General introduction
This thesis focuses on anxious distress in depression. To introduce and place anxious distress in depression in context, first, a broader description of depression nosology throughout history is provided. This will show that the definition and viewpoints of depression have been subject to continuous adjustments throughout history, a process that is still ongoing today.

**Major Depressive Disorder**

**Nosology of depression throughout history: from Hippocrates to Diagnostic and Statistical Manual of Mental Disorders (DSM)**

Despite the clinical recognition of mood disorders since ancient times, the diagnosis of mood disorders remains a challenging process. It was Hippocrates (460–377 before Christ [B.C.]), a Greek physician occasionally referred to as the ‘Father of Medicine’, who in 400 B.C. provided the first known description of depression [1]. He used the Greek name ‘melancholia’ for pathological states of depression and stated that ‘fear or sadness that last a long time means melancholia’ (Hippocrates). These symptoms could be accompanied by several other symptoms including aversion to food, despondency, sleeplessness, irritability, and restlessness [1]. Hippocrates and his devotees viewed both mental and physical diseases as a result of bodily imbalances in four basic humors including blood, phlegm, yellow bile and black bile. Melancholia was viewed as an excess of black bile. Several other Greek physicians, such as Aretaeus of Cappadocia (+ 150–200 B.C.) and Galen (+ 131–201 B.C.), elongated the Hippocratic view of melancholia which endured until the end of the eighteenth century [1].

In 1621, the English scientist Robert Burton published his masterpiece ‘The anatomy of melancholy’ in which he described mood, cognition, and physical symptoms as the three major components of depression, a view that still stands nowadays. Burton also distinguished melancholia as a disorder where symptoms occurred without a cause, and as a condition due to for instance grief [1]. In the seventeenth century, a radical change in the view of depression emerged and disease specificity started to receive more attention. The English physician Thomas Sydenham (1624–1689) suggested that every disease had natural forms with uniform presentations in different persons. It was also during this time that melancholia was divided into two major types of conditions based on disturbances of the brain and of the nervous system, namely melancholic conditions and neurotic conditions. These conditions were sharply distinguished by the nineteenth century, based on their causes, symptoms and treatment [1]. In the late nineteenth century, two leading but considerably opposing diagnosticians of depression were Emile Kraepelin (1856–1926) and Sigmund Freud (1856–1939) [1]. Kraepelin mainly focused on the melancholic type of
depression, whereas Freud—known as the founder of psychoanalysis—focused more on neurotic depression. Kraepelin proposed that mental disorders should be described based on symptom patterns and natural history. Also, he believed that psychiatric disorders originate from genetic and biologic causes. Freud also focused on the distinction between the normality of grief and melancholia as a disorder [1].

In the beginning of the twentieth century, depression was sharply split into melancholia linked to psychosis and neurotic depression. In 1952, the first edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-I) appeared and melancholia was classified as a category of psychotic disorders. The DSM-II was released in 1968 and grouped psychotic depression with states of mania. In 1980, the DSM-III appeared and depressive classifications were again unified into one single category. This was due to a group of psychiatrists of the Washington University, led by Samuel Guze and Eli Robins who developed the Feighner criteria [2]. Although empirical evidence for the Feighner criteria was very limited, it became the foundation for the DSM-III depression diagnosis. The DSM-III added the exclusion criterion of recent bereavement to the depression diagnosis. In subsequent editions of the DSM, the DSM-III-R (1987) and DSM-IV (1994), the MDD diagnostic criteria were unaltered.

