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

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