General introduction
Depressive and anxiety disorders affect millions of people every year, many of whom are parents. Children whose parents suffer from (one of) these conditions have an elevated risk to develop similar problems. The aim of this thesis is to improve our knowledge of the intergenerational transmission of depressive/anxiety disorders and to shed light on possibilities to decrease the risk that these disorders pass down from one generation to the next.

The epidemiology of depressive and anxiety disorders
The lifetime prevalences of depressive and anxiety disorders in European countries range from 5.2% to 22.3% and from 9.9% to 21.0% respectively. The most recent Dutch estimate of depression indicates that at least once in life about one fifth of the general population will suffer from a depressive episode. A similar estimate has been found for anxiety disorders. A brief overview of the clinical features of depressive and anxiety disorders is presented in Box 1 (see DSM-IV for a full description of diagnostic criteria). Depressive and anxiety disorders develop gradually and, although they can emerge at any age, the first clinical manifestation often occurs early in life. Social anxiety disorder is likely to emerge in late childhood or adolescence while panic disorder, agoraphobia, and generalized anxiety disorder typically have their first onset during late adolescence and young adulthood. The core risk period for the first onset of depressive disorders ranges from mid-late adolescence to the early 40s. Depressive and anxiety disorders are disabling conditions. Once developed, they tend to run a recurrent or chronic course frequently leading to substantial impairments in academic, occupational and social functioning that often persist during adulthood. From an economic perspective, society at large is faced with high costs due to the use of health care and the loss of productivity.

Intergenerational transmission
Hippocrates introduced the term ‘melancholia’ to describe a state characterized by affective symptoms, most importantly fear and sadness. From the oldest times it was already recognized that melancholia could be inherited: “Et patrum in natos abeunt cum semine morae.” (the character of the parent is transmitted to the children through the seed) (Burton, 1989, p. 205, The Anatomy of Melancholy). In the eighties of the last century, there has been renewed interest in the familial nature of psychiatric disorders. Professionals working in adult psychiatry noticed that many patients were raised in families with a mentally ill parent. Likewise in youth mental health care, professionals came across many children whose parents also suffer or suffered from psychiatric problems. During this period, the first cross-sectional and retrospective studies were conducted investigating the hypothesis that offspring of parents with depressive disorders have an elevated risk of mental health problems, in particular of depressive disorders, compared to children whose parents are unaffected. To date, a large body of literature exists showing that parental depression is among the most robust and well-replicated risk factors for depression.
Depressive disorders
The term depressive disorder in this thesis refers to major depressive disorder and dysthymic disorder according to DSM-IV criteria. Persons with a major depressive disorder experience a depressed mood and/or loss of interest and pleasure in almost all activities for two weeks or more. This condition is accompanied by at least four additional symptoms such as loss of energy, weight changes, insomnia or hypersomnia, suicidal thoughts and concentration problems. In dysthymic disorder symptoms are milder than in major depressive disorder but are continuously present for at least two years. Persons with bipolar disorder experience depressive episodes and extreme euphoric or irritable mood states called manic or hypomanic episodes. These episodes alternate with normal mood states. In a few chapters, the term mood disorder is used referring to all three disorders.

Anxiety disorders
The term anxiety disorder in this thesis refers to generalized anxiety disorder, social phobia, panic disorder and agoraphobia according to DSM-IV criteria. Persons with a generalized anxiety disorder experience excessive and uncontrollable anxiety and worry about many topics for at least six months. The disorder is accompanied by three (or more) symptoms such as restlessness, irritability, muscle tension and tiredness. Social phobia is characterized by a disproportionate fear of negative evaluation in social settings experienced for six months or longer. Persons with social phobia avoid such situations or endure them with significant distress. Panic disorder encompasses the occurrence of typically unanticipated and recurrent panic attacks not caused by a medical condition or a substance. Agoraphobia is defined as an intense fear of and/or avoidance of situations that may induce anxiety or panic and from which it is not easy to go away or where help is perceived to be unavailable (e.g., using public transportation).

Comorbidity
Importantly, comorbidity rates of depressive disorders with anxiety disorders are excessively high. Lamers and colleagues, for example, found that 75% of persons with a depressive disorder also had a lifetime comorbid anxiety disorder and 81% of persons with an anxiety disorder also had a lifetime depressive disorder. Lifetime comorbidity is thus more common than these disorders occurring in pure and isolated form. The present thesis therefore deals with the group of persons with a depressive and/or anxiety disorder further referred to as persons with depressive/anxiety disorders.

