Depressive and anxiety disorders as well as alcohol use disorders are among the most common psychiatric disorders in the general population. This is alarming as these disorders have a serious impact on a person’s physical, social and occupational functioning and constitute a large economic burden to society. This thesis focuses on the co-occurrence of depressive/anxiety disorders and alcohol use disorders, a phenomenon that occurs far more often than one would expect by chance. As persons with this comorbid condition suffer from more severe impairment, more suicidality and poorer treatment outcomes than persons with either depressive/anxiety disorders or alcohol use disorders, prevention and treatment strategies may offer the opportunity to greatly improve public health.

For this purpose, it is crucial to improve our understanding of the comorbidity of these disorders. How often do depressive/anxiety disorders and alcohol use disorders co-occur? What is the performance of a screening instrument for detecting alcohol use disorders in depressed/anxious persons? Which etiological pathways are involved in the development of this comorbid condition? And what are its consequences for the course of depressive/anxiety disorders as well as alcohol use disorders?

Comorbidity of depressive/anxiety disorders and alcohol use disorders
Chapter 2 reports on the lifetime prevalence of alcohol use disorders (i.e., alcohol abuse and alcohol dependence) in persons with and without lifetime depressive/anxiety disorders. Data were derived from the baseline assessment of the Netherlands Study of Depression and Anxiety (NESDA), an ongoing cohort study aimed at examining the course and consequences of depressive and anxiety disorders in the adult (18-65 years) population. Although only 5.5% of persons without a depressive/anxiety disorder met criteria for alcohol dependence, prevalence rates were significantly higher in persons with depressive or anxiety disorders (16.5% and 12.4%, respectively) and especially in persons with both depressive and anxiety disorders (20.3%). In contrast, alcohol abuse was not more common in persons with depressive and/or anxiety disorders than among healthy controls (overall prevalence of alcohol abuse: 11.8%).

Screening for alcohol use disorders
Although alcohol use disorders, and especially alcohol dependence, are highly prevalent in persons with depressive/anxiety disorders, these disorders often remain unrecognized in general psychiatric or somatic clinical settings. Adequate screening for alcohol use disorders may therefore help to identify those depressed/anxious persons suffering from this comorbid condition. Chapter 3 showed that the Alcohol Use Disorders Identification Test (AUDIT), as a time-efficient screening instrument including just ten items, accurately detected a DSM-IV diagnosis of alcohol dependence in depressed/anxious men and women of the NESDA study, which is comparable to its performance in healthy controls. The optimal cut-off point was ≥9 for men and ≥6 for women. The accuracy of the AUDIT in identifying alcohol abuse was, however, limited and no adequate cut-off points could be determined.
Possible pathways to comorbidity

To optimize prevention and treatment strategies for patients with comorbid depressive/anxiety disorders and alcohol use disorders, it is crucial to unravel the etiological pathways to comorbidity. Therefore, the present thesis prospectively examined whether depressive/anxiety disorders predicted the first-incidence of alcohol use disorders and/or vice versa. In addition, we explored the role of shared vulnerability factors in explaining the comorbidity of these disorders.

Chapter 4 examined the first-incidence of alcohol use disorders during a four-year follow-up in the NESDA sample. We found that the number of current depressive/anxiety disorders at baseline, as a measure for severity, was a strong and independent predictor of the first-incidence of alcohol dependence, but not of alcohol abuse. A possible underlying mechanism could be that depressed/anxious persons misuse alcohol to self-medicate their distressing symptoms and, consequently, have an increased risk of developing alcohol dependence.

In Chapter 5, we used data from the National Epidemiological Survey on Alcohol and Related Conditions (NESARC), a representative sample of the adult (≥18 years) civilian population in the United States, to examine the first-incidence of depressive disorders during three-year follow-up. We demonstrated that alcohol use disorder severity, as the count of all seven dependence and three abuse criteria, independently predicted the first-incidence of depressive disorders. Interpersonal and social consequences, often observed in (severe) alcohol use disorders, may cause the onset of depressive disorders. In addition, alcohol use may pharmaceutically induce the onset of depressive/anxiety disorders, for example, through chronic activation of physiological stress systems. This may be supported by Chapter 6 showing that heavy alcohol use was associated with dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis and the autonomic nervous system at the NESDA baseline assessment. Especially dysregulations of the HPA axis have been linked to depressive/anxiety disorders and may therefore contribute to the observed association between alcohol use disorder severity and first-incident depressive disorders.

