The interplay between depression, anxiety and physical health

Gerrits, M.J.G.

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Chapter 8

Longitudinal association between pain, and depression and anxiety over four years

Marloes M.J.G. Gerrits, Harm W.J. van Marwijk,
Patricia van Oppen, Henriëtte E. van der Horst,
Brenda W.J.H. Penninx

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ABSTRACT

The present study assessed longitudinal associations between depression and/or anxiety (D/A) and pain, and compared pain over time between D/A and healthy subjects. 2,676 participants of the Netherlands Study of Depression and Anxiety were followed up for four years. At three consecutive waves we assessed depressive and anxiety symptom severity and also four different (DSM-IV based) D/A disorder courses over time (n=2,093): incident, remitted, chronic, and no D/A (reference group). Pain was assessed by severity and number of locations. Change in D/A symptoms was positively associated with change in pain symptoms. Compared to healthy controls (n= 519), D/A subjects – incident (n=333), remitted (n=548) or chronic (n=693) - reported more severe pain (b=0.4-0.7, p<0.001) and more pain locations (b=0.8-1.4, p<.001) at all waves, with the highest ratings in chronic D/A. Remission of D/A during follow-up was associated with a significant decline in pain (severity; p=0.002, number of locations; p<.001), but pain levels remained significantly higher compared to healthy controls. This study largely confirms synchrony of change between depression, anxiety and pain. However, after depression and anxiety remission, subjects report higher pain ratings over time.

Perspective

These longitudinal results point to a significant negative impact of depressive and anxiety disorders on pain over time. In clinical practice assessing D/A (history) in patients with pain is important to identify and treat individuals at an increased risk of chronic severe pain.

INTRODUCTION

Pain is a major global health care problem which is often persistent over time[1;2]. Insight into factors that may influence the course of pain could help to optimize treatment strategies. Depressive and/or anxiety disorders (D/A) are highly prevalent in those with pain[3-10] and the combination of D/A and pain leads to reduced quality of life, major societal costs and even points to increased numbers of suicide death[11-14]. Furthermore, D/A are associated with reduced psychosocial functioning and inadequate coping strategies which could result in increased pain ratings over time[15;16]. D/A may also lead to changes in the insular cortex, abnormalities in hypothalamic-pituitary-adrenal axis and autonomic nervous system that could subsequently lead to or aggravate pain[15;17-22]. With these psychosocial and biological changes it is questionable whether D/A recovery will also result in decreasing pain levels. As the course of D/A is known to be diverse, ranging from a single short episode to be chronically persistent[23-26], the trajectory of D/A may be associated with pain course.

There are only a few short-term studies examining how change in D/A course is related to the course of pain over time. One study demonstrated that when depressive symptoms improved in 103 primary care patients, pain also improved over the course of 6 months[27]. A clinical trial with depressed and non-depressed subjects (n=500) showed that the increase of depressive symptoms during a preceding time interval was associated with more severe pain after 1 year, whereas depression relief was associated with less pain[28]. In another study with 483 neurology outpatients, depression severity predicted pain over the course 12 months[29]. And finally, in 526 patients with serious burn injuries, more depressive and anxiety symptoms were associated with greater pain at the subsequent time point over a two-year follow-up[30]. The findings from these relatively small and specific samples point to a synchrony of change over a short period of time, such that if depressive and anxiety symptoms change then pain symptoms will change in a similar direction. Of the above mentioned studies, four focused on depressive symptoms and only one on anxiety symptoms. In addition, it is clinically relevant to know how change at the depressive and anxiety disorder level is associated with pain over time, because in daily practice disorders are more closely aligned with clinical decision making. Whether chronic states of depression and anxiety have a different impact on pain over time than more temporary states of depression and anxiety has not yet been tested. Finally, information on how pain levels of depressed or anxious patients relate to pain levels in mentally healthy individuals over time is lacking. Our objectives were to determine how different courses of depressive and/or anxious symptoms and depressive and/or anxiety disorders (incident, remitted and chronic D/A versus healthy controls) are associated with pain over a four-year period in a large sample.

