are anxious themselves which further influences the parent-child interaction (Williams, Kertz, Schrock, & Woodruff-Borden, 2012). A recent study found parents' anxiety rather than parents' attention bias to prospectively predict young children's attention bias (Aktar, Van Bockstaele, Perez-Edgar, Wiers, & Bogels, 2018). Anxiety levels in parents may, therefore, be seen as a factor to be relevant across time and in more specific interactions or modeling situations, instead of the presence of previous emotional disorders.

Attention Bias Modification (ABM) concerns a new treatment that has been studied across different anxious populations in the past two decades, including its application for children and adolescents with anxiety disorders. Previous RCT studies showed contradicting results and relatively few studies investigated the online delivery of ABM and its combined effect with CBT. In line with four previous RCTs (Britton et al., 2013; Ollendick et al., 2019; Pergamin-Hight, Pine, Fox, & Bar-Haim, 2016; Shechner et al., 2014), we found that both ABM and its Attention Control Condition (ACC) resulted in reduced anxiety symptomology reported by clinicians, parents, and children when combined with CBT (chapter 6). Previous studies that used full online delivery of

ABM did not find a superior effect of ABM compared to ACC for different anxious populations either (for an overview, see chapter 6). A more recent study by Chang et al. (2019) did find more treatment responders in the ABM condition, but online delivery of ABM was combined with sessions in the laboratory. As both ABM and ACC are effective in alleviating anxiety, more research is needed to identify active elements of attention training as well as which children and adolescents are most likely to benefit from ABM. We also found that baseline attention bias and age of participants did not moderate treatment effects. Although larger treatment gains were previously found for older children (Pergamin-Hight et al., 2016), other studies (i.e. Ollendick et al., 2019) also did not show a moderating effect of baseline attention bias. The latter finding may be explained by the difficulty of capturing different facets of baseline attention bias with one single experimental measurement, as discussed later in this chapter.

Methodological Considerations

ATTENTIO study

As the studies in chapter 5 and 6 were carried out within the ATTENTIO study, methodological considerations of these studies can be found in the design and characteristics of this study and its sample. Originally, ATTENTIO concerned a single center RCT study within the Erasmus MC – Sophia Children's Hospital, a tertiary hospital in Rotterdam. In the Netherlands, the mental health care system is divided into primary, secondary, and tertiary care, with the latter intended for the most complex mental health problems. Therefore, children included in the study may concern a more heavily affected group. In a later phase of the study, we started recruiting children at secondary mental health centers as well. Because only six children (11%) from these mental health centers were included, comparisons between the different sites would not have led to meaningful results. In addition, several recruitment strategies were performed that included mailings to general practitioners, local newspapers, TV, radio, and informative websites on mental health in children. This may have led to a selection bias of participants that were reached via these media of parents with higher educational level and good mental health (Topolovec-Vranic & Natarajan, 2016). However, by combining traditional media with a web-based approach, we are more confident to have reached a broader group of parents. A strength of the study is that we had excellent inclusion (83%) and follow-up rates (84%). Nevertheless, as the study was terminated due to futility before the target sample size was reached, the small sample may have hampered the follow-up analyses for moderating and mediating effects which required more power in chapter 5 and 6. An explanation of the small sample size lies mainly in the reformation

and decentralization of the Dutch youth care system in 2015 as children with anxiety disorders without physical comorbidity were mainly treated in primary mental health care.

The RCT design of the current study resulted in a bottom-up study design for our study on the familial aggregation of cognitive biases of parents and children with anxiety disorders. As we did not include a group of parents with anxiety disorders with non-anxious children, it was not possible to examine the bidirectional transmission of cognitive biases. Previous studies with community samples have shown a reciprocal relationship with child threat cognitions predicting parents' expectancies, which further escalate child's cognitions (Creswell, O'Connor, & Brewin, 2006; Creswell, Shildrick, & Field, 2011). A strength of our design is that we included both fathers and mothers, whereas most previous studies did not assess cognitive biases in fathers. As put forward by Bögels and Phares (2008), mothers and fathers have different roles throughout the development of children's coping with anxiety. For example, fathers are assumed to have a larger role than mothers in play and challenge for young children. Anxiety in fathers could impact children's development by not encouraging risk taking or engaging in energetic play, whereas anxious mothers could still fulfill their task of providing care and protection. In adolescence, anxious fathers may be hindered in their role of helping their child in the transition to the outside world while anxious mothers could encounter more problems in letting go.

Measurement of attention bias

We did not find a significant attention bias in children and adolescents with anxiety disorders who participated in the ATTENTIO study. Also, we did not find anxiety disorder-congruent attention bias when taking the type of stimuli and classified anxiety disorders into account. The absence of attention bias in our study sample is in line with several studies that also found no attention bias (i.e. an attention bias not significantly different from zero) in clinically anxious children and adolescents (for reviews, see Mogg, Waters, & Bradley, 2017 and Van Bockstaele et al., 2014). A recent multi-site study by Abend et al. (2018) including over 1000 children and adolescents found small associations between attention bias and symptoms of social phobia and school phobia, but not other anxiety symptoms. This finding advocates that the relative role of attention bias in pediatric anxiety might be minor.

As the research on anxiety-related attention bias increases, evidence shows that attention bias is neither a unitary nor a stable construct (MacLeod, 2019). Both individual differences (symptom profile, level of trait anxiety), task-related variables (time-course of attention bias), and

situational variables (external stressors, temporal instability) have been related to attention bias (for an overview, see Mogg & Bradley, 2016). It should also be noted that attention bias can be distinguished between facilitated attention towards threat, difficulty with disengagement, and attention bias away from threat or threat avoidance (Cisler & Koster, 2010). Moreover, it has been proposed that more than one of these components of attention bias can be found within the same children depending on the task and situational differences described above (Mogg & Bradley, 2016). Because of the small sample size in the ATTENTIO study, we were not able to examine differences between the various types of attention bias. Still, the absence of general attention bias towards threat in our sample may also explain why we did find a superior effect of Attention Bias Modification over control training in chapter 6.

