The interplay between depression, anxiety and physical health

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Chapter 4

Pain and the onset of depressive and anxiety disorders

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ABSTRACT

Patients with pain may be at increased risk of developing a first episode of depressive or anxiety disorder. Insight into possible associations between specific pain characteristics and such a development could help clinicians to improve prevention and treatment strategies. The objectives of this study are to examine the impact of pain symptomatology on depression and anxiety onset and to determine whether these associations are independent of subthreshold depressive and anxiety symptoms. Data from the Netherlands Study of Depression and Anxiety, collected between 2004 and 2011, were used. 614 participants with no previous history and no current depression or anxiety at baseline were followed for four years. Onset of depressive or anxiety disorder was assessed at two and four year follow-up by CIDI. Baseline pain characteristics were location, duration and severity, as assessed by Chronic Pain Grade. Onset of depressive or anxiety disorder occurred in 15.5% of participants. Using Cox survival analyses, onset of depression and anxiety was associated with 6 pain locations (neck, back, head, orofacial area, abdomen and joints; HR=1.96-4.02; p<.05), increasing number of pain locations (HR=1.29; p<.001) and higher severity of pain (HR=1.57; p<.001). By contrast, there was no association with duration of pain symptoms (HR=1.47; p=.12). Independent of subthreshold affective symptoms, only joint pain and increasing number of pain locations were still significantly associated with depression and anxiety onset. Clinicians should be aware that regardless of affective symptoms, pain, particularly at multiple locations, is a risk indicator for developing depressive and anxiety disorders.

INTRODUCTION

Pain is usually defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage[1]. Pain is associated with functional impairment, (social) disability[2], pain-related anxiety and even anxiety sensitivity –the tendency to catastrophically misinterpret anxiety sensations-[3], which have all been linked to an increased development of depressive as well as anxiety disorders[4]. Data from epidemiological studies also suggest pain could be a risk indicator for depressive and anxiety disorder onset[5-7], but we know little about the specifics of such a relationship. The emotional, economic and societal burden of pain and depressive and anxiety disorders, separately and conjointly, is high[8-11]. An estimate of the contribution of pain to onset of depressive and anxiety disorders could support (the development of) new management strategies in clinical practice.

There are several methodological issues that hamper a sound estimation of this relationship. Firstly, most current studies are based on the onset of depressive or anxiety symptoms[6;12-16], but not all individuals with symptoms will ultimately develop a disorder[17-19]. Pain was found to be associated with increased risk of depressive and anxiety symptom onset in these studies, with one exception[15]. Secondly, most of these studies use a single determinant of pain such as location (joints[16], neck, back[13], unspecified[14]) or interference with daily life[6;12] to examine the impact on depression and anxiety onset. Two studies showed that having pain at a particular location (bladder, migraine, back) was associated with increased risk of incident major depressive disorder[20;21]. We did not find comparable studies for anxiety disorder onset. Thirdly, some studies include depression only, but the associations between pain and depression and anxiety should be studied in concert, due to the high co-morbidity of these disorders[22;23]. Moreover, the variation in pain characteristics associated with anxiety onset could be different than for depressive disorders[24]. Fourthly, some of the above-mentioned studies did not exclude participants with a depression or anxiety history[12;13] or did not specifically report on this[6;15;20]. The findings of these studies are more difficult to interpret since the associations could have been driven by a previous episode, which is an acknowledged predictor of recurrence[25;26]. Lastly, to our knowledge there are no studies examining the relationship between pain and depressive or anxiety disorder onset that also consider the important role of subthreshold depressive and anxiety symptoms. We already know that such symptoms are often associated with disorder onset[18;27]. Estimating the effect of pain over and beyond such subthreshold symptoms can help to determine whether pain is an independent risk indicator for depression and anxiety onset. If pain is indeed a risk indicator, independent of subthreshold symptoms, than adequate pain management - which is now frequently lacking[28;29] - could, besides improving pain symptoms, potentially also reduce depression and anxiety risk. Using a longitudinal study design, we will

examine the following questions: Which specific pain characteristics - location, severity, duration - are associated with onset of depressive and anxiety disorders? Is pain associated with depressive and/or anxiety disorder onset directly or indirectly through elevated subthreshold depressive and anxiety levels?

