Symptoms of depression and risk of low back pain: A prospective co-twin study

Running head: Symptoms of depression and risk of low back pain

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What's already known about this topic?

- The co-occurrence of low back pain (LBP) and depression is common, however the nature of this association remains unclear.

What does this study add?

- The observed association between depression and LBP is dependent on the method of assessment used for both conditions.
- The nature of the association is influenced by genetics and shared environmental factors, highlighting the complexity of this relationship.
- People with higher levels of depression are at higher risk of developing LBP, however this risk is small, presents only in more disabling cases of LBP, and is not significant when genetics and early environmental factors are considered.

Abstract

Background: Although the co-occurrence of low back pain (LBP) and depression is common, the nature of this association remains unclear. We aimed to investigate whether symptoms of depression increase the risk of LBP, after adjusting for genetic and environmental influences.

Methods: Baseline data of 1,607 twins from the Murcia Twin Registry (Spain) were collected in 2009-2011 and follow-up data in 2013. Twins answered questions on depression-related symptomatology and LBP. Only participants not reporting chronic LBP at baseline were included. The association between symptoms of depression at baseline and LBP at follow-up was investigated using logistic regression analysis including the complete sample. Subsequent matched within pair case-control analyses were performed with all complete dizygotic twin pairs discordant for LBP, followed by monozygotic twins.

Results: In the total sample analysis, symptoms of depression did not significantly increase the risk of chronic LBP (OR=1.40, 95%CI: 0.96-2.03), care seeking (OR=1.21, 95%CI: 0.81-1.81), or activity limitation (OR=1.09, 95%CI: 0.69-1.72). State-depression (participants' symptoms at the moment of the interview) was significantly associated with future care seeking (OR=1.06, 95%CI: 1.01-1.12), and activity limitation (OR=1.07, 95%CI: 1.01-1.14). A significant association was found between trait depression and activity limitation (OR=1.05, 95%CI: 1.01-1.10), but not for the other LBP outcomes. No significant association was observed in any of the subsequent case-control analyses.

Conclusions: The association between depression and LBP appears to be small and likely to be confounded by genetic and early shared environment influences. Our results

highlight the important influence of the methods of assessment on estimating this association.

Keywords: Low back pain; Depression; Case-control Twin study; Epidemiology; Risk factor.

1. Introduction

The latest Global Burden of Diseases study has indicated LBP as the leading cause of disability worldwide, where disability is assessed by years lived with disability (YLDs), while depression is responsible for the second highest burden of all diseases globally (Vos et al., 2012; Global Burden of Disease Study, 2015). These conditions commonly co-exist (Sullivan et al., 1992; Bair et al., 2003; Edit et al., 2013) and the association between them has been long discussed in the literature and clinical practice. In fact recent studies have established a link between them with pooled results from a recent systematic review showing that symptoms of depression increase the risk of future LBP (Pinheiro et al., 2015b). However, genetic factors have substantial influences in the development of both LBP (Nielsen et al., 2012; Ferreira et al., 2013) and depression (Sullivan et al., 2000) as well as in the association between symptoms of depression or anxiety and LBP (Reichborn-Kjennerud et al., 2002; Pinheiro et al., 2015a). None of the studies included in this systematic review (Pinheiro et al., 2015b) controlled for the effects of genetics or early shared environment on the relationship between depression and LBP.

A co-twin, cross-sectional study conducted by our research group found that the relationship between symptoms of depression and self-reported LBP disappears when genetic and common environmental influences are accounted for (Pinheiro et al., 2015a). This finding suggests that the proposed direct relationship between depression and LBP might be, in fact, driven by factors influencing both conditions such as genetic factors. Although the co-twin design allows for a better understanding of the nature of the association between these variables, our study (Pinheiro et al., 2015a) did not allow

for a firm conclusion about the causal relationship between symptoms of depression and LBP due to its cross-sectional design.

To fully understand the effect of symptoms of depression as a risk factor for LBP, a comprehensive approach considering genetic and environmental factors is required. Thus, the aim of this study was to investigate whether symptoms of depression increase the risk of chronic LBP with the use of a prospective study design, adjusting for important confounders including genetic factors.

2. Methods

2.1 Study design and sample

We conducted an observational longitudinal twin study investigating symptoms of depression as a risk factor for the development of chronic LBP in adult twins from the Murcia Twin Registry (MTR), which is a population-based Registry. For more information about the recruitment and inclusion criteria see manuscripts published elsewhere (Ordonana et al., 2006; Ordonana et al., 2013). The Research Ethics Committee of the University of Murcia approved all registry and data collection procedures involved in this study. The Helsinki Declaration, as well as applicable institutional and governmental regulations concerning the ethical use of human volunteers, were followed during all phases of this research.

2.2. Participants and Procedure

Data were collected between 2009 and 2011 (baseline) and 2013 (follow-up) for female, male and opposite-sex twin pairs. Information on demographics and self-reported health-related questionnaires were gathered. Trained assessors, blinded to the predictors

and outcomes of the study, collected all data using phone and face-to-face interviews. All questionnaires were self-reported.

Inclusion criteria for this study were: answering the questionnaire at both baseline and follow-up and being free of chronic LBP at baseline. We defined participants as being free of chronic LBP based on the answers to the following question: “Have you ever suffered from chronic LBP?” Those participants who answered “no” to this question at baseline were considered as free of chronic LBP and were included in the analysis.