Attention Bias Modification

In our study, we found a decrease in anxiety symptomatology with the online delivery of both ABM and ACC without successfully modifying baseline attention bias. A fundamental assumption of ABM is baseline (i.e. pre-existing) attention bias in participants. Hence, it has previously been argued that ABM can only be effective when it successfully targets baseline attention bias (MacLeod & Clarke, 2015; MacLeod & Grafton, 2016; Wiers, 2017). However, the lack of this baseline attention bias in anxious individuals together with research showing the different features of attention bias (see above) hampers this argument (Mogg et al., 2017). As discussed earlier, the lack of baseline attention bias could either be explained by the small role of this cognitive bias in children and adolescents with anxiety disorders or by difficulties with measuring a concept that is most likely made up of different components. The anxiolytic effect in our study may be explained by features that the ABM and ACC conditions shared, without the necessity of modifying attention bias. First, both conditions included a training in attentional control, whether attention was trained towards threat or not. Poor attentional control has previously been associated with attention bias in anxious individuals (Derryberry & Reed, 2002). Thus, enhanced attentional control may explain decreases in anxiety symptoms in both ACM and ACC. Second, these reductions in anxiety may be due to exposure of threatening stimuli (Mogg et al., 2017). Various studies have shown that exposure is a very effective strategy to alleviate anxiety disorders (Weisz et al., 2017). Because our study did not include a CBT only condition, or attention training without threatening stimuli, we were not able to determine which elements led to the decreased levels of anxiety symptomatology in our study.

Future Research

General recommendations for population-based studies

Regarding the development of anxiety and depression symptoms across age, the following three recommendations for future studies should be considered. First, we recommend the use of multi-informants across age. In early childhood, combining parent reports together with independent observations could increase the reliability of measured anxiety and depression symptoms. We strongly recommend children to report on their daily functioning, besides reports from their parents. In addition, peers and teachers may give a more representative picture of children's social competence as the behavior of children will vary across social situations and the persons involved (Renk & Phares, 2004). Second, because of the high comorbidity between internalizing and externalizing problems, we recommend studying developmental trajectories across age while taking both into account. Although trajectories of internalizing and externalizing symptoms have been found to be largely similar, trajectories of pure internalizing or externalizing symptoms may relate to specific phenotypes of psychopathology (Nivard et al., 2016). In addition, co-occurring high levels of internalizing and externalizing problems have been related to more risk-taking and deviant behavior towards peers (Fanti & Henrich, 2010). Third, we suggest that future studies continue to study individual differences in anxiety and depression symptoms after adolescence, as previous studies have shown that gender, contextual stressors, and support can influence developmental trajectories and these risk factors will have a more prominent role after puberty (Legerstee et al., 2013; Nelemans, Hale, Branje, Meeus, & Rudolph, 2017).

The AOO can be used as a vital statistic in the prevention, diagnosis and treatment of anxiety disorders by describing lifetime risk and specific periods of vulnerability in which symptoms can cross the threshold of a full-blown disorder. We showed that the design of the study in which the AOO is measured influences this statistic. Therefore, we recommend future studies to use a prospective design when studying AOO. Our meta-analysis showed a specific temporal pattern of AOO for anxiety disorder subtypes, showing a continuum of average anxiety onset from childhood to young adulthood. Future studies could examine AOO together with the temporal sequence of comorbid anxiety and other mental disorders in order to understand how age-related factors may explain comorbidity and homotypic or heterotypic continuity. A recent large population-based cohort study showed that the risk of developing comorbid disorders is the highest in the six months following the first anxiety or mood disorder, but remains high in the

next 15 years (Plana-Ripoll, Pedersen, Holtz, & et al., 2019). Therefore, future studies may also choose to use more dynamic models (i.e. psychopathology as a system instead of a category) to understand which individuals who show subthreshold (comorbid) anxiety symptoms will progress into a full-threshold disorder (Nelson, McGorry, Wichers, Wigman, & Hartmann, 2017). Time series methods with collecting data of individuals via mobile applications could then be used as repeated measures for different dimensions of psychopathology.

Cognitive bias research for anxiety disorders

Because of the high familial aggregation of anxiety disorders, it is worthwhile to further study how cognitive biases are transmitted. In order to do this, we recommend to study longitudinal associations between cognitive biases in children and parents in both community, at-risk, and clinical samples. With the use of these different prospective samples, the reciprocal transmission of cognitive biases can be assessed. In addition, this gives the possibility to study whether the clinical expression of anxiety, in either the child or parents, mediates the magnitude and direction of the transmission. Instead of lifetime emotional disorders, it may be more important to consider anxiety-disorder specific transmission and biases (Legerstee & Utens, 2018). A previous study showed that children of parents with panic disorder made more threatening interpretations compared to children from parents with social phobia or parents without anxiety disorders (van Niekerk et al., 2018). Moreover, the results of our study encourage to examine the aggregation of cognitive biases across different levels of information processing. However, before future studies examine the familial aggregation of attention bias, recent advances in the components and measurement of this cognitive bias should be taken into account.

For the measurement of attention bias, we would like to highlight different recommendations that have been given by previous studies to improve the reliability of attention bias. First, the reliability of the dot-probe task can be improved by averaging attention bias across assessments instead of one single assessment (Price et al., 2015). Second, to avoid including measurement error due to top/bottom attentional allocation, horizontal stimulus presentation is preferred (Price et al., 2015). Third, attention bias variability, another RT index, may be more reliable across sessions and has been related to differences in anxiety symptomatology (Iacoviello et al., 2014; Price et al., 2015). Fourth, eye-tracking-based indices of attention bias measure the direct eye-gaze of participants, and there is preliminary evidence that this measure is more reliable than attention bias (Price et al., 2015; Waechter, Nelson, Wright, Hyatt, & Oakman, 2014). Also, eye-

tracking can be used to assess different components of attention bias (Sagliano, D'Olimpio, Taglialatela Scafati, & Trojano, 2016).

Recent studies show that attention bias in orienting towards and away from threat depends on multi-component bottom-up and top-down cognitive systems which reciprocally influence each other (Mogg & Bradley, 2016). Hence, the anxiolytic effect of Attention Bias Modification (ABM) training will most likely be larger if it targets the balance between top-down (automatic) and bottom-up (strategic) systems. In order to target both bottom-up and top-down processes, engagement in the training may be of particular relevance. A series of studies that target cognitive biases with more goal-oriented methods have been published in which attention towards positive stimuli training is combined with top-down-processes and goal-directed search tasks (Waters, Pittaway, Mogg, Bradley, & Pine, 2013; Waters et al., 2015). These studies, in which the training has been delivered via the internet, have shown positive effects on clinician-rated outcomes and provide a promising application of the recent advances in ABM research. Future clinical trials may further study the mechanism of alleviating anxiety symptomatology of attention towards positive stimuli training. In general, we recommend that future studies are registered via a trial registry to examine possible publication bias in future review studies.