Nowadays, in the latest fifth edition of the DSM (DSM-5), the DSM-III classification was retained and the bereavement exclusion criterion was removed [3]. The DSM-5 diagnostic criteria of Major Depressive Disorder (MDD) requires presence of at least five out of nine symptoms: 1) depressed mood and/or 2) loss of interest or pleasure (at least one of these symptoms is mandatory), 3) significant weight loss or weight gain, or decrease or increase in appetite, 4) insomnia or hypersomnia, 5) psychomotor agitation or retardation, 6) fatigue or loss of energy, 7) feelings of worthlessness or excessive or inappropriate guilt, 8) diminished ability to think or concentrate or indecisiveness, and 9) recurrent thoughts of death or recurrent suicidal ideation or attempt [4]. The depressive symptoms have to cause clinically significant impairment of functioning and the depressive episode may not be attributable to the physiological effects of a substance or another medical condition [4]. In addition, the DSM-5 introduced a new anxious distress specifier to acknowledge the clinical significance of prominent anxiety features in MDD [4]. This specifier was derived from the study by Goldberg and colleagues, who produced a brief 5-item anxiety scale by item-response theory analyses to facilitate the diagnostic assessment of anxious depression [5]. The DSM-5 criteria for anxious distress are endorsement of at least two of the following five symptoms during the majority of a major depressive episode:
1) feeling keyed up or tense;
2) feeling unusually restless;
3) difficulty concentrating because of worry;
4) fear that something awful might happen;
5) feeling of losing control [4].

Clearly, the description and views of depression have been subject to continuous adjustments over a 2,500-year span, although the core symptoms of deep sadness and its variants (e.g. despondency, sorrow, despair) have remained consistent over time.

**Prevalence and burden of Major Depressive Disorder**

Of all mental disorders, MDD is one of the most prevalent disorders affecting nearly 300 million people worldwide [6]. In the Netherlands, the 12-month prevalence of depression is 5.2% and the lifetime depression prevalence is 18.7% [7]. MDD also often has a chronic course, especially when symptoms of closely related disorders such as anxiety symptoms are taken into account [8]. Furthermore, MDD is a major cause of disability as it is the second leading cause of global disease burden which is expressed in disability-adjusted life years, and accounted for 8.2% of the global disease burden [9]. The burden of MDD further extends to physical health as MDD has been associated with excess onset of a multitude of somatic diseases [10-12], for instance cardiovascular diseases (CVD) [13], diabetes [14] and to a lesser extent even cancer [15]. Presence of an MDD diagnosis plus somatic disease comorbidity likely increases the negative societal impact on public health and causes high societal costs.

**Heterogeneity of Major Depressive Disorder and clinical relevance**

The DSM diagnostic criteria of depression were largely welcomed in the field of Psychiatry as it provided a universal method to classify a uniform condition that can be used not only for clinical but also for research purposes. However, to date, no major neurobiological or genetic scientific breakthroughs have been discovered in depression research but some progress is being made. One of the possible explanations for the lack of these breakthroughs may be the heterogeneity of the MDD diagnosis. The DSM-5 field trials demonstrated that the reliability of the present MDD diagnosis was found to be in the ‘questionable’ range, implying that experienced clinicians could be expected to agree about the diagnosis only 15% more frequently than by chance alone [16]. With regard to the nine current diagnostic criteria of MDD, a total of 227 symptom combinations are possible [17], and therefore patients with depression may not even share a single depressive symptom but yet it is assumed that these patients suffer from the same condition. Furthermore, as a consequence of the removal of the bereavement criterion in the DSM-5, the context in which depressive symptoms may arise is now neglected. As a result, patients with severe and enduring symptoms as well as patients with symptoms that are common signs of distress are included by the DSM-5 MDD diagnosis. Thus, the current diagnosis of MDD seems to be heterogeneous.
Does this clinical heterogeneity of MDD actually have important public health consequences? Yes, since populations with MDD may differ considerably in their clinical presentation it is likely that subgroups of patients with depression may have differential correlates, and therefore it is difficult to study important correlates such as biological markers and risk factors for the overall condition of depression. Heterogeneity of the MDD diagnosis may thus hinder progress in depression research and ultimately hamper new developments in depression treatment. This is a major concern as, despite effectiveness of currently available antidepressant treatment in MDD, around 30% of patients still do not reach remission of their MDD, even after several treatment attempts [18]. This emphasizes the importance of developing new potential drug treatments and to establish differential treatment response, but this is greatly hampered by the heterogeneity of the MDD diagnosis. In order to establish new potential treatment targets, research focused on the potential neurobiological pathophysiology of MDD. Several neurobiological mechanisms have recently been implicated in the pathophysiology of MDD, such as alterations in regional brain volumes and disturbances in the main neurobiological stress-responsive systems including the hypothalamic-pituitary-adrenal axis, adrenal nervous system and the immune system [19]. It has been shown in patients with high baseline inflammatory biomarkers, that anti-inflammatory treatment with a tumor necrosis factor (TNF)-α antagonist may improve depressive symptoms [20]. A meta-analysis by Kohler and colleagues (2014) suggested positive antidepressant effects of anti-inflammatory drugs and cyclooxygenase-2 inhibitors in depression but this finding was uncertain because of heterogeneity across included trials [21]. This underlines the need to identify more homogeneous depressive subgroups that may benefit from differential treatment regimens. One important entity of MDD to study is anxious depression, as substantial evidence points out that it is of major clinical relevance [22,23].
Anxious depression

