Clinical Study

Chronic low back pain and the risk of depression or anxiety symptoms: insights from a longitudinal twin study

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Abstract

BACKGROUND CONTEXT: Pain is commonly associated with symptoms of depression or anxiety, although this relationship is considered bidirectional. There is limited knowledge regarding causal relationships.

PURPOSE: This study aims to investigate whether chronic low back pain (LBP) increases the risk of depression or anxiety symptoms, after adjusting for shared familial factors.

STUDY DESIGN: This is a longitudinal, genetically informative study design from the Murcia Twin Registry in Spain.

PATIENT SAMPLE: The patient sample included 1,269 adult twins with a mean age of 53 years.

OUTCOME MEASURES: The outcome of depression or anxiety symptoms was evaluated with EuroQol questionnaire.

METHODS: Using logistic regression analyses, twins were initially assessed as individuals in the total sample analysis, followed by a co-twin case-control, which was partially (dizygotic [DZ] twins) and fully (monozygotic [MZ] twins) adjusted for shared familial factors. There was no external funding for this study and no conflict of interest was declared.

RESULTS: There was a significant association between chronic LBP and the risk of depression or anxiety symptoms in the unadjusted total sample analysis (odds ratio [OR]: 1.81, 95% confidence interval [CI]: 1.34–2.44). After adjusting for confounders, the association remained significant (OR: 1.43, 95% CI: 1.05–1.95), although the adjusted co-twin case-control was non-significant in DZ (OR: 1.03, 95% CI: 0.50–2.13) and MZ twins (OR: 1.86, 95% CI: 0.63–5.51).

CONCLUSIONS: The relationship between chronic LBP and the future development of depression or anxiety symptoms is not causal. The relationship is likely to be explained by confounding from shared familial factors, given the non-statistically significant associations in the co-twin case-control analyses. © 2017 Elsevier Inc. All rights reserved.

Keywords: Anxiety; Chronic low back pain; Depression; Epidemiology; Genetics; Twins

Introduction

Low back pain (LBP) is the largest contributor to years lived with a disability worldwide [1]. Although the vast majority of LBP episodes resolve rapidly within a few weeks or months [2,3], some will continue to report ongoing complaints for 3 months or longer, predisposing them to chronic LBP [4]. Those who report chronic LBP generally have a poorer prognosis [4], and this can significantly impact on people's quality of life, including psychological disturbance with depression symptoms in particular, commonly associated with LBP [5].

Ranked second behind LBP in terms of years lived with a disability [1], depression is characterized by persistent low mood and a loss of interest and enjoyment in ordinary things. A review of the literature investigating the relationship between depression and pain showed that depression was present in up to 85% of those reporting painful conditions [6]. Moreover, individuals suffering from depression commonly report symptoms of anxiety, that is, feelings of worry, nervousness, or unease. For instance, the Netherlands Study of Depression and Anxiety showed that of the people who presented with depression, 67% had a current anxiety disorder, whereas among those who presented with anxiety, 63% had a current depressive disorder [7]. Anxiety with depression is associated with chronic pain [8] and both are known to negatively impact treatment [9], reduce quality of life, and increase societal cost [10–12].

Those who suffer LBP are more likely to suffer from depression or anxiety compared with non-LBP sufferers. A number of prevalence studies have identified this relationship, including a recent study of the general population of Qatar, where the prevalence of depression (13.7% vs. 8.5%) and anxiety disorders (9.5% vs. 6.2%) was higher in those with LBP compared with those without LBP [13]. Similarly, men with long-standing chronic LBP reported higher lifetime prevalence rates of depression (32% vs. 16%) and anxiety (30.9% vs. 14.3%) disorders over those not reporting chronic LBP [14]. However, few studies exist in regard to the risk of future depression and anxiety caused by chronic LBP. Adults from a Dutch population aged between 18 and 65 years who self-reported chronic LBP lasting longer than 3 months were at risk of developing depression or anxiety disorders [15]. Another Dutch study showed that those who reported pain in multiple locations (including the spine) were at higher risk of developing a first episode of depression or anxiety symptoms [16], whereas a similar cohort who reported chronic pain of greater than 90 days' duration was also associated with the future development of depressive and anxiety disorders [17]. Although pain is an established marker for future depression or anxiety, a review of the literature indicates that depression or anxiety can precede pain [18]. However, the exact nature of the relationship (ie, a causal relationship) between LBP and these specific psychological distress states is yet to be clarified.