In addition to these two causal models to comorbidity, common factors, such as the same personality traits, may independently cause the onset of depressive/anxiety disorders as well as alcohol use disorders. This was supported by Chapter 7, based on NESDA data, showing that all aspects of negative emotionality and some aspects of impulsivity (disinhibition and boredom susceptibility) were linked to pure as well as comorbid depressive/anxiety disorder and alcohol dependence, which may indicate that shared personality traits cause the onset of both disorders. However, persons with a primary depressive/anxiety disorder preceding alcohol dependence had higher scores of negative emotionality and lower scores of thrill and adventure seeking (i.e., more typical traits for depressive/anxiety disorders) than persons with alcohol dependence preceding depressive/anxiety disorders. This may indicate that these traits predispose persons to develop a depressive/anxiety disorder, which subsequently causes the onset of alcohol dependence.
The role of other risk factors
Other risk factors, such as sociodemographics and vulnerability factors, also played an important role in the development of a (comorbid) depressive/anxiety disorder or alcohol use disorder. One of the strongest predictors of the onset of psychopathology was gender. For example, Chapter 5 showed that the risk of developing a depressive disorder was doubled in women compared to men. In contrast, men had a two-fold increased risk of developing alcohol dependence compared to women (see Chapter 4). However, this association could largely be explained by the fact that men had already experienced more severe alcohol problems at baseline than women. Subthreshold symptoms also demonstrated to be strong and independent predictors of the first-incidence of psychopathology. For example, the severity of baseline major depressive disorder symptoms was an independent predictor of the first-incidence of depressive disorders (Chapter 5), whereas severity of baseline alcohol problems was a strong and independent predictor of first-incident alcohol dependence (Chapter 4).

Comorbidity and the impact on the course of disorders
As depressive/anxiety disorders and alcohol use disorders frequently co-occur, it is interesting to determine whether this comorbidity affects the course of disorders. Therefore, we used prospective data of the NESDA sample to examine the impact of comorbidity on the two-year course of alcohol dependence and depressive/anxiety disorders.

Chapter 8 demonstrated that severity of depressive and anxiety symptoms predicted the recurrence (i.e., relapse) of alcohol dependence during two-year follow-up in persons with remitted alcohol dependence at baseline. The recurrence of alcohol dependence may result from the same underlying mechanism as a first episode: persons misuse alcohol to self-medicate their distressing symptoms of depression and anxiety. However, depressive and anxiety symptoms did not predict the persistence of alcohol dependence in persons with current alcohol dependence at baseline, which may indicate that current alcohol dependence is a more autonomous condition involving loss of control over drinking and is therefore no longer dependent of mood states. Chapter 9 showed that (severe) alcohol dependence, but not alcohol abuse, independently predicted the persistence of depressive/anxiety disorders. Interpersonal and social problems, as specific characteristics of severe alcohol dependence, may cause the persistence of depressive/anxiety disorders.

Discussion
This thesis ends with a general discussion (Chapter 10) of the findings reported in Chapters 2 through 9. In conclusion, our findings suggest that depressive/anxiety disorders and alcohol use disorders have a bidirectional relationship as depressive/anxiety disorders promote the onset of alcohol dependence, whereas alcohol use disorder severity predicts the first-incidence of depressive disorders. In addition, comorbid alcohol dependence negatively affects the course of depressive/anxiety disorders, whereas comorbid
depressive/anxiety disorders have a negative impact on the recurrence of alcohol dependence. These findings provide evidence for a vicious cycle in which depressive/anxiety disorders and alcohol dependence are reinforcing each other. Suggestions for optimizing mental health care include screening for comorbid disorders as well as integrated care for persons suffering from this highly disabling comorbid condition of depressive/anxiety disorders and alcohol dependence.