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Original article

Familial aggregation and heritability of ankylosing spondylitis – a Swedish nested case–control study

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Abstract

Objectives. AS is known to be a highly heritable disease, but previous studies on the magnitude of the familial aggregation and heritability of AS have been small and inconclusive, with familial relative risks ranging from 17 to 94. We aimed to improve estimates of these factors by studying families of all subjects diagnosed with AS in Sweden over a period of 16 years and to investigate if familial risks vary by sex or type of relative.

Methods. In a nested case–control study, we identified AS index patients from the National Patient Register (NPR) and the Swedish Rheumatology Quality Register (SRQ) between 2001 and 2016. Each index patient was matched on age and sex to up to 50 general population controls. First-degree relatives of index patients and controls were identified through the Multi-Generation Register, with disease status ascertained in the NPR and SRQ. Familial risks were defined as odds ratios (ORs) of having AS when exposed to a first-degree relative with AS, using conditional logistic regression.

Results. The overall familial OR for AS was 19.4 (95% CI 18.1, 20.8). Estimates were similar for different relative types and by sex, but having more than one affected relative resulted in a higher risk [OR 68.0 (95% CI 51.3, 90.1)]. Heritability, estimated by assuming sibling risks were completely due to genetics, was 77% (95% CI 73, 80).

Conclusion. Although the familial risk and heritability of AS are higher than for most other diseases, we report estimates that are substantially lower than commonly referenced numbers for AS from other populations.

Key words: ankylosing spondylitis, familial aggregation, heritability, epidemiology

Rheumatology key messages

- Familial risks and heritability of AS are high, although not as high as previously reported.
- AS risk was similarly increased, about 20-fold, in parents, siblings and children of probands.
- The heritability proposed here might still be overestimating the influence of genetics on AS risk.

CLINICAL SCIENCE

Introduction

It is well known that AS displays strong familial aggregation [1]. Studies of mainly European populations have found the AS prevalence to be 0.1–0.4% [2–8], while in first-degree relatives of AS patients risks reaching 4–11% have been reported [9–11]. In addition, twin studies have reported a pairwise concordance rate of 25–75% in monozygotic twins and 4–15% in dizygotic twins [12–14]. Together, this suggests an important influence of genetic factors, and indeed a number of alleles linked to AS susceptibility have been identified. The strongest association by far is with HLA-B27, which is present in 85–95% of cases [15–17], but also in ∼10% of Caucasians overall [15–18].

The strong familial aggregation has several important implications: in directing aetiological research, making family history a diagnostic criterion and as a potential matter of concern for patients living with the disease. It is thus unfortunate that the precision of previous estimates of familial aggregation of AS have been limited by the small study size, and in some cases probable selection bias, of earlier studies. When compiling data from six studies, comprising 404 affected first-degree relatives of AS index patients, Brown *et al.* [19] reported a recurrence risk ratio of 82. In the absence of a control group, this estimate was based on (and is thus highly sensitive to) an assumed population prevalence. Studies in the Icelandic population have reported relative risks in

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first-degree relatives ranging from 75 to 94, based on data from 256 patients in total [20, 21]. In contrast, a register-based study of 3509 hospitalized AS patients in Sweden reported a sibling risk of 17 in siblings of affected individuals [22].

Similar uncertainties surround the heritability of AS. Heritability is defined as the proportion of variance in a phenotypic trait that is explained by genetic variation. Twin studies have indicated that the heritability of AS is 90–99% [12, 14], which would make AS one of the most heritable of all studied phenotypes [23], as compared with, for example, RA (40%) [24], IBD (65–75%) [25] and even adult height (80–90%) [26, 27]. The heritability studies on AS were severely underpowered however, including 27 and 40 twin pairs and only 12 concordant pairs in total [12, 14]. It is currently believed that slightly >20% of the heritability of AS is explained by HLA-B27, and an additional 8% is accounted for by other loci [28], but the majority of the heritability remains unexplained. If current figures of AS heritability are overestimated, this could explain part of this 'missing heritability'.

Against this background, we aimed to provide more accurate estimates of the familial aggregation and heritability of AS. To this end we performed a case–control study using Swedish nationwide registers including >13 000 AS patients together with general population controls and first-degree relatives of both groups.

