Deconstructing depression: unified syndrome or groups of symptoms?

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Chapter 8

Summary and General Discussion

The present dissertation aimed to expand our knowledge of depression by researching its symptom-specific longitudinal characteristics, its predictive factors, and methods for predicting depression and anxiety while taking individual symptoms into account. This dissertation mainly focused on depression, although anxiety has been studied as well, as anxiety is highly prevalent in patients with depression and share a common etiology. The following main research question was formulated: *Can major depressive disorder be characterized as a unified syndrome?* To answer this question we assessed the course of individual depressive symptoms over time (chapter 2), the relation between risk factors and the course of induvial symptoms and symptom domains of depression and anxiety (chapter 3-6), and examined if advanced statistical methods were more adequate to handle depression heterogeneity (chapter 7). We hypothesised that depression is a disorder with substantial within-person heterogeneity between symptoms in terms of intercepts, slopes, and variability. We expected that risk factors are associated with the course of specific symptoms, rather than depression as a homogeneous construct, with similar associations for each symptom. More specifically, we hypothesized that low-grade inflammation inflammatory markers demonstrate the strongest associations with symptoms that overlap with sickness behaviour. Lastly, we hypothesized that machine learning techniques are better in detecting complex patterns in the data and would outdo traditional regression analysis techniques and achieve higher levels of accuracy when predicting the course and onset of depression and anxiety, particularly when symptom-specific features of current depression and anxiety are included to predict future disorders. The first part of the present chapter will provide a summary of our findings. In the second half this chapter these findings will be discussed in light of the current literature, clinical implications and future research directions will be discussed.

8.1 Summary

Depression shows a large heterogeneity of symptoms between and within persons over time. However, most outcome studies have assessed depression as a single underlying latent construct, using the sum score on psychometric scales as a total indicator for depression severity. In **chapter 2,** we assessed the longitudinal symptom-specific trajectories and within-person variability of major depressive disorder over a 9-year period. The highest baseline severity scores were found for the items regarding energy and mood states. The core symptoms of depressed mood and anhedonia had the most favourable course, whereas sleeping problems and (psycho-) somatic symptoms were more persistent over 9-years follow-up. Within-person variability was highest for symptoms related to energy and lowest for suicidal ideation. The severity, course, and within-person variability differed remarkedly between depressive symptoms. Therefore, addressing depression at the syndrome level may obscure insights into both patient and symptom-specific characteristics. Our findings strengthen the idea that employing a symptom-focused approach in both clinical care and research is of value.

Individual symptoms demonstrate heterogeneity in their course over time, but this symptom-specific course is also related to different predictive factors. Preceding chronic depression and neuroticism are two of the most well established predictive factors for the course of depression. However, symptom-specific prospective studies are scarce. In **chapter 3,** we assessed if chronicity (i.e., being depressed for 24 months during a patient's preceding 48 months before baseline) and neuroticism at baseline could predict adverse course trajectories over 9 years of follow up with differential magnitudes for individual depressive symptoms. We found that patients with chronic depression or high levels of neuroticism showed similar absolute rates of decline over time compared to their counterparts. However, because symptoms had higher starting points for mood, cognitive, and somatic/vegetative symptoms (in that order), symptom severity remained higher over time. Findings for the effects of chronicity and neuroticism were remarkably similar, even when assessing the independent associations of both variables. Chronicity and neuroticism predict long-term persistence of diverse psychiatric symptoms, in particular low self-esteem and high interpersonal sensitivity.

Although neuroticism and chronicity are two of the most well-established predictor variables, current psychiatric symptoms are maybe the strongest predictor of all. Although this seems obvious, this is often ignored in scientific literature and previous studies have often failed to take baseline severity into account when assessing the effects of personality pathology. In **chapter 4,** we assessed the prognostic value of personality pathology (e.g. Emotional Dysregulation, measured with DAPP-SF) on treatment outcome among patients with depressive and/or anxiety disorders. Baseline symptom level (BSI-pretreatment) was considered as a mediator- or moderator variable. We found that personality pathology was strongly and significantly associated with treatment outcome. At first glance, this suggests that dimensional levels of personality pathology had a significant and seemingly clinically relevant effect on treatment outcome. However, when taking baseline symptom level into account, we found that patients with high symptom levels at baseline had substantially higher symptom levels after treatment, regardless of personality pathology level. These findings support our hypothesis that baseline symptom level was an important mediator. Furthermore, we found that the baseline symptom level also statistically moderated the predictive effects of Emotional Dysregulation and Inhibition, which were slightly more predictive of treatment outcome among participants with high baseline symptom level. However, the effect sizes of these interaction terms were small.

