

SUMMARY

Insomnia is a very common mental health problem. One in every three adults suffers from sleep problems such as difficulty falling asleep, difficulty maintaining asleep, or early morning awakenings. And for one in every ten people these problems are chronic. They suffer from sleep problems at least three nights a week, for at least three months, and it interferes with their daily functioning. These people suffer from insomnia disorder.

In addition to the discomfort that insomnia can cause at night and during the day, suffering from insomnia is also a risk factor for many medical and mental disorders. For example, insomnia increases the risk of depression, one of the most common and burdensome illnesses of our time. Insomnia can therefore have major health-consequences, both at present and in the future. Accordingly, it is very important to be able to understand who the people suffering from insomnia are. How do they differ from good sleepers? And why do some people with insomnia develop a depression, while others do not? To answer these questions will help us to identify, at an early stage, the people that are at risk, and to optimize the available treatments for insomnia.

Unfortunately, it proved difficult to answer these questions. This was mostly because, over the years, many findings on insomnia turned out to be inconsistent. While one research group found a certain brain circuit that seemed important for insomnia, this could not be replicated in a subsequent study and a different brain circuit appeared to be of importance. This was not only the case for brain circuits, but also in other areas such as cognition, mood, life history, family history and the microstructure of sleep. These inconsistencies hinder a better understanding of how insomnia is developed and maintained. At the same time, these inconsistencies may point to something else: it may be true that for some people with insomnia one brain circuit is important, while for a second group another brain circuit is important. In other words, perhaps these inconsistent findings are not inconsistencies, but point to the existence of different subgroups of people with insomnia.

The idea that insomnia may not be one homogeneous group, but consists of several subgroups, is the basis of the first part of this dissertation. This idea of subgroups within insomnia, however, is not new. Over the years, many different subgroups of insomnia have been proposed. For example, there was the idea of classifying people according to their dominant sleep complaint: difficulty falling asleep *versus* difficulty sleeping through the night *versus* problems with waking up too early. Unfortunately, this classification did not appear to be robust: even within a few months, people's dominant sleep complaint could change. This variability is problematic as we aim to find subgroups that are robust over time, so that we can ultimately understand the mechanisms behind insomnia better

in order to optimize its treatment. This ultimate goal becomes challenging when the types change over time. In that case, it suddenly matters whether someone comes to seek help in January, when difficulty falling asleep is the main complaint; or in June, when it may have turned into difficulty maintaining asleep being the dominant sleep complaint. An important condition in our research into subtypes of insomnia was therefore that they would be stable over time.

For this reason, we looked not only at the sleep problems themselves, but also at all kinds of other characteristics that may be important in the development and maintenance of insomnia: from personality traits to life-history, and from worrying and ruminating to the experience of happiness. All these characteristics have been shown to be relatively stable within persons and over time. Someone who tends to worry a lot, often has this tendency throughout his or her life. In this way, we had a very broad (multivariate) approach, in which we investigated whether different profiles might be captured within all these characteristics. Following this perspective, people's sleep problems may be the same, but it is actually the context in which the problems are developed and maintained that differs. It is thus not a single characteristic that is relevant to the different types, but rather a whole *system* in which the entire profile is of importance.

Based on this perspective, we collected a lot of data from many different people. This was made possible through the online platform of the Dutch Sleep Registry (www.slaapregister.nl), which was set up precisely for this reason. On the registry, anyone can create an account, which then gives access to many different questionnaires. From a very large group of more than 4000 good and bad sleepers we collected information on up to 34 different characteristics. Within the group of bad sleepers we found that, based on these characteristics, it is not one homogeneous group, but rather a heterogeneous group that can be better divided into five subgroups. Five types of insomnia: (1) a highly distressed type that experiences both many negative and very few positive emotions; two moderately distressed types that can be distinguished from each other because type (2) is mainly sensitive to stress, while type (3) is characterised by a lack of positive emotions; and two groups that are similar to people without insomnia in many respects, but one type (4) reacts strongly to life events and the other type (5) shows very little positive and negative emotions. A follow-up measurement showed that, even after a number of years, most people still belonged to the same subtype. The subtypes thus appeared to be stable over time.

