EFORT open reviews

INSTRUCTIONAL LECTURE: SPINE | 7:6 | 414–421

Idiopathic scoliosis: a systematic review and meta-analysis of heritability

Tian Cheng[1], Elisabet Einarsdottir[2], Juha Kere[3,4] and Paul Gerdhem[1,5]

[1]Department of Clinical Science, Intervention and Technology (CLINTEC), Karolinska Institutet, Stockholm, Sweden
[2]Department of Gene Technology, School of Engineering Sciences in Chemistry, Biotechnology and Health, Royal Institute of Technology, Stockholm, Sweden
[3]Department of Biosciences and Nutrition (BioNut), Karolinska Institutet, Stockholm, Sweden
[4]Folkhälsan Research Center, Helsinki, Finland
[5]Department of Reconstructive Orthopaedics, Karolinska University Hospital, Stockholm, Sweden

Correspondence should be addressed to P Gerdhem
Email
paul.gerdhem@ki.se

- *Purpose:* Idiopathic scoliosis is the most common spinal deformity and affects 1–3% of children and adolescents. Idiopathic scoliosis may run in families and the purpose of this systematic review was to describe the degree of heritability.
- *Methods:* We searched Medline, Web of Science and EMBASE for family and twin studies reporting heritability estimates for idiopathic scoliosis, or studies from which heritability estimates could be calculated. Reference lists were screened for additional papers. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. The protocol was registered at PROSPERO (registration number: CRD42022307329).
- *Results:* The literature search identified 1134 reports. After full-text screening, nine eligible reports were included for data extraction. Seven were twin studies containing between 5 and 526 pairs, and two were family studies with 1149 and 2732 individuals, respectively. Quality was 'good' in four studies and 'fair' in five studies. In general, studies with radiograph-confirmed diagnosis reported higher heritability estimates than studies with self-reported diagnosis. Population-based twin studies reported lower heritability estimates than clinic-based twin studies. Family-based studies reported higher heritability estimates than twin studies. Pairwise concordance for scoliosis ranged from 0.11 to 1.00 in monozygotic twins and from 0 to 1.0 in dizygotic twins. A meta-analysis of three studies resulted in a narrow sense heritability estimate of 0.57 (95% CI: 0.29–0.86).
- *Conclusion:* Twin and family studies indicate a hereditary component in idiopathic scoliosis, but study heterogeneity is large, and the degree of the heritability is uncertain. Nevertheless, known genetic variants associated with idiopathic scoliosis can still only explain a minor part of heritability.

Keywords

- scoliosis
- heritability
- genetics

EFORT Open Reviews (2022) **7**, 414–421

Introduction

Idiopathic scoliosis is the most common type of spinal deformity, occurring in 1–3% of children and adolescents worldwide (1, 2, 3). If progressive, untreated scoliosis may progress to a severe deformity with detrimental effect on pulmonary function (Fig. 1) (4). Surgery is the only available treatment for severe scoliosis.

The genetic component in idiopathic scoliosis is well established, yet poorly understood. Twin studies in idiopathic scoliosis have reported higher concordance rates in monozygotic twins compared to dizygotic twins (Fig. 2) (5, 6). Family studies have also reported a higher prevalence of scoliosis in relatives compared to the general population (7, 8, 9). Despite this, the inheritance pattern and the aetio-pathophysiology of idiopathic scoliosis are yet to be fully understood (10). Studies on familial forms of idiopathic scoliosis have identified several modes of inheritance including X-linked, autosomal dominant and multifactorial (11, 12). A few high penetrance risk loci have been identified (11, 12). However, the proportion of idiopathic scoliosis patients that follow these Mendelian inheritance patterns is small and today, idiopathic scoliosis is regarded as a complex trait (10, 12). Like other complex traits, they do not follow the Mendelian inheritance pattern and a combination of multiple low penetrance risk

www.efortopenreviews.org
https://doi.org/10.1530/EOR-22-0026

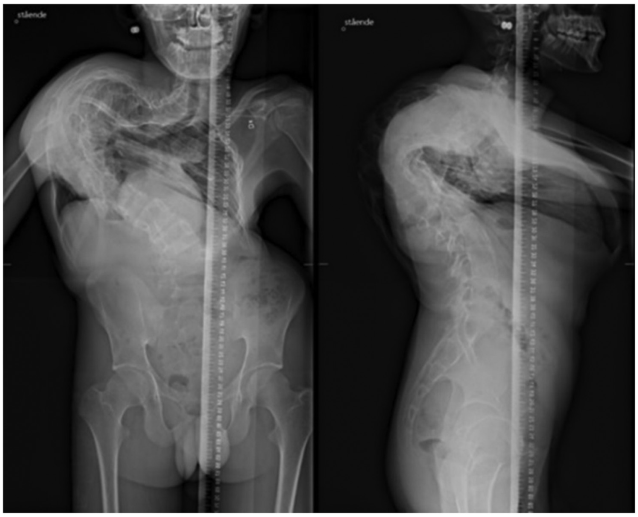

Figure 1
Severe untreated idiopathic scoliosis with severe restriction of the thoracic cage and pulmonary compromise in a male adolescent.