METHOD

Sample design

The Netherlands Study of Depression and Anxiety (NESDA) is a longitudinal ongoing cohort study comprising 2,981 participants (18 to 65 years) and is aimed at describing the course of depressive and anxiety disorders. Participants were recruited from the general population (n=564), primary care (n=1,610) and secondary mental health care (n=807). Non-response was higher among men and younger persons (<40 years). Neither psychiatric nor somatic health problems had any significant impact on willingness to participate[30]. Exclusion criteria were not being fluent in Dutch and having a primary diagnosis of psychotic, obsessive compulsive, bipolar or severe addiction disorder. A detailed description of the NESDA study design and sampling procedures has been provided[31]. The Ethics Committee of participating universities approved the research protocol and written informed consent was obtained from all individuals. Specially trained research staff conducted the interviews. All 2,981 participants were screened for depressive and anxiety disorder at baseline using the Composite International Diagnostic Interview (CIDI, version 2.1). CIDI is a DSM-IV based reliable and valid instrument for assessing depressive and anxiety disorders[32;33]. Included disorders were major depressive disorder, dysthymia, social phobia, generalized anxiety disorder, panic disorder and agoraphobia. Participants either had no prior history, a prior history or a current depressive and/or anxiety disorder. Baseline data collection took place between 2004 and 2007, with follow-up (FU) assessments, including the CIDI, two and four years later.

For this study, we studied 652 participants who reported never to have had a depressive or anxiety disorder during their lifetime. Of these, 38 (5.8%) did not undergo an assessment at both two- and four-year follow-up. Consequently, a total of 614 participants were followed up for four years.

Onset of depressive and/or anxiety disorder

Onset of a depressive or anxiety disorder (yes/no) was defined by a DSM-IV based CIDI diagnosis of depression or anxiety at two- or four-year follow-up. We calculated the *time to onset of a depressive or anxiety disorder* in months, with a maximum of 48 months, from the moment the participants were assessed at baseline until the moment a participant was diagnosed with a depressive or anxiety disorder at one of the FU assessments according to the CIDI. Participants who were diagnosed with a depressive and/or anxiety disorder at the 2- or 4-year follow-up assessment, were asked to indicate the recency of disorder onset: less than a month ago, between one and 6 months ago, between 6 and 12 months ago, 12 months ago and between 12 and 24 months ago. We used this information and calculated the median of a time interval to assign time of onset. For instance, if a participant reported a recency of disorder onset between 1 and 6 months ago (median 3 months ago) at the 4-year follow up interview (and no disorder was diagnosed at 2-year follow up), the time from baseline to be used in the analyses was (48-3=) 45 months. For participants not having a depressive or anxiety disorder during FU, time was censored as the time from the baseline assessment until the end of the FU period (48 months).

Measurements

Pain

To assess baseline pain over the last 6 months in various ways, the baseline interview contained four different measures: a) 7 specific common pain locations (neck, back, head, orofacial area, abdomen, chest and joints); b) the number of pain locations; c) duration of pain; and d) chronic pain severity, all determined by the Chronic Pain Grade(CPG)[34]. First, the number of pain locations (0-7) in the last six months was assessed. Next, the participant was asked to choose the most painful of the specific locations, to which all subsequent questions applied. Then, duration of pain in the last six months was dichotomized as ≥90 days versus <90 days, based on the most frequently used definition of chronic pain as lasting at least three months[35]. Last, chronic pain severity was based on the reported pain intensity and pain disability. Pain intensity is a 0-100 scale derived from the mean score of current pain, worst pain and average pain over the past 6 months, and classified as low pain intensity < 50 and high pain intensity ≥ 50. The pain disability score, also a 0-100 scale, was based on the mean of disability in daily activities, social activities and work activities. Disability points (0-6) were given for the number of days with experienced pain disability (0-3 points) and the disability score (0-3 points). The CPG scale developed by Von Korff et al[34] separated the following pain grades: grade 1: low intensity-low disability (intensity <50, <3 disability points), grade 2: high intensity-low disability (intensity ≥ 50, <3 points), grade 3: high disability-moderately limiting (3-4 points, regardless of intensity), grade 4: high disability-severely limiting (5-6 points, regardless of intensity).

Patients with no pain in the past six months are included in grade 1. To exclude pain symptoms that were very mild or occurred only sporadically in the past six months, we chose to adjust the pain location variables. The specific pain locations and the number of pain locations were only taken into account if at least grade 2 on the CPG was reported, so that the more severe locations of pain were measured.

Covariates

Covariates were selected a priori based on previous research on the association of depression and anxiety with pain. Socio-demographic characteristics included age, gender and years of education[36;37]. Since chronic diseases can exert an effect on both pain and depression/anxiety, the number of chronic diseases was assessed as the total number of disease categories for which participants reported being currently treated by a healthcare professional or using medication. The following disease categories were considered: cardiometabolic, respiratory, endocrine, neurological, musculoskeletal, digestive disorders, or cancer[38]. To check whether these factors could be moderators in the relationship we added interaction terms of pain with the covariates.