DNA was used to ascertain the zygosity in part of the sample (338 female twin pairs). When a DNA test was not performed, a 12-item questionnaire focusing on the degree of similarity and mistaken identity between twins was used. This questionnaire corresponds well with DNA testing for determining zygosity and the agreement between them is around 96% (Ordonana et al., 2013).

2.3. Measurements and Instruments

2.3.1. Outcomes

The three LBP measures collected at follow-up were the outcomes of this study: i) presence of chronic LBP, ii) medical care-seeking associated with chronic LBP, and iii) activity limitation associated with chronic LBP. All LBP outcomes were assessed through a dichotomous self-reported question. The chronic LBP question was derived from the Spanish National Health Survey (Ministerio de Sanidad Servicios Sociales e Igualdad, 2012.) while the other questions were based on consensual recommendations for the assessment of LBP in observational studies (de Vet et al., 2002; Dionne et al., 2008). Participants were instructed to consider chronic LBP as pain in the lower back

area that lasted for at least six months (including recurrent episodes). Those participants endorsing the question “Have you ever suffered from chronic LBP?” were considered as cases for having chronic LBP. This question was followed by: “Did you seek medical help because of this pain?” and “Was this pain bad enough to limit your usual activities or change your daily routine for more than one day?” Those participants who answered “yes” for these questions were considered as “cases” for medical care-seeking and for activity limitation respectively, while those participants who answered “no” for each of these questions, along with those who did not report chronic LBP in the first question, were considered as the non-cases for medical care-seeking and activity limitation outcomes.

2.3.2. Explanatory variables

Data on symptoms of depression were collected at baseline and were considered the explanatory variables. Participants were requested to answer two instruments, resulting in three different measures of symptoms of depression. Firstly, the Depression and Anxiety domain of the EuroQol-5 dimension questionnaire (EQ-5D) was used to assess symptoms of depression combined with anxiety (Szende and Williams, 2004). Participants were instructed to select the option that best described themselves on that day: i) “I am not anxious or depressed; ii) I am moderately anxious or depressed; iii) I am extremely anxious or depressed”. Due to the small number of participants in the extreme category, participants were divided into two groups: i) not depressed or anxious; ii) moderately or extremely depressed or anxious.

The second instrument used to assess symptoms of depression was the Spanish version of the State-Trait Depression Questionnaire (Spielberger et al., 2005). Only female twin

pairs answered this questionnaire. The State-Trait Depression Questionnaire is comprised of two sub-scales - state depression and trait depression scales. The state depression items refer to how participants felt “at the moment” of the interview, while the trait depression items refer to how participants “generally” felt. Each of the sub-scales is composed of 10 items with four-point scale answer options (1 to 4). The final score for each sub-scale ranges from 10 to 40 (Spielberger et al., 2008). The continuous scores for both state and trait depression were used in the analyses.

2.3.3.. Potential Confounders

Data on age, sex, sleep quality, body mass index, engagement in leisure physical activity, and smoking were collected at baseline and considered as possible confounding variables. Participants’ subjective sleep quality was assessed using the Spanish version of the Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989; Royuela Rico and Macías Fernández, 1997) and the dichotomous score was used for analysis, based on the total score cut off point of 5, with a score greater than 5 indicating poor sleep quality (Buysse et al., 1989). Participants were required to choose the option that best described their engagement in leisure physical activity: i) “I do not practice exercise. My leisure time is mostly sedentary (reading, watching TV, movies etc)”; ii) “Some sport or physical activity occasionally (walking, gardening, soft gym, light efforts etc)”; iii) “Regular physical activity several times a month (tennis, jogging, swimming, cycling, team sports etc)”; iv) “Physical training several times a week”. Engagement in leisure physical activity was dichotomized into two categories: i) no physical activity; ii) low, moderate or vigorous physical activity. In regards to smoking habits, participants were divided into two categories: i) ex or never smoker; ii) current smoker. Smoking and

physical activity questions were based on the Spanish National Health Survey questionnaire (Ministerio de Sanidad Servicios Sociales e Igualdad, 2012.).

2.4. Data Analysis

Descriptive statistics were used to characterize the sample, which was comprised of twins who participated in both data waves and did not report chronic LBP at baseline. The outcome variables investigated were chronic LBP, medical care-seeking associated with chronic LBP, and activity limitation associated with chronic LBP at follow-up. Explanatory variables were the three measures of symptoms of depression that were collected at baseline: symptoms of depression and anxiety, state depression, and trait depression. Potential confounders considered were age, sex, sleep quality, engagement in leisure physical activity, and smoking. As twins were followed up for different periods of time the total sample analyses were adjusted for follow-up length. Both twins within a pair were followed for the same period of time, therefore the within-pair case-control analyses were not adjusted for follow-up length. We analyzed the association between each depression measure and each LBP outcome in two stages, total sample analysis and within-pair twin case-control analysis, by means of logistic regressions.