Further research opportunities

Future research for children and adolescents with anxiety disorders may benefit from taking the following recommendations into account. For studies that report on the social and academic functioning of adolescents with anxiety disorders, we advise the use of a control group or norm scores to put their findings into perspective. Also, we highlight the importance of reporting inclusion and exclusion criteria and the use of multi-informant outcome assessment. While many steps are taken to improve our understanding of Attention Bias Modification for treating children and adolescents with anxiety disorders, other novel approaches of treatment have also been examined. First, a meta-analysis by Krebs and colleagues (2018) showed that modification of interpretation bias for youth with anxiety disorders may have potential effects as it has moderate effects on interpretation bias. However, because the effects on anxiety were small, more research in this field is warranted (Krebs et al., 2018). Second, many studies have examined the use of CBT over the internet, or internet-based cognitive behavioral therapy (iCBT). It has been concluded that iCBT is useful in treating mental health and medical illnesses with psychiatric comorbidities (Kumar, Sattar, Bseiso, Khan, & Rutkofsky, 2017). For children and adolescents with anxiety disorders, the feasibility of implementing iCBT in regular mental health care has been

successfully examined in rural areas (i.e. Jolstedt et al., 2017). Larger randomized controlled trials on the use of iCBT in clinical practice and its effect on treatment barriers of regular CBT are promising directions of future research.

Clinical Implications

Prevention policies

The main findings of this thesis result in three implications for prevention policies. First, prevention programs directed at children susceptible of developing elevated anxiety and depression symptoms (i.e. selected or indicated prevention instead of universal prevention) are most likely to be effective as the development of anxiety and depression symptoms can be predicted by child and family characteristics that can be measured before these symptoms develop. Selective and indicated prevention programs could benefit from taking risk factors into account when defining which children may develop anxiety and depression symptoms, such as parental psychopathology or indicators of socioeconomic status.

Second, the longitudinal course of anxiety and depression symptoms should be taken into account when selecting children who could benefit most from prevention programs. We showed that children with declining symptoms of anxiety and depression are not affected in their daily functioning at middle school. Thus, the measurement of these symptoms at one time point may include children in which these symptoms have a transient course. In the Netherlands, children are screened for mental health at elementary school via youth health care by the age of 6 and 10 (*Jeugdgezondheidszorg*). We recommend that children receive indicated prevention care when their parents report an increase in symptoms by the age 10 to prevent the development of clinical problems.

Third, although most prevention programs are directed at the elementary school period, prevention beyond the (primary) educational system and into early adulthood is ever-so needed. Adolescents are vulnerable and our findings indicate that they are faring badly when they develop anxiety disorders. Hence, prevention programs that specifically aim at this age group are warranted. We therefore strongly support the introduction of 'You and Your Health' (*Jij en Je Gezondheid*) in eight youth health care regions in the Netherlands in 2018, where adolescents are screened each subsequent year for multiple (mental) health problems when they are in secondary school. The different AOO we found in chapter 4 could guide prevention programs to target factors contributing to the emergence of anxiety disorders in key vulnerability periods. In

addition, macro-strategies to reduce risk and improve quality of life should be pursued such as strengthening community networks and reducing the stigma of mental health disorders (WHO, 2004).

Clinical practice

The findings of this thesis suggest that for adolescents with anxiety disorders, daily functioning evaluation should be part of regular clinical practice. Although daily impairments are already incorporated in the diagnosis of anxiety disorders, impairments in daily functioning should be targets of treatment as well. As a previous study showed that after CBT adolescents with alleviated anxiety still report low satisfaction across domains of friends, work, and community (Eng, Coles, Heimberg, & Safren, 2001), more efforts are needed to improve their daily functioning. For example, targeting self-efficacy may help adolescents besides challenging their anxious beliefs and thoughts. A recent study showed that social skills training has positive long-term effects on both alleviating anxiety and enhancing perceived social skills for adolescents with social phobia (Olivares-Olivares, Ortiz-González, & Olivares, 2019). Also, clinicians should be aware that problems with social functioning are of relevance for other subtypes of anxiety disorders than social phobia and comorbid disorders are the rule rather than the exception.

Despite the recent advances in the field of Attention Bias Modification for anxiety disorders, the implication of this treatment in clinical practice is not recommended yet. However, parents can play an important role in the transmission and maintenance of cognitive biases. Therefore, clinicians may involve parents in the treatment of children and adolescents by explaining how cognitive biases operate. Future studies have the opportunity to contribute to the translation of this growing body of research into practice.

