CHAPTER 1

General Introduction
“My daughter (9 years old) is very sensitive, she can’t handle it when I raise my voice. So she cries quickly, she is anxious, and scared sometimes, not really of me, but of what could come”. … “She senses me really perfectly, my mood. And she notices when I don’t feel good about myself, then she’s also rebellious”.

A mother (47), diagnosed with depression.

Anxiety and depression are mental problems that are highly prevalent and pose a huge burden on patients and their families. Children of parents with anxiety or depression are at high risk of developing these disorders as well. Starting point of this thesis (part I) was the challenge to design an intervention to prevent the development of anxiety and depression in children of patients with anxiety and depression, and to investigate its efficacy (the STERK study: Screening and Training: Enhancing Resilience in Kids). The focus of the STERK study was to screen offspring for increased high risk and to target specific modifiable risk factors in an individually tailored preventive intervention for high risk offspring. Additionally, parent perceptions regarding preventive activities for offspring of depressed and anxious patients were studied. Part II of this thesis will shed some light on offspring risk and protective factors for the development of anxiety and depression in childhood and adulthood. Finally, in part III, child and parent factors (such as parent and child temperament and parenting style), and their relation to negative and positive treatment outcome in childhood anxiety disorders will be examined.

In this introduction, I will argue the importance of prevention of anxiety and depressive disorders in offspring. In this light, anxiety and depressive disorder will be described, including their prevalence, characteristics, comorbidity, and burden of disease. Parental anxiety and depressive disorders as risk factor for anxiety and depression in offspring will be discussed, followed by an overview of studies evaluating preventive treatments for offspring. Additional risk factors for the development of anxiety and depression in offspring will be discussed, and clues for additional modifiable mechanisms of risk will be outlined. Furthermore, parent and child risk factors are discussed in light of their putative influence on treatment outcome in anxious children and adolescents. Finally, an outline of the chapters will be given.
BACKGROUND

ANXIETY AND DEPRESSIVE DISORDERS

Anxiety disorders and major depressive disorder are highly prevalent mental disorders that tend to be persistent and recurrent, often co-occur, and pose a huge burden on patients (de Graaf, Bijl, Smit, Vollebergh, & Spijker, 2002; de Graaf, ten Have, van Gool, & van Dorsselaer, 2012; Kessler, Avenevoli, & Merikangas, 2001; Kessler, Chiu, Demler, Merikangas, & Walters, 2005). Anxiety and depressive disorders are defined in the Diagnostic and Statistical Manual of Mental Disorders (DSM, current version DSM-5, American Psychiatric Association, 2013). Per chapter, it will be outlined which anxiety and depressive disorders are studied. Since the studies in this thesis were carried about before 2013, the fourth version of the DSM was used (DSM-IV-TR, American Psychiatric Association, 2000).

The term anxiety disorders in this thesis is an umbrella term including different anxiety disorders such as panic disorder, agoraphobia, generalized anxiety disorder, specific phobia, separation anxiety disorder, and social anxiety disorder. Anxiety disorders differ from developmentally normative fear or anxiety by being excessive and persisting beyond developmentally appropriate periods. They differ from transient fear or anxiety (which is often stress-induced) by being persistent, occurring more days than not for at least 6 months. In anxiety disorders, anxiety and worry are associated with physical symptoms such as restlessness, fatigue, irritability, muscle tension or sleep disturbances. People with an anxiety disorder are avoidant of feared objects or situations, which leads to clinically significant interference with daily functioning.

Depressive disorders in this thesis include major depressive disorder (including major depressive episode), and persistent depressive disorder (dysthymia). The common feature of all depressive disorders is the presence of depressive, sad, or empty mood, accompanied by somatic and cognitive changes that significantly affect the individual’s capacity to function. In children, mood can be irritable. People affected by depression lose interest in the activities they used to enjoy and can also be affected by physical symptoms such as disturbed sleep. In the DSM (2013), major depressive disorder is characterized by discrete episodes of at least 2 weeks’ duration (although most episodes last considerably longer) involving 5 or more of the following symptoms: depressed mood, loss of interest or pleasure, change in weight or appetite, insomnia or hypersomnia, observed psychomotor retardation or agitation, loss of energy or fatigue, worthlessness or guilt, impaired concentration or indecisiveness, thoughts of death or suicidal ideation or suicide attempt. A more chronic form of depression, persistent depressive disorder (dysthymia), can be diagnosed when the mood disturbance continues for at least 2 years in adults or 1 year in children.
Chapter 1

**Prevalence and persistence**

In the Netherlands, anxiety and depressive disorders are the most common mental disorders, with 19.6% of the adult population reporting anxiety disorders and 18.7% reporting major depressive disorder during their lifetime (de Graaf et al., 2012), with 12-month prevalence rates of 10.1% and 5.2%.