2.4.1. Total sample analysis

In the total sample analysis all participants, regardless of zygosity and concordance for LBP measures, were included. Therefore, twins were analyzed as individuals rather than pairs. The association between each depression measure and each LBP outcome was investigated using logistic regression analysis. We used a robust estimator for all total sample analyses to account for possible non-independence of data (*vce* function on STATA). All total sample analyses were adjusted for age and sex. To select other

confounding variables that should be included in each of the multivariable models, we conducted univariate logistic regression analyses investigating the association between sleep quality, engagement in leisure physical activity, or smoking and both the explanatory (depression related) and outcome (LBP related) variables. When a p-value < 0.20 for the association between the co-variable and both the explanatory and outcome variables was identified, this co-variable was considered a confounding variable and was included in the pertinent multivariate regression model. The co-variables included in the multivariate model for the total sample analysis were retained in all analytical phases, with all models generating comparable results for each outcome.

2.4.2. Within pair twin case-control analysis

In the within pair twin case-control analysis only complete twin pairs (i.e., data available for both twins) who were discordant for the LBP outcome (e.g. one twin reported chronic LBP while the co-twin did not) were included.

Twins were analyzed as matched pairs rather than individuals. These analyses were performed to investigate the association between depression measures and chronic LBP, adjusting for genetics and shared environment. The within-pair twin case-control analyses were adjusted for the same variables included in the total sample analysis (except age), with sex being included when appropriate only (e.g. DZ analyses). Conditional logistic regression was used to perform all within pair twin case-control analyses. Initially, only DZ twin pairs were included in the within pair twin case-control analysis. Subsequently, the analysis was performed for MZ twin pairs.

The levels of adjustment for confounders increase in each analytical phase, from total sample analysis to MZ only case-control analysis. In the total sample analysis, the adjustment of variables is derived from the data, while in the within pair twin case-control analysis adjustment for genetic and environment factors is also employed, in addition to data-driven confounders. DZ twins share approximately 50% of their genes, while MZ share approximately 100%, with both DZ and MZ twins considered to share 100% of the so-called common or shared environment. Therefore, the MZ model provides the most adjusted and therefore precise estimation of risks. In theory, if the magnitude of the association between two variables increases or remains significant and relevant across the analytical phases, this is consistent with a possible causal relationship, as the estimates become more direct and filtered throughout the analytical phases. However, if the magnitude of the association decreases or disappears, this is indicative of this association being confounded by other factors such as genetics (Figure 1) (Everitt and Howell, 2005).

<Figure 1 about here>

All analyses were conducted using STATA version 13. Results from regression models were presented using OR and 95% confidence interval (95%CI). The significance level was set at 0.05.

3. Results

3.1. Study sample

Of the 1,607 participants with data available at both baseline and follow-up, a total of 1,098 twins did not report chronic LBP at baseline and formed the basis for this analysis. Participants' age ranged from 43 to 71 years and 52.6% were men. The

incidence of chronic LBP during the follow-up period was 22.3%, 205 participants (18.7%) sought care for their LBP, and 171 participants (15.6%) had their activities limited because of their LBP. Overall, the prevalence of symptoms of depression at study entry, regardless of the measure used, was similar across participants with and without LBP. Twins with LBP reported worse sleep quality, engaged less in physical activity and were less likely to smoke (Table 1).

<Table 1 about here>

3.2. Chronic LBP

In the total sample analysis, symptoms of depression and anxiety at baseline did not significantly increase the risk of chronic LBP (OR = 1.40, 95%CI: 0.96 to 2.03) (Table 2). This risk presented a trend towards increasing in the DZ case-control analysis (OR = 2.15, 95%CI: 0.97 to 4.77), although this estimate was not statistically significant. When the analysis was conducted separately for MZ case-control pairs, no risk of chronic LBP was identified (OR = 1.00, 95%CI: 0.06 to 15.99).

<Table 2 about here>

Both measures of state and trait depression, available exclusively for women, did not increase the risk of chronic LBP in the total sample analyses (OR = 1.05, 95%CI: 0.99 to 1.11 and OR = 1.03, 95%CI: 0.99 to 1.08, respectively) (Table 2). The magnitude of the association did not change and remained non-significant in the DZ case-control analyses for both measures (OR = 1.05, 95%CI: 0.88 to 1.25 for state and OR = 1.01, 95%CI: 0.87 to 1.16 for trait-depression). In the MZ case-control analysis the association between state and trait depression and chronic LBP was similar to the

previous phases (OR = 1.01, 95%CI: 0.76 to 1.34 and OR = 1.28, 95%CI: 0.84 to 1.96, respectively) (Figure 2).

<Figure 2 about here>

3.3. Medical care-seeking associated with chronic LBP

In the total sample analysis, only state depression at baseline increased the risk of women seeking medical care for their chronic LBP (OR = 1.06, 95%CI: 1.01 to 1.12) (Table 3). No association was found for symptoms of depression (OR = 1.21, 95%CI: 0.81 - 1.81) or trait depression (OR = 1.04, 95%CI: 0.99 - 1.09) (Table 3). No subsequent case-control analysis was statistically significant. The magnitude of the association for symptoms of depression and state depression did not change substantially in the MZ phase (OR = 1.33, 95%CI: 0.07 to 25.91 and OR = 1.09, 95%CI: 0.80 to 1.50, respectively) (Figure 3).

