The interplay between depression, anxiety and physical health

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Chapter 7

Pain, not chronic disease, is associated with the recurrence of depressive and anxiety disorders

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ABSTRACT

Objective

To determine whether specific chronic diseases and pain characteristics are associated with depression and anxiety recurrence and to examine whether these associations were mediated by subthreshold depressive or anxiety symptoms.

Method

1,122 individuals with remitted depressive or anxiety disorder (Netherlands Study of Depression and Anxiety) were followed up till four years. The impact of specific chronic diseases and pain characteristics on recurrence was assessed using Cox regression and mediation analyses.

Results

Chronic diseases were not associated with recurrence. Pain of neck (HR 1.45, p<.01), chest (HR 1.65, p<.01), abdomen (HR 1.52, p<.01), increasing number of pain locations (HR 1.10, p<.01) and pain severity (HR 1.18, p=.01) were associated with an increased hazard of depression recurrence but not anxiety. Subthreshold depressive symptoms largely mediated the associations between pain and depression recurrence.

Conclusion

Pain, not chronic disease, increases the likelihood of depression recurrence, largely through its association with increased subthreshold depressive symptoms . These findings support the idea of a reinforcing mechanism between pain and depression and stress the importance of elucidating the neurobiological links to optimize pain and depression management.

INTRODUCTION

Depressive and anxiety disorders are often recurrent. Recurrence rates of 25 to 60% have been reported in studies differing in populations and methodology[1-11]. After over two to three years of being without a disorder, recurrence rates seem to stabilize and in the long run after a person stays well for a longer period recurrence appears less likely[1;11;12]. Insight into the contributions of risk factors for recurrence of depressive and anxiety disorders is necessary to find strategies to prevent new episodes and identify who might benefit from long-term treatment[13]. Suffering from chronic diseases or pain might pose an important -potentially modifiable- risk for recurrence of depressive and anxiety disorders for various reasons. Firstly, we previously assessed a negative impact of several chronic diseases and pain on the course of illness in depressed and anxious individuals and previous studies have also found a negative impact on prevalence and treatment outcome of depression and anxiety[14-21]. Secondly, chronic diseases and pain can lead to negative coping strategies, disability and reduced quality of life[22;23], which might lead to redeveloping a depressive or anxiety episode in people prone to affective disorders. Last, shared pathophysiological mechanisms have been postulated between chronic somatic diseases, pain and depression and anxiety[19;24;25]. So far, limited evidence for the role of chronic diseases, and especially particular diseases, and pain on depression and anxiety recurrence exists. One study found higher pain severity as predictor of depression relapse in 278 randomized trial subjects[26]. A treatment trial showed that cumulative chronic disease ratings significantly impacted on depression relapse(n=128)[27], whereas another found no effect of chronic conditions(n=251)[6]. Two longitudinal studies (n=585, n=687 respectively) found that chronic diseases[3;10] and chronic pain[3] did not predict depression recurrence. One study (n=429) found no effect of number of chronic diseases on anxiety recurrence in their multivariate model[28]. To the best of our knowledge, there are no studies reporting associations between pain and anxiety recurrence. Previous studies on risk factors for recurrence of depressive and anxiety disorders point to subthreshold depressive and anxiety symptoms as the most consistent predictive factors for depression and anxiety recurrence[1-7;9;10;13;21;26;29;30]. Since chronic diseases and pain can also increase subthreshold depressive and anxiety symptoms[31;32], associations of chronic diseases and pain with recurrence of depressive and anxiety disorders may be linked through increased subthreshold depressive and anxiety levels.

The objectives of this study were to examine to what extent (particular) chronic diseases and pain symptoms are associated with the recurrence of depressive and anxiety disorders in patients with a prior history of depressive and/or anxiety disorder in a large longitudinal study. And second, to determine whether subthreshold depressive and anxiety symptoms partly mediate associations between chronic diseases, pain and recurrence of depressive and anxiety disorders.

