Heredity of Low Back Pain in a Young Population: A Classical Twin Study

Lise Hestbaek[1], Ivan A. Iachine[2], Charlotte Leboeuf-Yde[3], Kirsten Ohm Kyvik[4], and Claus Manniche[1]

[1] *The Back Clinic, Ringe, Denmark.*
[2] *Department of Statistics, University of Southern Denmark, Odense.*
[3] *The Medical Research Unit, Ringkjøbing County, Ringkøbing, Denmark.*
[4] *The Danish Twin Registry, University of Southern Denmark, Odense.*

Important genetic influence on intervertebral disc degeneration has been shown previously. However, the role of the disc in pain production is not clear and the genetic influence on the development of the symptoms of low back pain is largely unknown. Therefore, data on lifetime prevalence of low back pain from the young cohort in The Danish Twin Registry (aged 12–41) were analyzed with respect to heredity. Casewise concordance rates, odds ratios, tetrachoric correlation coefficients and biometric liability models were estimated in relation to gender and age. Finally, age-adjusted heritability of liability estimates were obtained. Both concordance rates and odds ratios show significant genetic influence on the liability to develop low back pain. Also, tetrachoric correlation coefficients show genetic influence, but this is not statistically significant for all age groups. The biometric modeling demonstrates shared environment to be a strong component in the youngest age group (12–15), but not above age 15, and it also demonstrates some non-additive genetic effects in the older age groups. Age-adjusted heritability of liability is estimated to 44% (37–50) for males and 40% (34–46) for females aged 16 to 41. Thus, the various analyses all demonstrate significant genetic influence on the liability to low back pain. The shared environment is an important component until age 15. After age 15, this component is unimportant. As people grow older, the effect of the non-shared environment increases and non-additive genetic effects become more evident, indicating an increasing degree of genetic interaction as age increases.

To date there has been extensive focus on the influence of external risk factors in the etiology of low back pain (LBP). However, such risk factors most likely only offer part of the explanation, since variation in LBP-status within populations with similar exposures is common. Rather, various risk factors are likely to affect people differently according to their physical shape, mental condition, social network, genetic make-up and other unknown factors (i.e., some people are more frail than others).

Previous studies have shown an important genetic influence on intervertebral disc degeneration, as identified by magnetic resonance imaging, in adolescents as well as in adults (Battié et al. 1995; Sambrook et al., 1999). However, the role of the disc in pain production is unknown (Boden et al., 1990; Elfering et al., 2002; Jensen et al., 1994). Thus, although the disc is a primary suspect of symptoms, all other spinal structures are capable of producing pain (Battié et al., 1995) and the presence of degenerative disc disease does not necessarily correlate with the presence of LBP. Heikkilä et al. (1989) estimated the relative role of genetic factors in sciatica to be up to 20% but, as with degenerative disc disease, results relating to sciatica cannot be directly extrapolated to all people with LBP, since only a small subgroup is considered. To our knowledge, the relative importance of genetic and environmental factors on non-specific LBP has only been investigated by Bengtsson and Thorson (1991). They analysed LBP of functional importance for work and found strong indications of genetic influence in the etiology of LBP.

For a disease of multifactorial etiology, such as LBP (Von Korff, 1994), the genetic component can be expected to have its effect mainly in younger age groups whereas environmental influences would dominate in the elderly (Järvinen & Aho, 1994). Therefore, genetic predisposition might be an important risk factor for early development of LBP.

This study will concentrate on the relative importance of genetic and environmental components on the development of non-specific LBP, with specific focus on adolescents, who are still largely unaffected by various occupational risk factors.

Methods

Material

Analyses were based on data from the youngest cohort of the population-based Danish Twin Registry, which includes data from 20,888 twin pairs aged 12 to

Address for correspondence: Lise Hestbaek, Drammelsbækvej 54, DK-8300 Odder, Denmark. Email: hestbaek@vip.cypercity.dk

https://doi.org/10.1375/twin.7.1.16 Published online by Cambridge University Press

41 years (Kyvik et al., 1996). Twin individuals can be regarded as a subset of the general population because they have been shown to have the same mortality (Christensen et al., 1995) and the same prevalence as the general population of most diseases (e.g., insulin-dependent diabetes) (Kyvik et al., 1995). A postal survey about general health, including information about past and present back pain, was conducted in 1994–1995, where 34,076 twins were available for questioning, with a response rate of 86% (29,424 participants). Because LBP usually is considered to have a different pattern in males and females, only like-sex twin pairs were included in this study, in order to keep our analyses free from gender confounding. This resulted in a data set of 19,075 individuals (3818 complete MZ twin pairs and 4469 complete DZ twin pairs).

The question of relevance for this study was: "Have you ever had problems with the lower part of your back?" Furthermore, the questions: "How many days have you altogether had problems with the lower part of your back during the past year?" and "Have you had any problems with the lower part of your back today?" were used to test internal validity. This was accompanied by a drawing, specifying the low back as the area between the lower ribs and the lower gluteal folds. Thus the main outcome was lifetime prevalence of LBP.

Zygosity was determined by questions of similarity and mistaken identity, a method that has been shown to have a misclassification rate of < 5% (Hauge, 1981).

Validation

The *internal* validity of the LBP-data was evaluated by identifying logical errors. This was done by cross-tabulating "LBP today" with "LBP past year" and "LBP past year" with "LBP ever".

Prevalence of LBP and Dependence on Age, Sex, and Zygosity

The twins registered in the Danish Twin Register have an identification number with either an "A"- or a "B"-suffix *randomly assigned*, thus "A" and "B" make up a twin pair. Estimation of tetrachoric coefficients using biometric models assumes symmetry of the LBP distribution (i.e., the distribution of LBP must be similar for twins with suffix A and twins with suffix B). This assumption was tested by means of the McNemar test. Likewise, the prevalence of LBP must be equal in MZ- and DZ twins and this was tested by means of logistic regression, adjusted for age. For comparing "A twins" with "B twins", prevalence rates were computed on an individual level, whereas for other purposes prevalence rates were estimated by formula (1), to take account of the dependency within pairs and thus avoiding the decreased power from using a split file including only half the data set (Witte, 1999).

