Genetic and environmental influences to low back pain and symptoms of depression and anxiety: A population-based twin study

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ABSTRACT

Background: People suffering from chronic pain are more likely to experience symptoms of depression and anxiety. However, the mechanisms underlying this relationship remain largely unknown. In light of the moderate to large effects of genetic factors on chronic pain and depression and anxiety, we aimed to estimate the relative contribution of genetic and environmental factors to the relationship between these traits.

Methods: Using data from 2139 participants in the Murcia Twin Registry, we employed a bivariate analysis and structural equation modeling to estimate the relative influences of genetics and the environment on the covariation between low back pain and symptoms of depression and anxiety.

Results: We have obtained heritability estimates of 0.26 (95% Confidence Interval (CI) 0.11, 0.41) for chronic low back pain and 0.45 (95% CI 0.29, 0.50) for symptoms of depression and anxiety. The phenotypic, genetic, and unique environment correlations in the bivariate analytical model were, respectively, r_{ph} = 0.26 (95% CI 0.19, 0.33); r_G = 0.47 (95% CI 0.42, 0.70); r_E = 0.14 (95% CI -0.04, 0.25). The percentage of covariance between low back pain and symptoms of depression and anxiety attributable to additive genetic factors was 63.6%, and to unique environment 36.4%.

Conclusions: Our findings confirm the relationship between low back pain and symptoms of depression and anxiety in a non-clinical sample. Shared genetic factors affect significantly the covariation between these conditions, supporting the role of common biological and physiological pathways.

1. Introduction

People suffering from chronic low back pain are more likely to experience symptoms of depression and anxiety [3,4,7,14,24,46]. The prevalence of pain among people with depression can be as high as 65% [3], and the concomitant presence of symptoms of depression, anxiety, and pain is associated with worse health status for patients compared to the presence of one of these conditions alone [4,28]. Additionally, the co-occurrence of symptoms of depression and low back pain results in higher healthcare utilization costs [16]. For instance, the medical costs of people suffering from low back pain and depression are 2.8 times higher than of those with low back pain alone [44]. Despite the impact that comorbid depression, anxiety and low back pain brings for patients and society, the mechanisms underpinning this relationship remain largely unclear. The prevalent co-occurrence observed for these conditions could result from: genetic factors that contribute to the liability of both conditions (pleiotropy), familial environmental factors (shared factors), or individual environmental factors (unique factors) that could affect both conditions. A better understanding of such mechanisms could contribute to the development of management plans for patients suffering from both conditions.

In light of the moderate to large effects of genetic factors on low back pain [11] and depression [47], our research group has recently investigated the relationship between low back pain and symptoms of depression and anxiety while accounting for genetic and environmental factors by employing a co-twin case-control design [36,38]. The findings from these studies showed that once familial factors are accounted for, the association between low back pain and symptoms of depression

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and anxiety disappears, suggesting that genetic factors play an important role in this relationship. Although these studies gave a strong indication of the role of genetic influences to this association, the genetic and environmental contributions to the relationship were not estimated.

Previous studies have attempted to estimate the contribution of the environmental and genetic factors to the association between pain and symptoms of depression and anxiety. Overall, they found that the link between pain and symptoms of depression and anxiety is primarily explained by shared genetic influences between the two phenotypes, whereas shared environmental effects were not important [15,41]. These studies were performed with young samples (mean age ranging from 22 to 29 years), however it is likely that age, and other sample characteristics, such as sex composition or cultural background, as well as prevalence of pain and symptoms of depression and anxiety an impact on the genetic and environmental estimates [45]. The impact of genetic factors on health problems, such as low back pain and symptoms of depression and anxiety might vary considerably with age, and the expression of genes can change across the lifespan [9]. Additionally, changes in the prevalence of these conditions across the lifespan can also impact on the estimates. For instance, although the prevalence of symptoms of depression and anxiety seems to be stable across adulthood [21], the prevalence of low back pain is believed to reach its peak in middle aged adults [19,27]. Therefore, establishing the genetic and environmental contribution to the relationship between low back pain and symptoms of depression and anxiety across different aging and cultural groups is essential to enhance our understanding of the mechanisms explaining the relationship between these traits.