Besides psychological variables, we also assessed symptom-specific associations with biological variables. Multiple studies demonstrated an association between inflammatory markers and MDD. A cross-sectional relationship between low-grade inflammation and anxiety has also been reported, but the potential longitudinal relationship has been less well studied. People with chronic low-grade inflammation may be at an increased risk of MDD, often in the form of sickness behaviours. We hypothesized that inflammation is predictive of the severity and the course of a subset of MDD symptoms, especially symptoms that overlap with sickness behaviour, such as anhedonia, anorexia, low concentration, low energy, loss of libido, psychomotor slowness, irritability, and malaise. In **chapter 5** and **chapter 6** we tested the association between basal and lipopolysaccharide (LPS)-induced inflammatory markers with individual MDD symptoms and symptom domains of anxiety over a period of up to 9 years. We found that basal and LPS-stimulated inflammatory markers were more strongly associated with sickness behaviour symptoms over the course of 9-year follow up, compared

to non-sickness behaviour symptoms of depression. We also found associations with anxiety symptoms of somatic (arousal) symptoms and agoraphobia. However, the associations were attenuated by 25%-30% after adjusting for the presence of (comorbid) MDD, and the effect sizes of these associations were small. Inflammation was not related to depression as a unified syndrome but rather to the presence and the course of specific MDD symptoms, of which the majority were related to sickness behaviour. It is likely that many of the associations we found have to do with lifestyle and disease-related variables, as these factors are thought to be part of the causal pathway. Afterall, variables related to somatic diseases (e.g. obesity) may induce sickness behaviour, which includes (lifestyle) changes such as a decrease in physical activity. Another line of thought is that these somatic and lifestyle factors act as confounding variables as they are both related to inflammation and depression, though our conclusions remained when we adjusted our findings for the presence of chronic somatic diseases. Moreover, the fact that inflammation seems to be associated with symptoms related to sickness behaviour with the strongest magnitudes, suggests that the sickness behaviour theory is probable.

Due to the heterogeneity of depression and anxiety, predicting the onset and course of mood and anxiety disorders is of clinical importance but remains difficult. Perhaps more advanced statistical models are better suited to handle the complexity of mood and anxiety disorders and improve predictive accuracy. In **chapter 7,** we compared the predictive performances of traditional logistic regression, basic probabilistic machine learning methods, and advanced automated machine learning (Auto-sklearn). We compared how well multinomial logistic regression, a naïve Bayes classifier, and Auto-sklearn predicted depression and anxiety diagnoses at a 2-, 4-, 6-, and 9-year follow up, operationalized as binary or categorical variables. Predictor sets included demographic and self-report data, which can be easily collected in clinical practice at two initial time points (baseline and 1-year follow up). We additionally included predictor sets that took the current individual symptoms (item-scores) into account. The three methods were similarly successful in predicting (mental) health status, with correct predictions for up to 79% (95% CI 75–81%). When assessing a more complex dataset with individual item scores Auto-sklearn was superior but did not result in higher accuracy levels. Against our expectations, more advanced methods of automated machine learning added only limited value, compared to traditional data modelling, when predicting the onset and course of depression and anxiety.

8.2 General Discussion

8.2.1 Is the course of individual depressive symptoms uniform over time?

Although most studies approach depression as a unified construct, we found substantial heterogeneity between depressive symptoms in terms of symptom severity at baseline (i.e., intercepts), slopes over time, and within-person variability over time [1-3]. These findings are consistent with previous literature [4, 5], although in contrast with others [2, 6, 7].

Outcome measurements are generally based on a questionnaire sum score, in which the same weight is given to each of its items. This method would be valid in view of classic test theory; if MDD was a unified construct and all its symptoms contributed equally to its latent construct [8, 9]. However, MDD is unlikely to be a distinct illness with homogeneous symptomatology [8, 10, 11] and the symptom-specific severity, slopes and variability show that symptoms are not diagnostically equivalent and are not interchangeable [12]. Rather, MDD consists of individual symptoms that behave differently over time. These symptoms influence each other with different magnitudes on group level, but also may change within individuals over time [13].

