Heritability of neck pain: a population-based study of 33 794 Danish twins

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Objectives. To determine the heritability of neck pain in a large population-based study of twins.

Methods. Data on lifetime prevalence of neck pain from a population-based cross-sectional survey of Danish twins were used. To assess twin similarity, the probandwise concordance rates, zygosity-specific odds ratios and tetrachoric correlations were calculated and compared for monozygotic and dizygotic twins. Using biometric modelling (structural equation modelling), the genetic and environmental contributions of the liability to neck pain were estimated.

Results. A total of 33 794 twins (response rate 73%) answered the questions regarding neck pain. Probandwise concordance rates, zygosity-specific odds ratios and tetrachoric correlations showed a significant genetic effect on neck pain. An overall additive genetic component of 44% was found. The genetic effect decreased with age, accounting for only 10% in the oldest male group and 0% in the oldest female group. There was a statistically significant difference in heritability between males and females (34% vs 52%, \( P < 0.0001 \)).

Conclusions. Genes play a significant role in neck pain, particularly in women. However, the genetic influence becomes gradually less important with increasing age, and environmental factors dominate almost completely in the older age groups.

Key words: Neck pain, Heritability, Genes, Environment, Twin study, Prevalence, Cross-sectional, Survey, Questionnaire.

Neck pain (NP) is very common in Western countries, where more than one in two adults have had NP during their lifetime [1, 2]. Neck pain is a great socio-economic burden in terms of sick leave, disability and workers’ compensation benefits [3–6], and it is therefore important to study what causes NP in order to identify possible preventive measures. Studies on the aetiology of NP have largely focused on occupational [7] and psychosocial risk factors [8, 9]. Also, comorbidities [10] and a previous history of neck injury [10, 11] have been associated with NP, but much confusion exists regarding the true causes of this very common symptom.

Recently, a few studies have focused on whether genes play a role in relation to NP [12–14]. Sambrook et al. [12] found an important genetic influence in degenerative changes of the cervical intervertebral discs based on MRI. However, in women such changes are probably not associated with NP [13, 15]. In a recent study, MacGregor et al. [13] showed a genetic influence on neck pain in women. Unfortunately, the analysis was based on a non-population-based sample of volunteer twins and is therefore probably subject to selection bias. Hartvigsen et al. [14] studied NP in Danish twins aged 70 and older, and found that genes play only a minor role in the liability to NP in seniors. However, these results cannot be extrapolated to a younger twin cohort and so the heritability of NP in a population of young and middle-aged twins remains to be investigated.

The aim of this study was to determine the genetic and environmental contributions to neck pain in men and women aged between 20 and 71 yr. Population-based twin registries offer a valuable tool for investigating the effect of genes and environment in complex diseases such as NP [16]. This paper will therefore add to the understanding of the aetiology of NP.

Materials and methods

Study sample

The Danish twin Registry (DTR) was established in 1954 and covers birth cohorts from 1870 to 2001. It is among the largest and most comprehensive twin registries in the world and is considered representative of the general population in Denmark [17, 18].

All twins born between 1931 and 1982, registered in the DTR, who had previously agreed to participate in research projects, were included in this study. For ethical reasons no attempt was made to contact twins who had previously declined participation in research projects. A questionnaire was sent out in April 2002, followed by a reminder 3 weeks later.

The zygosity of the twins in this cohort has previously been determined with self-report questionnaires [19]. The accuracy of determining a correct zygosity classification within this cohort was 97%.

Questionnaire

We used a joint 20-page questionnaire (Omnibus-02 questionnaire) that included questions from several different research teams. Questions on NP were taken from the Standardised Nordic Questionnaire (SNQ) [20]. The SNQ has been validated in terms of test–retest reliability [20–22] and validity [20, 21]. The questions on NP have demonstrated kappa values ranging between 0.64 and 0.79 and a sensitivity of 0.90 (for the diagnosis of cervical spondylisis), and the SNQ was found to be reliable and suitable for use in epidemiological studies.