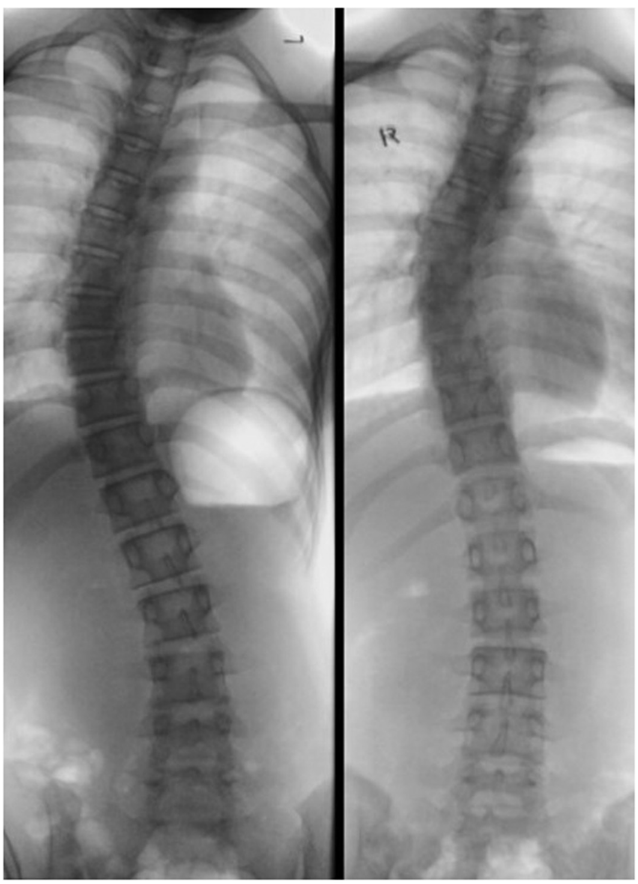

Figure 2
Female twin couple with moderate scoliosis.

loci and environmental factors are the most likely cause of the scoliosis phenotype (10, 12, 13).

Candidate gene studies and genome-wide association studies have identified several idiopathic scoliosis susceptibility loci, for example, near the genes *LBX1, GPR126/ADGRG6, PAX1 and BNC2* (14, 15, 16, 17, 18, 19). The mechanisms by which these susceptibility genes contribute to the phenotype of scoliosis are unclear. Furthermore, the currently well-known and replicated loci can only explain a small percentage of all possible loci and the missing heritability remains a concern (14, 15, 16, 17, 18, 19, 20).

Heritability is an important parameter in quantitative genetics and estimates the proportion of a specific phenotypic variance that is attributed to differences in genes in a specific population (21). Heritability, however, is not a direct measure of the genetic effect on a trait.

The heritability of idiopathic scoliosis has been reported in a few studies with different methodologies supporting the importance of hereditary factors (5, 7, 22). However, the proportion of the observed variance in idiopathic scoliosis that is attributed to genetics is highly uncertain. In this systematic review and meta-analysis, we aimed to describe the degree of heritability in idiopathic scoliosis estimated from twin or family studies.

Materials and methods

Preliminary searches were made in December 2021 and January 2022, to pilot the study selection process. The systematic review protocol was uploaded to the International prospective register of systematic reviews on January 26, 2022 (PROSPERO; www.crd.york.ac.uk/PROSPERO). The PROSPERO registration number is CRD42022307329. The review process was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Research question

How large is the degree of heritability in idiopathic scoliosis?

PECO outline

Population: Individuals investigated for idiopathic scoliosis.
Exposure: Relatedness (twin pairs or families).
Controls: Individuals without idiopathic scoliosis.
Outcome: Heritability estimates.

Inclusion criteria

Included were reports with estimates of heritability for idiopathic scoliosis from twin or family studies. Accepted estimates were concordance rates, twin correlations or

heritability estimates including broad or narrow sense heritability, as well as reports allowing calculation of heritability estimates. No age criteria were applied. Excluded were publications that did not report any new findings (such as reviews) and non-English reports.