The dynamic nature of these symptom profiles raise the question whether using a sum score of self-report questionnaires does justice to the heterogeneity between symptoms. The use of sum scores to estimate depression severity obscures insight into both patient- and symptom-specific characteristics and can lead to serious misinterpretations regarding depressive severity over time [8, 14]. For example, a patient who recovers by feeling less depressed will show a similar change in the depressive severity measure as a patient whose recovery takes place in another symptom domain, such as sleep. A clinically important change might be obscured by more trivial changes on other items.

In general, depression treatment focuses mainly on the core symptoms of depression. However, a more symptom-specific approach would reveal that other symptoms (e.g. sleeping problems) are more persistent. These residual symptoms are relevant, as they are known to form a risk factor for relapse and worse overall treatment outcome [15, 16]. Other techniques for measuring the course of depression symptomatology are needed and being developed, such as network analysis [17] and dynamic time warp analyses [18].

8.2.2 Are individual symptoms of depression related to the same risk factors?

If depression truly represents one unified latent disorder, all risk factors would have affected the individual symptoms with similar effect sizes. However, two comprehensive studies have demonstrated that individual symptoms have different risk factors [19, 20]. We extended these findings and demonstrated that history of chronic depression, neuroticism, and inflammation is not related to depression as a whole, but rather with specific symptoms with varying magnitudes. Our findings are discussed in the following paragraphs.

8.2.2.1 Preceding chronicity and neuroticism

Two of the most established prognostic factors for depression are a preceding chronic course and neuroticism. We found that a history of chronic depression at baseline was a predictor for the severity of most individual symptoms during 9 years of follow-up of MDD patients, albeit of varying magnitudes. Surprisingly, findings for the effects of chronicity and neuroticism were remarkably similar. Both baseline variables independently predicted an adverse course of symptoms of mood and cognitive symptom clusters, demonstrating the strongest link to 'low self-esteem' and 'interpersonal sensitivity'. The similar results for chronicity and neuroticism in relation to these two symptoms seem to suggest that either these symptoms might cause each other, or that a third dimension (e.g., general severity of MDD, chronic arousal and stress activation, or social isolation) underlies the reported relationships, or both. Although no longer in practice since the introduction of the DSM-III, our findings are relevant in light of a proposition to revive neurotic depression, a subtype of depression which is reactive to life events, persistent, and unlikely to benefit from antidepressants [21]. In light of one modern view of depression as a network of symptoms with between symptom causalities, it is likely that symptoms of low self-esteem and interpersonal sensitivity may be central in the network of patients with a neurotic-like expression of depression [12]. Low self-esteem and high levels of interpersonal sensitivity can play a role in the overall persistence and relapse of depression [22-25].

These findings are also interesting in light of an evolutionary approach of psychiatry. Within this approach, it is thought that the function of emotions is that they create a special state in an organism that allows it to cope effectively with adaptive challenges [26, 27]. In certain situations the effort of pursuing a goal does not match the potential benefits of success.

Feelings of low mood, anhedonia, and lack of energy may be beneficial in these circumstances, as they downregulate the tendency to put effort into the pursuit of unreachable goals, also known as the "*regulation of effort*" [26]. However, depression consists of more than these core symptoms, such as symptoms of increased interpersonal sensitivity and low self-esteem. Perhaps, specific symptoms have different functions for specific adaptive challenges. Price, among others, formulated the *social competition hypothesis of depression* [28, 29]. In this theory, symptoms of negative affect serve as signals in conflicts of hierarchy. In line with this theory, self-deception about one's abilities (low self-esteem) induces dominant others into thinking the individual is no threat. Perhaps symptoms of low self-esteem and feelings of worthlessness might specifically be induced by situations in which it is better to inhibit striving, signal submission and a wish for reconciliation [30-34]. In relation to our findings, perhaps in a subgroup of chronic patients with high levels of neuroticism, interpersonal relations are particularly problematic, therefore leading to symptoms of low self-esteem. Or, difficulties in interpersonal relationships are experienced as more stressful, which is in line with our findings of increased levels of interpersonal sensitivity. One can imagine that among patients with high level of neuroticism, symptoms of high interpersonal sensitivity and low self-esteem tend to bidirectionally influence each other, which could lead to a chronic course.