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Only the question on lifetime NP (‘Have you ever had neck trouble?’) was used for the statistical analyses, together with a drawing showing the area between the occiput and the third thoracic vertebra. The definition of trouble was ‘ache, pain or discomfort’. The question on ‘NP past year’ was used only to test for logical errors.

Analysis of data

The NP questions were validated for logical errors by cross-tabulating questions on ‘NP ever’ and ‘NP past year’. The prevalence of lifetime NP was calculated both totally and stratified by age and gender. Probandwise concordance rates, odds ratios and tetrachoric correlation coefficients (all with 95% confidence intervals) were calculated. By means of biometrical modelling (structural equation modelling), the sizes of the genetic and environmental variances of liability to NP were calculated.

Probandwise concordance rates

The probandwise concordance rate provides the most informative measure of concordance and estimates the risk that a twin is affected given an affected co-twin, and is used to assess the similarity of monozygotic (MZ) and dizygotic (DZ) twins. It is therefore directly comparable to disease risk rates in background populations [23]. Probandwise concordance rates are robust even in the presence of incomplete ascertainment, and hence are comparable between studies. The probandwise concordance rates are calculated using the formula \( \frac{2C_1 + C_2}{2C_1 + C_2 + D} \), where \( C_1 \) is the number of doubly ascertained concordant pairs, \( C_2 \) is the number of singly ascertained concordant pairs and \( D \) is the number of discordant pairs. In this case, where there was complete ascertainment, the formula is \( \frac{2C_1}{2C_1 + D} \), i.e. singly ascertained cases are not relevant.

Zygosity-specific odds ratios

The zygosity-specific odds ratio (OR) measures the association between NP in one twin (the ‘index’ twin) and NP in the co-twin, and thus provides an estimate of the increased risk of neck pain in one twin conditioned on the presence or absence of neck pain in the co-twin [24]. Odds ratios include additional information from twin pairs who are concordant for no neck pain and are calculated like normal ORs. By calculating the common ORs (the weighted average of the zygosity-specific OR) and using a Mantel–Haenszel test \( \chi^2_{MH} \), a statistically significant familial aggregation (genetic component) can be determined. To determine whether there is a genetic influence (whether the OR for MZ twins is greater than the OR for DZ twins), the difference in zygosity-specific ORs is tested \( \chi^2_G \). Furthermore, it can be investigated whether a common environmental effect is present \( \chi^2_E \) [24]. Zygosity-specific ORs were calculated using the Stata release 8.0 software package (StataCorp, College Station, TX, USA). For further reading we recommend the paper by Ramakrishnan et al. [24].

Tetrachoric correlations

Tetrachoric correlations provide a measure of the similarity of twin partners in susceptibility to disease, and are equivalent to intraclass correlation coefficients. Tetrachoric correlations are based on a multifactorial threshold model, assuming a normally distributed variation of liability to neck pain that is due to genetic and environmental factors [25]. In theory, NP becomes manifest when a certain threshold on the liability distribution is exceeded (e.g. the prevalence of NP). The impact of genetic and environmental effects is reflected in the similarity of the co-twin’s susceptibility to NP (i.e. the variance of liability to NP is the same in both twins). A genetic component is indicated when tetrachoric correlations for MZ twins are more than twice that of DZ twins \( r_{MZ} > 2r_{DZ} \). The term ‘liability’ not only includes susceptibility to NP but it also combines external factors that may increase (or decrease) the likelihood of developing NP. The point on the scale of liability above which all individuals are affected and below which all are normal is called the ‘threshold’. The tetrachoric correlations were calculated from raw data using the Mx software package [26].

