Chapter 1

General introduction
People with depressive disorders frequently come to see their general practitioner as these conditions are highly prevalent and a leading cause of disability (Global Burden of Disease Study Collaborators 2015; Whiteford et al. 2013). For many people, depression is a dark cloud raining on their parade; it negatively affects many aspects of life, such as social and occupational functioning (Ormel et al. 2008; Ormel et al. 1994; Paykel 2008; Alonso et al. 2004). In the Netherlands, 19% of the general population experience a major depressive disorder during their life and 5% in the previous year (de Graaf et al. 2012). In general practice, the key question is usually whether the mood problem is contextual (‘understandable’), for instance because there are financial problems or physical health problems. In this thesis, I focus on exploring determinants of onset and recurrence of depressive disorders and on the effectiveness of a preventive intervention for recurrence of depressive disorders. First, I describe the diagnostic criteria, course and disease burden of depressive disorders in this introduction. Thereafter, I briefly discuss determinants of occurrence, onset and recurrence of depressive disorders. Following this overview, I am going to discuss what the gaps in the current knowledge are around the treatment and prevention of depressive disorders from a public health or primary care perspective. Lastly, I present a concise overview of the research questions and an outline of this thesis.

**Definition and diagnostic criteria**

According to the Diagnostic and Statistical Manual of mental disorders (DSM IV-R; APA 1994), depressive disorders include major depressive disorder and dysthymic disorder. Major depressive disorder is the focus of this thesis and is characterized by either a depressed mood or a loss of interest or pleasure most of the day, nearly every day for a period of at least two weeks. In addition to a depressed mood or loss of interest, at least four of the following symptoms are present nearly every day during the same two-week period: significant weight change or change in appetite, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue or loss of energy, feeling of worthlessness or excessive guilt, diminished ability to think or concentrate, or recurrent thoughts of death or suicidal ideation/attempt. Moreover, the person experiences clinically significant distress or impaired social, occupational or educational functioning. Dysthymic disorder is characterized by a depressed mood and two or more of the symptoms described above for more days than not, for at least two years. In 2013, the Diagnostic and Statistical Manual of mental disorders was updated (APA 2013). In the DSM 5, the criteria for major depressive disorders are mainly conform the DSM-IV-R criteria. However, the section ‘depressive disorders’ now also includes disruptive mood dysregulation
disorder and premenstrual dysphoric disorder, and dysthyemic disorder has been replaced by persistent depressive disorder.

### Disease burden of depressive disorders

Depressive disorders were the second leading cause of global non-fatal burden of disease in 1999 -2013 (Global Burden of Disease Study Collaborators 2015; Whiteford et al. 2013). Major depressive disorder accounted for 8.2% (95% CI 5.9 to 10.8) of years lived with disability (YLD) in 2010 (Ferrari et al. 2013). Besides the high burden for patients, depressive disorders are associated with substantial societal costs because of increased healthcare utilization and productivity losses (Hendriks et al. 2015; Bosmans et al. 2010; Luppa et al. 2007; Smit et al. 2006). In Europe, healthcare costs and productivity loss costs for mood disorder, which included both unipolar and bipolar depressive disorders, were estimated at 113.4 billion euros in 2010 (Gustavsson et al. 2011). Healthcare costs for depressive disorders in the Netherlands are 966 million euros per year, which comprises 1.3% of total healthcare costs in 2007 (Slobbe et al. 2011).

### Comorbidity with anxiety disorders

Depressive disorders cause even more disability when there is also an anxiety disorder present. Comorbidity rates of depressive and anxiety disorders around 50% have been reported (Spinhoven et al. 2011; de Graaf et al. 2002; Fava et al. 2000). Comorbidity is not only associated with an unfavorable course of depressive and anxiety disorders but also with impaired functioning and higher healthcare utilization (de Graaf et al. 2002; Buist-Bouwman et al. 2004; Penninx et al. 2011; Hendriks et al. 2015). Since depressive and anxiety disorders often occur together and comorbidity negatively affects course and disease burden of depressive disorders, I have also taken anxiety disorders into account in the studies reported in this thesis.