8.2.2.2 Personality pathology and symptom levels

Personality pathology and depression are two highly intercorrelated constructs. We demonstrated that dimensional personality pathology constructs had a significant and seemingly clinically relevant effect on treatment outcome of patients with a depression or anxiety disorder. Our results replicate findings from previous studies, in which personality pathology was found to have a negative impact on treatment outcome in patients with anxiety and depressive disorders [35-39]. However, high symptom levels at baseline resulted in substantially higher symptom levels after treatment, regardless of personality pathology levels. It is plausible that personality pathology has less prognostic value when researchers would adjust for baseline symptom levels [35-41].

The presentation and expression of personality pathology and depression/anxiety are known to bidirectionally influence each other [42, 43]. Personality pathology cause patients to respond to stress with (or relapse in) higher levels of depression and anxiety. Patients who

report lower (depression) symptom levels after treatment also display a decrease in levels of personality pathology [44]. Patients who are very anxious or depressed may fail to provide accurate self-descriptions [42, 45, 46]. Clearly, the depressive symptom of feeling worthless would influence self-descriptions of self-esteem and vice versa. Moreover, social anxiety symptoms would influence patients descriptions of interpersonal sensitivity and vice versa. In this regard, to some extent, personality pathology and depression/anxiety can in part be manifestations of one and the same underlying common spectrum [42].

8.2.2.3 Inflammation and mood states

We demonstrated that basal inflammatory markers and the LPS-induced inflammatory markers predicted specific depressive symptoms over the course of 9 years. Also associations with somatic (arousal) symptoms of anxiety and agoraphobia were found, although part of these relationships tended to be explained by MDD comorbidity. Our findings are largely consistent with previous findings; signs of low-grade inflammation at baseline were associated with the long-term symptomatology of sickness behavior [47], which may explain some of the symptoms in certain cases of depression [48-50]. The sickness-behaviour theory may (partly) explain the relation between inflammation and depression. More specifically, this theory states that somatic triggers induce an inflammatory response accompanied by sickness behaviour, which include reward oriented behavioural and motivational changes [47, 51-53]. These behavioural changes also are thought to hold some evolutionary advantages as they may protect the individual and facilitate recovery, by preserving energy resources needed for healing infection or other diseases and may help to prevent the transmission of its potential infectious agent to kin [47, 53]. Sickness behaviour (including lifestyle factors such as lower activity) is related to, and is part of, the depressive symptomatology [54-56]. However, when depression is approached on a syndrome level the relation is often rather weak or sometimes conflicting [47]. Inflammation may only be predominantly related to symptoms of sickness behaviour that overlap with those of mood disorders, which demonstrates the importance of symptom-specific research. This was recently confirmed with a pooled analysis in which 15 studies, of which ours, were included [57]. This demonstrated stronger associations between CRP and IL-6 and symptoms that were related to sickness behaviour, such as physical symptoms (e.g. loss of energy) and anhedonia.

Symptoms that were not related to sickness behaviour demonstrated smaller, or no associations with CRP and IL-6 [57].

8.2.3 Are advanced statistical methods more adequate to handle depression heterogeneity?

Besides assessing the added value of symptom-specific predictions of depression course, we also assessed whether improving statistical methods could improve predictive accuracy. Although we earlier approached individual symptoms as outcomes, a current symptom profile might as well predict depression or anxiety at follow-up [2]. In line with our increasing understanding of the complexity and heterogeneity of affective disorders, we expected that complex patterns exist in the data (including nonlinear and higher dimensional), which can be detected when analyzing all available data regarding individual symptoms and multiple variables simultaneously [58, 59]. Although we hypothesized using more advanced machine learning methods would be better suited for this task and would outperform simpler and more traditional data models, our research could not be concluded unequivocally. In fact, in line with an earlier study, we found that depending on the set of predictor variables, more complex machine learning methods do not necessarily result in higher levels of accuracy when predicting future outcomes of affective disorders [60].

