Lumbar disc degeneration and genetic factors are the main risk factors for low back pain in women: the UK Twin Spine Study

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ABSTRACT

Objective Low back pain (LBP) is a common musculoskeletal disorder, but it is still unclear which individuals develop it. The authors examined the contribution of genetic factors, lumbar disc degeneration (LDD) and other risk factors in a female sample of the general population.

Material and Methods A cross-sectional study was conducted among 2256 women (371 and 698 monozygotic and dizygotic twin pairs and 29 sibling pairs) with a mean age of 50 years (18–84). A self-reported validated questionnaire was used to collect back pain data. Risk factors including body weight, smoking, occupation, physical exercise and MRI assessed LDD were measured. Data analysis included logistic regression and variance decomposition.

Results The major factors associated with LBP included genetic background, with OR approximately 6 if the monozygotic co-twin had LBP; 2.2 if she was a dizygotic co-twin. In addition, LDD and overweight were highly significantly (p<0.001) associated with non-specific LBP. The single most important risk factor was the amount of LDD. After adjustment for other risk factors, the individuals who exhibited advanced LDD (90% vs 10%) had 3.2 higher odds of manifesting LBP.

Conclusions The major risk factors for reported episodes of severe and disabling LBP in UK women include the degree of LDD as assessed by MRI, being overweight and genetic heritability.

Low back pain (LBP) is a common musculoskeletal condition in all ages worldwide1 and in Europe in particular.1 The lifetime prevalence of non-specific LBP may reach 80%, with the annual prevalence ranging between 25% and 60% in different ethnic groups.4–6 Radiological features of lumbar disc degeneration (LDD) are almost universal in adults,6 and have been proposed repeatedly as one of the main causes of LBP.7–9 Although an association has been demonstrated,10,11 the individual risk factors for LBP remain unclear and universal consensus regarding the extent of LDD–LBP association is lacking.12–15 The lack of standardised clinical criteria and radiological definitions has further hampered the undertaking of well-executed epidemiological studies. More sensitive imaging modalities, such as MRI, have fallen in cost and become more widely available and are paving the way for new, large-scale epidemiological studies of LDD.

Obesity, smoking and occupation have been reported to be associated with prevalent LBP, although the quantitative effect of the majority of these has been found to be negligible—even insignificant.16–19 On the other hand, several studies have consistently suggested the presence of a major genetic component underlying variation of LBP,10,20 although data remain scarce.

The main aim of this study, representing a continuation of our preliminary study,10 was to evaluate the association of non-specific LBP with LDD and putative genetic factors in a sample taken from the general population, using extensive data from the UK Twin Spine Study (TUTSS). The UK Twin Spine Study has one of the world’s largest samples for whom LBP data and important risk factors, including MRI-determined LDD status, are available in a subsample. Other relevant risk factors available for this study included age, anthropometrics, smoking and physical exercise. This allowed us to conduct rigorous association analysis of the LBP with LDD scores and genetic heritability, simultaneously controlling for the effect of other risk factors. Needless to say, the study does not consider several other potentially relevant risk factors, including inflammatory disease, fracture or the psychological component in back pain, which is an important contributor to pain and disability.21

PATIENTS AND METHODS

Study sample

A total of 2256 women (age range 18–84 years, with a mean of 50 years) was examined in this project and included 371 and 698 pairs of monzygotic and dizygotic twin pairs, 29 pairs of siblings and 60 singletons. This sample was taken from the TwinsUK register (http://www.twinsuk.ac.uk), a volunteer-based group of healthy adult twins drawn from the UK population.22 Participating twins underwent a nurse-led interview and had been sent, before their visit, a standardised questionnaire for completion, without conferring, relating to lifetime history of low back symptoms. The low back questions followed the format of the Medical Research Council Nurses Study,23 and included both questions and a mannequin diagram on which to demonstrate pain distribution. LBP was defined as being located between the 12th ribs and the gluteal folds. Pain associated with fever, menstruation or pregnancy was excluded. Our analyses focused on
pain associated with disability in ‘activities of daily living’ (see below), with LBP_12 defined as pain associated with disability that has lasted more than 1 day during the previous 12 months; LBP_1 was defined as pain associated with disability lasting more than 1 month ever. LBPI (and LBPI2) was defined as a binary trait (ie, 1 affected vs 0 non-affected) but we also considered LBP_1Q and LBP_1O as semiquantitative traits, in which the degree of LBPI was defined as the number of daily tasks not achievable in LBP episodes during the past 12 months and ever, respectively. ‘Activities of daily living’ were defined as any one of the following being impossible to achieve (as opposed to just ‘difficult’): walking around the house; standing for 15 min; getting up from a low chair; getting out of the bath; getting in and out of the car; going up and down stairs; putting on socks or stockings and cutting toenails. Details of potential confounding variables were recorded at the interview: height; weight; history of smoking; history of manual work including physical occupations such as cleaning or lifting and physical exercise. Physical exercise was defined by a positive answer to ‘Have you done any regular sporting activity at any time since you left school?’ Ethics committee approval had been obtained and the participants gave informed consent.