One way of disentangling the complex relationship between LBP and depression or anxiety is through the consideration of shared familial factors (ie, genetics and shared early environment) as its contribution is unclear, yet moderate heritability estimates for LBP (ranging from 21% to 67%) [19], anxiety (24%–39%) [20] and depression (31%–42%) have been reported [21]. The implementation of a discordant, within-pair twin case-control study design using twins (who share not only all [monozygotic {MZ}] or approximately half [dizygotic {DZ}] of their genes but also virtually their entire childhood environment into adolescence, because of their similar upbringing) is an effective way of controlling for previously unmeasured shared familial factors [22], thereby providing more precise estimates between two variables. By employing a genetically informative longitudinal design and providing insights into causation, our objective was to examine the influence of a history of chronic LBP on the future risk of depressive or anxiety symptoms, controlling for the effect of shared familial factors by means of a co-twin case-control design.

Methods

Study sample and data collection

Participants consisted of adults born in multiple births between 1940 and 1966, who were part of the Murcia Twin Registry (MTR) in Spain. The present study sample comprised adult twins with or without chronic LBP who were free of symptoms of depression or anxiety at baseline as assessed by the depression or anxiety dimension of the EuroQol (EQ-5D) health questionnaire [23]. The MTR is a community-based twin registry, and a description of recruitment methods and waves of data collection is provided elsewhere [24]. Briefly, baseline data collection via a health-related questionnaire was conducted between 2009 and 2011 with follow-up data collected in 2013. Data collection was done sequentially for female, male, and opposite-gender twin pairs. Both twins within a pair were followed up for the same period, with opposite-gender, same-gender male and female twin pairs being followed up for 2, 3, and 4 years, respectively [24]. In all recruitment phases, data on participant demographic, lifestyle, and health-related variables were collected either by telephone or face-to-face interview, with informed consent obtained during this period. All MTR procedures were approved by the Murcia University Research Ethics Committee. There was no external funding for the present study and no conflict of interest was declared.

Zygosity assessment

Zygosity was determined via responses to a 12-item questionnaire focusing on the degree of similarity and mistaken identity between twins—a method validated by genetic testing with an accuracy of approximately 96% [24].

Assessment of LBP

The exposure investigated was the participants' report of chronic LBP at baseline. Participants were initially asked: "Have you ever suffered from chronic LBP?" Those who responded positively were then asked: "Has a doctor told you that you suffered from chronic LBP?" An affirmative response to these questions confirmed the presence of chronic LBP. These questions were obtained from the Spanish National Health Survey [25], which described "chronic" as a condition of at least 6 months' in duration, including seasonal or recurrent episodes.

Assessment of depression or anxiety symptomatology

The outcome of interest was symptoms of depression or anxiety at follow-up and was assessed with the depression or anxiety dimension of the EQ-5D—the same measure used as the criterion for selecting the study sample at baseline. The EQ-5D is a generic quality of life instrument that requires participants to respond to five health domains (mobility, self-care, usual activities, pain or discomfort, and anxiety or depression) and has been shown to have adequate validity and responsiveness in patients with chronic pain [23]. Using the depression or anxiety domain, the participants were asked to answer a single question that best described them on that day, with answers classified as "I am not anxious or depressed," "I am moderately anxious or depressed," or "I am extremely anxious or depressed." The participants' answers were dichotomized into "I am not anxious or depressed" or "I am moderately/extremely anxious or depressed." Although the EQ-5D is unlikely to be a valid predictor of depression and anxiety disorders, evidence suggests that there is good sensitivity for similar one-item mood screening measures [26]. Additionally, the EQ-5D has been previously used as a survey screening measure of mental health [27–29] and has shown convergent validity with other screening measures of psychological distress [30,31].

