Chapter 1

Introduction
Depression and anxiety

Depression and anxiety, also referred to as emotional disorders, are common psychiatric problems. The life-time prevalence of diagnosed depression and anxiety disorders (DSM-IV) ranges from 4.6% to 20.8% for depressive disorders (Andrade et al., 2003; Bijl, Ravelli, & Van Zessen, 1998; Kessler et al., 2005; Ormel & Sytema, 1999) and from 10.5% to 28.8% for anxiety disorders (Alonso et al., 2003; Bijl, Ravelli, & Van Zessen, 1998; Kessler et al., 2005). In addition, many individuals report “sub-clinical” depressive and anxiety problems which do not meet DSM-IV criteria but cause suffering none the less (e.g., Kessler et al., 1994, 1997; Roberts et al., 1990). Depression is characterised by depressed mood or loss of interest or pleasure in nearly all activities (e.g., Zahn-Waxler et al., 2006). In addition, depression includes vegetative symptoms (e.g., changes in appetite or weight), cognitive symptoms (e.g., difficulty thinking and concentrating) and/or emotional symptoms (e.g., feelings of worthlessness or guilt). Anxiety is characterised by a sense of apprehension toward the future, continual attentiveness of signs of potential threat and a constant state of preparation and readiness to cope with potential dangers. In order to ward off anxiety, individuals can develop and pursue self-defeating behaviours, for example worry, thought suppression or behavioural avoidance (Barlow, 2000, 2002).

Many individuals with a life-time diagnosis of anxiety or depression experienced their first episodes during respectively late childhood or adolescence and late adolescence or young adulthood (Costello et al., 2003; Kim-Cohen et al., 2003; Lewinsohn et al., 2000; McGee et al., 1992). Depression in childhood is rare with a prevalence of 1%-3% (Cohen et al., 1993; Costello et al., 1996). In adolescence the prevalence of depression increases sharply to near-adult prevalence levels (Kessler, Avenevoli, & Merikangas, 2001; Lewinsohn, Rohde, & Seeley, 1998). Childhood anxiety disorder is more common than childhood depression and, with prevalence rates between 3.5% and 23.9%, almost as common as anxiety disorders in adulthood (Cartwright-Hatton, McNicol, & Doubleday, 2006). From childhood on anxiety disorder is more common in women than in men, while depression becomes more prevalent in women in adolescence (e.g., Hankin & Abramson, 1999; Lewinsohn, Rohde, & Seeley, 1998; Williams et al., 2005).

Etiology of depression and anxiety

Depression and anxiety are so-called multifactorial problems. The probability of developing these problems is influenced by a wide range of risk factors including genetic liability, neurophysiological dysfunctions, predisposing temperament or personality traits,
adverse childhood circumstances, limited interpersonal resources, long-term difficulties and traumatic events (e.g., Brown & Harris, 1978; Goodman & Gotlib, 1999; Hankin & Abela, 2005; Ornel & Neeleman, 2000; Williams et al., 2005). Since about twice as many women than men suffer from depression and anxiety problems, the female gender is often considered a risk factor for depression and anxiety as well.

Current knowledge indicates that the presence or occurrence of any given risk factor in itself is not sufficient to lead to psychiatric disorders such as depression and anxiety, instead the onset of these problems seems to require a combination of several risk factors (Rothman & Greenland, 1998). Risk factors seem to cluster (Bifulco, Moran, & Ball, 2002; Goodyer et al., 1993; Menard, Bandeen-Roche & Chilcoat, 2004; Walsh, MacMillan, & Prescott, 2002), such that, for example, environmental risk factors are more prevalent among those with a higher genetic liability. Besides increasing risk of depression and anxiety by adding to each others effects, risk factors affect each other in such a way that some risk factors mediate or moderate the effect of other risk factors (e.g., Goodman & Gotlib, 1999; Kendler et al., 2002). An example of mediation is that a genetic predisposition to depression and anxiety is thought to operate through the shaping of neurophysiological functions and subsequently the (interpersonal) environment (e.g., Goodman & Gotlib, 1999). An example of moderation is that the impact of stressful events on depression and anxiety is likely to be stronger when social resources are limited (e.g., Cohen & Wills, 1985; Windle, 1992). Many risk factors for depression and anxiety have been identified but the interplay and mechanisms by which risk factors result in depression and anxiety are by no means understood. Extending on existing research, this thesis studies the interplay of several personal and environmental risk factors of depression and anxiety.

