

Online Supplementary material

This file contains online support data for Westerlind et al “Siblings of patients with rheumatoid arthritis have an increased mortality rate, a Swedish cohort study”

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Supplementary Material

Data linkage, registers and data sources

The Swedish Rheumatology Quality (SRQ) register was established in 1996. At diagnosis, patients with rheumatoid arthritis (RA) are included at the rheumatology clinic and followed prospectively. SRQ is estimated to have a coverage of over 80% of the prevalent patients with RA.¹ SRQ was through the unique personal identification number (PIN) given to everyone residing in Sweden for a longer period of time, linked to a number of nationwide, virtually complete, registers, such as the National patient register (NPR), the Prescribed Drug Register (PDR), the multi-generation register (MGR), the total population register (TPR), the cause of death register and the Longitudinal integrated database for health insurance and labor market studies (LISA). This linkage and the registers included have previously been described elsewhere,² and we therefore here only provide a brief overview. NPR contains inpatient visits since 1964, and hospital-based outpatient care since 2001.³ Since 2005, data on all prescribed drugs, are collected in PDR. The TPR contains information on sex and date of birth for the Swedish population since the start in 1968.⁴ In events of death, the date, and cause thereof, is registered with the cause of death register. LISA contains information on income, marital status and educational level and through MGR, all individuals born 1932 or later and residing in Sweden since 1961 or later, can be linked to their parents.

REFERENCES

1. SRQ. Visualization and Analysis Platform (VAP). 2018 (accessed 2018-11-05).
2. Askling J, Fored CM, Geborek P, et al. Swedish registers to examine drug safety and clinical issues in RA. *Ann Rheum Dis* 2006; **65**(6): 707-12.
3. Ludvigsson JF, Andersson E, Ekbom A, et al. External review and validation of the Swedish national inpatient register. *BMC Public Health* 2011; **11**: 450.
4. Ludvigsson JF, Almqvist C, Bonamy AK, et al. Registers of the Swedish total population and their use in medical research. *Eur J Epidemiol* 2016; **31**(2): 125-36.

Supplementary Table S1. Demographics of the study population of Swedish incident RA and prevalent, respectively, patients identified through the national Patient Register, followed from RA diagnosis of the index patient (2006 through 2017) for all-cause mortality up until the end of 2018.

	Patients with RA	Full siblings of the patients with RA	Matched reference individuals in the general population	Full siblings of the matched reference individuals in the general population
Incident NPR cohort				
N	10,708	13,455	29,624	38,070
Median age (IQR)	56.2 (14.6)	56.2 (14.4)	55.3 (14.8)	55.4 (14.8)
Women (%)	7,373 (68.9)	6,543 (48.6)	20,334 (68.6)	18,893 (49.6)
Median years of follow-up (IQR)	6.2 (5.7)	6.4 (5.8)	6.3 (5.8)	6.4 (5.8)
Events	779	902	1,700	2,230
Age and sex standardized mortality rate (95%CI)	10.5 (9.7-11.3)	8.9 (8.3-9.5)	8.8 (8.4-9.3)	8.2 (7.9-8.5)
Hazard Ratio (95%CI)	1.19 (1.09-1.29) ^A	1.08 (1.00-1.16) ^B		
Rheumatoid factor positive RA				
N	6,279	7,985	17,371	22,528
Median age (IQR)	56.2 (14.3)	56.4 (14.0)	55.5 (14.5)	55.7 (14.5)
Women (%)	4,449 (70.9)	3,913 (49)	12,235 (70.4)	11,139 (49.4)
Median years of follow-up (IQR)	6.3 (5.6)	6.5 (5.8)	6.4 (5.8)	6.5 (5.7)
Events	531	562	1,001	1,386
Age and sex standardized mortality rate (95%CI)	12.6 (11.4-13.7)	9.3 (8.5-10.0)	8.9 (8.4-9.5)	8.5 (8.0-8.9)
Hazard Ratio (95%CI)	1.41 (1.27-1.57) ^A	1.08 (0.98-1.20) ^B		
Rheumatoid factor negative RA				
N	4,429	5,470	12,253	15,542
Median age (IQR)	56.0 (15.0)	56.0 (14.9)	55.0 (15.2)	55.0 (15.2)
Women (%)	2,924 (66.0)	2,630 (48.1)	8,099 (66.1)	7,754 (49.9)
Median years of follow-up (IQR)	6.2 (5.8)	6.3 (5.8)	6.2 (5.8)	6.3 (5.9)
Events	248	340	699	844
Age and sex standardized mortality rate (95%CI)	7.8 (6.8-8.8)	8.5 (7.5-9.4)	8.7 (8.0-9.4)	7.8 (7.3-8.3)
Hazard Ratio (95%CI)	0.89 (0.77-1.03) ^A	1.06 (0.94-1.21) ^B		