### Course of depressive disorders: recurrent nature

The high disease burden of depressive disorders partly stems from its recurrent course. A review by Steinert et al. (2014) reported recurrence rates of 7.3% after 3 years to 65% after 23 years in the general population and primary care. In the Netherlands, recurrence rates after two years are 5% in the general population (Hardeveld et al. 2010), 27% in primary care and 34% in specialized mental healthcare (Hardeveld et al. 2013). Furthermore, the risk of recurrence increases by 9-18% with each additional episode (Mueller et al. 1999; Bulloch et al. 2014).
Different concepts of the various stages of the course of depressive disorders exist and these are often used interchangeably or inconsistently. In our studies we used the commonly accepted conceptualization by Frank et al. (1991). According to their criteria, a person’s disease stage is defined on basis of symptom severity and duration. It starts with the asymptomatic period before a person’s first depressive episode, the disorder-free stage. A person can move from the disorder-free stage to a symptomatic stage characterized by a full syndromal expression of the disorder: a depressive episode. Then, spontaneously or after treatment, a person reaches remission: a period during which an improvement sets in and during which the person no longer meets diagnostic criteria and has minimal symptoms (partial remission) or no symptoms (full remission). When remission lasts for a certain period, mostly a period of six months is used, the person is considered to have recovered. A relapse is defined as a return of the depressive episode during the period of remission but before recovery, while recurrence is defined as a new depressive episode after recovery.

**Determinants of onset and course of depressive disorders**

As depressive disorders are a leading cause of disability, it is important to gain insight in factors that are associated with the onset and course of depressive disorders. Knowledge of predictors of the onset, course and consequences of depressive disorders is essential for matching limited treatment resources to the needs of patients and may result in more effective prevention and treatment of depressive disorders (Munoz et al. 2010; Penninx et al. 2008). Several important predictors of depressive disorders have been identified, but they explain only a proportion of the variance (Conradi et al. 2008; van Loo et al. 2015). Further study is needed to clarify determinants.

Subclinical depressive symptoms are among the main predictors of both onset and recurrence of depressive disorders (Horwath et al. 1992; Paykel 2008; Hardeveld et al. 2010). Judd et al. (1998), for instance, found that recovered patients who reported residual subclinical symptoms had higher odds of relapse (OR = 3.68; 95% CI 2.64 to 5.12) and relapsed more than three times faster (median = 68 vs. 231 weeks) than asymptomatic patients during the ten year-follow-up period. Besides subclinical symptoms, number of previous episodes is a strong predictor of relapse and recurrence (Hardeveld et al. 2010; Bulloch et al. 2014). Each self-reported additional episode increased the risk of recurrence by about 9%, according to a study by Bulloch et al. (2014) in the general population. Other factors that may predict relapse or recurrence are severity of the previous episode, psychosocial impairment after a depressive episode, comorbid psychopathology,
dysfunctional cognitive styles and neuroticism (Burcusa & Iacono 2007; Conradi et al. 2008; Hardeveld et al. 2010; Klein et al. 2011). Demographic factors such as gender, socio-economic and marital status, which are risk factors for the onset of a first depressive episode (de Graaf et al. 2013), do not seem to predict relapse or recurrence (Burcusa & Iacono 2007; Hardeveld et al. 2010). For other factors such as financial strain and somatization, mostly cross-sectional studies suggest a link with mental health problems, although the relation with depressive disorders is not yet fully understood. Associations of financial strain and somatization with the presence, onset and course of depressive disorders are further explored in this thesis.

Financial strain and income
Socio-economic characteristics such as low income, low education level, and unemployment are associated with higher rates of mental health problems (Fryers et al. 2003; Lorant et al. 2003). A meta-analysis by Lorant et al. (2003) showed that people with low socio-economic status (SES) had higher odds of having a depressive disorder (OR = 1.81) compared to people with high SES. The strength of the associations varies according to the way SES was defined (Lorant et al. 2003; Fryers et al. 2003; Wang et al. 2010). Mostly, objective indicators of socio-economic status such as education level or income are used. However, perceived financial strain, which could be considered as a negative stressor (Wang et al. 2010), might be a better predictor of mental health problems (Weich & Lewis 1998). Perceived financial strain is not only restricted to subjects with a low income but may also represent a tendency to worry (Weich & Lewis 1998). In a Canadian cohort study, perceived financial strain was associated with an increased risk of depressive disorders in working participants (Wang et al. 2010). Longitudinal studies on the associations of both perceived financial strain and income with the onset of a depressive or anxiety disorders have been limited so far. In this thesis, I therefore assess whether financial strain is associated with the onset of depressive disorders, independent of income.