Mediators

Subthreshold depressive and anxiety symptoms were assessed on severity scales for the week prior to the baseline interview. Since none of the participants had a current or lifetime history of depressive or anxiety disorder at baseline, we regarded all symptoms reported on the continuous symptom severity scales to be 'subthreshold'. Subthreshold symptoms may not be 'true' mediators of the associations, since these symptoms were assessed as baseline, when pain was also assessed. Also, there could be a reverse pathway from subthreshold symptoms to pain. However, since subthreshold depressive and anxiety symptoms are such important predictors of depressive and anxiety disorder onset, and because pain and these subthreshold symptoms are so closely linked, we chose mediation analyses to explore the role of subthreshold symptoms in the associations between pain and depressive and anxiety disorder onset. We measured the severity of depressive symptoms using the Quick Inventory of Depressive Symptomatology -self-report (QIDS), a reliable and valid instrument consisting of 16 items, not covering pain symptomatology (0-27 score)[39;40]. Self-reported severity of anxiety symptoms was assessed using the reliable and valid Beck Anxiety Inventory (BAI), consisting of 21 items (0-63 score) measuring the severity of mainly arousal-related symptoms of anxiety[41].

Statistical analysis

We used descriptive statistics to describe sample characteristics and pain symptoms across patients with and without onset of depressive and anxiety disorders. To examine the associations between pain and time to onset of a of depressive or anxiety disorder diagnosis, we performed univariate Cox regression analyses, before and after adjustment for covariates. We also checked whether these covariates could be moderators of the association between pain and depression or anxiety onset. Cox regression takes into account differences in time-at-risk for an event and censoring. Time-at-risk was either measured from baseline until the moment a participant had an event (onset of depressive or anxiety disorder) or it was censored when the participant did not have an onset during the follow-up period. Because depression and anxiety are often co-morbid, we first analysed depressive and/or anxiety disorder onset conjointly.

Next, we also analysed the time to onset of depressive or anxiety disorder separately, in order to explore whether the impact of pain is different for onset of depressive versus anxiety disorders.

To determine whether baseline subthreshold symptoms of depression and anxiety mediated the associations found between pain and first onset of depression or anxiety we used the indirect method by Preacher and Hayes for the analyses, which estimates the direct and indirect unstandardized effects of the independent variable on the dependent variable through the mediator variable, controlling for covariates[42].

RESULTS

Sample Characteristics

Table 1 shows the characteristics of the study sample (n=614). Mean age was 40.9 years and 60.7% were female. 12.9% of participants reported no pain in the past six months, 23% had pain for at least three months, and 19.4% had high intensity of pain symptoms, CPG≥2. Of the participants, 95 (15.5%) developed a first-incidence depressive and/or anxiety disorder during a follow-up of 43.3 months on average (SD 10.4). 3.9% of participants were diagnosed with both a depressive and anxiety disorder.

Impact of pain on onset of depression or anxiety

Table 2 shows the associations between pain symptoms and first onset of a depressive and/or anxiety disorder. After adjusting for covariates the results were very similar to those of the unadjusted analyses. Neck (HR=2.72, p<.001), back (HR=2.46, p<.001), head (HR=2.59, p<.001), orofacial (HR=4.02, p=.004), abdominal (HR=1.96, p=.02) and joint pain (HR 2.86, p<.001) were significantly associated with depression and/or anxiety onset, as was the number of pain locations (per pain location increase: HR=1.29, p<.001) and higher CPG (per grade increase: HR=1.57, p<.001). Age, gender, education and number of chronic diseases were no moderators of the associations between pain and depression and anxiety onset. As shown, the associations between pain and the risk of depressive disorder onset appeared slightly stronger than was the case for anxiety disorder onset. But since confidence intervals for the onset of depressive versus anxiety disorders were largely overlapping and pointed in the same direction, and because of decreasing sample sizes when studying depression and anxiety onset separately, we decided to further investigate the associations between pain and depression and/or anxiety onset conjointly.

Table 1: Sample Characteristics.

Characteristics	Population (n=614)
Sample characteristics	
Female gender, %	60.7
Age in years, Mean (SD)	40.9 (14.6)
Education in years, Mean (SD)	12.9 (3.2)
Subthreshold depressive symptoms (QIDS), Mean (SD)	3.4 (3.1)
Subthreshold anxiety symptoms (BAI), Mean (SD)	4.0 (4.7)
Number of chronic diseases, Mean (SD)	0.5 (0.7)
Pain location, %[1]	
Neck	10.7
Back	13.2
Head	13.4
Orofacial area	2.0
Chest	3.7
Abdomen	9.6
Joints	12.5
Number of pain locations, Mean (SD)[1]	0.7 (1.5)
Duration of Pain ≥ 90 days, %	23.0
Chronic Pain Grade, Mean (SD)	1.3 (0.7)
Grade 1, %	80.6
Grade 2, %	12.2
Grade 3, %	4.1
Grade 4, %	3.1
Outcome, %	
Onset of depressive disorder	11.6
Onset of anxiety disorder	7.8
Onset of depressive and/or anxiety disorder	15.5
Duration of follow up in months, Mean (SD)	43.3 (10.4)