Most adult mental disorders have their onset in childhood or adolescence (Costello, Mustillo, Erkanli, Keeler, & Angold, 2003; Kim-Cohen et al., 2003). Also, anxiety and depressive disorders in childhood and adolescence often persist into adulthood (Kessler et al., 2001). Anxiety and depression are highly prevalent in children and adolescents. In the general population, anxiety (Bernstein, Borchartd, & Perwien, 1996) and depression (Birmaher, Ryan, Williamson, Brent, & Kaufman, 1996) are comparatively common, with 9.9% and 9.5% of children developing any anxiety disorder or depressive disorder before age 16 (Costello et al., 2003). In the Netherlands, among children ages 13-18, 6-month prevalence rates for any anxiety disorder are 23.5%, and for any mood disorder 7.2% (Verhulst, van der Ende, Ferdinand, & Kasius, 1997), with numbers being comparable to more recent and international findings (Kessler et al., 2012). Anxiety has an earlier age of onset (median age of onset: age 11 years), compared to depression (median age of onset: age 30 years; Kessler et al., 2005).

Subclinical symptoms of anxiety in children and adolescents are associated with lower levels of well-being (Muris, 2006), and early-onset anxiety disorders are powerful predictors of the subsequent onset and persistence of other mental disorders (Kessler, Ruscio, Shear, & Wittchen, 2010). Also, subsyndromal depression is a powerful predictor of subsequent onset of major depressive disorder (Angst, Sellaro, & Merikangas, 2000). Early onset anxiety and depression are often chronic and recurrent (Birmaher et al., 1996; Costello et al., 2003; Kessler et al., 2001).

**Comorbidity between anxiety and depressive disorders**

Research over the last few decades suggests considerable overlap among the various anxiety and depressive disorders (Kessler et al., 2005), which is already manifest in children (Costello et al., 2003; Essau, 2003). This overlap is seen most clearly diagnostically, as evidenced by high rates of current and lifetime comorbidity (Kessler et al., 2005). There is increasing evidence that anxiety not only precedes and heightens the risk for subsequent depression (Essau, Karpinski, Petermann, & Conradt, 1998), but also results in a poorer course and prognosis of this subsequent mood disorder (Stein et al., 2001). Comorbidity is furthermore characterized by an earlier onset, more recurrence, and greater use of health care services including medication (Moffitt et al., 2007).

Also, there is considerable etiological overlap between anxiety and depression, meaning that the development of both can be influenced by a wide range of risk factors including genetic liability, parental psychopathology and other family factors, parenting, gender, temperament, and childhood adversity (Alloy, Abramson, Smith, Gibb, & Neeren, 2006; Goodman & Gotlib, 1999; Murray, Creswell, & Cooper, 2009; Rapee, 2012). Moreover, (preventive) treatment for
depression has a significantly positive effect on anxiety and vice versa (Teubert & Pinquart, 2011; Weisz, McCarty, & Valeri, 2006). This last finding offers some support for the option to treat youth depression and anxiety with an intervention encompassing both emotional disorders (e.g., Barrett, Farrell, Ollendick, & Dadds, 2006; Farchione et al., 2012; Moses & Barlow, 2006).

**Burden of disease**

Burden of disease for both anxiety and depression is high. Among all mental health disorders, anxiety and depression represent the top 2 mental disorders with the most disability adjusted life years (DALYs) and also are the leading cause of years lived with disability (YLDs) worldwide (Whiteford et al., 2013). Anxiety and depression in adulthood are related to increased rates of unemployment, welfare assistance, lost productivity, and an extensive use of the health care system, resulting in extremely high economic health costs in adults (Greenberg et al., 1999; Rice & Miller, 1998).

In childhood, anxiety and depressive disorders are associated with a wide range of psychosocial impairments, like low self-esteem, social impairment, and poor academic achievement (Bernstein et al., 1996; Birmaher et al., 1996; Kessler et al., 2001; Rapee, Kennedy, Ingram, Edwards, & Sweeney, 2005; Weissman et al., 1999). When compared with healthy controls, children with anxiety or depression are at risk of increased use of long-term psychiatric and medical services (Weissman et al., 1999), leading to high societal costs (Bodden, Dirksen, & Bögels, 2008; Lynch & Clarke, 2006). If left untreated, childhood anxiety and depression are also associated with significant risk of other psychological disorders (in both childhood and adulthood; Birmaher et al., 1996; Kessler et al., 2001; Weissman et al., 1999).

**ANXIETY AND DEPRESSIVE DISORDERS IN FAMILIES**

Anxiety and depression run in families (for reviews see Hettema, Neale, & Kendler, 2001; Rice, Harold, & Thaper, 2002; Sullivan, Neale, & Kendler, 2000). In the Netherlands, 864,000 parents meet the diagnostic criteria for a DSM axis 1 mental disorder annually (Bool, van der Zanden, & Smit, 2007). These parents have 1,600,000 children under the age of 22 (38.5%), 900,000 of which are younger than 12 (35.6%), and over 400,000 are younger than 6 years of age (35.3%; Bool et al., 2007). Children of anxious and depressed parents are at 3-4 times greater risk of developing anxiety, depression, and other psychiatric disorders than children in the general population (see Figure 1.1; Hirshfeld-Becker et al., 2012; Lieb, Isensee, Höfler, Pfister, & Wittchen, 2002; Micco et al., 2009).

