EXTENDED REPORT

Impact of parental history on patients' cardiovascular mortality in rheumatoid arthritis

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Background: Patients with rheumatoid arthritis are at increased risk of death from cardiovascular disease (CVD). This risk is influenced by the inflammatory activity of the rheumatoid arthritis as well as by traditional risk factors for CVD. However, little is known about whether or to what extent hereditary factors for CVD contribute additional risk in patients with rheumatoid arthritis.

Objective: To assess the clinical impact of a parental history of CVD in patients with rheumatoid arthritis.

Methods: Population based cohort study of 10 805 Swedish patients with rheumatoid arthritis aged 16–67 years during follow up (1990–2000). Parents, and cardiovascular deaths among patients and parents, were identified through register linkages. Relative risk of death v the general population was assessed using standardised mortality ratios (SMR), which were compared by Poisson regression.

Results: Rheumatoid patients with a parental history of fatal CVD had an SMR of death from CVD of 2.9 (95% confidence interval, 2.5 to 3.4). By contrast, rheumatoid patients without a parental history of fatal CVD had an SMR of 1.7 (1.2 to 2.3). A parental death from CVD was associated with a 70% increase in the risk of fatal CVD in rheumatoid arthritis (SMR ratio = 1.7 (1.2 to 2.4), and an increase in the 10 year mortality from CVD from 5% to 10% in men and from 2% to 4% in women aged 50 to 67 years.

Conclusions: Parental history of death from CVD is an important (and easily assessable) risk factor for fatal CVD in rheumatoid arthritis.

Patients with rheumatoid arthritis are at increased risk of premature death, mainly because of an increased occurrence of cardiovascular disease (CVD).^{1–3} As CVD is a serious medical condition, and as interventions among individuals at high risk may reduce their risk of CVD, identification of rheumatoid patients at high risk of CVD is an important task for rheumatologists—indeed probably the single most important measure that currently may prolong the lifespan in rheumatoid arthritis.⁴ Easily assessable clinical indices that differentiate between rheumatoid patients at high and low risk of CVD are therefore warranted. Recent studies aimed at exploring the occurrence and risk factors for CVD in rheumatoid arthritis suggest that most traditional risk factors for CVD are not more common in rheumatoid patients than in the general population, and hence are unlikely to explain the increased risk of CVD in the former, which instead appears to be linked to the inflammatory activity in rheumatoid arthritis.^{3–12} There is, however, some evidence for an increased occurrence of parental cardiovascular morbidity or mortality in patients with rheumatoid arthritis.^{3–13} From a clinical standpoint it is important to understand the influence of heredity, as information on this can be obtained by simple questioning and may influence the prediction of CVD risk in the patient.

In the general population, a parental history of CVD is a risk factor for CVD independently of risk factors such as systolic blood pressure, cholesterol level, and cigarette smoking, and has typically been associated with a 50–100% increased risk of fatal or non-fatal CVD in the offspring.^{14–18} If this familial association also holds true in rheumatoid arthritis, rheumatoid patients with a parental history of CVD may be at particularly high risk of death from CVD. In contrast to previous studies which have aimed at assessing the prevalence of,¹⁰ or have adjusted for but not displayed the intrinsic effect of,^{3–9} risk factors such as parental history, we therefore aimed to assess the clinical impact of a parental history of CVD in patients with rheumatoid arthritis. To do

this, we used nationwide and population based Swedish health and census registers to identify a cohort of over 12 000 patients, their parents, and the occurrence of fatal CVD among them.

METHODS

Data sources

Swedish inpatient care is public and population based. Referrals are based on geography rather than insurance. The national registration number (NRN), a unique 10 digit number assigned to all Swedish residents at birth, is recorded in all health and census registers and allows record linkage.¹⁹ In this study, we used the following registers:

- *The Swedish Hospital Discharge Register.* This contains information on all individual discharges from Swedish inpatient care, countywise since 1964, nationwide since 1987.²⁰ Discharge diagnoses (one principal and up to seven contributory) are coded according to the *International Classification of Diseases* (ICD) versions 7–10. The completeness of the register is over 99%. Scrutiny, within the framework of other studies, of almost 1000 medical files of individuals discharged with rheumatoid arthritis has indicated that close to 90% of these register diagnoses reflected true rheumatoid arthritis as defined by the American College of Rheumatology (ACR) criteria (the remainder chiefly being made up of other rheumatic diseases).²¹
- *The Swedish Multi-Generation Register.* This contains information on the identity (the NRN) of parents of Swedish residents born 1932 or later and alive in 1961. At least one parent may be identified for over 90% of such individuals who were alive in 1990. For these, parents may be

Abbreviations: ACR, American College of Rheumatology; CVD, cardiovascular disease; NRN, national registration number; SMR, standardised mortality ratio