[1] Pain locations were only taken into account when CPG ≥ 2

Mediation of subthreshold depressive and anxiety symptoms

We performed the analyses for the two presumed mediators - subthreshold depressive and anxiety symptoms - separately. Both were mediators in the associations between the pain variables and onset of depressive and anxiety disorders. Since the correlation coefficient between severity of subthreshold depressive and anxiety symptoms was moderate (Spearman's rho 0.55), we therefore decided to create a model which included both severity of subthreshold depressive and severity of subthreshold anxiety symptoms. In this model subthreshold anxiety was no longer a mediator between pain and onset of depression and/or anxiety, and associations with or without

entering subthreshold anxiety remained similar. Accordingly, we have presented the effects of subthreshold depressive symptoms on the associations between pain characteristics and the onset of depression and/or anxiety in Table 3. First, the analyses confirmed that pain is associated with higher severity of subthreshold depressive symptoms (a in Table 3) and that higher severity of subthreshold symptoms was significantly associated with depression and anxiety onset (b in Table 3). For joint pain (p=.015) and increasing number of pain locations (p=0.048) a significant direct effect (c' in Table 3) was found, suggesting that independent of subthreshold symptoms, joint pain and increasing number of pain locations predict the first onset of depressive and/or anxiety disorder. Almost reaching a significant direct effect on the first onset of depression and anxiety were the CPG (p=.054) and neck pain (p=.062) and back pain (p=.065). Significant indirect effects (a x b effects in Table 3) were seen for pain of the neck, back, head, face, abdomen, chest and joints, higher number of pain locations, chronic pain and higher CPG, suggesting there is an overall effect of all the pain variables on depressive and/or anxiety disorder onset, with subthreshold depressive symptoms mediating the associations.

Table 2: Associations between pain symptoms and onset of depressive and/or anxiety disorder during follow-up[1].

Pain characteristics	Time to onset of depressive and/or anxiety disorder unadjusted		Time to onset of depressive and/or anxiety disorder[3]		Time to onset of depressive disorder[3]		Time to onset of anxiety disorder[3]	
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
Pain location[2]								
Neck	2.37 (1.45-3.89)	.001	2.72 (1.59-4.67)	<.001	2.64 (1.42-4.91)	.002	1.95 (0.89-4.38)	.093
Back	2.28 (1.42-3.64)	.001	2.46 (1.49-4.09)	<.001	2.63 (1.47-4.68)	.001	1.41 (0.65-3.02)	.395
Head	2.55 (1.61-4.02)	<.001	2.59 (1.59-4.19)	<.001	2.86 (1.65-4.96)	<.001	1.52 (0.73-4.16)	.262
Orofacial area	3.33 (1.35-8.18)	.009	4.02 (1.57-10.3)	.004	6.06 (2.03-15.9)	<.001	2.25 (0.50-10.1)	.288
Chest	2.20 (1.02-4.75)	.051	2.14 (0.97-4.70)	.059	1.51 (0.54-4.25)	.426	2.21 (0.76-6.42)	.145
Abdomen	1.90 (1.09-3.30)	.023	1.96 (1.11-3.49)	.021	2.15 (1.13-4.10)	.021	1.01 (0.44-2.62)	.983
Joints	2.28 (1.42-3.68)	.001	2.86 (1.69-4.84)	<.001	2.68 (1.45-4.95)	.002	2.34 (1.12-4.92)	.024
Number of pain locations[2]	1.24 (1.12-1.37)	<.001	1.29 (1.15-1.44)	<.001	1.29 (1.13-1.48)	<.001	1.15 (0.98-1.36)	.097
Duration of pain ≥ 90 days	1.25 (0.79-1.97)	.342	1.47 (0.90-2.39)	.124	1.51 (0.86-2.66)	.148	1.26 (0.62-2.55)	.519
Chronic Pain Grade	1.49 (1.20-1.85)	<.001	1.57 (1.25-1.98)	<.001	1.58 (1.22-2.05)	.001	1.44 (1.03-2.02)	.035

[1] Using cox regression analyses

[2] Pain locations were only taken into account when CPG ≥ 2

[3] Adjusted for age, gender, years of education, number of chronic diseases

Table 3: Summary of Preacher and Hayes mediator model analyses (5000 bootstraps) between pain and onset of depressive and/or anxiety disorder (DV)[2].