Biometric modelling and heritability

Heritability was estimated using standard biometric modelling (structural equation modelling) [27]. Classical biometric analyses of twin data are based on the assumption that the total phenotypic variance in a trait \( V_P \) can be partitioned into components attributable to genetic and environmental effects. This can be written as \( V_P = V_G + V_E + V_C \), where \( V_G \) is the genetic variance and \( V_E \) the environmental variance. The total phenotypic variance can be further divided into \( V_P = V_A + V_D + V_E + V_C \), where \( V_A \) is the variance attributable to the additive effects of genes, \( V_D \) is the variance attributable to dominance (non-additive effects arising from the interaction of alleles at a locus), \( V_C \) refers to the variance attributable to shared environmental effects (environmental exposures shared by both twins and which contribute to twin similarity), and \( V_E \) is the variance attributable to non-shared environmental effects (environmental exposures unique to each twin and which contribute to twin dissimilarity), including the residual variation as well as any potential measurement errors. Monozygotic twins share all additive and non-additive genetic effects while DZ twins share on average half of all additive \( (A) \) and a quarter of all dominance \( (D) \) genetic effects \( (1/2A + 1/4D) \) [25]. The shared environmental influence is equal within both MZ and DZ pairs. By biometric modelling, ACE and ADE \( (C \) represents the common environmental effect, \( E \) represents the non-shared environmental effect) models were calculated, followed by a more parsimonious model \( (AE, CE, DE \) or \( E \) \). The best model fits were chosen based on the maximum log-likelihood test \( –2LL \) and the Akaike Information Criterion [28]. The Mx software package was used for the biometric modelling [26].

Results

Prevalence of neck pain

A total of 46 818 questionnaires were sent out. After one reminder, 35 315 (76%) questionnaires were returned. For various reasons (duplicates, blanks, ID numbers removed, etc.), some had to be discarded, giving a total of 33 794 (73%) questionnaires eligible for further analysis. The internal validity of the questionnaire on NP showed that no-one had answered yes to ‘NP within last year’ and no to ‘NP ever’, giving zero inconsistent answers.

The lifetime NP prevalence for the twin cohort was 44% (95% confidence interval 43.8–44.9). Females reported NP more often than men \( [51 \% vs 36\% \times \chi^2(1) = 702.9, P < 0.001] \). The lifetime prevalence of NP increased until about the age of 35 yr, when it stagnated, with a slight decrease from the age of approximately 50 yr. The lifetime prevalences of NP for MZ and DZ twins were not statistically significantly different.

Concordance rates, odds ratios and tetrachoric correlations

The numbers of concordant and discordant pairs are shown in Table 1 together with the probandwise concordance rates, zygosity-specific odds ratio and the tetrachoric correlations. The overall probandwise concordance rates for MZ and for DZ
TABLE 1. Probandwise concordance rates, odds ratios and tetrachoric correlations for neck pain ever by zygosity, sex and age