MATERIALS AND METHODS

Sample

Data of the current study are derived from the Netherlands Study of Depression and Anxiety (NESDA). This is an ongoing longitudinal cohort study among 2,981 participants (18 to 65 years) who were recruited from the community, general practice and specialized mental health care. The study was designed to recruit depressed and/or anxious patients as well as a group of healthy controls from different settings in order to study course and consequences of depressive and/or anxiety disorders (D/A). Participants were assessed for D/A using the DSM-IV based Composite International Diagnostic Interview at baseline and the 2- and 4-year follow-up assessments (CIDI, version 2.1). The CIDI is a structured interview with acceptable reliability and validity for assessing depressive (major depressive disorder, dysthymia) and anxiety (social phobia, generalized anxiety disorder, panic disorder, agoraphobia) disorders[31;32]. Exclusion criteria were not being fluent in Dutch and having a primary diagnosis of psychotic, obsessive compulsive, bipolar or severe addiction disorder. An extensive description of the NESDA study design and method of recruitment has been provided by Penninx et al[33]. At T0, 2,981 participants were recruited. Willingness to participate did not depend on somatic or mental health problems but was slightly lower in younger men[34]. Data were gathered in three waves: at baseline in 2004-2007 (T0), after 2 year follow-up (T1, 2006-2009) and after 4 year follow-up (T2, 2008-2011). In the present study, we included NESDA participants who participated in at least one of the two follow-up assessments (n=2,676). The 305 non-responders differed significantly in that they more often had a current depressive and/or anxiety disorder and also more severe pain and pain in more locations.

Depression and/or anxiety course

To examine depression and/or anxiety course over four years, we used two different indicators. The first was based on change in the course of depressive and anxiety symptoms and the second was based on the presence or absence of CIDI-based DSM-IV depressive and/or anxiety disorders over time.

Change in depressive and anxiety symptoms

Depressive and anxiety symptoms were assessed at the baseline interview (T0) and at the two- and four-year follow-up (T1, T2) covering symptomatology experienced in the past week. Depressive symptoms were measured using the Quick Inventory of Depressive Symptomatology -self-report (QIDS), a reliable and valid instrument consisting of 16 items, none of which covering pain symptomatology (0-27 score)[35;36]. Self-reported anxiety symptoms were measured using the reliable and valid Beck Anxiety Inventory (BAI), consisting of 21 items (0-63 score) measuring severity of mainly arousal-related symptoms of anxiety[37]. Next to the BAI, we also used the Fear questionnaire (FQ) measuring mainly avoidance symptoms, consisting of 15 items (0-120 score) with good reliability and validity[38;39]. To describe the change in course of depressive and anxiety symptoms, we calculated two changes scores for the QIDS, BAI and FQ symptoms separately: change between T0 and T1 (T1-T0) and between T1 and T2 (T2-T1).

Course of depressive and anxiety disorders

We were interested in examining how clinically relevant distinct courses of D/A - incident, remitted, chronic - compared to healthy controls are associated with pain over time. We defined these four trajectories as outlined below:

1. Healthy controls: participants who did not have a D/A diagnosis at all three waves and who did not have a D/A lifetime history. The healthy controls were regarded as the reference group.
2. Incident D/A: participants who did not have a D/A diagnosis at baseline but who developed a D/A diagnosis during follow-up.
3. Remitted D/A: participants who had a baseline D/A diagnosis (six-month prevalence) but who remitted during follow-up.
4. Chronic D/A: participants who had a baseline D/A diagnosis (six-month prevalence) and a D/A diagnosis at one of the two follow-up assessments with at least 24 months out of the 48 months of follow-up having reported symptoms. The latter was based on the Life Chart Interview (LCI)[40] included in each follow-up assessment. The LCI uses a calendar approach to recall life events to refresh memory, after which depressive and anxiety symptoms were determined for each month during follow-up.

Since depression and anxiety are often comorbid (in the NESDA sample in 67% of all cases[41]) we assessed the association of depressive and anxiety disorders with pain over time conjointly. However, compared to depression, the link between anxiety and pain is less investigated[3]. Consequently, we additionally explored whether the longitudinal pain associations were comparable for depression and anxiety course trajectories by examining depression and anxiety disorders separately.

