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Genetic and environmental influences on non-specific neck pain in early adolescence: A classical twin study

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Abstract

Background—Prevalence of neck pain has increased among adolescents. The origins of adult chronic neck pain may lie in late childhood, but for early prevention, more information is needed about its aetiology. We investigated the relative roles of genetic and environmental factors in early adolescent neck pain with a classic twin study.

Methods—Frequency of neck pain was assessed with a validated pain questionnaire in a population-based sample of nearly 1800 pairs of 11–12-year-old Finnish twins. Twin pair similarity for neck pain was quantified by polychoric correlations, and variance components were estimated with biometric structural equation modelling.

Results—Prevalence of neck pain reported at least once monthly was 38% and at least once weekly 16%, with no significant differences between gender or zygosity. A greater polychoric correlation in liability to neck pain was found in monozygotic (0.67) than for dizygotic pairs (0.38), suggesting strong genetic influences. Model-fitting indicated that 68% (95% CI 62 to 74) of the variation in liability to neck pain could be attributed to genetic effects, with the remainder attributed to unshared environmental effects. No evidence for sex-specific genetic effects or for sex differences in the magnitude of genetic effects was found.

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Conflict of interest: none

Author contributions

Marja Mikkelsson, Jouko Salminen, Lea Pulkkinen, Richard J. Rose and Jaakko Kaprio made substantial contributions to the study's conception and design. Minna Ståhl, Ashraf El-Metwally and Jaakko Kaprio analysed and interpretated the data. Minna Ståhl drafted the article and all the other authors discussed the results and contributed to the critical revision of the manuscript for important intellectual content. All authors made the final approval of the version to be published.

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Conclusions—Genetic and unique environmental factors seem to play the most important roles in liability to neck pain in early adolescence. Future research should be directed to identifying pathways for genetic influences on neck pain and in exploring effectiveness of interventions that target already identified environmental risk factors.

Keywords

neck pain; heritability; genetic; risk factor; child; adolescent; musculoskeletal pain

Introduction

Already in preadolescence, non-specific neck pain is quite prevalent (Balagué et al., 1994; Mikkelsson et al., 1997$_a$; Kajer et al., 2011). A substantial increase in prevalence rates with female overrepresentation appears first in adolescence (Ståhl et al., 2004), and prevalence rates approximate adult levels by age 18 (Grimmer et al., 2006; Jeffries et al., 2007). Neck pain seems to be the most recurrent/persistent musculoskeletal pain from preadolescence to adolescence (El-Metwally et al., 2004) and chronic neck pain in adulthood may have its origin in childhood (Hertzberg et al., 1985; Brattberg, 2004; Siivola et al., 2004). During the past two decades, a steady increase in prevalence of neck pain has been reported among adolescents in western countries (King et al., 1996; Hakala et al., 2002), perhaps predictive of increasing numbers of adults with persistent neck pain in the future. To reduce the burden of health care, effective prevention programs directed toward children and adolescents must be created. But to do so, more information about the aetiology of neck pain in childhood and adolescence, which is likely multifactorial, is necessary. Previous epidemiological studies among school-aged children have focused on identifying environmental risk factors, but the contribution of genetic factors is unknown.

Twin data estimate genetic contributions to a trait through comparison of the phenotypic resemblance of monozygotic (MZ) and dizygotic (DZ) twins (Boomsma et al., 2002; Posthuma et al., 2003). MZ twins reared together share 100% of their genes, i.e. have the same genomic sequence, and through childhood and early adolescence, much of their environmental experience: resemblance between them is attributed to these two sources. The extent to which MZ co-twins differ from one another is ascribed to unique, non-shared environmental factors, which also includes measurement error. DZ twins reared together share, on average, 50% of their segregating genes and much of their environmental experience, so resemblance between them due to genetic influences will be lower than for MZ pairs. Differences between DZ co-twins are attributed to non-shared environmental factors and non-shared genetic influences. In adult twin studies of neck pain, genes play a significant role in neck pain, particularly in women(Fejer et al., 2006$_a$). Genetic influence becomes gradually less important with increasing age, and environmental factors dominate almost completely in older age groups (Harvigsen et al., 2005; Fejer et al., 2006$_a$). The aim of this study was to evaluate the relative contribution of genetic and environmental factors to neck pain in early adolescent girls and boys.