Pain variables (IV)[1]	Subthreshold depression (S)	Effect of IV on S (a)	Effect of S on DV (b)	Direct effect (c') of IV on DV		Indirect effect of IV on DV (a x b)	95% CI (a x b)
				effect	p		
Neck	QIDS	2.08*	0.29*	0.69	.062	.65	(.30-1.05)**
Back	QIDS	1.37*	0.31*	0.63	.065	.49	(.21-.82)**
Head	QIDS	2.22*	0.30*	0.48	.140	.69	(.39-1.04)**
Orofacial area	QIDS	3.05*	0.31*	0.97	.176	.98	(.21-2.00)**
Chest	QIDS	2.45*	0.31*	0.24	.668	.77	(.26-1.73)**
Abdomen	QIDS	2.11*	0.31*	0.12	.757	.68	(.33-1.11)**
Joints	QIDS	1.68*	0.31*	0.87	.015	.53	(.22-.90)**
Number of pain locations	QIDS	0.54*	0.30*	0.16	.048	.17	(.09-.25)**
Chronic Pain Grade	QIDS	0.96*	0.31*	0.31	.055	.30	(.15-.48)**

Abbreviation: QIDS= Quick Inventory of Depressive Symptoms, IV= Independent Variable, S=Subthreshold depression, DV= Dependent Variable

* $p<0.001$

** significant based on 95% confidence interval (CI)

[1] Pain location was only taken into account when CPG ≥ 2

[2] Adjusted for age, gender, years of education, number of chronic diseases

DISCUSSION

The purpose of this study was to examine whether particular pain characteristics are associated with first onset of depressive and anxiety disorders and if so, whether these associations are independent of or mediated by subthreshold depressive and anxiety symptoms. Our results show that several different pain locations, increasing number of pain locations and higher chronic pain severity are associated with the onset of depressive and anxiety disorders. Joint pain and increasing number of pain locations are associated with an elevated risk of developing a depressive or anxiety disorder, independent of subthreshold symptoms.

Our findings that pain can be a risk indicator of depression underline the findings of Fishbain et al.[5]. In their review of the literature on links between chronic pain and depression, they found evidence for pain preceding depression. Their review points to a bidirectional relationship because they also found evidence for depression preceding pain. We found that increasing pain, as measured with a larger number of painful locations but also with increasing intensity and disability, is associated with a higher risk of developing a first depressive or anxiety disorder; only the duration of pain for more than three months was not associated with depression and anxiety onset. A pain risk score based on severity was also a better predictor of future daily functioning and pain worrying than duration of pain[43]. One previous study found no significant effect of increasing pain intensity and disability on onset of depressive symptoms, but these different findings might be explained by the study design[15]. The authors used depressive symptoms instead of disorder as an outcome, and also studied a small elderly population. Furthermore, they did not include anxiety and they examined not only first onset but also recurrence of depressive disorders.

Our findings for specific pain locations concur with other studies that have examined the associations between particular pain locations (joints, neck, back) and the onset of depressive and anxiety symptoms and disorders[13;16;20;21]. Of the particular pain locations, only joint pain was directly associated with onset of depression and anxiety, independent of subthreshold depressive symptoms in our study. In a previous study we also discovered that joint pain, independent of symptom severity, is associated with a worse course of depressive and anxiety disorders[44]. The explanation for the relationship between joint pain and depression and anxiety has yet to be clarified. One of the reasons could be that these patients in particular are severely hindered in physical activity, resulting in greater role impairment and increased morbidity[28]. From a biopsychosocial perspective several mechanisms could be explanatory in the link between pain and depressive and anxiety disorder onset[45]. Recent discoveries of underlying biological pathways via neuroimaging studies, for instance, have shown that pain and emotion are closely connected at the brain level[46]. Reduced levels of the neurotransmitters norepinephrine and serotonin are being linked to a hampered gate-control mechanism of pain and development

of mood disorders[24]. Systemically increased inflammatory markers in both pain and affective disorders point to shared underlying pathways[8;24]. There is also evidence for psychosocial links between pain and depression and anxiety. Stress, maladaptive coping strategies, underlying disability and greater role impairment due to pain are likely to induce depression and anxiety[5;24;28].

In this sample the associations between pain and onset of depression and anxiety were consistent across age and gender. Therefore, irrespective of being young or old pain seems to be a risk indicator of incident depressive and anxiety disorder. It is, however, important to note that this was a study conducted in adults and findings could thus still be different in children and elderly. Also females, compared to males, more often display pain symptoms and also more frequently have depressive and anxiety disorders then males, this may have led to the finding that the association between pain and depressive and anxiety disorder onset was not moderated by gender.