Literature search

Searches were made in MEDLINE, EMBASE and Web of Science. The final literature search for this systematic review was made by experienced librarians on February 4, 2022. The search terms are available in Supplementary Appendix 1 (see section on supplementary materials given at the end of this article).

Report selection

In the initial screening, titles and abstracts were screened by the authors TC and PG with the Rayyan software (23) to identify the reports fulfilling the inclusion criteria. Articles were stored in the Rayyan software and in a citation manager (Endnote). Full-text reading on reports that were identified in the initial screening was performed independently by the authors TC and PG. Reference lists of the identified reports were screened for additional reports that fulfilled the inclusion criteria. Discrepancies in report selection were solved by discussion by authors TC and PG and if needed after reading the full-length reports or with the help of a third reviewer (EE).

Data extraction

The following data (when available) was extracted and tabulated.

- Study type (twin/family)
- Country of origin for study
- Study size
- Scoliosis diagnosis
- Method of determining zygosity
- Data on curve size
- Concordance for monozygotic (MZ) twins (pairwise and probandwise)
- Concordance for dizygotic (DZ) twins (pairwise and probandwise)
- Tetrachoric correlations for monozygotic twins (dichotomous trait)
- Tetrachoric correlations for dizygotic twins (dichotomous trait)
- Correlations for monozygotic twins (continuous trait)
- Correlations for dizygotic twins (continuous trait)
- Broad sense heritability
- Narrow sense heritability
- Structural equation modelling data

Calculation of heritability estimates

Heritability estimates were calculated in reports that lacked heritability estimates but contained available relevant data for calculation.

Pairwise concordance estimates the probability of both siblings in a twin pair being affected when one twin in the pair is affected. Pairwise concordance was extracted from the report if available or calculated as follows: $C/(C+D)$. C is the number of concordant pairs and D is the number of discordant pairs (24).

Probandwise concordance estimates the probability of the other twin being affected when one twin is affected (24). Probandwise concordance was extracted from the report if available or calculated as follows: $2C/(2C+D)$.

Correlations for the curve severity (Cobb angle) were extracted from the report, or if data were available in the report calculated as Spearman rank correlations (95% CIs).

Broad sense heritability represents all the genetic contribution to the phenotypic variance in the population and includes additive, dominant, epistatic effects, as well as maternal and paternal effects (25). It was calculated using Falconer's formula $(H^2 = 2(r_{MZ} - r_{DZ})$ for continuous data (26) or Holzinger's formula $(H^2 = (concordance_{MZ} - concordance_{DZ})/(1 - concordance_{DZ}))$ for concordance measures from dichotomous data if these were not available in the report. 'r' represents the correlation for the trait from the tetrachoric or the Spearman correlations in monozygotic and dizygotic twins, respectively.

Heritability assumptions

In twin studies, the concordance rate of idiopathic scoliosis between monozygotic and dizygotic twins was used to calculate the heritability estimates. This method assumes that 100% of the genome is shared between monozygotic twins while 50% of the genome is shared between dizygotic twins. The twin method is a robust way to minimize environmental confounding (27).

In family studies, the prevalence of idiopathic scoliosis in family members and controls were used to calculate heritability estimates. This method assumes that 50% of the genome is shared between a parent and a child and between two siblings. The genome shared between first-degree cousins is assumed to be 12.5% (27).

Narrow sense heritability represents the proportion of phenotypic variance due to additive genetic variation (25).

Statistical analysis

Meta-analysis was performed with a restricted maximum likelihood model in which narrow sense heritability and S.E. was entered. Spearman correlations (95% CI) were

calculated for studies with available data for curve severity. SPSS version 27 was used for statistical analysis.

Risk of bias assessment

Risk of bias assessment was performed due to its potential impact on the results and conclusions. Quality of the reports was assessed by semi-quantitative grading using the Study Quality Assessment Tools for case–control studies, available at www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools independently by TC and PG. Discrepancies in the quality assessment were solved by discussion by TC and PG. The overall quality was assessed as good, fair or poor.

Results

Report selection

Figure 3 shows the flowchart of report selection. A total of 1870 reports were identified in the initial search. After deduplication, including a comparison of digital object identifiers (28), 1134 reports remained and were screened for eligibility. After initial screening for title and abstracts, 20 out of the available 1134 reports qualified for full-text screening. An additional 12 reports were identified from the reference lists of the identified reports and were also qualified for full-text screening. Nine reports were found eligible after full-text screening (5, 6, 7, 22, 29, 30, 31, 32, 33). Among the 23 excluded reports, 21 lacked heritability estimates or data sufficient for the calculation of heritability estimates, one report included non-idiopathic scoliosis and one report was not in English.