Methods

Study design

We performed a nested case–control study by linking data from Swedish nationwide population and health registers. Index patients with AS were identified from two sources: the National Patient Register (NPR) and the Swedish Rheumatology Quality Register (SRQ). The NPR contains data on diagnoses from hospital visits for inpatient care since 1964 and for specialist outpatient care since 2001. A validation of NPR has found the positive predictive value for a diagnosis of AS to be 79–85% according to the Assessment of SpondyloArthritis international Society (ASAS) criteria and 70–80% with respect to the modified New York criteria [29]. The SRQ is a clinical register that longitudinally captures disease activity, disease characteristics and anti-rheumatic therapy as registered by the treating rheumatologist. Initially started for RA in 1995, the SRQ was later extended to patients with AS and other rheumatic diseases, especially those on treatment with biologic agents [30].

For each index patient, general population controls were randomly selected from a subset of the Swedish Total Population Register. This subset of 1 537 147 individuals had previously been selected as controls (matched 5:1 by sex, birth year and place of residence) to a larger cohort of patients with chronic inflammatory arthritis. Because of the low AS prevalence in the general population and an expected high familial aggregation of AS, we resampled from the total pool of controls to reach 50 controls per case in order to sufficiently increase the number of affected relatives of controls included in the study. Eligible controls were alive, living in Sweden and with no history of AS at the date of the first AS diagnosis in the index patient. Controls were matched to index patients by sex and birth year. First-degree relatives, i.e. parents, children and full siblings, of index patients and controls were identified through the Multi-Generation Register. This register holds information on parents of Swedish residents born after 1931 and ever registered as living in Sweden since 1961, which also allowed for the identification of siblings and children of index patients. The study was approved by the Regional Ethics Review Board in Stockholm (2015/1844-31/2). Participant consent was not obtained, as this was a register-based study with anonymized data.

Identification of study population and exposure

We identified all patients in the NPR having at least one visit to a specialist clinic in rheumatology or internal medicine listing an AS diagnosis [International Classification of Diseases, 10th Revision (ICD-10); code M45 or M08.1] from 1 January 2001 through 31 December 2016. This corresponded to the disease definition in the validation study of AS in the NPR [29]. To further increase validity, we also required index patients to have at least one more visit between 1987 and 2016 with an AS diagnosis (also including ICD-9 code 720A). Additional index patients were further identified among individuals included in the SRQ with an AS diagnosis between 2001 and 2016. Together, these patients represented the main AS definition. Index patients from the SRQ were also analysed separately. Demographic characteristics of index patients were extracted from the Swedish Total Population Register and AS-related comorbidity conditions of index patients were identified from the NPR (for ICD codes used to define comorbidity conditions see Supplementary Table S1, available at *Rheumatology* online). Index patients and controls with missing data for county of residence were excluded, as were individuals with no first-degree relatives recorded in the Multi-Generation Register (if parents of an individual were missing because of register truncations, this also made connections to potential siblings impossible).

While requiring two or more visits with AS is expected to increase the validity of the diagnosis, it also reduced the sample size. Thus separate analyses were made using a wider definition, including index patients with at least one visit listing an AS diagnosis in the NPR at a specialist clinic in rheumatology or internal medicine (corresponding to the definition from the validation study [29]) or a listing in the SRQ from 2001 to 2016.

Among relatives, individuals were considered affected, and thus an exposure to the index patient according to the same requirements, i.e. if they had two or more specialist visits in the NPR between 1987 and 2016 with an AS diagnosis or were registered in the SRQ with an AS diagnosis between 2001 and 2016. For the wider AS

definition, one visit in the NPR or inclusion in the SRQ was sufficient for a relative to be considered affected.

Statistical analyses

Familial risks were calculated as odds ratios (ORs) using conditional logistic regression in SAS 9.4 (SAS Institute, Cary, NC, USA). Each relative pair was treated separately and a relative's AS status was assessed independent of the time of AS onset in the index patient. For instance, in a pair of brothers with AS, each of them would occur in the analysis once as an index patient and once as an affected relative. Familial risks were estimated overall, for siblings, parents and children separately and for having more than one affected relative. The analyses were stratified by sex and adjusted for county of residence. Because of the clustered data structure, robust standard errors were used to correct the CIs.

As familial risks have been seen to differ by age at disease onset in other similar diseases (e.g. RA [24]), familial risks were also compared for index patients with disease onset before and after the median age at onset of 25 years. This analysis was restricted to the SRQ population, where information on age at onset was available. We also performed an analysis including only index patients born in Sweden to take into account that HLA-B27 positivity and other genetic factors vary with ethnic origin. Further, familial risks were calculated excluding index patients that had received a diagnosis of psoriasis or PsA, since PsA is known to have a noticeably lower familial aggregation than AS [31]. These analyses were both made for the main AS definition.