Pain

During the baseline interview and at the two- and four-year follow-up, participants were systematically questioned about pain symptoms in the past six months using the Chronic Pain Grade Questionnaire by von Korff et al[42]. An inventory was made of pain symptoms of joints in the extremities, back, neck, abdomen, chest, head and orofacial area in the last six months. Next, the participant was asked to choose the most painful location, for which pain intensity and pain-related disability were assessed. Pain intensity was based on the mean of present pain, average and worst pain over the past six months on a 0-100 scale. Pain related disability was calculated from the mean interference of pain with usual activities, work/housework activities and social

activities in the prior six months (0-100 scale) and disability days in the prior 6 months (score 0–180). Of all mentioned pain locations, the number of pain locations was calculated (0-7).

We used two different outcome measures for pain:

a. Pain severity: We combined the continuous scales for intensity and disability into one measure of pain severity. We transformed the pain intensity and disability into standardized Z-scores and the pain severity measure was based on the mean of the intensity and disability Z-scores.
b. Number of pain locations: based on the number of pain locations (0-7) the participant reported.

These two continuous measures cover several relevant aspects of pain symptomatology. For the continuous measures we calculated change scores for both measures (change between T0 and T1 (T1-T0) and between T1 and T2 (T2-T1)).

Covariates

Covariates were selected a priori on the basis of previously reported associations between both pain and depressive and/or anxiety disorders. Baseline socio-demographic characteristics included age, sex and years of education[8;43;44]. Baseline chronic disease status was based on self-reported diagnoses of the following disease categories: cardiometabolic, respiratory, digestive, neurological, musculoskeletal, endocrine and cancer[45]. To assess diseases most 'objectively', somatic disease was only considered present if treated by a healthcare professional or when medication was used. From these categories we calculated the number of self-reported somatic disease categories. To account for possible psychoactive and pain medication effects, medication use over 4 years was assessed based on drug container inspection of all drugs used in the month prior to each interview and classified according to the World Health Organization Anatomical Therapeutic Chemical (ATC) classification[46]. As effects of psychoactive medications are unlikely to be clinically significant when used infrequently, use of these medications was only considered present when taken on a regular basis (on average at least 50% of the time). Similarly, pain medication was only considered when taken on a regular basis (on average at least 50% of the time). Antidepressants included selective serotonin reuptake inhibitors (ATC-code N06AB), tricyclic antidepressants (N06AA) and other antidepressants (N06AF/N06AX). Benzodiazepines included ATC-codes N03AE, N05BA, N05CD and N05CF. Pain medication included paracetamol (N02BE01), acetylsalicylic acid (N02BA), non-steroidal anti-inflammatory drugs (M01A, M01B), and opioids (N02A).

Statistical analysis

We used descriptive statistics to present sample characteristics of the 2,676 participants at T0, T1 and T2. Both number of pain locations and pain severity showed normal distributions.

To study associations of change in depressive and anxiety symptoms with change in pain over time we used linear mixed models (LMM)[47]. With LMM, regression analyses can be performed with repeated measures data. This method takes into account the dependency of the repeated observations from the same participant over time and missing values, which reduces bias due to selective loss to follow up. By using change scores, LMM can estimate how changes in the main predictor variable affect changes in the dependent variable over time. To adjust for regression to the mean effects, we used baseline pain severity and baseline number of pain locations as a covariate in the analyses between change in D/A symptoms and change in pain severity and number of pain locations, respectively. Additional LMM analyses were performed to test the impact of covariates on the associations between change in D/A and change in pain.

Then, the distribution of the baseline characteristics of participants across the D/A disorder course groups and the control group were compared using two-tailed chi-square statistics (for categorical variables) and one-way-analysis of variance statistics (ANOVA; for continuous variables).

LMM were used to examine the association between D/A disorder course with pain during four years of follow up (T0, T1, and T2). In order to examine whether the disorder courses show differential change in pain over time, we tested an interaction term between course trajectory*time. An interaction-term was considered significant when the p-value of the interaction term was below 0.05. Additional analyses of the associations between D/A disorder course and pain were adjusted for covariates. All the covariates were entered in the model as fixed factors. All statistical analyses were performed in SPSS 20 for Windows (SPSS inc, Chicago, Ill).

