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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

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Objective. **To estimate familial aggregation of rheumatoid arthritis (RA) in 3 large population-representative samples and to test if familial aggregation is affected by rheumatoid factor (RF)/anti–citrullinated protein antibody (ACPA) status, type of relative, sex, and age at onset of RA.**

Methods. **A register-based nested case–control study was performed in the Swedish total population. Data on patients with RA were ascertained through the nationwide Swedish Patient Register (n = 88,639), the clinical Swedish Rheumatology Quality Register (n = 11,519), and the Epidemiological Investigation of Rheumatoid Arthritis case–control study (n = 2,871). Data on first- and second-degree relatives were obtained through the Swedish Multigeneration Register. Familial risks were calculated using conditional logistic regression.**

Results. **Consistent across data sources, the familial odds ratio for RA was ~3 in first-degree relatives of RA patients and 2 in second-degree relatives. Familial risks were similar among siblings, parents, and offspring. Familial aggregation was not modified by sex, but was higher in RA patients with early-onset disease and in RF/ACPA-positive RA patients. The observed familial risks were consistent with a heritability of ~50% for ACPA-positive RA and ~20% for ACPA-negative RA.**

Conclusion. **The pattern of risks suggests that familial factors influence RA in men and women equally and that these factors are of less importance for late-onset RA. Familial factors are more important for seropositive RA, but there is significant familial overlap between seropositive RA and seronegative RA. Even if the familial risk is assumed to be completely due to genetics, the observed risks suggest that heritability of RA is lower than previously reported, in particular for ACPA-negative RA.**

Rheumatoid arthritis (RA) is a complex disease, believed to be caused by a combination of genetic and environmental factors. In addition to alleles in the HLA system, investigators have identified >40 loci that contribute to the risk of developing RA in recent genome-wide association studies, albeit with individually modest effect sizes (1,2). Despite these breakthroughs, it is generally believed that many additional risk alleles for RA remain to be identified (3). Taken together, the identified loci have been estimated to explain 50–60% and 30–50% of the genetic liability to develop anti–citrullinated protein antibody (ACPA)–positive RA and ACPA-negative RA, respectively (2). The remaining genes constitute the "missing heritability" of RA, a concept that intrinsically depends on the estimated proportion of a disease that is due to genetic factors. Traditionally, estimation of this proportion is based on the strength of the familial aggregation.

Despite the clinically well-known familial aggregation of RA, surprisingly few population-based studies have addressed its strength and nature. Most studies

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have been based on clinical cohorts and have not included control groups (Table 1). A review that compared the reported prevalence of RA among relatives of RA patients versus the expected population prevalence of RA yielded estimates of sibling relative risk (RR) ranging from 2 to 17 (4). These estimates are sensitive not only to the validity and generalizability of the original studies, but also to the estimated general population prevalence of RA. In studies that have included a representative control group, the age- and sex-adjusted RR of RA among first-degree relatives of RA patients has been estimated as somewhat lower (RR 1.5–4.5) (5–10).

Although ACPA has higher specificity and prognostic value (11), presence of rheumatoid factor (RF) is used as a diagnostic criterion for distinguishing seropositive and seronegative RA in, for example, the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10) (12). Among RA patients, ACPA and RF show high correspondence, and RF/ACPA-positive RA is ~2–4 times more common than RF/ACPA-negative RA. In light of evidence of distinct etiologies and differences in the number of identified susceptibility genes for RF/ACPA-positive RA compared to RF/ACPA-negative RA, one might expect that familial risks should be higher for RF-positive RA; this hypothesis is supported by a single study (13), although several other studies have not supported the theory (6,7,10,14). In one of few studies to address familial aggregation by ACPA rather than RF, the heritability of ACPA-positive and ACPA-negative RA was reported to be equally strong (68% versus 66%), although the study was small, with 11 ACPA-positive and 2 ACPA-negative concordant twin pairs (15). Sex and age at onset of RA have been suggested as other factors that modify familial aggregation of RA (16), but as with RF/ACPA status, the evidence is so far inconclusive because of the small and possibly nongeneralizable samples that have been studied.

For the above reasons, in the current study we aimed to provide more precise estimates of the familial aggregation of RA than have been previously reported, using 3 large and population-representative samples. We further aimed to extend these precise overall estimates to provide more specific estimates of familial aggregation by type of relative, sex of RA patient and relative, RF/ACPA status, and age at RA onset.

MATERIALS AND METHODS

We linked records from several Swedish population registers using unique personal identification numbers as the (deterministic) linkage key and performed a nested case–control study. Three different sources were used to identify cases: the nationwide Swedish Patient Register, the Swedish Rheumatology Quality (SRQ) Register, and the Epidemiological Investigation of Rheumatoid Arthritis (EIRA) case–control study. For each case, 5 controls were randomly selected from the Swedish Total Population Register and matched with the case subjects for sex, birth year, county of residence, and marital status. First- and second-degree relatives of cases and controls were identified through the Swedish Multigeneration Register. A relative was considered to have RA (and the index individuals thus considered "exposed") if the relative had ever met the criteria for RA as defined in any of the 3 data sources. Patients identified through each data source were referred to as "index patients," where "index" refers to the individual whose relatives are considered, since both outcome (in the index individual) and exposure (in the index individual's relatives) is defined as being an RA patient. For example, if identified through the same data source, 2 sisters with RA would appear as 2 index patients, each "exposed" by her sister's disease status.