Heritability, defined as the proportion of phenotypic variance that is due to additive genetic variance, was calculated for the main AS definition overall and stratified by sex. For an in-depth description of the heritability concept, see Falconer [32] and Frisell *et al.* [33]. In short, the heritability of a trait may be calculated by dividing the observed phenotypic correlation of relatives by their genetic correlation, given the assumption that relatives are only similar due to shared genetic factors. As this approach cannot distinguish between additive genetic effects and common environmental effects between relatives, the heritability obtained can be seen as an upper limit of heritability in the population. Further details of heritability calculations are described elsewhere [24].

The heritability estimate is dependent on the population prevalence of disease, which is not directly estimable in our case–control sample. We therefore used the AS prevalence previously estimated from the NPR [4] and adjusted it to our stricter main AS definition. To cover a range of plausible prevalence figures, heritability was calculated for both half and double the adjusted prevalence. When looking at only male or only female relatives, sex-specific prevalences were applied. Heritability was estimated from both overall and sibling-specific familial risks. Sibling-specific familial risks are often considered superior, because calendar time trends (including data truncations) are likely to affect siblings equally. Approximate 95% CIs around the heritability estimate were obtained by plugging the 95% confidence limits of the familial risk into the calculations.

Results

We identified 13 659 patients from the NPR with two or more visits with an AS diagnosis and 4770 patients from the SRQ. These populations were largely overlapping, giving 14 240 unique index patients. The 581 individuals from the SRQ not identified from the NPR were all present in the NPR with diagnoses typical for AS comorbidities. Excluding 431 index patients with no first-degree relatives recorded in the Multi-Generation Register and 21 with missing data for county of residence, our main study population included 13 795 index patients and 668 936 controls. From the SRQ alone, 4651 index patients and 226 874 controls were included in the analysis. As shown in Table 1, the male:female ratio of index patients was about 2:1, similar to previous findings based on Swedish registers [4, 22]. Index patients

Table 1 Descriptive characteristics of AS index patients from two different sources

Characteristics	Source of index patients	
	NPR + SRQ (n = 13 795)	SRQ only (n = 4651)
Birth year, mean (range)	1960 (1909–2000)	1967 (1924–1999)
Age at first observed AS diagnosis, years, mean (range)	48 (9–98)	41 (12–86)
Females, *n* (%)	4761 (34.5)	1490 (32.0)
Region of birth, *n* (%)		
Sweden	12 280 (89.0)	4063 (87.4)
Other Nordic country	478 (3.5)	127 (2.7)
Other EU country	505 (3.7)	207 (4.5)
Other	532 (3.9)	254 (5.5)
Comorbidity conditions[a] in NPR, *n* (%)		
PsA	861 (6.2)	272 (5.8)
Psoriasis	876 (6.4)	287 (6.2)
Other specified inflammatory SpAs	2676 (19.4)	1002 (21.5)
Inflammatory SpA, unspecified	1382 (10.0)	517 (11.1)
Crohn's disease	749 (5.4)	243 (5.2)
Ulcerative colitis	701 (5.1)	232 (5.0)
Uveitis/iritis	3880 (28.1)	1556 (33.5)
Retinitis	86 (0.6)	33 (0.7)
Prostatitis	264 (1.9)	78 (1.7)
AV block	290 (2.1)	51 (1.1)
JIA	732 (5.3)	374 (8.0)

[a]For ICD codes used to define comorbidity conditions see Supplementary Table S1, available at *Rheumatology* online.
EU, European Union.

TABLE 2 Number of first-degree relatives in total and relatives with AS among index patients and controls

Relatives	Index patients		Controls	
	Relatives, *n*	Relatives with AS, *n* (%)	Relatives, *n*	Relatives with AS, *n* (%)
NPR + SRQ[a]				
Siblings	19 152	683 (3.6)	919 342	1739 (0.19)
Parents	23 723	535 (2.3)	1 140 593	1357 (0.12)
Children	23 840	498 (2.1)	1 194 324	1221 (0.10)
SRQ only[b]				
Siblings	6599	220 (3.3)	320 507	553 (0.17)
Parents	8335	234 (2.8)	406 740	592 (0.15)
Children	7333	151 (2.1)	371 318	258 (0.07)

[a]*n* = 13 795 index patients and 668 936 controls.
[b]*n* = 4651 index patients and 226 874 controls.

from the SRQ were born on average 7 years later than index patients from the two registers combined and were to a greater extent born outside of Sweden. The most common AS-related comorbidity in both groups was uveitis/iritis, with the highest proportion in the SRQ. In contrast, patients from the SRQ had somewhat lower rates of PsA and psoriasis diagnoses compared with the combined dataset.