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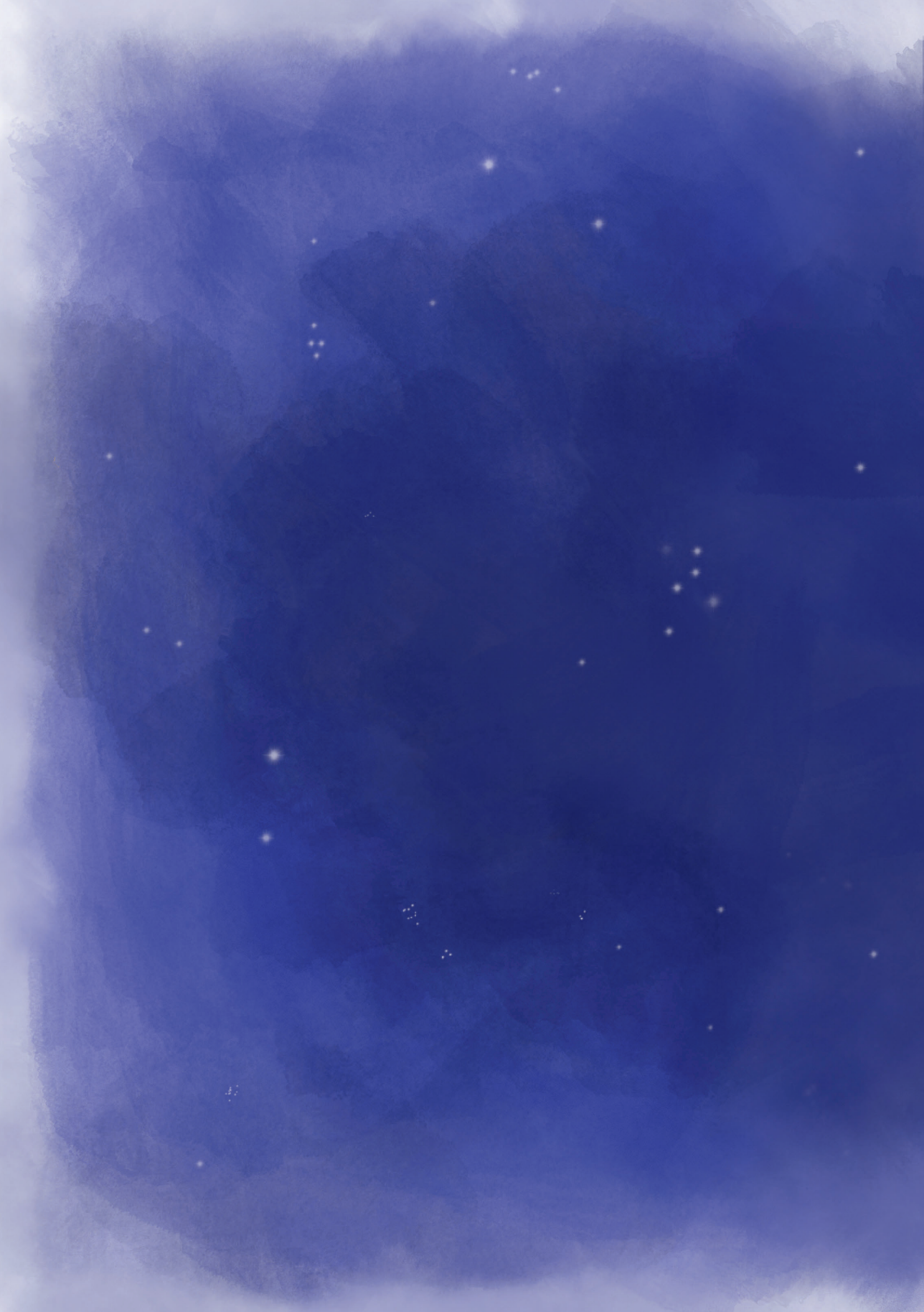


Chapter 8

Summary
Samenvatting

Summary

Anxiety disorders are the most common mental disorders among children and adolescents and are associated with adverse outcomes in later life, including other psychiatric disorders. As anxiety disorders often continue from childhood into adolescence and adulthood, identifying these disorders at an early stage is of utmost importance. Previous studies have shown that symptoms of anxiety interfere with daily functioning and understanding the consequences of anxiety disorders across the development of children and adolescents could contribute to diagnosis and treatment. Also, research in the past two decades has expanded on the role of information processes or cognitive biases in the transmission, maintenance, and treatment of anxiety disorders in children in adolescents. The first aim of this thesis, addressed in part I (chapter 2, 3, and 4), was to provide more insight into age-related characteristics of anxiety disorders. The second aim of this thesis, addressed in part II (chapter 5 and 6), was to gain more knowledge about the role of cognitive biases in the familial aggregation and treatment of anxiety disorders in children and adolescents. The second part of this thesis is based on the results of the ATTENTIO study, a multicenter randomized controlled trial (RCT) in which children and adolescents with an anxiety disorder participated with their parent(s). More detailed information regarding the aims of this thesis is provided in chapter 1.

In chapter 2, we aimed to describe different patterns of anxiety and depression symptoms in a sample from the Dutch general population (Generation R study). In this large sample of 7,499 children followed between the ages of 1.5 and 10 years, we found four different trajectories of anxiety and depression symptoms (parent-report). Whereas most children showed low, stable levels of anxiety and depression, smaller groups of children showed either decreasing, increasing, or preschool-limited (i.e. increasing symptoms up to age 6, followed by a decrease between to age 10) trajectories of these symptoms. Furthermore, these smaller trajectories could be distinguished from both the low group and each other by both maternal and paternal psychopathology during pregnancy, maternal education, and child ethnicity. We also found that children in the increasing trajectory and preschool-limited trajectory had diminished psychosocial outcomes (i.e. lower self-esteem and diminished friendship quality) and worse school outcomes (i.e. lower school performance and more school problems) compared to the other trajectories. Thus, developmental trajectories of anxiety and depression symptoms across childhood can be predicted by family characteristics before birth and are associated with differences in daily functioning at 10 years. These findings can help to guide prevention policies that aim to reduce

clinical problems in children and underline that also sub-clinical levels of anxiety and depression are associated with suboptimal daily functioning in childhood.

In chapter 3 a systemic review of studies on social and academic functioning of adolescents with anxiety disorders is presented. In total, 14 studies were included that reported on different aspects of these two domains. Taken together, these studies showed that adolescents with anxiety disorders experience several problems with social functioning and to a lesser degree problems with academic functioning. Evidence was found for lower social competence, problems with interpersonal relationships, and victimization for adolescents with anxiety disorders compared to healthy peers. Although the results were most evident for adolescents with a social anxiety disorder, also other anxiety disorders were associated with problems with social functioning. In addition, adolescents with anxiety disorders experience problems at school (e.g. attending and concentrating), but we found no evidence for their actual academic performance being lower compared to their non-anxious peers. The results of our systematic review highlight the various ways in which anxiety disorders interfere with daily functioning for adolescents and emphasize the importance of incorporating these domains in clinical practice regarding both diagnosis and treatment.

Chapter 4 of this thesis aimed to estimate the age of onset (AOO) of anxiety disorders in general and subtypes of anxiety disorders by carrying out a systematic review and meta-analysis of studies that were conducted in samples from the general population. In total, 24 studies resulted in an average AOO of 21.3 years for anxiety disorders in general. Separation anxiety disorder, specific phobia, and social anxiety disorder had a mean onset before the age of 15. Agoraphobia, obsessive-compulsive disorder, post-traumatic stress disorder, panic disorder, and generalized anxiety disorder began, on average, between 21.1 and 34.9 years. We found no evidence for an earlier AOO for women compared to men. A prospective study design, the number of anxiety disorders assessed, and the developmental index of the study country were associated with an earlier AOO. The results of our meta-analysis partly confirm the findings of previous review studies on the AOO of anxiety disorders. In addition, we found that study design is an important characteristic to take into account when examining AOO. These findings provide vulnerability periods for the development of anxiety disorder subtypes that can be informative for prevention policies and could help to elucidate the pathogenesis of anxiety disorders.