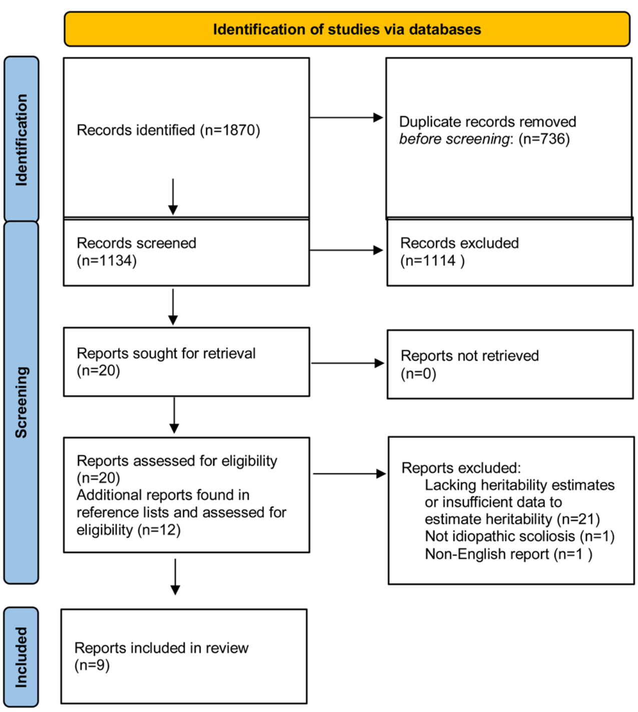

Figure 3
PRISMA flowchart.

Sample characteristics

The studies originated from countries in East Asia, Europe and North America. Seven were twin studies and two were family studies. The publication years for the included studies ranged from 1967 to 2016. The sample sizes ranged between 5 and 526 pairs in the twin studies, and 1149 and 2732 individuals in the family studies.

Results synthesis

The summary of extracted data from the nine studies is presented in Table 1.

Twin studies

Scoliosis diagnosis was confirmed by radiographs in five studies and was self-reported in two studies, both from Scandinavia. In the twin study from Sweden, the diagnosis was partially based on self-reported data and partially based on data from the National Patient Register.

Our results show that pairwise concordance rates for monozygotic twins (spanning from 0.11 to 1.0) were approximately twice the pairwise concordance rates for dizygotic twins (spanning from 0 to 1.0) in most studies. Broad sense heritability spanned between 0.13 and 1.0, whereas the only available narrow sense heritability estimate in a twin study was 0.38.

Family studies

The scoliosis diagnosis was confirmed for the probands using radiographs in both studies. Narrow sense heritability estimates were 0.49 and 0.88, respectively.

Meta-analysis

A meta-analysis of three studies resulted in a narrow sense heritability estimate of 0.57 (95% CI: 0.29-0.86) (Fig. 4).

Discussion

Twin and family studies indicate a hereditary component in idiopathic scoliosis, but study heterogeneity is large, and the degree of the heritability is uncertain.

Few studies received the 'good' overall score in the risk of bias assessment. Two twin studies were population-based and included a large population from the Swedish twin registry and the Danish twin registry (5, 6). Despite this, a major drawback was that scoliosis was self-reported instead of radiographically confirmed hence receiving

Table 1 Summary of the data extraction from the nine included studies. Data within parentheses are CIs if not stated otherwise.