Box 1. Brief overview of the clinical features of depressive and anxiety disorders

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Several mechanisms have been proposed to explain the intergenerational transmission of depressive and anxiety disorders\textsuperscript{30,31}, but it should be noted that a complete picture of the processes involved remain a distant goal. Offspring may inherit genes that make them vulnerable to develop these conditions (i.e., direct genetic transmission) or they may for instance inherit personality traits that place them at increased risk (i.e., indirect genetic transmission).\textsuperscript{32,33} In addition to these genetic influences, environmental risk factors may also play an important role.\textsuperscript{34,35} For example, parents with depression more often display negative cognitions, emotions and behaviors, which may adversely affect offspring in social learning and through the parent being less able to align with offspring’s social and emotional needs.\textsuperscript{36,37} Further, increased exposure to stressful life events that accompany a parental disorder (e.g., financial problems and marital discord) may contribute to psychopathology in offspring.\textsuperscript{38-40} These genetic influences and contextual challenges are likely to operate in complex ways and interact with other risk factors. For a more extensive developmental model for understanding intergenerational transmission of depression see Goodman and Gotlib.\textsuperscript{30} The intergenerational transmission of anxiety has been studied less extensively than depression. Available literature on the intergenerational transmission of anxiety disorders show a similar picture.\textsuperscript{31}

**Psychiatric outcomes in offspring**

Previous studies reveal that offspring of depressed/anxious parents have a two- to three-fold increased risk of developing these disorders when compared to offspring whose parents are unaffected.\textsuperscript{41-44} While this estimate of a two- to three-fold increased risk seems to be fairly stable across studies, the absolute rates vary widely. Cumulative incidence rates from about 10% to 50\%\textsuperscript{45-51} were found in cross-sectional and short-term follow-up studies in high-risk offspring samples. These type of studies may have underestimated offspring risk due to possible failure to recall past episodes.\textsuperscript{52,53} It has been shown that longitudinal studies with repeated measurements of outcomes produce more accurate estimates of lifetime prevalence of depressive/anxiety disorders when compared to those obtained from retrospectively reported data.\textsuperscript{54,55} In addition, studies in relatively young offspring are limited in that lifetime prevalence rates are established before the peak periods of vulnerability for depressive/anxiety disorders have passed.\textsuperscript{7,56} For example, if offspring were assessed at age 15, a substantial part of them will develop depression later on and consequently, these incident cases were not covered in the study and the absolute risk estimates are too low. Few long-term high-risk offspring studies have been carried out (≥10 years)\textsuperscript{42,43}, only one of which has followed offspring into adulthood.\textsuperscript{41} In the present thesis we will determine the cumulative incidence of mood/anxiety disorders in a large cohort of offspring of depressed/anxious patients, who have been repeatedly assessed into adulthood (baseline age: 13-25 years). This information may be valuable for planning policies and/or prevention and treatment as well as for raising awareness of this issue. It is clear that offspring risk is the result of a complex interplay between a range of risk- and protective factors, both of which need to be evaluated when looking at intergenerational transmission. Other factors must be considered, so in this thesis we also
look at the potential impact of the family situation and of other parental characteristics and characteristics in offspring. These results may shed new light on subgroups that need extra attention and on factors that protect against risk of developing a mood/anxiety disorder.

While much research has been devoted to the onset of depression/anxiety in the context of parental depression/anxiety e.g., far less is known about the clinical course after offspring have experienced a first depressive/anxiety episode. High-risk offspring studies that do present course characteristics (e.g., recurrence, chronicity) indicate that in many cases symptoms persist or recur, suggesting that offspring risk is certainly not of a temporary nature. As these studies report on very small samples of affected offspring or provide relatively rough course descriptions, the present thesis aims to more precisely describe the prospective course of depressive/anxiety disorders in offspring. The above also evokes interest in whether a parental history of depression/anxiety not only predicts the first clinical manifestation of depression/anxiety in offspring but also foreshadows a less favorable clinical course. The latter needs empirical study, since factors involved in the onset of these conditions need not be the same as those affecting its course. Previous findings are inconclusive with regard to this as some studies suggest parental history to be related to a worse course of depressive/anxiety disorders, while others do not find such a relation. A part of this thesis is devoted to this topic.