Data sources and RA ascertainment. *The Swedish Patient Register.* The Swedish Patient Register contains date of admission, date of discharge, and primary and secondary diagnoses (coded according to ICD versions 7–10) as assigned by the treating (discharging) physician. Information on inpatient treatment is available from 1964 onward, with virtually complete nationwide coverage for RA beginning in 1987 (17). Diagnoses based on outpatient visits to non–primary care facilities have been recorded since 2001. We had access to data in the Patient Register through 2009, and identified all individuals listed with the following ICD codes: ICD-10 codes M05, M060, M06.2, M06.3, M06.8, M06.9, M12.3; ICD-9 codes 714.0–2, 714.8, 719.3; ICD-8 codes 712.10, 712.20, 712.38, 712.39. Diagnostic validity in the Patient Register has been assessed by reviewing the medical charts of almost 1,000 patients admitted to a hospital with an RA diagnosis, as well as the records of 114 patients with a non–primary care outpatient visit with an RA diagnosis. Approximately 90% of patients, whether admitted to a hospital or treated at an outpatient facility (18,19), fulfilled the American College of Rheumatology (ACR) criteria for RA (20). To increase diagnostic validity, 2 or more separate visits with RA diagnoses were required and at least 1 of these visits had to be to a specialist in rheumatology or internal medicine.

The SRQ Register. The SRQ Register is run by the Swedish Rheumatology Association and is primarily a clinical database. It is a web-based surveillance system initiated in the mid-1990s, and it contains baseline patient information (including the diagnosis, onset of symptoms, ACR criteria, RF status, and disease activity) collected at first entry, with longitudinal information on disease progress collected at subsequent visits. For the purpose of this study, only those patients who, according to the ACR criteria, were classified as having RA within 12 months of symptom onset were included. We had access to data in the SRQ Register through 2010.

The EIRA case–control study. The EIRA study is a population-based case–control study of incident RA. The study started in 1996, and new cases and controls are still being enrolled. For the purpose of this study, we included all EIRA cases recruited through 2009. EIRA investigators invite all newly diagnosed Swedish-speaking RA patients ages 18–70

Table 1. Seminal studies on the familial aggregation of RA published after 1980*

Author, year (ref.)	Country	RA ascertainment		No. of patients	No. of relatives	Reference group	Estimate†	Comment
		Index patients	Relatives					
Thomas et al, 1983 (34)	UK	RA outpatient clinic	Reported by index patient	295	Not reported	None	22% reported having FDR with RA	
Del Junco et al, 1984 (7)	US	RA outpatient clinic	Chart review; clinical examination	78	496 FDR	General population	FDR rate ratio 1.7 (1.0–2.9)	No effect modification by RF, age, or sex
Aho et al, 1986 (6)	Finland	Nationwide sickness insurance register	Reported by index patient	261	82 MZ twin pairs, 179 DZ twin pairs	General population of twins	Age and sex adjusted RR 8.6 (3.9–16.3) in MZ twins, 3.4 (1.2–7.4) in DZ twins	No effect modification by RF
Wolfe et al, 1988 (14)	US	RA outpatient clinic	Reported by index patient; chart review	985	Not reported	None	11% (10% of RF+ and 8% of RF−) had FDR with RA	No effect of RF
Bellamy et al, 1992 (35)	Australia	Self-report; questionnaire; questions to treating physician	Same as index patient	186	186 twins	None	Concordance rate 21% (6–44) in MZ twins, 0% (0–25) in DZ twins	3 concordant MZ twin pairs, 0 concordant DZ twin pairs
Deighton and Walker, 1992 (36)	UK	RA outpatient clinic	Clinical examination	243	Not reported	None	13% had sibling with RA	No effect of RF
Silman et al, 1993 (31)	UK	Recruited through clinics and a media campaign; clinical examination	Same as index patient	203	91 MZ twin pairs, 112 DZ twin pairs	None	Concordance rate 15.4% in MZ twins, 3.6% in DZ twins	14 concordant MZ twin pairs, 4 concordant DZ twin pairs
Pritchard, 1994 (37)	UK	RA outpatient clinic	Reported by index patient	719	Not reported	None	18% reported having FDR or SDR with RA	
Lynn et al, 1995 (38)	US	Hospitalized	Reported by index patient	166	1,257 FDR	None	18% had FDR with RA	More familial for men, younger age at onset
Jones et al, 1996 (9)	UK	Norfolk Arthritis Register	Questionnaire; clinical examination	207	518 FDR	180 controls	FDR RR 1.6 (0.3–8.7), age and sex adjusted 2.2 (0.2–20.6)	
Koumantaki et al, 1997 (10)	Greece	Hospitalizations and outpatient visits	Reported by index patient	126	Not reported	94 controls	FDR OR 4.4 (1.7–11.1)	No effect modification by RF
Lin et al, 1998 (39)	US	NIH registry	Questionnaire; chart review	29	218 FDR	14 controls (friends of patients)	Age/sex-adjusted FDR OR 15.5 (2.0–121.5)	
Barrera et al, 1999 (13)	The Netherlands	RA outpatient clinic	Reported by index patient; chart review	683	Not reported	None	10% had sibling with RA	Possible effect modification by RF
Grant et al, 2001 (5)	Iceland	RA outpatient clinic	Same as index patient	1,412	Not reported	General population	RR 4.4 (3.3–5.7) in siblings, 2.8 (1.6–4.2) in offspring, 3.9 (2.6–5.5) in parents	
Svendsen et al, 2002 (40)	Denmark	Questionnaire, clinical examination	Clinical examination	49	13 MZ twin pairs; 36 DZ twin pairs	None	Proband concordance rate 0 (0–25) in MZ twins, 9 (2–24) in DZ twins	
Hemminki et al, 2009 (8)	Sweden	Hospitalized	Same as index patient	47,361	Not reported	General population	Age, sex, period adjusted RR 4.6 (3.0 –7.2) in siblings, 3.0 (2.8 –3.2) in parents	
Rojas-Villarraga et al, 2009 (41)	Colombia	RA outpatient clinic	Reported by index patient; clinical examination	157	Not reported	None	7% had FDR with RA	
Somers et al, 2013 (42)	Denmark	Hospitalizations and outpatient visits	Same as index patient	9,118	All parents	General population	HR 2.7 (2.4–3.1) in mother–daughter, HR 2.9 (2.2–3.8) in father–son	No effect modification by sex