Methods

The study population

This study is part of an on-going longitudinal, population-based twin-family study of behavioural development and health issues in five consecutive Finnish twin cohorts, born 1983–1987 (Kaprio et al., 2002). The data are from baseline assessments of 4 of the 5 nationwide birth cohorts. Pain items used for this analysis were not included in questionnaires administered in the first year of data collection. From 1995 to 1998, Finnish families (n = 2,487) with 11–12- year-old twins (median age 11.4 years, 95% CI 10.9 – 11.9

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years) were identified from the nation's Central Population Registryand approximately 85% responded to an initial family questionnaire on the twins' gestation, delivery, zygosity, family structure, childhood development and medical history, day care and school (Kaprio et al., 1990). The return of this family questionnaire was immediately followed by individual questionnaires to both parents and the two co-twins. All questionnaires were mailed in late autumn of the year twins reached age 11, with a response rate among twins of 96%.

Questionnaires were received from 3,917 individual twins, but 89 had missing data on neck pain from their co-twins. Zygosity of same-sex twin pairs was determined from their perceived similarity and confusability of appearance as separately reported by twins and their parents in mailed questionnaires (Sarna et al., 1978; Goldsmith, 1991) Confirmation of zygosity in some pairs was enhanced by comparisons of school photographs and additional information obtained from twins' mothers. In study of same-sex pairs enrolled in laboratory research during 2006–2009, zygosity was confirmed for 97% of tested pairs (n=397) with genetic markers. But in 117 cases from the full sample, zygosity could not be assigned due to missing or ambiguous information, and these pairs were excluded. The final study sample consisted of 1,797 twin pairs with confirmed zygosity and complete data from both co-twins; included were 611 MZ pairs (297 female and 314 male MZ pairs), 598 same-sex DZ pairs (273 sister-sister and 325 brother-brother DZ pairs) and 588 opposite-sex DZ pairs.

Measurements

Musculoskeletal pain symptoms were assessed using questionnaire items developed by Mikkelsson el al.(1997_b). Test-retest reliability of the questionnaire in detecting those reporting pain at least once a week was satisfactory ($\kappa = 0.9$) (Mikklesson et al., 1996). The observed agreement between of questionnaire and interview was 86% with a Cohen Kappa (κ) of 0.67 (Mikklesson et al., 1997_b). The pain questionnaire included site-specific questions of pain in seven different areas of the body (neck, upper limb, chest, lower limb, upper back, lower back and buttocks). Adjacent to the pain questions, the questionnaire included a manikin (front and back) divided into seven different body parts analogous to the anatomic area of each question. Musculoskeletal pain symptoms were assessed with a 5-level frequency classification (pain seldom or never, once a month, once a week, more than once a week, almost daily) from the preceding summer until the time of survey (an approximate period of three months). For analyses, pain frequencies once a week, more than once a week and almost daily were combined and categorized "at least once a week".

Statistical methods

Biometric modelling was used to estimate genetic and environmental contributions to the liability towards neck pain. In the basic model, an individual's deviation from the population mean is assumed to result from both genetic and environmental effects. The total amount of genetic influence on neck pain is the sum of additive (i.e., effect of one allele is added to the effect of another allele at a locus) and dominance (the deviation from purely additive effects) effects of alleles at multiple loci, plus variance due to the interaction of alleles at different loci (epistasis). Environmental effects are partitioned into those shared (in households, schools and neighbourhoods) by co-twins reared together and those non-shared (e.g., in interactions with different peers). The corresponding phenotypic variance is assumed to result from genetic and environmental variances. Data from twins permit us to estimate these variance components.

With data from twins reared together, four separate parameters can be modelled: additive genetic (A) and dominant genetic (D) components, shared (C) and non-shared (E) environmental components. Their influence on the phenotype is given by parameters (a, d, c, and e) that are equivalent to the standardized regression coefficients of the phenotype on the

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corresponding components (A, D, C, and E, respectively) (Neale and Cardon, 1992). The square of these parameters estimates the proportion of variance due to each component. Models are fit based on different combinations of these parameters: AE, ACE, ADE, and CE, but effects due to dominance and shared environmental effects cannot be simultaneously modelled with data limited to that from twins reared together (Neale and Cardon, 1992). Given the observed pattern of correlations with DZ correlations greater than one-half the MZ correlations (see results), ACE model is preferred over the ADE model as the initial model. Because our data included twins of both sexes and opposite-sex twin pairs, additional hypotheses regarding sex-specific effects could be tested (Neale and Cardon, 1992).