Among all relatives identified from the Multi-Generation Register, the proportions of affected relatives were similar for index patients from the SRQ alone and from the NPR and SRQ together (Table 2). Index patients had higher proportions of affected relatives compared with controls for all types of relatives (also stratified by sex in Supplementary Table S2, available at *Rheumatology* online). In total, 11.1% of index patients had one or more affected relative, compared with 0.6% of controls (Supplementary Table S3, available at *Rheumatology* online). The mean number of relatives did not differ significantly between index patients and controls (Supplementary Table S4, available at *Rheumatology* online).

Familial risks and heritability

Figure 1 shows the OR of AS when having an affected relative, by type of relative and by sex for index patients from the main AS definition (combining the NPR and SRQ). The overall OR of AS when having an affected relative was 19.4 (95% CI 18.1, 20.8). The estimates were similar for exposures from different types of relatives, but having more than one affected relative resulted in a considerably higher risk [OR 68.0 (95% CI 51.3, 90.1)]. Heritability was 77% (95% CI 73, 80) when estimated from sibling risks, assuming a prevalence of 0.11% (Table 3). Depending on the choice of prevalence, from 0.055% to 0.22%, heritability varied from 72% (95% CI 69, 75) to 82% (95% CI 78, 86) (Supplementary Table S5, available at *Rheumatology* online). Overall, women had an elevated familial risk if the affected relative was female, but with the lower prevalence of AS among women, this translated into similar or slightly lower heritability compared with males. The increased familial risk was only observed for mother–daughter pairs, while sisters had the same familial risk as brothers (Fig. 1).

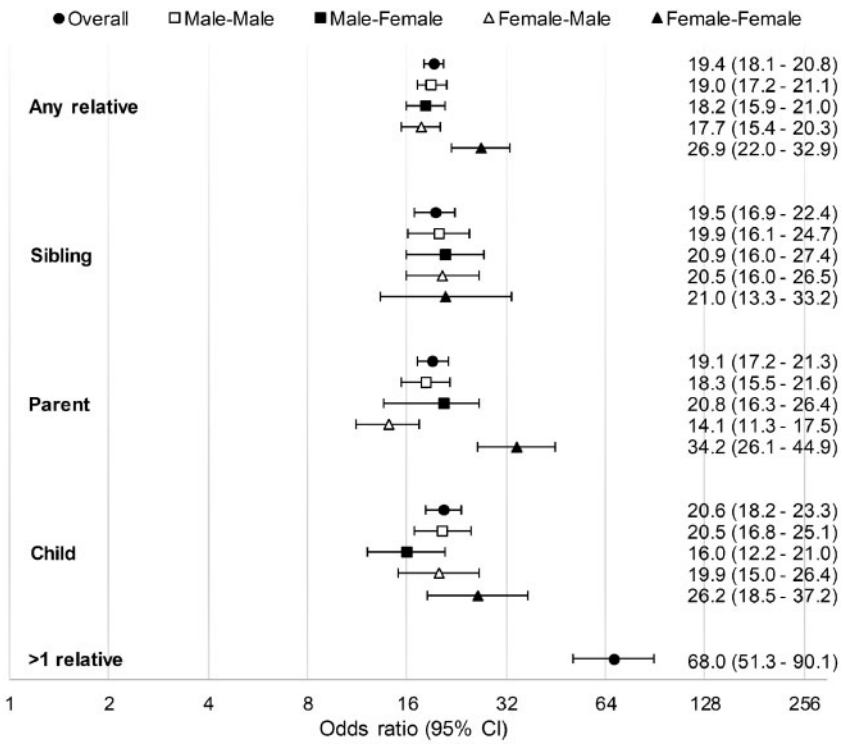
For patients from the SRQ, risks were somewhat higher than in the NPR and SRQ combined, but CIs were broader (Table 4). When stratified by age at disease onset, a trend towards an increased familial risk was seen for patients with disease onset before age 25 years compared with those with disease onset after age 25 years. This trend was consistent for all types of relatives, although CIs were overlapping. With the wider AS definition (at least one visit) we identified 17 738 index patients, and the risk of AS when having an affected relative of any kind was 16.9 (95% CI 15.9, 18.0) (Supplementary Table S6, available at *Rheumatology* online). Restricting analysis to the 12 280 index patients born in Sweden did not affect the main results (Supplementary Table S7, available at *Rheumatology* online). Neither was any difference detected when excluding 1373 index patients with psoriasis or PsA diagnoses from the analysis (Supplementary Table S8, available at *Rheumatology* online).

