The interplay between depression, anxiety and physical health

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Chapter 9

General discussion

The aim of these studies was to enhance the understanding of how pain and (specific) chronic somatic diseases are associated with depressive and anxiety disorders in order to help tailor and improve management strategies for individuals suffering from both physical and mental health problems. First, we examined whether general practitioners' recognition of depression and anxiety is associated with physical health problems such as pain or chronic somatic diseases. Then, we assessed how pain and depressive and anxiety disorders are associated both cross-sectionally and longitudinally (onset, recurrence and chronicity). Next, we examined how chronic somatic diseases are associated with depressive and anxiety disorders over time. Finally, we determined the effect of depressive and anxiety disorder course on pain over time. For all these studies, we used data from the Netherlands Study of Depression and Anxiety (NESDA), which recruited 2,981 individuals in the age of 18 to 65 years. In this Chapter, the main findings from *Chapters 2 to 8* will be reviewed. Also methodological considerations, potential implications for clinical practice and future research will be delineated.

MAIN FINDINGS IN THE CONTEXT OF CURRENT SCIENTIFIC LITERATURE

Table 1 summarizes the main results of *Chapters 2 through 7*. In the first column, we show that reporting severe pain was associated with increased GP recognition. Having chronic somatic disease did not have a major impact on the recognition of depressive and anxiety disorders by general practitioners. In the second column, we show that having migraines in particular but also having pain in general, regardless of its location, was associated with increased odds of having a depressive and/or anxiety disorder. The third column shows that several pain locations, increasing number of locations and increasing severity of locations were associated with onset of depressive and anxiety disorders. When taking into account subthreshold depressive and anxiety symptoms, pain of the joints and increasing number of pain locations was still associated with depression and anxiety onset. As shown in the fourth column, having pain in multiple locations and of increasing severity was also associated with recurrence of depression, but this was largely through the effect of pain on subthreshold depressive symptoms. Diabetes was associated with depressive and anxiety disorder recurrence, whereas no other somatic disease was. Increasing number of pain locations and increasing severity of pain were also associated with a chronic course as shown in the last column. The results described in *Chapter 8* are not presented in this Table. In *Chapter 8* we showed a synchrony of change between depressive and anxiety symptoms and pain symptoms, and also that over time patients with depressive and anxiety disorder – whether incident, remitted or chronic – had worse pain symptoms compared to healthy individuals. Even after depression or anxiety remission, pain symptoms were worse compared to healthy controls.

Table 1: Main results of Chapters 2 through 7 for the association between pain, somatic diseases and depressive and anxiety disorders.

	Depressive and/or anxiety disorder*				
	GP Recognition	Prevalence	Onset	Recurrence[a]	Chronicity
	Chapter 2	Chapter 3	Chapter 4	Chapter 5,6,7	Chapter 5,6
Physical health					
Pain					
Neck	0	+	+	+	0
Back	0	+	+	+	0
Head	0	+	+	+	0
Orofacial	0	+	+	0	0
Chest	+	+	0	+	0
Abdomen	0	+	+	+	0
Joints	0	+	++	+	++
No of locations	0	+	++	+	+
Severity	+	n.e.	+	+	+
Duration	0	n.e.	0	0	+
Somatic disease					
Cardiac	0	n.e.	n.e.	0	0
Respiratory	0	n.e.	n.e.	0	0
Digestive	0	n.e.	n.e.	0	0
Diabetes	0	n.e.	n.e.	+	0
Musculoskeletal	0	n.e.	n.e.	0	+
Neurological	0	n.e.	n.e.	0	0
Thyroid	0	n.e.	n.e.	0	0
Cancer	0	n.e.	n.e.	0	0
Migraine	n.e.	+	n.e.	n.e.	n.e.
No of diseases	0	n.e.	n.e.	0	0

++ = significant positive association between physical health and depressive and/or anxiety disorder outcome, even after taking into account depressive/anxiety severity

+ = significant positive association between physical health variable and depressive and/or anxiety disorder outcome, not considering depressive/anxiety severity

0 = no significant association between physical health variable and depressive and/or anxiety disorder outcome

n.e. = not examined

* all associations were adjusted for gender, age and education

[a] significant associations between pain and depressive but not anxiety disorder recurrence