ARIADNE

The studies described in this thesis were conducted in the context of the ARIADNE project. ARIADNE stands for ‘Adolescents at Risk of Anxiety and Depression; A combined Neurobiological and Epidemiological approach’. ARIADNE’s aim is to further our understanding of the etiological mechanisms involved in the onset and course of depression and anxiety disorders. The prospective design incorporates measures of familial liability and neurobiological, neuropsychological, interpersonal and environmental factors in order to examine associations and interplay between risk factors. Participants were adolescent and young-adult offspring of parents (formerly) treated for emotional disorders (for recruitment and sample characteristics see Chapter 2). The research design
adopted in the ARIADNE study has two major advantages: a) the inclusion of adolescents and young-adults increases the chances that we can examine pathways to first onset, b) etiological mechanisms are more likely to surface in high-risk samples since these offer a higher prevalence of and more variation in both risk factors and levels of depression and anxiety than general population samples. Moreover, due to a relatively large sample size of 524 respondents, ARIADNE provides adequate statistical power to formally test the effects and interplay of multiple risk factors.

**The present thesis**

My work in ARIADNE targeted the etiological role of and interplay between familial liability, gender, temperament, and stress and the extent to which these factors have generic or specific effects on depression and anxiety. As described above, our studies were conducted in a high-risk sample of offspring of parents with a history of emotional disorder. Parental emotional disorder increases offspring risk of these disorders by means of a complex interplay of genetic and environmental effects on offspring emotional health (Downey & Coyne, 1990; Goodman & Gotlib, 1999; Nomura, Warner, & Wickramaratne, 2001; Zahn-Waxler et al., 2006). Goodman and Gotlib (1999) illustrated this intergenerational transmission of risk of depression in an adaptation of general etiological models for depression and anxiety (see Figure 1). This model focuses specifically on maternal depression, but in our opinion it can be used in the wider context of this thesis to illustrate the assumed effects of paternal and maternal emotional disorder as well as the interplay of these and other personal and environmental risk factors.

Goodman and Gotlib distinguish between moderators, mediators (or mechanisms), and offspring vulnerabilities in the intergenerational transmission of risk. Moderators are factors that can alter the effect and the prevalence of other risk factors for offspring disorder. Goodman and Gotlib consider temperament, gender and intellectual and social-cognitive skills to be moderators of risk. Besides these offspring characteristics, they identify timing and course of parental disorder and availability and mental health of the other parent as moderators specific to the intergenerational transmission of risk. The mediators in the model are those risk factors through which parental emotional disorder increases offspring risk of psychiatric disorders or mental health problems. These mediators include a) heritability of mental disorder, b) innate dysfunctional neuroregulatory mechanisms, c) exposure to parent’s negative and/or maladaptive cognitions, behaviours, and affect, and d) exposure to a stressful environment. Goodman and Gotlib tied these factors to maternal depression, but they are likely to be general risk
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factors, that is, the presence of these factors is not always or fully the result of parental disorder. Offspring vulnerabilities include psychobiological dysfunction and deficits or maladaptive styles/tendencies in cognition, affection, or (interpersonal) behaviour. As mentioned above, the studies in the present thesis examined the roles of familial liability, gender, temperament, stress and the extent to which effects are generic or specific for depression and anxiety.

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<th>Risk</th>
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<td>Depressed mother</td>
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<td>Psychobiological dysfunction</td>
<td>Childhood or adolescent depression</td>
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<td>Innate dysfunctional neuroregulatory mechanisms</td>
<td>Skills deficits or maladaptive styles or behavioral tendencies</td>
<td>Other disorders</td>
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<td>Exposure to mother’s negative and/or maladaptive cognitions, behaviors, and affect</td>
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<td>Behavioral or interpersonal</td>
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Figure 1 An integrative model for the transmission of risk to offspring of depressed mothers (Goodman & Gotlib, 1999)