RESULTS

At baseline 66.3% was female and the mean age was 42.0 years (SD 13.0) (Table 1). Almost a quarter of individuals used antidepressants on a regular basis (≥50% of the time). Benzodiazepines and pain medication were regularly used by less than 10% of individuals. Over time the regular use of antidepressants and benzodiazepines slightly decreased, whereas the use of pain medication increased. Overall depressive and anxiety symptom scores slightly decreased, and a similar pattern was shown for pain intensity, disability, severity and locations.

Change in depressive and anxiety symptoms and pain

Table 2 shows associations between changes in depressive and anxiety symptoms with changes in pain symptoms (severity and number of pain locations) over time. There was synchrony of change between depressive symptoms and pain symptoms (severity; B=0.01, p<.001, number of locations; B=0.03, p<.001) and between anxiety symptoms and pain (severity; BAI: B=0.006, p<.001, Fear: B=0.005, p<.001, number of locations; BAI: B=0.03, p<.001, Fear: B=0.007, p<.001), indicating that an increase or decrease in depressive and anxiety symptomatology was associated

with an increase or decrease of pain, respectively. Also, the baseline values of pain severity and number of pain locations were significantly negatively associated with change in pain severity and number of pain locations, indicating that when baseline pain levels are high there is on average a larger decrease in pain over time. We only showed the model adjusted for covariates, since the unadjusted model yielded similar results indicating that the other covariates had hardly any impact on the D/A and pain longitudinal associations.

Table 1: Sample characteristics.

	Baseline	Two year FU	Four year FU
	n=2,676	n=2,596	n=2,402
Socio-demographics			
Female gender, %	66.3		
Age in years, Mean (SD)	42.0 (13.0)		
Education in years, Mean (SD)	12.3 (3.3)		
Number of chronic diseases, Mean (SD)	0.6 (0.8)		
*Medication use**			
Antidepressants, %	22.1	19.7	18.2
Benzodiazepines, %	6.7	4.3	4.3
Pain medication, %	7.8	8.8	9.2
Depressive and anxiety symptoms			
QIDS, Mean (SD)	8.1 (5.6)	6.1 (4.8)	6.0 (4.8)
BAI, Mean (SD)	11.7 (10.4)	8.7 (8.7)	8.1 (8.4)
FQ, Mean (SD)	24.9 (20.0)	20.3 (18.3)	18.7 (18.3)
Pain			
Pain intensity, Mean (SD)	39.6 (20.6)	39.6 (20.4)	39.2 (21.2)
Pain disability, Mean (SD)	26.0 (25.4)	25.5 (25.0)	24.6 (24.6)
Pain severity, Z score, Mean (SD)	0.01 (0.9)	0.01 (0.9)	0.01 (0.9)
Number of pain locations, Mean (SD)	3.2 (1.7)	3.1 (1.8)	2.9 (1.8)

Abbreviations: QIDS= Quick Inventory of Depressive Symptomatology, BAI=Beck Anxiety Inventory, FQ= Fear questionnaire, FU= follow-up

* using medication ≥ 50% of the time

Table 2: Association between changes in depressive (QIDS) or anxiety (BAI, FQ) symptom severity and changes in pain over 4 years using random coefficient analyses (n=2,676)[1].

	Δ Pain Severity		Δ Number of pain locations	
	B[2]	p	B[2]	p
Model 1				
Δ QIDS	0.01 (0.005-0.02)	<.001	0.03 (0.02-0.04)	<.001
BL pain severity	-0.26 (-0.29- -0.23)	<.001	n.a.	
BL pain locations	n.a.		-0.21 (-0.23- -0.18)	<.001
Model 2				
Δ BAI	0.007 (0.003-0.01)	<.001	0.03 (0.02-0.03)	<.001
BL pain severity	-0.26 (-0.28- -0.22)	<.001	n.a.	
BL pain locations	n.a.		-0.21 (-0.24- -0.18)	<.001
Model 3				
Δ Fear	0.005 (0.003-0.007)	<.001	0.007 (0.003-0.01)	<.001
BL pain severity	-0.26 (-0.29- -0.23)	<.001	n.a.	
BL pain locations	n.a.		-0.21 (-0.24- -0.19)	<.001