Chapter 5 focuses on the familial aggregation of cognitive biases (i.e. attention bias and interpretation bias) in children and adolescents with anxiety disorders and their parents. contradicting results emerged from previous studies on the association of cognitive biases between parents and children in clinical samples. Also, the mechanisms by which cognitive biases between parents and children are transmitted are less well understood. We found that greater attention bias for mothers was associated with larger interpretation bias for children and adolescents with anxiety disorders (baseline sample ATTENTIO study, *n* = 55). Attention bias between mothers and children was not related and we found no association between cognitive biases between fathers and children. Neither lifetime maternal emotional disorders moderated nor maternal rearing styles (i.e. emotional warmth, rejection, and overprotection) mediated the association between cognitive biases in mothers and children. This study showed that cognitive biases between mothers and children may influence each other at different stages of information processing. Also, more specific behavioral interactions between mothers and children may explain the familial aggregation of cognitive biases instead of general rearing styles and lifetime maternal psychopathology.

Finally, chapter 6 of this thesis examined the efficacy of Attention Bias Modification (ABM) combined with Cognitive Behavioral Treatment (CBT) in a double-blinded RCT for children and adolescents with anxiety disorders. Previous studies showed contradicting results of the efficacy of ABM versus placebo Attention Control Condition and few studies examined the online delivery of ABM and its combined effect with CBT. The results of the ATTENTIO study (*n* = 55) revealed that both online ABM combined with CBT as well as ACC with CBT resulted in alleviated anxiety symptomatology after treatment and at 6-months follow-up. In addition, baseline attention bias and age did not moderate treatment effects. The ATTENTIO study contributes to the growing body of literature that questions the effectiveness of ABM for changing attention bias in children and adolescents with anxiety disorders. Future studies may further clarify which elements of ABM and ACC contribute to alleviating anxiety in children and adolescents, such as exposure or enhanced attentional control in participants. There needs to be a greater understanding of the effect and potential working mechanisms of ABM before the implementation of (online) ABM in clinical practice.

Samenvatting

Angststoornissen zijn de meest voorkomende psychische stoornissen bij kinderen en adolescenten en worden op latere leeftijd geassocieerd met nadelige effecten, waaronder andere psychiatrische stoornissen. Aangezien angststoornissen vaak voortduren van de kindertijd tot in de adolescentie en de volwassenheid, is het van zeer groot belang om angststoornissen in een vroeg stadium te herkennen. Eerdere studies hebben aangetoond dat symptomen van angst het dagelijks functioneren belemmeren. Een beter begrip van de gevolgen van angststoornissen bij kinderen en adolescenten kan een belangrijke bijdrage leveren aan diagnostisering en behandeling. Tevens is er in de afgelopen twee decennia toenemende aandacht voor de rol van informatieprocessen of cognitieve *biases* bij de overdracht, het aanhouden en de behandeling van angststoornissen bij kinderen bij adolescenten. Het eerste doel van dit proefschrift, besproken in deel I (hoofdstuk 2, 3 en 4), was om meer inzicht te verkrijgen in leeftijd-gerelateerde kenmerken van angststoornissen. Het tweede doel van dit proefschrift, behandeld in deel II (hoofdstuk 5 en 6) was om meer kennis te vergaren over de rol van cognitieve biases bij zowel de familiale aggregatie als de behandeling van angststoornissen bij kinderen en adolescenten. Dit deel van het proefschrift is gebaseerd op de resultaten van de ATTENTIO-studie, een multicenter gerandomiseerde gecontroleerde trial (RCT) waarbij kinderen en adolescenten met een angststoornis en hun ouder(s) hebben deelgenomen. Meer achtergrondinformatie over de doelstellingen van dit proefschrift wordt gegeven in hoofdstuk 1.

In hoofdstuk 2 beschreven wij verschillende patronen van angst- en depressiesymptomen in een steekproef uit de algemene Nederlandse bevolking (Generation R). In een grote steekproef van kinderen tussen 1,5 en 10 jaar oud (*n* = 7.499) vonden we vier verschillende trajecten angst- en depressiesymptomen (door ouders gerapporteerd). Terwijl de meeste kinderen lage, stabiele niveaus van angst en depressie lieten zien, vertoonden kleinere subgroepen afnemende, stijgende of verhoogde symptomen tijdens de kleuterleeftijd (een toename van symptomen tot de leeftijd van 6 jaar, gevolgd door een afname tot de leeftijd van 10 jaar). Psychopathologie tijdens de zwangerschap, van zowel de moeder als de vader, voorspelden de kleinere trajecten. Het opleidingsniveau van moeders en de etniciteit van het kind onderscheidden deze trajecten van de lage, stabiele groep en van elkaar. We hebben ook geconstateerd dat kinderen in het stijgende traject en kinderen met verhoogde symptomen tijdens de kleuterleeftijd lager scoorden op psychosociaal welbevinden (verminderd zelfvertrouwen en een lagere kwaliteit van vriendschappen) en slechtere schoolresultaten (slechtere schoolprestaties en meer

schoolproblemen) hadden in vergelijking met kinderen in de andere trajecten. Ontwikkelingstrajecten van angst- en depressiesymptomen gedurende de kindertijd kunnen dus voorspeld worden door familiekenmerken (voor de geboorte) en zijn geassocieerd met verschillen in het dagelijks functioneren op de leeftijd van 10 jaar. Deze bevindingen kunnen helpen bij preventiebeleid gericht op het verminderen van klinisch relevante angstproblemen bij kinderen en benadrukken dat ook subklinische niveaus van angst en depressie geassocieerd zijn met een verminderd dagelijks functioneren in de kindertijd.