Familial liability

The more relatives suffer from emotional disorder, the higher the individual’s risk to develop psychiatric problems seems to be (Bijl, Cuijpers, & Smit, 2002; Lewinsohn et al., 2003; Merikangas et al., 1998; Warner et al., 1999; Weissman et al., 2005). For the present thesis familial liability was defined as the number of affected parents. A second affected parent has been found to increase risk of emotional problems in offspring of parents with Major Depressive Disorder (MDD) (e.g., Birmaher et al., 1996; Brennan et al., 2002, Foley.
et al., 2001; Marmorstein, Malone, & Iacono, 2004; McCauley, Pavlidis, & Kendall, 2001; Nomura, Warner, & Wickramaratne, 2001; Warner, Mufson, & Weissman, 1995). This operates through both genetic and environmental factors (Brennan et al., 2002; Dierker, Merikangas, & Szatmari, 1999; Nomura, Warner, & Wickramaratne, 2001), probably by both adding genetic and environmental risk and reduction of resources to counterbalance the adverse effects of the disorder in the other parent (Downey & Coyne, 1990; Tannenbaum & Forehand, 1994). According to Goodman and Gotlib the presence of a second affected parent also acts as a moderator. This implies that the effects of parental emotional disorder and associated risk factors, such as adverse familial circumstances, differ according to the presence of a second affected parent. Important in this context are differences in the effects of maternal versus paternal disorder and the relative importance of environmental factors to offspring mental health when genetic risk increases. Maternal emotional disorder is found to be more strongly associated with offspring emotional health and parent-offspring relation quality than paternal emotional disorder (Connell & Goodman, 2002; Field, Hossain, & Malphurs, 1999; Goodman & Gotlib, 1999; Jacob & Johnson, 1997; Johnson et al., 1999; Kendler et al., 2001; Phares & Compas, 1992). While paternal emotional disorder may increase offspring risk when the mother is unaffected, it may not significantly increase offspring risk further when the mother is affected. Environmental risk factors for depression and anxiety are more prevalent among offspring of parents with an emotional disorder than in offspring of unaffected parents (Bifulco, Moran, & Ball, 2002; Goodyer et al., 1993; Walsh, MacMillan, & Jamieson, 2002) and there is evidence that the effect of parental disorder on offspring emotional health is partially mediated by environmental factors such as parent-offspring relationship quality (e.g., Hammen, Brennan, & Shih, 2004; Pilowsky et al., 2006). However, it is not clear whether such environmental factors affect offspring emotional health relatively more or less when genetic risk is higher (e.g., Hammen, Brennan, & Shih, 2004; Pilowsky et al., 2006). In this thesis, we examined the effect of a second affected parent on offspring depression and anxiety and its interplay with parent and offspring gender and parent-offspring relational stress.

**Gender**

About twice as many women than men suffer from depression and anxiety (e.g., Costello & Angold, 1995; Hankin & Abramson, 1999; Ormel & Sytema, 1999; Williams et al., 2005). This gender difference in anxiety is already found in childhood, while the female preponderance in depression appears in adolescence (e.g., Hankin & Abramson, 1999; Lewinsohn, Rohde, & Seeley, 1998; Williams et al., 2005). Although the gender difference
is consistently reported, it has not been convincingly explained (Bebbington, 1996; Hettema et al., 2005; Kendler, Gardner, & Prescott, 2002; Lichtenstein & Annas, 2000), but other studies failed to present such evidence (Kendler, Gardner, & Prescott, 2001; Murray & Sines, 1996). Multifactorial studies in adults by Kendler and associates indicate that the underlying structure of the genetic and environmental risk factors for depression and anxiety is similar between men and women (Hettema et al., 2005; Kendler, Gardner, & Prescott, 2002, 2006). This is in line with findings that suggest that risk factors for emotional disorder do not differ between men and women, but that these factors are more prevalent and have a larger impact in women. (Cyranowski et al., 2000; Else-Quest, Hyde, & Goldsmith, 2006; Hankin & Abramson, 2001; Kagan, 2001; Nolen-Hoeksema & Girgus, 1994). Cyranowski et al. (2000) especially stress the importance of interpersonal relations and interpersonal stressors. According to these authors women develop a greater need for affiliation which makes them especially vulnerable to emotional problems following negative interpersonal events.

Goodman and Gotlib consider offspring gender to be a moderator, implying that associations between risk factors and offspring emotional health are different between sons and daughters. For example, daughters are thought to experience more and be more vulnerable to the (interpersonal) effects of parental emotional disorder than sons (e.g., Davies & Windle, 1997; Hops, 1996). In this thesis we examined the interplay of gender and familial liability and gender differences in the interplay between social support and parent-offspring problems in relation to depression and anxiety problems.