Understanding whether low back pain and symptoms of depression and anxiety are influenced by the same genetic and environmental factors is a relevant question and could have promising impact for management of patients with these conditions. If genetic factors indeed largely explain the covariance between low back pain and symptoms of depression and anxiety, this suggests an overlap in the set of genes influencing both traits. In this case, a common physiological pathway might explain the co-occurrence of these traits and therefore understanding this pathway and/or identifying the specific genes could help with management of these conditions. The aim of this study was to estimate the genetic and environmental sources of covariance among low back pain and symptoms of depression and anxiety by using a classical twin design and a large sample of middle-aged Spanish twins.

2. Method

2.1. Participants

Cross-sectional data from a population-based sample of twins registered in the Murcia Twin Register (MTR) [33,34] were used for this study. The MTR is a community-based twin registry, it is comprised of female and male adult twins who were born between 1940 and 1966 in the Region of Murcia, Spain, and representative of the general population in the region [35]. Additional details about the MTR can be found elsewhere [33,34]. The Committee of Research Ethics of the University of Murcia approved the registry and all data collection procedures for this study. Additionally, the MTR follows all national and institutional regulations regarding personal data protection and ethical use of human volunteers.

2.2. Data collection

Trained assessors collected data on demographic information and self-reported health-related questionnaires through phone and face-to-face interviews for all participants. Data collection for this study took place between 2009 and 2011.

2.2.1. Zygosity ascertainment

A sample of 338 twin pairs had their zygosity ascertained by DNA test. The remaining of the participants answered a 12-item questionnaire that assesses the degree of similarity and mistaken identity between twins. This questionnaire has been validated against DNA test and an agreement of approximately 96% has been found [34].

2.2.2. Assessment of low back pain and symptoms of depression and anxiety

Prevalence of low back pain was assessed through the following dichotomous self-reported question derived from the Spanish National Health Survey: "Have you ever suffered from chronic low back pain?" Participants were instructed to consider chronic low back pain as pain in the lower back area that lasted for at least six months, including recurrent episodes.

Data on symptoms of depression and anxiety were collected using the "Depression and Anxiety" domain of the EuroQol-5 dimension (EQ5D) questionnaire [50]. This is a self-reported questionnaire and participants are given three options and are instructed to select the one that best describe themselves at the day they were answering the questionnaire. The response options included: (1) "I am not anxious or depressed"; (2) "I am moderately anxious or depressed"; and (3) "I am extremely anxious or depressed." Nonetheless, since there was small number of participants in the third category, participants' answers were dichotomized into not depressed or anxious versus moderately or very depressed or anxious. The EQ5D has adequate validity when used for people with chronic pain,[32] and it offers a reasonable valid prediction of depression and anxiety disorders.[23,48] Additionally, the EQ5D is substantially correlated with other measures of psychological distress, suggesting good convergent validity [20].

2.3. Statistical analysis

2.3.1. Twin data

Classic twin analysis is typically aimed at disentangling the genetic and environmental influences that might contribute to individual differences in a trait. These influences may be estimated using twin data because identical twins (monozygotic, MZ) share all their genes, while non-identical twins (dizygotic, DZ) share on average half of their segregating genes [10]. When phenotypic data is available on MZ and DZ twin pairs, the total variance of the trait can be decomposed into variance due to additive (A; i.e., summed allelic effects across multiple genes) and non-additive (D; i.e., genetic dominance, possibly including epistasis) genetic factors, as well as shared (C; i.e., common/family environment) and individual (E; i.e., idiosyncratic experiences, including measurement error) environmental factors. Components C and D cannot be estimated simultaneously in a classical twin model. The pattern of MZ and DZ correlations will determine whether C or D will be modelled. As a general rule, C is estimated if the DZ twin correlation is greater than half of the MZ twin correlation, and D is estimated if the DZ twin correlation is less than half of the MZ correlation [29,52]. If data from more than one variable are analyzed (e.g. low back pain and symptoms of depression and anxiety), it is possible to investigate the potential overlap in genetic and environmental factors that could explain the co-occurrence of these traits.

2.3.2. Structural equation modeling

The variance in a trait that is explained by each of the latent components (i.e. A, C or D, E) is commonly investigated by employing Structural Equation Models (SEM). Additional details of the twin design can be found elsewhere [29,40,52].

