

## Supplemental Material for: *Familial aggregation of arthritis-related diseases in seropositive and seronegative rheumatoid arthritis – a register-based case-control study in Sweden*

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### **This supplemental material contains:**

Table S1: Validity of register-based RA serology

Table S2: Familial risks in siblings, offspring, and parents

Table S3: Familial risks by proband's sex

Figure S1: Venn diagram of RA cases ascertained from different data sources

Table S4: Descriptive statistics of the sample ascertained through the SRQ

Table S5: Replication of main findings using the SRQ

Table S6: Risk of RA associated with multiple affected relatives (Figure 2 in manuscript)

**Table S1.** Correspondence of RA serology in the NPR, the SRQ, and the EIRA study.

	Serology based on algorithm in NPR			Serology from diagnosis in SRQ			RF measured in EIRA			ACPA measured in EIRA		
	N	PPV	NPV	N	PPV	NPV	N	PPV	NPV	N	PPV	NPV
Diagnosis NPR	60998	1.00	1.00	24047	0.87	0.90	2572	0.80	0.93	2582	0.77	0.84
Diagnosis SRQ	24047	0.98	0.57	25733	1.00	1.00	2423	0.95	0.93	2435	0.86	0.75
RF EIRA	2572	0.98	0.48	2423	0.97	0.89	2822	1.00	1.00	2772	0.85	0.75
ACPA EIRA	2582	0.96	0.43	2435	0.88	0.72	2772	0.87	0.71	2829	1.00	1.00

**Notes:** NPR, national patient register; SRQ, Swedish Rheumatology Quality of care register; PPV, row-wise positive predictive value; NPV, row-wise negative predictive value.

**Table S2.** Arthritis-related diseases in first degree relatives associated to proband's RA, by proband's serostatus and type of relative. RA probands ascertained through the NPR.

Disease in FDR	Type of relative	Seropositive RA, OR (95% CI)	Seronegative RA, OR (95% CI)
Seropositive RA	Offspring	4.02 (3.60-4.48)	2.52 (2.06-3.08)
	Parent	3.88 (3.51-4.28)	2.70 (2.26-3.22)
	Sibling	4.06 (3.57-4.63)	2.25 (1.87-2.71)
Seronegative RA	Offspring	2.72 (2.29-3.24)	2.78 (2.03-3.80)
	Parent	2.34 (1.95-2.81)	2.32 (1.72-3.13)
	Sibling	2.33 (1.93-2.81)	3.36 (2.24-5.06)
Juvenile idiopathic arthritis	Offspring	3.80 (2.82-5.12)	5.04 (3.00-8.46)
	Parent	*	*
	Sibling	7.69 (3.12-18.95)	7.08 (2.02-24.82)
Other inflammatory arthritis	Offspring	1.65 (1.50-1.82)	1.76 (1.49-2.08)
	Parent	1.42 (1.21-1.66)	1.41 (1.09-1.83)
	Sibling	1.76 (1.55-2.00)	1.49 (1.18-1.88)
Spondyloarthropathies	Offspring	1.17 (1.11-1.23)	1.32 (1.21-1.44)
	Parent	1.25 (1.15-1.37)	1.35 (1.17-1.56)
	Sibling	1.20 (1.12-1.28)	1.33 (1.19-1.49)
Psoriasis/ Psoriatic arthritis	Offspring	1.20 (1.12-1.29)	1.48 (1.33-1.66)
	Parent	1.20 (1.07-1.34)	1.25 (1.05-1.49)
	Sibling	1.24 (1.14-1.34)	1.41 (1.22-1.62)
Lupus	Offspring	1.73 (1.38-2.17)	1.26 (0.80-1.96)
	Parent	1.98 (1.37-2.86)	2.44 (1.42-4.20)
	Sibling	2.04 (1.59-2.62)	2.02 (1.18-3.48)
Connective tissue diseases	Offspring	2.15 (1.76-2.64)	1.66 (1.16-2.37)
	Parent	2.08 (1.66-2.60)	1.63 (1.09-2.43)
	Sibling	1.86 (1.54-2.24)	2.00 (1.40-2.85)
Arthralgia	Offspring	1.34 (1.27-1.41)	1.29 (1.17-1.43)
	Parent	1.05 (0.92-1.20)	1.17 (0.96-1.44)
	Sibling	1.08 (0.99-1.19)	1.24 (1.06-1.44)
Osteoarthritis	Offspring	1.05 (1.00-1.11)	1.10 (1.01-1.19)
	Parent	0.96 (0.91-1.01)	0.96 (0.89-1.05)
	Sibling	1.02 (0.98-1.07)	1.07 (0.99-1.17)

**Notes:** \*: Not possible to compute due to sparse data.

**Table S3.** Arthritis-related diseases in first degree relatives associated to proband's RA, by proband's serostatus and sex. RA probands ascertained through the NPR.