* RA = rheumatoid arthritis; FDR = first-degree relative; MZ = monozygotic; DZ = dizygotic; RF = rheumatoid factor; SDR = second-degree relative; RR = relative risk; OR = odds ratio; NIH = National Institutes of Health; HR = hazard ratio.
† Values in parentheses are the 95% confidence intervals.

years, who are treated at one of the collaborating rheumatology departments. Of invited cases, participation has been estimated to be 96% (21).

The Multigeneration Register. The Multigeneration Register identifies biological and adoptive parents of Swedish residents born in 1932 or thereafter and registered as living in Sweden at any time since 1961. For individuals born in Sweden in 1968 or later, the register has almost perfect coverage (22). Through the parents, it is possible to identify other relatives, for instance, siblings are identified as all individuals who have the same biological mother and father.

RF and ACPA status. For cases identified through the SRQ register, RF status was defined according to the reporting clinician. For cases identified through the EIRA study, RF was measured by nephelometry, with the cutoff for RF positivity specified at each respective laboratory. For RA cases exclusively identified through the Swedish Patient Register, we used a probabilistic algorithm to determine their RF status based on their history of ICD-10 diagnoses of seropositive RA or seronegative RA. Most subjects (76%) had exclusively received codes corresponding to either seropositive RA or seronegative RA. For the remaining subjects, RF status was defined as seropositive if subjects had received more diagnoses of seropositive RA than of seronegative RA and as seronegative if subjects had received more diagnoses of seronegative RA than of seropositive RA. RF status was considered unknown in subjects who had received an equal number of seropositive RA and seronegative RA diagnoses and in subjects who had received diagnoses based on ICD-8 or ICD-9 criteria only. We tested this classification scheme on the subjects with known RF status in the SRQ Register and EIRA study and found that it predicted the correct RF status in 91% and 92% of all classified cases, respectively.

ACPA was directly measured for cases in the EIRA study using an Immunoscan RA Mark 2 (Euro-Diagnostica) anti–cyclic citrullinated peptide 2 enzyme-linked immunosorbent assay (23). ACPA was considered to be present when detected in concentrations of >25 units/ml.

Statistical analysis. We first compared the family structures of RA cases with those of their matched controls to ensure that any familial observations were not simply due to differences in, for example, the number of identified relatives of a particular type. Thereafter, familial risks were estimated by conditional logistic regression using SAS version 9.3. In all analyses, RA in relatives was defined as RA identified in any of the contributing data sources. The occurrence of RA in a first-degree relative was assessed from 1964 until 2009, irrespective of the date of RA onset in the index patient. In additional analyses, we also assessed the relative risk of family history of RA (i.e., only taking into account RA in the relatives who were diagnosed before the case's disease onset), but found very similar distribution and magnitude of relative risks (estimates in combined sample <10% different) (data not shown).

Familial risks were estimated both by treating each relationship pair separately and, to increase power, by creating identifiers for having any relative (≥1) with a diagnosis of RA. In the first instance, each individual potentially contributes multiple observations, one for each relative of the relevant type. To correct confidence intervals (CIs) for the correlated data structure, robust standard errors were calculated using the sandwich covariance estimator by Lin and Wei (24), implemented in Proc Phreg, SAS version 9.3. Familial risks were stratified by type of relative and by sex (in the combined sample of the Swedish Patient Register, SRQ Register, and EIRA study), RF status (in the combined sample, and in the SRQ Register and the EIRA study separately), ACPA status (only in the EIRA study), and age at disease onset in the case (only in the SRQ Register and the EIRA study).