<Table 3 about here>

<Figure 3 about here>

3.4 Activity limitation associated with chronic LBP

Both state and trait depression were statistically associated with future activity limitation associated with chronic LBP in the total sample analysis (OR = 1.07, 95%CI: 1.01 to 1.14 and OR = 1.05, 95%CI: 1.01 to 1.10, respectively) (Table 4). No statistically significant association was found for symptoms of depression (OR = 1.09, 95%CI: 0.69 to 1.72). No subsequent analysis was statistically significant (Figure 4).

<Table 4 about here>

<Figure 4 about here>

4. Discussion and conclusions

The aim of this longitudinal co-twin study was to investigate whether symptoms of depression increase the risk for chronic LBP and to examine the influences of genetics and early shared environmental factors in this postulated association. Our results suggest that the relationship between depression and LBP is small and likely to be influenced by the definition used for both conditions and whether genetic and early environmental factors are considered in the case-control analysis. The presence of symptoms of depression or anxiety does not appear to increase the risk of LBP in the future, regardless of whether LBP is sufficiently severe for people to seek medical care or reduce their routine activities. However, higher levels of current depressive symptomatology (state depression) and dispositional or trait depression appear to be associated with future care seeking for LBP. Dispositional or trait depression appears to also increase the risk of limiting their activity because of LBP. Trait depression refers to how participants generally feel (Spielberger et al., 2005). This measure is more likely to capture symptoms of depression as a feature throughout life as opposed to the other measures of depression that refer only to the current and possibly temporary symptoms.

The results of this study are consistent with the findings of our previous cross-sectional co-twin study in which the same analytical phases were used (Pinheiro et al., 2015a). However, the current results for state and trait depression are different from the previous investigation, where we previously found no association between these variables and LBP. Possible reasons for this discrepancy include the cross-sectional nature of the previous investigation, and the selection of subjects which excluded those with a longer history of LBP (Pinheiro et al., 2015a). Additionally, the present study investigated other LBP outcomes, in addition to chronic LBP, including medical care seeking and activity limitation associated with LBP, and the statistically significant associations of

the current study were found for these variables only. This is especially important as the insights on the relationship between LBP and depression might be different depending on the depression and LBP phenotypes. In previous longitudinal studies this relationship was only observed in participants with more severe, persistent and limiting LBP (Croft et al., 1995; Carroll et al., 2004; Hartvigsen et al., 2006; Makris et al., 2014), which is consistent with the findings of the present study and do not contradict the previous one (Pinheiro et al., 2015a) either.

The results of this study provide a different interpretation to previous studies that have identified an increased risk of LBP in people with symptoms of depression (Mannion et al., 1996; Muramatsu et al., 1997; Adams et al., 1999; Carroll et al., 2004; Larson et al., 2004; Currie and Wang, 2005; Hartvigsen et al., 2006; Patten et al., 2008; Docking et al., 2011; Makris et al., 2014). The effect size we observed in the total sample analysis for symptoms of depression and anxiety and chronic LBP (OR = 1.40) was similar to other non-twin studies published in the field (Pinheiro et al., 2015b). However, with our twin data, no association was observed in the within-pair case-control analysis, particularly in MZ twins. The MZ within-pair twin case-control analysis generates the most precise estimates of association between two variables, as twins are matched for genetic and familial confounders (MacGregor et al., 2000). Therefore, the fact that the association between depression and LBP disappeared in the MZ case-control analysis suggests that genetics and early shared environment factors confound this association. We argue that the previous increase in risk of LBP identified in non-twin studies (with similar estimates to our total sample approach) could possibly be confounded by these factors. However, we emphasize that this hypothesis needs to be tested in future studies, due to the small numbers in the MZ analyses observed in the current study.

Although LBP and symptoms of depression are conditions likely to present concurrently, based on the results of this study, particularly the interpretation of statistical significance and generated confidence intervals, a direct causal link between these conditions seems to be unlikely. Based on the results of the current study we cannot rule out that the association between LBP and depression could be the result of an interaction of factors instead of linear direct causation paths (Bair et al., 2003). The suggested lack of a causal relationship between depression and LBP might assist in the understanding of the limited effects of interventions targeting depression in patients presenting with co-morbid symptoms of depression and LBP to improve LBP related outcomes, such as use of antidepressants. Unfortunately, these treatments have proved to be ineffective with a recent Cochrane systematic review showing that there is no clear evidence that antidepressants are more effective than placebo in the management of patients with chronic LBP and comorbid depression (Urquhart et al., 2008). However, clinicians should not disregard the importance of diagnosing symptoms of depression in patients with LBP. Especially in primary care settings, depression is often overlooked due to physical complaints (Panzarino, 1998) and the neglect of managing symptoms of depression leads to worse outcomes for patients with increases in mortality rates, morbidity, and management costs (Panzarino, 1998).

This study has several strengths such as the use of a longitudinal design, several measures of LBP, and a case-control twin analytical approach. However, some limitations should be discussed. Firstly, the LBP measures used to classify participants as free of LBP at baseline assessed *chronic* LBP and therefore it is likely that participants with a history of acute LBP (e.g. LBP lasting for less than 6 months) could

be included in the analysis. This might have influenced the results, since a previous history of LBP is a risk factor for developing a new episode in the future (Stanton et al., 2008). We only had data available for state and trait depression for women, which limits the generalizability of the findings of this study. Data on symptoms of depression could include an anxiety component due to the characteristic of the instrument. Additionally, our measure of depression assessed symptoms of depression and not depression diagnosed by a health professional, although previous investigations have demonstrated the validity of screening questionnaires when compared to the gold standard to diagnose depression (Choi et al., 2014). Lastly, the sample sizes for the case-control analyses were overall small. Therefore, the results of this study should be interpreted with caution.