^A Adjusted for age, sex and calendar period of inclusion, and compared to the general population comparator subjects

^B Adjusted for age, sex and calendar period of inclusion, and compared to the siblings of the general population comparator subjects

Supplementary Table S2. Hazard ratio (HR) for mortality among incident patients with RA, identified from two overlapping data sources, compared to the general population comparator subjects, and among siblings of the patients with RA compared to the siblings of the general population comparator subjects, stratified by time since the index RA patient's diagnosis.

	Incident RA from the Swedish Rheumatology Quality register			
	HR (95% CI)			
	Patients with RA	Full siblings of the patients with RA	Matched reference individuals in the general population	Full siblings of the matched reference individuals in the general population
	< 1 year			
N (% women)	8137 (68.8)	10261 (48.8)	22457 (68.4)	28878 (49.6)
Median years of follow-up (IQR)	1.0 (0.0)	1.0 (0.0)	1.0 (0.0)	1.0 (0.0)
Events	37	64	157	164
Age and sex standardized mortality rate (95%CI)	5.6 (3.8-7.4)	7.2 (5.4-9.0)	8.7 (7.3-10.1)	6.8 (5.7-7.9)
Hazard Ratio (95% CI)	0.59 (0.41-0.84) ^A	1.08 (0.81-1.42) ^A		
	1 - <5 years			
N (% women)	8097 (68.9)	10178 (48.8)	22244 (68.5)	28664 (49.7)
Median years of follow-up (IQR)	5.0 (1.1)	5.0 (1.1)	5.0 (1.1)	5.0 (1.1)
Events	221	320	588	732
Age and sex standardized mortality rate (95%CI)	7.5 (6.4-8.5)	8.0 (7.1-8.9)	7.9 (7.2-8.5)	6.9 (6.3-7.4)
Hazard Ratio (95% CI)	0.96 (0.82-1.12) ^A	1.16 (1.02-1.32) ^B		
	5 - < 10 years			
N (% women)	5320 (70.6)	6733 (48.8)	14533 (70.3)	19052 (49.8)
Median years of follow-up (IQR)	9.6 (2.9)	9.7 (2.8)	9.7 (2.9)	9.7 (2.8)
Events	231	235	457	607
Age and sex standardized mortality rate (95%CI)	11.6 (10.0-13.1)	8.4 (7.3-9.5)	8.9 (8.0-9.7)	8.0 (7.3-8.6)
Hazard Ratio (95% CI)	1.28 (1.09-1.50) ^A	1.03 (0.89-1.20) ^B		
	>= 10 years			
N (% women)	2440 (72.6)	3172 (49.4)	6709 (71.6)	9027 (49.6)
Median years of follow-up (IQR)	13.1 (3.9)	13.2 (3.9)	13.2 (4.0)	13.2 (4.0)
Events	124	146	209	352
Age and sex standardized mortality rate (95%CI)	12.1 (9.7-14.5)	9.2 (7.6-10.8)	7.7 (6.5-9.0)	8.5 (7.6-9.5)
Hazard Ratio (95% CI)	1.55 (1.24-1.94) ^A	1.10 (0.91-1.34) ^B		
	NPR incident			
	< 1 years			
N (% women)	10708(68.9)	13455(48.6)	29624(68.6)	38070(49.6)
Median years of follow-up (IQR)	1.0(0.0)	1.0(0.0)	1.0(0.0)	1.0(0.0)
Events	47	97	221	243
Age and sex standardized mortality rate (95%CI)	5.2 (3.7-6.7)	8.0 (6.3-9.6)	8.7 (7.6-9.9)	8.0 (6.1-7.9)
Hazard Ratio (95% CI)	0.55 (0.40-0.75) ^A	1.08 (0.85.36) ^B		
	1 - < 5 years			