For comparison with previous studies and as a complementary measure of familial aggregation, we calculated the heritability of RA overall and stratified by sex and RF/ACPA status. Heritability is a theoretical concept defined as the proportion of a population's phenotypic variance that is attributable to genetic variation. Consistent with classic quantitative genetics, the heritability of a dichotomous trait may be calculated from relatives' tetrachoric correlation by assuming a liability threshold model of the trait, where everyone has a liability to develop the trait, but only those scoring above a threshold value do so. Under the further assumption that only additive genetic factors contribute to similarity among relatives with regard to the trait and that mating is random with regard to the genes underlying the trait, the heritability may be estimated as twice the observed tetrachoric correlation among first-degree relatives (25). To calculate the tetrachoric correlation from case–control sampled data, the population prevalence of the trait must be known. To assess the sensitivity to the assumed prevalence, we calculated the heritability for a range of estimated prevalences, in turn informed by previous prevalence studies of RA based on the same data (26). Further details on these calculations are available on the *Arthritis & Rheumatism* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.38097/abstract.

RESULTS

Of 90,372 cases with RA, 88,639 were identified through the Swedish Patient Register, 11,519 through the SRQ Register, and 2,871 through the EIRA study. The 3 data sources were hierarchically overlapping, as shown in Figure 1, with 77,654 cases identified only through the Patient Register, and 9,458 identified

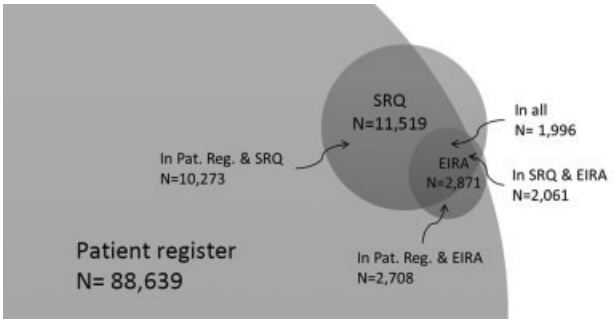

Figure 1. Venn diagram of hierarchically overlapping data sources. The combined sample (from the Swedish Patient Register [Pat. Reg.], the Swedish Rheumatology Quality [SRQ] Register, and the Epidemiological Investigation of Rheumatoid Arthritis [EIRA] study) includes 90,372 patients.

Table 2. First-degree relatives of Swedish patients with rheumatoid arthritis (RA) identified in 3 overlapping data sources and matched general-population controls*

Data source	No. of relatives per case or control, mean ± SD			No. of relatives with RA (% of all relatives)		
	Siblings	Parents	Offspring	Siblings	Parents	Offspring
Swedish Patient Register						
Cases	0.69 ± 1.32	0.80 ± 0.97	1.76 ± 1.39	2,182 (3.5)	2,751 (3.9)	2,817 (1.8)
Controls	0.66 ± 1.29	0.79 ± 0.96	1.78 ± 1.39	3,130 (1.0)	4,549 (1.3)	4,552 (0.6)
SRQ Register						
Cases	1.16 ± 1.53	1.37 ± 0.91	1.91 ± 1.28	352 (2.6)	582 (3.7)	178 (0.9)
Controls	1.10 ± 1.47	1.34 ± 0.92	1.88 ± 1.29	588 (0.8)	1,011 (1.3)	316 (0.3)
EIRA study						
Cases	1.37 ± 1.50	1.68 ± 0.70	1.85 ± 1.23	92 (2.6)	192 (4.0)	30 (0.6)
Controls	1.25 ± 1.45	1.58 ± 0.78	1.83 ± 1.26	174 (0.9)	299 (1.3)	53 (0.2)

* Irrespective of patients' birth-year cohort, which is a strong determinant for the possibility of identifying relatives, and which differs across data from the Swedish Patient Register, the Swedish Rheumatology Quality (SRQ) Register, and the Epidemiological Investigation of Rheumatoid Arthritis (EIRA) study.

through the SRQ Register but not the EIRA study. Most patients who were not identified in the Patient Register were registered in 2010 (n = 715), when we only had data from the SRQ Register, or had been registered only once or outside of specialist care (n = 389).

Table 2 is a summary of the mean number of relatives for cases and controls. The number of identifiable relatives depends on birth cohort, which differed across the 3 cohorts studied. Excluding individuals born before 1932, no difference was seen among the data sources (available on the *Arthritis & Rheumatism* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.38097/abstract). Case subjects had the same number of offspring as the controls, but the number of parents and siblings identified was higher. The difference was small, however, and adjustment for the number of relatives did not affect the estimated familial risks (data not shown).