The purpose of assessing different pain characteristics in relation to depressive and anxiety disorder onset was to provide information for practitioners regarding which characteristics of pain are associated with onset of psychopathology. Our results show that intensity of and disability related to pain symptoms, as well as pain in several locations, are associated with an increased likelihood of developing a depressive or anxiety disorder, whereas duration of pain symptoms is not. Also, patients with severe pain of the joints and in multiple locations are at increased risk for developing a disorder, even before they display depressive and anxiety symptoms. Clinicians should be aware that a patient with multiple painful symptoms, particularly involving the joints, has a heightened risk of developing depression or anxiety in the future. Ideally, treatment regimens for pain should not only target pain symptoms but should also aim to prevent depressive and anxiety disorders. Cognitive-behavioural therapies have shown some efficacy in reducing pain and psychological distress in chronic pain populations[16;29;47-49] A number of medications have been proven effective in patients with severe pain, and there is evidence that effectively treating pain alleviates mood symptoms[24;28]. Theoretically, more benefit might be expected from drugs that have analgesic effects and stimulate mood. Of certain antidepressants it is claimed they have such dual action[50;51]. In any case, it is unknown whether such pain treatments could eventually prevent depressive or anxiety disorders. Moreover, there are downsides to all treatments such as non-response for the majority of patients with severe chronic pain and the dangers of side effects in pharmacological interventions[28;52].

Strengths and limitations

In this prospective longitudinal study, we had the opportunity to examine the onset of depressive and anxiety disorders, based on structured diagnostic interviews. Participants with a previous history of depressive and anxiety disorders were excluded, as the focus was on first onset of psychopathology. Besides depressive disorder only, we also examined anxiety disorders. Our

study population was not selected on the basis of the presence of pain; therefore, even though selected to examine depression and anxiety longitudinally, this population may reasonably reflect of the presence of particular pain characteristics in the normal population.

This study also had some limitations. NESDA provides information on the most common depressive and anxiety disorders and therefore results cannot be generalized to other specific disorders such as PTSD or bipolar depression. We found that the impact of pain on onset of depression and anxiety separately was similar, but the incidence of these disorders was quite low. Since there is little evidence for the link between pain and anxiety onset, future studies could focus on pain and anxiety onset only. Due to the small percentage of patients developing both a depressive and anxiety disorder over four years of follow-up we were unable to investigate the impact of pain on this affective comorbidity. The method of dating the onset of depressive or anxiety disorder was not very exact. However, when we did not consider time to onset (by repeating our analyses using logistic regression analyses), we found very similar results.

The pain variables were not completely time independent. So over the course of 4 years the pain symptoms could vary, and we have not accounted for that change in the analyses. However, we have used multiple pain measures which may well captivate a broad range of pain symptomatology. The findings for orofacial pain and chest pain should be viewed with caution because of the small number of participants in our study experiencing these pain symptoms. We did not assess whether the participant had a pain disorder at baseline. Nor did we ask whether there was a specific cause for the pain, such as tissue damage or a particular disease, and we did not perform a physical examination, so these findings do not specifically apply to persons with medically unexplained pain. We did, however, correct for having chronic somatic diseases, which hardly changed the associations. Lastly, the statistical mediation model assumes temporal direction of the independent variable preceding the mediator, which precedes the outcome variable, but both pain and subthreshold symptoms were measured at baseline. Epidemiological studies such as ours cannot definitely prove that there is a single causal pathway from pain (via subthreshold symptoms) towards depressive and anxiety disorders. With our longitudinal study we were able to show that experiencing pain is a risk indicator for developing depressive and anxiety disorders. But evidence in the reverse direction of depression and anxiety preceding pain also exists[5;36;53;54]. The associations we found linking pain to depression and anxiety onset may also reflect some shared genetic and environmental influences, and for different individuals these influences might contribute to the relationship to a greater or lesser degree[55].

Conclusions

This study shows that patients with pain in multiple locations, particularly involving pain of the joints, are more prone towards developing a first onset of depressive and anxiety disorders. Clinicians should be aware of this heightened risk. If chronic pain could be tackled with effective treatment strategies in the future resulting in more pain free individuals, then the depression and anxiety burden could be reduced.