(1): $P = (2n_{11}+n_d)/2n$, n_{11} = concordant pairs, n_d = discordant pairs

Dependence of LBP on age and sex was investigated and the significance of differences between sexes or age groups were established by the use of logistic regression. Significance tests were based on the robust Huber-White variance estimators to account for the dependence between the LBP-status of the twins, as implemented in the Stata statistical package (Stata Corp., 2001).

Based on the change in prevalence over age, the cohort was divided into age groups for further analyses, but since this study is part of an ongoing project about LBP in adolescents aged 12 to 22, one of the cut points was set pre-hoc at age 22. Dependence of zygosity on age and sex was investigated and the significance of differences in the percentages of MZ and DZ twins in different sex and age groups were established by the use of logistic regression.

Casewise Concordance Rates

These were calculated with 95% confidence intervals as suggested by formula 6 on page 293 in Witte et al. (1999). In this case there was complete ascertainment and therefore the casewise concordance rates are similar to the probandwise concordance rates. Due to dependency on population prevalence, the concordance rates are presented alongside the lifetime prevalence rates of LBP.

Odds Ratios

Odds ratios have some advantages over concordance rates. Unlike concordance rates, they are not affected by the background rate of disease in the population and odds ratios also consider the information from concordantly unaffected pairs. First, odds ratios for having LBP in case of an affected co-twin, regardless of zygosity, were calculated for each year of birth and presented as a graph to illustrate the change with age. Next, zygosity-specific odds ratios were calculated for each age- and sex-group including 95% confidence intervals as described by Ramakrishnan et al. (1992), using twin "A" as the index twin. Common odds ratios for MZ and DZ pairs within each age- and sex-group as well as for the total sample, including 95% confidence intervals, were also calculated. Additionally, the MZ and DZ odds ratios were compared.

Tetrachoric Correlation Coefficients and Biometric Modeling

Due to the dichotomous nature of the outcome, tetrachoric correlation coefficients (i.e., correlation coefficients of liability to LBP) were estimated for MZ and DZ twin-pairs (rMZ and rDZ). Furthermore, biometric modeling (path analysis) was done and the ACE, ADE, DCE, AE, DE, CE and E models were fitted to the data (Neale, 1998). For comparisons of non-nested models the Akaike Information Criterion (AIC) was used (Akaike, 1987).

Age-adjusted Heritability Estimates

Finally an age-adjusted estimate of heritability of liability based on the maximum likelihood method was calculated by using the bivariate probit model. This

https://doi.org/10.1375/twin.7.1.16 Published online by Cambridge University Press

model is based on the assumption of an underlying bivariate normal liability distribution. An individual is affected if the respective individual liability variable exceeds a certain threshold. It is assumed that genetic and environmental influences on the LBP status are mediated through the liability variable. To account for the changing LBP prevalence the liability variable is allowed to depend on age by means of a linear regression model. This approach allows for simultaneous estimation of heritability of liability and the marginal effects of age (Kohler & Rodgers, 1999). It is based on DeFries' and Fulker's (1985) regression procedure for estimating heritability, and is used to avoid an inflated estimate of the effect of shared environment due to a general increase in LBP prevalence with increasing age. The estimation procedure has been implemented by Kohler and Rodgers in Stata 7 statistical software package.

The age-group specific tetrachoric correlation coefficients and biometric model estimates were computed using the Mx software package (Neale, 1995). All other analyses were performed using the Stata statistical software package 7.0 with the inclusion of a program for "DF-like" analysis of binary, ordered and censored variables using probit and tobit approaches (Kohler & Rodgers, 1999). Statistical significance was defined as $p < .05$.

Results

Validation

The cross-tabulations between different LBP-parameters demonstrate an acceptable agreement. Only 181/18,649 answered "yes" to "Do you have LBP today" while reporting to have had LBP 0 days during the past year. Conversely, of those reporting never having had LBP in the past 222/18,923 said that they had LBP during the past year. This gives a definitely unacceptable response in 1% of the cases (181/18,649 and 222/18,923), which we consider to be an acceptable level of illegal answers in a questionnaire survey.

Prevalence of LBP and Dependence on Age, Sex and Zygosity

There is a significant increase in the lifetime prevalence rates of LBP with increasing age ($p < .001$). Furthermore, LBP is significantly more common among females than males for all ages combined ($p < .001$), but not in the oldest age group ($p = .650$). Lifetime prevalence by age and sex is graphically presented in Figure 1. There is a strong increase in prevalence from age 12 to 22, therefore this age group is further subdivided into: 12–14, 15–18 and 19–22. After age 22 there is only a slight increase, and thus this group is only divided into two subgroups: 23–32 and 33–41. The prevalence of LBP is 55.1% (54.1–56.1) for twins with suffix A and 54.6% (53.6–55.6) for those with suffix B ($p = .3640$) (i.e., the dataset is symmetric). This is true when testing across all age groups as well as within age groups. Likewise, zygosity does not affect the LBP-prevalence when adjusted for age ($p = .884$), but the overall prevalence is higher among DZ twins (55.0% (53.7–56.4) vs. 52.2% (50.7–53.7) in MZ twins). This difference is due to an increase in the proportion of DZ twins with age, combined with increasing prevalence of LBP with age.

Dependence of Zygosity on Age and Sex

The results indicate that MZ/DZ ratio varies with age and sex. The proportion of DZ twins increases with age (from 53% (50–55) in age group 1 to 62% (61–64) in age group 5, $p < .001$) and there is an overrepresentation of females among monozygotic twins (54% (53–55) of MZ twins are females, $p < .001$). This is accounted for by presenting results stratified for age and sex.