Disease in FDR	Data source	Female			Male		
		Seropositive RA, OR (95% CI)	Seronegative RA, OR (95% CI)	Ratio of ORs (95% CI)	Seropositive RA, OR (95% CI)	Seronegative RA, OR (95% CI)	Ratio of ORs (95% CI)
Seropositive RA	NPR	3.90 (3.65-4.18)	2.48 (2.19-2.79)	1.58 (1.37-1.81)	4.08 (3.65-4.56)	2.35 (1.94-2.86)	1.73 (1.38-2.17)
	SRQ	4.11 (3.73-4.53)	2.68 (2.27-3.18)	1.53 (1.26-1.86)	4.14 (3.51-4.89)	2.44 (1.87-3.19)	1.70 (1.24-2.33)
Seronegative RA	NPR	2.38 (2.12-2.66)	2.69 (2.18-3.31)	0.88 (0.70-1.12)	2.76 (2.28-3.35)	3.14 (2.27-4.33)	0.88 (0.61-1.28)
	SRQ	2.34 (2.00-2.75)	2.77 (2.03-3.78)	0.85 (0.60-1.20)	2.64 (1.98-3.53)	2.81 (1.78-4.44)	0.94 (0.55-1.61)
Juvenile idiopathic arthritis	NPR	3.99 (2.91-5.47)	6.47 (3.47-12.06)	0.62 (0.31-1.24)	3.92 (2.15-7.14)	4.02 (1.75-9.22)	0.97 (0.35-2.72)
	SRQ	2.51 (1.59-3.97)	5.10 (2.44-10.64)	0.49 (0.21-1.17)	3.76 (1.73-8.16)	3.25 (1.37-7.74)	1.15 (0.36-3.70)
Other infl. arthritis	NPR	1.69 (1.57-1.82)	1.60 (1.39-1.84)	1.06 (0.90-1.24)	1.44 (1.27-1.64)	1.41 (1.14-1.74)	1.03 (0.80-1.31)
	SRQ	1.45 (1.29-1.63)	1.58 (1.30-1.92)	0.92 (0.73-1.15)	1.40 (1.16-1.69)	1.19 (0.87-1.63)	1.17 (0.82-1.69)
Spondyloarthropathies	NPR	1.21 (1.16-1.26)	1.30 (1.21-1.39)	0.93 (0.86-1.01)	1.18 (1.10-1.27)	1.35 (1.20-1.50)	0.88 (0.77-1.00)
	SRQ	1.17 (1.10-1.24)	1.22 (1.10-1.36)	0.95 (0.84-1.08)	1.17 (1.05-1.29)	1.18 (1.00-1.40)	0.99 (0.81-1.20)
Psoriasis/Psoriatic arthritis	NPR	1.24 (1.17-1.31)	1.40 (1.28-1.53)	0.89 (0.80-0.98)	1.21 (1.11-1.32)	1.40 (1.21-1.60)	0.87 (0.73-1.02)
	SRQ	1.16 (1.07-1.26)	1.41 (1.24-1.61)	0.82 (0.71-0.96)	1.13 (0.98-1.29)	1.07 (0.87-1.32)	1.05 (0.82-1.35)
Lupus	NPR	2.05 (1.71-2.44)	1.45 (1.03-2.05)	1.41 (0.96-2.08)	1.73 (1.30-2.31)	2.87 (1.74-4.72)	0.60 (0.34-1.07)
	SRQ	1.99 (1.53-2.59)	1.76 (1.11-2.79)	1.13 (0.67-1.92)	2.07 (1.36-3.17)	2.23 (1.17-4.26)	0.93 (0.43-2.01)
Connective tissue diseases	NPR	2.08 (1.83-2.37)	1.67 (1.29-2.15)	1.25 (0.94-1.66)	1.92 (1.55-2.38)	1.98 (1.39-2.82)	0.97 (0.64-1.47)
	SRQ	1.82 (1.50-2.21)	1.19 (0.80-1.77)	1.53 (0.99-2.36)	2.05 (1.49-2.83)	1.73 (0.98-3.05)	1.19 (0.62-2.28)
Arthralgia	NPR	1.26 (1.20-1.32)	1.33 (1.22-1.45)	0.94 (0.86-1.04)	1.17 (1.07-1.26)	1.09 (0.94-1.25)	1.07 (0.91-1.26)
	SRQ	1.20 (1.11-1.29)	1.31 (1.16-1.47)	0.92 (0.80-1.05)	1.19 (1.06-1.34)	1.05 (0.87-1.26)	1.14 (0.91-1.42)
Osteoarthritis	NPR	1.03 (1.00-1.06)	1.06 (1.00-1.11)	0.97 (0.92-1.04)	1.02 (0.97-1.08)	1.02 (0.94-1.11)	1.00 (0.91-1.11)
	SRQ	1.03 (0.99-1.08)	1.09 (1.01-1.17)	0.95 (0.87-1.04)	1.00 (0.93-1.08)	1.07 (0.95-1.21)	0.93 (0.81-1.08)