This means that while in the general population approximately 10% of children and adolescents develop an anxiety or depressive disorder before age 16 (Costello et al., 2003), up to 40% of children of depressed and anxious parents develop a depressive or anxiety disorder (Beardslee, Versage, & Gladstone, 1998; Hirshfeld-Becker et al., 2012; Micco et al., 2009;
In addition, offspring risk is diverse. Offspring of depressed or anxious parents are at risk for a number of different disorders. Children of anxious parents have greater risk for both anxiety and depressive disorders than children of healthy controls (ORs = 3.9, and 2.7 respectively; Micco et al., 2009). Children of depressed parents show an increased risk for depressive (OR = 4.0; Rice et al., 2002; OR = 3.3; Weissman et al., 2006) and anxiety disorders when compared with controls (OR = 2.9; Weissman et al., 2006).

Furthermore, these percentages increase even further when taking additional risk factors into account. For example, in a large sample of adolescent offspring of depressed parents, additional factors that put offspring at high risk of anxiety or depressive disorder were studied (de Vries et al., 2002). Three factors were found to be associated with increased risk: female gender, having two affected parents, and suicide attempt(s) of one of the parents. Risk of developing anxiety or depression before age 20 increased from 24% in offspring without additional risk factors up to 74% for those meeting two of three of the identified risk factors.

Figure 1.1. Rates of lifetime disorders at 10-year follow-up in offspring of parents with panic disorder or major depressive disorder or both, and in offspring of comparison parents (Hirshfeld-Becker et al., 2012)
Besides the substantial risk for psychopathology, offspring of depressed or anxious parents are also more likely to exhibit general difficulties in functioning, increased social impairment, increased guilt, and interpersonal difficulties, as well as attachment problems (Beardslee et al., 1998; Weissman et al., 2006). Parent depression or anxiety predict lower general assessment of functioning in offspring, both current and lifetime, greater risk for hospitalization, and lower academic achievements (Hirshfeld-Becker et al., 2012). Thus, offspring risk for both general and mental health problems is substantial.

**IN CONCLUSION**

The results summarized here document that anxiety and depression are highly prevalent, and comorbid mental disorders, that often have their onset in childhood or adolescence and tend to persist into adulthood. Anxiety and depressive disorders are associated with a wide range of psychosocial impairments and an extensive use of the health care system, resulting in extremely high economic health costs. In addition, offspring of depressed and anxious parents are at increased risk for developing these and other mental health disorders (Beidel & Turner, 1997; Hirshfeld-Becker et al., 2012; Micco et al., 2009). Therefore, research on the prevention of anxiety and depression in offspring is of the utmost importance.
PART I: PREVENTING ANXIETY AND DEPRESSION IN OFFSPRING

PREVENTION OF ANXIETY AND DEPRESSION

“There could be no wiser investment (in our country) than a commitment to foster the prevention of mental disorders and the promotion of mental health through rigorous research with the highest of methodological standards” (Mrazek & Haggerty, Institute of Medicine, 1994, p.483).

The last two decades, a variety of programs has been developed to prevent anxiety and depression in children and adolescents. Primary preventive interventions can be defined as either universal, selective, or indicated (see Table 1.1, Mrazek & Haggerty, 1994). Universal interventions target whole population groups, selective interventions involve individuals identified as at risk of anxiety and depression, and indicated interventions target individuals identified with mild to moderate symptoms of anxiety or depression.

The results of universal prevention programs (aimed at the general public without any predetermination of risk or vulnerability status, for example school programs) are disappointing for both anxiety and depression symptomatology (Horowitz & Garber, 2006; Sutton, 2007; Tak, Lichtwarck-Aschoff, Gillham, Zundert, & Engels, 2016; Teubert & Pinquart, 2011). Also, studies examining universal prevention are hardly feasible, as the number of subjects needed for sufficient power is very high (>10,000, Cuijpers, 2003).

The more promising longitudinal results have been found in studies of indicated prevention (targeting children or adolescents with elevated symptoms; e.g., Simon, Bögels, & Voncken, 2011; Sportel, de Hullu, de Jong, & Nauta, 2013) and selective prevention (targeting high risk groups who have not yet developed a mental disorder, e.g., offspring of depressed or anxious parents; for a review see Sutton, 2007). Combining indicated and selective prevention, for example by targeting offspring with elevated symptoms or additional risk factors, might even further increase statistical power and prevention efficacy (Cuijpers, 2003).

PREVENTION OF ANXIETY AND DEPRESSION IN OFFSPRING

Preventive interventions for anxiety and depression in offspring

Despite of the high risk in offspring of depressed and anxious parents, the number of randomized controlled trials testing the efficacy of selective and indicated prevention is very limited. To date, five randomized controlled prevention trials have specifically focused on preventing anxiety and depressive symptomatology in offspring of depressed or anxious parents (i.e., selective or indicated prevention; see Table 1.2). A recent systematic review and meta-analysis summarized the effectiveness of these (and other) preventive interventions (Siegenthaler, Munder, & Egger, 2012), and concluded that interventions to prevent mental disorders and psychological symptoms in the offspring of parents with a range of different mental disorders appear to be
effective. Of the 13 trials included, 6 studies examined the incidence in the child of the same mental disorder present in the parent, i.e., one study on opiate abuse and dependence (Haggerty, Skinner, Fleming, Gainey, & Catalano, 2008) and five studies on anxiety and depression (Beardslee, Wright, Gladstone, & Forbes, 2007; Clarke et al., 2001; Compas et al., 2009; Garber et al., 2009; Ginsburg, 2009). These 6 interventions decreased the risk of developing a mental disorder by 40% (combined relative risk 0.60, 95% CI 0.45-0.79, \( p = .001 \)). The relative risk of the five RCTs specifically examining the incidence of anxiety or depressive disorders in children of parents with anxiety or depressive disorders, as calculated by Siegenthaler et al. (2012), is displayed in Table 1.2. Summarizing, the results seem positive, with room for improvement: the risk of developing the same anxiety or depressive disorder as the parent was decreased by 41% (combined relative risk = 0.59).