The similarity of co-twins for reported neck pain was quantified by polychoric correlations, and models were fitted to these polychoric correlations using weighted least squares, which is an asymptotically distribution-free procedure. In computing polychoric correlations, it was assumed that the distribution of the underlying liability to the trait is continuous and normal, with two thresholds depicting our 3-fold categorization of subjects. We tested the underlying liability model for bivariate normality in all pairs and that model could not be rejected ($p = 0.14$), suggesting that a single, continuous measure of liability to neck pain frequency accounts well for the data.

We also tested some assumptions central to twin analyses. These tests evaluate the assumption that first and second twins, twins of both zygosities, and male and female twins all represent the same population. Distributions of neck pain frequency were studied using maximum likelihood estimation for raw data observations. An initial fully-saturated model, in which all distributions for first and second twins in all zygosity-sex groups were free to vary, was compared to successively more constrained models by likelihood ratio tests. The distributions were first set equal for first- and second-born co-twins, then for MZ and DZ pairs, and finally set equal in males and females. If no significant differences are observed, neither birth order, zygosity, nor sex differences, respectively, are of major importance. We also tested whether correlations for male and female MZ pairs differed, and those for male DZ, female DZ and opposite-sex DZ pairs differed using a single test for the fit between a model allowing the correlations to differ and one constraining the correlations to equality across zygosities.

Variance component estimation was then carried out using the Mx program to build structural equation models for multiple groups. Chi-square goodness-of-fit statistics were used to assess how well models fit the data. The superiority of alternative, hierarchically nested models was assessed by the difference in chi-square values of the models, which is, itself, distributed as chi-square with degrees of freedom equal to the difference in degrees of freedom of the models to be compared. This was done to compare models where different components of variance have been specified. Based on the best model, variance components were computed, and 95% confidence intervals estimated. Model fitting was based on scripts available at the Genomeutwin-project Mx-library (http://www.psy.vu.nl/mxbib/). Because the models take better account of the data, the heritability estimate from the model is more accurate (and comes with 95% confidence intervals) than estimating heritability directly based on the MZ and DZ correlations (Posthuma et al., 2003).

Results

Prevalence of neck pain

A total number of 3,917 individual twins (1,886 girls and 2,031 boys) had responded to the question about neck pain. The 3-month period prevalence was 38.3% (95% CI 36.5 to 40.0)

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for neck pain at least once a month and 16.3% (95% CI 14.9 to 17.4) for neck pain at least once a week, with neither significant gender (p=0.36) nor zygosity differences (p=0.13).

Twin similarity and genetic modeling

Polychoric correlations of liability to neck pain were 0.66 (CI 95% 0.59 to 0.73) in MZ twins and 0.38 (CI 95% 0.30 to 0.45) in DZ twins, suggesting a strong genetic influence (Table 1). We found no evidence that MZ correlations differed by sex, or that correlations for male DZ, female DZ, and opposite-sex pairs differed (p=0.37).

Table 2 shows steps of biometric modelling which began by estimating parameters indicative of the relative strength of genetic and environmental influences. The first model was a full-sex differences model (ACE) in which estimates for a, c and e are allowed to differ in magnitude between boys and girls, and allows for a sex-specific genetic component. The next model with no sex-specific genetic component provided a good fit to the data and fit was further improved with a model assuming equal-magnitude genetic effects in liability to neck pain among boys and girls. This was the model against which we tested other models. Because the estimate for the environmental component, C (point estimate in the ACE models for c^2 was less than 10%) was non-significant, it could be dropped from the model. The AE model with no sex-specific effects fit the data well. Dropping A resulted in a significant deterioration of model fit, so AE model was chosen as the best fitting model. Results obtained from that final model showed that 68% (95 % CI 62 to 74) of the variance in liability to neck pain could be attributed to genetic effects, and 32% (26 to 38) to unshared environmental effects. This is in line with the pattern of MZ and DZ correlations of 0.66 and 0.38 respectively. The MZ correlation is a close estimate of the genetic component, when shared environmental effects are absent.

Discussion and conclusions

Using a classical twin study design, we found that 68% of variance in liability to non-specific neck pain at the ages of 11–12 could be attributed to genetic factors and 32% of the phenotypic variation to individual environmental factors in both genders. Shared environmental factors (e.g. rearing environments, socio-economic conditions, and activities engaged in by both twins) seemed to play a minor role.