MATERIALS AND METHODS

Sample

The Netherlands Study of Depression and Anxiety (NESDA) is a longitudinal cohort study, which was designed to examine the long-term course and consequences of depressive and anxiety disorders[33]. At baseline, 2,981 participants (18 to 65 years), were included from the general population (n=564), general practices (n=1,610) and mental health care organizations (n=807). Exclusion criteria were not being fluent in Dutch and having a primary diagnosis of psychotic, obsessive compulsive, bipolar or severe addiction disorder. The Ethical Committee of participating universities approved the research protocol and a written informed consent was obtained from all patients. Baseline data collection took place between 2004 and 2007, with follow-up assessments including the CIDI two and four years later. The face-to-face interview assessments included a standardized diagnostic psychiatric interview and demographic and personal characteristics. Specially trained research staff conducted the interviews.

All 2,981 participants were screened for depression and anxiety at baseline using the DSM-IV based Composite International Diagnostic Interview (CIDI, version 2.1), a highly reliable and valid instrument for assessing depressive (major depressive disorder, dysthymia) and anxiety (social phobia, generalized anxiety disorder, panic disorder, agoraphobia) disorders[34]. Participants could have either no history, a prior history or a current depressive and/or anxiety disorder.

For this study, we examined 1,236 participants who reported to have had a depressive or anxiety disorder in the past, but were currently remitted according to the CIDI, which meant they did not have a diagnosis of depressive or anxiety disorder (in the prior six months) either at baseline (n=628) or at the two year follow-up assessment (n=608). Of these, 114 (9.2%) were lost to follow-up, who did not differ significantly differ in age, gender, education and subthreshold depressive or anxiety symptoms at baseline. Consequently, a total of 1,122 participants were followed up for up to four years.

Recurrence of depressive and anxiety disorders

Recurrence of a depressive or anxiety disorder (yes/no) was defined by the DSM-IV based CIDI in the subsequent assessments. We calculated the *time to recurrence of a depressive or anxiety disorder* in months (maximum of 48 months) from the moment the participant was assessed as being remitted (did not have a current diagnosis) until the moment a participant was diagnosed with a depressive or anxiety disorder in one of the follow up assessments according to the CIDI. When a participant was diagnosed with a recurrence of depressive and/or anxiety disorder at the 2- or 4-year follow up assessment, participants 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 retrospectively. We used this information and calculated the median of the time interval to recurrence. So, for instance, if a participant reported a recurrence of depressive or anxiety disorder with a recency of onset between 1 and 6 months ago (median 3 months ago) at the 4-year follow up interview (and no disorder at the two year follow up was diagnosed), the time from baseline to recurrence to be used in the analyses was (48-3=) 45 months. For participants not experiencing a recurrence of depression or anxiety, time was censored as the time from the assessment in which remission was defined until the end of the follow up period.

Measurements

Data on self-reported chronic diseases and pain, both indicators of physical health, were assessed at the time point at which the participants were defined as remitted (either at baseline or at the two-year follow up assessment).

Chronic disease

First, patients were asked in a face-to-face interview whether they had been diagnosed with any of the mentioned chronic somatic diseases (Table 1). In order to assess the chronic diseases most 'objectively', we considered chronic disease only to be present if the participant stated that the disease was being treated by a healthcare professional or he or she was using medication for the disease. As in a previous study[18], we classified the chronic diseases into seven main categories; cardiometabolic, respiratory, endocrine, neurological, musculoskeletal, digestive disorders or cancer. We defined the number of chronic diseases as the number of disease categories to which a participant had been classified.

Pain

To assess pain over the last 6 months in various ways, the interview contained four different measures: a) 7 specific common pain locations (neck, back, head, orofacial area, abdomen, chest and joints); b) the number of locations; c) duration and; d) severity determined by the Chronic Pain Grade(CPG)[35]. First, the number of pain locations (0-7) in the last six months was assessed. Then, the participant was asked to choose the most painful of the locations, to which all subsequent questions applied. Next, duration of pain in the last six months was dichotomized as ≥90 versus <90 days, based on the most frequently used definition of chronic pain. Last, severity was graded by measuring the intensity of pain and disability caused by pain using the CPG scale:

- grade 1: low intensity-low disability
- grade 2: high intensity-low disability
- grade 3: high disability-moderately limiting
- grade 4: high disability-severely limiting

To exclude pain symptoms that were mild or occurred only sporadically in the past six months, only pain locations with at least a grade 2 on the CPG were taken into account, so that the more severe locations of pain (at least high intensity of pain and low disability caused by pain) were measured.