What is anxious depression?
Depression often co-occurs with anxiety [24] and has been extensively studied, but various concepts and definitions have been used for this co-occurrence [22,25]. Generally, the term ‘anxious depression’ has been used interchangeably throughout the literature to denote three common dichotomous anxiety-depression definitions:
1) MDD with the DSM-5 anxious distress specifier (i.e. at least 2 out of 5 general anxiety symptoms);
2) MDD with a comorbid full-blown anxiety disorder;
3) MDD with anxiety symptoms measured as an above cut-off score on an anxiety severity scale [22].

This thesis mainly focuses on the first definition of MDD with the anxious distress specifier, but the other two anxious depression definitions are examined as well. While prior studies have often focused on dichotomous classifiers for anxious depression, others have expressed the concept as a continuous dimension. Consequently, various definitions for anxious depression are being used across studies, making results not always directly comparable.

Clinical relevance and current evidence
Why is anxious depression worth clinical and research attention, and does its exact assessment play an important role in this? The clinical relevance becomes clear from recent studies illustrating that patients with anxious depression compared to patients with ‘pure depression’ generally may have greater depression chronicity and severity [24,26-29], higher suicide risks [30-32], lower treatment response [23,33-37] and a differential neurobiological profile [38]. Thus, while these important clinical implications underscore the need for further investigation, the use of inconsistent diagnostic criteria has resulted in significant variability in the samples studied. This hampers our ability to draw conclusions about the anxious depression population and the efficacy of treatment interventions. However, new developments in the field of anxious depression may contribute to a more uniform, clinically relevant definition as the DSM-5 includes a new anxious distress specifier [4].

It is of significant interest to establish how well this anxious distress specifier predicts clinical outcomes, when compared with a formal comorbid anxiety disorder diagnosis. This has important implications in that assessment of anxiety by means of a short specifier is much easier and less time-consuming than formally diagnosing a full-blown DSM-based anxiety disorder. The anxious distress specifier might also aid in identifying
patients with significant anxiety not meeting full criteria for anxiety disorder, but who may require a different treatment strategy than patients without anxiety or anxiety disorder. Further, it is important to establish whether anxious distress in depression is characterized by a differential neurobiological basis, which may aid its recognition as a distinct depressive symptom profile and ultimately its treatment by providing insight into more specific biological treatment targets [38]. Because MDD is also associated with substantial consequences on somatic health [10], it is important to examine the impact of anxious distress in MDD on the incidence of common somatic diseases. By gaining insight into whether anxious distress contributes to somatic disease onset in patients with MDD, prevention and treatment strategies may be more focused on somatic disease development in these patients.

