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ORIGINAL ARTICLE

Heritability of scoliosis

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Abstract
Purpose To estimate the heritability of scoliosis in the Swedish Twin Registry.
Methods Self-reported data on scoliosis from 64,578 twins in the Swedish Twin Registry were analysed. Prevalence, pair- and probandwise concordances and tetrachoric correlations in mono- and dizygotic same-sex twins were calculated. The relative importance of genetic variance, i.e. the heritability, and unique and shared environmental variance was estimated using structural equation modelling in Mx software. In addition, all twins in the twin registry were matched against the Swedish Inpatient Register on the primary diagnosis idiopathic scoliosis.
Results The prevalence of scoliosis was 4%. Pair- and probandwise concordance was 0.11/0.17 for mono- and 0.04/0.08 for same-sex dizygotic twins. The tetrachoric correlation (95% CI) was 0.41 (0.33–0.49) in mono- and 0.18 (0.09–0.29) in dizygotic twins. The most favourable model in the Mx analyses estimated the additive genetic effects (95% CI) to 0.38 (0.18–0.46) and the unique environmental effects to 0.62 (0.54–0.70). Shared environmental effects were not significant. The pairwise/probandwise concordance for idiopathic scoliosis in the Swedish Inpatient Register was 0.08/0.15 for monozygotic and zero/zero for same-sex dizygotic twins.
Conclusion Using self-reported data on scoliosis from the Swedish Twin Registry, we estimate that 38% of the variance in the liability to develop scoliosis is due to additive genetic effects and 62% to unique environmental effects. This is the first study of sufficient size to make heritability estimates of scoliosis.

Keywords Adolescent idiopathic scoliosis · Heritability estimates · Twin studies · Population based

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Introduction

The aetiology of idiopathic scoliosis is still unknown. Relatives to patients with idiopathic scoliosis have a higher prevalence of this condition than the population in general, suggesting the importance of hereditary factors [1–3]. Pedigree studies and genetic analyses have so far shown inconsistent results both regarding the mode of heritability and possible genetic determinants associated with the scoliotic phenotype [4–6].

Twin studies are useful to distinguish whether a family history of disease is the result of shared environmental or hereditary factors, based on the assumption that identical (monozygotic) twins share 100% of their genome and fraternal (dizygotic) twins 50% of their segregating genes. A higher proportion of concordant pairs, i.e. both twins affected, in monozygotic compared to dizygotic twins indicate that hereditary factors are important [7]. With statistical methods it is possible to quantify the relative

importance of hereditary factors, i.e. the heritability, and environmental factors on variation in a trait [8].

Earlier twin studies of idiopathic scoliosis report higher concordances in monozygotic compared to dizygotic twin pairs [7, 9, 10]. However, due to sample size constraints, they have not been able to report heritability estimates.

The population-based Swedish Twin Registry contains the largest collection of twins in the world. The aim of this study was to compare scoliosis concordances in mono- and dizygotic twins, as well as studying the heritability of scoliosis in the Swedish Twin Registry.

Materials and methods

Twin registry

The Swedish Twin Registry was created in the late 1950s, containing information on 171,196 twins born between 1886 and 2000.

Survey

During the years 1998–2002 and 2005–2006 all twins, born 1985 and earlier, alive and living in Sweden ($n = 104{,}349$), were asked to participate in two large surveys on health status and exposures, the so-called SALT and STAGE cohorts. Among other questions the twins were asked: "Do you have or have had scoliosis?" Details of these cohorts and the questionnaires have been published elsewhere [11, 12]. The surveys were approved by the local ethics committee and informed consent was obtained from all subjects.

Zygosity

Zygosity was assigned based on DNA or intrasimilarity questions during childhood [11]. The latter method has been proven to correctly diagnose more than 95% of Swedish twins as well as twins from other nationalities [13–15].

Concordances

A pair is denoted concordant for a trait when both twins in a pair are affected and discordant when only one twin is affected. A higher concordance in monozygotic (MZ) than in dizygotic (DZ) twins indicates a genetic contribution. We calculated both pairwise and probandwise concordances according to Hopper [16]. Pairwise concordance estimates the probability of both members in a twin pair being affected when one twin in the pair is affected. Pairwise concordance is calculated as follows: concordant affected pairs/discordant pairs. The probandwise concordance estimates the probability of a twin being affected given that his/her twin partner is affected. Probandwise concordance is calculated as follows: $2 \times$ concordant affected pairs/($2 \times$ concordant affected pairs + discordant pairs).