Physical health and GP recognition of depressive and anxiety disorders

Almost 60% of depressed and anxious individuals were recognized as such by their GP. This is rather high compared to other studies on GP recognition[1-7] and agrees with the finding that, in an international comparison on GP recognition of depression by Mitchell et al.[8], Dutch GP's recognized depression best. Also, we used the report of diagnoses of depression and anxiety and other psychological problems together with data on antidepressant medication and referral to mental health care, to define GP recognition. We were not able to use free text in the EMRs that the GP may use for indication of depression or anxiety. Use of free text could have led to even higher rates [3;4]. Our study showed that having chronic somatic disease is not significantly associated with GP recognition of depression and anxiety, which concurs with previous studies[6;9;10]. However, other studies found either lower[11-14] or higher recognition rates[15]. A reason for these differences might be that GP recognition could differ in different countries with different health care settings and different cultures[8]. Also, over the last decade international (GP) guidelines have reported on the attention that should be paid to depressive and anxiety symptoms in the physically ill[16;17]. The studies that found lower recognition rates when considering the patient's physical health status are at least ten years old. If increased awareness regarding depression and anxiety in the physically ill is indeed the reason why we did not find lower recognition rates in the physically ill, then higher recognition rates found by Robbins et al.[15] who performed their study in 1994 are surprising. However, the patients in their study were interviewed directly after a consultation with the GP, and the GP's were asked to fill in forms regarding diagnosing emotional problems, which may have caused increased attention during the consultations.

Our goal in *Chapter 2* was also to estimate to what extent particular physical health problems are associated with GP recognition of depressive and anxiety disorders. We found no significant association between several particular somatic diseases, i.e. diabetes, hypertension, heart disease, arthritis and GP recognition. Two studies[18;19] found similar results for diabetes and myocardial infarction. In contrast to our findings, however, they reported that hypertension was associated with increased GP recognition of depression and anxiety respectively. It could be argued that hypertension may cause feelings of anxiousness in some cultures but not in others. These studies did not take pain ratings into account. The association between hypertension in these studies could have been driven by the reporting of chest pain to the GPs by these patients which would then agree with our findings. It could be expected that patients with hypertension who report chest pain will be examined for possible cardiac causes of the pain. Once a cardiac diagnosis is ruled out, a depressive or particularly an anxiety disorder would be a differential diagnosis to consider. When depressive and anxiety severity were taken into account, we found that pain severity is related to depressive and anxiety severity and that through this pathway pain seems to impact on GP recognition. The display of severe pain symptoms, such as chest pain without an organic cause, may trigger the GP to consider a diagnosis of depressive or anxiety disorder. But it could also be that it was only the severity of depressive and anxiety symptoms that triggered the GP report on depression and anxiety in the EMR. With our data we were not able to differentiate between reasons the GP had to diagnose or treat a patient as depressed or anxious. All-in-all these findings provide a more in-depth proof supporting previous findings that being physically ill in general does not have a major impact on GP recognition of depressive and anxiety disorders.

Comorbidity of physical health problems and depressive and anxiety disorders

Comorbidity of pain and depressive and anxiety disorders

In *Chapter 3*, we examined the associations between pain locations and depressive and anxiety disorders cross-sectionally. We were interested in examining whether the associations between pain and depression and anxiety could be independent of anatomical site. Also, we had a particular interest in whether migraine was associated with depressive and anxiety disorders and we wanted to examine whether there was a consistent association between migraine and pain in other locations independent of depression and anxiety. Previous studies have reported associations between migraine and depressive and anxiety disorders and also between other pain locations and depression and anxiety. However, many studies focused on specific pain locations in relation to depression and anxiety, but did not aim to include information about other possible comorbid pain locations[20-22]. We assessed six different pain locations; neck, back, orofacial area, chest, abdomen, chest and joints. Having headaches was classified as mild nonmigrainous, probable migraine and strict migraine, depending on pain severity, duration, frequency and migraine specific symptoms. We found that pain of the back, neck, orofacial area, abdomen and chest as well as nonmigrainous headache, probable migraine and strict migraine were associated with remitted and - more strongly - with current depressive, anxiety and comorbid depressive and anxiety disorder. These findings point to a significant association between pain and depressive and anxiety disorders, which does not seem to be depending on the location of the pain. We also found that a change in pain was associated with a change in depressive and anxiety symptoms in a similar direction. There were some differences in the strengths of the associations between the different pain locations and depression and anxiety, for instance strict migraine was associated more strongly with depression, anxiety and comorbid depression and anxiety than back and joint pain. However, the definition used for having strict migraine was considerably more extensive than the reporting of pain in the other six locations over the past six months and therefore this particularly strong association may have been found due to a stronger association between more severe pain that does not have to be specific for migraine. A consistent association was also found between migraine and pain in all other anatomical sites, but when taking into account depression and anxiety these associations weakened.