At the start of this thesis, hardly any studies had been conducted on the validity of the anxious distress specifier, although the importance of testing the specifier as a predictor and prognostic indicator was emphasized by several researchers [39,40]. One exception was the study by Zimmerman (2014), in which a self-report measure was developed to test the DSM-5 anxious distress specifier [41]. After examining its psychometric properties, association with clinician anxiety ratings and clinical characteristics, the self-report measure was found to be reliable and valid, and patients with the anxious distress specifier had worse outcomes [41]. However, the Zimmerman study provided no longitudinal data. Therefore, although potentially of great clinical value, the longitudinal validity of the DSM-5 anxious distress specifier for clinical and treatment outcomes in patients with MDD was largely unknown. Furthermore, during this thesis, very few studies were conducted on the possible underlying neurobiological basis of anxious distress in depression. Only two studies have examined the link between inflammation and depression with concurrent anxiety. One study showed higher monocyte counts in patients with MDD and moderate-severe to severe anxious distress than in those with mild to moderate anxious distress [42]. The other study found decreased venous blood basophil counts and increased fragmented neutrophils in patients with MDD and high levels of anxiety [43]. The findings of these studies reflect alterations in white blood cell subset counts and indirectly may point to alterations in the immune system, suggesting the role of inflammation in the development of anxious depression. With regard to onset risks of somatic diseases, during the conduct of this thesis, only one study assessed the impact of anxious distress on CVD [44]. This study showed an increased risk of CVD in patients with depression plus anxious distress [44] but whether onset risks of other common somatic diseases are also increased in patients with anxious depression is unknown. Moreover, almost no studies have been conducted that examined the impact of specific clinical depression characteristics on the incidence risks of a multitude of somatic disease categories simultaneously, while taking important lifestyle factors into account. Exploring
the role of anxious distress in depression and other clinical depression characteristics on incidence risks of somatic diseases may help to improve prevention strategies and may provide specific treatment targets, from which both patients with depression as well as society may greatly benefit.

Central aims of this thesis

The main objective of this thesis is to establish whether anxious distress in depression is a distinct and clinically important depressive symptom profile. In order to address this matter from different perspectives, several sub aims were defined in this thesis.

Aim: to establish whether anxious distress in depression is a distinct and clinically important depressive symptom profile.

The first sub aim is to establish the longitudinal predictive validity of the DSM-5 anxious distress specifier for clinical outcomes in patients with current MDD, and to validate the specifier’s predictive validity against that of comorbid DSM-IV-based anxiety disorder diagnoses (Chapter 2). The second sub aim is to establish the ability of the DSM-5 anxious distress specifier to predict treatment outcomes and frequency of antidepressant side effects in patients with current MDD starting adequate antidepressant treatment, and to compare the specifier’s predictive validity against that of comorbid DSM-IV-based anxiety disorder diagnoses (Chapter 3). The third sub aim is to establish whether anxious distress and other related dimensional anxiety scales are associated with differential basal inflammatory markers and innate cytokine production capacity in patients with current MDD (Chapter 4). The fourth sub aim is to establish the value and place of anxious distress in depression within the field of anxious depression, while considering clinical course trajectories and outcomes, treatment outcomes, and its possible underlying neurobiological dysregulations (Chapter 5). The final sub aim is to establish whether anxious distress in depression, and also other clinical depression characteristics, impacts the onset risk of somatic diseases in patients with MDD over 6 year time (Chapter 6).
Methods