Probandwise concordance refers to the risk at the individual rather than the pair level, and can be compared to risk rates for other familial pairings as well as the population prevalence. In addition, probandwise is not as sensitive as pairwise concordance to differences between studies in the ascertainment of affected twins. The use of probandwise concordance is therefore generally advocated in twin studies [17]. However, we report both, since most other twin studies of scoliosis report pairwise concordance only.

Tetrachoric correlations

The phenotypic, i.e. the tetrachoric, correlations, in MZ and DZ twin pairs were estimated. Differences provide information about the presence of genetic effects. When you have a dichotomous variable, e.g. having or not having scoliosis, this estimate assumes an underlying normally distributed susceptibility to the phenotype. A higher tetrachoric correlation in MZ compared to DZ twins indicates a genetic contribution. If the tetrachoric correlation in DZ twins is *approximately half* the value in MZ twins it indicates an additive genetic effect (A). If the tetrachoric correlation in DZ twins is *less than half* the value in MZ twins, it indicates a dominant or non-additive genetic effect (D). Dominant genetic effects refer to the non-additive effects of one allele at loci responsible for the effect, and additive genetic effects to when both alleles contribute across all responsible loci.

Variance partitioning

The phenotypic variance can be attributed to genetic, shared environmental and unique environmental effects. Statistical model fitting can be used to quantify the importance of these effects [18]. Heritability represents the relative importance of the genetic variance. Genetic variance, or broad sense heritability, reflects additive (A) and/or dominant (D) genetic effects. Shared environmental variance (C) reflects factors affecting twin similarity shared during upbringing (e.g. early household environment), while unique environmental variance (E) reflects environmental factors unique to each twin (e.g. a traffic accident).

Assuming that MZ twins have identical genomes, DZ twins share 50% of their segregating genes, and that twin pairs of both zygosities share 100% of their early

household environment, the correlations in genetic effects between twins can be set to 1 for MZ and 0.5 for DZ twins, and the correlations in shared environmental effects to 1 for both zygosities. Structural equation modelling can then be used to test different models for the variance partitioning and estimate the relative size of the contributing parameters. Full and nested models (ACE-AE-A and ADE-DE-D) were investigated as well as sex-limited models. These analyses were carried out in the Mx software program, which implements maximum likelihood methods [18]. The principle of parsimony was used to determine which nested model was to be preferred (e.g. ACE or AE) when the Chi-square goodness of fit test was not significant. The principle of parsimony means that the simplest explanation of the data is preferred. Akaike's information criterion (AIC) was used to compare goodness of fit between non-nested models (e.g. ACE and ADE).

National Patient Register

In Sweden, all citizens receive a unique social security number, which enables cross-matching between different registers. The National Patient Register consists of data on all inpatient visits in Sweden, by law, in designated areas of Sweden since 1964 and in all of Sweden since 1987. Data on outpatient visits has nationwide coverage since 2001, but primary healthcare is not yet covered. The register contains information on International Classification of Diseases (ICD) codes. The Swedish National Patient Register was used for two purposes: For identification of twins with more severe idiopathic scoliosis and for identification of twins with diagnoses that could be related to a non-idiopathic scoliosis.

All twins in the Swedish twin registry, not only those participating in the aforementioned surveys, were matched against inpatient data on the primary diagnosis idiopathic scoliosis. We used the following ICD codes for the primary diagnosis of idiopathic scoliosis: M41.1, M41.2 (ICD10), 737D, (ICD9), 735.99 (ICD8) 745.99 (ICD7). A pair was denoted concordant when both, and discordant when only one, twin/s were identified in the National Patient Register. Information on zygosity was retrieved from the Swedish Twin Registry.

Twins who replied "Yes" to the scoliosis question in the Twin Registry surveys and had ever received any of the ICD codes for diseases of the nervous system, congenital anomalies, congenital deformities, chromosomal aberrations and juvenile osteochondrosis (Scheuermann) were not considered in the analysis of prevalence. *Twin pairs* in which one of the twins had answered "Yes" to the scoliosis question and had received any of these diagnoses were not considered in the analysis of concordance, tetrachoric correlation and structural equation modelling.

Statistical software

Tetrachoric correlations and Chi-square for comparisons of prevalence were calculated in SAS version 9.2 (SAS Institute, Cary, NC, USA). Structural equation modelling was performed in Mx statistical program (version 1.54) [18].