<table>
<thead>
<tr>
<th>Age group (yr)</th>
<th>Total number</th>
<th>Prevalence</th>
<th>Discordant pairs for NP</th>
<th>Concordant pairs for NP</th>
<th>Zygosity-specific odds ratios (95% CI)</th>
<th>Tetrachoric correlations (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>MZ, M</td>
<td>DZ, M</td>
<td>MZ, F</td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>3976</td>
<td>0.35 (0.34–0.37)</td>
<td>0.40 (044-0.53)***</td>
<td>0.48 (048-0.67)***</td>
<td>0.41 (033–0.49)****</td>
<td>0.41 (033–0.49)****</td>
</tr>
<tr>
<td>DZ, M</td>
<td>6092</td>
<td>0.36 (0.35–0.37)</td>
<td>0.40 (044-0.53)***</td>
<td>0.47 (045-0.67)***</td>
<td>0.41 (033–0.49)****</td>
<td>0.41 (033–0.49)****</td>
</tr>
<tr>
<td>MZ, F</td>
<td>5024</td>
<td>0.49 (0.48–0.51)</td>
<td>0.51 (050-0.66)***</td>
<td>0.61 (060-0.70)***</td>
<td>0.47 (040–0.50)****</td>
<td>0.47 (040–0.50)****</td>
</tr>
<tr>
<td>DZ, M</td>
<td>1589</td>
<td>0.31 (0.29–0.34)</td>
<td>0.30 (029-0.42)</td>
<td>0.30 (029-0.42)</td>
<td>0.27 (018–0.37)**</td>
<td>0.27 (018–0.37)**</td>
</tr>
<tr>
<td>MZ, F</td>
<td>2093</td>
<td>0.42 (0.39–0.44)</td>
<td>0.50 (049-0.67)***</td>
<td>0.61 (060-0.70)***</td>
<td>0.47 (040–0.50)****</td>
<td>0.47 (040–0.50)****</td>
</tr>
<tr>
<td>DZ, M</td>
<td>2039</td>
<td>0.42 (0.39–0.44)</td>
<td>0.49 (049-0.61)***</td>
<td>0.58 (050-0.70)***</td>
<td>0.47 (040–0.50)****</td>
<td>0.47 (040–0.50)****</td>
</tr>
<tr>
<td>MZ, F</td>
<td>1551</td>
<td>0.60 (0.58–0.63)</td>
<td>0.61 (060-0.70)***</td>
<td>0.73 (070-0.80)***</td>
<td>0.53 (042–0.63)****</td>
<td>0.53 (042–0.63)****</td>
</tr>
<tr>
<td>51–71</td>
<td>1220</td>
<td>0.35 (0.32–0.38)</td>
<td>0.35 (028-0.42)</td>
<td>0.46 (039-0.53)</td>
<td>0.35 (019–0.49)**</td>
<td>0.35 (019–0.49)**</td>
</tr>
<tr>
<td>DZ, M</td>
<td>2464</td>
<td>0.35 (0.33–0.37)</td>
<td>0.34 (029-0.42)</td>
<td>0.34 (029-0.42)</td>
<td>0.03 (–0.11 to 0.17)</td>
<td>0.03 (–0.11 to 0.17)</td>
</tr>
<tr>
<td>MZ, F</td>
<td>1380</td>
<td>0.48 (0.45–0.51)</td>
<td>0.49 (049-0.67)***</td>
<td>0.61 (060-0.70)***</td>
<td>0.53 (040–0.50)****</td>
<td>0.53 (040–0.50)****</td>
</tr>
<tr>
<td>DZ, F</td>
<td>2566</td>
<td>0.50 (0.48–0.53)</td>
<td>0.49 (049-0.67)***</td>
<td>0.61 (060-0.70)***</td>
<td>0.30 (019–0.49)**</td>
<td>0.30 (019–0.49)**</td>
</tr>
</tbody>
</table>

Heritability of neck pain

Monozygotic estimates are significantly larger than the corresponding dizygotic estimates: **P < 0.01; ***P < 0.001. The numbers of concordant and discordant pairs are based on complete pairs only, hence the difference to the total number of twins in the survey and number of twin pairs. CI, confidence interval.

Discussion

With this study we have demonstrated that the overall heritability of lifetime NP is 44%. Heritability differs between men and women, being highest for women (33 vs 51%). In other words, nearly half of the variation with regard to NP in the young and middle-aged population is a result of genetic variation; in women, slightly more than half of the liability to NP is caused by genetic variation, whereas in men the proportion is only one-third. Hence, environmental influence plays a larger role with regard to the development of NP in men than in women. The gender difference in the perception and experience of pain is well documented and is believed to be a combination of psychological and biological factors [29]. Recently, willingness to report pain has been raised as an explanation for the gender differences in pain reporting [30]. Interestingly, when willingness to report pain was measured in a questionnaire—and subsequently controlled for—ambiguous results were seen: sex was not a predictor of the pain threshold, but remained a significant predictor in pain tolerance [31]. Therefore, psychosocial factors as well as biological factors are viable explanations for gender differences in (experimental) pain [31]. However, our heritability estimates were performed on each gender separately and thus the willingness to report NP will not
have influenced the gender-specific heritability estimates. However, the significant difference in the heritability of NP between genders may be influenced by the willingness to report NP. Further studies are needed to elucidate whether this difference can be explained by this phenomenon.