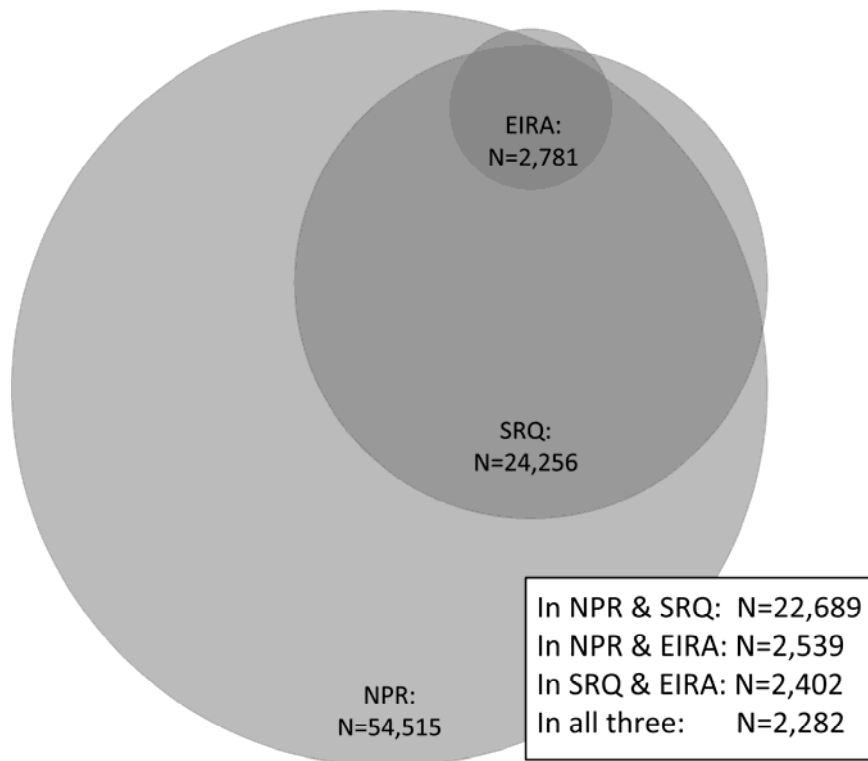


Figure S1. Venn diagram of RA cases retrieved from the National Patient Register (NPR), the Swedish Rheumatology's Quality of Care Register (SRQ), and the Epidemiological Investigation of Rheumatoid Arthritis (EIRA) case-control study.

**Table S4. Descriptive statistics of RA cases ascertained through the Swedish Rheumatology Quality of Care Register, their matched controls, and index individuals' first degree relatives.**

Index individuals:	Seropositive RA		Seronegative RA	
	Cases	Controls	Cases	Controls
N	17968	86404	6288	30440
Male, %	27.4%	27.2%	30.6%	30.4%
Age at inclusion, yrs, median (1st -3rd quartile)	60 (50-68)	59 (50-68)	60 (49-70)	60 (49-70)
<b>First degree relatives:</b>				
N	71183	347149	24785	120182
Male, %	50.9%	51.5%	51.0%	51.8%
Birth year, median (1st-3rd quartile)	1969 (1958-1980)	1970 (1960-1982)	1969 (1957-1982)	1969 (1958-1983)
Seropositive RA	1618 (2.27%)	1944 (0.56%)	352 (1.42%)	679 (0.56%)
Seronegative RA	333 (0.47%)	680 (0.20%)	121 (0.49%)	210 (0.17%)
Juvenile idiopathic arthritis	45 (0.06%)	84 (0.02%)	29 (0.12%)	30 (0.02%)
Other inflammatory arthritis	548 (0.77%)	1888 (0.54%)	203 (0.82%)	675 (0.56%)
Spondyloarthropathies	1985 (2.79%)	8268 (2.38%)	697 (2.81%)	2791 (2.32%)
Psoriasis/ psoriatic arthritis	1141 (1.60%)	4805 (1.38%)	458 (1.85%)	1713 (1.43%)
Lupus	123 (0.17%)	304 (0.09%)	39 (0.16%)	104 (0.09%)
Connective tissue diseases	215 (0.30%)	549 (0.16%)	51 (0.21%)	188 (0.16%)
Arthralgia	1337 (1.88%)	5496 (1.58%)	523 (2.11%)	2053 (1.71%)
Osteoarthritis	3794 (5.33%)	18089 (5.21%)	1397 (5.64%)	6215 (5.17%)