Table 1 Characteristics of the analytical cohort of 10 805 Swedish patients with rheumatoid arthritis born in 1932 or later and admitted to hospital with adult rheumatoid arthritis at least once between 1964 and 1999

Number of patients	10 805
Sex	
Female	7840
Male	2965
Year of birth	
1932–1939	3665
1940–1949	4248
1950–1959	1783
1960–1969	860
1970–1982	249
Year of first inpatient RA diagnosis	
1964–1979	2081
1980–1989	3620
1990–1998	5104
Median age (range) at start of follow up (y)	48 (16 to 67)
Person-years of follow up	75 906

RA, rheumatoid arthritis; y, years.

identified independently of the vital status of each individual in the parent–offspring pair. The most common reason for incomplete information on the NRNs of parents is foreign country of birth.

- *The Swedish Register of Population and Population Changes.* This is the Swedish census register and contains information on vital status and any date of emigration for Swedish residents.

Patients

In the Hospital Discharge Register, we identified all individuals who were born 1932 or later—to comply with the coverage of the Multi-Generation Register—and who were discharged with adult rheumatoid arthritis at least once between 1 January 1964 and 31 December 1999. The ICD codes used were ICD-7: 722, ICD-8: 712.1, 712.3, 714.93, ICD-9: 714 A-C, and ICD-10: M05-06. After exclusion of

individuals with data inconsistencies precluding follow up ($n = 40$), those who at some other point in time also had a discharge diagnosis of either psoriatic arthritis, ankylosing spondylitis, or systemic lupus erythematosus ($n = 1157$), and those who died within one year following first admission listing rheumatoid arthritis ($n = 901$), this primary cohort consisted of 14 390 patients with rheumatoid arthritis; 72% were female, and the median age at entry was 49 years (range 16 to 67).

Parents

By linking the rheumatoid arthritis cohort to the Swedish Multi-Generation Register we identified 22 856 parents. For 12 051 (91%) we identified at least one parent, and for 10 805 (75%), we identified both parents. Characteristics of the 10 805 patients with complete parental information are given in table 1.

Follow up

Rheumatoid patients were followed for mortality from 1990 to 1999. By linking all individuals (rheumatoid arthritis patients and their parents) to the Cause of Death Register and to the Register of Population and Population Changes, we collected information on vital status and deaths from CVD (1990 to 1999 for patients, 1964 to 1999 for parents). Rheumatoid patients started follow up at the time of their first discharge listing rheumatoid arthritis, or on 1 January 1990 if the date of first discharge predated 1990, and ended follow up at the earliest of date of death, emigration, or 31 December 1999.

Statistical methods

We calculated standardised mortality ratios (SMR)—that is, the ratio between the observed and the expected numbers of deaths—as measure of relative risk of death in the rheumatoid arthritis cohort *v* the general population. Expected numbers were calculated by multiplying the age, sex, and calendar period specific person-years of follow up by the corresponding mortality rates in the entire Swedish population. Confidence intervals (CI) were calculated assuming a Poisson distribution for the observed cases. We

Table 2 Standardised mortality ratio (SMR) and multivariate SMR ratio (relative risk) of cardiovascular disease derived from Poisson regression in 10 805 Swedish patients with rheumatoid arthritis followed up between 1990 and 1999

Variable	No of patients	Person-years	O	E	SMR	RR (95% CI)
Number of parents dying from CVD						
Neither	5034	34 424	42	24.9	1.7	1
At least one	5771	41 482	151	51.8	2.9	1.7 (1.2 to 2.4)
Sex of patient						
Male	2965	20 325	100	42.1	2.4	1
Female	7840	55 581	93	34.6	2.7	1.1 (0.9 to 1.5)
Years since first discharge with rheumatoid arthritis 1964–1999						
1–4 years	7167*	19 942	43	18.5	2.3	1
5–9 years	6136*	20 105	37	19.6	1.9	0.8 (0.5 to 1.3)
10+ years	5604*	35 859	113	38.7	2.9	1.3 (0.9 to 1.8)
Attained age during follow up						
<50 years	6098*	31 731	15	7.6	2.0	1
50–54 years	5676*	16 270	26	12.1	2.1	1.1 (0.6 to 2.1)
55–59 years	5410*	16 735	64	24.4	2.6	1.3 (0.8 to 2.3)
60–64 years	3519*	9932	67	26.6	2.5	1.3 (0.7 to 2.2)
65–69 years	1047*	1238	21	6.0	3.5	1.8 (0.9 to 3.4)

Multivariate model including all variables displayed in the table.

*Each patient may be included in more than one category.

CI, confidence interval; CVD, cardiovascular disease; E, expected number of deaths; O, observed number of deaths; RR, relative risk.