Early detection of anxiety and depression in offspring seems to be crucial, as this would allow the treatment of early manifestations of symptoms before they cause clinical impairment. Additionally, screening for additional risk factors that put offspring at increased risk would allow for targeting specific risk factors in preventive treatment, increasing treatment efficacy. Only two of the five studies in Table 1.2 have conducted such a combined indicated and selective prevention trial, by targeting offspring (selective prevention) at increased risk of depression by screening for history of depression or subsyndromal depressive symptoms (indicated prevention; Table 1.1. Classification of preventive interventions for mental health problems and mental disorders

<table>
<thead>
<tr>
<th>Prevention</th>
<th>Aimed at the general public without any predetermination of risk or vulnerability status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selective prevention</td>
<td>Intended for groups with a higher risk of developing a disorder than the general population at large</td>
</tr>
<tr>
<td>Indicated prevention</td>
<td>Targeted towards individuals who are developing early signs and symptoms of a disorder</td>
</tr>
</tbody>
</table>

Source: Adapted from Mrazek and Haggerty (1994).

Table 1.2. RCT’s studying the prevention of anxiety or depression in offspring of depressed or anxious parents: Effectiveness.

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Prevention</th>
<th>Relative Risk (95% CI)</th>
<th>Follow-up time (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beardslee et al.</td>
<td>1997, 2003, 2007</td>
<td>Selective</td>
<td>0.68 (0.28-1.67)</td>
<td>4.5</td>
</tr>
<tr>
<td>Clarke et al.</td>
<td>2001</td>
<td>Selective and indicated</td>
<td>0.36 (0.13-1.04)</td>
<td>1</td>
</tr>
<tr>
<td>Compas et al.</td>
<td>2009, 2010</td>
<td>Selective</td>
<td>0.43 (0.16-1.17)</td>
<td>1</td>
</tr>
<tr>
<td>Garber et al.</td>
<td>2009</td>
<td>Selective and indicated</td>
<td>0.66 (0.45-0.96)</td>
<td>0.5</td>
</tr>
<tr>
<td>Ginsburg</td>
<td>2009</td>
<td>Selective</td>
<td>0.08 (0.45-0.79)</td>
<td>1</td>
</tr>
</tbody>
</table>

Source: Adapted from Siegenthaler et al. (2012).
<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Preven-</th>
<th>Parental disorder</th>
<th>Child age</th>
<th>Child inclusion</th>
<th>Intervention</th>
<th>Intervention format</th>
<th>Intervention strategies</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Beardslee, Gladstone, Wright, &amp; Cooper, 2003; Beardslee et al., 2007)</td>
<td>138</td>
<td>S</td>
<td>At least 1 episode of mood disorder in the 18 months before contact</td>
<td>8-15, $M = 11.6$</td>
<td>Never diagnosed with or treated for a mood disorder</td>
<td>Random assignment to either 2 informational lectures or a 6-11 sessions clinician facilitated intervention, including separate meetings with parents and children, and a family meeting</td>
<td>Family</td>
<td>(1) Assessing all family members, (2) presenting psychoeducational material about mood disorders and about risk and resilience in children, (3) linking the psychoeducational material to the family’s life experiences (4) decreasing feelings of guilt and blame in children, (5) helping the children to develop relationships both within and outside of the family to facilitate their independent functioning</td>
</tr>
<tr>
<td>(Clarke et al., 2001)</td>
<td>94</td>
<td>S&amp;I</td>
<td>Current episode of major depression and/or dysthymia, or an episode in the past 12 months</td>
<td>13-18, $M = 14.6$</td>
<td>Subclinical depressive symptoms or history of depression</td>
<td>Randomly assigned to either an abbreviated version of the adolescent depression treatment program Coping with Stress, with 15 one-hour group sessions and 3 parent sessions, or usual HMO care</td>
<td>Adolescent group</td>
<td>Teaching of cognitive restructuring techniques to identify and challenge irrational unrealistic or overly negative thoughts, with special focus on having a depressed parent. Parents were only informed about the program.</td>
</tr>
<tr>
<td>(Compas et al., 2009; Compas et al., 2010)</td>
<td>155</td>
<td>S</td>
<td>Current or past (but during lifetime of the child) major depressive disorder</td>
<td>9-15, $M = 11.5$</td>
<td>No anxiety or depression related exclusion criteria</td>
<td>Randomly assigned to either a 12 session cognitive behavioral preventive intervention, with 8 weekly and 4 monthly sessions, or a self-study written information condition</td>
<td>Family group</td>
<td>Providing information/education and teaching cognitive-behavioral skills to parents and children: focus on stressful parent-child interactions (focus on effective parenting, with focus on warmth and structure) and on the way children cope</td>
</tr>
<tr>
<td>(Garber et al., 2009)</td>
<td>316</td>
<td>S&amp;I</td>
<td>Current or prior depression</td>
<td>13-17, $M = 14.8$</td>
<td>Subclinical depressive symptoms or history of depression</td>
<td>Randomization to an adolescent cognitive behavioral prevention program (modification of Clarke et al., 2001), with 8 weekly 90 minute sessions and 6 monthly group sessions, or to usual care</td>
<td>Adolescent group</td>
<td>Adolescents were taught cognitive restructuring techniques to identify and challenge unrealistic and overly negative thoughts and problem-solving skills (Coping with depression), teaching new skills like behavioral activation, relaxation and assertiveness</td>
</tr>
<tr>
<td>(Ginsburg, 2009)</td>
<td>40</td>
<td>S</td>
<td>Current or lifetime diagnosis of an anxiety disorder</td>
<td>7-12, $M = 8.94$</td>
<td>No presence of an anxiety disorder</td>
<td>Random assignment to either a cognitive behavioral intervention (the Coping and Promoting Strengths program), 6-8 weekly 60 minute sessions and 3 monthly booster sessions or a waitlist control condition</td>
<td>Family</td>
<td>Focusing on child risk factors: anxiety management, cognitive restructuring, problem-solving skills and on parent/family factors: anxiety management, contingency management, communication &amp; problem-solving skills</td>
</tr>
</tbody>
</table>
None of the studies intended to target offspring at high risk by screening for additional risk factors.