	Simony *et al.* (33)*	Grauers *et al.* (5)	Andersen *et al.* (6)*	Inoue *et al.* (32)	Kesling & Reinker (31)	Carr (30)	Fisher & DeGeorge (29)	Tang *et al.* (7)	Yang *et al.* (22)
Study type (twin/family)	Twin	Twin	Twin	Twin	Twin	Twin	Twin	Family	Family
Study size	21 pairs	526 pairs[a]	135 pairs	21 pairs	5 pairs[b]	6 pairs	14 pairs	1149 individuals	2732 individuals
Country of origin for study	Denmark	Sweden	Denmark	Japan	USA	UK	USA	HongKong	China
Scoliosis diagnosis	Radiographs	Self-assessment	Self-assessment	Radiographs	Radiographs	Radiographs	Radiographs	Radiographs	Radiographs
Zygosity determined by	DNA	Question-naire	Question-naire	DNA	Blood chemistry	DNA	Blood chemistry, clinical		
Data on curve size available	Partly	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Concordance for monozygotic twins (pairwise)	0.40 (0.10 to 0.70)	0.11	0.13 (0.05 to 0.27)	0.92	0.50[c]	0.67	1.00[d]		
Concordance for monozygotic twins (probandwise)	0.45 (0.16 to 0.74)	0.17	0.25 (0.17 to 0.37)	0.96[c]	0.33[c]	0.33[c]	0.50[c, d]		
Concordance for dizygotic twins (pairwise)	0.05 (−0.05 to 0.15)	0.04	0.00 (0.00 to 0.03)	0.62	1.0[c]	0.0	0.57[d]		
Concordance for dizygotic twins (probandwise)	0.10 (−0.03 to 0.23)	0.08	0.00	0.77[c]	0.5[c]	0.0[c]	0.36[c, d]		
Tetrachoric correlations for monozygotic twins (dichotomous trait)		0.41 (0.33 to 0.49)							
Tetrachoric correlations for dizygotic twins (dichotomous trait)		0.19 (0.09 to 0.29)							
Correlations for monozygotic twins (continuous trait)				0.84 (0.53 to 0.95)			0.49 (−0.56 to 0.94)[c]		
Correlations for dizygotic twins (continuous trait)				0.52 (−0.32 to 0.90)			−0.96 (−0.99 to −0.70)[c]		
Broad sense heritability	0.70[c]	0.44[c]	0.13[c]	0.79[c]		0.67[c]	1.0[c]		
Narrow sense heritability		0.38 (s.e. = 0.10)						0.88 (s.e. = 0.11)	0.49 (s.e. = 0.03)
Quality assessment	Good	Fair	Fair	Fair	Fair	Good	Good	Good	Fair

*These studies partly overlap; [a]Additional cohort with 152 twin pairs with separately presented data. MZ pairwise concordance 0.08, DZ pairwise concordance 0; [b]Five pairs with available data; [c]Calculated data (see methods section); [d]Concordance rate calculated with 10 degree Cobb as threshold for affected.

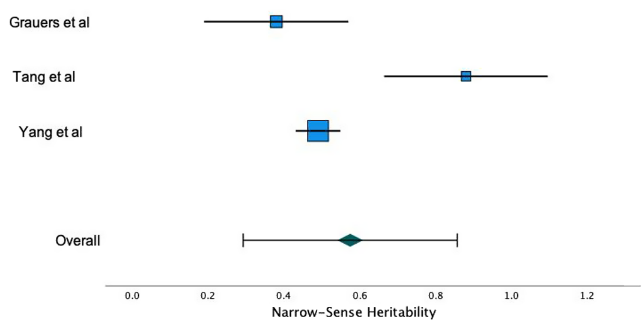

Figure 4

Forest plot for narrow sense heritability data (95% CI). The I^2 statistic was 90%, indicating a high degree of heterogeneity for the three studies.

the 'fair' overall score. Both studies yielded relatively low heritability estimates and concordance rates. For the remaining five twin studies, the diagnosis was confirmed with radiographs, but the included population was smaller (5–21 twin pairs for each study). Studies that received the 'fair' overall score lacked detailed reporting on the recruiting process and a complete lack of reporting on one twin pair (31, 32).

The five twin studies included were performed in Scandinavia, United Kingdom, United States and Japan while both family studies were performed in China (Hong Kong and Mainland) (5, 6, 7, 22, 29, 30, 31, 32, 33). The ethnicity of the population included was however not fully reported on. Therefore, we could not draw any conclusion on the differences in heritability in different ethnic groups. Since females are predominantly represented in idiopathic scoliosis, few males were included in the reports and we were thus unable to draw any conclusions about heritability, taking the patient's sex into consideration.

Heritability differences between studies

There is considerable heterogeneity between the studies regarding study design, diagnosis method, zygosity method, study population and heritability estimation methods, predictably resulting in large differences in the estimated heritability (21, 27). It is important, however, to point out that heritability is a concept specific to the population and trait in the specific environment it is estimated in. Heritability is the proportion of phenotypic variance caused by genetic factors and is not the proportion of a phenotype that is due to genetic factors (21, 27). Heritability estimates are therefore not constant and depend on, for example, allele frequencies, environmental factors, age at sampling and if new variants are introduced. The effect of genetics may also be modified by treatment. Therefore, heritability estimates only predict the heritability in the studied population. Despite this, it is also important to point out that heritability is fairly constant across populations and is therefore a particularly useful concept in understanding genetic influence on traits (21, 27).