Table 3 Relative risk of death measured as standardised mortality ratios (SMR) for 10 805 Swedish patients with rheumatoid arthritis followed up between 1990 and 1999

Deceased parents	Parental cause of death	No of patients	All cause mortality			Cardiovascular death		
			O	E	SMR (95%CI)	O	E	SMR (95% CI)
Neither	–	2216	42	24.9	1.7 (1.2 to 2.3)	4	5.2	0.8 (0.2 to 2.0)
One	Not from CVD	1793	59	39.9	1.5 (1.1 to 1.9)	18	9.9	1.8 (1.1 to 2.9)
	From CVD	1827	108	45.7	2.4 (1.9 to 2.9)	40	11.5	3.5 (2.5 to 4.7)
Both	Neither from CVD	1025	67	35.2	1.9 (1.5 to 2.4)	20	9.8	2.0 (1.2 to 3.1)
	One from CVD	2399	170	85.5	2.0 (1.7 to 2.3)	57	23.9	2.4 (1.8 to 3.1)
	Both from CVD	1545	113	57.6	2.0 (1.6 to 2.4)	54	16.4	3.3 (2.5 to 4.3)
All RA patients irrespective of parental history		10 805	559	288	1.9 (1.8–2.1)	193	76.7	2.5 (2.1 to 2.8)

Cause specific standardised mortality ratios by parental vital status and parental cause of death (cardiovascular and all other causes).

CI, confidence interval; CVD, cardiovascular disease; E, expected number of deaths; O, observed number of deaths; RA, rheumatoid arthritis.

compared SMRs for rheumatoid patients with and without a parental history of fatal CVD using Poisson regression. We used Kaplan–Meier curves to assess cumulative incidence.

For reasons of simplicity and to remove any bias resulting from the mere identification of a parent rather than their cause of death, all analyses were done on the cohort of 10 805 rheumatoid patients for whom we had information on both parents. Likewise, we excluded the first 365 days of follow up to minimise the inclusion of patients with an impending death. (Analyses based on the 12 051 rheumatoid patients for whom we had information on at least one parent and analyses including the first year of follow up yielded similar results; data not shown).

Figure 1 Cumulative incidence of death from cardiovascular disease in 10 805 Swedish patients with rheumatoid arthritis aged 16 to 67 years and followed for mortality between 1990 and 1999, according to sex of patient, age at entry, and parental history of cardiovascular death.

RESULTS

Overall, rheumatoid patients were at a 93% increased risk of death from all causes (SMR = 1.93 (95% CI, 1.8 to 2.1), number of deaths = 559), at a 150% increased risk of death from CVD (SMR = 2.5 (2.1 to 2.8), number of deaths = 193), and at a 125% increased risk of fatal coronary heart disease (SMR = 2.3 (1.8 to 2.8), number of deaths = 85).

Rheumatoid patients with at least one parent who had died from a CVD had an SMR of death from CVD of 2.9 (2.5 to 3.4). In contrast, rheumatoid patients who did not have any parent who had died from CVD had an SMR of 1.7 (1.2 to 2.3) (table 2). When these SMRs were compared, a parental death from CVD was associated with a 70% increase in the risk of death from CVD in the offspring patients with rheumatoid arthritis (SMR = 1.7 (1.2 to 2.4)) (table 2), and a corresponding and significant 20% increase in patients' overall mortality, after adjustment for age, sex, and time of follow up (data not shown).

The association with parental death from CVD and risk of death from CVD in rheumatoid arthritis showed a dose-response pattern: from an SMR of 1.7 (as indicated above) for no parental history of death from CVD, through 2.7 (95% CI, 2.2 to 3.3) for a single parental death from CVD, to 3.3 (2.5 to 4.3) for both parents dead from CVD (p for trend = 0.001). Stratification showed that CVD entailed a higher relative risks in the offspring than did other parental causes of death (table 3), and conversely that offsprings' increase in overall mortality was almost entirely accounted for by deaths from CVD (data not shown). The association between parental CVD and patients' CVD was of equal magnitude for maternal and paternal history of fatal CVD, and when both exposure and outcome was restricted to death from acute myocardial infarction (data not shown).

Cumulative incidence of death by parental history

Death from CVD was uncommon before 50 years of age (fig 1). Among rheumatoid patients aged 50 or more but below the maximum of 67 years, a parental history of fatal CVD was associated with an increase in the 10 year probability of death from CVD from 5% to 10% in men and from 2% to 4% in women.

DISCUSSION

The results of our large, population based cohort study of patients with rheumatoid arthritis followed for mortality during the 1990s confirm the increased mortality from CVD in rheumatoid arthritis, and further indicate that a parental history of death from CVD is associated with a similar relative risk for CVD in rheumatoid arthritis as in the general population.^{14 15} Because of this, and because of the already increased risk of death from CVD in rheumatoid arthritis, our results stress that the clinical impact of a parental history of

fatal CVD is much greater in rheumatoid patients than in the general population.