Temperament

Temperament represents basic person characteristics in emotional reactivity and self-regulation (e.g., Rothbart, Ahadi, & Evans, 2000) and affects mental health in interaction with the environment (Dadds & Salmon, 2003; Oldehinkel et al., 2006). Temperament is shaped by the environment to some extent through parenting and other experiences, but it appears to be moderately stable during adolescence and young adulthood (Caspi & Roberts, 2001). In the present thesis, I focus on the temperament domains of negative affectivity, extraversion and effortful control as assessed by the Adult Temperament Questionnaire (Rothbart, Ahadi, & Evans, 2000). Negative affectivity is highly related to the adult personality trait of neuroticism, while effortful control is related to conscientiousness (Rothbart, Ahadi, & Evans, 2000). Neuroticism, extraversion, and
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Conscientiousness represent the three most salient temperament/personality domains across all major theories of temperament/personality (e.g., Cloninger, 1986; Eysenck & Eysenck, 1985; McCrae & Costa, 1997; Rothbart, Ahadi, & Evans, 2000). Negative affectivity describes a tendency to experience negative emotions or emotional instability (Eysenck, 1967; Eysenck & Rachman, 1965; John, 1990), extraversion may be described as the tendency to engage in the pursuit of pleasurable experiences (Carver, Sutton, & Scheier, 2000; Depue & Collins, 1999; Derryberry & Tucker, 2006) and effortful control describes the ability to voluntarily regulate attention and behavior (Derryberry, 2002; Rueda, Posner, & Rothbart, 2004). Negative affectivity has a strong positive association with both depression and anxiety (e.g., Caspi et al., 1996; Jorm et al., 2000; Lonigan et al., 1997; Ormel, Oldehinkel, & Brilman, 2001; Roberts & Kendler, 1999) while extraversion has a negative association with emotional problems (e.g., Angst, 1998; Bienvenu et al., 2001a; Brown, Chorpita, & Barlow, 1998; Carver, 2004; Clark, Watson, & Mineka, 1994; Davidson, 1995; Depue & Iacono, 1989; Trull & Sher, 1994). Due to these associations, high negative affectivity and low extraversion are considered to be risk factors for depression and anxiety. Effortful control has been studied less in relation to depression or anxiety, but recent findings show a negative, that is protective, effect of this trait (Eisenberg et al., 2001; Lemery, Essex, & Smider, 2002; Lengua, West, & Sandler, 1998; Lengua, Long, & Smith, 2005; Muris, De Jong, & Engelen, 2004). Temperament characteristics thus are directly associated with risk of emotional disorder, but have also been shown to alter effects of other risk factors (Gothelf et al., 2004; Kendler, Kuhn, & Prescott, 2004a; Ormel Oldehinkel, & Brilman, 2001; Van Os & Jones, 1999) or even each other's effects (Gershuny & Sher, 1998; Muris, 2006; Oldehinkel et al., 2007). In the model of Goodman and Gotlib temperament is proposed to be a moderator in the intergenerational transmission of risk. In the present thesis we examined the interplay of the temperament domains of effortful control, negative affectivity and extraversion, as well as mediation and moderation by these domains in the association between sexual assault and emotional problems.

Stress

Stress can be defined as “environmental events or chronic conditions that objectively threaten the physical and/or psychological health or well-being of individuals of a particular age in a particular society” (Grant et al., 2003, p.449). Since the onset of depression and anxiety disorders is often associated with the experience of stress it is an important factor in many etiological models of depression and anxiety (e.g., Brown & Harris, 1978; Goodman & Gotlib, 1999; Hankin & Abela, 2005; Ormel & Neeleman,
 Nonetheless, the majority of individuals that encounter stress do not develop emotional problems (e.g., Hankin & Abela, 2005). The extent to which stress affects emotional health is therefore thought to differ according to its nature, severity or chronicity, as well as to the presence or absence of other stress factors. Moreover, the extent to which events and conditions are appraised as stressful and affecting well being differs according to individual characteristics such as genetic factors, biological processes, temperamental features, cognitive structures, interpersonal interacting styles and emotion regulation (Goodman & Gotlib, 1999; Hankin & Abela, 2005; Williams et al., 2005).

Offspring of parents with emotional disorder encounter more stress, ranging from poverty, parental divorce, disturbed parent-offspring relations and poor family functioning to sexual and physical abuse (e.g., Bifulco, Moran, & Ball, 2002; Downey & Coyne, 1990; Goodman & Gotlib, 1999; Goodyer, 1990; Walsh, MacMillan, & Jamieson, 2002). In addition, parental emotional disorder may increase the extent to which offspring experience stress through its effect on the individual characteristics described above. Goodman and Gotlib therefore consider stress to be a mediator in the intergenerational transmission of risk.