In this systematic review, heritability estimates varied largely, as expected. In all seven twin studies, both the pairwise and probandwise concordance rates were about two times higher in monozygotic twins than in dizygotic twins. The self-reported twin studies yielded lower heritability estimates than studies with radiograph-confirmed scoliosis. This was expected, as the self-reported studies were population-based and included a much larger sample size. Furthermore, mild scoliosis can have little or no symptoms and be difficult to detect. It is likely that some twin pairs with self-reported 'no' to scoliosis can have a Cobb angle of more than 10° if radiographed. On the contrary, it is also likely that some individuals might have self-reported 'yes' to scoliosis despite not having confirmed scoliosis or other spinal deformities (33). Ideally, a population-based approach using a twin registry together with radiographically confirmed diagnosis will yield the most accurate concordance rate and heritability estimates (33). For the five studies where the diagnosis was confirmed by radiograph, we could not calculate the heritability estimate for one study as only one dizygotic twin pair was available (31). Broad sense heritability was significantly higher for the remaining studies. This might be because the included participants were not recruited through a population-based approach, with the risk of selection bias and overestimation of heritability.

Although the hereditary component in idiopathic scoliosis has been well established, few studies have studied heritability (12). As with other complex traits of polygenic nature, inheriting one risk allele for idiopathic scoliosis would not necessarily result in the scoliosis phenotype (10). The risk allele is most likely one of many contributing risk factors together with other genetic and environmental factors that in combination cause the disease. However, quantifying heritability gives a notion of how much of a trait is explained by genetics and could thereafter inform genetic risk estimation (21). Ultimately, it could help to lead to a better understanding of the pathogenesis of idiopathic scoliosis.

Candidate gene studies and genome-wide associations have identified several susceptibility loci in idiopathic scoliosis. The most replicated candidate genes include among others *LBX1*, *GPR126/ADGRG6*, *PAX1* and *BNC2* (14, 15, 16, 17, 18, 19). Several other loci have been identified, but most could not be replicated in other populations. The mechanisms through which the candidate loci may be driving idiopathic scoliosis susceptibility are yet to be understood. Furthermore, these variants only account for a very small percentage of all the risk variants, and most of the risk factors contributing to idiopathic scoliosis are yet to be identified (12).

The study's strengths include the robust study design following PRISMA guidelines and with prespecified protocol registered in PROSPERO. A literature search was performed in three major databases by senior librarians with previous experience with systematic reviews. Our research group also has previous experience in scoliosis and heritability research possibly improving the ability to select eligible studies. We also did not limit the inclusion criteria to only studies reporting heritability estimates but also included reports where heritability estimates could be calculated.

This study is not without its limitations. As discussed above, two twin studies included self-reported diagnosis for idiopathic scoliosis with potential for sampling bias. For the other twin studies, sample sizes were fairly small with the potential risk of selection bias. Furthermore, only English reports were included with the potential risk of missing data. However, we consider this risk low. Non-English reports were few, had small sample sizes and were mostly published more than half a century ago. Kesling *et al.* performed a meta-analysis in MZ and DZ twins in idiopathic scoliosis including non-English reports. The majority of the reports included contained less than 8 pairs of twins apart from one German study by Berquet *et al.* that included 29 twin pairs and further 16 twin pairs were 'cited in German literature' (34). The meta-analysis reported a MZ concordance of 0.73 and DZ concordance of 0.36 (31).

We included only classical study designs for heritability estimates, twin and family studies. These classical designs have the limitation of assuming shared environmental influences among twins and family members and additive genetic variances which may not be true, hence overestimating the heritability (21, 27). Novel study designs using genome-wide association studies for heritability estimate can be helpful in understanding the missing heritability in the future. However, current limitations to this method include sample size requirements and small effect sizes for each variant (21, 27).

In conclusion, this systematic review confirms that twin and family studies indicate a hereditary component in idiopathic scoliosis, but study heterogeneity is large, and the degree of the hereditary component is variable.

Supplementary materials

This is linked to the online version of the paper at https://doi.org/10.1530/EOR-22-0026.

ICMJE Conflict of Interest Statement

P G reports receiving lecture fees from Depuy Synthes, Johnson & Johnson and royalties from Studentlitteratur, Lund, Sweden not related to the work presented here. All other authors have nothing to disclose.

Funding Statement

The work for this review was funded by a grant from CIMED/Karolinska Institutet, the Swedish Research Council (number 2012-02275 and 2017-01639) and the Region Stockholm ALF-support. Paul Gerdhem was supported by Region Stockholm in a clinical research appointment.

Acknowledgement

The authors thank Jonas Pettersson and Narcisa Hennerz, librarians at the Karolinska Institutet, Sweden, for help with the systematic literature search.