Also, although anxiety and depression are highly comorbid, prevention studies to date have been designed to prevent either anxiety or depression (see Table 1.3). Furthermore, most prevention interventions were group-based, whereas individual programs allow for more tailoring to specific needs. Many prevention programs have mainly focused on symptom reduction. However, building resilience and targeting multiple risk and protective factors in a preventive intervention might also be very important.

Therefore, the STERK study (Screening and Training: Enhancing Resilience in Kids) was designed as a combined selective and indicated randomized controlled prevention trial aimed at targeting both anxiety and depression (see Chapter 2). To enhance treatment impact, an ultra high risk group of offspring participants was selected using additional risk factors (see paragraph ‘anxiety and depressive disorders in families’). The STERK study furthermore adds to existing studies by including mediators and moderators of change in the assessments, and studying cost-effectiveness.

The STERK intervention was designed as an individually tailored, behavioral preventive training, aimed at increasing strengths and resilience by targeting modifiable risk and protective factors that were hypothesized to decrease the risk of developing anxiety and depression in offspring. The intervention encompassed 10 individual child sessions and 2 parent sessions, including multiple intervention components, each of which addressed risk and protective factors across different domains (Garber, 2006). The intervention was designed to reduce symptoms of anxiety and depression by increasing behavioral activation (Dimidjian, Martell, Addis, & Herman-Dunn, 2008) and increasing exposure to feared stimuli and situations (Nauta & Scholing, 1997). Furthermore, the intervention focused on increasing offspring strengths, resilience and optimism by building support networks (Beardslee, Versage, Salt, & Wright, 1999), increasing active coping and problem solving skills (Compas et al., 2009; Jaser et al., 2005; Jaser et al., 2007), increasing self-understanding (Beardslee & Podorefsky, 1988), focusing on positive feelings and activities, and enhancing parent-offspring communication and shared understanding of parent psychopathology (Beardslee et al., 1999). The study was designed to contribute to the knowledge on risk and protective factors influencing the intergenerational transmission of risk, by studying parent and offspring mediators and moderators of change, like optimism, coping, self-esteem, and implicit associations.

**Parent perspectives on offspring prevention**

Numerous challenges were encountered during the process of conducting the STERK study. As evident in Table 1.4, the few other research groups that attempted to recruit families with a depressed or anxious parent to participate in a randomized controlled prevention trial for offspring encountered recruitment difficulties and high dropout rates. For example, in the
sample used by Clarke et al. (2001), the 94 adolescent offspring (aged 13-18) of adults treated for depression were derived from an initial sample of nearly 3000 parents and 3400 youth, with 2250 families actively declining participation (others did not meet inclusion criteria). While the preventive intervention was found to be effective (Clarke et al., 2001), the reasons why families seemed so reluctant to participate remained unclear.

For the STERK study, recruitment difficulties, such as parents declining participation, prevented completion of the original project (see Chapter 3). In order to unravel parents’ reasons for declining participation, a qualitative approach was chosen to investigate parents’ perceptions on offspring risk and need for prevention. Qualitative research methods are suitable for exploring actual experiences and perceptions. These methods give space to peoples stories without being narrowed down by specific hypotheses of the researcher, and without being led by questionnaires and predefined items. Also, they are especially helpful when little is known about the researched phenomenon.