Abbreviations: Δ= change in, QIDS= Quick Inventory of Depressive Symptomatology, BAI=Beck Anxiety Inventory, FQ= Fear questionnaire, BL= baseline, n.a.= not applicable

[1] Models adjusted for age, gender, years of education, number of chronic diseases

[2] B=regression coefficient

Course of depressive and anxiety disorders and pain

Of the 2,676 individuals we selected at baseline, there were 2,093 individuals who could be assigned to one of the 4 different defined disorder course groups. There were 519 (24.8%) controls, who had never had a lifetime D/A. 333 individuals (15.9%), who did not have a baseline disorder, developed a depressive and/or anxiety disorder over time. Of the individuals with a depressive and/or anxiety disorder at baseline, 548 (26.2%) remitted over time and 693 (33.1%) were chronically depressed and/or anxious over the 4-year period. Those who did not fit our predefined categories (n=583) because they had a lifetime D/A diagnosis but did not develop a new disorder or because they had a fluctuating course of D/A remission and recurrence over time were excluded. In Table 3, the baseline sample characteristics are shown for the 4 distinct disorder groups (n=2,093). As shown, compared to the healthy controls there were more females with incident, remitted and chronic D/A. Baseline use of antidepressants, benzodiazepines and pain medication was increased in all D/A groups compared to in the healthy controls (p<.001) with the highest rates of antidepressants and benzodiazepines in the chronic D/A group. Pain medication was used significantly more by the individuals who developed D/A over time, compared to the healthy controls (p<.001) and remitted D/A individuals (p=0.03). As expected, depressive and anxiety symptoms were highest in the chronically depressed and anxious, and differed

significantly compared to healthy, incident D/A and remitted D/A individuals (p<.001). Baseline pain ratings were highest in the chronically depressed and anxious, and differed significantly compared to healthy, incident D/A and remitted D/A individuals (p<.001).

Table 4 displays adjusted associations between the D/A disorder course groups and pain outcomes over four years of follow up (again, unadjusted results were largely similar). Regarding the pain outcomes, the mean score of pain severity increased over time as seen by the time factor (B=0.05, p=0.01), whereas the number of pain locations remained the same (B=-0.04, p=0.21). Compared to the healthy controls, individuals in the three distinct D/A groups (either incident D/A, remitted D/A or chronic D/A) all had significantly greater pain severity (incident D/A: B=0.4, remitted D/A: B=0.5, chronic D/A: B= 0.7, all p<.001) and number of pain locations (incident D/A: B=0.8, D/A remission: B=1.0, chronic D/A: B= 1.4, all p<.001) at baseline, and also at two- and four-year follow-up. Over time, individuals who had a remitted D/A showed a stronger decline on both pain severity (B=-0.08, p=0.002) and number of pain locations (B=-0.24, p<.001). As compared to controls, subjects with incident D/A or chronic D/A did not show significantly larger or smaller change in pain outcomes over 4 years. We tested whether the use of antidepressants, benzodiazepines or pain medication had an impact on the longitudinal associations, but these medications showed to be no confounders of the associations (data not shown).

Table 3: Baseline sample characteristics according to D/A disorder course type[1].