N (% women)	10655(69.0)	13331(48.7)	29350(68.8)	37767(49.7)
Median years of follow-up (IQR)	5.0(1.2)	5.0(1.2)	5.0(1.2)	5.0(1.2)
Events	363	432	814	1007
Age and sex standardized mortality rate (95%CI)	10.2 (9.1-11.3)	9.0 (8.2-9.9)	8.8 (8.2-9.4)	7.8 (8.2-9.4)
Hazard Ratio (95% CI)	1.14 (1.01-1.29) ^A	1.14 (1.02-1.28) ^B		
5 - <10 years				
N (% women)	6652(70.4)	8502(48.6)	18405(70.0)	24045(49.7)
Median years of follow-up (IQR)	8.5(3.3)	8.6(3.2)	8.6(3.3)	8.6(3.2)
Events	316	314	590	843
Age and sex standardized mortality rate (95%CI)	12.3 (10.9-13.8)	8.4 (7.5-9.4)	8.9 (8.1-9.6)	8.6 (8.0-9.2)
Hazard Ratio (95% CI)	1.40 (1.22-1.61) ^A	0.97 (0.86-1.11) ^B		
>= 10 years				
N (% women)	2172(72.7)	2830(49.5)	6212(71.9)	8222(49.9)
Median years of follow-up (IQR)	11.5(1.6)	11.5(1.7)	11.5(1.7)	11.5(1.7)
Events	62	67	99	165
Age and sex standardized mortality rate (95%CI)	12.4 (8.8-16.0)	9.7 (6.9-12.4)	7.5 (5.7-9.3)	9.2 (7.7-10.8)
Hazard Ratio (95% CI)	1.75 (1.27-2.40) ^A	1.11 (0.84-1.47) ^B		

^A Adjusted for age, sex and calendar period of inclusion, and compared to the general population comparator subjects

^B Adjusted for age, sex and calendar period of inclusion, and compared to the siblings of the general population comparator subjects

Supplementary Table S3. Hazard ratio (HR) and 95% confidence intervals (CI) for mortality among the general comparator subjects in the main analysis, using income, education and marital status as covariates.

Covariate	Frequency among the general population comparator subjects and their siblings	HR (95%CI)^A
N total	50,382	
Educational level > 12 years	15,437	1.00 (Ref)
Educational level 10-12 years	23,460	1.60 (1.45-1.77)
Educational level <= 9 years	11,485	1.88 (1.69-2.09)
Income*		1.15 (1.13-1.17)
Married	33,712	1.00 (Ref)
Marriage “unmarried”	14,310	1.75 (1.60-1.92)
Marriage widow/-er	2,360	1.25 (1.09-1.43)

* Adjusted for inflation and divided into deciles with highest income as reference group

^A Adjusted for sex, age and calendar period of inclusion

Supplementary Table S4. Hazard ratio (HR) and 95% confidence intervals (CI) for mortality among the patients with RA in the incident cohort diagnosed 2001-2017 and identified through the Swedish Rheumatology Quality register compared to their matched general population comparator subjects and the siblings of the incident patients with RA compared to the siblings of the general population comparator subjects, after adjusting for income, education and marital status,

	Patients with RA	Full siblings of the patients with RA	Matched reference individuals in the general population	Full siblings of the matched reference individuals in the general population
N (% women)	8,036 (68.8)	10,083 (48.8)	22,108 (68.3)	28,274 (49.7)
Income*				
HR (95%CI)	1.13 (1.03-1.25) ^A	1.09 (1.00-1.19) ^B		
HR among men (95% CI)	1.12 (0.96-1.29)	0.99 (0.88-1.12)		
HR among women (95% CI)	1.15 (0.99-1.32)	1.27 (1.10-1.47)		
Educational level				
<= 9 years (N events)	2,020 (238)	2,708 (301)	4,696 (507)	6,789 (655)
10-12 years (N events)	3,832 (256)	4,809 (304)	10,149 (569)	13,311 (802)
> 12 years [†] (N events)	2,184 (94)	2,566 (115)	7,263 (236)	8,174 (284)
HR (95%CI)	1.11 (1.01-1.22) ^A	1.09 (1.00-1.19) ^B		
HR among men (95% CI)	1.07 (0.92-1.24)	1.00 (0.89-1.12)		
HR among women (95% CI)	1.12 (0.97-1.30)	1.25 (1.08-1.45)		
Marital status				
Married [†] (N events)	5,428 (425)	6,743 (519)	14,840 (922)	18,872 (1,212)
Marriage “unmarried” (N events)	2,175 (104)	2,869 (149)	6,144 (280)	8,166 (397)
Marriage widow/-er (N events)	433 (62)	471 (59)	1,124 (123)	1,236 (145)
HR (95%CI)	1.14 (1.03-1.26) ^A	1.10 (1.01-1.20) ^B		
HR among men (95% CI)	1.12 (0.97-1.30)	1.01 (0.90-1.13)		
HR among women (95% CI)	1.15 (0.99-1.32)	1.27 (1.10-1.47)		
Combined model with all three covariates				
HR (95%CI)	1.12 (1.01-1.23) ^A	1.09 (1.00-1.19) ^B		
HR among men (95% CI)	1.09 (0.94-1.26)	0.99 (0.88-1.11)		
HR among women (95% CI)	1.13 (0.98-1.30)	1.26 (1.09-1.45)		