Covariates

Sociodemographic characteristics included age, gender and years of education. The recency of the last episode of depressive or anxiety disorder, more than one year ago or one year or less, was determined at the time participants had a remitted depressive or anxiety disorder, since the time from remittance might impact on the recurrence of depression and anxiety[1].

Mediators

A mediator is an intervening variable that may account for the association between the independent variables, chronic disease and pain, and the dependent variable, the recurrence of depression or anxiety. We assessed the subthreshold symptoms of depression and anxiety using the severity of symptoms at the time participants had a remitted diagnosis of depressive or anxiety disorders. We expected subthreshold symptoms to be partial mediators since the presence of chronic diseases and pain have shown to increase severity of symptoms of depression and anxiety[31;32], which could in turn result in depression or anxiety recurrence[1-7;26;29;30]. The severity of depressive symptoms was measured using the Quick Inventory of Depressive Symptomatology -self-report (QIDS), a reliable and valid instrument consisting of 16 items (0-27 score)[36;37]. Self-reported severity of anxiety symptoms was 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[38].

Statistical analysis

To examine the associations of chronic diseases and pain with the time to recurrence of a diagnosis of depression or anxiety, we performed Cox regression analyses, before and after adjustment for covariates. Cox regression takes into account differences in time at risk for an event and censoring. Time at risk was measured from the moment the participant was assessed as being remitted until either the moment a participant had an event, a recurrent depressive or anxiety disorder, or was censored when the participant did not have a recurrence during follow up period. We also analyzed the time to recurrence of depressive or anxiety disorder separately, in order to explore whether the impact of chronic diseases and pain is different for recurrence of depression versus anxiety.

To determine whether subthreshold symptoms of depression and anxiety mediated the associations found between chronic diseases, pain and recurrence of depression or anxiety we conducted mediation analyses, through the indirect method by Preacher and Hayes involving bootstrapping approximations[39]. The indirect method estimates the total, direct, and indirect unstandardized effects of the independent variables on the dependent variable through the mediator variable, controlling for covariates.

RESULTS

Sample characteristics

Table 1 shows the characteristics of the study sample (n=1,122). Mean age of the study sample was 43.4 years and 68.2% was female. The average number of chronic diseases was 0.6 (SD 0.8), 59.4% of participants had no chronic disease. The mean number of pain locations was 1.2 (SD 1.9), 35.8% had a CPG of at least 2. Of participants, 424 (37.8%) had a recurrence of a depressive and/or anxiety disorder during the follow-up period. The average follow-up period was 30.0 months (SD 13.4).

Impact of chronic diseases and pain on recurrence

In Table 2 the adjusted associations between chronic diseases, pain symptoms and recurrence of a depressive or anxiety disorder are shown. Unadjusted analyses showed rather similar results (not shown). For the chronic disease categories no associations recurrence of depression or anxiety were found. For pain we did find significant positive associations with recurrence of depression and/or anxiety. However, the associations were driven by the recurrence of depressive disorder and not anxiety. Severe neck (HR=1.45, p=.005), chest (HR=1.65, p=.008) and abdominal (HR=1.52, p=.003) pain were significantly associated with depression recurrence, as was the number of pain locations (per location increase: HR=1.10, p=.002) and higher CPG (per grade increase: HR=1.18, p=.01).

Table 1: Sample characteristics.

Characteristics	Population (n=1,122)
Sample characteristics	
Female gender, %	68.2
Age in years, Mean (SD)	43.4 (12.8)
Education in years, Mean (SD)	12.5 (3.2)
Recency of last episode (≤1 year), %	14.3
History of both depression and anxiety, %	48.4
QIDS score, Mean (SD)	5.4 (3.7)
BAI, Mean (SD)	7.2 (6.4)

Table 1 continued.