Concordance Rates

The number of concordant and discordant pairs can be seen in Table 1 alongside the case wise concordance

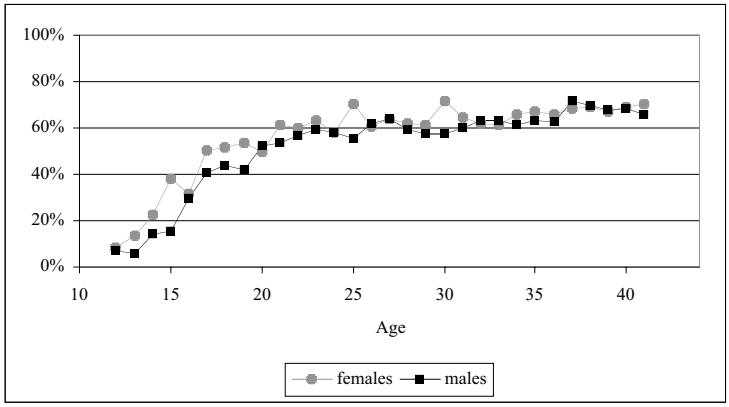

Figure 1
Lifetime prevalence of LBP.

https://doi.org/10.1375/twin.7.1.16 Published online by Cambridge University Press

rates (Pc). Casewise concordance rates are 7–49% higher for MZ twins than DZ twins, with the difference slightly decreasing as the Pc increases with age.

Odds Ratios

The overall odds ratios for LBP in case of an affected co-twin decreases rapidly from age 12 to age 19, but remains fairly stable thereafter. Odds ratios are similar for males and females. The odds ratios for MZ twins are 2–3 times higher than for DZ twins in all age groups, except females aged 15–18, where the OR is increased six fold for MZ twins. The common odds ratio for each age- and sex group is significantly above one, with the common odds ratio for the whole sample being 3.35 (3.06–3.67), indicating a definite familial disposition. The difference between MZ and DZ twins is also statistically significant for all groups, and the difference between MZ and DZ twins across all age- and sex-groups is 2.76 (2.30–3.32), which indicates genetic influence. Age group-, sex- and zygosity-specific odds ratios are shown in Figure 2a and 2b.

Tetrachoric Correlations

There is an inverse relationship between age and the tetrachoric correlation coefficients which may be interpreted as a decrease of genetic and familial effects on the liability to LBP with age. The differences between MZ and DZ correlations are statistically significant, except for the youngest age group and males aged 19 to 22. Exact results are presented in Table 1. When rMZ equals rDZ there is no genetic components, when rDZ is half of rMZ, it illustrates a perfect additive model, the AE-model, and when rDZ is one quarter of rMZ it indicates a dominant genetic influence, the DE-model. Figures 3a and 3b shows rDZ in relation to rMZ, indicating which models gives the best fit for different age- and sex groups. One quarter and one half of the respective rMZs are shown in the figures and the DZ correlations are added. Thus, the best-fitting model can be determined on basis of the placement in relation to the three rMZ-graphs. This shows a change from an ACE- in the youngest age-group, via an AE-model, to a DE-model in the oldest age-group. There is a rather strong c^2-component for the 12- to 15-year-olds, hardly any c^2-components for the older age-groups, and more dominant genetic effects with age.

The only component present in all models is the non-shared environment (e^2), thus this is used in Figure 4 to illustrate the increasing importance of the

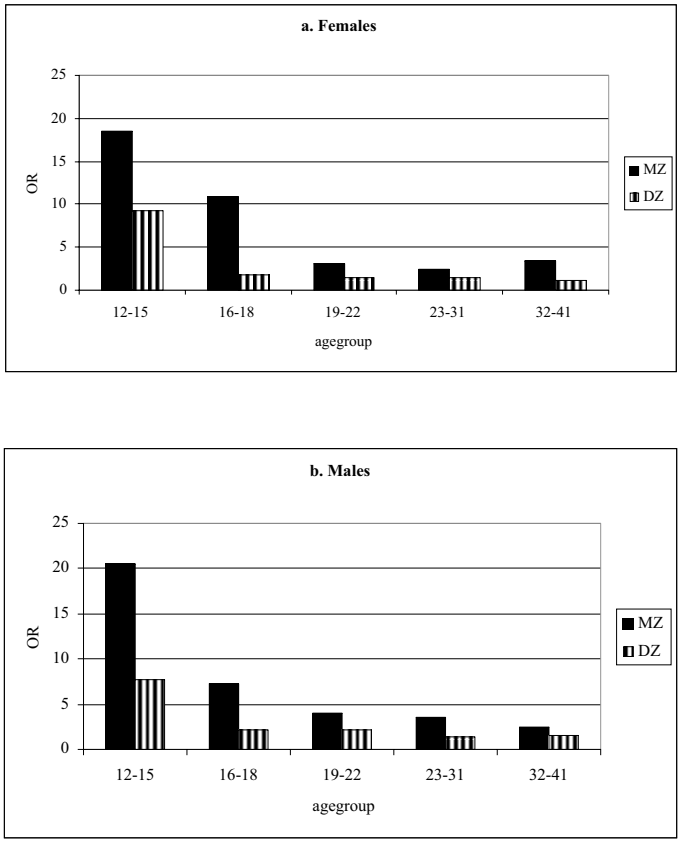

Figure 2a–b

Odds ratios for having LBP if the co-twin is affected by sex, age, and zygosity.

https://doi.org/10.1375/twin.7.1.16 Published online by Cambridge University Press

Table 1

Lifetime Prevalence of LBP, Casewise Concordance Rates, and Tetrachoric Correlations by Age Group, Sex, and Zygosity