Next, the most important question was whether these subtypes are clinically relevant: can we actually meaningfully distinguish people with insomnia from each other based on these subtypes? We made a small start in this respect and found, for example, that the development of sleep problems throughout the course of life differed greatly between the various types; and that cognitive behavioural therapy may have a different effect on the various types. One finding that is specifically important for the rest of this dissertation was that

the degree of depression problems that people with insomnia reported, both in the past and in the present, differed greatly depending on the type to which they belonged. While more than one-half of the people with type 1 had ever had a depression, and more than one-third had current mood problems; for type 4 this was less than 10 and 1 percent, respectively. Perhaps we can thus use these subtypes to identify people with insomnia who are at greater risk of developing a depression. By identifying the people with the highest risk at an early stage, we may even be able to prevent the depression.

This link between insomnia and depression formed the basis for the second part of this dissertation. A lot of research has already been done into this relationship. For example, it has been shown repeatedly that people with insomnia are at a higher risk for developing a depression; that 80% of people with depression also suffer from sleep problems (co-morbidity); and that when people with co-morbid insomnia and depression problems are treated for their insomnia, this not only reduces the sleep problems but also the depression problems. All these studies thus highlight the strong relationship between the two disorders. However, if we critically and carefully consider what it means to get a diagnosis of insomnia or depression, the interpretation of these results becomes more complex. Insomnia is after all not only a disorder of the night, but also a disorder of the day. In order to diagnose insomnia, a person has to suffer both from sleep problems at night and from reduced functioning during the day. Similarly, a diagnosis of depression can also include sleep problems. This strong overlap in symptomatology therefore raises the question of how we can meaningfully distinguish between these two disorders. Can this overlap in symptoms be an alternative explanation for the strong link that has been found between the two disorders? Can insomnia be a risk factor for depression simply because it is a symptom of depression?

In two studies we tried to re-examine the link between insomnia and depression, while taking this complexity of symptom overlap into account. We did so by investigating insomnia and depression not as two separate 'disorders', but rather as networks of interrelated symptoms. In this way, the direct relationships between symptoms are at the heart of the system and we can investigate the role of specific complaints in this system of symptoms. First of all, we investigated whether sleep problems increase the risk of depression, when viewed from this system's perspective. Instead of looking at insomnia as a disorder, in which people already have to suffer from daytime problems as well, we looked at the system of daytime and nighttime complaints and identified which specific complaints within that system are predictive for the development of a depression. Five complaints were found to increase the risk of depression, including difficulties falling asleep. This finding confirms that sleep problems increase the risk of depression, even if we take the relationship between the various day and nighttime complaints into account. This finding is important in identifying people who are at increased risk for developing a depression, such that we can ultimately prevent rather than treat depression.

At present, however, depression is very common, and often in combination with insomnia. In this respect, the results that point to the potential role of insomnia for its treatment are promising; as the successful treatment of insomnia seems to also reduce the symptoms of depression. At the same time, the question remained: do these effects really originate from the treatment of sleep problems at night? Or does the treatment possibly focus on the daytime complaints, such as worry and sad mood, both symptoms being part of insomnia as well? Again, we did not look at the individual symptoms or disorders, but at the system of day and nighttime complaints. Within this system, we investigated which specific complaints were targeted by the treatment using a new analysis that we introduced, called *Network Intervention Analysis*. This new analysis showed that indeed mainly sleep problems were tackled by the treatment; and specifically problems with sleeping through the night and early morning awakenings. So it does seem to be the case that the successful treatment of sleep problems is a driving force for the improvement of the depression problems. These studies together thus indicate that insomnia is of primary importance in predicting, preventing and alleviating depression.

Although the questions that are central to this dissertation are not novel, the way in which we investigated them is. Instead of merely focusing on the sleep problems to find subtypes, we broadened our perspective. This turned out to yield stable subtypes and the first results in terms of their clinical utility are promising. We moreover investigated the relationship between insomnia and depression from a new perspective, that is, as a system of symptoms. These investigations offer new starting points and suggest that the path from insomnia to depression (via problems with falling asleep) does not have to be the same as the path back (via problems with maintaining asleep and early morning awakenings). Together, all studies in this dissertation have an important common denominator: by changing our perspective, from single symptoms to complex systems, we can learn a lot about psychopathology in general, and the link between insomnia and depression in particular.