Impact of pain on onset and course of depressive and anxiety disorders

Bair et al.[21] and Asmundson et al.[20] provide an overview on the link between pain and depressive, and anxiety disorders respectively, both finding more studies on the effect of depression and anxiety on pain than vice versa. Therefore, we wanted to examine how pain is associated with incidence and prognosis of depressive and anxiety disorders. In *Chapter 4*, we found a dose-response relationship where increasing severity and number of pain locations were associated with an increased likelihood of developing a depressive and anxiety disorder. The site of pain in these associations seemed less relevant to the association. Previous studies already reported pain as a risk indicator of depressive and anxiety symptoms, but information on the onset of depressive and anxiety disorders was very limited[23-30]. Our finding that pain is associated with new onset of depressive and anxiety disorders was recently confirmed by Barry et al.[31]. In *Chapter 5,* we found that pain is not only associated with onset of depression and anxiety, but also with the increased likelihood of a worse depression and anxiety course. There was a significant association between joint pain and a worse course, but we did not find significant associations for other particular locations. For these analyses, we took any pain mentioned into account whereas we decided to only take pain into account when participants reported high pain intensity or pain-related disability for the other analyses. We feel it is not surprising that when examining more severe forms of pain in relation to depression and anxiety more significant associations were found. This is in line with the significant associations between increasing severity and number of locations and the likelihood of onset and worse course of depressive and anxiety disorders. Also, in *Chapter 7* we found significant associations between several pain locations and depression recurrence, these findings were however largely explained through severity of subthreshold symptoms. In our longitudinal studies, the experience of joint pain - irrespective of the cause of pain - in particular was strongly associated with onset (*Chapter 4*) and course (*Chapter 5*) of depression and anxiety, even over and beyond the severity of depressive and anxiety symptoms. Also, the self-report of musculoskeletal diseases (*Chapter 6*) was associated with a chronic course of depressive and anxiety disorders. This may suggest that there are particular reasons why the combination of joint pain, which is also the core symptom of most musculoskeletal diseases, with depressive and anxiety disorders may lead to a worse depression and anxiety course. In the section regarding theoretical models below we outline our hypotheses on these particular associations.

Impact of chronic somatic diseases on course of depressive and anxiety disorders

Musculoskeletal disease was associated with a worse course of depression and anxiety. Diabetes was associated with an increased likelihood of a remitting and recurrent course over two years. When we focused on depression and anxiety remission and recurrence over the course of four years in *Chapter 7* we could not reproduce the associations between diabetes and depression and anxiety recurrence. We did not detect any association between other somatic diseases and depression and anxiety course, even though several other somatic diseases - such as cardiac diseases, COPD or cancer - are associated with increased prevalence of depression and anxiety. The NESDA study has a large sample size, but the prevalence of self-reported chronic somatic diseases was in general very low. Since our evidence was limited to a small number of somatic diseases, definite conclusions regarding the associations between (specific) chronic diseases and depressive and anxiety disorder course cannot be drawn. Most studies regarding the longitudinal associations between somatic diseases and depression and anxiety have focused on particular somatic disease populations such as patients with arthritis, diabetics or patients who recently have had a myocardial infarction. Our findings concerning musculoskeletal diseases (with arthritis in particular) agree with earlier evidence that musculoskeletal disorders are associated with worse depression and anxiety course[32]. Several meta-analyses and reviews report increased prevalence of depression and anxiety in diabetics and a negative impact of depression and anxiety on diabetes control and its complications[33;34]. Another NESDA study examined diabetes incidence in depressed/anxious and healthy individuals. They found a rather low diabetes incidence, but a higher diabetes onset in current depressed and anxious individuals compared to healthy individuals[35]. The effect of diabetes on depression and anxiety course is still not well described. Our findings contribute to previous findings in which (badly controlled) diabetes is associated with worse depression course and decreased antidepressant treatment response in depressed individuals[34;36]. However, other studies[32;37] did not find an association between diabetes and depression and anxiety course. Therefore, the evidence regarding the impact of diabetes on depression and anxiety course is still limited, and could be depending on the severity of diabetes and its complications.