References

1. Fong DY, Lee CF, Cheung KM, Cheng JC, Ng BK, Lam TP, Mak KH, Yip PS & Luk KD. A meta-analysis of the clinical effectiveness of school scoliosis screening. *Spine* 2010 **35** 1061–1071. (https://doi.org/10.1097/BRS.0b013e3181bcc835)

2. Luk KD, Lee CF, Cheung KM, Cheng JC, Ng BK, Lam TP, Mak KH, Yip PS & Fong DY. Clinical effectiveness of school screening for adolescent idiopathic scoliosis: a large population-based retrospective cohort study. *Spine* 2010 **35** 1607–1614. (https://doi.org/10.1097/BRS.0b013e3181c7cb8c)

3. Willner S & Udén A. A prospective prevalence study of scoliosis in Southern Sweden. *Acta Orthopaedica Scandinavica* 1982 **53** 233–237. (https://doi.org/10.3109/17453678208992208)

4. Pehrsson K, Larsson S, Oden A & Nachemson A. Long-term follow-up of patients with untreated scoliosis. A study of mortality, causes of death, and symptoms. *Spine* 1992 **17** 1091–1096. (https://doi.org/10.1097/00007632-199209000-00014)

5. Grauers A, Rahman I & Gerdhem P. Heritability of scoliosis. *European Spine Journal* 2012 **21** 1069–1074. (https://doi.org/10.1007/s00586-011-2074-1)

6. Andersen MO, Thomsen K & Kyvik KO. Adolescent idiopathic scoliosis in twins: a population-based survey. *Spine* 2007 **32** 927–930. (https://doi.org/10.1097/01.brs.0000259865.08984.00)

7. Tang NL, Yeung HY, Hung VW, Di Liao C, Lam TP, Yeung HM, Lee KM, Ng BK & Cheng JC. Genetic epidemiology and heritability of AIS: a study of 415 Chinese female patients. *Journal of Orthopaedic Research* 2012 **30** 1464–1469. (https://doi.org/10.1002/jor.22090)

8. Riseborough EJ & Wynne-Davies R. A genetic survey of idiopathic scoliosis in Boston, Massachusetts. *Journal of Bone and Joint Surgery: American Volume* 1973 **55** 974–982. (https://doi.org/10.2106/00004623-197355050-00006)

9. Wynne-Davies R. Familial (idiopathic) scoliosis. A family survey. *Journal of Bone and Joint Surgery: British Volume* 1968 **50** 24–30.

10. Cheng JC, Castelein RM, Chu WC, Danielsson AJ, Dobbs MB, Grivas TB, Gurnett CA, Luk KD, Moreau A, Newton PO, *et al.* Adolescent idiopathic scoliosis. *Nature Reviews: Disease Primers* 2015 **1** 15030. (https://doi.org/10.1038/nrdp.2015.30)

11. Khanshour A & Wise C. The Genetic Architecture of Adolescent Idiopathic Scoliosis.*In: Pathogenesis of Idiopathic Scoliosis* (Eds) M Machida, M Weinstein, J Dubousset, Springer: Tokyo, Japan 2018. (https://doi.org/10.1007/978-4-431-56541-3_3)

12. Tang NLS, Dobbs MB, Gurnett CA, Qiu Y, Lam TP, Cheng JCY & Hadley-Miller N. A decade after idiopathic scoliosis was first called a complex trait-a tribute to the late Dr. Yves Cotrel for his support in studies of etiology of scoliosis. *Genes* 2021 **12** 1033.

13. Cheng JC, Tang NL, Yeung HY & Miller N. Genetic association of complex traits: using idiopathic scoliosis as an example. *Clinical Orthopaedics and Related Research* 2007 **462** 38–44. (https://doi.org/10.1097/BLO.0b013e3180d09dcc)

14. Takahashi Y, Kou I, Takahashi A, Johnson TA, Kono K, Kawakami N, Uno K, Ito M, Minami S, Yanagida H, *et al.* A genome-wide association study identifies common variants near LBX1 associated with adolescent idiopathic scoliosis. *Nature Genetics* 2011 **43** 1237–1240. (https://doi.org/10.1038/ng.974)

15. Kou I, Takahashi Y, Johnson TA, Takahashi A, Guo L, Dai J, Qiu X, Sharma S, Takimoto A, Ogura Y, *et al.* Genetic variants in GPR126 are associated with adolescent idiopathic scoliosis. *Nature Genetics* 2013 **45** 676–679. (https://doi.org/10.1038/ng.2639)

16. Sharma S, Londono D, Eckalbar WL, Gao X, Zhang D, Mauldin K, Kou I, Takahashi A, Matsumoto M, Kamiya N, *et al.* A PAX1 enhancer locus is associated with susceptibility to idiopathic scoliosis in females. *Nature Communications* 2015 **6** 6452. (https://doi.org/10.1038/ncomms7452)