Discussion

In this large population-based study, familial aggregation of AS was assessed for different types of first-degree relatives and by sex. We concluded that there was a 20-fold increase in the odds of AS among first-degree relatives of AS patients, which is substantially lower than commonly referenced numbers from other populations. We could also show that the OR was similar by type of relative and sex. Although high compared with most other diseases, the heritability estimate of 77% was also lower than previous reports for AS [12, 14].

The familial risk estimates are considerably lower than two reports from Iceland [20, 21]. The risk ratios of 75 (95% CI 60, 94) and 94 (95% CI 74, 114) observed in those studies are more in line with our result for having more than one affected relative [OR 68.0 (95% CI 51.3, 90.1)]. It is difficult to see why our studies should get

FIG. 1 ORs of AS when having a first-degree relative with the disease



Familial ORs (95% CIs) by type of relative and sex. For sex-specific estimates, e.g. 'male–female' refers to a male index patient and a female relative. Sibling/parent/child refers to a relative in relation to the index patient, so that estimates in, for example, the subgroup 'parent' are ORs of AS when having a parent with AS.

TABLE 3 Heritability of AS based on sibling and first-degree relative familial risks, overall and by sex

Sex of relatives	Heritability, proportion (95% CI)	
	Sibling	Any relative
Overall[a]	0.77 (0.73, 0.80)	0.81 (0.80, 0.83)
Male–male[b]	0.80 (0.74, 0.85)	0.80 (0.77, 0.82)
Male–female[a]	0.73 (0.67, 0.78)	0.71 (0.68, 0.74)
Female–male[a]	0.77 (0.72, 0.83)	0.75 (0.72, 0.79)
Female–female[c]	0.71 (0.61, 0.81)	0.81 (0.76, 0.85)

Heritability based on familial risk estimates. For sex-specific estimates, e.g. 'male–female' refers to a male index patient and a female relative. Estimated using a population prevalence of [a]0.11%, [b]0.15% and [c]0.08%.

such different results. While the ethnic composition may differ due to differences in immigration rates, excluding index patients born outside of Sweden did not affect the results in our study. In the Icelandic studies, all cases were clinically verified and patients with PsA-associated axial disease were excluded. Our results were not materially changed by excluding patients ever diagnosed with psoriasis or PsA however, and neither did a restriction to index patients identified from the SRQ, with presumably higher diagnostic validity than the NPR. One speculation may be that the difference is a result of some particular clustering of the limited number of Icelandic cases in families.

An equally high familial risk as in Iceland has been reported in another publication [19], where the pooled, observed prevalence of AS in first-degree relatives of AS patients from six studies in the UK, Finland and the Netherlands (8.2%) was divided by an assumed population prevalence of 0.1%, resulting in a recurrence risk ratio of 82. This estimate is clearly highly dependent on the assumed population prevalence. Together with the small sample size of the original studies, this could explain at least part of the discrepancy from our results. It also seems likely that individuals with familial AS may be more prone to participate in a study on this specific topic, which may be expected to lead to some overestimation. In contrast, our results are in line with a previous Swedish report that included 3509 patients hospitalized for AS between 1973 and 2004 [22]. Based on 102 sibling cases, they concluded the sibling risk to be 17.1 (95% CI 9.9, 29.4). Despite the differences in study size, study period and AS definition, these results are similar to the sibling risk from our wider definition [OR 16.6 (95% CI 14.8, 18.7); Supplementary Table S6, available at *Rheumatology* online].