While recent studies have made the important discovery that the association between rheumatoid arthritis and CVD goes beyond traditional risk factors for CVD, there is little information on the clinical impact of factors such as parental history on mortality in rheumatoid patients.^{3, 5–12} They show, however, that parental history of death from CVD is a relatively common experience (36–48%) in the age group containing the typical rheumatoid arthritis patient.^{3, 9, 10} In a recent study by Maradit-Kremers *et al* of 603 subjects with rheumatoid arthritis, family history was not associated with cardiovascular death.²² This apparent discrepancy compared with our study might reflect the substantial differences in design between the two studies: Maradit-Kramers *et al* assessed self reported non-fatal or fatal CVD in any first degree relative at the time of onset of patients' rheumatoid arthritis, and appear to have had 25% missing observations, whereas we assessed parental death from CVD as it occurred using register data, with very few losses. The follow up periods were also different, as Maradit-Kramers *et al* assessed deaths from 1955 to 2001, and we assessed mortality in the rheumatoid patients during the 1990s.

When dichotomised into yes/no, a parental history of death from CVD in our study was in itself associated with a 70% increase in the risk of offspring dying from CVD. We further noted a stronger association if both parents had died from CVD than if only one of them had, which is also in line with findings in the general population.^{15, 17} In addition, our analyses indicate the specificity of the association with parental history: although a parental death from any cause was associated with an increased risk of offspring dying from CVD, parental deaths from CVD entailed higher relative risks for offspring dying of CVD than other causes of parental death. Conversely, much of the effect on mortality in rheumatoid arthritis associated with a parental history of death from CVD was mediated through an increased patient mortality from CVD rather than from other causes. The comparatively low attained age (16 to 67 years of age) of our cohort explains the comparatively moderate proportion of all observed deaths that were attributed to CVD,¹ and the moderate impact of a parental history of death from CVD on patients' all cause mortality.

The main strengths of this study are the large population based rheumatoid cohort that we identified, the large proportion of all eligible parents who were identified, and the non-differential follow up. Importantly, the vital status of the patient did not affect the chance of identifying the parents (and vice versa). The register based identification of family history further ruled out recall bias, and the causes of death were assigned independently of each other. Although CVD may represent, for example, both coronary and cerebrovascular deaths, we noted similarly strong associations for any CVD (in the parent and offspring) as for acute myocardial infarction only. The quality of the rheumatoid arthritis diagnosis, as recorded in the Hospital Discharge Register, is high. In an ongoing study including scrutiny of the medical files of over 1000 individuals admitted to hospital with rheumatoid arthritis between 1965 and 1995, nearly 90% of the registered rheumatoid arthritis diagnoses fulfilled the ACR criteria.²¹ In any case, any resulting bias is likely to be non-differential and unlikely to explain the associations found. As we included patients with rheumatoid arthritis ever discharged from inpatient care, there may be a selection of more severe cases. Against a background of a true prevalence of rheumatoid arthritis of around 0.4–0.5% in the age groups covered by our study (16 to 67 years of age)^{23, 24}—and an estimated prevalence in that age range of 0.25% when using our rheumatoid cohort who were alive in

1999 as the definition of rheumatoid arthritis—it is fair to assume that by and large our cohort included around half of all true cases of rheumatoid arthritis in the source population.

Although family history of CVD in the general population is an independent risk factor for CVD, it is likely to be made up by a mix of genetic and environmental susceptibility factors.^{17, 18} In our study, we had limited possibilities to study such putative components, or other risk factors, any further. Importantly, however, irrespective of the exact mechanism of action (nature or nurture), a parental history of CVD still serves as a common clinical marker that will identify patients at high risk of lethal CVD.

In order to avoid bias from surveillance, diagnostic intensity, and non-biological factors leading to hospital admission in patients or families with rheumatoid arthritis, we defined outcome as death from rather than admission for CVD. Although our results therefore do not allow comparison of the effects of parental history between incident and fatal CVD, studies in the general population indicate that it is a risk factor for both types of outcome.¹⁶ Furthermore, the primary and secondary CVD prevention strategies in rheumatoid arthritis are relatively similar. As not all CVD is fatal, and as the risk of CVD increases with age (we followed the rheumatoid patients until they were 67), and because the association between parental history and risk of CVD in the general population applies also to non-fatal CVD,¹⁶ our results may be an underestimate of the true difference in cumulative incidence with respect to *incident* cardiovascular events between rheumatoid patients (of all ages) with and without a parental history of CVD.

In summary, our study suggests that a parental history of fatal CVD may signal an additional increase in the already increased risk of CVD in rheumatoid arthritis, and highlights the importance of including an assessment of cardiovascular risk factors among patients with this disease.

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