LDD status was established using MRI, performed in 909 subjects using a Siemens (Munich, Germany) 1.0-tesla superconducting magnet between 1998 and 2001. The method is described in detail elsewhere.24 The following radiographic coding on a scale of 0–3 was made for each of the five intervertebral discs in the lumbar spine: (1) disc signal intensity within the nucleus pulposus; (2) disc height; (3) disc extension and (4) anterior osteophytes. Each trait code was summed over the five lumbar discs to produce a summary variable (LSIG, LHT, LBUL, LOST) and the summary variables were added to provide an overall summary score, LSUM.

Statistical and genetic analysis

The analysis was conducted in two stages. First, identification of the potential confounder effect on LBP was examined. We conducted a series of variance (for discrete LBP variables) and correlation (for semiquantitative LBP variables) analyses with LSUM and its structural components with the above confounders as independent predictors. To verify the consistency and the extent of the associations between the four LBP variables and LDD traits we performed canonical correlation analysis between these two arrays of traits. This measures the association of two canonical variables, one representing a set of dependent variables (LBP status variables), the other a set of independent variables (LDD traits, etc) and evaluates simultaneously the contribution of each variable to the observed correlation. Variables showing significant association with LBP status were used to predict the risk of LBP in multiple logistic regression analysis. We evaluated the extent of association of the cumulative degenerative score, LSUM, and its components with LBPI, simultaneously adjusting for age, weight and other predictors for the risk of LBP. This analysis also included the LBPI status of the twin, and estimated the OR added by affected dizygotic and monozygotic twin, respectively.

In the second stage, the effects of potential covariates (eg, age, weight) on LBP variation were estimated simultaneously with the effect of the putative genetic factors, using variance component analysis.25 In these analyses, the total variance (V_T) of the phenotype of interest (LBP, LSUM) is decomposed into genetic (V_G) and environmental components. The latter in turn may include common family environment (V_CE) and unexplained residual influences (V_RS). Theoretically, monozygotic twins have all their genes in common, while dizygotic pairs share on average half of their segregating genes. When the phenotypic correlation between monozygotic twin pairs is greater than that of dizygotic twin pairs, it is assumed that genetic influences underlie the increased familial aggregation. Using the maximum likelihood ratio test (LRT) as a model-fitting technique, a best fitting and most parsimonious model was obtained after excluding all non-significant parameters from the general model (backward elimination).

As significant correlations were observed between LBP and LDD variables, we assumed that these correlations were attributable to common genes and/or common environmental factors. To test this hypothesis we used bivariate variance component analysis, which evaluates to what extent the observed phenotypic correlation can be caused by pleiotropic genetic factors (measured by additive genetic correlation, r_G), and/or by shared environmental factors (measured by environmental correlation, r_E).26 While genetic correlation is a quantitative measure of the shared effects of genes on each of the two traits under analysis, environmental correlation estimates the extent to which these traits share a common environment.