**Table S5. Arthritis-related diseases in first degree relatives associated to proband's RA, by proband's serostatus. Cases ascertained through the Swedish Rheumatology Quality of Care Register.**

Disease in relative	Seropositive RA, OR (95% CI)	Seronegative RA, OR (95% CI)	Ratio of ORs (95% CI)
Seropositive RA	4.12 (3.79-4.49)	2.61 (2.26-3.01)	1.58 (1.34-1.87)
Seronegative RA	2.41 (2.10-2.77)	2.78 (2.15-3.60)	0.87 (0.65-1.16)
Juvenile idiopathic arthritis	2.78 (1.88-4.10)	4.54 (2.53-8.14)	0.61 (0.30-1.24)
Other infl. arthritis	1.44 (1.30-1.59)	1.46 (1.24-1.72)	0.99 (0.81-1.19)
Spondyloarthropathies	1.17 (1.11-1.23)	1.21 (1.11-1.32)	0.96 (0.87-1.07)
Psoriasis/ psoriatic arthritis	1.15 (1.08-1.24)	1.31 (1.17-1.46)	0.88 (0.77-1.01)
Lupus	2.01 (1.61-2.52)	1.90 (1.31-2.77)	1.06 (0.69-1.63)
Connective tissue diseases	1.88 (1.59-2.22)	1.34 (0.97-1.85)	1.41 (0.98-2.02)
Arthralgia	1.20 (1.12-1.27)	1.22 (1.11-1.35)	0.98 (0.87-1.10)
Osteoarthritis	1.02 (0.99-1.06)	1.08 (1.02-1.15)	0.95 (0.88-1.02)

**Table S6. Odds ratios (95% CI) for combinations of arthritis-related disease in first degree relatives associated to proband's RA ascertained through the NPR, by serostatus.**

Disease in FDR:	Seropositive RA in proband			Seronegative RA in proband		
	FDR with seropositive RA and a second FDR with disease in row	FDR with seronegative RA and a second FDR with disease in row	2+ FDRs with disease in row	FDR with seropositive RA and a second FDR with disease in row	FDR with seronegative RA and a second FDR with disease in row	2+ FDRs with disease in row
Seropositive RA	8.92 (6.97-11.42)	6.63 (4.65-9.44)	8.92 (6.97-11.42)	4.10 (2.65-6.34)	6.47 (3.36-12.45)	4.10 (2.65-6.34)
Seronegative RA	6.63 (4.65-9.44)	4.88 (1.93-12.31)	4.88 (1.93-12.31)	6.47 (3.36-12.45)	1.67 (0.17-16.02)	1.67 (0.17-16.02)
JIA	9.86 (3.26-29.77)	6.45 (1.47-28.32)	17.41 (3.46-87.67)	11.17 (2.93-42.57)	*	7.46 (1.25-44.56)
Other infl. arthritis	4.88 (3.61-6.59)	2.58 (1.46-4.58)	3.10 (2.02-4.77)	2.35 (1.37-4.03)	5.13 (2.42-10.87)	3.20 (1.33-7.74)
Spondyloarthropathies	3.87 (3.42-4.38)	2.73 (2.20-3.39)	1.43 (1.26-1.62)	2.79 (2.22-3.52)	2.61 (1.82-3.76)	1.45 (1.17-1.80)
Psoriasis/psoriatic arthritis	3.62 (3.10-4.23)	3.03 (2.39-3.84)	1.41 (1.19-1.67)	3.24 (2.47-4.26)	2.49 (1.55-4.00)	1.58 (1.18-2.11)
Lupus	3.39 (2.29-5.04)	2.40 (1.16-4.97)	1.47 (0.40-5.39)	2.36 (0.99-5.67)	1.50 (0.49-4.56)	1.57 (0.16-15.71)
Connective tissue diseases	3.50 (2.74-4.49)	3.66 (2.25-5.95)	4.04 (1.59-10.27)	2.68 (1.74-4.13)	2.06 (0.94-4.51)	9.65 (1.80-51.78)
Arthralgia	3.57 (2.93-4.35)	3.47 (2.52-4.76)	1.27 (1.04-1.56)	2.73 (1.95-3.82)	2.73 (1.47-5.05)	1.80 (1.30-2.49)
Osteoarthritis	3.67 (3.23-4.17)	2.32 (1.88-2.86)	1.06 (0.99-1.15)	2.33 (1.87-2.89)	2.69 (1.79-4.05)	1.13 (1.00-1.28)

**Notes:** FDR: first degree relative. JIA: Juvenile idiopathic arthritis. \*: Not possible to compute.