Initially, assumptions of the twin design were tested and univariate ACE/ADE models were fitted separately for each variable (i.e: low back pain and symptoms of depression and anxiety). Afterwards, a bivariate Cholesky model including both variables was fitted. The Cholesky factorization ensure that the estimated A, C or D, and E matrices are positive definite, restriction that follows from the fact that they are
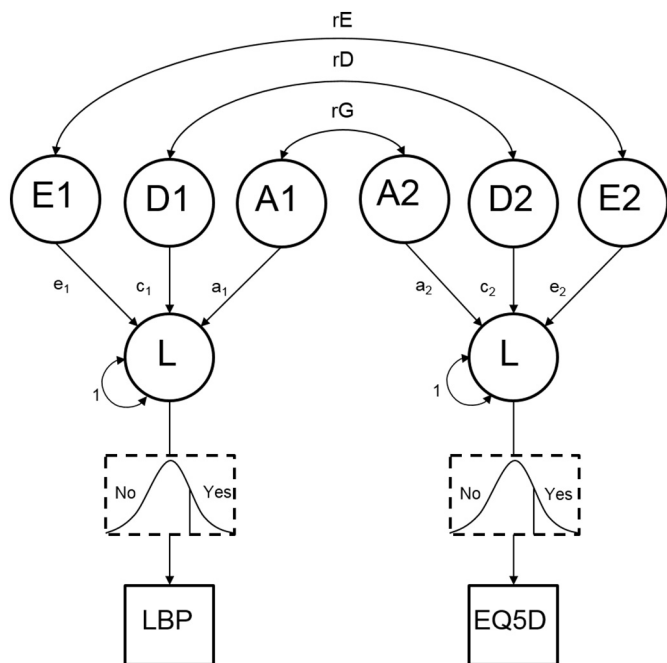
Fig. 1. Path diagram of the bivariate model with the latent factors A, D and E and their influence on the liability to low back pain (LBP) and symptoms of depression and anxiety (EQ5D) as modelled in the liability threshold model.

- L = liability, LBP = low back pain, EQ5D = EuroQol-5 dimension. Variables in circles represent latent variables or factors. Variables in boxes represent observed variables. Single-headed arrows (paths) represent causal relationship between the latent and observed variables. Double-headed arrows define correlations between variables. Paths: $a_{(1\ or\ 2)}$, $c_{(1\ or\ 2)}$, $e_{(1\ or\ 2)}$, additive genetic, common environmental, and unshared environmental paths corresponding to univariate analyses of low back pain and EQ5D. Correlations: r_G, r_C, and r_E, additive genetic, common environmental, and unshared environmental correlations between corresponding components of low back pain and EQ5D.

covariance matrices [30]. In the case of the bivariate model, Cholesky results were transformed, prior interpretation, into a correlated factor solution [25]. Such transformation was conducted because no specific relationship or order between low back pain and symptoms of depression and anxiety was hypothesized, and the Cholesky factorizarion implies that there is a specific ordering of the variables. In the correlated factor solution, each variable is separately decomposed into its genetic and environmental components (latent variables), and the correlations of these components across variables are estimated. For instance, a high genetic correlation (rG) between the two traits suggests that genetic influences on low back pain also affect symptoms of depression and anxiety, whereas a genetic correlation of 0 indicates independence in the genetic factors influencing each variable (Fig. 1). The same principle applies to the C, D and E components. Finally, the proportion of covariance of the traits explained by genetic and environmental factors is estimated as well.

In every case, the full models were tested against nested submodels, where A component, C/D component or both (AC/AD) were fixed to zero. If there was no statistically significant difference between two models, the simplest one was chosen (parsimony principle). Given that the estimation of a significant genetic dominance component in the complete absence of additive genetic variance, although theoretically possible, is practically unlikely, DE models were not fit.

The log-likelihood ratio test (LRT) was used compare the fit of the different models and submodels. The difference in minus two times the log-likelihood ($-2LL$) between two models has a χ^2 distribution with the degrees of freedom (*df*) equaling the difference in *df* between the two models. Additionally, the model fit was evaluated using Akaike's information criterion (AIC) [1] which is a parsimony-adjusted statistic

used to select among competing models. This fit index is based on a hypothetical replication of the same population and of the same size as the analyses. The model with the smallest AIC is chosen as it is most likely to replicate as opposed to more complex models that are less likely to replicate [22].