17. Ogura Y, Kou I, Miura S, Takahashi A, Xu L, Takeda K, Takahashi Y, Kono K, Kawakami N, Uno K, *et al.* A functional SNP in BNC2 is associated with adolescent idiopathic scoliosis. *American Journal of Human Genetics* 2015 **97** 337–342. (https://doi.org/10.1016/j.ajhg.2015.06.012)

18. Ogura Y, Takeda K, Kou I, Khanshour A, Grauers A, Zhou H, Liu G, Fan Y-H, Zhou T, Wu Z, *et al.* An international meta-analysis confirms the association of BNC2 with adolescent idiopathic scoliosis. *Scientific Reports* 2018 **8** 4730.

19. Khanshour AM, Kou I, Fan Y, Einarsdottir E, Makki N, Kidane YH, Kere J, Grauers A, Johnson TA, Paria N, *et al.* Genome-wide meta-analysis and replication studies in multiple ethnicities identify novel adolescent idiopathic scoliosis susceptibility loci. *Human Molecular Genetics* 2018 **27** 3986–3998. (https://doi.org/10.1093/hmg/ddy306)

20. Young AI. Solving the missing heritability problem. *PLoS Genetics* 2019 **15** e1008222. (https://doi.org/10.1371/journal.pgen.1008222)

21. Visscher PM, Hill WG & Wray NR. Heritability in the genomics era – concepts and misconceptions. *Nature Reviews: Genetics* 2008 **9** 255–266. (https://doi.org/10.1038/nrg2322)

22. Yang T, Jia Q, Guo H, Xu J, Bai Y, Yang K, Luo F, Zhang Z & Hou T. Epidemiological survey of idiopathic scoliosis and sequence alignment analysis of multiple candidate genes. *International Orthopaedics* 2012 **36** 1307–1314. (https://doi.org/10.1007/s00264-011-1419-z)

23. Ouzzani M, Hammady H, Fedorowicz Z & Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. *Systematic Reviews* 2016 **5** 210. (https://doi.org/10.1186/s13643-016-0384-4)

24. Allen G, Harvald B & Shields J. Measures of twin concordance. *Acta Genetica et Statistica Medica* 1967 **17** 475–481. (https://doi.org/10.1159/000152101)

25. Knopik VS, Neiderhiser JM, DeFries JC & Plomin R. *Behavioral Genetics*. Worth Publishers, Macmillan Learning, 2017.

26. Falconer DS. *Introduction to Quantitative Genetics*. India: Pearson Education, 1996.

27. Mayhew AJ & Meyre D. Assessing the heritability of complex traits in humans: methodological challenges and opportunities. *Current Genomics* 2017 **18** 332–340. (https://doi.org/10.2174/1389202918666170307161450)

28. Bramer WM, Giustini D, de Jonge GB, Holland L & Bekhuis T. De-duplication of database search results for systematic reviews in EndNote. *Journal of the Medical Library Association* 2016 **104** 240–243. (https://doi.org/10.3163/1536-5050.104.3.014)

29. Fisher RL & De George FV. A twin study of idiopathic scoliosis. *Clinical Orthopaedics* 1967 **55** 117–126.

30. Carr AJ. Adolescent idiopathic scoliosis in identical twins. *Journal of Bone and Joint Surgery: British Volume* 1990 **72** 1077. (https://doi.org/10.1302/0301-620X.72B6.2246294)

31. Kesling KL & Reinker KA. Scoliosis in twins. A meta-analysis of the literature and report of six cases. *Spine* 1997 **22** 2009–2014; discussion 15. (https://doi.org/10.1097/00007632-199709010-00014)

32. Inoue M, Minami S, Kitahara H, Otsuka Y, Nakata Y, Takaso M & Moriya H. Idiopathic scoliosis in twins studied by DNA fingerprinting: the incidence and type of scoliosis. *Journal of Bone and Joint Surgery: British Volume* 1998 **80** 212–217. (https://doi.org/10.1302/0301-620x.80b2.7544)

33. Simony A, Carreon LY, H Jmark K, Kyvik KO & Andersen MØ. Concordance rates of adolescent idiopathic scoliosis in a Danish twin population. *Spine* 2016 **41** 1503–1507. (https://doi.org/10.1097/BRS.0000000000001681)

34. Berquet KH. Considerations on heredity in idiopathic scoliosis. *Zeitschrift Fur Orthopadie und Ihre Grenzgebiete* 1966 **101** 197–209.