Prevention

Given the very high public health burden of depressive/anxiety disorders and the limited success of treatment, there is a growing interest in possibilities of prevention or early intervention to reduce the incidence of these disorders and favorably affect its course. Evidence of the increased risk of mental health problems in offspring of affected parents and the challenges they face has raised awareness that they are an important target group for prevention or early intervention. This has resulted in the development of several programs in the Netherlands and in other countries aimed at preventing the transmission of mental disorders from parents to offspring. These programs can be classified as selective preventive interventions: they target a subpopulation showing an increased risk. This type of prevention differs from universal strategies addressing an entire population regardless of their at-risk status and indicated prevention strategies directed at persons already experiencing subclinical symptoms. There are several types of such selective prevention programs including face-to-face and online child-, parent- and family-interventions. A meta-analysis of prevention programs in children of parents with mental disorders in general states that these programs decreased the risk of developing a mental disorder in children by 40%. A recent meta-analysis focusing on prevention programs in children of depressed parents in particular yields similar results.

Previous meta-analyses mainly focuses on determining the efficacy of prevention programs, but implementation of evidence-based programs into clinical practice requires sufficiently detailed intervention descriptions. This is also important from a research
perspective in order to be able to replicate or build on previous findings. The present thesis adds to the existing literature by systematically reviewing trials assessing the efficacy of a prevention program for children of parents with a mood or anxiety disorder and, describing these programs conforming to the recently introduced Template for Intervention Description and Replication (TIDieR). To increase knowledge of what has exactly been done in these programs, an overview of techniques used in prevention programs will additionally be provided. These intervention characteristics and techniques may be taken into account as potential mediating or moderating factors of intervention effect in future meta-analyses. Practitioners as well as researchers have emphasized that recruiting families for such programs is quite a challenge. Recruitment strategies used to approach families or offspring to participate in these trials and difficulties encountered will therefore also be considered in this thesis. Lastly, we will evaluate the efficacy of these programs in terms of their ability to prevent the onset of mood/anxiety disorders and to reduce mood/anxiety symptoms. Other than Loechner and colleagues, our meta-analysis also includes prevention programs for children of parents with an anxiety disorder.

Treatment
Preventive approaches are a major area of interest in studies on families in which a parent has a mental illness, but far less is known about help-seeking in offspring who already suffer from these conditions. A few high-risk studies have reported on the treatment history of offspring as part of their larger investigations into the consequences for children of depressed or anxious parents. A recent study of Weissman and colleagues, for example, shows that 76.3% of offspring of depressed parents, had received mental health treatment at some point in their life. Importantly, previous offspring studies present lifetime treatment rates; they do not report on the timing of treatment, that is the time between the onset of a mental disorder and initial help-seeking. This is relevant as previous findings suggest that the shorter the time between onset and treatment the better the response outcomes. To address this gap in literature, this thesis examines the time to initial help-seeking in offspring who have a parent with depression or anxiety and who have developed (one of) these conditions themselves. In addition, we aim to identify subgroups of offspring who tend to be late in seeking professional help and who may be an important target for strategies to reduce help-seeking delays.

Framework of studies
The present thesis presents work from two longitudinal cohort studies.

Adolescents at Risk of Anxiety and Depression: a Neurobiological and Epidemiological approach (ARIADNE)
ARIADNE is a cohort study examining the onset and course of mood and anxiety disorders among 523 offspring (baseline age, 13-25 years; recruited from 2000-2002) of 366 patients who had received specialized treatment for depressive (i.e., major depressive disorder,
dysthymia) and/or anxiety disorder (i.e., panic disorder with or without agoraphobia, obsessive-compulsive disorder) in the 10 years previous to the study. ARIADNE’s study design has been previously described. Briefly, patients (also referred to as index parents) were recruited through 16 psychiatric services in the northern provinces of the Netherlands and were not eligible to participate if they had a history of a schizophrenia spectrum diagnosis, a history of post-traumatic stress disorder, or insufficient command of the Dutch language. At baseline face-to-face assessments, including a psychiatric diagnostic interview (i.e., the Composite International Diagnostic Interview; CIDI), were conducted with the index parents: 320 had a depressive disorder (87.4%; of which 43.1% had a pure depressive disorder and 56.9% had a comorbid anxiety disorder), 207 had an anxiety disorder (56.6%; of which 12.1% had a pure anxiety disorder and 87.9% had a comorbid depressive disorder) and 5.5% of the index parents had no formal diagnosis. During the baseline assessment, offspring were also assessed by means of a psychiatric diagnostic interview. In addition, offspring completed self-report questionnaires at baseline, one-year, two-year and four-year follow-up, assessing temperament, social support, coping, family functioning, parent-adolescent communication, and a wide range of DSM-IV symptoms.