REFERENCE LIST

1. Recommended by the IASP Subcommittee on Taxonomy. Pain Terms: A List With Definitions And Notes On Usage. *Pain* 1979;6:247-252.
2. Romera I, Montejo AL, Caballero F et al. Functional impairment related to painful physical symptoms in patients with generalized anxiety disorder with or without comorbid major depressive disorder: post hoc analysis of a cross-sectional study. *BMC Psychiatry* 2011;11:69.
3. Ocanez KL, McHugh RK, Otto MW. A meta-analytic review of the association between anxiety sensitivity and pain. *Depress Anxiety* 2010;27:760-767.
4. Carleton RN, Abrams MP, Asmundson GJ, Antony MM, McCabe RE. Pain-related anxiety and anxiety sensitivity across anxiety and depressive disorders. *J Anxiety Disord* 2009;23:791-798.
5. Fishbain DA, Cutler R, Rosomoff HL, Rosomoff RS. Chronic pain-associated depression: antecedent or consequence of chronic pain? A review. *Clin J Pain* 1997;13:116-137.
6. Hilderink PH, Burger H, Deeg DJ, Beekman AT, Oude Voshaar RC. The temporal relation between pain and depression: results from the longitudinal aging study amsterdam. *Psychosom Med* 2012;74:945-951.
7. Asmundson GJ, Katz J. Understanding the co-occurrence of anxiety disorders and chronic pain: state-of-the-art. *Depress Anxiety* 2009;26:888-901.
8. Bair MJ, Robinson RL, Katon W, Kroenke K. Depression and pain comorbidity: a literature review. *Arch Intern Med* 2003;163:2433-2445.
9. Bekkering GE, Bala MM, Reid K et al. Epidemiology of chronic pain and its treatment in The Netherlands. *Neth J Med* 2011;69:141-153.
10. Wittchen HU, Jacobi F, Rehm J et al. The size and burden of mental disorders and other disorders of the brain in Europe 2010. *Eur Neuropsychopharmacol* 2011;21:655-679.
11. Gustavsson A, Svensson M, Jacobi F et al. Cost of disorders of the brain in Europe 2010. *Eur Neuropsychopharmacol* 2011;21:718-779.
12. Arola HM, Nicholls E, Mallen C, Thomas E. Self-reported pain interference and symptoms of anxiety and depression in community-dwelling older adults: can a temporal relationship be determined? *Eur J Pain* 2010;14:966-971.
13. Carroll LJ, Cassidy JD, Cote P. Factors associated with the onset of an episode of depressive symptoms in the general population. *J Clin Epidemiol* 2003;56:651-658.
14. Harris T, Cook DG, Victor C, DeWilde S, Beighton C. Onset and persistence of depression in older people--results from a 2-year community follow-up study. *Age Ageing* 2006;35:25-32.
15. Livingston G, Watkin V, Milne B, Manela MV, Katona C. Who becomes depressed? The Islington community study of older people. *J Affect Disord* 2000;58:125-133.
16. Magni G, Moreschi C, Rigatti-Luchini S, Merskey H. Prospective study on the relationship between depressive symptoms and chronic musculoskeletal pain. *Pain* 1994;56:289-297.
17. Acarturk C, Smit F, de Graaf R, van Straten A, Ten Have M, Cuijpers P. Incidence of social phobia and identification of its risk indicators: a model for prevention. *Acta Psychiatr Scand* 2009;119:62-70.
18. Cuijpers P, Smit F. Subthreshold depression as a risk indicator for major depressive disorder: a systematic review of prospective studies. *Acta Psychiatr Scand* 2004;109:325-331.
19. Karsten J, Hartman CA, Smit JH et al. Psychiatric history and subthreshold symptoms as predictors of the occurrence of depressive or anxiety disorder within 2 years. *Br J Psychiatry* 2011;198:206-212.
20. Keller JJ, Liu SP, Lin HC. Increased risk of depressive disorder following diagnosis with bladder pain syndrome/interstitial cystitis. *Neurourol Urodyn* 2012.
21. Patten SB. Long-term medical conditions and major depression in a Canadian population study at waves 1 and 2. *J Affect Disord* 2001;63:35-41.
22. Lamers F, van OP, Comijs HC et al. Comorbidity patterns of anxiety and depressive disorders in a large cohort study: the Netherlands Study of Depression and Anxiety (NESDA). *J Clin Psychiatry* 2011;72:341-348.
23. Kessler RC, Chiu WT, Demler O, Merikangas KR, Walters EE. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry* 2005;62:617-627.
24. Dersh J, Polatin PB, Gatchel RJ. Chronic pain and psychopathology: research findings and theoretical considerations. *Psychosom Med* 2002;64:773-786.
25. Bruce SE, Yonkers KA, Otto MW et al. Influence of psychiatric comorbidity on recovery and recurrence in generalized anxiety disorder, social phobia, and panic disorder: a 12-year prospective study. *Am J Psychiatry* 2005;162:1179-1187.
26. Colman I, Naicker K, Zeng Y, Ataullahjan A, Senthilselvan A, Patten SB. Predictors of long-term prognosis of depression. *CMAJ* 2011;183:1969-1976.
27. Shankman SA, Lewinsohn PM, Klein DN, Small JW, Seeley JR, Altman SE. Subthreshold conditions as precursors for full syndrome disorders: a 15-year longitudinal study of multiple diagnostic classes. *J Child Psychol Psychiatry* 2009;50:1485-1494.
28. Moore R.A. What works for whom? Determining the efficacy and harm of treatments for pain. *Pain*. In press.
29. Williams AC, Eccleston C, Morley S. Psychological therapies for the management of chronic pain (excluding headache) in adults. *Cochrane Database Syst Rev* 2012;11:CD007407.
30. van der Veen W, van der Meer K, Penninx BWJH. Screening for depression and anxiety: correlates of non-response and cohort attrition in the Netherlands study of depression and anxiety (NESDA). *Int J Methods Psychiatr Res* 2009;18:229-239.
31. Penninx BW, Beekman AT, Smit JH et al. The Netherlands Study of Depression and Anxiety (NESDA): rationale, objectives and methods. *Int J Methods Psychiatr Res* 2008;17:121-140.
32. Wittchen HU, Robins LN, Cottler LB, Sartorius N, Burke JD, Regier D. Cross-cultural feasibility, reliability and sources of variance of the Composite International Diagnostic Interview (CIDI). The Multicentre WHO/ ADAMHA Field Trials. *Br J Psychiatry* 1991;159:645-53, 658.
33. Wittchen HU. Reliability and validity studies of the WHO--Composite International Diagnostic Interview (CIDI): a critical review. *J Psychiatr Res* 1994;28:57-84.
34. Von Korff M, Ormel J, Keefe FJ, Dworkin SF. Grading the severity of chronic pain. *Pain* 1992;50:133-149.
35. International Association for the study of Pain: Classification of chronic pain: descriptions of chronic pain syndromes and definitions of pain terms. *Pain* 1986;1-222.