	Healthy control	Incident D/A	Remitted D/A	Chronic D/A	D/A groups compared to controls	Between D/A groups
	n=519	n=333	n=548	n=693	p	p
Socio-demographics						
Female gender, %	59.3	74.5	66.6	64.4	<.001	inc-rem 0.01, inc-chr 0.001
Age in years, Mean (SD)	41.7 (14.6)	41.3 (13.5)	40.5 (12.8)	42.8 (11.7)	0.015	rem-chr 0.01
Education in years, Mean (SD)	12.9 (3.2)	12.3 (3.1)	12.0 (3.1)	11.6 (3.4)	<.001	inc-chr 0.02
Number of chronic diseases, Mean (SD)	0.5 (0.7)	0.6 (0.9)	0.6 (0.8)	0.7 (0.9)	0.001	-
*Medication use**						
Antidepressants, %	0.4	15.0	29.9	38.7	<.001	inc-rem, inc-chr, rem-chr <.001
Benzodiazepines, %	0.0	1.8	8.2	14.0	<.001	inc-rem, inc-chr, rem-chr <.001
Pain medication, %	4.6	11.7	7.3	8.2	0.002	inc-rem 0.03
Depressive and anxiety symptoms						inc-rem,
QIDS score, Mean (SD)	2.9 (2.6)	6.6 (4.0)	9.5 (4.8)	12.5 (4.9)	<.001	inc-chr,
BAI score, Mean (SD)	3.3 (4.2)	8.7 (7.0)	13.6 (9.6)	19.3 (10.9)	<.001	rem-chr
Fear score, Mean (SD)	11.2 (11.5)	19.2 (14.1)	25.6 (18.2)	37.5 (20.8)	<.001	<0.001
Pain						
Pain intensity (0-100), Mean (SD)	27.9 (18.7)	40.0 (18.9)	42.0 (20.1)	46.6 (20.0)	<.001	inc-chr,
Pain disability (0-100), Mean (SD)	15.5 (20.6)	24.9 (23.6)	28.4 (25.9)	34.0 (26.7)	<.001	rem-chr
Pain severity, Z score, Mean (SD)	-0.5 (0.8)	-0.02 (0.8)	0.09 (0.9)	0.3 (0.9)	<.001	<0.001
Number of pain locations (0-7), Mean (SD)	2.1 (1.5)	3.1 (1.6)	3.4 (1.7)	3.8 (1.7)	<.001	

Abbreviations: D/A= depressive and/or anxiety disorder, QIDS= Quick Inventory of Depressive Symptomatology, BAI=Beck's Anxiety Inventory, FQ= Fear questionnaire, inc=incident, rem=remitted, chr=chronic, * using medication >=50% of the time

[1] p-value based on one-way ANOVA for continuous variables and Chi square test for categorical variables

The outcomes of Table 4 are summarized graphically in Figure 1. The individuals with D/A - incident, remission and chronic - had significantly higher pain severity and higher number of pain locations compared to healthy controls at T0, T1, and T2 (see Figure 1a. and 1b, respectively). In particular, individuals with chronic D/A had highest pain ratings over the whole follow-up period. As shown in the Figure, for the healthy controls and individuals with incident or chronic D/A there was hardly any change in pain severity and number of pain locations over time, whereas for individuals who achieved D/A remission, there was a strong decline in pain ratings over time. However, even remitted patients did not reach comparable levels of pain severity and number of pain locations as compared to the healthy controls. We performed the analyses for depressive (D) course trajectories and anxiety (A) course trajectories - depression (n=1752; healthy controls n=519, incident D n=441, D remission n=496, chronic D n=296) and anxiety (n=1785; healthy controls n=519, incident A n=298, A remission n=504, chronic A n=464) - separately. Compared to the healthy controls, we found positive associations between depression - incident, remitted or chronic - and both pain severity (incident D: B=0.5, D remission: B=0.6, chronic D: B= 0.8, all p<.001) and number of pain locations (incident D: B=1.1, D remission: B=1.2, chronic D: B= 1.7, all p<.001). Over time persons who had remission of D showed a stronger decline on both pain severity (B=-0.08, p=0.002) and number of pain locations (B=-0.2, p=.001). Very similarly, compared to the healthy controls, we found positive associations between anxiety - incident, remitted or chronic - and both pain severity (incident D: B=0.5, D remission: B=0.5, chronic D: B= 0.7, all p<.001) and number of pain locations (incident D: B=0.9, D remission: B=1.2, chronic D B= 1.5, all p<.001) was found. Over time persons who had remission of A showed a stronger decline on pain severity (B=-0.06, p=0.05) and number of pain locations (B=-0.3, p<.001). To conclude, findings were very comparable across depression and anxiety course trajectories.

Table 4: Adjusted association between D/A disorder course types and pain over 4 years using random coefficient analyses (n=2,093)[1].