2.3.3. Liability-threshold model

The liability-threshold model was used to analyze low back pain and symptoms of depression and anxiety since these are dichotomous variables [42]. This model assumes that an unobserved liability underlies the measured categories of low back pain and symptoms of depression and anxiety. The liability is assumed to be normally distributed with a mean value of 0 and a variance of 1, but the correlation between them is unknown and the shape of such distribution is determined by the correlation. The liability can be influenced either by the individual's exposure to environmental factors or by the genetic make-up. A trait is expressed when the liability exceeds a certain threshold value. The number of standard deviations away from the mean is used to calculate the thresholds. The area under the curve corresponds to the probability to be in a certain category of low back pain or symptoms of depression and anxiety (Fig. 1). Polychoric correlation between the liability distributions is used to estimate twin similarity.

Tetrachoric twin correlations and cross-twin cross-trait correlations (the correlation between low back pain in one twin and symptoms of depression and anxiety in the co-twin) were estimated within a model, named saturated model, in which the correlations and thresholds are freely estimated over the different zygosity groups. Then, thresholds were constrained to be equal over the different groups to test for effects of twin order, zygosity and sex. The fit of these models was compared with the saturated model.

All models were fitted to the individual observations using full information maximum likelihood (FIML) within the OpenMx package v2.7.9 [31] from R v3.3.3. The role of covariates on the traits of interest was tested by introducing them in the model of means, which performs a linear regression on the observed scores and proceeds to use the residuals for estimating the weights of each variance component [6]. Subsequently likelihood ratio tests between a model with free parameters for the effect of the covariates on the main variable, and the models where each one of those parameters was fixed to zero were carried out. Data manipulation and descriptive and preliminary analyses were performed both in SPSS v.19 and R v. 3.2.3 (R Core Team [53]). Correlations were classified as follows: < 0.25 as low, between 0.25 and 0.50 as fair, between 0.50 and 0.75 as moderate to good, and > 0.75 as high [39].

3. Results

3.1. Sample characteristics

A total of 2139 twins formed the study sample for this cross-sectional study. The mean age of all participants was 53.7 years (*SD*: 7.3; range: 43–71), and female participants accounted for 54.6% of the sample (Table 1). There were 962 complete twin pairs [196 MZ female (MZF) pairs, 129 MZ male (MZM) pairs, 188 DZ female (DZF), 163 DZ male (DZM), and 286 opposite sex dizygotic (OSDZ) pairs] and 215 incomplete twin pairs (17 MZF twins, 28 MZM twins, 30 DZF twins, 35 DZM twins, and 105 OSDZ twins).Overall the prevalence of low back pain was 32.3% and of symptoms of depression and anxiety was 21.9%.

3.2. Assumption testing

There was no evidence of statistically significant differences in prevalence of low back pain and symptoms of depression and anxiety among members in a pair or between MZ, SSDZ and OSDZ twins. In the saturated model, thresholds for both variables could be constrained to

Table 1
Characteristics of included participants stratified by zygosity.

	Total		MZM		MZF		DZM		DZF		DZOS	
	n	Mean ± SD (range) or %	n	Mean ± SD (range) or %	n	Mean ± SD (range) or %	n	Mean ± SD (range) or %	n	Mean ± SD (range) or %	n	Mean ± SD (range) or %
Age (years)	2139	53.7 ± 7.3 (43–71)	286	52.4 ± 6.7 (44–70)	409	52.0 ± 7.1 (43–70)	361	52.6 ± 7.1 (43–70)	406	53.2 ± 7.7 (43–69)	677	56.2 ± 7 (45–71)
Sex (female)	1167	54.6	0	0	409	100	0	0	406	100	352	52.0
Low back pain	689	32.3	59	20.6	177	43.3	85	23.5	180	44.4	188	28.0
Depression/anxiety*	466	21.9	34	11.9	95	23.4	41	11.4	108	26.7	188	27.9

* Indicate the presence of symptoms of depression and anxiety, MZM = monozygotic male, MZF = monozygotic female, DZM = dizygotic male, DZF = dizygotic female, DZOS = dizygotic opposite sex.

Table 2
Results of the regression of the thresholds of low back pain and symptoms of depression and anxiety on age, sex and wave of data collection.

Model	Low back pain		Depression/anxiety*	
	χ^2	p value	χ^2	p value
1. Drop age	0.056	0.8121	1.384	0.2394
2. Drop sex	68.147	< 0.0001	36.667	< 0.0001
3. Drop wave	8.044	0.004	9.798	0.002

* Indicates symptoms of depression and anxiety.

be equal over all groups without a significant worsening of fit. Prevalence of low back pain and symptoms of depression and anxiety, within zygosity groups is shown in Table 1.