Age	Zygosity and sex	*n* (individuals)	Lifetime prevalence of LBP (95%CI)	Concordant pairs	Discordant pairs	Casewise concordance rates (95%CI)	Tetrachoric correlation (*r*) (95%CI)	$r_{mz} = r_{dz}$ *p*
12–15	MZ-m	514	11% (8–15)	16	26	0.55 (0.40–0.71)	0.77 (0.59–0.89)	0.617
	DZ-m	576	10% (7–14)	11	37	0.37 (0.27–0.53)	0.58 (0.33–0.76)	
	MZ-f	514	21% (17–26)	36	38	0.65 (0.55–0.76)	0.80 (0.67–0.89)	0.500
	DZ-f	556	21% (17–26)	33	53	0.55(0.45–0.66)	0.67 (0.51–0.80)	
16-18	MZ-m	456	35% (29–41)	50	59	0.63 (0.54–0.72)	0.64 (0.49-0.77)	0.005
	DZ-m	400	42% (35–48)	44	79	0.53 (0.44–0.62)	0.30 (0.08–0.49)	
	MZ-f	526	45% (40–51)	89	61	0.74 (0.68–0.81)	0.74 (0.62–0.84)	0.001
	DZ-f	326	42% (35–49)	35	68	0.51 (0.41–0.61)	0.23 (–0.01–0.45)	
19–22	MZ-m	514	49% (43–55)	83	86	0.66 (0.59–0.73)	0.50 (0.33–0.64)	0.364
	DZ-m	528	52% (47–58)	85	107	0.61 (0.55–0.68)	0.29 (0.11–0.46)	
	MZ-f	704	57% (52–62)	137	126	0.69 (0.63–0.74)	0.42 (0.26–0.55)	0.032
	DZ-f	578	56% (50–61)	95	131	0.59 (0.53–0.66)	0.13 (–0.05–0.31)	
23–32	MZ-m	1106	58% (54–62)	225	188	0.71 (0.67–0.75)	0.46 (0.34–0.57)	0.000
	DZ-m	1466	61% (58–64)	284	326	0.64 (0.60–0.67)	0.11 (–0.01–0.22)	
	MZ-f	1588	63% (60–67)	357	292	0.71 (0.68–0.74)	0.32 (0.22–0.40)	0.000
	DZ-f	1794	64% (61–67)	386	377	0.67 (0.64–0.70)	0.16 (0.05–0.26)	
33–41	MZ-m	878	67% (63–72)	219	154	0.74 (0.70–0.78)	0.17 (0.06–0.29)	0.000
	DZ-m	1366	65% (61–68)	301	283	0.68 (0.64–0.72)	0.03 (–0.11–0.16)	
	MZ-f	836	64% (59–68)	198	138	0.74 (0.70–0.78)	0.44 (0.30–0.57)	0.000
	DZ-f	1348	68% (65–71)	317	285	0.69 (0.66–0.72)	0.04 (–0.08–0.17)	

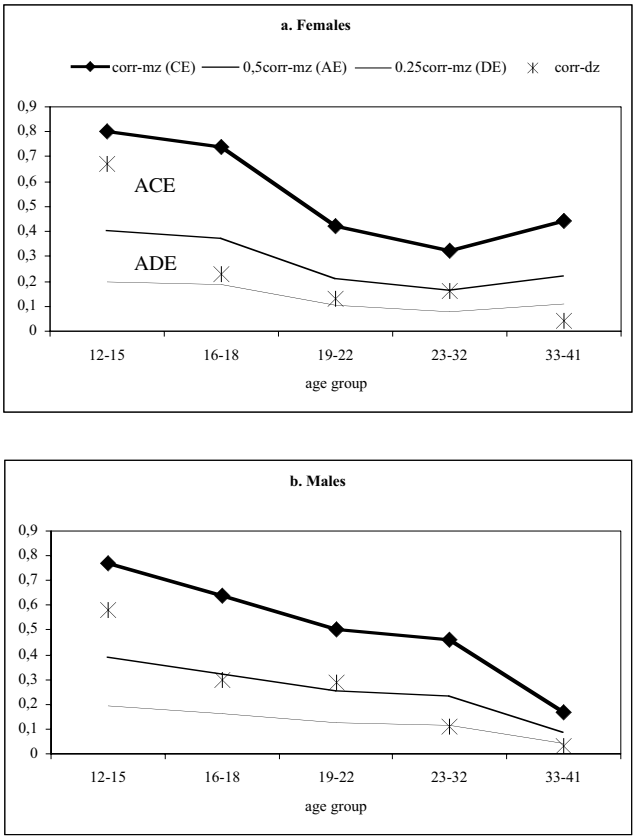

Figure 3a–b

Tetrachoric correlations for MZ twins in relation to DZ twins in a figure indicating the best-fitting models.

https://doi.org/10.1375/twin.7.1.16 Published online by Cambridge University Press

non-shared environment, reflecting the decrease in genetic influence, with age.

Biometric Modeling

Like the correlation coefficients, the biometric modeling shows a strong c^2-component in the youngest age group (age 12–15), which is not the case for the rest of the cohort. Therefore, the CE-model gives the best fit for females and the ACE/DCE-model the best fit for males aged 12–15. To test if the effect of common environment was inflated by the large increase in LBP-prevalence with age within the youngest age group, the modeling was done separately for each year of birth within that age group (1979–1982), but all ages still yielded significant c^2-values (data not shown). After age 15 the best fit is a DE- or an AE-model, with the AE-model having the best overall fit. The variance components and the model fit statistics can be seen in Table 2. The biometric modeling shows that the observed LBP pattern is consistent with the presence of genetic influence on liability to LBP with heritability values ranging from 24% to 85%. Figure 5 shows the combined effect of additive and dominant genetic components, according to the best-fitting model for each age group. The heritability estimate does not change much in females after age 22, whereas there seems to be a decrease with age in males across the whole sample, although there is a considerable overlap of the confidence intervals.