Before the present study there was only limited data on the possible gender difference in familial aggregation

TABLE 4 ORs of AS in index patients from the SRQ by age at disease onset

Relative with AS	Familial risk, OR (95% CI)		
	All ages combined	Age at onset <25 years	Age at onset ≥25 years
Any first-degree relative	21.7 (19.3, 24.4)	25.1 (21.3, 29.6)	18.4 (15.6, 21.7)
Sibling	20.1 (16.1, 25.1)	24.0 (17.6, 32.9)	16.5 (12.1, 22.6)
Parent	20.0 (17.0, 23.5)	22.3 (18.2, 27.3)	15.9 (12.1, 20.9)
Child	31.2 (24.2, 40.1)	38.4 (24.5, 60.1)	28.0 (20.5, 38.2)
>1 relative	101.9 (64.0, 162.0)	NA[a]	NA[a]

[a]OR not calculated due to the small number of observations.
NA, not available.

of AS. Whereas a previous study saw a 3-fold risk increase for fathers of AS patients compared with mothers [20], we could not detect such a difference. Conversely, we saw an increased risk for daughters of affected mothers compared with daughters of affected fathers. Overall, ORs were somewhat higher in female–female relative pairs than in male–male pairs. However, this should be seen in the context of lower disease prevalence in females, and indeed the increased OR did not translate into an increased heritability for female AS. If anything, the heritability of AS based on sibling risks was lower among females than among males. For males, familial risks were similar regardless of the sex of the affected relative. The cross-gender heritability was very similar to the within-gender heritability, suggesting that the same heritable factors influence AS in men and women.

One factor that seemed to affect the familial risk in our study was age at AS onset in the index patients. Patients with disease onset before age 25 years had a higher risk compared with patients with disease onset after age 25 years. Thus family history seems more important for disease with onset at a young age. It could be that people with a strong genetic predisposition develop the disease early, while those who require more environmental factors to cross the liability threshold take longer time to develop the disease.

SpA, to which AS belongs, is a heterogeneous group of diseases with considerable overlap between conditions. We aimed to focus on patients fulfilling the ASAS classification criteria for axial SpA, which corresponds fairly well with an AS diagnosis in the NPR according to a recent validation study [29]. Patients with other types of SpA sometimes presenting with axial involvement (e.g. PsA and IBD with SpA) and who only occur in the registers under their primary diagnosis would not be included in this study. We calculated familial risks based on two different AS definitions. The wider definition, requiring at least one visit with AS in the register, corresponded to the definition used in the previous validation of AS in the NPR [29]. Our main definition required two registered visits with AS. By tightening the definition, ORs increased from 16.9 to 19.4, and we would argue that this reflects reduced misclassification. An AS diagnosis in the specialized clinical register SRQ is expected to have even higher validity than a diagnosis from the NPR, explaining part of the higher risk seen in SRQ patients. Patients in the SRQ are also more commonly on treatment with anti-rheumatic therapy, including biologic agents, indicative of more severe disease. On the other hand, patients with mild AS disease might only be diagnosed and managed in primary health care, which do not report to the NPR. Assuming that there could be an association between familial risks and disease activity/severity, this might have had an impact on our results.

Some caution is warranted for the interpretation of the heritability reported. Estimation of heritability from case–control data is dependent on the (observed) familial risk and the (unobserved) disease prevalence in the population. Our most precise estimate, based on sibling risk and 0.11% population prevalence, put the heritability of AS at 77% (95% CI 73, 80%). However, uncertainty regarding the prevalence is not covered by the CIs and we therefore calculated heritability based on different prevalence estimates (Supplementary Table S5, available at *Rheumatology* online). Notably, heritability did not reach the previously reported >90% [12, 14], even when more extreme prevalence figures were applied. Furthermore, our study design does not allow for a separation of the effects of additive genetics and common environmental exposures, and the heritability was calculated assuming that the familial aggregation was purely due to shared genetics. If family-shared environmental risk factors influence AS risk, heritability is overestimated with this approach. If heritability is lower than previously believed, this has implications for aetiological studies aimed at identifying disease-associated genes, as it explains part of the 'missing heritability'.

The use of population-based data has many advantages compared with using clinical cohorts. The large sample size enabled us to reach precise estimates of the familial aggregation and heritability and to stratify these estimates by sex and type of relative. Prospective, nationwide data collection minimizes selection bias, and disease ascertainment in relatives is not reliant on reports from index patients. In contrast, the accuracy of self-reported family history of disease is likely to differ

between index patients and controls, as is the willingness of relatives to participate in a study.