In hoofdstuk 3 werd een overzicht gegeven van studies naar het sociaal en academisch functioneren van adolescenten met angststoornissen middels een systematisch review. In totaal werden er 14 studies meegenomen waarin verschillende aspecten van deze twee domeinen werden onderzocht. Tezamen toonden deze studies aan dat adolescenten met angststoornissen verschillende problemen ervaren op sociaal gebied en in mindere mate problemen hebben op academisch gebied. In vergelijking met leeftijdsgenoten zonder angst, hebben adolescenten met angststoornissen minder sociale vaardigheden, meer problemen met interpersoonlijke relaties en zijn zij vaker het slachtoffer van pesten. Hoewel de resultaten het duidelijkst waren voor adolescenten met een sociale angststoornis, waren ook andere typen angststoornissen geassocieerd met problemen op sociaal gebied. Voorts ervaren jongeren met angststoornissen problemen op school (bijvoorbeeld verzuim en concentratie), maar we vonden geen bewijs dat hun schoolprestaties daadwerkelijk lager waren in vergelijking met hun niet-angstige leeftijdsgenoten. De resultaten van onze systematische review belichten de verschillende manieren waarop angststoornissen het dagelijks functioneren van adolescenten belemmeren en benadrukken het belang van het overwegen van deze domeinen op sociaal en academisch gebied in de klinische praktijk met betrekking tot diagnostisering en behandeling.

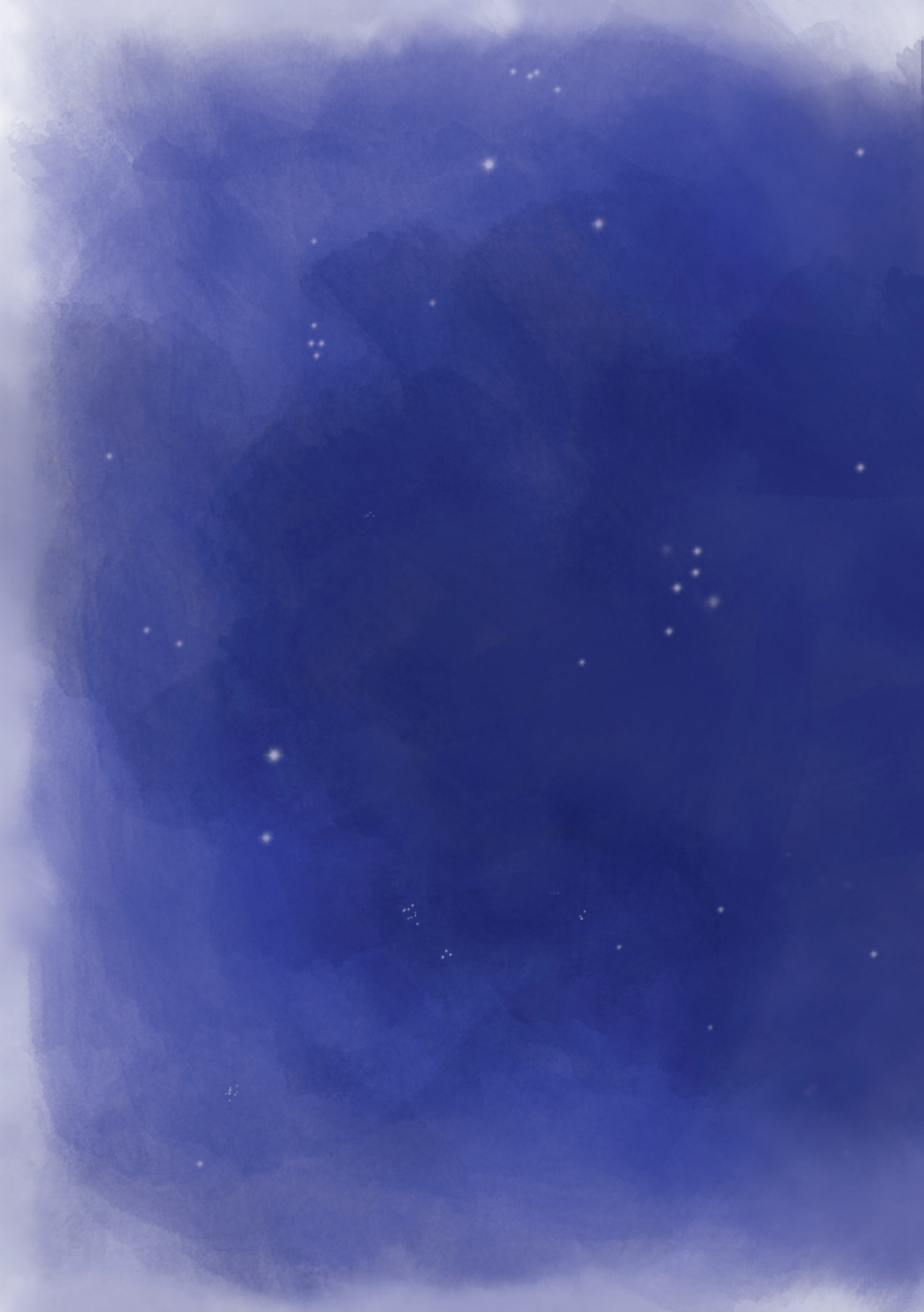
Hoofdstuk 4 van dit proefschrift beschreef een systematische review en meta-analyse van populatiestudies gericht op het schatten van de beginleeftijd van angststoornissen. De bevindingen van in totaal 24 studies resulteerden in een gemiddelde beginleeftijd van 21,3 jaar voor angststoornissen in het algemeen. Separatieangststoornis, specifieke fobie en sociale angststoornis hadden een gemiddelde beginleeftijd voor het 15^{e} levensjaar. Agorafobie, obsessief-compulsieve stoornis, posttraumatische stressstoornis, paniekstoornis en gegeneraliseerde angststoornis begonnen gemiddeld tussen 21,1 en 34,9 jaar. Wij vonden geen bewijs voor een vroegere beginleeftijd van angststoornissen voor vrouwen in vergelijking met mannen. Een prospectieve onderzoeksopzet, het aantal onderzochte angststoornissen en de ontwikkelings-

index van het land waar de studie werd uitgevoerd, werden geassocieerd met een vroegere beginleeftijd. De resultaten van onze meta-analyse bevestigen gedeeltelijk de bevindingen van eerdere overzichtsstudies over de beginleeftijd van angststoornissen. Daarnaast hebben we laten zien dat de opzet van een onderzoek van groot belang is waarmee rekening gehouden moet worden bij het bestuderen van de beginleeftijd van mentale stoornissen. De bevindingen suggereren dat preventiebeleid gericht zou moeten zijn op factoren die geassocieerd zijn met de ontwikkeling van subtypes van angststoornissen in de leeftijdsgroepen met de grootste gevoeligheid voor het ontwikkelen van die stoornissen.