As shown in Table 3, overall familial risks of RA were similar among first-degree relatives (OR 3.1 [95% CI 2.9–3.3] for parents, and OR 3.6 [95% CI 3.1–4.0] for siblings) and lower for second-degree relatives (OR 1.9 [95% CI 1.7–2.2] overall). Having >1 first-degree relative who had RA doubled the OR (with 1 first-degree relative, OR 3.2 [95% CI 3.0–3.3], with 2 or more first-degree relatives, OR 7.0 [95% CI 6.1–8.0]).

There were no significant differences between the sexes, although ORs tended to be slightly higher for male index patients and male–male relationships (e.g., for brothers, OR 4.5 [95% CI 2.8–7.2] and for sisters, OR 3.5 [95% CI 2.8–4.3]). Odds ratios among grandparents were similar for maternal and paternal grandparents (OR 1.9 [95% CI 1.6–2.2] and OR 1.7 [95% CI 1.4–2.0], respectively). Familial risk for both sexes combined was of the same magnitude as sex-specific risk. Despite the differences in the way cases were ascertained, overall familial risks were similar in the 3 data

Table 3. Risk of rheumatoid arthritis (RA) in relatives of patients with RA compared to the occurrence of RA in relatives of matched general-population controls in the combined sample

Relationship to patient	Familial risk, OR (95% CI)*				
	Overall	Male–male	Female–male	Male–female	Female–female
Any first-degree relative	3.2 (3.0–3.3)	3.8 (3.3–4.2)	3.1 (2.8–3.3)	3.3 (3.0–3.5)	3.1 (2.9–3.3)
≥2 first-degree relatives	7.0 (6.1–8.0)	6.6 (3.3–13.1)	7.3 (4.7–11.2)	6.3 (5.0–7.9)	7.4 (5.2–10.4)
Siblings	3.6 (3.1–4.0)	4.5 (2.8–7.2)	3.3 (2.6–4.3)	3.7 (2.8–4.8)	3.5 (2.8–4.3)
Parents	3.1 (2.9–3.3)	3.7 (3.0–4.6)	3.1 (2.7–3.5)	3.0 (2.6–3.4)	3.1 (2.8–3.3)
Children	3.2 (3.0–3.5)	3.6 (2.7–4.9)	3.1 (2.6–3.7)	3.3 (2.7–3.9)	3.2 (2.9–3.6)
Any second-degree relative	1.9 (1.7–2.2)	2.8 (1.9–4.2)	2.0 (1.6–2.5)	1.7 (1.4–2.2)	1.9 (1.6–2.2)
Half siblings	2.0 (0.7–6.2)	1.1 (0.0–65.8)	2.0 (0.4–11.1)	2.2 (0.1–59.1)	3.1 (0.2–42.7)
Maternal grandparents	1.9 (1.6–2.2)	2.3 (1.2–4.5)	2.0 (1.4–2.9)	2.1 (1.4–3.1)	1.7 (1.4–2.2)
Paternal grandparents	1.7 (1.4–2.0)	3.3 (1.5–7.5)	1.7 (1.1–2.6)	1.2 (0.8–1.8)	1.7 (1.3–2.3)

* Odds ratios (ORs) with 95% confidence intervals (95% CIs) estimated with conditional logistic regression and calculated with a robust variance estimator.

Table 4. Familial risk of RA by RF/ACPA status of the index patient and relative*

Data source	No. of index patients	First-degree relatives by serologic status, OR (95% CI)		
		Any	RF positive	RF negative
Combined sample				
Overall	90,372	3.2 (3.0–3.3)	3.4 (3.3–3.6)	2.5 (2.3–2.8)
RF-positive RA	45,851	3.5 (3.3–3.7)	3.9 (3.6–4.1)	2.6 (2.3–3.0)
RF-negative RA	12,959	2.6 (2.4–2.9)	2.5 (2.2–2.8)	3.1 (2.5–3.8)
SRQ Register				
Overall	11,519	2.9 (2.6–3.2)	3.1 (2.8–3.6)	2.4 (1.9–3.1)
RF-positive RA	7,410	3.3 (2.9–3.7)	3.7 (3.2–4.2)	2.4 (1.8–3.2)
RF-negative RA	4,020	2.2 (1.9–2.7)	2.2 (1.7–2.8)	2.5 (1.6–3.8)
EIRA study				
Overall	2,871	3.0 (2.5–3.7)	3.4 (2.7–4.4)	2.2 (1.4–3.4)
RF-positive RA	1,839	3.7 (2.9–4.6)	4.3 (3.2–5.7)	2.6 (1.5–4.6)
RF-negative RA	934	2.2 (1.5–3.0)	2.1 (1.4–3.4)	1.6 (0.7–3.7)
ACPA-positive RA	1,652	3.7 (2.9–4.7)	4.6 (3.4–6.1)	2.2 (1.3–3.9)
ACPA-negative RA	873	2.1 (1.5–3.1)	1.8 (1.1–2.9)	2.2 (0.9–5.3)

* Combined sample includes data from the Swedish Patient Register, the Swedish Rheumatology Quality (SRQ) Register, and the Epidemiological Investigation of Rheumatoid Arthritis (EIRA) study. Odds ratios (ORs) with 95% confidence intervals (95% CIs) were estimated with conditional logistic regression and calculated with a robust variance estimator. RA = rheumatoid arthritis; RF = rheumatoid factor; ACPA = anti–citrullinated protein antibody.

sources, with an OR of 3.2 (95% CI 3.0–3.3) in the combined sample, 2.9 (95% CI 2.6–3.2) in the SRQ Register, and 3.0 (95% CI 2.5–3.7) in the EIRA study.