Results

Descriptive data

In total 64,587 out of 104,349 individuals answered the question on scoliosis, giving a response rate of 62%.

Out of the 64,587 respondents, 2,571 twins (1,910 women and 661 men) with the mean age of 50 years replied "Yes" to the scoliosis question, giving a prevalence of 4.0% (5.4% for women and 2.2% for men). In 22,470 pairs, comprising 6,853 MZ and 7,779 same-sex DZ pairs, both twins responded. There was no significant difference in prevalence of scoliosis in MZ and same-sex DZ twin pairs ($p = 0.42$).

Concordances

We found 476 MZ pairs discordant for scoliosis and 50 concordant MZ pairs, compared to 546 discordant and 24 concordant same-sex DZ pairs. The pairwise concordances for MZ and DZ twins were 0.11 and 0.04 and the probandwise concordances 0.17 and 0.08, respectively. In order to avoid confounding by degenerative scoliosis we excluded all twins aged 50 years and older when answering the questionnaire ($n = 34{,}585$) but the results did not change substantially (data not shown).

Tetrachoric correlations

The tetrachoric correlation was higher in MZ twins compared to DZ twins (Table 1).

Variance partitioning

An AE model was found to be the most favourable model, according to the test statistics and the principle of parsimony, estimating that 0.38 of the variance in the liability to develop scoliosis is due to additive genetic effects and 0.62 to unique environmental effects (Table 2).

National Patient Register

One hundred and sixty-one twins were registered as inpatients due to idiopathic scoliosis in the National Patient

Table 1 Pair- and probandwise concordances and tetrachoric correlations of self-assessed scoliosis in the Swedish Twin Registry

	All	MZ	DZ same sex
Complete pairs (*n*)	22,470	6,853	7,779
Discordant pairs (*n*)	1,645	476	546
Concordant pairs (*n*)	94	50	24
Pairwise concordance	–	0.11	0.04
Probandwise concordance	–	0.17	0.08
Tetrachoric correlations (95% CI)	–	0.41 (0.33–0.49)	0.19 (0.09–0.29)

Complete pairs (*n*) = number of pairs where both twins have answered the scoliosis question. Discordant pairs (*n*) = number of pairs where one twin has scoliosis and the other does not. Concordant pairs (*n*) = number of pairs where both twins have scoliosis. The pair- and probandwise concordance is higher in mono- compared to dizygotic twins, indicating a genetic effect in the aetiology of scoliosis. The tetrachoric correlation in dizygotic twin pairs is approximately half the value in the monozygotic twin pairs, indicating an additive genetic effect

MZ monozygotic twins, *DZ* dizygotic twins, *CI* confidence interval

Table 2 Estimated effects of hereditary and environmental factors on the susceptibility to scoliosis in the Swedish Twin Registry

Fitted model	Genetic component	Shared environmental component	Unique environmental component	Chi-square goodness of fit
ACE	0.38 (0.18–0.46)	0.00 (0.00–0.17)	0.62 (0.54–0.70)	18.00
AE	0.38 (0.18–0.46)	–	0.62 (0.54–0.70)	18.00

Results are presented as proportion of variance (95% CI)

The AE model is found to be the most favourable according to the principle of parsimony, since there was no difference in Chi-square goodness of fit between the ACE and the AE model. Sex-specific models or models implying a dominant genetic effect did not have significantly better goodness of fit (data not shown)

ACE model implying additive genetic effects (A), shared environmental effects (C) and unique environmental effects (E); *AE* nested model implying additive genetic effects (A) and unique environmental effects (E) only

Register (1964–2008). Information on zygosity existed on 152 of these 161 twins in the Swedish Twin Registry. We found two concordant and 22 discordant MZ pairs compared to zero concordant and 25 discordant same-sex DZ twin pairs, giving pairwise/probandwise concordances of 0.08/0.15, respectively, for MZ twins, and zero/zero for same-sex DZ twins. We were able to estimate neither the tetrachoric correlations nor the heritability for inpatient twins since we found no concordant same-sex dizygotic pairs.

Discussion

Using a classic twin study approach, we have estimated the relative importance of hereditary and environmental factors in the aetiology of scoliosis. In this large population-based study we found that (1) idiopathic scoliosis is a hereditary condition, (2) the absolute risk of developing scoliosis for the twin of a person with scoliosis is estimated to be 0.15–0.17 in monozygotic and 0.00–0.08 in same-sex dizygotic twins, and (3) genetic effects explain 38% of the susceptibility to scoliosis.