RESULTS

Descriptive statistics and covariates effect

The preliminary statistical analysis showed highly significant (p<0.001) correlations between all LBP variables. We therefore selected two moderately intercorrelated (r=0.62) variables, LBPI and LBPI_1Q (both defined in the Patients and methods section), for further analysis. These variables were selected because they reflect pain episodes lasting for more than 1 month over life time and therefore are a more reliable measure than LBP_12 variables. The second reason was the results of the canonical and regular correlation analyses showing LBPI_1 to have the strongest association with LDD phenotypes (see below). As we are interested in the consistency of the results with respect to other LBP phenotypes, we chose semiquantitative phenotype LBPI_1Q (vs binary LBP_1). The prevalence of LBPI_1 in the total sample was approximately 24% with no difference between the dizygotic and monozygotic twins (0.242 vs 0.243). However, the concordance rate in the total sample was significantly higher in monozygotic twins versus dizygotic twins (χ²=8.02, p=0.008), with corresponding tetrachoric correlations, 0.641 and 0.375, respectively (p<0.001, for both).

Table 1 shows basic characteristics of the twins and the available sample sizes by LBPI status. Women with disabling episodes of back pain were more likely to be older, heavier and taller, to have done manual work and to perform physical exercise. In addition, all LDD and LBP variables were significantly higher in the LBPI group. We found no association between LBPI and smoking, and age had a minimal effect on back pain status. As weight and body mass index (BMI) were strongly correlated (r=0.91, p<0.001), to avoid redundancy and collinearity in multivariable analysis, and as weight was more highly correlated with LBP than BMI, only weight was considered in the following analysis.

As associations between all LDD traits and LBP status were highly statistically significant (table 1), we tested the consistency of the associations using correlation and canonical correlation analyses (table 2). The latter was performed on adjusted and non-adjusted variables and showed a highly significant (p<0.001) association between the two arrays of variables. The magnitude of canonical correlations was approximately the
same (R = 0.250) regardless of adjustment and whether LSUM or its four structural components were used. Considering LBP and LDD variables adjusted for significant covariates (table 2), it is worth mentioning that canonical weights (not shown), representing a variable’s unique contribution, were of comparable magnitude for LSUM components, ranging from 0.278 (LSIG) to 0.409 (LHT). However, the contribution of LBP variables varied much more, from 0.179 (LBP_1Q) to 0.853 (LBP_1). One interpretation of these findings is that all four MRI traits make a significant and similar contribution to LBP, but especially to LBP1.

### Independent risk factors for LBP

This was tested using multiple logistic regression for the effect of all significant variables (table 1) on LBP1. First, to preserve sample size, LDD traits were not included in the analysis. Body weight, exercise and LBP status of the co-twin were highly significantly (p<0.001 for each covariate) associated with LBP1. Next, we added the LDD status avoiding collinearity, by examining LSUM and its constituent traits separately. LSUM, weight, physical exercise and LBP1 status of the co-twin were all found to be significant predictors of back pain (table 3). Testing the association with the four MRI traits of LDD, only disc height (p = 0.0013) and disc bulge (p = 0.0311) were independent significant predictors. However, the OR of each of them was substantially lower than the corresponding effect for the summary trait LSUM. Comparison of the upper versus the lower 10% of the predictor variables distribution suggested that LSUM is the major potential risk factor for LBP (table 3). The contribution of monozygotic co-twins to LBP risk was virtually twice the effect of dizygotic twins: 1.757 (SE 0.317) versus 0.782 (SE 0.253), with p<0.001, clearly highlighting the contribution of genetic factors to LBP.

### Contribution of genetic factors

Next we examined the contribution of genetic factors to LBP1. Taking the LBP status of the co-twin into account, logistic regression analysis suggested a significant genetic background (table 3), which is also supported by high and zygosity-dependent tetrachoric correlations between the twins (see above). The correlations between dizygotic and monozygotic twins in LBP_1Q scores were also in accord, 0.374 and 0.467 (p<0.001 for both). We therefore submitted both LBP variables to univariate and bivariate variance component analyses with LSUM (table 4) to evaluate the extent of the genetic influence and to examine the shared genetic effects between LBP and MRI-determined LDD. We found significant heritability for both LBP variables and LSUM. By LRT, the most parsimonious model (balancing fit of data with minimum complexity) displayed a significant heritability estimate of 43.5% (LBP1) to 68.2% (LSUM) of the residual variation adjusted for significant covariates. Both LBP1 and LBP1Q variables displayed highly significant (p<0.001) genetic correlations with LSUM (table 4). However, we found no common environmental factors simultaneously affecting LBP1 (or LBP_1Q) and LSUM variations.
The major aim of this study was to assess to what extent genetic factors and LDD contribute to reports of previous episodes of non-specific LBP within the middle-aged female population. As consistency is lacking in the association between back pain and the degeneration process of intervertebral discs, the substantial genetic component in LBP observed in variance component analysis is confirmed by concordance rates differing between the monozygotic and dizygotic twins (0.641 vs 0.375, p=0.018) and by multiple logistic regression analysis (table 3). In the total sample, the regression coefficient β for the dizygotic twin effect was 0.782±0.253 (with OR 2.19); however, if the sibling is monozygotic the effect was virtually twice as large (1.757±0.317, OR 5.79), and reliably significant, p=0.0009.