Assessment of potential confounding factors

Given their known association with symptoms of depression, anxiety, and LBP, we investigated smoking status, level of physical activity, and sleep quality as potential confounders assessed at baseline. The participants were asked about smoking habits, with answers dichotomized as ex- or never smoker, or current or occasional smoker. Physical activity was examined by the participants' engagement in leisure physical activity and was based on four options: (1) "I do not practice exercise. My leisure time is mostly sedentary (reading, watching TV, movies, etc)"; (2) "Some sport or physical activity occasionally (walking, gardening, soft gym, light efforts etc)"; (3) "Regular physical activity several times a month (tennis, jogging, swimming, cycling, team sports etc)"; and (4) "Physical training several times a week." This variable was dichotomized into sedentary or no physical activity engagement in recreational physical activity or mild, moderate,

or vigorous physical activity engagement. Both smoking and leisure physical activity questions originated from the Spanish National Health Survey questionnaire [25]. Sleep quality was assessed using the Spanish version of the Pittsburgh Sleep Quality Index (PSQI) [32]. The total score is composed of the sum of scores from seven domains, ranging from 0 to 21, where higher scores represent worse sleep quality. A total score of greater than 5 indicates poor sleep quality. The PSQI scores were dichotomized into good sleep (scores ≤5 points) and poor sleep (scores >5 points) for analyses.

Analysis

Descriptive analyses were conducted for all included variables. Logistic regression models were built to analyze the association between chronic LBP and the risk of depressive and anxiety symptoms while controlling for potential confounders. Statistical significance was set at p<.05 for the estimates of association in all models, whereas the strength of associations was measured with odds ratios (ORs) and the precision of these estimates was given by their 95% confidence intervals (CI). Data analysis was conducted using STATA 12 statistical software (version 12.0; StataCorp LP, College Station, TX, USA).

To determine the associations of interest, we initially calculated the unadjusted ORs and 95% CIs for the outcome of depression or anxiety symptoms caused by chronic LBP exposure. Next, by way of univariate logistic regression, all variables associated with the outcome and exposure were considered confounders, if the p values for both associations were less than .2. Lastly, all cofounders identified in the prior step were incorporated into the final multivariable (adjusted) models. The analyses were conducted in two stages: (1) total sample (individual) analysis and (2.a) co-twin case-control for DZ twins followed by (2.b) co-twin case-control for MZ twins. Final models were adjusted for age and gender (except for the MZ analysis) and for those variables that were detected as possible confounders.

Total sample analysis

All participants were included in the total sample analysis (n=1,269) using complete or incomplete twin pairs regardless of the concordance or discordance of depression or anxiety status. Because twin pairs were followed up at different time points, the total sample analysis was adjusted for follow-up length. Multivariate logistic regression models were used for each analysis. Regression analyses in the total sample were based on the sandwich or Huber-White variance estimator, which adjusts estimated standard errors to account for data dependence between twins in a pair and provides statistical tests that are robust to model assumptions.

Co-twin case-control analyses

To investigate causality, a co-twin case-control analysis in all MZ and DZ complete and discordant pairs for

Table 1
Study sample characteristics based on depression or anxiety response at follow-up

Characteristics	Depression or anxiety		No depression or anxiety		All participants	
	n	Mean±SD or %	n	Mean±SD or %	n	Mean±SD or %
Age (y)	249	53.5±7.4	1,020	53.3±7.3	1,269	53.3±7.3
Gender—male	81	32.5	545	53.4	626	49.3
Gender—female	168	67.5	475	46.6	643	50.7
MZ	94	37.8	366	35.9	460	36.3
DZ	155	62.2	654	64.1	809	63.7
Chronic LBP*	96	38.6	252	24.7	348	27.4
Smoker[†]	112	45.2	389	38.3	501	39.6
Sleep quality[‡]	129	51.8	353	34.6	482	37.0
Physical activity[§]	125	50.2	597	58.8	722	57.1

SD, standard deviation; LBP, low back pain; MZ, monozygotic; DZ, dizygotic.

* Indicates chronic LBP of at least 6 months' duration at baseline.

[†] Indicates current smokers.

[‡] Indicates poor sleep quality.