Although expectations that machine learning methods will one day unravel the complex nature of psychiatry are still high, recent studies found that machine learning was only of limited added value in research compared to traditional regression models [61-63], and is limited in its clinical usefulness [64]. Within other fields, the proposed added value of machine learning is increasingly criticized [e.g., 62, 65, 66]. That aside, our findings as well as the literature suggest that machine learning might hold some benefits, especially when handling large and complex datasets [67]. Perhaps, the complexity and random chance effects, and therefore our inability to predict, is an inherent part of the nature of affective disorders, rather than a result of errors in our measuring and statistical methods. Although some progress in predicting psychiatry is still likely to be made, and might even be of some clinical usefulness (e.g. [68]), large accuracy levels are likely difficult to accomplish [69]. Small events could lead to dramatic changes in behaviour over time (also known as butterfly effects), such as certain childhood experiences or a treatment intervention in an early stage of the disease [70]. Moreover, the courses of psychiatric disorders are vastly influenced by factors outside

of mental healthcare such as individual choices and circumstances in social, economic, and lifestyles. More advanced models and more elaborate datasets might not be able to solve this. The field of psychiatry may benefit from acknowledging its chaos and complexity, while avoiding defeatism [71, 72].

8.2.4 Clinical implications and future research

Our results regarding symptom-specific associations with risk factors might contribute to the develoment of symptom-specific personalized treatments in the future. Moreover, we hope to have contributed to better understand the relation between inflammation and depression. However, as we made use of data from two cohortstudies without testing the use of certain interventions in clinical practice, we wish to be modest when it comes to giving advise for clinical implementations. Moreover, symptom-specific research on intervention level is only beginning to emerge and much more research is needed. Therefore, we integrated possible clinical implementations of our results with future research recommendations in the present paragraph.

8.2.4.1 Core symptoms

For clinical practice and research, more emphasis should be laid on the subjectively experienced phenomenology of symptoms instead of syndromes. When seeking help, patients do not describe that they experience a particular disorder, but instead they describe symptoms (e.g. “I feel depressed all the time”; “I can’t sleep”; “When I am in the supermarket, it feels like I am going to have a heart attack”). In theory, clinicians should then ask about DSM-5 criteria to classify patients. For example, when a patient is complaining about a depressed mood, clinicians should check if the patient has at least five out of nine symptoms. In practice, however, clinicians under time constraints want to provide care and not to categorize. Perhaps focusing on the reported core symptoms might be more important [73].

Research on personalized medicine in mental health care [74-76] and treatment of specific (residual) symptoms has highlighted that a symptom-specific approach may be beneficial [77-79]. Because a causal relationship exists between symptoms [80, 81], targeting the key symptoms (i.e., more central in the causal network of depressive symptoms) in clinical care may benefit a patient’s recovery [82]. Patients with similar DSM-5 classification may often have similar symptoms that are central in their symptomatology. For example, for most

patients with MDD, central symptoms would be a sad mood and anhedonia, although research also demonstrated that loss of energy is a highly central symptom [81]. For panic disorder, this might be “fear of internal sensations of physical arrousal” [83]. For generalized anxiety disorder, this often is “rumination”. For social anxiety, this often is “fear of social rejection”. However, most of these assumed “central” core symptoms are not researched suffiently with longitudinal network analyses. Most of these studies have used cross-sectional approaches, on the group level.

Although some stereotypical core symptoms per disorder could probably be identified on the group level, patients differ substantially on the individual level. Individual patients vary in the symptoms that are most central in their symptomatology. Only recently have idiographic analysis techniques been used more frequently to study time series of depressive symptoms in a single patient [84]. Especially when taking the vast comorbidity between depression and anxiety into account; patient A may experience a sad mood as a reaction to prolonged symptoms of panic, and patient B may experience panic after increasing levels of persistent sad mood. Patient A may thus benefit more from targeting panic in therapy than patient B. Moreover, other symptoms (e.g., sleeping problems) may be more persistent and can be a risk factor for relapse; therefore, it might be important to identify these symptoms in later stages of treatment [15, 16].