To conclude, we found evidence musculoskeletal diseases and diabetes are negatively associated with depression and anxiety course. To answer our questions regarding the associations between particular somatic diseases and the development and course of depressive and anxiety disorders larger study cohorts are needed. Also, due to the low prevalence of somatic diseases, we were also not able to examine whether particular somatic diseases are risk indicators of depression and anxiety onset or whether depressive and anxiety disorders are predictive of somatic disease incidence or course.

Course trajectories of depression and anxiety associated with pain over time

We already found that change in the number of pain locations between baseline and two years later was modestly positively correlated with changes in depressive and anxiety symptoms over two years in *Chapter 2*. Similarly, change in D/A symptoms was positively associated with change in pain severity and number of pain locations over the course of four years in *Chapter 8*. This findings point to a synchrony of change in a way that an increase or decrease in pain is accompanied by an increase or decrease in depression and anxiety. Next to examining these associations at symptom

level, we were interested in whether a synchrony of change can be detected when examining change in the course of depressive and anxiety disorders. As expected, compared to healthy controls, we found that incidence, remittance and chronic course of depression and anxiety were associated with more severe pain and more pain locations, with the highest pain ratings in the chronically depressed and anxious. Supporting the synchrony of change we found that remission of depression and anxiety was associated with a significant decline in pain. However, pain levels remained significantly higher compared to healthy controls. A possible explanation for this finding could be that the depressive or anxiety disorder leads to a 'scarring' process which results in higher pain sensitivity. Not supporting the idea of synchrony of change was our finding that patients who developed a depression or anxiety over time, already had high pain ratings at baseline. Also, these patients did not show significant increases along with the development of depression and anxiety. These findings suggest that pain could be antecedent to depressive and anxiety disorders or increase vulnerability to the development of these disorders. In the next section, we will further delineate possible theoretical models behind the interplay of physical and mental health problems.

THEORETICAL MODELS AND PATHOPHYSIOLOGICAL PATHWAYS

Theoretical models

In the previous sections we combined our findings with previous research and provided evidence for bidirectional relationships between physical health problems, particularly pain, and depressive and anxiety disorders. Regarding the developing and perpetuating of these debilitating conditions, possible theoretical models have been described. As such, sensitizing or scarring mechanisms – with cognitive processes and personality changes – have been described in the development and perpetuation of pain and depressive and anxiety disorders[38]. The example that follows will focus on the effect of physical health on depression and anxiety because it best suits our data, but the pathway could also be reversed. Life stress is associated with onset of both pain and depressive and anxiety disorders[39;40]. Distress -for instance due to pain or somatic diseases- brings about elevations in vulnerability such that episodes of depression/anxiety occur before the onset of physical ill health and predispose to depression onset after physical ill health onset . The experience of pain itself, particularly when severe and widespread, can lead to anxiety sensitivity – which refers to the perception that bodily symptoms are harmful -, avoidance of pain, dysfunctional cognitions (such as pain catastrophizing or perceived helplessness), personality changes and reduced activity levels which can subsequently cause significant distress and ultimately contribute to the development and maintenance of both depressive and anxiety disorders. Due to pain, individuals may also have difficulty maintaining social relationships and have increased risk of losing their job which can subsequently lead to more distress, finally resulting in (worse) depressive and anxiety disorders[20;21]. Several somatic diseases may also lead to changes in role functioning in daily life and result in depression and anxiety. Also, often somatic diseases have pain as a core symptom and so pain could be a major link between somatic disease and depressive and anxiety disorder, particularly when remembering our findings regarding the negative impact that migraine has on depression and anxiety prevalence or musculoskeletal disease on depression and anxiety course. Even for diabetes, our findings could have been driven by the pain caused by peripheral neuropathy. Musculoskeletal diseases and diabetes are also associated with inflammatory and metabolic changes which may contribute to vulnerability in developing depression and anxiety. Consistent with and complementary to this psychological perspective, a neurobiological framework has also been developed. Next to behavioural changes, stress in response to (the experience of) threat activates genetically determined neuronal and hormonal programs. The dysregulation of these stress and inflammatory pathways promote alterations in brain circuitry that modulates stress, depression, anxiety and pain[41]. It is hypothesized that dysregulation of hypothalamic-pituitary-adrenal axis (HPA-axis), the autonomic nervous system (ANS) and the immune system (IMS) have a crucial role in the processes of central sensitization in pain disorders and "kindling" in depression and thus in the progression and (self-)perpetuation of chronic pain and depressive and anxiety disorders[42;43]. In the section below we will outline current evidence for these neurobiological links between physical and mental health problems.