Age-adjusted Heritability Estimate

Since the youngest age group displays a very different pattern of heritability from the rest, there is no point in making overall estimates for the whole cohort. Therefore the youngest age group has been excluded and the age-adjusted heritability for the group aged 16 to 41 calculated. Because the AE-model shows the best overall fit above age 16, this is used to estimate the age-adjusted heritability by applying a DF-like method. In this way the age-adjusted heritability of liability is estimated to 40% (34–46) for females aged 16 to 41 and 44% (37–50) for males in the same age group.

Discussion

Our findings demonstrate a considerable genetic influence on the etiology of LBP with age-adjusted heritability measures above 40%. Common environment seems to be a strong component in the youngest age group, aged 12 to 15, whereas it is almost non-existing in the older age groups. This implies that the common environment mainly has an effect while the children actually live in the same environment, whereas they do not carry the effect with them after leaving home (no spill-over effect). As adolescents

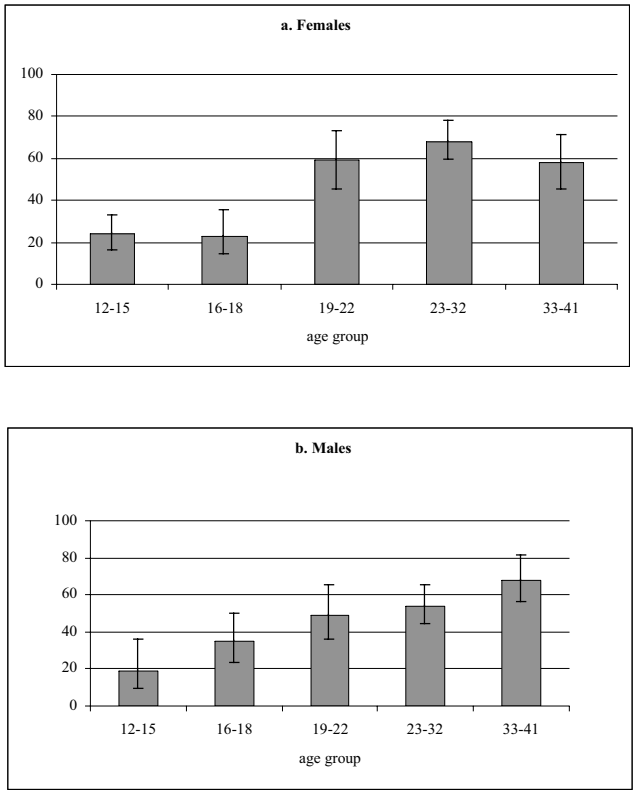

Figure 4a–b

e^2 according to the best-fitting model based on AIC, by sex and age group.

https://doi.org/10.1375/twin.7.1.16 Published online by Cambridge University Press

Table 2

Biometrical Models for LBP: Variance Components and Model Fit Statistics by Age Group, Sex and Zygosity (The Lowest AIC (Indicating the Best-fitting Model) for Each Group Indicated with Bold Characters)

Age	Sex	Component	ACE	ADE	DCE	AE	DE	CE	E
12–15	Female	a^2	0.26 (0.00–0.63)	0.85 (0.63–0.92)	—	0.85 (0.76–0.92)	—	—	—
		d^2	—	0.00 (0.00–0.22)	0.15 (0.00–0.38)	—	0.83 (0.68–0.92)	—	—
		c^2	0.56 (0.22–0.81)	—	0.67 (0.46–0.82)	—	—	0.76 (0.67–0.84)	—
		e^2	0.18 (0.10–0.31)	0.15 (0.08–0.47)	0.18 (0.10–0.31)	0.15 (0.08–0.24)	0.17 (0.08–0.32)	0.24 (0.16–0.33)	1.00 (1.00–1.00)
		AIC	–5.412	6.225	–5.412	4.225	0.828	–5.805	116.898
	Male	a^2	0.45 (0.00–0.90)	0.83 (0.27–0.92)	—	0.83 (0.68–0.92)	—	—	—
		d^2	—	0.00 (0.00–0.56)	0.30 (0.00–0.66)	—	0.85 (0.74–0.92)	—	—
		c^2	0.36 (0.00–0.76)	—	0.51 (0.18–0.76)	—	—	0.70 (0.56–0.81)	—
		e^2	0.19 (0.09–0.36)	0.17 (0.08–0.32)	0.19 (0.09–0.36)	0.17 (0.08–0.32)	0.15 (0.08–0.26)	0.30 (0.19–0.44)	1.00 (1.00–1.00)
		AIC	–5.529	–3.521	–5.529	–5.521	21.863	–4.394	77.908
16–18	Female	a^2	0.75 (0.48–0.84)	0.14 (0.00–0.82)	—	0.75 (0.63–0.84)	—	—	—
		d^2	—	0.62 (0.00–0.86)	0.72 (0.38–0.86)	—	0.77 (0.65–0.86)	—	—
		c^2	0.00 (0.00–0.24)	—	0.05 (0.00–0.35)	—	—	0.59 (0.47–0.69)	—
		e^2	0.25 (0.16–0.37)	0.23 (0.14–0.35)	0.23 (0.14–0.35)	0.25 (0.16–0.37)	0.23 (0.14–0.35)	0.41 (0.31–0.53)	1.00 (1.00–1.00)
		AIC	–2.831	–4.500	–4.500	–4.831	–6.417	12.406	54.601
	Male	a^2	0.65 (0.18–0.77)	0.58 (0.00–0.77)	—	0.65 (0.50–0.77)	—	—	—
		d^2	—	0.07 (0.00–0.76)	0.46 (0.13–0.76)	—	0.67 (0.52–0.79)	—	—
		c^2	0.00 (0.00–0.38)	—	0.19 (0.00–0.46)	—	—	0.50 (0.36–0.61)	—
		e^2	0.35 (0.23–0.51)	0.34 (0.22–0.50)	0.34 (0.22–0.51)	0.35 (0.23–0.50)	0.33 (0.21–0.48)	0.50 (0.39–0.64)	1.00 (1.00–1.00)
		AIC	1.808	1.782	1.782	–0.192	1.559	7.055	49.814
19–22	Female	a^2	0.39 (0.03–0.52)	0.18 (0.00–0.52)	—	0.39 (0.25–0.64)	—	—	—
		d^2	—	0.23 (0.00–0.55)	0.35 (0.04–0.54)	—	0.41 (0.27–0.55)	—	—
		c^2	0.00 (0.00–0.29)	—	0.06 (0.00–0.30)	—	—	0.29 (0.17–0.40)	—
		e^2	0.61 (0.36–0.67)	0.59 (0.36–0.65)	0.59 (0.45–0.75)	0.61 (0.48–0.75)	0.59 (0.45–0.73)	0.71 (0.60–0.83)	1.00 (1.00–1.00)
		AIC	0.414	0.089	0.089	–1.586	–1.678	7.055	23.367
	Male	a^2	0.44 (0.00–0.64)	0.51 (0.00–0.64)	—	0.51 (0.35–0.64)	—	—	—
		d^2	—	0.00 (0.00–0.61)	0.29 (0.00–0.61)	—	0.52 (0.36–0.66)	—	—