Familial risks were greatly modified by RF/ACPA status (Table 4). In all samples, there was a stronger aggregation of RF-positive RA compared to RF-negative RA or RA overall (e.g., in the SRQ Register, ORs were 3.7, 2.5, and 2.9, respectively). Familial risk of RF-negative RA showed weaker or no specificity, with a similar association with RF-positive RA and RF-negative RA in the SRQ Register and EIRA study, albeit with a slightly stronger association with RF-negative RA than with RF-positive RA in the combined sample. The strongest familial risk was the prediction, by RF-positive RA in first-degree relatives, of ACPA-positive RA in index patients (OR 4.6 [95% CI 3.4–6.1]). Among the RA patients with unknown RF status, the degree of familial aggregation was intermediate between the risks of RF-positive RA and RF-negative RA. (In the combined sample, the OR for the association between unknown RF status in the proband and any RA in first-degree relative was 2.8 [95% CI 2.6–3.0]; the OR for the association between any RA in the proband and unknown RF status in first-degree relative was 2.9 [95% CI 2.7–3.]).

Familial risks were also modified by the proband's age at onset of disease (Figure 2). The familial OR was almost twice as high among probands with disease onset before age 40 (OR 4.3 [95% CI 3.3–5.4]) compared to probands with disease onset after age 60 (OR 2.3 [95% CI 1.9–2.7]). The age interaction was further modified by RF status; it was even more pronounced for RF-positive RA, but weak for RF-negative RA. In the EIRA study, a similar pattern was found after stratification for the proband's ACPA status and age (Figure 2), but because of lack of power it was not informative to further narrow the analyses according to the relatives' RF status.

The familial risks were consistent with an overall heritability of RA of 40%. This estimate was not particularly sensitive to the assumed population prevalence of RA, ranging from 38% (using a population prevalence estimate of 0.5%) to 45% (using a population prevalence estimate of 2%) (available on the *Arthritis & Rheumatism* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.38097/abstract). On the heritability scale, there was no visible difference between the sexes, since higher ORs in men were counteracted by lower disease prevalence. The difference in familial aggregation of RA by RF/ACPA status was more pronounced on the heritability scale, since the higher familial OR for RF/ACPA-positive RA coincided with higher disease prevalence. In the combined sample, heritability of RF-positive RA was estimated to be ~44% and heritability of RF-negative RA, ~27%. In the EIRA study, a comparison between ACPA in index patients and RF in first-degree relatives revealed a heritability estimate of ~50% for ACPA-positive RA and ~20% for ACPA-negative RA.