* Adjusted for inflation and divided into deciles with highest income as reference group

[†] Reference group

^A Adjusted for age, sex and calendar period of inclusion, and compared to the general population comparator subjects

^B Adjusted for age, sex and calendar period of inclusion, and compared to the siblings of the general population comparator subjects

Supplementary Table S5. Age standardized mortality rates with 95% confidence intervals, and hazard ratio (HR) with 95% confidence intervals (CI) stratified by sex and status, for all three cohorts. The mortality rates were standardized against the incident SRQ cohort, using 10 year age strata.

	Patients with RA	Full siblings of the patients with RA	Matched reference individuals in the general population	Full siblings of the matched reference individuals in the general population
Incident SRQ cohort				
N men (N events)	2,541 (277)	5,256 (440)	7,086 (660)	14,543 (1,119)
N women (N events)	5,596 (331)	5,005 (316)	15,371 (737)	14,335 (714)
Mortality rate men (95% CI)	12.3 (11.3-13.4)	10.8 (10.1-11.5)	11.3 (10.7-12.0)	10.4 (10.0-10.8)
Mortality rate women (95% CI)	8.0 (7.4-8.6)	7.7 (7.1-8.3)	7.0 (6.6-7.4)	6.4 (6.0-6.7)
HR among men (95% CI)	1.09 (0.95-1.26) ^A	1.03 (0.91-1.15) ^B		
HR among women (95% CI)	1.13 (0.99-1.29) ^A	1.21 (1.06-1.38) ^B		
Incident NPR cohort				
N men (N events)	3,335 (353)	6,912 (543)	9,290 (820)	19,177 (1,352)
N women (N events)	7,373 (426)	6,543 (359)	20,334 (880)	18,893 (878)
Mortality rate men (95% CI)	13.2 (12.2-14.3)	11.0 (10.4-10.9)	11.6 (11.0-12.2)	10.5 (10.1-10.9)
Mortality rate women (95% CI)	8.4 (7.9-9.0)	7.3 (6.8-7.9)	6.7 (6.4-7.1)	6.5 (6.2-6.8)
HR among men (95% CI)	1.14 (1.01-1.29)	1.04 (0.95-1.15)		
HR among women (95% CI)	1.23 (1.10-1.39)	1.12 (0.99-1.27)		
Prevalent NPR cohort				
N men (N events)	7,320 (1,158)	16,731 (1,851)	19,818 (2,144)	46,030 (4,559)
N women (N events)	18,144 (1,868)	15,866 (1,235)	48,856 (3,128)	45,516 (2,928)
Mortality rate men (95% CI)	15.3 (14.6-15.9)	11.2 (10.8-11.5)	10.9 (10.6-11.3)	10.6 (10.4-10.8)
Mortality rate women (95% CI)	10.6 (10.3-10.9)	7.4 (7.1-7.7)	7.0 (6.9-7.2)	6.4 (6.2-6.5)
HR among men (95% CI)	1.39 (1.29-1.49) ^A	1.04 (0.99-1.10) ^B		
HR among women (95% CI)	1.50 (1.42-1.59) ^A	1.15 (1.08-1.23) ^B		