https://doi.org/10.1375/twin.7.1.16 Published online by Cambridge University Press

Table 2 continued

Age	Sex	Component	ACE	ADE	DCE	AE	DE	CE	E
19–22	Male	c^2	0.06 (0.00–0.44)	—	0.21 (0.00–0.44)	—	—	0.39 (0.27–0.51)	—
		e^2	0.50 (0.36–0.67)	0.49 (0.36–0.65)	0.50 (0.36–0.67)	0.49 (0.36–0.65)	0.48 (0.34–0.64)	0.61 (0.49–0.74)	1.00 (1.00–1.00)
		AIC	–4.157	–4.064	–4.157	–6.064	–3.619	–3.040	28.741
23–32	Female	a^2	0.32 (0.07–0.41)	0.24 (0.00–0.41)	—	0.32 (0.22–0.41)	—	—	—
		d^2	—	0.09 (0.00–0.42)	0.25 (0.05–0.42)	—	0.34 (0.24–0.44)	—	—
		c^2	0.00 (0.00–0.21)	—	0.08 (0.00–0.22)	—	—	0.23 (0.16–0.31)	—
		e^2	0.57 (0.26–0.64)	0.67 (0.57–0.77)	0.67 (0.57–0.78)	0.68 (0.59–0.78)	0.66 (0.56–0.76)	0.77 (0.69–0.84)	1.00 (1.00–1.00)
		AIC	–4.720	–4.854	–4.854	–6.720	–5.696	–0.890	31.982
	Male	a^2	0.41 (0.25–0.51)	0.00 (0.00–0.44)	—	0.41 (0.30–0.51)	—	—	—
		d^2	—	0.46 (0.00–0.56)	0.46 (0.26–0.56)	—	0.46 (0.35–0.56)	—	—
		c^2	0.00 (0.00–0.11)	—	0.00 (0.00–0.15)	—	—	0.27 (0.18–0.35)	—
		e^2	0.59 (0.49–0.70)	0.54 (0.44–0.66)	0.54 (0.44–0.66)	0.59 (0.49–0.70)	0.54 (0.44–0.65)	0.73 (0.65–0.82)	1.00 (1.00–1.00)
		AIC	3.784	0.197	0.197	1.784	–1.803	15.994	5.182
33–41	Female	a^2	0.36 (0.19–0.48)	0.00 (0.00–0.33)	—	0.36 (0.23–0.48)	—	—	—
		d^2	—	0.42 0.05–0.55)	0.42 (0.00–0.46)	—	0.42 (0.29–0.55)	—	—
		c^2	0.00 (0.00–0.10)	—	0.09 (0.00–0.26)	—	—	0.21 (0.11–0.31)	—
		e^2	0.64 (0.52–0.77)	0.58 (0.45–0.71)	0.58 (0.45–0.71)	0.64 (0.52–0.77)	0.58 (0.45–0.65)	0.46 (0.34–0.55)	1.00 (1.00–1.00)
		AIC	4.618	–0.054	–0.053	2.618	–2.054	13.413	29.641
	Male	a^2	0.32 (0.00–0.44)	0.27 (0.00–0.44)	—	0.32 (0.19–0.44)	—	—	—
		d^2	—	0.06 (0.00–0.46)	0.24 (0.00–0.46)	—	0.35 (0.21–0.79)	—	—
		c^2	0.00 (0.00–0.25)	—	0.09 (0.00–0.26)	—	—	0.22 (0.12–0.31)	—
		e^2	0.57 (0.00–0.66)	0.67 (0.63–0.81)	0.67 (0.53–0.82)	0.68 (0.56–0.81)	0.65 (0.52–0.79)	0.78 (0.69–0.89)	1.00 (1.00–1.00)
		AIC	–3.282	–3.324	–3.324	–5.282	–4.237	–1.959	16.015

become adults, the influence from the non-shared environment increases in relation to the genetic components. A strong component of this effect may be work-related when the grown-up twins obtain different employment. There seems to be some genetic dominance for LBP above age 15, which becomes stronger with age. However, since a full ADCE-model cannot be estimated, the division of the total hereditary components into A and D components is highly speculative, but we can conclude that there is evidence of non-additive genetic effects, maybe indicating an increasing degree of genetic interaction with increasing age.