This study has several strengths. Firstly, it is based on a large and representative sample of Finnish 11–12-year-old twins. Secondly, zygosity was comprehensively ascertained by both twins and parents' reports (previously validated against DNA markers) (Bønnelykke et al., 1989; Christiansen et al., 2003; Gao et al., 2006) and confirmed by genetic markers in a subset of this sample. Thirdly, we used a questionnaire with acceptable validity and reliability in assessing musculoskeletal pains. Recall bias was minimized by limiting recall period to the previous three months with an easily identified starting point "since the summer". Our 3-fold categorisation of neck pain (none/once a month/at least once a week) did not affect on our results, because additional analyses indicated that the underlying liability model for neck pain is single and continuous (i.e. the underlying etiological factors are the same for all frequencies of neck pain), consistent with a study of tension-type headache in a large adult twin sample from Denmark (Russel et al., 2007). Although intensity of pain was not assessed, our previous findings suggest that frequency of neck pain reflects intensity of pain fairly well (Ståhl et al., 2004). The limitations of the study are that the impact of neck pain on children's lives remains unknown and seek of medical care was not evaluated. Thus, our results should not be directly extrapolated to children with troublesome neck pain presenting to healthcare professionals. In these cases, a possible serious underlying cause of neck pain must always be excluded before interventions towards possible environmental risk factors among those with a family history of chronic neck pain.

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Generalizing results from twin population to singletons is debatable. However, adolescent twins and singletons do not differ in behavioural traits (Pulkkinen et al., 2003), academic performance (Christensen et al., 2006), or personality (Johnson et al., 2002). Nor are adult twin-singleton differences observed in disease-related physical and lifestyle characteristics (Andrew et al., 2001). In addition, the prevalence of weekly and monthly neck pain in this twin population matched the prevalence, with the same frequency categorisation, found during the same time period among Finnish schoolchildren aged 9–12 years (Ståhl et al., 2008), and the prevalence of low back pain (El-Metwally et al., 2008)and headache (Virtanen et al., 2004)in our twin data was similar to that found in other population studies. The absence of gender differences in prevalence of neck pain in these young twins is consistent with earlier findings among singletons where elevated prevalence of neck pain in females is not pronounced until later adolescence (Ståhl et al., 2004). Jointly, these observations suggest that our results from Finnish twins can be generalized to the general population.

To our knowledge, this is the first study investigating genetic contributions to neck pain in school-aged children. Since heritability estimates are age-, time- and population-specific, and bound to how pain is defined and assessed, relevant comparisons may be problematic. Three previous studies investigated genetic contributions to adult neck pain. In a Danish study of twins, ages 20–71, heritability of lifetime neck pain was estimated at 44% with genetic contributions declining with increasing age (Fejer et al., 2006_a). Among individuals ≥70 years of age, environmental factor mostly explained the liability to neck pain (Hartvigsen et al., 2006). Our study and those on adult twins suggest that individual differences in neck pain are strongly influenced genetically in younger ages but more environmentally in older age groups.

We found no evidence for sex-specific genetic effects; nor did we find evidence of sex differences in the relative magnitude of genetic influence: the relative contribution of genes and environments does not appear to differ in boys and girls at this age. But gender difference in prevalence does appear after puberty (Ståhl et al., 2004) and continues through adulthood (Hogg-Johnsson et al., 2008), so the situation could be different from adolescence on. In study of adults, larger estimates of heritability of liability to neck pain were found in women, but no evidence of a sex-specific genetic effect was found (Fejer et al., 2006_a; Fejer et al., 2006_b). Thus, the same genes appear to be influencing neck pain in both sexes across the life span.

Pain symptoms seem to cluster and overlap in population-based epidemiological studies among children and adolescents (Kristjansdottir, 1997; Mikklesson et al., 1997_a; Perquin et al., 2000; Fichtel and Larsson, 2002; El-Metwally et al., 2004; Ghandour et al., 2004; Stahl et al., 2004; Petersen et al., 2006; Auvinen et al., 2009). It has been suggested that frequent pain symptoms in children should be regarded as a potential general pain disorder, rather than merely a localized body disorder (Petersen et al., 2006). In the study among adult twins by Williams et al. (2010) pain reporting at different body sites was explained by a single underlying genetic factor. On the contrary, in our data set we found very low estimates for genetic components for low back pain (El-Metwally et al., 2008) and widespread pain (Mikklesson et al., 2001), but a strong genetic component for neck pain in 11–12-year-olds. Further comparison of different musculoskeletal pain symptoms in school-age children shows additional differences: neck pain is clearly the most prevalent and persistent musculoskeletal pain (Mikklesson et al., 1997_a; El-Metwally et al., 2004), and the prevalence of neck pain has increased more rapidly than the prevalence of low back pain during the last decades (Hakala et al., 2002). These findings argue against a common underlying aetiology and mechanism for all sources of pain in childhood/adolescence. Theoretically, multivariate genetic modeling could help resolve whether this is the case or