After completion of the four-year ARIADNE study, all offspring were asked if they were willing to participate in a new study: the Netherlands Study of Depression and Anxiety (NESDA). This procedure unfortunately resulted in a large drop-out (i.e., 50.1%). Nevertheless, a substantial number of offspring of the ARIADNE cohort are still being followed in the context of NESDA (n=261 offspring participated in the NESDA baseline assessment) for up to 13 years now.

**Netherlands Study of Depression and Anxiety (NESDA)**

NESDA is an ongoing naturalistic cohort study aimed at examining the long-term course and consequences of depressive and anxiety disorders in adults (baseline age: 18-65 years; recruited from 2004-2007). A detailed description of objectives, recruitment, and methods of NESDA is described elsewhere. Briefly, the NESDA cohort comprises 2981 adults including patients with a current depressive and/or anxiety disorder (57%), persons with a remitted depressive and/or anxiety disorder (21%) and healthy control participants (22%). In order to represent various settings and stages of psychopathology participants were recruited from primary care (n=1610, 54%), specialized mental health care (n=807, 27%) and from two previous cohort studies including community participants (n=564, 19%; selected from the Netherlands Mental Health Service and Incidence Study, n=303, 10%) and offspring of patients who had received specialized treatment for depressive and/or anxiety disorders (n=261, 9%; selected from the above described ARIADNE cohort). Persons were not eligible to participate in the NESDA study if they did not sufficiently master the Dutch language or had a primary clinical diagnosis of a psychotic disorder, obsessive-compulsive disorder, bipolar disorder, or substance use disorder. The baseline assessment (2004-2007) included a four-hour interview during which a standardized psychiatric interview (i.e., the CIDI) was conducted to assess...
the lifetime presence of psychiatric disorders. In addition, information was gathered on demographic, psychosocial, clinical and biological determinants. Until now, follow-up assessments have been conducted after two-year follow-up (response: 87%), four-year follow-up (response: 81%), six-year follow-up (response: 76%) and nine-year follow-up (response: 69%) after the baseline assessment.

Outline of this thesis
The objective of this thesis is to expand our knowledge of the intergenerational transmission of depressive/anxiety disorders and to shed light on possibilities to decrease the risk that these disorders are passed on from generation to generation. The term ‘offspring’ is used to refer to persons with a parental history of depressive/anxiety disorders. In the first part of this thesis, we examine the onset and course of depressive/anxiety disorders in the context of parental depression/anxiety (Chapters 2, 3, 4, 5). The second part of this thesis reviews existing prevention programs specifically targeting offspring and focuses on help-seeking in offspring already suffering from depressive/anxiety disorders (Chapters 6 and 7). Table 1 presents an overview of the chapters included in this thesis.

Chapter 2 examines the cumulative incidence of mood/anxiety disorders in offspring of depressed/anxious patients using 10-year follow-up data of the ARIADNE cohort. In addition, this study investigates which parental-, family-, and offspring characteristics are associated with offspring risk for mood/anxiety disorders. In Chapter 3, in response to a recently published paper demonstrating the independent effects of paternal and maternal depressive symptoms on offspring depressive symptoms84, we discuss the possibility that the risk associated with both parents being affected may be worse than additive. Chapter 4 looks at adulthood and investigates whether a parental history of depressive/anxiety disorders is

Table 1. Overview of the chapters presented in this thesis

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Opportunities for intervention

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predictive of the first onset of depressive/anxiety disorders in this period of life. In addition, we investigate whether a parental history predicts recurrence and long-term persistence of these conditions. Clinical- and treatment factors are considered to examine whether they contribute to these potential prospective associations. This paper is based on nine-year follow-up data of the NESDA study. Chapter 5 is based on six-year follow-up data of the NESDA study and considers various course indicators of depressive/anxiety disorders in offspring with a lifetime depressive/anxiety disorder at baseline. The course is described for all offspring, and for offspring with and without a depressive/anxiety diagnosis during follow-up, separately. In addition, course trajectories in offspring are compared to those of controls without a parental history. Chapter 6 systematically reviews randomized controlled trials of prevention programs designed to reduce the risk of mood/anxiety disorders in children of parents with a mood or anxiety disorder. A comprehensive description of these prevention programs and recruitment strategies is provided as well as a meta-analysis of their effectiveness. Chapter 7 examines the time between the first onset and offspring’s initial help-seeking and its determinants. In addition, we investigate whether offspring receive specialized treatment. This chapter is based on 10-year follow-up data of the ARIADNE cohort. Finally, Chapter 8 summarizes and discusses the main findings of this thesis.
REFERENCES