The major strengths of our study are the large sample size and the possibility of studying the change in the determinants of LBP with age. It turned out, not unexpectedly, that the relative contributions of hereditary and environmental components to the

https://doi.org/10.1375/twin.7.1.16 Published online by Cambridge University Press

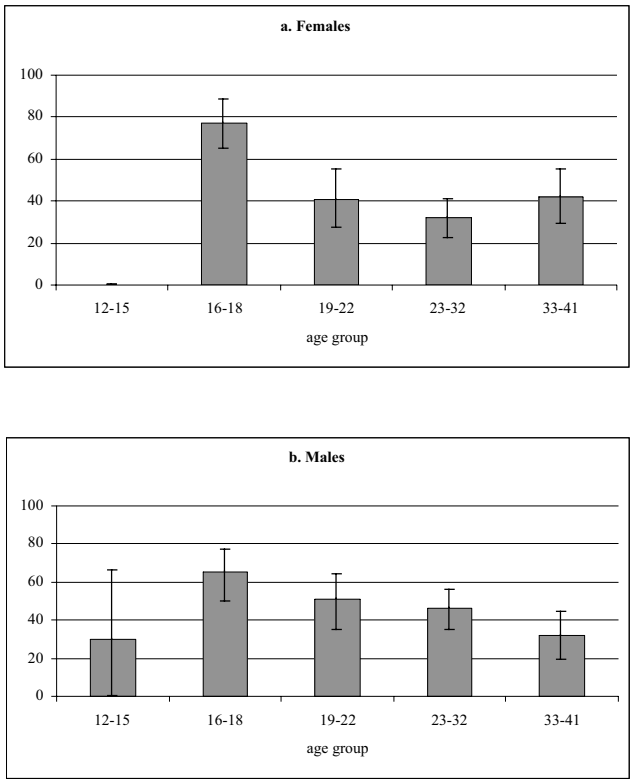

Figure 5a–b

H^2 ($a^2 + d^2$) = genetic determination/broad sense heritability according to the best fitting model, by sex and age group.

liability to develop LBP differ in relation to age, but not in relation to sex. In a future study, male and female data could be modeled separately in the same analysis and data from opposite sex twin-pairs could be included. This way the issues of sex differences and sex limitations could be explored in more detail.

One of the conditions for the results to be extrapolated to the general population is that the prevalence must be the same for twins and singletons. The 1-year prevalence rate of the 30- to 40-year-old part of our cohort is 54%, which corresponds well with the findings of a previous study of a Danish 30- to 50-year-old general population who had a 1-year prevalence of 56% (Hestbaek, 2003). Other studies of general populations in the Nordic countries (Leboeuf & Lauritzen, 1995) have shown similar prevalences. Furthermore, the cohort has previously been shown to be comparable to the general population with respect to morbidity and mortality (Christensen et al., 1995; Kyvik et al., 1995). In our cohort we found some dependency of zygosity on sex and age, but this was compensated for by stratifying the data by sex and age, since LBP prevalence is independent of zygosity when adjusted for sex and age. It is also important that the zygosity diagnosis is accurate. In the Danish Twin Register the error rate has been estimated to less than 5% (Hauge, 1981), which we consider to be satisfactory for our purposes. Another important consideration is the equal environment assumption. However, we consider this assumption to be satisfyingly supported (Kyvik, 2000).

Our "diagnosis" might also be considered problematic by some. However, we consider the broad diagnosis of unspecific LBP as a strength. Previous studies have investigated disc degeneration (Battié et al., 1995; Elfering et al., 2002; Sambrook et al., 1999) or sciatica (Heikkilä, 1989), which both are subgroups of LBP, which may or may not have the same etiology as other types of LBP-disorders. LBP can rarely be diagnosed specifically (Deyo, 1993), and trying to categorize study-subjects into specific LBP-diagnoses could be a source of error rather than precision.

There is no previous research into the genetic influence on non-specific LBP in young populations. Bengtsson and Thorson (1991), estimated concordance rates for LBP of functional importance in twins, aged 15–47, from the Swedish Twin Register and found strong indications that genetic factors are of importance for LBP. They demonstrated concordance rates within MZ pairs to be 37%–100% higher than in DZ pairs. Other previous studies have been concerned with disc degeneration (Battié et al., 1995; Matsui, 1998; Sambrook et al., 1999), reporting familial history of operated lumbar disc herniation to have a

https://doi.org/10.1375/twin.7.1.16 Published online by Cambridge University Press

significant implication in lumbar degenerative disc disease (Matsui, 1998) and that co-twin status accounted for 54% of the variance in lumbar degenerative disc disease (Battié et al., 1995). The only study, to our knowledge, which has performed path analysis in relation to the back investigated heritability of intervertebral disc degeneration as assessed by MRI. They found an AE model to be the most parsimonious and gave heritability estimates of 63% to 74% (Sambrook et al., 1999). However, they only included 172 MZ and 154 DZ twins and did not stratify for age, thus a possible dominant effect could be hidden within the overall age-adjusted results. Furthermore, as mentioned previously, the role of the disc in pain production is largely unknown (Battié et al., 1995).

Our results are consistent with previous findings, indicating that the influence of genetic factors decreases with age in disorders of multifactorial origin (Järvinen, 1994). Therefore, it is very important for future research to stratify analyses by age. A future scientific challenge is to determine whether LBP in subjects with a high genetic liability becomes more severe than LBP with a more environmentally based etiology. This could be indicated if those with an early onset are more prone to chronicity/disability later in life than those with late onset-LBP.

Conclusion

The various analyses all demonstrate significant genetic influence on the liability to LBP with an increasing effect of the non-shared environment as people grow older. It remains to be seen whether the more severe and long-lasting cases of LBP have an earlier onset than the less severe and/or transient cases. If this is the case, it might indicate that genetic components have a stronger influence on the liability of severe LBP whereas the transient cases may be more environment-determined. Therefore, analyses of subgroups of LBP should be performed in the future.

Acknowledgments

The first author was funded by The Foundation for Chiropractic Research and Postgraduate Education, Denmark.

References

Akaike, H. (1987). Factor analysis and AIC. *Psychometrika, 52*(3), 317–332.