Netherlands Study of Depression and Anxiety (NESDA)
To address the above mentioned research aims, all studies included in this thesis used baseline, 1-, 2-, 4- or 6-year follow-up data from the Netherlands Study of Depression and Anxiety (NESDA) [45]. The NESDA study is an ongoing longitudinal, observational cohort study designed to examine the long-term course of depressive and anxiety disorders. A total of 2,981 persons were included in the baseline assessment between September 2004 to February 2007 from three study sites in the Netherlands (Amsterdam, Leiden and Groningen). The NESDA sample consists of participants aged between 18 and 65 years with a current (57%) or remitted (21%) depressive and/or anxiety disorder and healthy controls (22%). Participants were recruited from the community (19%), primary care (54%) and outpatient mental healthcare services (27%) reflecting different settings and stages of psychopathology. Exclusion criteria were insufficient command of the Dutch language and a primary clinical psychiatric disorder diagnosis other than depressive or anxiety disorders including a bipolar disorder, an obsessive-compulsive disorder, a posttraumatic stress disorder, a substance use disorder or a psychotic disorder. At baseline, 2- (n=2,596; 87.1%), 4- (n=2,402; 80.6%) and 6-year (n=2,256; 75.7%) follow-up, broad assessments took place for all participants and included a face-to-face interview, self-report questionnaires, blood collection and a physical examination performed by trained research staff. Data of 1-year follow-up (n=2,445; 82%) were acquired by a self-report questionnaire including measures of depression symptom severity and medication use. The rationale, objectives and recruitment strategy of the NESDA study can be found in a study design paper [45].

Measurements of key concepts in this thesis
Major Depressive Disorder
Diagnoses of current (6-month or 1-month recency) and remitted (presence of a lifetime MDD diagnosis but without an MDD diagnosis or any anxiety disorder in the past 6 months) MDD were established in a face-to-face-interview by the Composite International Diagnostic Interview according to DSM-IV criteria algorithms (CIDI, version 2.1) performed by trained research staff [46].

Anxious distress
The anxious distress specifier was constructed by selecting five items from self-reported questionnaires administered within NESDA that matched the five DSM-5 anxious distress criteria: the Inventory of Depressive Symptomatology (IDS) [47] and the Beck Anxiety Inventory (BAI) [48]. Both questionnaires assess the presence of specific symptoms in the past week on a 0–3 (not at all–severely) scale. The selected IDS items were: item 7
'Feeling anxious or tense' (DSM-5 criterion 1), item 15 'Concentration/decision making' (DSM-5 criterion 3) and item 24 'Feeling restless' (DSM-5 criterion 2). The selected BAI items were: item 5 ‘Fear of worst happening’ (DSM-5 criterion 4) and item 14 ‘Fear of losing control’ (DSM-5 criterion 5). Symptoms that were scored with at least two (i.e. moderate or severe options) on the 0–3 scale, were considered present. When at least two symptoms were present, the specifier was considered present (dichotomous indicator). We also constructed a continuous indicator by counting the number of anxious components present (range, 0–5 symptoms).

As indicated above, in addition to the anxious distress specifier, we also used other methods to classify anxious depression in order to compare these with the anxious distress specifier. Anxious depression was also determined by the presence of comorbid DSM-IV-based current (6-month recency) anxiety disorders (Social Phobia, Panic Disorder with or without Agoraphobia, Agoraphobia and Generalized Anxiety Disorder) using the CIDI. In addition, different anxiety (sub)scales were assessed: The Inventory of Depressive Symptomatology anxiety arousal subscale (IDS-AA) [49], BAI [48], Fear Questionnaire (FQ) [50], Mood and Anxiety Symptoms Questionnaire Anxious Arousal subscale (MASQ-AA) [51], Anxiety Sensitivity Index (ASI) [52] and the Penn-State Worry Questionnaire (PSWQ) anxiety subscale [53]. Some of these scales focus more on somatic anxiety symptoms (i.e. IDS-AA, BAI and MASQ-AA), others more on cognitive anxiety symptoms (i.e. anxious distress specifier, FQ, ASI, PSWQ).