Hoofdstuk 5 richtte zich op de familiale aggregatie van cognitieve biases bij kinderen en adolescenten met angststoornissen en hun ouders. Voorgaande studies in klinische steekproeven vonden tegenstrijdige resultaten met betrekking tot de associatie van cognitieve biases tussen ouders en kinderen. Tevens is er minder bekend over de mechanismen waardoor cognitieve biases tussen ouders en kinderen worden overgedragen. Wij vonden een positieve associatie tussen de aandachtbias bij moeders en interpretatiebias bij kinderen en adolescenten met angststoornissen (baseline-steekproef ATTENTIO-onderzoek, *n* = 55). Cognitieve biases tussen vaders en kinderen en aandachtbias tussen moeders en kinderen waren niet gerelateerd. Emotionele stoornissen van de moeder had geen modererend effect en moederlijke opvoedingsstijlen (emotionele warmte, afwijzing en overbescherming) van de moeder had geen mediërend effect in de associatie tussen cognitieve biases van moeders en kinderen. Deze studie toonde aan dat cognitieve biases van moeders en kinderen elkaar kunnen beïnvloeden in verschillende stadia van informatieprocessen. Daarnaast verwachten wij dat meer specifieke interacties tussen moeders en kinderen de familiale aggregatie van cognitieve biases verklaren in plaats van algemene opvoedingsstijlen en de (eerdere) aanwezigheid van psychopathologie bij moeders.

Tot slot werd in hoofdstuk 6 van dit proefschrift de effectiviteit van Aandacht Bias Modificatie (ABM) gecombineerd met Cognitieve Gedragstherapie (CGT) onderzocht in een RCT voor kinderen en adolescenten met angststoornissen. Eerdere studies hebben tegenstrijdige resultaten voortgebracht over de effectiviteit van ABM versus de placebo Aandacht Controle Conditie (ACC). Ook hebben slechts enkele studies de online toepassing van ABM en het gecombineerde effect van ABM met CGT onderzocht. De resultaten van de ATTENTIO-studie (n = 55) toonden aan dat zowel online ABM gecombineerd met CGT als ACC met CGT resulteerden in een vermindering van angstsymptomen na de behandeling en na een follow-up van 6 maanden. Bovendien vonden wij geen invloed van baseline AB en leeftijd op de behandelingseffecten.

De ATTENTIO-studie draagt bij aan de toenemende kennis over de effectiviteit van ABM bij het veranderen van aandachtbias bij kinderen en adolescenten met angststoornissen. In de toekomst dient te worden onderzocht welke elementen van ABM en ACC bijdragen aan het verminderen van angst bij kinderen en adolescenten, zoals blootstelling aan beangstigende stimuli (exposure) of door een verbeterde, algemene, controle van de aandacht bij deelnemers. Dit is een voorwaarde voor de implementatie van deze (online) behandeling in de klinische praktijk.



Appendices

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Publications

de Lijster, J. M., Dieleman, G. C., Utens, E. M. W. J., Dierckx, B., Wierenga, M., Verhulst, F. C., & Legerstee, J. S. (2018). Social and academic functioning in adolescents with anxiety disorders: A systematic review. *Journal of Affective Disorders, 230,* 108 – 117.

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de Lijster, J. M., Utens, E. M. W. J., Dieleman, G. C., Alexander, T. M., Hillegers, M. H. J., & Legerstee, J. S. (2019). Familial aggregation of cognitive biases for children with anxiety disorders. *Cognitive Therapy and Research, advance online publication.*

Legerstee, J. S., Dierckx, B, Utens, E. M. W. J., Verhulst, F. C., Zieldorff, C., Dieleman, G. C., & de Lijster, J. M. (2019). The age of onset of anxiety disorders. In G. de Girolamo, P. D. McGorry, & N. Sartorius (Eds.), *Age of Onset of Mental Disorders.* Cham, Switzerland: Springer.

About the author

Jasmijn de Lijster was born on July 3rd 1988, in Rotterdam, the Netherlands. In 2006, she finished pre-university education at the Farel College in Ridderkerk. With the completion of her Bachelor degree in Psychology at Tilburg University, she continued with a Research Master in the Social and Behavioral Sciences. She formalized her track Psychology and Health towards developmental psychology and graduated cum laude in 2012. After her graduation, she worked as an instructor at the Department of Developmental and Forensic Psychology of Tilburg University and as an assistant research associate at Yulius Academy. She started her PhD in September 2013 at the Department of Child and Adolescent Psychiatry/Psychology of the Erasmus MC Sophia Children's Hospital, under the supervision of prof. dr. F.C. Verhulst, prof. dr. M.H.J. Hillegers and dr. J.S. Legerstee which resulted in the work described in this thesis. This is part of the ATTENTIO study, a multicenter randomized controlled trial on the effect of Attention Bias Modification for children and adolescents with anxiety disorders. Participating mental health care centers were locations around Rotterdam from Lucertis and the Sophia Children's Hospital. Jasmijn was responsible for implementing and coordinating the study at these centers, the data-management, data analyses, and conducted all assessments with participating families. In addition, she worked as a psychologist at the outpatient clinic of the Department of Child and Adolescent Psychiatry/Psychology. As part of her PhD, she graduated from the Master Clinical Epidemiology, Netherlands Institute of Health Sciences in August 2016. In June 2018, she started working as a project manager for the European Commission funded Horizon2020 LifeCycle Project at Erasmus MC, Generation R. Her ambition is to continue her work in making an effort for children and adolescents with mental health problems as a psychologist and researcher.