In conclusion, our results suggest that the relationship between symptoms of depression and LBP is small and dependent on the definition used for both conditions. Symptoms of depression or anxiety do not increase the risk of future LBP, regardless of the LBP outcome measure used. A higher score in the more specific state and trait depression scales, increases the risk of more disabling LBP (medical care seeking and activity limitation), but not overall LBP. Additionally, the results of the current study do not suggest a possible causal link between depression and LBP given that no association was found when genetic and early environmental factors are controlled for, and even when the association was observed in the total sample analysis (with no adjustment for genetics) the observed magnitude was small.

Additional studies are needed to confirm the results of the present investigation in a larger sample and in populations with different cultural and genetic backgrounds.

Specifically, future investigations should consider genetic and common environment confounding factors when possible. Common factors influencing both LBP and depression, preferably modifiable factors, should also be investigated in future research so that treatment and preventative strategies could be designed for these common health problems. Interaction of risk factors should also be considered in the investigation of the depression-LBP link, as it has been shown that depression interacts with other variables such as obesity, and potentially alters people's risk of developing health conditions. For instance, the risk of developing asthma is higher for people with depression and obesity than for those only with depression (Brumpton et al., 2013). Additionally, the ability to differentiate phenotypes of LBP in the future, as well as depression, may show different aspects of these conditions. The need for these studies highlights the complexity of what was previously thought to be a simple, direct relationship between depression and chronic LBP.

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Author Contributions

All authors discussed the results of this study, critically revised the manuscript for important intellectual content and approved the final version of the manuscript.

- Pinheiro MB: conception and design, analysis and interpretation of data, drafting and revision of the manuscript and approval of the final version.
- Ferreira ML: conception and design, interpretation of data and results, drafting and revision of the manuscript and approval of the final version.

- Refshauge K: conception and design, interpretation of data and results, revision of the manuscript and approval of the final version.
- Colodro-Conde L: acquisition and assembly of data, interpretation of data and results, revision of the manuscript and final approval of the final version.
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- Ferreira PF: conception and design, analysis and interpretation of data and results, drafting and revision of the manuscript and approval of the final version.

References

Adams, M.A., Mannion, A.F., and Dolan, P. (1999). Personal risk factors for first-time low back pain. *Spine* **24**, 2497-2505.

Bair, M.J., Robinson, R.L., Katon, W., and Kroenke, K. (2003). Depression and pain comorbidity: a literature review. *Arch Intern Med* **163**, 2433-2445.

Brumpton, B.M., Leivseth, L., Romundstad, P.R., Langhammer, A., Chen, Y., Camargo, C.A., and Mai, X.M. (2013). The joint association of anxiety, depression and obesity with incident asthma in adults: the HUNT study. *Int J Epidemiol* **42**, 1455-1463.

Buysse, D.J., Reynolds, C.F., Monk, T.H., Berman, S.R., and Kupfer, D.J. (1989). The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res* **28**, 193-213.

Carroll, L.J., Cassidy, J.D., and Cote, P. (2004). Depression as a risk factor for onset of an episode of troublesome neck and low back pain. *Pain* **107**, 134-139.

Choi, Y., Mayer, T.G., Williams, M.J., and Gatchel, R.J. (2014). What is the best screening test for depression in chronic spinal pain patients? *Spine J* **14**, 1175-1182.

Croft, P.R., Papageorgiou, A.C., Ferry, S., Thomas, E., Jayson, M.I.V., and Silman, A.J. (1995). Psychologic distress and low back pain - Evidence from a prospective study in the general population. *Spine* **20**, 2731-2737.

Currie, S.R., and Wang, J.L. (2005). More data on major depression as an antecedent risk factor for first onset of chronic back pain. *Psychol Med* **35**, 1275-1282.

de Vet, H.C.W., Heymans, M.W., Dunn, K.M., Pope, D.P., van der Beek, A.J., Macfarlane, G.J., Bouter, L.M., and Croft, P.R. (2002). Episodes of low back pain - A proposal for uniform definitions to be used in research. *Spine* **27**, 2409-2416.

Dionne, C.E., Dunn, K.M., Croft, P.R., Nachemson, A.L., Buchbinder, R., Walker, B.F., Wyatt, M., Cassidy, J.D., Rossignol, M., Leboeuf-Yde, C., Hartvigsen, J., Leino-Arjas, P., Latza, U., Reis, S., Gil Del Real, M.T., Kovacs, F.M., Oberg, B., Cedraschi, C., Bouter, L.M., Koes, B.W., Picavet, H.S., van Tulder, M.W., Burton, K., Foster, N.E., Macfarlane, G.J., Thomas, E., Underwood, M., Waddell, G., Shekelle, P., Volinn, E., and Von Korff, M. (2008). A consensus approach toward the standardization of back pain definitions for use in prevalence studies. *Spine* **33**, 95-103.