Effects of age, sex and wave of data collection (either 2009, 2010, or 2011) were regressed out from the observed scores via a linear regression using the FIML procedure in OpenMx. Subsequently, SEM were fitted to the residual scores. These predictors were fixed to zero one by one, and tested for a significant difference in model fit using log-likelihood ratio tests (Table 2). Sex and wave of data collection showed a significant effect on both variables, while no significant effect of age on any variable was found. Therefore, age was dropped from the model.

Tetrachoric twin correlations and the cross-twin cross-trait correlations from the saturated model are presented in Table 3. The within-trait and the cross-twin cross-trait correlations were higher in MZ than in DZ twins, supporting the hypothesis of genetic influences on low back pain and symptoms of depression and anxiety and on the covariation between the traits.

In the univariate case, MZ-DZ correlation patterns lead us to fitting different variance models (ACE/ADE) for low back pain and symptoms of depression and anxiety. For the former, an ACE model showed a better fit (A = 0.24 [0.01 0.34], C = 0.02 [0.00 0.26], and E = 0.74 [0.59 0.91]); for the latter, an ADE model was the most appropriate (A = 0.14 [0.00 0.57], D = 0.37 [0.00 0.67], and E = 0.49 [0.35 0.67]). In the bivariate case, however, the ADE model showed the best fit (lowest -2LL and AIC values). Therefore, although there was no a priori/theoretical reason to exclude the impact of shared environment, D factor was modelled, instead of C.

Fit comparisons for the bivariate decompositions are presented in Table 4. There was no deterioration of fit after dropping C/D from the model, neither in the univariate nor the bivariate case when comparisons were performed between ACE/ADE models and more restrictive AE and E models. The AE model was the most parsimonious model, as indicated by the lowest AIC values and better fit. These results suggest that non-additive genetic (D) and shared environmental effects (C) did not contribute significantly to low back pain and symptoms of depression and anxiety (or their covariance) in this sample.

In order to express the proportion of variance explained by each component according to the full genetic and the more restrictive AE model, the obtained maximum-likelihood parameter estimates of the A, D, and E (e.g., $a_{(1\ or\ 2)}$, $d_{(1\ or\ 2)}$, $e_{(1\ or\ 2)}$) (Fig. 1) variance components were squared (e.g., a_1^2 and e_1^2) (Table 5).

The phenotypic, genetic, and unique environment correlations in the AE Model were, respectively, r_{ph} = 0.26 (0.19, 0.33); r_G = 0.47 (0.42, 0.70); r_E = 0.14 (−0.04, 0.25). The percentage of covariance

Table 3
Polychoric twin correlations based on maximum likelihood estimates of a liability model with two categories.

	Low back pain twin correlation	Depression/anxiety* twin correlation	Cross-trait cross-twin correlation
MZ	0.25 (0.07, 0.42)	0.50 (0.31, 0.66)	0.24 (0.10, 0.27)
DZ	0.14 (0.00, 0.27)	0.16 (0.00, 0.30)	− 0.01 (− 0.12, 0.09)

* Indicates symptoms of depression and anxiety, MZ = monozygotic, DZ = dizygotic.

Table 4
Model fitting results for the univariate and bivariate models of low back pain (LBP) and symptoms of depression and anxiety.

Variables	Model	− 2LL	AIC	Parameters	Comparison	χ^2	Δdf	*p* value
LBP	1. ACE	2572.784	− 1679.200	7				
	2. ADE	2572.800	− 1679.200	7				
	3. AE	**2572.800**	**− 1681.200**	**6**	**ACE**	**0.016**	**1**	**0.900**
	4. CE	2573.849	− 1680.151	6	ACE	1.065	1	0.302
	5. E	2584.346	− 1671.654	5	AE	11.547	1	0.0007
Depression/anxiety*	1. ACE	2125.985	− 2116.015	7				
	2. ADE	2124.934	− 2117.066	7				
	3. AE	**2125.985**	**− 2128.015**	**6**	**ADE**	**1.051**	**1**	**0.305**
	4. CE	2132.546	− 2111.454	6	ACE	6.560	1	0.010
	5. E	2152.090	− 2093.909	5	AE	26.105	1	< 0.0001
LBP and Depression/anxiety*	1. ACE	4654.890	− 3833.110	17				
	2. ADE	4653.134	− 3834.866	17				
	3. AE	**4656.337**	**− 3837.663**	**14**	**ADE**	**3.203**	**3**	**0.361**
	4. CE	4664.974	− 3829.026	14	ACE	10.084	3	0.018
	5. E	4694.046	− 3805.953	11	AE	37.709	3	< 0.0001

* Indicates symptoms of depression and anxiety; AIC = Akaike's Information Criterion, − 2LL = negative 2 log-likelihood, df = degrees of freedom, LBP = low back pain, EQ5D = symptoms of depression and anxiety, A = additive genetic influences, C = common environmental influences, E = unique environmental influences. The best fitting model is shown in boldtype.