### Table 1.4. RCTs studying the prevention of anxiety or depression in offspring of depressed or anxious parents: Recruitment of participants

<table>
<thead>
<tr>
<th>Study</th>
<th>Families contacted</th>
<th>Families screened at baseline</th>
<th>Children enrolled</th>
<th>Recruited via</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beardslee et al.</td>
<td>Not described</td>
<td>Unknown</td>
<td>138 (105 families, 190 parents)</td>
<td>HMO(^1) + referral from mental health practitioners</td>
</tr>
<tr>
<td>2003, 2007</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clarke et al., 2001</td>
<td>2995 (i.e., 3374 children)</td>
<td>481</td>
<td>94</td>
<td>HMO computerized pharmacy database</td>
</tr>
<tr>
<td>Compas et al.,</td>
<td>574</td>
<td>309</td>
<td>155 (111 parents)</td>
<td>Recruitment through several sources, including mental health clinics, family and general medical practices, and media outlets</td>
</tr>
<tr>
<td>2009, 2010</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Garber et al.,</td>
<td>2494</td>
<td>393 (442 adolescents)</td>
<td>316</td>
<td>Inclusion through several sources including an HMO computerized database, a university medical center email listserv, letters to physicians in the community, letters to parents of students in local schools, and newspaper, radio and television advertisements</td>
</tr>
<tr>
<td>2009</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ginsburg, 2009</td>
<td>Not described</td>
<td>51</td>
<td>40</td>
<td>Advertisements, mailings to local physicians and psychiatrists, community flyers</td>
</tr>
</tbody>
</table>

\(^1\) A Health Maintenance Organization (HMO) is an organization that provides or arranges managed care in the United States.
The qualitative study described in Chapter 3 intended to answer five questions: What are parents’ experiences regarding (1) their own depressive and anxiety disorders and their children’s vulnerability and resilience, (2) their own depressive and anxiety disorders and parenting, (3) help for offspring mental problems, and preventive interventions for their children, (4) participating in randomized controlled trials? Furthermore, (5) we intended to shed light on parents’ reasons for (not) participating in a preventive randomized controlled trial with their children.

In addition, mental health care professionals working in child and adult psychiatry were asked about the health care services provided for offspring of depressed or anxious parents. In Chapter 4, professionals’ experiences with patients who are parents, and the need for and barriers to offspring preventive care are discussed. Focus groups were conducted to obtain insight into professionals’ experiences with offspring of patients with anxiety and depression, and the role of adult and child mental health centers with regard to providing (preventive) care for offspring.

PART II: RISK AND RESILIENCE

RISK AND PROTECTIVE FACTORS

A risk factor is any condition or circumstance that increases the likelihood that psychopathology will develop. Not all children who are at risk become anxious or depressed. Factors that promote or maintain healthy development are called protective factors. The list of potential risk and protective factors for the development of anxiety and depressive disorders is extensive and spans different contexts (i.e., family, individual, and environmental; Kerig, Ludlow, & Wenar, 2012).

Reviews investigating the intergenerational transmission of risk of anxiety and depression have described a wide variety of factors in order to gain a better understanding of the risks to children of parents with anxiety or depression (Beardslee, Gladstone, & O’Connor, 2011; Goodman & Gotlib, 1999; Goodman & Gotlib, 2002; Murray et al., 2009). Summarizing these reviews, in a family context, risk for anxiety or depression may involve heritability, the course, timing and recurrence of the parental disorder, (inadequate) parenting styles, modelling, and parent-child communication. In the individual context, child risk and protective factors may include gender, dysfunctional neuroregulatory mechanisms in infancy, temperament, information processing biases, and maladaptive cognitive styles. In the environmental context, stressful life events, bullying, and exposure to negative information may present a risk, whereas adequate social support may be a protective factor.

Risk and protective factors can be divided into modifiable and non-modifiable factors. Non-modifiable risk factors, such as gender or heritability, can be used for screening for high risk. Modifiable risk factors related to the development of anxiety and depression in offspring are important since specifically targeting these factors may increase effectiveness of (preventive) interventions.
Chapter 1

**INTERGENERATIONAL TRANSMISSION OF RISK**

In this thesis, we focus on factors associated with anxiety and depression in adults and tested whether these factors already exist in childhood. Would that be the case, then prevention can focus on these factors in childhood, decreasing offspring risk. The focus of *Chapter 5* is on the potential impact of being exposed to maladaptive parental behavior as reflected in perceived emotional maltreatment in childhood and negative offspring self-associations. Whether these factors were potentially mediating in the intergenerational transmission of risk will be investigated.

Furthermore, a considerable number of children of depressed or anxious parents do not develop a disorder, which indicates that parental psychopathology alone does not adequately explain the problem. A complex variety of risk and protective factors is involved. In the models proposed in reviews mentioned previously, thus far, putative protective factors have received relatively little attention. In *Chapter 6*, optimism and positive self-associations are examined in relation to anxiety and depression in children growing up with and without a depressed or anxious parent.

**Implicit positive and negative self-associations**

Cognitive theorists and researchers suggest that cognitive vulnerability develops in childhood, primarily via children’s negative interactions with their parents (Abramson & Alloy, 2006; Ingram, 2003; Ingram, Miranda, & Segal, 2006), and that negative beliefs play an important role in the development and maintenance of anxiety and depression (Beck, 1976; Beck, 2005; Kendall, 1985). Current dual system models emphasize the importance of differentiating between more deliberate, ‘explicit’ beliefs versus more automatically activated, ‘implicit’ associations (Gawronski & Bodenhausen, 2006). Implicit associations are hypothesized to be evaluations about ourselves and our environment that are formed in childhood. They are hypothesized to be more stable and less easy to change than explicit beliefs. The development of negative and positive implicit associations is thought to stem from long-term socialization processes and to precede the development of more explicit beliefs (e.g., Petty, Tormala, Briñol, & Jarvis, 2006; Wilson, Lindsey, & Schooler, 2000). Positive early experiences, e.g., resulting from growing up in a positive rearing environment, can be hypothesized to result in stronger positive affective self-associations. However, negative early experiences (for example emotional maltreatment in childhood) could contribute to the development of stronger negative affective self-associations.