A new field of research is beginning to emerge in which patient-specific symptom networks are assessed [85]. In order to identify these networks, a patient is asked to report their symptoms over the course of several weeks, multiple times a day [86]. This method of intensive, acute, and real-life measurement is also known as ecological momentary assessment (EMA) [87]. This produces a rich dataset that allowes to assess which symptom potentially causes other symptoms, and therefore might be important to target with a personalized treatment. Altough this method is innovative and promissing, the vast effort that is needed by the patient makes it less likely to be implemented on a large scale in clinical practice. Novel analytical techniques are required to analyze panel data and time series data with a less intensive number of assessment [88], such as using Dynamic Time Warp [18, 89].

More research is also needed in order to assess other methods of determining patient-specific central symptoms. Paulhus and Vazire (2005, p. 227 [90]) stated that “no one else has access to more information than oneself”. Perhaps patients are able to assess their own central

symptoms when aided by professionals and a self-report questionnaire. Clinical practice may benefit from interview guidelines to identify patient-specific central symptoms through anamnesis and self-report. As is demonstrated with the Leiden Index of Depression Sensivitiy (LEIDS), patients are willing and able to self-report on their cognivity reactivity without mood induction [91]. Research is needed to assess if patients are able to report on the symptoms that are central in their depression.

8.2.4.2 Symptom-specific treatments

Although our current treatments often approach depression and anxiety on syndrome level when researched and implemented, in reality they are often already symptom-specific. The first-choice antidepressant (Selective Serotonin Reuptake Inhibitor) has demonstrated to have an effect on sadness and anhedonia that is more than twice as high, compared to the other symptoms of depression [92]. Furthermore, antidepressants even produce as negative side effects certain depression related symptoms, such as weight gain, sleeping problems, and psychomotor problems [8]. Symptom-specific cognitive behavioural therapy and pharmacological treatment, for instance, for insomnia appears to have a positive effect on depression as a whole [93, 94]. Multiple evidence-based treatments are available for the symptoms of low self-esteem, such as Competitive Memory Training [COMET; 95, 96] and mindfulness-based cognitive behavioural therapy [97, 98]. Interpersonal sensitivity is an important treatment target in interpersonal therapy [99]. Of course, keeping in mind depression as a network of symptoms, treating one symptom will likely effect other symptoms of depression, although not necessarily the full syndrome. Though, it might be beneficial to treat the person-specific “core symptom” first, before treating symptoms that are less central in the patients network [13]. More research is needed to assess the symptom-specific effects of these treatments, and whether a personalized symptom-specific treatment approach is indeed beneficial for the patient [79].

We found that inflammatory markers are related to specific depressive symptoms that overlap with sickness behaviour. Not all patients exhibit symptoms related to sickness behaviour, and only one third of MDD patients exhibit elevated inflammatory markers [100]. Our findings could have implications for anti-inflammatory treatment [101, 102] and personalized care [103-106]. Perhaps symptom-specific strategies could be developed in order to detect the subgroup of depressed patients for which anti-inflammatory treatments

could be valuable [107]. Instead of treating whole groups of patients with these interventions, only specific patients should be targeted that exhibit sickness related depressive symptoms [57]. Subsequently, inflammatory markers could be assessed before treating them with anti-inflammatory medication [108]. More research is needed in order to test the feasibility of this personalized medicine approach.

Based on our research, candidates for sickness-behaviour related depressive symptoms that also demonstrated significant association with most inflammatory markers are demonstrated in table 2. These symptoms include DSM-5 symptoms or IDS-SR symptoms that are often found in patients with MDD.

Table 2. Sickness-behaviour depressive symptoms that could be indicative elevated inflammatory markers *

1. Low energy
2. Psychomotor retardation
3. Anhedonia
4. Hyposomnia
5. Reduced libido
6. Leaden paralysis
7. Changes in appetite
8. Chances in weight
9. Somatic complaints, e.g. aches, pains and bowel problems