Characteristics	Population (n=1,122)
Physical health characteristics	
Chronic disease category, %	
Cardiometabolic hypertension, angina pectoris, history of cardiac disease, stroke, diabetes	16.5
Respiratory asthma, chronic bronchitis, pulmonary emphysema	7.8
Musculoskeletal osteoarthritis, rheumatoid arthritis, systemic lupus erythematodes, fibromyalgia	10.0
Digestive ulcer, irritable bowel syndrome, Crohn's disease, colitis ulcerosa, diverticulitis, liver cirrhosis, hepatitis, constipation	9.0
Neurological migraine, epilepsy, multiple sclerosis, peripheral neuropathy, hernia	4.3
Endocrine thyroid dysfunction	3.2
Cancer throat, thyroid, lymphoid, lung, esophagus, bowel, stomach, liver, uterus, cervix, ovary, bladder, testicle, prostate, skin, brain, blood	7.4
Number of chronic diseases, Mean (SD)	0.6 (0.8)
Pain Location, %[1]	
Neck	21.2
Back	26.5
Head	25.7
Orofacial	5.3
Abdominal	16.8
Joints	21.8
Chest	7.1
Number of pain locations, Mean (SD) [1]	1.2 (1.9)
Duration of Pain ≥ 90 days, %	31.6
Chronic Pain Grade, Mean (SD)	1.5 (0.8)
Outcome, %	
Recurrence of depression disorder	26.0
Recurrence of anxiety disorder	22.7
Recurrence of depressive and/or anxiety disorder	37.8
Duration of follow up in months, Mean (SD)	30.0 (13.4)

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

Abbreviations: CPG= Chronic Pain Grade, QIDS= Quick Inventory of Depressive Symptoms, BAI= Beck Anxiety Inventory

Table 2: Associations between somatic health variables and time to recurrence of depressive and/or anxiety disorder during follow-up (n=1,122)[a].

Physical health characteristics	Time to recurrence of depressive and/or anxiety disorder[c]		Time to recurrence of depressive disorder[c]		Time to recurrence of anxiety disorder[c]	
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
Chronic disease category						
Cardiometabolic	0.94 (0.71-1.25)	.66	0.86 (0.61-1.21)	.38	1.11 (0.78-1.59)	.57
Respiratory	1.17 (0.84-1.65)	.36	1.31 (0.89-1.93)	.18	1.10 (0.70-1.71)	.69
Musculoskeletal	1.13 (0.83-1.55)	.44	1.35 (0.94-1.92)	.11	1.19 (0.80-1.77)	.39
Digestive	1.26 (0.92-1.73)	.15	1.19 (0.82-1.75)	.36	1.22 (0.81-1.84)	.34
Neurological	1.17 (0.74-1.86)	.50	1.22 (0.71-2.09)	.47	0.89 (0.46-1.74)	.74
Endocrine	1.09 (0.65-1.83)	.76	1.07 (0.57-2.02)	.84	1.53 (0.85-2.75)	.15
Cancer	1.13 (0.80-1.60)	.49	1.11 (0.73-1.68)	.62	1.21 (0.78-1.86)	.40
Number of chronic diseases	1.09 (0.97-1.23)	.16	1.11 (0.96-1.27)	.16	1.13 (0.97-1.31)	.12
Pain location[b]						
Neck	1.31 (1.05-1.64)	.02	1.45 (1.12-1.89)	.005	1.15 (0.86-1.55)	.35
Back	1.15 (0.93-1.43)	.21	1.30 (1.00-1.67)	.05	0.93 (0.70-1.24)	.65
Head	1.21 (0.98-1.50)	.08	1.29 (1.00-1.67)	.05	1.26 (0.95-1.66)	.11
Orofacial	1.34 (0.92-1.96)	.13	1.46 (0.94-2.27)	.09	1.20 (0.72-2.00)	.49
Chest	1.51 (1.09-2.08)	.01	1.65 (1.14-2.39)	.008	1.41 (0.93-2.14)	.11
Abdominal	1.33 (1.05-1.68)	.02	1.52 (1.16-2.02)	.003	1.13 (0.82-1.55)	.45
Joints	1.20 (0.96-1.51)	.12	1.31 (1.00-1.71)	.05	0.99 (0.73-1.34)	.94
Number of pain locations[b]	1.07 (1.02-1.12)	.009	1.10 (1.04-1.16)	.002	1.03 (0.97-1.10)	.34
Duration of pain ≥ 90 days	1.10 (0.89-1.35)	.38	1.24 (0.96-1.58)	.11	0.99 (0.75-1.30)	.94
Chronic Pain Grade	1.11 (0.99-1.24)	.06	1.18 (1.04-1.35)	.01	1.07 (0.93-1.24)	.35

a Using univariate cox regression analyses

b Pain locations were only taken into account when CPG ≥ 2

c Adjusted for age, gender, years of education and recency of last episode of depressive or anxiety disorder