Docking, R.E., Fleming, J., Brayne, C., Zhao, J., Macfarlane, G.J., Jones, G.T., and Cambridge City over-75s Cohort Study collaboration (2011). Epidemiology of back pain in older adults: prevalence and risk factors for back pain onset. *Rheumatology* **50**, 1645-1653.

Edit, V., Eva, S., Maria, K., Istvan, R., Agnes, C., Zsolt, N., Eva, P., Laszlo, H., Peter, T.I., Emese, K., Klara, T., Gyula, P., Edit, V., Eva, S., Maria, K., Istvan, R., Agnes, C., Zsolt, N., Eva, P., Laszlo, H., Peter, T.I., Emese, K., Klara, T., and Gyula, P. (2013). Psychosocial, educational, and somatic factors in chronic nonspecific low back pain. *Rheumatol Int* **33**, 587-592.

Everitt, B.S., and Howell, D.C. (2005). Co-twin control methods. In Encyclopedia of Statistics in Behavioral Science, B.S. Everitt, ed. (West Sussex: Wiley).

Ferreira, P.H., Beckenkamp, P., Maher, C.G., Hopper, J.L., and Ferreira, M.L. (2013). Nature or nurture in low back pain? Results of a systematic review of studies based on twin samples. *Eur J Pain* **17**, 957-971.

Global Burden of Disease Study, C. (2015). Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* **386**, 743-800.

Hartvigsen, J., Frederiksen, H., and Christensen, K. (2006). Physical and mental function and incident low back pain in seniors - A population-based two-year prospective study of 1387 Danish twins aged 70 to 100 years. *Spine* **31**, 1628-1632.

Larson, S., Clark, M., and Eaton, W. (2004). Depressive disorder as a long-term antecedent risk factor for incident back pain: A 13-year follow-up study from the Baltimore Epidemiological Catchment Area Sample. *Psychol Med* **34**, 211-219.

MacGregor, A.J., Snieder, H., Schork, N.J., and Spector, T.D. (2000). Twins. Novel uses to study complex traits and genetic diseases. *Trends Genet* **16**, 131-134.

Makris, U.E., Fraenkel, L., Han, L., Leo-Summers, L., and Gill, T.M. (2014). Risk factors for restricting back pain in older persons. *J Am Med Dir Assoc* **15**, 62-67.

Mannion, A.F., Dolan, P., and Adams, M.A. (1996). Psychological questionnaires: Do "abnormal" scores precede or follow first-time low back pain? *Spine* **21**, 2603-2611.

Ministerio de Sanidad Servicios Sociales e Igualdad (2012.). Encuesta Nacional de Salud 2011-2012 [Spanish National Health Survey 2011-2012]. (Ministerio de Sanidad, Servicios Sociales e Igualdad,).

Muramatsu, N., Liang, J., and Sugisawa, H. (1997). Transitions in chronic low back pain in Japanese older adults: a sociomedical perspective. *J Gerontol B Psychol Sci Soc Sci* **52B**, S222-234.

Nielsen, C.S., Knudsen, G.P., and Steingrimsdottir, O.A. (2012). Twin studies of pain. *Clin Genet* **82**, 331-340.

Ordonana, J.R., Perez-Riquelme, F., Gonzalez-Javier, F., Carrillo, E., Gomez-Amor, J., and Martinez-Selva, J.M. (2006). An initiative in Spain for the study of women's health: the Murcia Twin Registry. *Twin Res Hum Genet* **9**, 865-867.

Ordonana, J.R., Rebollo-Mesa, I., Carrillo, E., Colodro-Conde, L., Garcia-Palomo, F.J., Gonzalez-Javier, F., Sanchez-Romera, J.F., Oviedo, J.M.A., de Pancorbo, M.M., and Perez-Riquelme, F. (2013). The Murcia Twin Registry: A Population-Based Registry of Adult Multiples in Spain. *Twin Res Hum Genet* **16**, 302-306.

Panzarino, P.J., Jr. (1998). The costs of depression: direct and indirect; treatment versus nontreatment. *J Clin Psychiatry* **59 Suppl 20**, 11-14.

Patten, S.B., Williams, J.V., Lavorato, D.H., Modgill, G., Jette, N., and Eliasziw, M. (2008). Major depression as a risk factor for chronic disease incidence: longitudinal analyses in a general population cohort. *Gen Hosp Psychiatry* **30**, 407-413.

Pinheiro, M.B., Ferreira, M.L., Refshauge, K., Colodro-Conde, L., Carrillo, E., Hopper, J.L., Ordonana, J.R., and Ferreira, P.H. (2015a). Genetics and the environment affect the relationship between depression and low back pain: a co-twin control study of Spanish twins. *Pain* **156**, 496-503.

Pinheiro, M.B., Ferreira, M.L., Refshauge, K., Ordonana, J.R., Machado, G.C., Prado, L.R., Maher, C.G., and Ferreira, P.H. (2015b). Symptoms of Depression and Risk of New Episodes of Low Back Pain: A Systematic Review and Meta-Analysis. *Arthritis Care Res (Hoboken)* **67**, 1591-1603.

Reichborn-Kjennerud, T., Stoltenberg, C., Tambs, K., Roysamb, E., Kringlen, E., Torgersen, S., and Harris, J.R. (2002). Back-neck pain and symptoms of anxiety and depression: a population-based twin study. *Psychol Med* **32**, 1009-1020.