Working with register data also has limitations. One is the inability to validate each diagnosis, as previously discussed. Furthermore, diagnostic data were mostly available since the start of the outpatient register in 2001, leading to underestimation of AS in older relatives, who may have been treated mainly before this date. Conversely, patients with recent disease onset might be missed because of long diagnostic delays for AS. We investigated the influence of these truncations by stratifying the analysis by decade of birth of index patients and could not see any significant differences in familial risks (data not shown). Because of the low population prevalence of AS, and the limited amount of data available for older relatives, we did not have enough power to look at risks in twins or second- or third-degree relatives. As we did not have information on zygosity, twins were treated as ordinary siblings in the analysis.

Another limitation is that we lacked data on HLA-B27 status. This strong risk allele is expected to explain part of the familial risk, and several studies have shown a higher familiality for HLA-B27-positive patients [12, 13]. As the prevalence of both HLA-B27 and AS is thought to vary in different parts of Sweden [4], we adjusted the analysis for county of residence of index patients and controls. This study is done in a predominantly Nordic ethnic group and generalizability to regions with very different prevalences of AS and HLA-B27 might be limited. It is important to note, however, that HLA-B27 is not likely to drive the familial aggregation completely. Using data from Reveille *et al.* [16], where HLA-B27 occurred in 87.8% of white AS patients and 7.6% of controls, and assuming a population prevalence of AS of 0.11%, the familial risk conveyed by HLA-B27 would be 5.8 (for calculations, see supplementary material, section 'Expected familial risk from HLA-B27', available at *Rheumatology* online). Notably, that is only one-third of the overall familial risk in this study. It roughly corresponds to reports from genetic studies where HLA-B27 is estimated to explain 20% of AS heritability [28]. While HLA-B27 remains an important factor in AS susceptibility, other factors are responsible for the majority of the familial aggregation.

In conclusion, we found that while familial risks and heritability of AS were very high, they were lower than previous reports from other countries. The heritability proposed might still be an overestimate of the true influence of genetics on disease risk and efforts should also be directed at identifying risk factors for AS that are not of genetic origin. From a clinical perspective, this strong familiality should motivate further research to evaluate if and how knowledge about a family history of AS may help to predict disease activity, prognosis and treatment outcomes.

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Supplementary data

Supplementary data are available at *Rheumatology* online.

References

1 de Blecourt JJ, Polman A, de Blecourt-Meindersma T, Erlee TJD, Drion EF. Hereditary factors in rheumatoid arthritis and ankylosing spondylitis. Ann Rheum Dis 1961;20:215–20.

2 Bakland G, Nossent HC, Gran JT. Incidence and prevalence of ankylosing spondylitis in northern Norway. Arthritis Rheum 2005;53:850–5.

3 De Angelis R, Salaffi F, Grassi W. Prevalence of spondyloarthropathies in an Italian population sample: a regional community-based study. Scand J Rheumatol 2007;36:14–21.

4 Exarchou S, Lindström U, Askling J *et al*. The prevalence of clinically diagnosed ankylosing spondylitis and its clinical manifestations: a nationwide register study. Arthritis Res Ther 2015;17:118.

5 Haglund E, Bremander AB, Petersson IF *et al*. Prevalence of spondyloarthritis and its subtypes in southern Sweden. Ann Rheum Dis 2011;70:943–8.

6 Trontzas P, Andrianakos A, Miyakis S *et al*. Seronegative spondyloarthropathies in Greece: a population-based study of prevalence, clinical pattern, and management. The ESORDIG study. Clin Rheumatol 2005;24:583–9.

7 van der Linden SM, Valkenburg HA, de Jongh BM, Cats A. The risk of developing ankylosing spondylitis in HLA-B27 positive individuals. A comparison of relatives of spondylitis patients with the general population. Arthritis Rheum 1984;27:241–9.

8 Stolwijk C, van Onna M, Boonen A, van Tubergen A. Global prevalence of spondyloarthritis: a systematic review and meta-regression analysis. Arthritis Care Res 2016;68:1320–31.

9 Emery AE, Lawrence JS. Genetics of ankylosing spondylitis. J Med Genet 1967;4:239–44.

10 Calin A, Brophy S, Blake D. Impact of sex on inheritance of ankylosing spondylitis: a cohort study. Lancet 1999;354:1687–90.

11 Carter N, Williamson L, Kennedy LG, Brown MA, Wordsworth BP. Susceptibility to ankylosing spondylitis. Rheumatology (Oxford) 2000;39:445.

12 Brown MA, Kennedy LG, MacGregor AJ *et al*. Susceptibility to ankylosing spondylitis in twins: the role of genes, HLA, and the environment. Arthritis Rheum 1997;40:1823–8.