Therefore, in this thesis, the question will be answered whether negative childhood experiences (i.e., perceived childhood emotional maltreatment) are related to the development of negative self-associations in offspring, and if this pathway can account for the intergenerational transmission of risk (*Chapter 5*). Furthermore, it will be examined whether children from parents with anxiety or depression are characterized by weaker positive (happy, calm) and stronger
negative (sad, anxious) affective self-associations than children from parents without anxiety or depression (Chapter 6).

**Childhood emotional maltreatment**

Childhood emotional maltreatment is the most frequent form of maltreatment experienced by children and adolescents (Kaplan, Pelcovitz, & Labruna, 1999; Stoltenborgh, Bakermans-Kranenburg, Alink, & van IJzendoorn, 2012; Stoltenborgh, Bakermans-Kranenburg, & van IJzendoorn, 2013). It involves acts of commission, such as degrading, terrorizing, belittling, blaming, and exploiting (which is known as psychological abuse), and/or acts of omission, such as isolation, rejection, and denying emotional responsiveness (which is known as emotional neglect). Emotional maltreatment by parents is harmful to the child’s emotional development, making the child feel worthless, unloved and unwanted (Binggeli, Hart, & Brassard, 2001; Egeland, 2009; Hornor, 2012). For similar definitions, see the American Professional Society on the Abuse of Children (APSAC).

Depressed and anxious parents are likely to expose their children to more negative cognitions, affect, and behaviors than do parents without psychopathology (for reviews see Beardslee et al., 1998; Downey & Coyne, 1990; Goodman & Gotlib, 1999). Additionally, anxious and depressed parents are hypothesized to have more difficulties meeting the child’s social and emotional needs (Goodman & Gotlib, 1999). For example, a loss of interest or pleasure in daily activities and fatigue or loss of energy are symptoms of depression that could make parental rearing more withdrawn and less consistent, while hostility and irritability symptoms of depression may result in a more critical parenting style with less positive interaction (Downey & Coyne, 1990). In Chapter 5, we hypothesize that especially when parental disorder leads to child perceived negative experiences, this will put offspring at increased risk of anxiety and depression.

**Optimism and pessimism**

Optimism and pessimism can be defined as a set of generally positive or negative expectations about the future (Scheier & Carver, 1985; Scheier, Carver, & Bridges, 1994). It appears that people who dispositionally hold positive expectations about the future respond to difficulty and adversity in more adaptive ways than people who hold negative expectations (Carver, Scheier, & Segerstrom, 2010). Expectancies influence how people approach both stressors and opportunities, and they influence the success with which people deal with them. In children, optimism has been linked to self-reported competence and hopefulness, and with more overall positive attributions about possible events (Ey et al., 2005). Furthermore, children’s reports of optimism at the beginning of the school year have been associated with fewer depressive symptoms three months later. By contrast, children’s reports of pessimism were related to an increase in anxiety symptoms (Ey et al., 2005). Optimism might serve as a protective factor in offspring of depressed or anxious parents, while pessimism could put children at increased risk.
In Chapter 6, it will be examined if explicit reports of optimism and pessimism differentiate between children with and without parents with anxiety or depression. Furthermore, whether optimism and pessimism are related to implicit negative and positive affective self-associations, and anxiety and depressive symptoms will be explored.

PART III: CHILD TREATMENT AND PARENT FACTORS

THE ROLE OF PARENTS IN THEIR CHILDREN’S TREATMENT SUCCESS

Once children have developed an anxiety or mood disorder, treatment options are ample. From an evidence-based perspective, child focused cognitive behavioral therapy (CBT) is currently the treatment of choice for both anxiety and depressive disorders in children and adolescence (for a review see Compton et al., 2004). Given the high comorbidity and etiological commonalities, some researchers have proposed a unified treatment for anxiety and depressive symptoms (Barlow, 2004). However, since anxiety commonly precedes depression, anxiety has an earlier age of onset than depression, making anxiety disorders more prevalent in younger children.

CBT for anxiety in children and adolescents is an effective treatment in 49-79% of cases (95% CI) in terms of symptom reduction and diagnostic recovery rates (Reynolds, Wilson, Austin, & Hooper, 2012; Silverman, Pina, & Viswesvaran, 2008). This means that large amounts of children still do not benefit sufficiently from the treatments currently offered in mental health care.

Treatment benefits proved rather robust across characteristics of treated youths (age, gender) and across variations in the format (e.g., group and individual treatment, with or without parental involvement; Silverman et al., 2008). However, there may be other characteristics that can be influenced to enhance treatment outcome. There is a need for identifying predictors of treatment outcome, which can be targeted by adapting treatment to putative predictors in order to enhance treatment outcome. Given the fact that child and parent factors, such as temperament and parenting, are important in the development and maintenance of symptomatology and disorders (for a review see Degnan, Almas, & Fox, 2010), in this thesis we will investigate role of parent temperament, parenting, and child temperament, in children’s treatment success or failure (Chapter 7).