Pathophysiological pathways

One of the pathophysiological pathways that has been associated with both depressive and anxiety disorders is dysregulation of the hypothalamic-pituitary-adrenal (HPA) stress axis. When depressed and/or anxious individuals are compared to mentally healthy individuals they show increased levels of cortisol[44;45]. However, in relation to chronic courses of depressive and anxiety disorders lower levels of cortisol have also been found, possibly pointing to an exhaustion of the stress system[46]. Dysregulation of the HPA axis has also been described in relation to painful conditions such as fibromyalgia. Interestingly, Riva et al. found that shoulder and neck pain were associated with hypercortisolism, whereas more severely affected pain patients with fibromyalgia had lower level of cortisol compared to healthy controls. The authors suggest that the regional (musculoskeletal) pain and associated hypercortisolism may constitute a preliminary stage towards the development of a hypocortisolism in widespread musculoskeletal pain[47;48]. Longitudinal studies on HPA axis abnormalities should integrate both pain and depression and anxiety to examine their separate and conjoint effects on this stress system. Dysregulation of the autonomic nervous system (ANS), increased sympathetic or decreased parasympathetic tone, has also been linked to both pain, with chronic widespread pain in particular, and depressive and anxiety disorders[49-51]. Evidence regarding ANS dysregulation has been associated consistently

with metabolic syndrome and could be a risk indicator of cardiovascular diseases and diabetes and ultimately be linked to depressive and anxiety disorders[33;52;53]. In turn, depressive and anxiety disorders could lead to pathophysiological and psychological changes (leading to passive behaviors such as physical inactivity) which contribute to development or worsening of metabolic syndrome and diabetes[33;53;54]. Dysregulation of HPA-axis and ANS contribute to immune activation and release of inflammatory markers (e.g. IL-6, CRP), which are associated to depressive and anxiety disorders and to several chronic somatic diseases such as cardiovascular diseases and arthritis[41;55;56]. Also several neurotransmitters, particularly serotonin and norepinephrine, are involved in both pain processing and emotion regulation[42;57]. Neuroimaging studies show significant overlap in brain areas, both functionally and/or structurally, for pain and emotion and in the descending pathways of the nervous system. For instance, studies have shown alterations in pain processing areas in depressed individuals. Therefore the presence of either pain or depression or anxiety may lead to the development or the worsening of the other[41].

"When pain will not wane it is only in the brain?"

Comorbidity of pain and depression and anxiety seems more a rule than an exception. Yet, in the DSM IV, pain is not listed as a symptom of any mood disorder. In the DSM 5, pain symptoms have not been incorporated differently in the criteria for depressive or anxiety disorders. Also, depressive and anxiety complaints are strikingly marginalized in the list of symptoms required to meet criteria for a chronic pain disorder[41]. Our findings, which show quite consistent associations between pain - particularly when in multiple locations and of increasing severity - and prevalence, incidence and course of depression and anxiety, seem to support the view that pain might be considered as a symptom of depression or anxiety as is sometimes postulated[21;58;59]. When also considering the above described possible psychological and pathophysiological pathways, then the separation of pain and mood and anxiety disorders might not be applicable for the majority of patients that can be found in clinical practice. However, it could also be argued that each condition also often exists without the other and the onset of pain and depression or anxiety do not typically coincide[38]. Further clarification of the associations between pain and depression and anxiety is needed before diagnostic criteria could be adapted.

METHODOLOGICAL CONSIDERATIONS

Several methodological issues have already been addressed in the previous Chapters. In this section, we will discuss the limitations of our study in general. An important remark is that the results are derived from an observational study, which does not allow us to make definitive statements on causal relationships between mental and physical health problems.