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not, but it is unlikely to help resolve this issue in this age-group, given that no significant genetic component was observed in the univariate analyses of LBP or widespread pain. A much larger sample size would be required to detect smaller genetic components, if they are present.

Does substantial heritability imply that neck pain is difficult to prevent in school-aged children? It is not that simple. Heritability estimates do not refer directly to neck pain at an individual level, but rather to an underlying theoretical construct - namely liability towards neck pain in the population -- the proportion of variation in susceptibility to neck pain to be ascribed to inter-individual genetic differences. While the structure of genes does not change, their action and expression can be modified to prevent diseases. Also, genetic and environmental factors interact in diseases; for example, genes can influence a person's response to an environmental risk factor, which means that an identified risk factor causes symptoms/disease only in subjects with certain genetic structure. In the recent systematic review, it was concluded that duration of static sitting posture and psychosocial factors, especially depression, mental stress, and psychosomatic complaints, have an influence on the development of upper quadrant musculoskeletal pain in children and adolescents (Prins et al., 2008). Daily use of computers exceeding 2–3h seems to be a threshold for neck and shoulder pain (Hakala et al., 2006). The association between neck pain and psychological factors could be genetically mediated, as was among adult female twins (MacGregor et al., 2004).

Conclusions

Adult chronic neck pain might have its origin in childhood or adolescence. Genetic factors, same for boys and girls, seem to play the most important role in liability to non-specific neck pain in early adolescent boys and girls. Unique environmental factors are also of importance. Future research should aim to identify different pathways by which genes influence neck pain and also explore the effectiveness of preventive interventions targeted against already identified psychological and physical environmental risk factors, especially among those with chronic neck pain sufferers in the family or in their close relatives.

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What's already known about this topic

- Prevalence of neck pain has constantly increased among school-age children during the last decades.
- The origins of adult chronic neck pain may lie in childhood, but for early prevention, more information is needed about its aetiology.
- Contribution of genetic factors is unknown.

What does this study add

- Genetic factors, same for boys and girls, seem play the most important role in liability to neck pain in early adolescence.
- Unique environmental factors seem also to play a role, while common environmental factors are of minor importance.

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Table 1

Within-pair polychoric correlations in monozygotic (MZ) and dizygotic (DZ) twin pairs regarding neck pain.

	Correlation coefficient (r)	95% confidence intervals (CI)
MZ boys	0.63	0.52 – 0.73
DZ same sex boys	0.42	0.28 – 0.56
MZ girls	0.72	0.63 – 0.81
DZ same sex girls	0.47	0.33 – 0.61
DZ opposite sex	0.31	0.20 – 0.42

LCL=mean − (1.96*s.e.)

UCL=mean + (1.96*s.e.)

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Table 2

Genetic modelling analysis for neck pain to evaluate the best model for variance components A, E and C.

Model	χ^2	*df*	AIC	$\Delta\chi^2$	Δdf	*P*
I ACE, no restrictions	47.93	31	−14.07	-	-	-
II ACE	51.37	34	−16.63	3.44	3	0.33
III ACE equal boys and girls	53.34	36	−18.66	1.97	2	0.37
IV AE	**54.59**	**37**	**−19.41**	**1.25**	**1**	**0.26**
V CE	82.46	37	8.46	29.12	1	<0.001
VI E	312.65	38	236.65	259.31	2	<0.001

A=additive genetic, C=common environmental, and E=unique environmental component

Model I allows for different A, C and E effects in boys and girls, sex-specific genetic effects, and different prevalences in boys and girls

Model II is Model I, but restricting prevalences to be the same in boys and girls with no sex-genetic effects

Model III A, C and E effects of equal size for boys and girls, compared to model II

Models IV, V and VI are compared to model III

Best fitting model in bold

AIC (akaike information criterion) $\chi^2 - 2df$