[§] Indicates engagement in leisure physical activity.

depression or anxiety status was performed using conditional logistic regression. The same variables adjusted for in the total sample stage were retained and used for the case-control analysis, allowing a comparison of all analytical stages. Separate co-twin case-control analyses were conducted for DZ and MZ twin pairs, respectively, increasingly controlling for genetic and early shared environmental confounding. Discordant MZ twins are ideal case-control pairs in this instance, as all genes and early common environmental factors are shared. In theory, if an initial association between chronic LBP and depression or anxiety is partially attenuated in DZ twins and fully in MZ twins, the association is likely due to genetic factors. If an association is fully attenuated in both DZ and MZ twins, the relationship may be due to shared familial factors. Lastly, if an association persists in both DZ and MZ analyses, the relationship is likely due to independent factors consistent with a causal path [33]. As a result, the discordant twin design is potentially more informative and precise than using unrelated case-control samples.

Results

Sample characteristics

A total of 1,269 participants reported no symptoms of depression or anxiety at baseline, forming the sample for the present study (Table 1). The mean age was 53.3 (standard deviation=7.3) years and 32.5% were male participants. Participants who showed symptoms of depression or anxiety at follow-up were more likely to be female (67.5%), had chronic LBP (38.6% vs. 24.7%), smoke, were less likely to engage in leisure physical activity, and reported poorer sleep quality.

Chronic LBP and symptoms of depression or anxiety

For the unadjusted total sample analysis, chronic LBP was significantly associated with a higher risk of depression or anxiety symptoms (OR: 1.81, 95% CI: 1.34–2.44) (Table 2).

When potential confounders: age, gender, smoking, sleep quality, and leisure physical activity were entered into the multivariate model in the adjusted total sample analysis, the relationship was attenuated, although chronic LBP was still significantly associated with a higher risk of depression or anxiety symptoms (OR: 1.43, 95% CI: 1.05–1.95). In the co-twin case-control analysis, a total of 123 pairs of twins were discordant for symptoms of depression or anxiety (78 pairs

Table 2
Total sample and co-twin case-control analyses for the relationship between chronic low back pain and the presence of depression or anxiety symptoms at follow-up

	Unadjusted OR (95% CI)	p
Total sample analysis (n=1,268)*		
Chronic low back pain	1.81 (1.34–2.44)	<.001
	Adjusted OR (95% CI)	**p**
Total sample analysis (n=1,259)*		
Chronic low back pain	1.43 (1.04–1.96)	.026
Age	1.00 (0.98–1.03)	.708
Gender	0.46 (0.33–0.65)	<.001
Smoking	1.44 (1.06–1.94)	.018
Leisure physical activity	0.86 (0.64–1.14)	.29
Sleep quality	1.89 (1.41–2.53)	<.001
Case-control DZ only (n=78 pairs)[†]		
Chronic low back pain	1.03 (0.49–2.13)	.945
Gender	0.74 (0.35–1.56)	.425
Smoking	1.43 (0.66–3.10)	.365
Leisure physical activity	1.09 (0.51–2.37)	.819
Sleep quality	1.79 (0.80–3.98)	.154
Case-control MZ only (n=45 pairs)[†]		
Chronic low back pain	1.86 (0.63–5.51)	.262
Smoking	1.69 (0.46–6.15)	.429
Leisure physical activity	0.29 (.07–1.16)	.08
Sleep quality	1.12 (0.36–3.51)	.848

MZ, monozygotic; DZ, dizygotic; OR, odds ratio; CI, confidence interval.

* Adjusted for follow-up length.

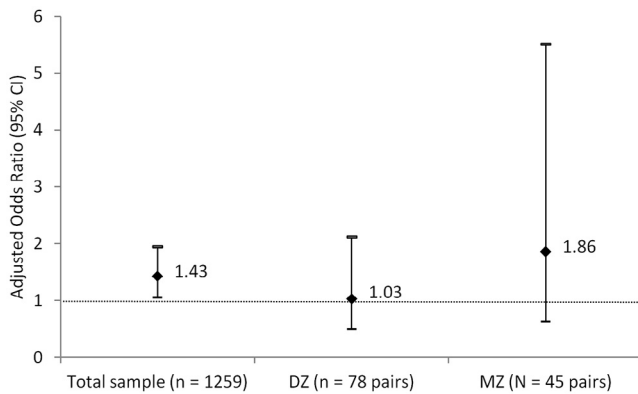[†] Number of complete and discordant twin pairs.