The environmental influences increase with age and the genetic component becomes negligible in the oldest age groups, especially among females, in whom the liability to NP is almost entirely due to environmental factors. Thus, environmental influences are more likely to be the major cause of the liability to NP in older age groups. This is not surprising, since NP is associated with several physical and psychosocial risk factors that may manifest later in life [7, 10, 11]. Unfortunately, it was not possible to measure and subsequently adjust for these well-known psychosocial risk factors in our study.

In order for biometric modelling to be valid, two major assumptions need to be fulfilled. First, the heritability estimates calculated from twins are based on the assumption that the heritability can be extrapolated to the general population. This generalizability has been supported by several studies, as it has been shown that the Danish twin cohort is representative of the Danish population in terms of many common diseases and mortality rate [17, 18, 32]. However, the lifetime NP prevalence in the Danish population remains to be confirmed in other studies and it is therefore impossible to determine whether the prevalence of NP in our twin cohort is equal to the prevalence of NP in other cohorts. Second, the assumption of equal environment assumes that MZ and DZ twins are equally exposed to environmental factors aetiologically related to the trait under study (in this case NP). Monozygotic twins are treated more similarly than DZ twins by their parents [33]. However, this similarity is not due to their greater phenotypic similarity, but is rather a consequence of their genetic identity and the greater similarity in responses that this elicits from the environment [34]. Thus, twins are treated according to their actual zygosity, not their perceived zygosity [33]. In our study, the prevalence estimates among MZ and DZ twins were identical, and therefore no violation of the equal environment assumption was detected.

The zygosity determination must be accurate in order for the results to be valid. The zygosity of twins has previously been determined via self-reported questionnaires, showing a misclassification rate of 3%, which is considered acceptable [19]. Since more MZ than DZ twins were misclassified, any effect on the accuracy of the heritability estimates is in the conservative direction.

Also, non-differentiated misclassification due to unspecified disease definition will tend to lower the heritability estimates. Even though the definition of NP was clearly stated and accompanied by a drawing marking the area of interest, a positive answer indicating lifetime occurrence of NP in an individual remains a source of subjective interpretation. Furthermore, this definition includes both specific and non-specific causes of NP [35]. Consequently, the heritability estimates presented in this paper should be considered only as an overall estimate of the genetic contribution to NP and the real genetic effect in specific subgroups may be larger.

Another potential limitation of this study is non-response and selection bias. Although the unadjusted response rate was 73%, we did not see significant differences between non-responders in terms of zygosity. In addition, a potential non-response bias specifically regarding our parameter (lifetime NP prevalence) is unlikely as this question was nested in a large 20-page general health survey. Thus, if bias was present it is related to other factors (for example, the size of the questionnaire) and not specifically to one single parameter such as NP.

The use of lifetime NP raises the issue of recall bias, which affects the prevalence estimates. This may explain the decline in NP prevalence in the oldest age group. However, this age-related drop in prevalence estimates could also reflect a birth cohort effect due to different levels of exposure to risk factors. Only a follow-up study could further investigate possible explanations of recall bias. Nevertheless, recall bias is assumed to be equal between MZ and DZ twins and, as the heritability estimates are comparisons between MZ and DZ twin pairs, possible recall bias does not affect our heritability estimates.

This is the first study on heritability of NP in young and middle-aged men and women, and it has several major strengths. First, it is based on a twin cohort with nearly complete ascertainment, resulting in less biased heritability estimates. Second, the large sample size and the high response rate made it possible to estimate differences in heritability between men and women with high accuracy (i.e. small confidence intervals). Third, the wide age span made it possible to study how the genetic and environmental contributions change in different age groups. Finally, the Danish twin cohort has been shown to be representative of the general population and so our findings can be extrapolated to the background population.