Battié, M. C., Videman, T., Gibbons, L. E., Fisher, L. D., Manninen, H., & Gill, K. (1995). Determinants of lumbar disc degeneration. A study relating lifetime exposures and magnetic resonance imaging findings in identical twins. *Spine, 20,* 2601–2612.

Bengtsson, B., & Thorson, J. (1991). Back pain: A study of twins. *Acta Geneticae Medicae et Gemellologiae, 40,* 83–90.

Boden, S. D., Davis, D. O., & Diana, T. S., et al. (1990). Abnormal magnetic resonance scans of the lumbar spine in asymptomatic subjects. *Journal of Bone and Joint Surgery [Ame], 72,* 403–408.

Christensen, K., Vaupel, J. W., Holm, N. V., & Yashin, A. (1995). Mortality among twins after age 6: Fetal origins hypothesis versus twin-method. *British Medical Journal, 310,* 432–436.

DeFries, J., & Fulker, D. (1985). Multiple regression analysis of twin data. *Behavior Genetics, 15,* 467–473.

Deyo, R. A. (1993). Practice variations, treatment fads, rising disability. Do we need a new clinical research paradigm? *Spine, 18,* 2153–2162.

Elfering, A., Semmer, N., Birkhofer, D., Zanetti, M., Hodler, J., & Boes, N. (2002). Risk factors for lumbar disc degeneration: A 5-year prospective magnetic resonance imaging study in asymptomatic individuals. *Spine, 27,* 125–134.

Gao, X. J., Klar, N., & Donner, A. (1997). Comparison of methods for analyzing binary data arising from two-sample twin studies. *Genetic Epidemiology, 14,* 349–363

Hauge, M. (1981). The Danish twin register. In S. A. Mednich, A. E. Baert, & B. P. Bachmann (Eds.), *Prospective longitudinal research* (pp. 217–222). Oxford: Oxford Medical Publications.

Heikkilä, J. K., Koskenvuo, M., & Heliövaara, M., et al. (1989). Genetic and environmental factors in sciatica. Evidence from a nationwide panel of 9365 adult twin pairs. *Annals of Medicine, 21,* 393–398.

Hestbaek, L., Leboeuf-Yde, C., Engberg, M., Lauritzen, T., Bruun, N. H., & Manniche, C. (in press). The course of low back pain in a general population. Results from a five-year prospective study. *Journal of Manipulative Physiological Therapy.*

Järvinen, P., & Aho, K. (1994). Twin studies in rheumatic diseases. *Seminars in Arthritis and Rheumatism, 24,* 19–28.

Jensen, M. C., Brant-Zawadski, M. N., Obuchowski, N., Mdic, M. T., Malkasian, D., & Ross, J. S. (1994). Magnetic resonance imaging of the lumbar spine in people without back pain. *New England Journal of Medicine, 331,* 69–73.

Khoury, M. J., Beaty, T. H., & Cohen, B. H. (1993). Fundamentals of genetic epidemiology. Oxford: Oxford University Press.

Kohler, H. P., & Rodgers, J. L. (1999). DF-like analyses of binary, ordered and censored variables using probit and tobit approaches. *Behavior Genetics, 29*(4), 221–232.

Kohler, H. P., & Rodgers, J. L. (2003). Programs for DF-like analyses of binary, ordered and censored variables using probit and tobit approaches. http://user.demogr.mpg.de/kohler.

Kyvik, K. O., Christensen, K., Skytthe, A., Harvald, B., & Holm, N. V. (1996). The Danish Twin Register. *Danish Medical Bulletin, 43,* 467–470.

Kyvik, K.O., Green, A., & Beck-Nielsen, H. (1995). Concordance rates of insulin-dependent diabetes

mellitus. A population based study of young Danish twins. *British Medical Journal, 311,* 913–917.

Kyvik, K. O. (2000). Generalizability and assumptions of twin studies. In T. D. Spector, H. Snieder, & A. MacGregor (Eds.), *Advances in twin and sib-pair analysis* (p. 72). Oxford: Oxford University Press.

Leboeuf-Yde, C., & Lauritzen, J. M. (1995). The prevalence of low back pain in the literature. A structured review of 26 Nordic studies from 1954 to 1993. *Spine, 20,* 2112–2118.

Matsui, H., Kanamori, M., Ishihara, H., Yudoh, K., Naruse, Y., & Tsuji, H. (1998). Familial predisposition for lumbar degenerative disc disease. *Spine, 23,* 1029–1034.

Neale, M. C. (1995). *Mx: Statistical modeling* (3rd ed.). Richmond: Medical College of Virginia, Virginia Commonwealth University.

Neale, M. C. (1998). Twin analysis. In P. Arbitrage, & T. Colton (Eds.), *Encyclopaedia of biostatistics* (6th ed.; pp. 4614–1616). London: Wiley.

Ramakrishnan, V., Goldberg, J., Henderson, W. G., Elisen, S. A., True, W., Lyons, M. J., & Tsuang, M. T. (1992). Elementary methods for the analysis of dichotomous outcomes in unselected samples of twins. *Genetic Epidemiology, 9,* 273–287.

Sambrook, P. N., MacGregor, A. J., & Spector, T. D. (1999). Genetic influences on cervical and lumbar disc degeneration. A magnetic resonance imaging study in twins. *Arthritis and Rheumatism, 42,* 366–372.

Todorov, A. A., & Suarez, B. K. (1998). Genetic liability model. In P. Armitrage, & T. Colton (Eds.), *Encyclopaedia of biostatistics* (6th ed; pp. 1680–1685). London: Wiley.

Von Korff, M. (1994). Studying the natural history of low back pain. *Spine, 19*(18S), 2041S–2046S.

Witte, J. S., Carlin, J. B., & Hopper, J. L. (1999). Likelihood-based approach to estimating twin concordance for dichotomous outcome. *Genetic Epidemiology, 15,* 290–304.

https://doi.org/10.1375/twin.7.1.16 Published online by Cambridge University Press