We used a large sample of adults with the advantage of inclusion of several important covariates. All the results in this thesis are based on adults who are aged between 18 and 65 years. As mentioned before, findings might therefore differ in children, adolescents and the elderly. Suffering from chronic somatic disease or pain at a young age may pose an even higher burden on daily life and may predispose to developing depression and anxiety and may possibly also lead to a worse course[60;61]. Also, compared to parents of healthy children, parents of chronically ill children may experience more distress and consequently have mood and anxiety disorders, which is known to increase risk of depression or anxiety in their offspring[62-64]. In an older population, the (longitudinal) associations between physical and mental health could be stronger due to multimorbidity and polypharmacy and decreased probability of adequate treatment for depression and anxiety. Compared to our study population of physically rather healthy individuals, elderly populations have increased incidence and prevalence of severe and multiple somatic health problems such as severe CVD and Parkinson's diseases which are associated with increased risk of depressive or anxiety disorders[65;66]. Also, they are more likely to use several medications some of which could induce affective problems [67]. However, previous studies also indicate that the prevalence of depressive and anxiety disorders decreases with age and several other factors such as loneliness and poor social support may be more important risk factors than the physical health problems[66].

Assessment of psychopathology

DSM-IV based CIDI diagnoses for the most common depressive and anxiety disorders were assessed. The longitudinal design of the NESDA study allowed us to examine associations between physical health and the incidence and course of depressive and anxiety disorders. In the NESDA study we included a heterogeneous sample of individuals (recruited from community, general practice and secondary mental health care services) with depressive and anxiety disorders, which is a major strength. However, with including only the most common DSM-IV depressive and anxiety disorders, we did not diagnose post-traumatic stress disorder (PTSD) and obsessive-compulsive disorder (OCD). Previous studies have reported strong links between physical health problems and PTSD, with pain in particular[20]. Therefore the reported associations between physical health and anxiety disorders may be underestimates.

Assessment of GP recognition

We were interested the associations between physical health and the GP recognition of depression and anxiety, and analysed this by comparing GP electronic medical records with a diagnosis in the diagnostic interview. We found a recognition rate of 60% which is rather high, nonetheless some factors may have negatively influenced this recognition rate. First of all, some patients do not perceive their problems as depression or anxiety or are reluctant to report these, which will increase the difficulty for GPs to accurately diagnose these disorders. Also, we did not

use the free text in the EMRs. It could be that GPs reported depressive or anxiety issues but did not report this as a diagnosis for instance to avoid stigma or because patients reported multiple problems during one consultation of which depressed mood or anxiety was the last one (the so called 'the doorknob phenomenon'). GP recordings of depression and anxiety were based on ICPC coding[68] which can be used to register disorders, but also symptoms descriptions such as depressive symptoms, distress or feelings of anxiousness. We chose to include both these symptom descriptions as well as disorder diagnoses as part of GP recognition of depression and anxiety. We feel that these are part of a spectrum of severity that may change during consecutive consultations, but which will not necessarily lead to adaptation of the recorded (symptom) diagnosis. We used a window of one year before and after the baseline diagnostic interview as an interval in which the GPs might have recorded a diagnosis. It could thus be that at the time of consultation the symptoms were more or less severe or even not present at all. Even though it is not recommended in the Dutch GP guidelines to prescribe antidepressants for pain complaints, some antidepressants may have been described for pain instead of depression or anxiety and this may have led to falsely high recognition rates. However, when excluding patients who were solely diagnosed based on antidepressant prescribing, we found similar associations between physical health and GP recognition.