	Pain severity		Number of pain locations	
	B[2]	p	B[2]	p
Intercept	-0.6 (-0.7- -0.5)	<.001	2.0 (1.8-2.1)	<.001
D/A status				
Healthy control	REFERENCE		REFERENCE	
Incident D/A	0.4 (0.3-0.5)	<.001	0.8 (0.6-1.0)	<.001
Remission of D/A	0.5 (0.4-0.6)	<.001	1.0 (0.9-1.2)	<.001
Chronic D/A	0.7 (0.6-0.8)	<.001	1.4 (1.3-1.6)	<.001
Time (per two years)	0.05 (0.0-0.1)	.01	-.04 (-.12-0.03)	.21
Interaction D/A status*Time				
Healthy control*Time	REFERENCE		REFERENCE	
Incident D/A*Time	-0.01 (-0.1-0.1)	.88	0.02 (-0.09- 0.1)	.69
Remission of D/A*Time	-0.08 (-0.1- -0.03)	.002	-0.24 (-0.3- -0.1)	<.001
Chronic D/A*Time	-0.03 (-0.08-0.02)	.18	-0.04 (-0.1-0.06)	.44

Abbreviations: D/A= depressive and/or anxiety disorder

[1] Model adjusted for time, age, gender, years of education, number of chronic diseases

[2] B=regression coefficient

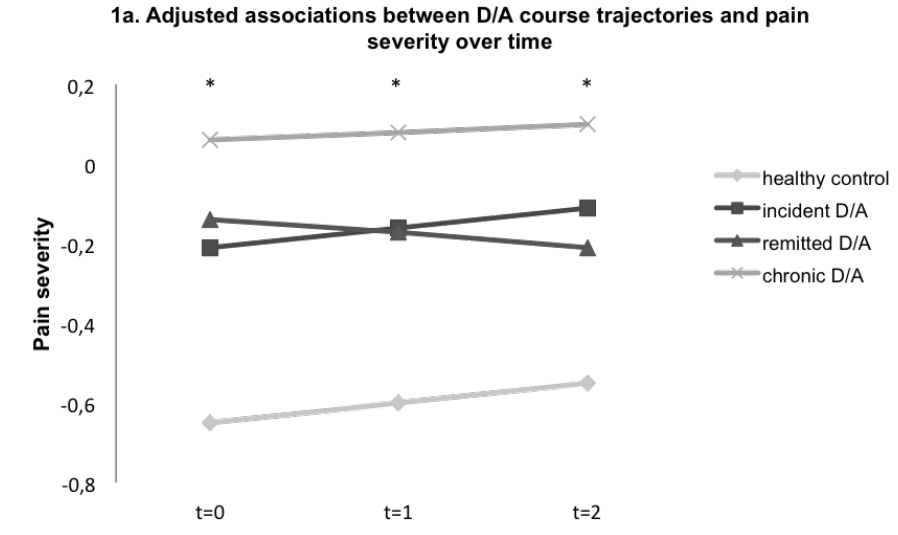

Figure 1 The association between depressive and/or anxiety disorder course and pain severity (1a.) and pain locations (1b.) over 4 years of follow-up based on random coefficient analyses.
*All D/A courses differed significantly in pain ratings from the healthy controls at all waves (p<.001)

DISCUSSION

This study used a longitudinal design to determine the associations between changes in depressive and anxiety symptoms and disorders with changes in pain. First, at depressive and anxiety symptom level we found a synchrony of change between change in depressive and anxiety symptoms and change in pain, which concurs with previous evidence[27-30]. Next, we found that depressive and anxiety disorders - whether incident, remitting or chronic- are associated with worse pain severity and higher number of pain locations over time compared to being mentally healthy. Chronically depressed and anxious individuals show the greatest pain ratings and even if individuals recover from the depressive or anxiety disorder their pain ratings are still significantly greater than of mentally healthy individuals. Surprisingly, when individuals developed a depressive or anxiety disorder over time, pain levels were already high before depression or anxiety onset and pain ratings did not significantly increase over time. Depressive and anxiety disorder courses separately exert rather a similar impact on pain over time, suggesting it seems sensible to study these affective disorders conjointly.