Mediation of subthreshold depressive and anxiety symptoms

In Table 3 we show the mediation of subthreshold depressive symptoms on the associations between pain and recurrence of depression which were (borderline) significant in the Cox regression analyses (p<.10). We did not conduct these analyses for chronic diseases or for recurrence of anxiety, since we did not find any significant associations for these indicators in earlier analyses. First, mediation analyses confirmed that pain is associated with higher severity of subthreshold symptoms (a in Table 3) and that higher severity of subthreshold symptoms was significantly associated with depression recurrence (b in Table 3). For all pain variables the direct paths turned insignificant, although the direct paths of abdominal and chest pain remained borderline significant (c' in Table 3). The indirect effects (a x b in Table 3) were significant for pain of the neck, back, head, abdomen, chest and joints, higher number of pain locations and higher CPG, suggesting that there is an overall effect of the pain variables on depression recurrence through increased subthreshold depressive symptoms.

Table 3: Summary of Preacher and Hayes mediator model analyses (5000 bootstraps) between pain[1](IV), and recurrence of depressive disorder (DV)[2].

Pain variables (IV)	Mediating variable (M)	Dependent variable (DV)	Effect of IV on M (a)	Effect of M on DV (b)	Direct effect (c')		Indirect effect (a x b)	95% CI (ab)	Total effect (c)	
					effect	p			effect	p
Neck	Depression severity, QIDS	Recurrence of depression	1.55**	.16**	.25	.14	.25	(.14-.36)^	.47	.004
Back	Depression severity, QIDS	Recurrence of depression	1.40**	.16**	.05	.76	.23	(.13-.34)^	.27	.09
Head	Depression severity, QIDS	Recurrence of depression	1.25**	.16**	.12	.48	.20	(.11-.31)^	.30	.05
Abdominal	Depression severity, QIDS	Recurrence of depression	1.79**	.16**	.35	.06	.28	(.17-.41)^	.60	.001
Chest	Depression severity, QIDS	Recurrence of depression	2.51**	.16**	.43	.10	.40	(.23-.59)^	.77	.002
Joints	Depression severity, QIDS	Recurrence of depression	1.21**	.16**	.16	.37	.19	(.10-.30)^	.34	.04
Number of pain locations	Depression severity, QIDS	Recurrence of depression	.42**	.15**	.06	.12	.07	(.04-.09)^	.12	.001
CPG	Depression severity, QIDS	Recurrence of depression	.74**	.16**	.08	.36	.12	(.07-.18)^	.18	.02

* p<.05, ** p<.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 and recency of last episode of depressive and/or anxiety disorder

DISCUSSION

The purpose of this study was to examine whether chronic diseases and pain are associated with recurrence of depressive and anxiety disorders and if so, whether these associations are partly mediated by subthreshold depressive and anxiety symptoms. In this large study with a mean follow up of 2,5 years, 37.8% of people experienced a recurrence, which corresponds reasonably well with percentages of recurrence in previous research[1-11]. We did not detect an association between the presence of chronic diseases with recurrence of depressive and anxiety disorders. Severe neck, chest and abdominal pain, a higher number of pain locations and higher severity of pain were significantly associated with recurrence of depressive disorder, but not of anxiety. Subthreshold depressive symptoms mediated the associations between pain and depression recurrence.

The finding that chronic diseases are not associated with the recurrence of depression or anxiety in this study agrees with previous findings[3;6;10;28]. Iosifescu et al. found that increasing cumulative chronic disease ratings did predict relapse in a treatment trial[27]. Contrary to the measures used by Iosifescu et al., we had no information on the severity of the chronic diseases and we had a relatively healthy population with on average 0.6 chronic diseases. Also, our and the above mentioned studies consisted of rather young populations with mean age around forty years[3;6;10;27]. Chronic diseases often progress over time therefore associations with depression and anxiety recurrence might be different in studies examining older multi-morbid populations.