Assessment of physical health

The NESDA sample was selected to study the long-term course and consequences of depressive and anxiety disorders and was not specifically selected for studying pain or particular chronic somatic diseases. The prevalence of several somatic diseases was quite low. Both the assessments of somatic diseases and pain were based on self-reports during face-to-face interviews. Compared to GP's EMR this information could be less accurate but if the EMRs are not complete, it could also be a benefit to study self-report. A previous study regarding self-reports of somatic diseases revealed fairly accurate diagnoses. However, the diagnosis of arthritis was not very accurate with both over- and underreporting compared to information obtained by the GP[69]. It is therefore possible, as we have stated before, that the positive association between musculoskeletal diseases and worse course of depression and anxiety was driven by pain. To provide the most accurate information on somatic diseases, next to also examining EMR data, radiographic or laboratory results should also be obtained. However, this would lead to tremendous costs for research and would probably lead to minor changes in disease prevalence. Also, for some symptoms all the effort will still not provide a definite diagnosis. In our chronic somatic disease questionnaire we specifically enquired after migraine. Of all 2,981 participants, only 60 reported having a migraine diagnosis at baseline. In the written questionnaire aimed at detecting migraine we found 453 individuals with symptoms fitting the definition of strict migraine. For the existence of some diseases both patients and GPs could thus be unaware.

We used a subjective measure for the experience of pain. The Chronic Pain Grade Scale is a multidimensional measure, which has previously been used in epidemiologic studies and clinical trials to evaluate pain severity across groups, in response to treatment effects and in clinical practice[70]. It is a valid and reliable tool and has shown to be responsive to change. We used the Chronic Pain Grade Scale to assess pain. It is well possible that pain disorders, such as migraine, fibromyalgia or irritable bowel syndrome, may be more strongly associated with depressive and anxiety disorder onset and course than our assessment of headache, joint pain and abdominal pain. Next to subjective pain measures, there are studies on experimental pain induction even in relation to depressive disorder. These studies comparing depressed individuals with controls have shown inconsistencies with hyperalgesia for deep pain such as invasive ischemic muscle pain and hypoalgesia in superficial experimental pain such as heat pain[71]. It could be that there is a difference in the associations between depression, anxiety and certain types of pain such as nociceptive (visceral, superficial or deep somatic pain) versus neuropathic pain. However, if these objective pain measures were to be used in longitudinal research participants would have to undergo multiple test moments, which would probably lead to very low response rates.

Statistical methods

We have used mediator models to examine the associations between physical health and depression and anxiety when taking into account possible mediators, of which the most important variables were the severity of depressive and anxiety symptom severity. A mediator is an intervening variable that may account (statistically) for the relationship between the independent and dependent variable[72]. We met an important demand to perform mediation analyses in that we demonstrated strong associations between the independent physical health variables and the mediating variables and also we found strong associations between the mediating variables and the depression and anxiety outcomes. Another important criterion for establishing mediation is to demonstrate the plausibility of the associations between independent, mediator and dependent variables which we have provided in the previous Chapters. The severity depressive and anxiety symptoms, in particular, are known to be the most important predictors of both occurrence and course of depression and anxiety. It is therefore apprehensible to expect an intervening role of these symptoms in the associations between physical and mental health. However, to perform mediation analyses it is proposed that a timeline should be established to infer a causal relation or mediator of change. The independent variable should precede the mediator variable in time, and that is a demand that we have not met. We do feel, however, that these analyses have provided a more in-depth insight in the associations between mental and physical health than if we had regarded severity of depressive and anxiety symptoms as confounders or moderators of the associations only.

CLINICAL IMPLICATIONS

One of the most important findings of this thesis is that pain is a risk indicator of onset and a worse course of depression and anxiety (*Chapters 4, 5 and 7*), with the severity of depressive and anxiety symptoms also being an important contributor to this association. The Dutch (GP) guidelines on depression and anxiety care were recently changed and recommend a stepped care model, in which the severity of depression and anxiety should guide the clinician to the appropriate intensity of treatment. Treatment for depressive and anxiety disorders relies mostly on cognitive behavioral therapy and antidepressant medication.

Current scientific knowledge points to shared biological underpinnings for several diseases, pain and depressive and anxiety disorders. Adequate management should probably focus on treatments that target both physical and mental health problems. There is evidence that some antidepressants, such as amitriptyline or duloxetine, may be beneficial in the treatment of certain pain conditions and depressive and anxiety disorders, but evidence is not conclusive[73-75]. Also, the downside of using pharmacological interventions– not only antidepressants but also analgesics - can be side effects and interactions with other medications, the last of which is particularly important in patients with comorbidity or even multimorbidity. Cognitive behavioral therapies have proven efficacy in symptom relief in both pain and depressive and anxiety disorders[29;76]. Currently, there is some evidence that targeting treatment at both pain and depression and anxiety (for instance via antidepressant treatment and a pain self-management program) has some efficacy compared to care as usual (which does not involve special attention to both problems)[77].