Somatization
Somatization is defined as “the tendency to experience and communicate somatic distress and symptoms unaccounted for by pathological findings, to attribute them to physical illness, and to seek medical help for them” (Lipowski 1988). While experiencing some physical symptoms unaccounted for by pathological findings is a common phenomenon, experiencing multiple unexplained physical symptoms from different organ systems often implies somatization (Terluin et al. 2006).
Somatization is especially prevalent in people who have mental health problems, such as depressive and anxiety disorders (Kroenke 2003). In the Netherlands, one out of two primary care patients with a depressive or anxiety disorder had a comorbid somatoform disorder (De Waal et al. 2004). The presence of somatization increases the burden and disability of depressive disorders as it negatively affects physical and mental health status, recognition and treatment response in depressed patients (Tylee & Gandhi 2005; Huijbregts et al. 2010).

Several underlying mechanisms have been proposed that may explain how somatization, depressive and anxiety disorders are related. It has been suggested that depressive and anxiety disorders may be a reaction to somatization; somatization may be part of, or a consequence of depressive and anxiety disorders; It has also be suggested that all of these conditions are just different expressions and dimensions of a common underlying form of distress (Lieb et al. 2007). As most studies assessing the relations between somatization, depressive and anxiety disorders have been cross-sectional, they were unable to differentiate between these proposed underlying mechanisms. In this thesis, I focused on the first mechanism and examined the impact of somatization on the onset and recurrence of depressive and anxiety disorders in a longitudinal cohort study, the Netherlands Study of Depression and Anxiety (NESDA, which is described in the next paragraph).

In NESDA, somatization is operationalized as the presence of multiple physical symptoms. It does not take into account whether the symptoms were explained by some medical condition. The Four-Dimensional Symptom Questionnaire (4DSQ) was used to measure somatization (Terluin 1996; Terluin et al. 2006). This self-report questionnaire has been developed in primary care to distinguish non-specific general distress from depression, anxiety and somatization. The somatization subscale of the 4DSQ operationalizes somatization as a high number and frequency of physical symptoms and consists of 16 symptoms a person may have had in the past week (e.g. “During the past week did you suffer from dizziness?”). Besides the 4DSQ, the Patient Health Questionnaire (PHQ-15; Kroenke et al. 2002) and several other self-report questionnaires are used to measure somatization. The measurement properties of these various questionnaires to measure somatization have not been compared in primary care. To date, it remains unclear which questionnaire can be used best for measuring somatization in primary care. Therefore, in chapter 5 we critically appraise the evidence on the measurement properties of self-report questionnaires measuring somatization in adult primary care patients.
The Netherlands Study of Depression and Anxiety

I used data from the Netherlands study of Depression and Anxiety (NESDA) to examine the associations of financial strain and somatization with depressive and anxiety disorders. NESDA is an ongoing, multi-site, naturalistic cohort study to describe the long-term course and consequences of depressive and anxiety disorders in different healthcare settings, and integrates biological and psychosocial research paradigms within an epidemiological approach (Penninx et al. 2008). At baseline (2004-2007), 2981 participants aged 18 through 65 years have been included from the general population, primary care, and specialized mental health services. The study population consists of healthy controls; persons with a prior history of a depressive or anxiety disorder; persons with a high risk because of a family history or subthreshold depressive or anxiety symptoms; and persons with a current depressive or anxiety disorders. Exclusion criteria were a primary diagnosis of obsessive compulsive disorder, bipolar disorder or severe addiction disorder, and not being fluent in Dutch. Baseline and follow-up assessments consist of a diagnostic psychiatric interview, questionnaires, and a medical assessment. In this thesis, I used data from the baseline and one-year, two-year and four-year follow-up assessments.