**More research is needed before clinical implication*

8.2.4.3 Using statistics in clinical practice

Deciding what information to collect from patients and making predictions on the micro level are important aspects of a clinician's skill set. This includes predictions regarding suicide risk, violence, the efficacy of treatment options, and the prognoses on the course of disorders [109]. The accuracy of these predictions is of vital importance for individual patients. Two major approaches to predict clinical outcomes can be identified: the clinical and the statistical method. The clinical approach refers to an informal and intuitive process. A clinician's experience, mentalization, and theoretical perspective combined with patient characteristics and circumstances determine how that clinician recalls and interprets these bits of information [109]. With a statistical approach, statistical methods are applied on objectively

measured variables in order to make predictions and prognoses based on probabilities [109]. Two meta-analyses demonstrated that statistical approaches were more accurate than clinical methods [109, 110]. In this dissertation, we demonstrated that moderate levels of accuracy can be accomplished based on data that can be easily collected in clinical practice, confirming that integrating statistical methods into clinical decision making could have an added benefit. Current mental healthcare is already partly digitalized, and the development of automated digital tools to assist clinicians should be attainable, providing clinicians with fast and cheap support in decision making. However, statistical reasoning may have certain ethical and clinical disadvantages, such as the inability to take into account patient specific circumstances. This could potentially lead to an inequality in access to care and stigmatisation [111]. Although Automated ML might be usefulness in healthcare practice [112], it should be used to assist and not to replace a clinicians decision-making.

A first step in the process toward statistically assisted clinical decision-making could be to bring more awareness about base rates into clinical practice. Research demonstrated that clinicians are often not aware of, or ignore, base rates and instead focus on patient-specific characteristics when making predictions. This is also known as the *base rate fallacy* [113, 114]. Using base rates when making clinical discissions is fundamental for clinical decision-making [114]. It can provide rough predictions for the prognosis of a disease, which could be important to take into account for both the clinician as the patient. Moreover, it could help to estimate the quality of care. For example, It would be important to notice when the percentage of successful CBT treatments goes down or is lower in one department compared with others [115]. However, calculating region-specific or clinic-specific base rates could be important.

8.2.5 Limitations

Some main limitations of our research need to be discussed.

- In both the NESDA and the Leiden Routine Outcome Monitoring study datasets, patients were selected at baseline when they met criteria for DSM disorders. Therefore, our data is subject to regression to the mean effects which resulted in a strong initial decrease in symptoms for most patients [116]. Although we tried to take baseline severity into account when assessing the course of symptoms over time, it is possible that patients were selected based on certain high (core) symptoms, which could therefore have coloured our findings.
- Individual symptoms of depression were assessed with items of the IDS-SR. Assessing individual symptoms based on single items presents psychometric hazards. Single items are more strongly affected by random error than sum scores of items [117]. Moreover, the ordinal scores per item are somewhat arbitrary and might differ in weight per item. For example, a score of "2. I think about about suicide or death several times a day", might be a more severe symptom than "2. I can feel the need to move and feel quite restless". Future research should preferable use multi-item measures per symptom such as – among others – the Inventory of Depression and Anxiety Symptoms, which incorporates multiple questions per symptom domain, for instance suicidal ideation is measured with six different items [118].
- Both NESDA and the Leiden Routine Outcome Monitoring Study have gathered limited data on the given treatments. Thus, we could not assess whether some types of treatment (pharmacological or psychological) were more effective with regard to certain variables (e.g., inflammation and neuroticism) than others.
- The time intervals between measures of the NESDA population ranged from a year to two years. We have no data on the course of symptoms between measurements. Therefore, it would be possible that patients remitted and relapsed between measurements.
- Most of our predictor and outcome variables relied on self-report. Self-report measures require patients to possess a certain level of insight, which may be lacking when levels of psychopathology are high, resulting in non-random errors of measurement.

8.2.6 General conclusion

The present dissertation aimed to expand our knowledge of depression by researching the symptom-specific longitudinal characteristics, its risk-factors, and methods for dealing with depression heterogeneity. The following main research question was formulated: *Can major depressive disorder be characterized as a unified syndrome?* Taken these findings together, our answer to this main research question is a resounding *no.* We demonstrated that individual depressive symptoms are not synchronized over time within patients and in groups of patients. We found that individual symptoms of depression are associated to different risk factors, as preceding chronicity, neuroticism, and inflammation were related to individual symptoms with vastly different magnitudes. With this dissertation, we hope to have contributed to the development of alternative ways to define and study depression and its symptoms. We are only at the beginning of a transition from one-fits-all syndromes to patient-specific symptoms. We hope to make a small contribution to the pavement of new ways of personalized symptom-specific treatments [79].

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