Three previous studies have focused on genes in relation to NP. Hartvigsen et al. [14] estimated the genetic and environmental contribution in NP in people aged 70 and older and concluded that the genetic effect plays only a minor role in old age. Their study supports our findings that the environmental effect gradually increases with age and that the genetic effect diminishes as people get old. Thus, environmental risk factors are more important in developing NP over time than any genetic component(s).

In the UK, MacGregor et al. [13] investigated the heritability of NP in female twins. Although their heritability estimates (48%) were very close to ours (51%), this may be a coincidence as their study was based on volunteers found through media campaigns and thus subject to severe selection bias. Also, they did not stratify by age, making it impossible to evaluate how age might have affected their results.

Sambrook et al. [12] showed a high genetic influence in cervical disc degeneration, with a genetic contribution varying between 63% and 79%. However, these results were based on two different cohorts (Australia and UK) with different selection criteria and with overrepresentation of females, and thus again selection bias may partly explain the high heritability estimates. Further, the outcome (cervical disc degeneration) is probably not directly associated with NP [13, 15].
Although NP is heritable, it is not known how genes specifically influence the presence of NP. However, as genes play a lesser role with increasing age, efforts should be made to minimize any documented environmental risk factors that may cause or aggravate NP (e.g. physical and psychosocial risk factors). Neck pain may be considered a heterogeneous cluster of more specific conditions with pain localized in the neck area as a common feature. In addition, there may be genetic differences in, for example, the duration and severity of NP (i.e. chronic NP vs acute NP, or one episode of NP vs many episodes of NP). Unfortunately, it was not possible to investigate these factors because of practical limitations (i.e. it was impossible to include additional questions) in the survey. Future studies should therefore be directed at investigating whether the genetic contributions in the various subdefinitions of people with NP are significantly different from each other. Attempts should be made to adjust for well-known psychosocial risk factors if possible [13]. Furthermore, studies should be conducted to investigate whether genetic differences between men and women are based on different genes or whether it is the same set of genes or shared environmental experiences that contributes to NP.

Conclusion

With this study we have demonstrated the importance of genes in the liability to NP in a large twin cohort representative of the background population. The genetic component accounts for about half of the liability to NP in women and one-third in men. Genes become gradually less important with increasing age, and thus environmental influences dominate in older age groups.

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The authors have declared no conflicts of interest.

References


Clinical Vignette

Proximal muscle weakness and elevated creatinine kinase

A 67-yr-old lady was admitted with proximal muscle weakness and painful lower limbs. Her symptoms developed suddenly when rising from the toilet chair. Examination confirmed the proximal weakness in the lower limbs, with no other significant neurological abnormality. Her past medical history was of chronic renal impairment secondary to hypertension, which was managed conservatively. She is not diabetic or on steroid therapy. Blood tests showed urea 14.3 mmol/l and creatinine 181 mmol/l; creatinine kinase (CK) was 9463 IU/l (normal values < 200 IU/l). MRI showed high signal changes within the biceps femoris muscles bilaterally, indicating trophic changes after the rupture. In addition there were small avulsion fractures present at the origin of the long head of the biceps in the region of the ischial tuberosities.

The patient recovered with physiotherapy and her CK level normalized over 1 week.

Spontaneous muscle rupture is rare but is a well-recognized manifestation, particularly in elderly or obese people, in patients on long-term steroid therapy, in metabolic diseases [1, 2] such as hyperparathyroidism and diabetes mellitus, and in chronic renal failure [3].

Muscle rupture in renal failure is either due to muscle degeneration related to acidosis or due to secondary hyperparathyroidism, which leads to bone resorption and avulsion of the muscle attachment.

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