Treatment of depressive disorders

In accordance with the stages of the course of depressive disorders described by Frank et al. (1991), treatment for depressive disorders can be categorized into acute-phase treatment, continuation treatment, and maintenance treatment. According to the Dutch general practitioners guideline (Van Weel-Baumgarten et al. 2012) and the Dutch Multidisciplinary Guideline for Depression (Spijker et al. 2013), acute-phase treatment should preferably consist of psychoeducation, activity scheduling, and a low intensity psychosocial intervention, such as problem solving treatment or supported self-help. If the depressive disorder persists despite these interventions, intensification with psychotherapy (e.g. Cognitive behavioral Therapy) or antidepressant medication is recommended. Besides psycho-education and activity scheduling, treatment for patients with a severe depressive disorder preferably consists of a combination of psychotherapy and antidepressants. Continuation treatment can be offered during remission and aims to sustain remission and prevent relapse. Clinical guidelines (Spijker et al. 2013; Van Weel-Baumgarten et al. 2012; National Collaborating Centre for Mental Health 2009) recommend continuation of antidepressants for at least six months after remission for patients who have benefited from taking antidepressants. The continuation period of six months is not evidence-based but based on consensus,
as the optimal duration of continuation of antidepressants is not yet known (Glue et al. 2010). After recovery, maintenance therapy can be offered in order to prevent recurrence. For patients who are at high risk of relapse, for instance patients with three or more previous depressive episodes or residual depressive symptoms, continuation of antidepressants for at least two years is advised, augmented with a psychological intervention (National Collaborating Centre for Mental Health 2009; Spijker et al. 2013; Van Weel-Baumgarten et al. 2012).

**Prevention of depressive disorders**

Current treatments can avert about 20-30% of the years lived with disability due to depressive disorders (Munoz et al. 2010). People with depressive disorders are often not diagnosed as such, do not acknowledge their problem as such or do not receive treatment. Even if all persons affected by a depressive disorder were treated with evidence-based treatments, the effect on averted disease burden would be limited because of the limited efficacy of currently available treatments and the steady influx of new patients (Cuijpers et al. 2012). According to Smit et al. (2006), a substantial part of costs of mental disorders is caused by new cases, almost 40%. Therefore, they argue for strengthening the role of preventive psychiatry in public health with the aim to reduce incidence and avoid future costs. A review by Cuijpers et al. (2008), including 19 randomized trials, showed that preventive interventions reduced the incidence of depressive disorders by 22%. So, besides treatment, preventive interventions can offer an important opportunity to reduce the high disease burden of depressive disorders. Munoz et al. (2010) state that preventive interventions should focus on people with a high risk of developing a depressive episode in the near future. A high level of subclinical depressive symptoms and having a history of depressive episodes are important high-risk markers. Interventions aimed at the prevention of relapse or recurrence could reduce the disease burden of depressive disorders by approximately 50% (Vos et al. 2004). Strategies to reduce the high disease burden of depressive disorders should, therefore, not only focus on preventing incident cases of depressive disorders but also on preventing relapse or recurrence. A commonly used strategy for preventing relapse or recurrence is continuation of antidepressants (Hansen et al. 2008; Olfson & Marcus 2009). However, many patients find long-term use of antidepressants unattractive and non-adherence is high (van Schaik et al. 2004; ten Doesschate et al. 2009). Also, the optimal duration of continuation is unknown (Glue et al. 2010). Psychological interventions offered after recovery have proven to be effective in reducing the risk of relapse and recurrence of depressive disorders, compared to treatment as
usual or continuation of antidepressants (Vittengl et al. 2007; Biesheuvel-Leliefeld et al. 2015). For instance, Preventive Cognitive Therapy (PCT) in group sessions, which is an adapted version of cognitive therapy for acute depression (Beck 1979) that aims to prevent relapse and recurrence, reduced the risk of recurrence during 5.5 years by 20% for patients with a history of four or more depressive episodes (recurrence rate: PCT = 75% vs treatment as usual = 95%) (Bockting et al. 2009). Most psychological interventions take place in secondary care, drawing on scarce resources in terms of therapists’ time and costs. A minimally supported intervention for prevention of relapse and recurrence would help overcome this problem. The majority of depressed patients visit their general practitioner first. Primary care, therefore, seems the most appropriate setting for such preventive interventions. For several years, more and more general practices in the Netherlands employ a mental health nurse (“POH GGZ”). For cost-effectiveness and pragmatic reasons, it would be attractive to have mental health nurses administer a minimal intervention for preventing relapse and recurrence in recurrently depressed patients. The effectiveness of a minimal intervention by mental health nurses in primary care for preventing relapse or recurrence has not yet been studied. Also, it is not yet known to whom minimal preventive interventions can be successfully applied. We assessed the effectiveness of such preventive intervention in "the Parade study", and aimed to identify subgroups for which the intervention was particularly (cost)effective.