Royuela Rico, A., and Macías Fernández, J.A. (1997). Propiedades clinimétricas de la versión castellana del cuestionario de Pittsburgh *Vigilia-Sueño* **9**, 81-94.

Spielberger, C., Buela-Casal, G., Agudelo, D., Carretero-Dios, H., and Santolaya, F. (2005). Analysis of convergent and discriminant validity of the Spanish experimental version of the State-Trait Depression Questionnaire (ST-DEP). *Actas Esp Psiquiatr* **33**, 374-382.

Spielberger, C.D., Buela-Casal, G., and Agudelo Vélez, D. (2008). Inventario de Depresión Estado-Rasgo. Manual. (Madrid: TEA Ediciones).
Stanton, T.R., Henschke, N., Maher, C.G., Refshauge, K.M., Latimer, J., and McAuley, J.H. (2008). After an episode of acute low back pain, recurrence is unpredictable and not as common as previously thought. *Spine (Phila Pa 1976)* **33**, 2923-2928.

Sullivan, M.J., Reesor, K., Mikail, S., and Fisher, R. (1992). The treatment of depression in chronic low back pain: review and recommendations. *Pain* **50**, 5-13.

Sullivan, P.F., Neale, M.C., and Kendler, K.S. (2000). Genetic epidemiology of major depression: review and meta-analysis. *Am J Psychiatry* **157**, 1552-1562.

Szende, A., and Williams, A. (2004). Measuring self-reported population health: an international perspective based on EQ-5D (Netherlands: SpringMed publishing).
Urquhart, D.M., Hoving, J.L., Assendelft, W.W., Roland, M., and van Tulder, M.W. (2008). Antidepressants for non-specific low back pain. *Cochrane Database Syst Rev*, CD001703.

Vos, T., Flaxman, A.D., Naghavi, M., Lozano, R., Michaud, C., Ezzati, M., Shibuya, K., Salomon, J.A., Abdalla, S., Aboyans, V., Abraham, J., Ackerman, I., Aggarwal, R., Ahn, S.Y., Ali, M.K., Alvarado, M., Anderson, H.R., Anderson, L.M., Andrews, K.G., Atkinson, C., Baddour, L.M., Bahalim, A.N., Barker-Collo, S., Barrero, L.H., Bartels, D.H., Basanez, M.G., Baxter, A., Bell, M.L., Benjamin, E.J., Bennett, D., Bernabe, E., Bhalla, K., Bhandari, B., Bikbov, B., Bin Abdulhak, A., Birbeck, G., Black, J.A., Blencowe, H., Blore, J.D., Blyth, F., Bolliger, I., Bonaventure, A., Boufous, S., Bourne, R., Boussinesq, M., Braithwaite, T., Brayne, C., Bridgett, L., Brooker, S., Brooks, P., Brugha, T.S., Bryan-Hancock, C., Bucello, C., Buchbinder, R., Buckle, G., Budke, C.M., Burch, M., Burney, P., Burstein, R., Calabria, B., Campbell, B., Canter, C.E., Carabin, H., Carapetis, J., Carmona, L., Cella, C., Charlson, F., Chen, H., Cheng, A.T., Chou, D., Chugh, S.S., Coffeng, L.E., Colan, S.D., Colquhoun, S., Colson, K.E., Condon, J., Connor, M.D., Cooper, L.T., Corriere, M., Cortinovis, M., de Vaccaro, K.C., Couser, W., Cowie, B.C., Criqui, M.H., Cross, M., Dabhadkar, K.C., Dahiya, M., Dahodwala, N., Damsere-Derry, J., Danaei, G., Davis, A., De Leo, D., Degenhardt, L., Dellavalle, R., Delossantos, A., Denenberg, J., Derrett, S., Des Jarlais, D.C., Dharmaratne, S.D., Dherani, M., Diaz-Torne, C., Dolk, H., Dorsey, E.R., Driscoll, T., Duber, H., Ebel, B., Edmond, K., Elbaz, A., Ali, S.E., Erskine, H., Erwin, P.J., Espindola, P., Ewoigbokhan, S.E., Farzadfar, F., Feigin, V., Felson, D.T., Ferrari, A., Ferri, C.P., Fevre, E.M., Finucane, M.M., Flaxman, S., Flood, L., Foreman, K., Forouzanfar, M.H., Fowkes, F.G., Franklin, R., Fransen, M., Freeman, M.K., Gabbe,