**Other clinical depression characteristics**

In addition to examining anxious distress in MDD, the impact of other clinical depression characteristics was evaluated in our study on somatic disease development. These characteristics included depression severity, depressive symptom clusters, individual depressive symptoms and other depressive subtypes than anxious distress in MDD (MDD with atypical or melancholic features). The 30-item self-report IDS [47] was used to assess overall depression severity, depressive symptom clusters and individual depressive symptoms. The IDS assesses all DSM-IV criterion symptom domains of MDD, plus commonly associated symptoms and symptoms relevant to melancholic and atypical features. For depression severity, the total IDS score (range, 0–84) was used, with a higher score indicating a higher severity. Depressive symptom clusters were created by classifying the 30 individual IDS items into a mood, cognitive and somatic/vegetative cluster that were based on previous factor-analytic symptom clusters [54]. Sum scores were created of the included dichotomized mood (10 items; range, 0–10), cognitive (4 items; range, 0–4) and somatic/vegetative IDS symptoms (16 items; range, 0–16). Presence of individual depressive symptoms were assessed by 30 individual IDS items on a 0–3 (not at all–severe) scale, and were then dichotomized and considered present when scored ≥2 (i.e. moder-
ate or severe). The depressive subtypes included next to the anxious distress specifier (methodology is described above), an atypical and a typical/melancholic depressive subtype which were previously identified in the NESDA sample using Latent Class Analysis (LCA) based on CIDI items [55]. In total, three classes were identified and were labelled moderate, severe atypical and severe typical/melancholic depression [56]. It is important to note that these LCA-based atypical and melancholic classes do not refer to the DSM atypical and melancholic specifiers, but are mostly differentiated by the neurovegetative symptoms appetite and weight change.
Outline of this thesis

This thesis investigates whether anxious distress in depression indicates a distinct and clinically important depressive symptom profile. In order to address this topic from different perspectives, several studies were carried out to examine the longitudinal predictive validity and the role of anxious distress in clinical course trajectories, treatment outcomes, somatic health consequences and touches upon its potential underlying neurobiology in light of the immune system in patients with current MDD. Also, the value and place of anxious distress in depression within the field of anxious depression was explored.

In Chapter 2 the discriminant performance, convergent validity, and longitudinal predictive validity of the DSM-5 anxious distress specifier is tested in a large cohort of patients with current MDD. Also, the specifier’s longitudinal validity is validated against comorbid DSM-IV-based anxiety disorder diagnoses. Chapter 3 examines whether the DSM-5 anxious distress specifier predicts treatment outcomes and frequency of antidepressant side effects in a group of patients with new-onset MDD on recently initiated adequate antidepressant treatment, and compares the longitudinal predictive validity of the specifier to that of comorbid DSM-IV-based anxiety disorders. Chapter 4 investigates within a large cohort of patients with current MDD whether anxious distress and related anxiety features were associated with differential basal inflammatory markers and innate cytokine production capacity. In order to place these research findings on anxious distress in depression in light of the research field of anxious depression, Chapter 5 includes a comprehensive review of anxious depression including anxious distress in depression. This review provides an overview of the latest literature on the impact of co-occurring anxiety in patients with depression on clinical course trajectories and outcomes, treatment outcomes, and its possible underlying neurobiological dysregulations. Chapter 6 examines the impact of anxious distress in depression and other clinical depression characteristics on 6-year incidence of common somatic diseases within persons with current and remitted MDD, and healthy controls who were initially free of the somatic diseases under study, while adjusting for important lifestyle factors. The incidence of five somatic disease categories (cardiometabolic, respiratory, musculoskeletal and digestive diseases, and cancer) was examined. In addition to the role of anxious distress in depression, the role of depression severity, depressive symptom clusters, individual depressive symptoms and depressive subtypes, including MDD with atypical and melancholic features, were explored. Finally, Chapter 7 provides a summary of the main findings, discussion and conclusion. A schematic overview of the outline of this thesis is shown in Figure 1 below.
Figure 1. Schematic overview of thesis outline by chapter.

Numbers correspond with chapter numbers.
References