This is the first observational study to systematically examine the associations between pain symptoms and depression and anxiety recurrence. We found that several pain measures are associated with an increased hazard of depression recurrence, which concurs with results of Fava et al. who found that higher levels of pain severity predicted relapse of depression in trial subjects[26]. Since all pain locations were (borderline) significant, the particular location of the pain seems less relevant in predicting depressive disorder recurrence. Our results point to a dose-response relationship, where increasing number of pain locations and increasing severity of pain seem to increase the hazard of depression recurrence. Our findings, with subthreshold depression levels largely mediating the associations, illustrate that a reinforcing mechanism between pain and depression might exist[24]. In support of such possible bidirectional relationship, a study found that change in pain was a strong predictor of subsequent depression symptom severity and vice versa, in both non-depressed and depressed individuals[40]. The proposed vicious cycle could then be due to negative coping mechanisms as a consequence of impaired physical and social role functioning caused by both the pain and affective symptoms[41]. Also, evidence for various shared pathophysiological pathways has been postulated. Neuroimaging studies have shown overlap of the neuronal networks of affect and pain, particularly of the (pre)frontal cortical regions[42]. The experienced pain could have caused changes such as dysregulation of the HPA axis (increasing cortisol levels), and of the autonomic nervous system (increasing sympathetic or

reducing parasympathetic functions) which consequently resulted in a new depressive disorder episode. It might also be possible that through these same pathways, the previous depressive episode(s) have made patients more vulnerable to pain[21;24;41;43;44].

Contrary to what we expected, we did not find a significant relationship between pain and anxiety recurrence. Although the same pathophysiological pathways for depression and pain are mentioned in research regarding anxiety and pain, associations might be different or they might be linked through depressive disorders. For instance, HPA-axis abnormalities were found to be strongly associated with depressive disorder and co-morbid depression and anxiety, but they were not present for most types of anxiety disorders[43;45]. A cross-sectional study found that depression partly mediated the relationship between pain and anxiety[16]. Also, a previous NESDA study found that anxiety predicted the recurrence of anxiety only, whereas depression predicted the recurrence of both depression and anxiety[46]. Since research on anxiety and co-morbid depressive and anxiety disorders is still limited compared to depressive disorder alone, more research, regarding anxiety especially, is needed to further explore links.

This study shows that the experience of pain makes a patient vulnerable to recurrence of depressive disorders. The experience of pain is one of the most common reasons to consult a physician, so it is very likely that patients with pain who also have a depressive history will contact their physician. The physician is then in the opportunity to enquire after depressive symptoms and if necessary start treatment. Unfortunately, previous studies have shown that pain negatively impacts depression treatment and vice versa[24]. Specific relapse prevention trials could focus on distinctions between patients with and without pain in order to find new strategies to prevent depression relapse in patients with pain. Some evidence has been found for alleviating chronic pain and depressive symptoms with collaborative care aimed at chronic pain patients[47]. Collaborative care trials have proven their efficacy on sustained recovery of depressive disorder and continuation and maintenance therapies can reduce recurrence[48;49]. Tailored collaborative care interventions with maintenance therapies for patients who recovered from a depressive disorder but who are experiencing pain might reduce recurrence risk in this particular subpopulation of vulnerable patients. Based on the continuously growing evidence regarding shared neurobiological pathways new effective interventions need to be explored.

Strong aspects of our study are the large sample size, the prospective design and the systematic investigation of the role of various chronic diseases and pain on the recurrence of both depression and anxiety. Also, we used full diagnostic interviews to assess the presence of depressive and anxiety disorders with questions regarding the recency of experienced periods which enabled us to assess time to recurrence more accurately. This study also had some limitations. The prevalence of specific chronic diseases (like myocardial infarction, epilepsy etc.) were quite low, so power was limited to study the role of all diseases individually. This study was conducted with patients of 18 to 65 years old, findings could be different in populations with younger individuals or elderly people. The last limitation is that 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 during the same assessment.

The presence of chronic diseases does not increase the risk of recurrence of depressive and anxiety disorders. Pain increases the likelihood of the recurrence of depressive disorder. Since pain was associated with increased subthreshold depressive symptoms, this largely mediated the found effects. Likely, reinforcing neurobiological mechanisms between pain and depressive disorders exist, which might be addressed in future treatment modalities, to prevent recurrences.

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