The measures of stress we used in the present thesis concern interpersonal stress, that is stress that occurs in or as a result of interactions between individuals. This type of stress in particular seems to lead to emotional problems (Garber & Flynn, 2001). In this thesis we examined the role of parent-offspring relational stress in the association between familial liability and offspring emotional problems, the interplay of parent-offspring communicational stress and social support, and the interplay of sexual assault and temperament.

**Generic and specific effects on depression and anxiety**

Several studies indicate that depression and anxiety are transmitted independently within families (Avenevoli et al., 2001; Klein et al., 2003; Weissman et al., 1993), implying that offspring of depressed parents are particularly at risk of depression and offspring of parents with anxiety are particularly at risk of anxiety. Depression and anxiety are however strongly associated. The onset of depression is often preceded by anxiety (e.g., Avenevoli et al., 2001; Cohen et al., 1993) and depression and anxiety are much more often co-morbid than would be expected by chance (e.g., Angold, Costello, & Erkanli, 1999; Brown et al., 2001; Mineka, Watson, & Clark, 1998; Williamson et al., 2005). Depression and anxiety can be distinguished from each other by low positive affect or hopelessness in depression and physiological hyper-arousal in anxiety (Brown, Chorpita, & Barlow, 1998;
Mineka, Watson, & Clark, 1998), but they share a common factor of psychological distress based on broad individual differences in general negative affect (Brown, Chorpita, & Barlow, 1998; Clark & Watson, 1991). Behavior-genetic and several family studies (Eley & Stevenson, 2000; Kendler et al., 1987, 1992; cf. Middeldorp et al., 2005; Thapar & McGuffin, 1997) indicate that depression and anxiety share an underlying genetic risk. This underlying risk may be differentially expressed as depression or anxiety dependent of exposure to environmental factors (Eley & Stevenson, 2000; Kendler et al., 1987, 1992). To fully understand the etiology of depression and anxiety, it is important to distinguish between generic effects of risk factors on psychological distress associated with both depression and anxiety, and specific effects on distress unique for either depression or anxiety. Throughout this thesis we distinguished between offspring depression and anxiety in studying the interplay of familial liability, gender, temperament and/or interpersonal stress.

Outline of this thesis

This thesis continues in Chapter 2 with a description of the ARIADNE data collection procedure and sample characteristics. Chapters 3 through 7 describe empirical studies into the interplay between personal and environmental risk factors.

Chapter 3 examines differences in offspring risk of depression and anxiety disorders according to familial liability and parent and offspring gender. We determined whether a second parent with a history of emotional problems increased risk of depression and anxiety in offspring of depressed parents and whether this effect varied according to whether mother or father was affected and whether offspring were sons or daughters. So far, research on the effect of a second affected parent as well as research formally testing differences in risk according to the parent-offspring gender dyad is scarce.

Chapter 4 examines the role of parent-offspring relational stress in the association between familial liability and offspring emotional problems. Although it is clear that parental emotional disorder is associated with troubled parent-offspring relations, empirical findings concerning the relative contribution to offspring problems in low versus high risk offspring seem contradictory, suggesting either an increased or decreased contribution. We sought to shed further light on these contradictory findings.

In Chapter 5 we examined whether the association between parent-offspring stress and offspring depression and anxiety was buffered by social support and whether this effect was different for male and female offspring. Perceived social support is thought to moderate the association between stress and emotional problems, such that high perceived
social support may decrease the effect of stress on emotional problems. In addition, women are thought to be affected more by social support as well as interpersonal stress. Very few studies have addressed this three-way interaction between gender, stress and support.

Chapter 6 is a longitudinal study into the interplay of the temperament domains of negative affectivity, extraversion and effortful control in relation to depression and anxiety. The aim was to determine whether effortful control could alter the effects of negative affectivity and extraversion on depression and anxiety. So far, only a few studies examined the potentially protective role of effortful control, in particular its subcomponents attentional, inhibitory and activation control.

Chapter 7 describes a study among the female participants of ARIADNE that examined the role of temperament in the association between sexual assault and emotional problems. Although it is widely suggested that sexual assault increases emotional problems partially through altering temperament characteristics (i.e., mediation), empirical studies that formally test this are scarce. In addition we examined whether the association between sexual assault and emotional problems may differ according to temperament (i.e., moderation). Although the literature shows such an effect of temperament on the effect of many stressors, researchers have not considered temperament as a potential moderator of the effect of sexual assault so far.

In the final chapter (Chapter 8), I will discuss our findings and their clinical and research implications.