Figure. Adjusted odds ratios and 95% CIs from multivariate models for the relationship between chronic low back pain and depression or anxiety symptoms. CI, confidence interval; DZ, dizygotic; MZ, monozygotic.

being DZ and 45 MZ), with gender (except in MZ twins), smoking, leisure physical activity, and sleep quality all considered confounding variables and entered into the multivariate analysis. There was no statistical increase in the risk of depression or anxiety symptoms associated with chronic LBP when the analyses were performed for DZ (OR: 1.03, 95% CI: 0.50–2.13) or MZ pairs (OR: 1.86, 95% CI: 0.63–5.51) (Table 2), suggesting the possible influence of familial factors (Figure).

Discussion

In this large, genetically informative study, the relationship between chronic LBP and later symptoms of depression or anxiety is not causal. Rather, unobserved shared familial factors appear to be influencing the relationship between chronic LBP and psychological distress—as non-statistically significant associations were observed in the co-twin case-control analyses.

The results of our total sample analysis were similar to previous non-twin studies. The presence of chronic pain (ie, longer than 90 days' duration) was associated with depression and anxiety disorders (OR: 1.40, 95% CI: 1.09–1.79), as was joint pain in the previous 6 months, which included LBP, neck pain, and extremities (OR: 1.64, 95% CI: 1.29–2.10) in a 2-year follow-up of a large population aged 18–65 years in the Netherlands [17]. Primary care patients with a previous history of frequent LBP with a mean age of 51 years reported psychological stress (including depression or anxiety) at 18 months' follow-up (OR: 1.47, 95% CI: 1.20–1.78) [34], whereas data from the Netherlands Mental Health Survey and Incidence Study showed those aged between 18 and 65 years, who reported chronic LBP, had a higher risk of developing later depression (OR: 2.37, 95% CI: 1.60–3.52) or anxiety (OR: 1.74, 95% CI: 1.13–2.67) disorders at 3 years' follow-up [15]. The risk in our study was marginally smaller (OR: 1.43) in comparison to

previous studies, and may be attributed to methodological differences in our exposure, study samples, and outcome measures.

Despite the large population size in the present study, the association between exposure and outcome effectively disappeared in the co-twin case-control analyses, suggesting that this relationship could be due to partial or complete shared familial confounding. However, cautious interpretation of results is encouraged, as firm conclusions cannot be made from our study, with the wide confidence intervals in the co-twin case-control analyses likely caused by the limited number of discordant pairs—reducing statistical power. With sufficient informative twin pairs a common challenge in discordant twin designs, this hypothesis needs to be tested with larger twin samples to fully capture this relationship [35]. In light of this limitation, the possible influence of shared familial confounding in our study is, to some degree, in agreement with a large Swedish twin prevalence study, which found that both major depression and generalized anxiety disorder were no longer significantly associated with chronic widespread pain when controlling for genetics and family environment, implying that these factors played a confounding role [36]. Similarly, a previous cross-sectional study of Spanish twins also showed that the relationship between LBP and depression or anxiety symptoms is confounded by shared familial factors [37].

The likely presence of shared familial confounding suggests that similar factors may affect both pain and psychological distress. For instance, it is hypothesized that the activation of genetically determined biochemical compounds, neurobiological mechanisms, or common cortical regions could explain this complex association, by way of shared pathophysiological pathways where pain can predispose to depression or anxiety symptoms. For instance, reduced descending inhibitory neurotransmitter projections from the brain (ie, serotonin and norepinephrine) can hamper the gate-control mechanism of pain, with neurotransmitter depletion implicated in the pathophysiology of depressive or anxious states [38,39]. Hypothalamic-pituitary-adrenal stress axis dysregulation can result in abnormally elevated cortisol levels in depressed [40] or anxious [41] people, as well as in those reporting regional and widespread pain [42]. Similarly, autonomic nervous system impairment via increased sympathetic or decreased parasympathetic function has also been implicated in widespread pain and psychological distress [43]. Abnormalities in both the hypothalamic-pituitary-adrenal stress axis and autonomic nervous system are known to generate inflammatory responses in pain and psychological distress [43,44]. More recently, neuroimaging studies point to emotion being closely connected (or overlapping) with the pain network in multiple brain regions, including the insula, the prefrontal cortex, and the anterior cingulate cortex [45,46]. Although less plausible, the influence of early shared childhood experiences shaping future adult health and disease is strong [47] and cannot be completely discounted either.