36. Tunks ER, Crook J, Weir R. Epidemiology of chronic pain with psychological comorbidity: prevalence, risk, course, and prognosis. *Can J Psychiatry* 2008;53:224-234.
37. Miller LR, Cano A. Comorbid chronic pain and depression: who is at risk? *J Pain* 2009;10:619-627.
38. Gerrits MM, van Oppen P, Van Marwijk HW, van der Horst H, Penninx BW. The impact of chronic somatic diseases on the course of depressive and anxiety disorders. *Psychother Psychosom* 2013;82:64-66.
39. Rush AJ, Gullion CM, Basco MR, Jarrett RB, Trivedi MH. The Inventory of Depressive Symptomatology (IDS): psychometric properties. *Psychol Med* 1996;26:477-486.
40. Rush AJ, Trivedi MH, Ibrahim HM et al. The 16-Item Quick Inventory of Depressive Symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. *Biol Psychiatry* 2003;54:573-583.
41. Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety: psychometric properties. *J Consult Clin Psychol* 1988;56:893-897.
42. Preacher KJ, Hayes AF. Asymptotic and resampling strategies for assessing and comparing indirect effects in multiple mediator models. *Behav Res Methods* 2008;40:879-891.
43. Von Korff M, Dunn KM. Chronic pain reconsidered. *Pain* 2008;138:267-276.
44. Gerrits MM, Vogelzangs N, van Oppen P, Van Marwijk HW, van der Horst H, Penninx BW. Impact of pain on the course of depressive and anxiety disorders. *Pain* 2012;153:429-436.
45. Campbell LC, Clauw DJ, Keefe FJ. Persistent pain and depression: a biopsychosocial perspective. *Biol Psychiatry* 2003;54:399-409.
46. Borsook D, Sava S, Becerra L. The pain imaging revolution: advancing pain into the 21st century. *Neuroscientist* 2010;16:171-185.
47. Fernandez E, Turk DC. The utility of cognitive coping strategies for altering pain perception: a meta-analysis. *Pain* 1989;38:123-135.
48. Jensen MP. Psychosocial approaches to pain management: an organizational framework. *Pain* 2011;152:717-725.
49. Peres MF, Lucchetti G. Coping strategies in chronic pain. *Curr Pain Headache Rep* 2010;14:331-338.
50. Marangell LB, Clauw DJ, Choy E et al. Comparative pain and mood effects in patients with comorbid fibromyalgia and major depressive disorder: secondary analyses of four pooled randomized controlled trials of duloxetine. *Pain* 2011;152:31-37.
51. Hauser W, Wolfe F, Tolle T, Uceyler N, Sommer C. The role of antidepressants in the management of fibromyalgia syndrome: a systematic review and meta-analysis. *CNS Drugs* 2012;26:297-307.
52. Kroenke K, Krebs EE, Bair MJ. Pharmacotherapy of chronic pain: a synthesis of recommendations from systematic reviews. *Gen Hosp Psychiatry* 2009;31:206-219.
53. Aggarwal VR, Macfarlane GJ, Farragher TM, McBeth J. Risk factors for onset of chronic oro-facial pain--results of the North Cheshire oro-facial pain prospective population study. *Pain* 2010;149:354-359.
54. Knaster P, Karlsson H, Estlander AM, Kalso E. Psychiatric disorders as assessed with SCID in chronic pain patients: the anxiety disorders precede the onset of pain. *Gen Hosp Psychiatry* 2012;34:46-52.
55. Kato K, Sullivan PF, Evengard B, Pedersen NL. Chronic widespread pain and its comorbidities: a population-based study. *Arch Intern Med* 2006;166:1649-1654.