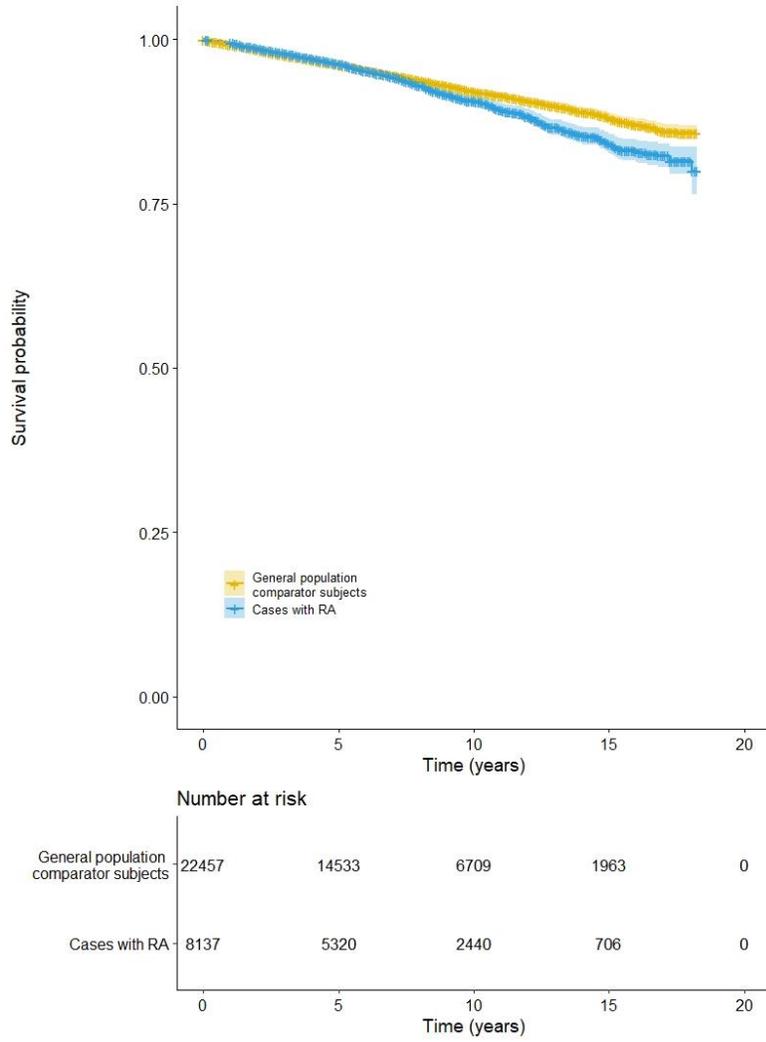
^A Adjusted for age and time of inclusion, and compared to the general population comparator subjects

^B Adjusted for age and time of inclusion, and compared to the siblings of the general population comparator subjects

Supplementary Table S6 Number and proportion of events per ICD chapter as the listed cause of death among the full siblings of new-onset patients with RA identified in the Swedish Rheumatology Quality Registers 2001-2017 and full siblings of their matched reference individuals in the general population.

	Full siblings of the patients with RA	Full siblings of the matched reference individuals in the general population
Listed cause of death	N (%)	N (%)
missing	125 (17)	311 (17)
A	6 (1)	16 (1)
B	4 (1)	9 (0)
C	231 (31)	626 (34)
D	7 (1)	15 (1)
E	20 (3)	53 (3)
F	13 (2)	36 (2)
G	26 (3)	69 (4)
H	0 (0)	1 (0)
I	186 (25)	416 (23)
J	52 (7)	92 (5)
K	19 (3)	48 (3)
L	2 (0)	4 (0)
M	6 (1)	12 (1)
N	7 (1)	13 (1)
O	0 (0)	0 (0)
P	0 (0)	0 (0)
Q	2 (0)	3 (0)
R	16 (2)	17 (1)
S	0 (0)	0 (0)
T	0 (0)	0 (0)
U	0 (0)	0 (0)
V	3 (0)	10 (1)
W	5 (1)	22 (1)
X	22 (3)	43 (2)
Y	4 (1)	17 (1)
Total	756	1833

Supplementary Figure S1. Kaplan-Meier curve for the 8,137 Swedish patients with new-onset RA identified in the Swedish Rheumatology Quality Register, and followed from the RA diagnosis of the index patient (2001 through 2017) for all-cause mortality up until the end of 2018, and their 22,457 matched reference individuals from the general population



Supplementary Figure S2. Kaplan-Meier curve for the 10,261 siblings of the Swedish patients with new-onset RA identified in the Swedish Rheumatology Quality Register, and followed from the RA diagnosis of the index patient (2001 through 2017) for all-cause mortality up until the end of 2018, and 28,878 full siblings of the matched reference individuals from the general population.