In the GPs' depression guideline, but not the anxiety guideline, pain is mentioned as a risk indicator for the onset and a worse course of depression. With this thesis we provide evidence for mentioning pain as risk indicator. There is no advice to systematically gain insight in the experience of pain symptoms and in pain management (e.g. is an appropriate analgesic being prescribed and used?), therefore in future guidelines the emphasis on pain could be improved. We also found that depressive and anxiety disorders lead to worse pain over time, even after depression and anxiety remission. We would advise that the future GP guideline regarding chronic pain will also point to the importance of adequately assessing and treating depressive and anxiety symptoms/disorders. The negative impact of having chronic somatic disease is mentioned in the depression and anxiety guidelines, and particularly in the depression guideline it is advised to assess self-management and treatment adherence for the somatic disease. We feel this should not be changed, because even though we did not find strong associations between having somatic disease and depression and anxiety, we did find associations between diabetes and musculoskeletal diseases with worse depression and anxiety course and also many chronic diseases harbor pain as a core symptom.

With the conventional treatments for both chronic pain and depression and anxiety many patients have proven treatment resistant. Therefore, there is a need for trials that search for optimal integrated (psychological and pharmacological) treatment interventions to be of most benefit to patients with both pain and an affective disorder. Moreover, future research should focus on new treatment modalities. Clearly, future studies are needed to tailor management for patients with physical and mental health problems.

FUTURE RESEARCH

This thesis has contributed to the longitudinal associations between physical and mental health problems. More research is however needed and directions for future research will be discussed below.

NESDA included participants who were 18 to 65 years old. As discussed previously, our findings are not representative of younger and older populations. Future studies in children, adolescents and the elderly would provide additional information.

Future large longitudinal studies would probably provide larger numbers of specific chronic somatic diseases and could thus focus on 'gaps' that remain to be filled in the associations between somatic diseases and onset of depressive and anxiety disorders. Not only focusing on somatic disease prevalence but also on its severity in the associations with onset and course of depression and anxiety may provide a better understanding of this form of comorbidity.

In this thesis we have specifically aimed at clarifying the role of physical health, particularly pain, in depressive and anxiety onset and course. Future longitudinal studies on depression and anxiety should examine pain next to other risk factors such as personality and coping.

Previous NESDA research has added knowledge to the evidence on the links between dysregulation of the HPA axis, the autonomic nervous system and metabolic and inflammatory pathways and depressive and anxiety disorders. Some evidence for the associations between these pathophysiological processes and pain has been found. But the studies are mostly cross-sectional and used small sample sizes. Another NESDA PhD project will involve the associations between these pathophysiological pathways and the reporting of pain. There is a need for longitudinal studies to evaluate the link between these pathophysiological pathways and physical and mental health.

Next to subjective pain ratings, experimentally induced pain may also help to unravel the pathophysiological changes that are associated with chronic pain states and chronic depressive and anxiety disorders.

Our findings that pain is strongly associated with onset and course of depression and anxiety suggests that future research should be aimed at randomized controlled trials examining integrated treatment targeting both pain and affective symptoms in order to optimize treatment.

IN CONCLUSION

This thesis shows that pain increases the likelihood of being recognized as depressed or anxious by the GP, mainly through increased severity of depressive and anxiety symptoms. Pain, particularly when in multiple locations and of increasing severity, is an important risk indicator of the onset of depression and anxiety and is negatively affecting depression and anxiety course. Likewise having a depressive or anxiety disorder is associated with increased pain, even when the depressive or anxiety disorder has faded. These findings provide evidence for a vicious cycle in which pain and depressive and anxiety disorders are reinforcing each other and show that the comorbidity of pain and depression and anxiety is a major health care problem. This thesis shows that chronic somatic diseases do not impact on GP recognition of depression or anxiety. Also, most chronic somatic diseases are not associated with depression and anxiety course, only diabetes and musculoskeletal diseases are associated with worse depression and anxiety prognosis. Both pain patients and depressed and anxious individuals are often non-responders in current treatment strategies and since the comorbidity is associated with even worse prognosis, we suggest that integrated care may improve response, and that novel treatment strategies should be developed.

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