Parent temperament

Although parent factors are related to the development and maintenance of anxiety disorder in children, there is little research on the role of parents in child treatment outcome. In general, parental involvement in child individual or group treatment does not influence effectivity (Silverman et al., 2008). However, there is ample evidence that parent anxiety and depression negatively affect children’s treatment outcome (Berman, Weems, Silverman, & Kurtines, 2000;
Hudson et al., 2015; Liber et al., 2008; Rapee, 2000; Southam-Gerow, Kendall, & Weersing, 2001).

Whether more stable temperament traits have a similar adverse effect on treatment has not yet been investigated. Temperament is reflected in stable individual differences in reactivity and self-regulation, which respectively encompass emotionally driven responses to change in the environment (such as negative affect and extraversion), and modulation of these responses (such as effortful control; Rothbart & Derryberry, 1981).

Some parent temperament traits can be hypothesized to obstruct the way to effective treatment, while others may facilitate treatment success. In Chapter 7 it is hypothesized that high parental negative affect, i.e., parents displaying a proneness to sadness, fear, frustration, or anxiety, has a negative effect on child treatment outcome, whereas effortful control and extraversion are hypothesized to increase the effectiveness of child CBT for anxiety.

Parenting style
Parenting styles (i.e., over-involve, rejection, emotional warmth) have been extensively studied as a factor in the development and maintenance of anxiety disorders in children, resulting in overall modest associations (McLeod, Weisz, & Wood, 2007). However, parenting may especially be of influence when trying to change children's anxious thoughts and behaviors in treatment. Empirical studies have already found that maternal over-involve and paternal rejection were related to a less favorable treatment outcome in anxious children and adolescents (Creswell, Willetts, Murray, Singhal, & Cooper, 2008; Liber et al., 2008).

However, parenting can also be hypothesized to positively influence children's treatment outcome. A parent high in emotional warmth, for example, could provide the safe environment a child needs when practicing new behaviors and approach fear-evoking situations in treatment.

Child temperament
Elucidating the role of individual differences in children's response to treatment may help understand pathways to effective treatment. Child temperament has been related to increased risk of developing anxiety disorders (e.g., Nigg, 2006). However, if these stable traits also play a role in children's treatment success has not yet been studied.

Child temperament characteristics can pose as a risk or protective factor for treatment success. Children with increased levels of extraversion are less likely to develop internalizing problems (Ormel et al., 2005). Child negative affect is characterized by fear and shyness, with stronger core beliefs about threat, which may make cognitive restructuring in CBT a harder and more time consuming process. Children's ability to self-regulate emotions, attention and behaviors on the other hand (i.e., effortful control) may facilitate children's ability to change their cognitions and (avoidant) behaviors.
In sum

In Chapter 7, parent and child temperament and parenting styles are studied, which can promote risk or resilience, as predictors of treatment success and failure. Possible venues for tailoring anxiety interventions to increase effectiveness will be discussed.

OUTLINE OF THIS THESIS

In the following chapters, five studies will be described concerning parent and offspring anxiety and depression, more specifically: (i) the prevention of anxiety and depression in offspring of depressed and anxious patients; (ii) perceptions of parents regarding offspring risk and prevention; (iii) putative risk factors and pathways underlying the intergenerational transmission of risk; and (iv) factors that might influence child anxiety treatment outcome.

In Chapter 2, the STERK study will be described in detail. The procedures regarding referral, recruitment, and screening are outlined. The assessments and the preventive intervention are described and supported with evidence. While conducting the study, we encountered numerous recruitment challenges. In order to get more insight into these recruitment problems, a qualitative approach was chosen to investigate parents’ and professionals’ perceptions on offspring risk and the need for offspring prevention (Chapter 3 and Chapter 4).

In Chapter 5, it will be examined whether childhood emotional maltreatment increases offspring implicit negative self-associations and whether these factors together mediate the relationship between parent and offspring psychopathology. Serial mediation analyses were used to investigate whether parent psychopathology increases offspring perceived emotional maltreatment, which might strengthen offspring implicit negative self-associations, influencing offspring psychopathology. Additionally, we will investigate whether this proposed pathway from parent disorder via emotional maltreatment and implicit self-associations to offspring anxiety and depression is more pronounced when both parents have anxiety or depressive disorders (instead of one parent).

Chapter 6 examined underlying processes related to the intergenerational transmission of risk for anxiety and depression by investigating if high risk offspring are already at an early age characterized by a more pessimistic view of the future and stronger negative implicit self-associations and if already in childhood these associations are related to increased levels of anxiety and depression symptomatology. It will be tested whether high risk offspring report higher pessimism and lower optimism scores, stronger negative self-anxious and self-depressed associations, and weaker associations between self and positive feelings than low risk youth.

Chapter 7 examined if specific parent and child factors influence the outcome of child CBT for anxiety disorders. Finally, in Chapter 8 the results will be summarized and integrated. This final chapter will also discuss some important remaining issues that call for future research and closes with addressing the implications for clinical practice.
PART I

Preventing anxiety and depression in offspring