PhD portfolio

Name PhD student:	J.M. de Lijster
Erasmus MC Department:	Child and Adolescent Psychiatry/psychology
Promotor(s):	Prof. dr. M.H.J. Hillegers
Supervisor(s)/co-promotor:	Dr. J.S. Legerstee
Research school:	Netherlands Institute for Health Sciences (NIHES)

1. PhD training	Year	Workload (ECTS)
General courses		
Master Health Sciences, specialization Clinical Epidemiology, NIHES Erasmus University Rotterdam, the Netherlands		
Introductory courses		
Principles of Research in Medicine (ESP01)	2014	0.7
Clinical Trials (ESP14)	2014	0.7
Methods of Public Health Research (ESP11)	2014	0.7
Fundamentals of Medical Decision Making (ESP70)	2014	0.7
The practice of Epidemiological Analysis (ESP65)	2014	0.7
Health Economics (ESP25)	2015	0.7
English language	Exemption	1.4
Introduction to Medical Writing	Exemption	1.1
Core courses		
Study Design (CC01)	2014	4.3
Biostatistical Methods I (CC02)	Exemption	5.7
Clinical Epidemiology (CE02)	2016	5.7
Methodologic Topics in Epidemiologic Research (EP02)	2014	1.4
Biostatistical Methods II (EP03)	2016	4.3
Courses for Quantitative Researcher (SC17)	Exemption	-
Advanced courses		
Health Services: Research and Practice (HS15)	2015	1.1
Maternal and Child Health (HS09)	2015	0.9
Causal Inference (ESP48)	2015	0.7
Psychiatric Epidemiology (EP12)	2015	1.1
Missing Values in Clinical Research (EP16)	2016	0.7
Causal mediation analysis (ESP69)	2016	0.7
Psychopharmacology (MP03)	2017	1.4
Advanced Topics in Clinical Research (EWP10)	2017	1.9
Repeated Measurements (CE08)	2017	1.4
Research		
Developmental Research Proposal	2016	2.5
Research period PIN Health Sciences	2017	28.7
Oral Research Presentation	2017	1.4

Research skills		
Patient Oriented Research (CPO): design, conduct and analysis, Erasmus MC, Rotterdam	2014	0.3
EndNote and PubMed (and other databases) courses, Erasmus MC, Rotterdam	2014	1.0
BROK (Good Clinical Practice), Erasmus MC, Rotterdam	2014	1.0
Scientific Integrity for PhD students, Erasmus MC, Rotterdam	2015	0.3
Biomedical English Writing and Communication, Erasmus MC, Rotterdam	2017	4.0

Clinical training		
Developmental, Dimensional and Diagnostic Interview (3Di) training, Yulius, Papendrecht	2015	0.3
'Psychotherapy of anxiety disorders', European Psychiatry Association, Madrid, Spain	2016	0.3
ADOS basic training, modules 1, 2, 3, and 4, Yulius, Barendrecht	2016	0.9

International conferences		
European Psychiatry Association, Madrid, Spain (presentation)	2016	0.9
European Society for Child and Adolescent Psychiatry, Genève, Switzerland (poster)	2017	0.9

Workshops, meetings and symposia		
Research meetings Child and Adolescent Psychiatry for PhD students, Erasmus MC, Rotterdam	2013 - 2018	3.6
Various presentations about the ATTENTION study and childhood anxiety disorders at primary schools, expert centers regarding educational services and participating research centers	2014 - 2016	3.6
Research colloquium Child and Adolescent Psychiatry (1 oral presentation)	2014 - 2018	0.3
Sophia Research Day, Erasmus MC, Rotterdam (1 oral presentation, award winning)	2016	0.3
Generation R research meetings, Erasmus MC, Rotterdam	2017	0.9
Training 'Netwerken helpt!', Career center, Erasmus MC, Rotterdam	2017	0.2
Seminar Major Milestones in child & adolescent psychiatry, Erasmus University, Rotterdam	2017	0.3
Seminar 'Het psychisch kwetsbare kind', Amsterdam Medical Centre, Amsterdam	2017	0.3
Symposium Vereniging Cognitieve en Gedragstherapie, Veldhoven (presentation)	2017	0.9
Career Guidance Programme, Promeras and Postdoc Network, Erasmus MC, Rotterdam	2017 - 2018	1.8
Postdoc Workshop 'Negotiation', Postdoc Network, Erasmus MC, Rotterdam	2018	0.2
Sophia Research Day, Erasmus MC, Rotterdam (1 oral presentation)	2019	0.3

2. Teaching

Supervising Master's Theses		
Inge van Hattem (Clinical Neuropsychology, Leiden University) *The exploration of associations between working memory capacity, cognitive inhibition and attention bias in clinically anxious children and adolescents*	2014 - 2015	3.0
Salwan Hassani (Master Medicine, Erasmus Medical Center) *Transmissie van angststoornissen van ouder op kind*	2014	3.0
Eline Tigges (Child- and Adolescent Psychology, Leiden University) *The association between attentional bias, interpretation bias and parental overprotection in clinically anxious youths*	2015	3.0
Yermilla Fitz-Jim (Child and Adolescent Psychology, Erasmus University) *Predictors of children's attentional bias and anxiety: the influence of parental attentional bias and psychopathology*	2015	3.0
Elle van der Kroon (Pedagogical Sciences, Erasmus University) *The influence of parental attention bias on the relation between parental rearing styles and child anxiety*	2015	3.0
Wijnand Dijkshoorn (Clinical Neuropsychology, Leiden University) *Exploring association between attention bias and interpretation bias with anxiety in clinically anxious youth: Evidence for the combined cognitive biases hypothesis*	2016	3.0
Esraa Marouf (Clinical Neuropsychology, Leiden University) *The relationship between attention bias and interpretation bias, parent's attention bias, and psychopathology in children with an anxiety disorder*	2017	3.0

Other teaching tasks		
Supervising research internship:		
Helene van Rest (Child- and Adolescent Psychology, Erasmus University)	2013 - 2014	2.0
Aleksandra Kubica (Child- and Adolescent Psychology, Leiden University)	2015 - 2016	2.0
Lyenne ten Holt (Clinical Neuropsychology, Leiden University)	2016 - 2017	2.0
Supervising and lecturing 2nd year medical students, Erasmus University, Rotterdam	2013 – 2018	3.0
Lecture Erasmus Master Pedagogical Sciences, University, Rotterdam	2014	0.1
Supervising workgroup 3rd year medical students, Erasmus University, Rotterdam	2014 - 2018	1.2

1 ECTS (European Credit Transfer System) is equal to a workload of 28 hours.

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Ik ben niet bang meer

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- naar Sneeuwwitje, Noord-Nederlands-Toneel