The finding that there is synchrony of change at symptom level may imply that when depressive and anxiety symptoms subside then the patient's pain will also disappear. A stable mental health situation, thus being a healthy control or having chronic depression or anxiety, was associated with stable pain ratings over time, but chronically depressed or anxious patients have significantly higher pain ratings at all times. Depression and anxiety remission -as expected- is associated with a decrease in pain ratings, but does not lead to similar levels of pain as observed in persons without lifetime depressive or anxiety disorders. These findings may imply that there are other factors involved in the association between depression, anxiety and pain and in the evolution of pain symptoms over time. Functional imaging studies have shown some evidence that emotional processing within the insula in depressed and anxious patients, is topologically shifted toward the prefrontal areas which are normally involved in pain processing, which might explain increased pain reporting in depressed and anxious individuals[19;20]. These changes in brain processing might persist after recovery of depression and anxiety and might also be negatively affected by the pain experience itself[19]. There is a growing body of literature about the biological consequences of depression and anxiety. In depressed and anxious individuals systemic inflammation and hyperactivity of the HPA-axis and autonomic dysregulation have been observed, which have also been linked to chronic pain[3;15;17;18;48;49]. Also, when individuals are depressed or anxious, they on average eat unhealthier diets, have decreased physical functioning and increased sedentary behavior[48;50;51]. These lifestyle factors have also been associated to chronic pain[19;21;22;52]. We were surprised to find that incidence of depression and anxiety over time shows no significant increases in pain ratings. However, these individuals already reported high pain ratings at the baseline assessment, which may reflect previous findings that pain can also be a risk indicator of depressive and anxiety disorder onset[3;53;54]. A diathesis-stress perspective on the link between D/A and pain suggests that certain diatheses – predisposing psychological characteristics of the individual - before the onset of chronic pain are activated by the stress of the pain. The resulting D/A may then be related to maintaining greater pain ratings compared to healthy individuals[53].

In concordance with our findings and since depression, anxiety and pain seem to be so closely linked, one could imagine that once an individual has suffered from a depressive or anxiety disorder, it is very unlikely that the person will reach pain ratings comparable to those of mentally healthy individuals over the course of many years. Likely, a downward spiral of depression or anxiety increasing pain perception, and pain leading to more depression and anxiety might result. To prevent this vicious cycle, interventions integrating treatments for depressive and anxiety problems as well as pain symptoms may show more favorable results than treating either affective or pain symptoms. There is evidence that both antidepressants and psychotherapy can be effective for depression, anxiety and pain symptoms[55-58]. But since evidence points to less effective treatment outcomes when patients have both affective and pain problems[3;4;59;60], new management options should be investigated. Ideally, these treatment could reduce both affective and pain symptomatology in the future.

This study had several strengths. We used a large longitudinal data set to analyze the effects of change in not only depressive and but also anxiety symptomatology with change in pain over the course of four years. We were able to analyze how different depressive and anxiety disorder courses are associated with pain symptoms over time. Studying disorders rather than symptoms in relation to pain can prevent an overestimation of the associations due to symptom overlap. Also, the use of disorder course types seems more clinically relevant since in daily practice depressive and anxiety disorders are mostly of interest to be managed by clinicians. We used two pain characteristics as outcome measure to examine the associations between depression and anxiety and pain. This study also had some limitations. NESDA provides information on the most common depressive and anxiety disorders and therefore results cannot be generalized to specific other disorders such as PTSD or bipolar depression. We collected data at three time points and although for depressive and anxiety disorders we had information over the whole period using a Life Chart method, regarding pain we only had information about pain symptoms in the 6 months previous to each interview. The use of a Life Chart method for pain symptomatology could give a more accurate picture of the pain symptoms over the whole period. We did not assess in the interview or by physical examination whether there was an organic cause for the reported pain. We did adjust the analyses for chronic somatic diseases, but this hardly changed associations. Lastly, we did not assess the reason why medication was being used, possibly antidepressants could have been taken for pain, however, the use of medication did not change the associations between depression, anxiety and pain.

To conclude, the results of our study indicate that there is a synchrony of change between depressive and anxiety symptoms and pain. Having an incident, a remitted or a chronic depressive and/or anxiety disorder is associated with greater pain ratings over time. On the long-term, depression and anxiety exert negative effects on pain ratings, even after remission of depression and anxiety. Our findings imply that it is important to consider depression and anxiety when diagnosing and treating pain in clinical practice. Reducing depression and anxiety burden might lead to reduced burden of pain, however, even when patients are recovered of depression or anxiety it is very likely that they will report more pain than patients without a history of depression or anxiety.

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