B.J., Gabriel, S.E., Gakidou, E., Ganatra, H.A., Garcia, B., Gaspari, F., Gillum, R.F., Gmel, G., Gosselin, R., Grainger, R., Groeger, J., Guillemin, F., Gunnell, D., Gupta, R., Haagsma, J., Hagan, H., Halasa, Y.A., Hall, W., Haring, D., Haro, J.M., Harrison, J.E., Havmoeller, R., Hay, R.J., Higashi, H., Hill, C., Hoen, B., Hoffman, H., Hotez, P.J., Hoy, D., Huang, J.J., Ibeanusi, S.E., Jacobsen, K.H., James, S.L., Jarvis, D., Jasrasaria, R., Jayaraman, S., Johns, N., Jonas, J.B., Karthikeyan, G., Kassebaum, N., Kawakami, N., Keren, A., Khoo, J.P., King, C.H., Knowlton, L.M., Kobusingye, O., Koranteng, A., Krishnamurthi, R., Lalloo, R., Laslett, L.L., Lathlean, T., Leasher, J.L., Lee, Y.Y., Leigh, J., Lim, S.S., Limb, E., Lin, J.K., Lipnick, M., Lipshultz, S.E., Liu, W., Loane, M., Ohno, S.L., Lyons, R., Ma, J., Mabweijano, J., MacIntyre, M.F., Malekzadeh, R., Mallinger, L., Manivannan, S., Marcenes, W., March, L., Margolis, D.J., Marks, G.B., Marks, R., Matsumori, A., Matzopoulos, R., Mayosi, B.M., McAnulty, J.H., McDermott, M.M., McGill, N., McGrath, J., Medina-Mora, M.E., Meltzer, M., Mensah, G.A., Merriman, T.R., Meyer, A.C., Miglioli, V., Miller, M., Miller, T.R., Mitchell, P.B., Mocumbi, A.O., Moffitt, T.E., Mokdad, A.A., Monasta, L., Montico, M., Moradi-Lakeh, M., Moran, A., Morawska, L., Mori, R., Murdoch, M.E., Mwaniki, M.K., Naidoo, K., Nair, M.N., Naldi, L., Narayan, K.M., Nelson, P.K., Nelson, R.G., Nevitt, M.C., Newton, C.R., Nolte, S., Norman, P., Norman, R., O'Donnell, M., O'Hanlon, S., Olives, C., Omer, S.B., Ortblad, K., Osborne, R., Ozgediz, D., Page, A., Pahari, B., Pandian, J.D., Rivero, A.P., Patten, S.B., Pearce, N., Padilla, R.P., Perez-Ruiz, F., Perico, N., Pesudovs, K., Phillips, D., Phillips, M.R., Pierce, K., Pion, S., Polanczyk, G.V., Polinder, S., Pope, C.A., 3rd, Popova, S., Porrini, E., Pourmalek, F., Prince, M., Pullan, R.L., Ramaiah, K.D., Ranganathan, D., Razavi, H., Regan, M., Rehm, J.T., Rein, D.B., Remuzzi, G., Richardson, K., Rivara, F.P., Roberts, T., Robinson, C., De Leon, F.R., Ronfani, L., Room, R., Rosenfeld, L.C., Rushton, L., Sacco, R.L., Saha, S., Sampson, U., Sanchez-Riera, L., Sanman, E., Schwebel, D.C., Scott, J.G., Segui-Gomez, M., Shahraz, S., Shepard, D.S., Shin, H., Shivakoti, R., Singh, D., Singh, G.M., Singh, J.A., Singleton, J., Sleet, D.A., Sliwa, K., Smith, E., Smith, J.L., Stapelberg, N.J., Steer, A., Steiner, T., Stolk, W.A., Stovner, L.J., Sudfeld, C., Syed, S., Tamburlini, G., Tavakkoli, M., Taylor, H.R., Taylor, J.A., Taylor, W.J., Thomas, B., Thomson, W.M., Thurston, G.D., Tleyjeh, I.M., Tonelli, M., Towbin, J.A., Truelsen, T., Tsilimbaris, M.K., Ubeda, C., Undurraga, E.A., van der Werf, M.J., van Os, J., Vavilala, M.S., Venketasubramanian, N., Wang, M., Wang, W., Watt, K., Weatherall, D.J., Weinstock, M.A., Weintraub, R., Weisskopf, M.G., Weissman, M.M., White, R.A., Whiteford, H., Wiersma, S.T., Wilkinson, J.D., Williams, H.C., Williams, S.R., Witt, E., Wolfe, F., Woolf, A.D., Wulf, S., Yeh, P.H., Zaidi, A.K., Zheng, Z.J., Zonies, D., Lopez, A.D., Murray, C.J., AlMazroa, M.A., and Memish, Z.A. (2012). Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* **380**, 2163-2196.

Figure captions

Figure 1. Sequence of analytical stages from the total sample to the within-pair twin case-control analyses.

An increase in the association from the total sample to the MZ within-pair twin case-control analyses (panel a) is indicative of an association consistent with causation, while a decrease (panel b) is consistent with genetics or early environment confounding the relationship. A stable and non-changed association (not depicted) is indicative of genetics or early environment not having a significant effect in the relationship. MZ = Monozygotic; DZ = Dizygotic.

Figure 2. Results from multivariate models for the relationship between all depression measures and chronic low back pain for all analytical phases.

MZ = Monozygotic; DZ = Dizygotic; OR = Odds Ratio; CI = Confidence Interval.

Figure 3. Results from multivariate models for the relationship between all depression measures and medical care-seeking associated with chronic low back pain for all analytical phases.

MZ = Monozygotic; DZ = Dizygotic; OR = Odds Ratio; CI = Confidence Interval.

Figure 4. Results from multivariate models for the relationship between all depression measures and activity limitation associated with chronic low back pain for all analytical phases.

MZ = Monozygotic; DZ = Dizygotic; OR = Odds Ratio; CI = Confidence Interval.