Table 5
Estimates of additive genetic (A), non-additive genetic (D), and unique environmental (E) variance components for low back pain and symptoms of depression and anxiety, computed from bivariate Cholesky decomposition model (correlated factors solution).

		Cholesky model (correlated factor solution)		
		a^2 (95% CI)	d^2 (95% CI)	e^2 (95% CI)
ADE model	Low back pain	0.10 (0.00, 0.36)	0.19 (0.00, 0.41)	0.71 (0.56, 0.87)
	Depression/anxiety[£]	0.07 (0.00, 0.49)	0.44 (0.00, 0.66)	0.48 (0.33, 0.66)
AE model	Low back pain	0.26 (0.11, 0.41)	0*	0.74 (0.59, 0.89)
	Depression/anxiety[£]	0.45 (0.29, 0.50)	0*	0.55 (0.39, 0.71)

* Fixed value
[£] Indicates symptoms of depression and anxiety.

between low back pain and symptoms of depression and anxiety attributable to A factor (additive genetic) was 63.6%, and to E factor (unique environment) was 36.4%.

4. Discussion

4.1. Summary

In this study we investigated the association between low back pain and symptoms of depression and anxiety by employing a classic twin design to estimate to what extent these two conditions are influenced by the same genetic and environmental factors. The phenotypic correlation between low back pain and symptoms of depression and anxiety was fair $r_{ph} = 0.26$ (95% CI 0.19, 0.33) and additive genetic factors explained 64% of the covariance between them. There was a fair genetic correlation ($r_G = 0.47$, 95% CI 0.42, 0.70) between the genetic factors influencing each condition, suggesting an overlap in the genes affecting low back pain and symptoms of depression and anxiety. Unique environmental factors made a smaller contribution to the association between low back pain and symptoms of depression and anxiety, explaining the remaining 36% of this relationship. Since the unique environment correlation was low and non-significant ($r_E = 0.14$, 95% CI -0.04, 0.25), this suggests that the type of unique environmental factors influencing low back pain are largely different from those impacting on symptoms of depression and anxiety.

4.2. Comparison with previous investigations

The heritability estimates (i.e. proportion of a phenotype's total variance that can be attributable to additive genetic effects) [42] found

for low back pain (26%) and symptoms of depression and anxiety (45%) were consistent with previous investigations, where low back pain heritability ranged between 21% and 67% [11], whereas symptoms of depression and anxiety ranged between 39% to 53% [15,41]. The phenotypic association found between low back pain and symptoms of depression and anxiety in the present study ($r_{ph} = 0.26$) was also similar to a previous study investigating the genetic and environmental contribution to pain in general and depression ($r_{ph} = 0.29$) [15] and another study investigating low back and neck pain and symptoms of depression and anxiety ($r_{ph} = 0.31$) [41]. Similarly, our results are in agreement with the mentioned investigations in finding that the correlation between pain and depression and anxiety is primarily due to genetic factors, with the unique environment playing a smaller role, whereas the shared environment (C) does not have a noticeable effect on these traits in adults [15,41].

A similar genetic correlation was found by Gasperi et al. [15] ($r_G = 0.56$ vs $r_G = 0.47$), [15] even though estimates of heritability and genetic effects can be affected by several factors, as previously highlighted [11,45]. Gasperi et al. [15] investigated a smaller and selected sample ($n = 400$) of younger participants (mean age = 29 years) from a diverse background (USA), and the pain phenotype investigated was different from the present study (recent or current pain in general vs lifetime history of chronic low back pain). Despite those differences, all of our estimates fell close to those previously reported, which could be a reflection of the robustness of the results. Furthermore, our findings provide additional support to the role of common genetic factors between pain and symptoms of depression and anxiety.