Although no single theoretical model or mechanism is likely to explain the complex interaction of this relationship, our results should not be taken as a complete refutation of a causal link, which may be present in some instances [18]. From a psychosocial (ie, behavioral) perspective, the experience of severe or long-lasting pain can create a perception of harmfulness, which can reduce physical activity, resulting in catastrophizing, a sense of disability, helplessness, and a lack of confidence in managing or coping with pain [5,48], all of which contribute to depression or anxiety development.

Our study had a number of strengths, including its longitudinal design and controlling for previously unobserved shared familial factors in a population-based sample of twins. Furthermore, our chronic LBP and depression or anxiety questions were nested within a general health survey, and by not singling out the primary aim of our study, bias may have been avoided. We also considered a number of variables that could exert an effect on both chronic LBP and depression or anxiety symptoms. Some limitations, however, need to be acknowledged. There was the possibility of participants being in remission at baseline, with prior psychological episodes known to predispose to new onset of depression or anxiety symptoms. Our follow-up time period varied from 2 to 4 years as twins were recruited sequentially by gender, and although we adjusted the varied follow-up length, depression or anxiety disease disorders can vary from being a short, single episode to being chronically persistent throughout this time span [49]. Nevertheless, our goal was to investigate whether baseline chronic LBP predicts subsequent psychological distress, and our findings were consistent with previous studies, verifying our results. Additionally, the depression or anxiety domain of the EQ-5D instrument focuses on a single-day situation, which may limit the accuracy of our findings. Given that the EQ-5D is not a validated method in identifying mood disorders, a more comprehensive measure would have been preferable, such as the Hospital Anxiety and Depression Scale [50]. However, evidence suggests that similar single-item mood screening questionnaires have good sensitivity, performing similarly to validated questionnaires [26], and we can therefore be reasonably confident of having identified participants with psychological distress. Moreover, the EQ-5D has been previously used as a quick, single-item screening tool to identify people with psychological distress in other studies [27–29] and could provide useful information in clinical settings where time is limited. Lastly, we were also unable to tease out symptoms of depression from symptoms of anxiety when using the EQ-5D, even though both conditions are commonly and closely linked [18], with pain having a similar impact on the course of depressive and anxiety disorders [17].

As for the exposure, participants answering the chronic LBP questionnaire may have been subjected to "recall bias," particularly if they experienced an episode of LBP some time ago. Moreover, our assessment did not include a clinical evaluation or identify LBP pain severity, with the latter possibly increasing the likelihood of developing more severe depression or anxiety symptoms [16]. Registry-based research seldom includes detailed and objective performance-based assessments, hence our reliance on self-report measures, although generally good agreement has been found between self-report and medical record data [51]. Our study was conducted in a population of adults with a mean age of 53.3 years (standard deviation=7.3), and results could therefore differ in children, adolescents, and particularly older adults, where chronic pain is reportedly more prevalent [52]. Also, we cannot completely rule out reverse causation as depression or anxiety has been found to precede pain [16] and there may have been residual confounders that we did not control for, including socioeconomic factors, antidepressant medication use, and factors that may not be shared by twin pairs, that is, occupational exposure. Although our study findings indicate that the relationship between chronic LBP and psychological distress may (to some degree) be due to shared genetic and environmental influence, the degree of this influence (or possible susceptibility) is presently not clear. Lastly, our confounders could have acted as mediators during the follow-up period, potentially transmitting their effects in a causal sequence between chronic LBP and psychological distress.

Conclusions

This large longitudinal study showed a non-causal relationship between a history of chronic LBP and the future risk of depression or anxiety symptoms. The relationship is likely due to a possible confounding effect from genetic and early shared environmental influences, as it disappeared in the subsequent co-twin case-control analyses. To further understand the role of underlying shared familial factors, as a plausible mechanism, on the relationship between chronic LBP and psychological distress, future studies using a larger sample of discordant twin pairs is encouraged.

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