There was notable agreement between the results of multiple logistic regression of the risk of LBP and bivariate genetic analysis of the LSUM, weight and affected twin zygosity effect on individual probability to have LBP1 are shown in the supplementary table. There were 49% LBP1 individuals in the fourth quartile of LSUM distribution, compared with only 6.9% in the first. Comparison of the first affected monozygotic vs dizygotic twin effect on the probability that the second twin will have LBP1, were statistically reliably significant ($\chi^2=10.99$, df=1, p=0.0009).

Table 3  Multiple logistic regression of LBP taking into account LDD status effect

| Risk factor* | Coefficient | Standard error | Wald's $\chi^2$ | p Value | OR (95% CI) |
|--------------|-------------|----------------|---------------|--------|-------------|
| Constant     | -4.164      | 0.584          | 50.903        | <0.0001| –           |
| Regression coefficients |  |  |  |  |  |
| LSUM         | 0.061       | 0.013          | 21.801        | <0.0001| 1.063 (1.036 to 1.091) |
| Weight       | 0.021       | 0.008          | 6.773         | 0.0091 | 1.021 (1.005 to 1.037) |
| Exercise     | 0.461       | 0.120          | 5.319         | 0.0210 | 1.617 (1.074 to 2.435) |
| LBP(DZ_sib)  | 0.762       | 0.028          | 8.529         | 0.0020 | 2.186 (1.329 to 3.595) |
| LBP(MZ_sib)  | 1.757       | 0.317          | 30.777        | <0.0001| 5.794 (3.112 to 10.789) |

*All variables showing significant association with LBP_1 in the preliminary analysis (table 1) were included into a multiple logistic regression analysis. However, only variables making independent significant contributions are presented in the table. To account for contribution of the affection status of siblings in the logistic regression model, including twins of different zygosity, the following definitions were introduced: LBP(DZ_sib)=1 if an individual has affected dizygotic sibling, otherwise 0; LBP(MZ_sib)=1 if an individual has affected monzygotic sibling, otherwise 0.

† '90% vs 10%' means that OR was estimated contrasting the variable upper vs lower 10 percentiles of the distribution. The corresponding results of univariate analysis of the LSUM, weight and affected twin zygosity effect on individual probability to have LBP1 are shown in the supplementary table. There were 49% LBP1 individuals in the fourth quartile of LSUM distribution, compared with only 6.9% in the first. Comparison of the first affected monozygotic vs dizygotic twin effect on the probability that the second twin will have LBP1, were statistically reliably significant ($\chi^2=10.99$, df=1, p=0.0009).