13 Jarvinen P. Occurrence of ankylosing spondylitis in a nationwide series of twins. Arthritis Rheum 1995;38:381–3.

14 Pedersen OB, Svendsen AJ, Ejstrup L *et al*. Ankylosing spondylitis in Danish and Norwegian twins: occurrence and the relative importance of genetic vs. environmental effectors in disease causation. Scand J Rheumatol 2008;37:120–6.

15 Brown MA, Pile KD, Kennedy LG *et al*. HLA class I associations of ankylosing spondylitis in the white

population in the United Kingdom. Ann Rheum Dis 1996; 55:268–70.

16 Reveille JD, Zhou X, Lee M *et al*. HLA class I and II alleles in susceptibility to ankylosing spondylitis. Ann Rheum Dis 2019;78:66.

17 Roberts RL, Wallace MC, Jones GT *et al*. Prevalence of HLA-B27 in the New Zealand population: effect of age and ethnicity. Arthritis Res Ther 2013;15:R158.

18 Hakansson U, Eitrem R, Low B, Winblad S. HLA-antigen b27 in cases with joint affections in an outbreak of salmonellosis. Scand J Infect Dis 1976;8:245–8.

19 Brown MA, Laval SH, Brophy S, Calin A. Recurrence risk modelling of the genetic susceptibility to ankylosing spondylitis. Ann Rheum Dis 2000;59:883–6.

20 Geirsson AJ, Kristjansson K, Gudbjornsson B. A strong familiality of ankylosing spondylitis through several generations. Ann Rheum Dis 2010;69:1346–8.

21 Thjodleifsson B, Geirsson AJ, Bjornsson S, Bjarnason I. A common genetic background for inflammatory bowel disease and ankylosing spondylitis: a genealogic study in Iceland. Arthritis Rheum 2007;56:2633–9.

22 Sundquist K, Martineus JC, Li X, Hemminki K, Sundquist J. Concordant and discordant associations between rheumatoid arthritis, systemic lupus erythematosus and ankylosing spondylitis based on all hospitalizations in Sweden between 1973 and 2004. Rheumatology (Oxford) 2008;47:1199–202.

23 Polderman TJ, Benyamin B, de Leeuw CA *et al*. Meta-analysis of the heritability of human traits based on fifty years of twin studies. Nat Genet 2015;47: 702–9.

24 Frisell T, Holmqvist M, Kallberg H *et al*. Familial risks and heritability of rheumatoid arthritis: role of rheumatoid factor/anti-citrullinated protein antibody status, number and type of affected relatives, sex, and age. Arthritis Rheum 2013;65:2773–82.

25 Chen GB, Lee SH, Brion MJ *et al*. Estimation and partitioning of (co)heritability of inflammatory bowel disease from GWAS and immunochip data. Hum Mol Genet 2014;23:4710–20.

26 Silventoinen K, Sammalisto S, Perola M *et al*. Heritability of adult body height: a comparative study of twin cohorts in eight countries. Twin Res 2003;6:399–408.

27 Visscher PM, Medland SE, Ferreira MA *et al*. Assumption-free estimation of heritability from genome-wide identity-by-descent sharing between full siblings. PLoS Genet 2006;2:e41.

28 Ellinghaus D, Jostins L, Spain SL *et al*. Analysis of five chronic inflammatory diseases identifies 27 new associations and highlights disease-specific patterns at shared loci. Nat Genet 2016;48:510.

29 Lindstrom U, Exarchou S, Sigurdardottir V *et al*. Validity of ankylosing spondylitis and undifferentiated spondyloarthritis diagnoses in the Swedish National Patient Register. Scand J Rheumatol 2015;44:369–76.

30 Eriksson JK, Askling J, Arkema EV. The Swedish Rheumatology Quality Register: optimisation of rheumatic disease assessments using register-enriched data. Clin Exp Rheumatol 2014;32(Suppl 85):S147–9.

31 Karason A, Love TJ, Gudbjornsson B. A strong heritability of psoriatic arthritis over four generations—the Reykjavik Psoriatic Arthritis Study. Rheumatology (Oxford) 2009;48:1424–8.

32 Falconer DS. Introduction to quantitative genetics, 4th edn. Harlow: Longman, 1996.

33 Frisell T, Saevarsdottir S, Askling J. Family history of rheumatoid arthritis: an old concept with new developments. Nat Rev Rheumatol 2016;12:335.