All but one of the previous twin studies of scoliosis have been based on smaller clinical or case-series of twin pairs, showing higher pairwise concordances for monozygotic (0.76–0.92) compared to dizygotic twins (0.36–0.63), thus indicating a strong genetic effect [10, 11]. A population-based study from the Danish Twin Registry show pair-/probandwise concordances for self-assessed scoliosis in parity with our results: 0.13/0.25 in monozygotic and zero/zero in dizygotic twins [7]. One could hypothesize that the population-based study design, including all cases regardless of severity, explains the lower concordance figures.

In the present study, we analysed a cohort of more severe twin cases as well by cross-matching the Swedish Twin Registry with the National Patient Register on the primary diagnosis of idiopathic scoliosis. These twins, to be recorded in the National Patient Register, have either been treated with surgery, or started their brace treatment as inpatients. The pair- and probandwise concordances for these twins were in parity with the results from the self-assessment question of scoliosis, in both the Swedish and the Danish Twin Registry. The higher concordance rates in the clinical or case-series studies are as such likely to be due to sampling biases. The results from the present study and the previous population-based twin study indicate a genetic component but not as strong as that in the former studies.

Due to sample size constraints, previous twin studies of scoliosis have been able to report only concordance

analyses but no heritability estimates. Concordance analyses can only indicate a genetic effect while heritability studies estimate the magnitude of a genetic effect in the aetiology of a disorder. We have estimated that 38% of the variance in the liability to develop scoliosis is due to additive genetic effects, or in other words, the heritability of this condition is 38%.

Other studies have suggested a dominant genetic effect as a cause of idiopathic scoliosis [5]. Our findings do not support this since the models with an additive genetic effect provided a better fit in the variance partitioning than the models implying a dominant genetic effect. This is in agreement with a recent report proposing a polygenic inheritance of idiopathic scoliosis [3].

The major limitation of our study design is the use of self-assessment data, and accordingly, the lack of information on type and degree of scoliosis. However, the results from cross-matching with the National Patient Register strengthen the validity of our data for idiopathic scoliosis. In an effort to avoid confounding by degenerative scoliosis in the present study, we excluded all twins aged 50 years and older when answering the questionnaire, but the results did not change substantially. It therefore seems that degenerative scoliosis does not influence the results significantly.

The prevalence of X-ray verified scoliosis in the adult Swedish population is not known. We found a self-assessed prevalence of scoliosis of 4.0%, almost three times as high as that in the Danish Twin Registry (1.36%), despite the use of similar questions [7]. Differences in prevalence rates could be due to a true difference in prevalence, or a misclassification of the subjects answering the questionnaire. Reported prevalence rates of X-ray verified idiopathic scoliosis in girls (Cobb $\geq 10°$) have been similar in Sweden (3.2% among girls 7–16 years) and in Denmark (4.1% among girls 10–17 years) [19, 20]. The prevalence of scoliosis in adults, based on X-ray, has ranged between 2.7 and 11.9% [21, 22].

Classical twin studies, as the present study, are limited by their general assumptions of random mating, no gene–environment interaction and the equal environment assumption [23]. They cannot account for possible differences in the early developmental environment between twins and singletons, between monozygotic and dizygotic twins or between monozygotic twins themselves [24]. During childhood, monozygotic twins may be treated more similarly than dizygotic twins, which in the case of scoliosis might make parents more attentive to differences in physical appearance and as such more prone to discover a mild scoliosis in monozygotic than in dizygotic twins. Whether the prevalence of scoliosis differs between twins and singletons is not known. However, relatives to patients with idiopathic scoliosis have a higher prevalence of this condition than the population in general [1–3], and studies of twins do not differ from other family studies in this respect.

The major strength of this study is the large population-based sample. To our knowledge, this is both the largest population-based study of scoliosis, as well as the first study estimating the magnitude of genetic effects on the susceptibility to scoliosis. So far, genetic studies have not been able to reveal the responsible gene or genes. The reason could be a polygenetic background, a low penetrance of the phenotype [3] or the lack of homogenous families. Recent data indicate that a panel of genetic markers selected after a genome wide association analysis may be useful to predict progression of idiopathic scoliosis [25]. In conclusion, our results confirm a genetic component in the aetiology of idiopathic scoliosis, still indicating that other factors, so far unknown, might be important for the development of scoliosis.

The surveys were approved by the local ethics committee and informed consent was obtained from all subjects.

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Conflict of interest None.

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