DISCUSSION

The major aim of this study was to assess to what extent genetic factors and LDD contribute to reports of previous episodes of non-specific LBP within the middle-aged female population. As consistency is lacking in the association between back pain and the degeneration process of intervertebral discs, the major contribution of common genetic and non-genetic factors with their potential association are of interest. The main results of this study, summarised in figure 1, show a major contribution of the specific genetic factors to variation of the LBP1 and LDD phenotypes, respectively. This figure illustrates a potentially strong effect of LDD on LBP1 appearance, and also the extent of association of both LBP1 and LDD with common covariates. The major risk factors for LBP were genetic factors, which gave OR of approximately 6, if the monozygotic co-twin had LBP or 2.2 (if she was a dizygotic co-twin), being overweight and, the most important, the amount of MRI-determined LDD. Therefore, after adjustment for other risk factors, the individuals who exhibited advanced LDD (90% vs 10%) had 3.2 higher odds of manifesting LBP. The data also showed the existence of a significant genetic correlation between LBP and LSUM measurements. The $R^2_{AD}$ suggests that approximately 11–13% of the genetic effects were shared in this sample. Similar results were obtained when we tested binary trait LBP1, and with the semicontinuous trait LBP_1Q. The parameter estimates in these analyses (table 4) are probably not very accurate, but they are nevertheless highly significant by LRT. The substantial genetic component in LBP1 observed in variance component analysis is confirmed by concordance rates differing between the monozygotic and dizygotic twins (tetrachoric correlation in monozygotic vs dizygotic twins 0.641 vs 0.375, p=0.018) and by multiple logistic regression analysis (table 3). In the total sample, the regression coefficient β for the dizygotic twin effect was 0.782±0.253 (with OR 2.19); however, if the sibling is monozygotic the effect was virtually twice as large (1.757±0.317, OR 5.79), and reliably significant, p=0.0009.

There was notable agreement between the results of multiple logistic regression of the risk of LBP and bivariate genetic analysis (tables 3 and 4). The former suggests that the disc degeneration is a highly important risk factor for LBP (p<0.0001) and remains such in univariate and multivariate analyses, regardless...
of adjustment. While several studies have been equivocal in reporting an association between LDD and LBP, other studies of large samples find a convincing correlation between LBP and the severity of MRI LDD. In our study, age was a major risk factor for LDD, but of interest, it exerted no independent effect on the risk of reported episodes of LBP.

The present results are in good agreement with published limited data, including a previous study from TwinsUK suggesting a significant contribution of genetic factors to the variation of different indicators of LBP in adults. The latter study used several back pain definitions in male twins, and found substantially higher intraclass correlations for all of them in monozygotic twins (compared with dizygotic). These led to heritability estimates of 0.30–0.46, which are comparable to estimates obtained in the present study, but at odds with the findings in Finnish children that twins’ shared environment, and not genetic factors, is responsible for the similarity in LBP status. Contrary to this, and in agreement with other studies using adults, including a preliminary study of this sample, our estimates gave significantly higher tetrachoric correlations in monozygotic versus dizygotic twins (0.641 vs 0.575, p<0.02 for difference) and substantial estimates of heritability.

Our data are also in agreement with the Battie study with respect to a significant estimate of heritability for LHT and LBP, and genetic correlation between the two, despite the different assessment of LBP in the two studies. The studies agree that only a portion of the genetic effects on LBP was caused by genes governing the variation of MRI variables, and an even smaller portion by environmental factors shared by LBP and LSUM. This suggests the existence of specific genetic effects and additional risk factors for both LBP and LSUM. Of these, we highlight weight, which in our study showed that overweight individuals have a greater risk of LBP in comparison with lean women (table 3). Significant genetic association between LSUM and LBP may have an important implication for future studies. It may suggest the existence of common metabolic pathways leading to the manifestation of both phenotypes and thus direct research towards the specific candidate genes, such as those involved in the metabolism and ageing of nucleus pulposus. LBP and LDD is governed by some common, but mostly independent, genetic factors the nature of which remain to be determined.

Certain limitations can be recognised in this study. Based on a female sample the results should not be extrapolated to men—there is also less exposure to heavy manual work in our subjects. Although we are not aware of the sex-specific genetic effects for LBP, differences may exist in the physiological background, as well as in lifestyle. The second limitation is the cross-sectional design of the study to derive conclusions in an age-dependent condition. Finally, questionnaire assessment of pain is subjective and may not be fully comparable between studies. In the present project, however, there was a very strong association between different LBP measures, as seen in table 1, and a remarkable similarity in association between them and LDD variables in canonical correlation analysis (table 2).

In conclusion, this cross-sectional study of a large sample of female twins shows that in addition to genetic predisposition, episodes of LBP are strongly associated with the extent of LDD as assessed by MRI. In addition, genetic variation of LBP and LDD is governed by some but mostly independent genetic factors, the nature of which remain to be determined.

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