Our findings are somewhat in disagreement with one previous study that concluded that the relationship between low back pain and depression is not confounded by underlying genetic or early

environmental factors [49]. In this previous co-twin case control study a sample of male twins from the United States were investigated and the association between low back pain and depression remained unchanged after adjusting for genetic and early environmental factors [49]. Estimates of heritability and shared environmental effects are time and context-dependent and may be affected by several factors. There were numerous differences between our study and the previous co-twin study, including instruments used to assess low back pain and depression as well as participants' characteristics, especially gender, which may have impacted the results.

4.3. Interpretation of findings and implications

The genetic correlation found in this study ($r_G = 0.47$) can be interpreted as the magnitude of genetic overlap among low back pain and symptoms of depression and anxiety, and the likelihood that these conditions share the same genes. Since a moderate genetic correlation was found, this suggests that shared genetic factors affect significantly the covariation between these conditions, supporting the theories of common biological and physiological pathways. Previous research suggests that pain and symptoms of depression and anxiety share similar biological pathways and neurotransmitters [12,13,26]. For instance, a dysregulation or decrease of the serotonin and norepinephrine is one of the proposed biological mechanism for depression and anxiety and these neurotransmitters are associated with pain modulation and are believed to reduce peripheral pain signals [3]. A dysfunction in the mesolimbic dopamine system has also been proposed as a mechanism underlying bidirectional processes between these phenotypes and neural function [13]. Previous research using functional magnetic resonance to investigate brain activation has shown that brain regions involved in the modulation of emotion and mood (e.g. amygdala) send many projections to structures involved in the modulation of pain [4,12,26]. Additional research is needed to further our understanding of such mechanisms and pathways.

The moderate genetic correlation suggests that the genetic architecture for one trait (e.g. low back pain), partially overlaps with that of the other trait (e.g. symptoms of depression and anxiety). Therefore, the next reasonable step would be to investigate which specific genes are associated with both traits. However, before pursuing this approach one should consider that the phenotypic correlation between low back pain and symptoms of depression and anxiety was only fair. Although our findings suggest that genetic influences largely contribute to the co-ocurrence between low back pain and symptoms of depression and anxiety, each phenotype also has unique genetic influences. Finding the genes that influence both traits might prove challenging.

Our findings suggest that there is far less overlap on the unique environmental factors affecting the association between low back pain and symptoms of depression and anxiety. A possible explanation is that there are a wide range of environmental factors that might impact on the development of pain and symptoms of depression and anxiety, and therefore it is less likely that twins will be similar with regards to these exposures. The finding of low unique environmental correlation between low back pain and symptoms of depression and anxiety implies that the environmental intervention method effective for one condition would not be a potential successful option for the other condition. Therefore, modifiable environmental factors that influence each variable (i.e., low back pain and symptoms of depression and anxiety) independently should be investigated.

4.4. Limitations and directions for future studies

Despite the strengths of this study, such as large and non-clinical sample size, this study has limitations that need to be considered when interpreting the findings. The low back pain measurement was somewhat simplistic and did not take into account pain severity, frequency, or activity limitation. This should be considered when interpreting the

results of this study, given that genetic influence is higher for more disabling and chronic types of low back pain [11]. Similarly, we assessed symptoms of depression and anxiety, rather than depression diagnosed by a health professional or a specific questionnaire, and previous studies have shown that the definition and measurement method used for assessing depression impact on its relationship with low back pain [37,38].

Our results do not take into consideration potential interactions of components, such as gene-environment interaction or gene-environment correlation. For instance, factors that are traditionally considered as environmental factors, such as physical activity engagement and sleep habits, could impact on both low back pain and symptoms of depression and anxiety [2,8,17,18,51]. However, these factors have also been demonstrated to have a strong genetic influence [5,43]. Future studies should consider this potential gene-environment interaction. Additionally, more research is needed to further our understanding of the biological mechanisms underlying this association.

5. Conclusions

Our findings confirm the relationship between low back pain and symptoms of depression and anxiety in a non-clinical sample. The association between low back pain and symptoms of depression and anxiety is mainly explained by shared genetic influences, suggesting an overlap on the set of genes that influence each trait. Additionally the types of individual-specific (non-shared) environmental factors that influence low back pain are largely not the same as those influencing symptoms of depression and anxiety. The present study extends the previous findings of genetic and environmental aetiologies of the comorbidity between pain and symptoms of depression and anxiety to the Spanish setting, contributing to the cross-cultural generality of this research field.

Conflict of interest

None.

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