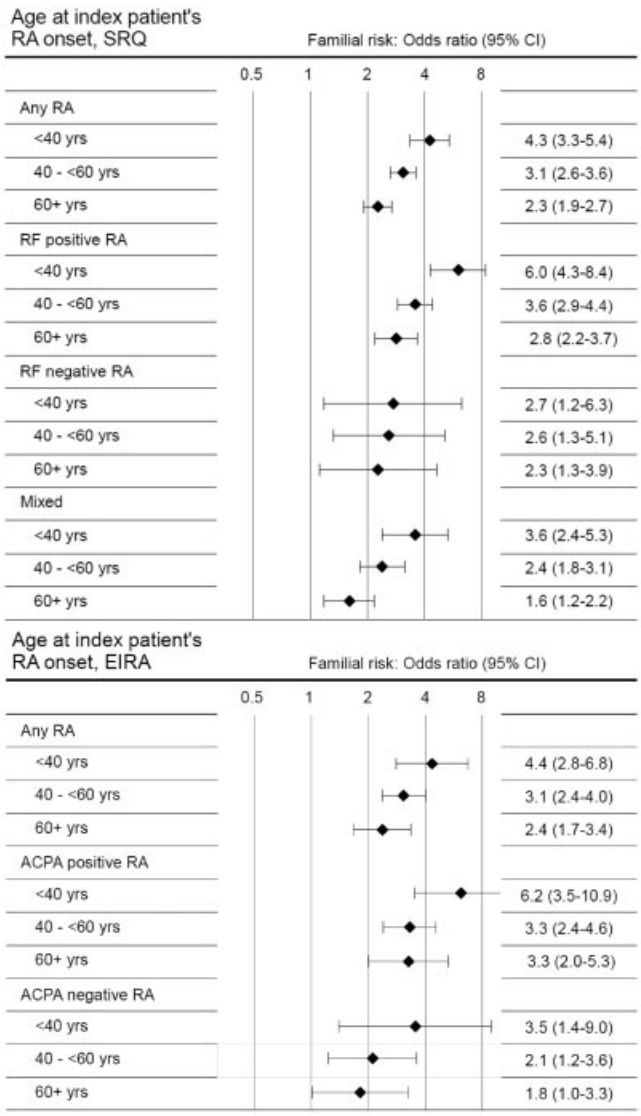

Figure 2. Relative risk of rheumatoid arthritis (RA) (familial risk) in Swedish patients with RA identified in the Swedish Rheumatology Quality Register (SRQ) and the Epidemiological Investigation of Rheumatoid Arthritis (EIRA) study (versus matched controls from a general population register), stratified by the index patient's age at onset of RA. In the SRQ Register, rheumatoid factor (RF) status refers to both index patients and relatives, i.e., RF-positive RA in first-degree relatives is regressed on RF-positive RA in index patients. In the Epidemiological Investigation of Rheumatoid Arthritis (EIRA) study, anti–citrullinated protein antibody (ACPA) status refers only to the index patient, and any RA in first-degree relatives is used for all analyses. 95% CI = 95% confidence interval.

DISCUSSION

Swedish nationwide registers were used in this study to assess the familial aggregation of RA in 3 hierarchically clustered population-based samples. We replicated population-based estimates of the familial risk of RA and were able to extend previous research in several ways.

First, in terms of family structure, we found that RA patients did not differ substantially from age-matched controls. There was no difference in the number of offspring, which raises doubt about the lowered rates of fertility or fecundity that have been previously reported in individuals with RA (27,28). RA patients were found to have a slightly higher number of siblings, which may indicate a socioeconomic difference in families with a history of RA (29). Regardless, this increased number of siblings had no effect on the estimated familial aggregation.

Further, we found familial risks that corresponded to those in previous studies of population-based samples; however, in general, the familial risks in the present study were lower than those shown in earlier studies that were based on selected or clinical samples. In a previous study that also used Swedish registers (8), a sibling risk of 4.6 was found, which is higher than our estimate and higher than the offspring risk found in that same study (standardized incidence ratio 3.0), while we found similar risks in offspring and siblings. In that study, RA was identified on the basis of hospitalizations only (and no data on RF or ACPA status were available). It might thus be that the considerably higher relative risks in the earlier study were reflective of disease severity, and, importantly, by health-seeking behavior that may be familial. The results may also be influenced by left truncation or different length of followup resulting in different age distributions, since we have shown that the familial risks are modified by age at disease onset.

The familial risks seen in our study were similar for first-degree relatives, and lower for second-degree relatives. This is consistent with the notion that familial risk is predominantly due to genetic factors, which would be similarly shared by all relatives at the same genetic distance, although environmental factors may follow a similar pattern and cannot be ruled out as contributing to familial risk. The familial risks were consistent with a heritability of 40%, which is lower than the often-cited ~60% heritability of RA (30). This previously reported heritability estimate is based on data from 2 twin samples, each with somewhat different heritability estimates (53% versus 65%), and a total of only 33 concordant twin pairs (6,30,31). Using genome-wide single-nucleotide polymorphisms (SNPs), the heritability of RA was recently estimated to be 52% (SE 8%) (32).

There may be many reasons why our estimate differs from earlier estimates. The classic twin model is known to result in overestimated heritability when monozygotic twins have more shared environment than dizygotic twins, when there are statistical interactions between genes at the same or different loci, or when there are statistical gene–environment interactions (6). It is also possible that when both twins in a twin pair have RA, they are more willing to participate, which would inflate concordance rates and heritability estimates. Our estimate of 40% is less sensitive to departures from additivity, since interactions contribute less to the sibling correlation than to the monozygotic twin correlation. That our estimate was also lower than the SNP-based estimate may be due to differences in case ascertainment or true differences between the populations studied (UK versus Swedish), but it may also be explained by random variation. Although lower than previously reported, our heritability estimate should still be an overestimate, since it assumes that nongenetic factors do not have an effect on sibling similarity.

Our results suggest that familial associations of RA are equal in men and women, and combined-sex familiality was similar in strength to sex-specific risk. Although familial ORs tended to be somewhat higher for male index patients, this is not surprising in light of the lower disease prevalence among men. Indeed, on the heritability scale, there was no visible difference (available on the *Arthritis & Rheumatism* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.38097/abstract). This absence of an interaction suggests that despite the strong difference between the sexes with regard to disease prevalence, the genetic contribution to RA seems to be similar in men and women, and we should perhaps not expect to find genes with a marked difference in effect by sex.

We found higher familial aggregation of RF/ACPA-positive RA than RF/ACPA-negative RA. The difference was more evident in the SRQ Register and EIRA study, where RF was more reliably measured. Generally, the association was even greater for ACPA than for RF, which would be expected if ACPA is a better indicator of an underlying diagnostic differentiation. This finding supports the notion that seropositive RA and seronegative RA have different etiologies, and that familial factors such as genetics are more important for the development of seropositive RA. The diseases are not independent, however. Despite a clear difference in familial aggregation, the cross-phenotype familial OR was ~2, suggesting that many genetic or family-related environmental factors influence both types of RA. This is consistent with findings of molecular genetic studies, which suggest that there are both similarities and differences in genetic risk factors for seropositive RA and seronegative RA (33).