Parade study

The Parade study (Biesheuvel-Leliefeld et al. 2012) aimed to evaluate whether supported self-help Preventive Cognitive Therapy (S-PCT) in primary care is (cost)effective for patients with recurrent depressive disorders in comparison with treatment as usual. Furthermore, we aimed to examine whether S-PCT for patients with recurrent depressive disorders is (cost)effective in certain subgroups of patients. It is not yet clear which patients respond particularly well to preventive interventions for recurrent depression. Identifying characteristics of patients that benefited is important to determine to whom these treatments should be offered. We performed a pragmatic randomized controlled trial with two parallel groups: S-PCT plus treatment as usual compared to treatment as usual only. Patients with recurrent depressive disorders who were at that time remitted (at least eight weeks but no longer than five years), were recruited in primary care practices and specialized mental healthcare institutions in the Netherlands, and were followed for twelve months.
The intervention consisted of a supported self-help treatment based on PCT (Bockting et al. 2005; Bockting & van Valen 2009). Patients were offered a self-help book with eight weekly modules and were supported by mental health nurses and psychologists during weekly telephone calls. S-PCT starts with the identification of negative thoughts and dysfunctional attitudes. Then, the focus of S-PCT is directed on changing these attitudes by using various cognitive techniques such as identification of positive attitudes and enhancing specific memories of positive experiences. Lastly, specific relapse and recurrence prevention strategies are formulated in a personal prevention plan.

Relapse or recurrence of a depressive disorder during the twelve month observation period was assessed by the Structured Clinical Interview for DSM-IV (SCID-I; First et al. 1995) after six and twelve months. In addition to relapse or recurrence, healthcare use and productivity loss costs, severity of depressive symptoms, self-efficacy, pain, fatigue, and comorbid anxiety, distress and somatization were repeatedly measured during the observation period.

**Research questions and outline of this thesis**

The research questions of this thesis are:

- Are somatization and financial strain associated with the presence, onset and recurrence of depressive and anxiety disorders? (part I);
- What is the evidence on measurement properties of self-report questionnaires measuring somatization in primary care? (part II);
- Is a minimal psychological intervention (S-PCT) in primary care effective in preventing relapse and recurrence of depressive disorders, compared to treatment as usual, in remitted, recurrently depressed patients? (part III);
- In which subgroups of patients is a minimal psychological intervention (S-PCT) aimed at preventing relapse and recurrence of depressive disorders particularly (cost)effective? (part III).

Part I of this thesis focuses on determinants of depressive and anxiety disorders. In chapter 2, we examine the associations of financial strain and income with the presence and onset of depressive and anxiety disorders. In chapter 3, we study the association between somatization and onset of depressive and anxiety disorders. In chapter 4, I focus on the associations between somatization and recurrence of depressive and anxiety disorders. In both chapter 3 and 4, we examine the role of depressive and anxiety symptoms as these symptoms are related to somatization and are main predictors of onset and recurrence of depressive and anxiety disorders.
In part II (chapter 5), we assess the measurement properties of self-report questionnaires measuring somatization in primary care.

Part III of this thesis focuses on an intervention program (S-PCT) aimed at preventing the relapse and recurrence of depressive disorders, the Parade study. In chapter 6, we assess the effectiveness of S-PCT. Thereafter, in chapter 7, we aim to identify subgroups for which S-PCT is particularly (cost)effective.

Finally, in chapter 8, I discuss the findings and methodological considerations of the studies included in this thesis and elaborate on the clinical implications of our findings and possibilities for future research.