In terms of heritability, we estimated that ACPA-positive RA had a heritability of ~50% and ACPA-negative RA ~20%. This has direct implications for the discussion on the missing heritability of RA. In calculations based on a heritability of RA of ~60% (with no distinction made in the heritability of ACPA-positive versus ACPA-negative RA), it was estimated that identified genes explain 50–60% and 30–50% of the genetic liability to develop ACPA-positive RA and ACPA-negative RA, respectively (2). If the heritability of RA is lower overall, then there is less missing knowledge on the involved genes, and we may already have identified a larger proportion of the loci that influence these traits.

A higher familial OR was found in RA with disease onset at a younger age, and a lower familial OR for RA with disease onset at an older age. The higher relative risk in individuals with earlier-onset RA is expected given that incidence of the disease peaks at 50–60 years of age. At the same heritability of a disease, the relative risk is expected to be higher at an age when the disease is rarer. The finding of lower familial risk of RA in subjects age >60 years, a time when incidence of RA is also lower, suggests that genetic and other familial factors are proportionally less important for the development of late-onset RA. It may be that individuals who are genetically predisposed to develop RA do so at an earlier age, while individuals who develop RA later have lower innate liability and need to accumulate more exposure to environmental factors for the disease to clinically manifest.

Interestingly, the age trend in familial risk was more pronounced for RF/ACPA-positive RA and weaker or absent for RF/ACPA-negative RA. This further stresses the etiologic differences between the 2 types of RA and that inborn or early-life factors seem more important for RF/ACPA-positive RA.

This study has several strengths. By using large Swedish registers we were able to provide fairly precise estimates for the familial aggregation of RA over all first- and second-degree relatives. The use of nationwide, prospectively collected patient information removed the risk of selective participation, recall bias, or misclassification due to case-reported RA in relatives. RA diagnoses recorded in the population registers have been shown to have high validity compared to chart reviews. By combining RA cases from 3 sources, we could capitalize on the statistical strength of the nation-

wide Swedish Patient Register to provide sufficient statistical power for precise estimates of sex-stratified familial risks, while taking advantage of the more clinically detailed information on age at onset and RF/ACPA status in the SRQ Register and EIRA study, to provide more nuanced estimates than those based on hospitalization data only. Familial risk estimates were consistent across data sources, supporting the notion that findings from the 2 smaller samples may be generalized to the general Swedish population.

Nevertheless, some limitations should be acknowledged. RF status and ACPA status were based on results of laboratory tests performed at one time point, as recorded in the SRQ Register and EIRA study. For the combined sample, and for relatives in each separate study population, RF status was based on the number of RF-informative RA diagnoses that were recorded in the Swedish Patient Register. It is likely that RF status is subject to some degree of misclassification. In theory, it is possible that the cross-phenotype familiality we observed for RF-positive and RF-negative RA is simply due to misdiagnosis of RF-positive RA as RF-negative RA. To explore this idea, we calculated the degree of misclassification that would be necessary for the observed OR in index patients with RF-negative RA and first-degree relatives with RF-positive RA to be due to a proportion of individuals with correctly classified RF-negative RA and with a familial OR of 1, plus a proportion of individuals with misclassified RF and an OR equal to that observed for index patients with RF-positive RA and first-degree relatives with RF-positive RA. We found that the proportion of index patients classified as having RF-negative RA who would need to actually have had RF-positive RA in order to explain the OR was roughly 50% in the combined sample and 40% in the EIRA sample. This seems unlikely, and we conclude that whereas the cross-phenotype familial risk might be inflated, a null association is unlikely.

Another limitation concerns the interpretation of familial risk. Family history of a disease may be due to genes or the nongenetic biologic, physical, or social factors shared by relatives. By comparing relatives known to share different degrees of genetic or environmental factors, it may be possible to assess the comparative importance of these factors. Unfortunately, we lacked information on adoptive relatives, monozygotic twins, and other types of relatives that would have been informative, and we were not able to test any hypotheses about the comparative importance of environmental and genetic factors. This caveat also applies to the heritability estimates, which were based on the strong assumption that only additive genetic factors contributed to familial aggregation of RA.

In conclusion, we found that the risk of developing RA was 3 times higher in first-degree relatives of RA patients. The pattern of familial risks suggests that familial factors influence RA in men and women equally and that familial factors are of less importance for late-onset RA. Familial factors were more important for RF/ACPA-positive RA, but there was a significant familial overlap between RF/ACPA-positive RA and RF/ACPA-negative RA. Even if familial risk is assumed to be completely due to genetics, the observed risks suggest a heritability of RA that is lower than previously reported, in particular for RF/ACPA-negative RA. It will now be an important task to assess to what extent the observed familial risks are driven by known RA risk genes and environmental factors.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Frisell had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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