National Study of Cause-Specific Mortality in Rheumatoid Arthritis, Juvenile Chronic Arthritis, and Other Rheumatic Conditions: A 20 Year Followup Study

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ABSTRACT. ***Objective.*** To quantify risks for cause-specific mortality among hospitalized patients with rheumatoid arthritis (RA), juvenile chronic arthritis (JCA), and 4 other rheumatic conditions in a nationwide, population based cohort over a 20 year period.

Methods. All subjects were identified from Scottish hospital inpatient records from 1981 to 2000 and were followed up by computer linkage to the national registry of deaths. Expected mortality was calculated from national mortality rates and was related to the observed incidence by the standardized mortality ratio (SMR) and the corresponding 95% confidence interval (95% CI).

Results. Overall mortality was elevated in each of the 6 rheumatic conditions examined, most notably in JCA (males: SMR 3.4, 95% CI 2.0,5.5; females: SMR 5.1, 95% CI 3.2,7.8). Among patients with RA, there was an increased risk for death in all *International Classification of Disease* chapters other than those relating to mental disorders. Specific causes of death with an increased risk for subjects with RA included lung cancer [males: 1.4 (1.2,1.5); females: 1.6 (1.5,1.8)], hematopoietic malignancies [M: 1.8 (1.4,2.3); F: 2.0 (1.7,2.3)], coronary artery disease (CAD) [M: 1.6 (1.5,1.7); F: 1.95 (1.9,2.0)], respiratory infections [M: 1.9 (1.7,2.2); F: 2.4 (2.3,2.6)], chronic obstructive pulmonary disease [M: 1.8 (1.6,2.0); F: 2.1 (1.9,2.3)], and renal failure [M: 3.1 (2.5,3.9); F: 3.5 (3.0,4.0)]. Conversely, RA subjects were less likely to die from gastrointestinal tract malignancies [M: 0.82 (0.7,1.0); F: 0.8 (0.7,0.9)].

Conclusion. Population studies for primary data collection are required to extend our knowledge about the underlying mechanisms of early mortality in patients with rheumatic conditions. (J Rheumatol 2003;30:958–65)

Key Indexing Terms:
MORTALITY
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RHEUMATOID ARTHRITIS
HOSPITAL COHORT

Since the early 1950s, clinic based studies have shown an increase in mortality for patients diagnosed with rheumatoid arthritis (RA), with risks compared to the general population ranging between 1.1 and 3.0[1]. Mortality in population based studies of RA has tended to be lower[2,3]. However, many of the previous studies had insufficient subjects to examine specific causes of death.

In addition to RA, several other rheumatic conditions have also been linked with increased mortality. Studies have reported increased death rates compared to the general population in systemic sclerosis (SSc)[4-6], Sjögren's syndrome (SS)[7,8], and juvenile chronic arthritis (JCA)[9].

Our aim was to quantify and compare risks for mortality, overall and from specific conditions, among patients with RA and 5 other rheumatic conditions (SSc, SS, arthropathies associated with infection, Felty's syndrome, and JCA) in a nationwide, population based cohort of over 40,000 persons who were hospitalized in Scotland during the period 1981 to 2000.

MATERIALS AND METHODS

Scottish inpatient records were examined for the period January 1, 1981, to December 31, 2000. These include diagnoses coded according to the 9th or (from April 1, 1996) the 10th revision of the *International Classification of*

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Disease (ICD)[10,11]. The first hospital admission in the period 1981–2000 was identified for all patients, of any age, who were recorded as having a rheumatic condition coded to one of the following 6 categories (ICD-9; ICD-10): SSc (710.1; M34.0–M34.9), SS (710.2; M35.0), arthropathies associated with infection (711.0–711.9; M00.0–M03.9), RA (714.0–714.2; M05.0–M06.9), Felty's syndrome (a subgroup of people with RA) (714.1; M05.0), and JCA (714.3; M08.0–M08.9). Information was also recorded on whether or not the rheumatic condition was the reason for hospitalization or was simply recorded for a patient admitted for another reason. The diagnosis data are taken from the hospital discharge sheet that is completed by the treating physician during admission. The discharge sheet records the main reason for the admission plus any underlying conditions. These are all clinical diagnoses and are not based on whether patients satisfied any set of classification criteria.

Deaths were identified by linkage of hospital inpatient records to the national register of deaths. Linkage was achieved by computerized probabilistic matching on the following variables, supplemented by targeted clerical checking: Soundex-coded surname (including maiden name), forename, sex, date of birth, and postcode of residence. It is estimated that this method of record linkage results in mismatched records in less than 2% of cases[12]. The followup period for mortality was to December 31, 2000. The experience of this cohort with respect to cancer incidence has been reported[13].

Statistical methods. Person-years at risk (of death) were calculated, for each subject, from the date of first hospital admission, after January 1, 1981, until the earliest date of death or the end of the observation period (December 31, 2000). Results are presented separately by sex. Expected mortality was calculated by multiplying the observed person-years at risk by the national mortality rates of Scotland specific for cause of death, sex, age group, and calendar period. Deaths were coded according to the 9th or (from January 1, 2000) the 10th revision of the ICD[10,11] and deaths coded to ICD-10 were mapped to the corresponding ICD-9 chapter or specific code. The measure used to evaluate risk was the standardized mortality ratio (SMR), the ratio of the "observed" to "expected" number of deaths. By assuming that the number of observed deaths follows a Poisson distribution, 95% confidence intervals (95% CI) were calculated using exact Poisson limits[14]. Analysis was carried out within each of the 6 rheumatic groups to determine the relationship with overall mortality.

Concentrating on the RA cohort, deaths according to ICD-9 chapters were also examined. For ICD chapters where a significantly increased or decreased risk was observed, and at least 50 deaths were recorded, further analyses were carried out. First, the data were stratified by time since the index hospitalization (0–5, 5–10, 10–15, 15–20 years) to determine whether the strength of the mortality relationship altered with duration of followup. Second, for those with RA, a stratified analysis was carried out according to whether RA was recorded as the principal reason for the index admission. This analysis was performed to ascertain whether the magnitudes of the relationships were different in those patients with RA, but who were hospitalized for another reason, who might be considered to have milder disease. Finally, where numbers allowed, SMR analysis was carried out for specific causes of death. All analyses were carried out using Stata 6.0[15] and Microsoft Excel 97.

RESULTS

A total of 44,363 patients (30,472 female, 13,891 male) were identified with a diagnosis of RA or one of the other 5 rheumatic conditions under study. Patients were excluded for whom the period from hospitalization to death (n = 2624) or end of the study period (n = 395) was less than 3 months. The final cohort consisted of 41,344 patients (28,451 female, 12,893 male) with a mean age at admission of 58.1 years. The cohort had a total of 291,428 years of followup (females 201,076, males 90,352), an average of 7.05 years, and a maximum of 20 years (Table 1). A total of 17,650 deaths (12,577 females, 5073 males) occurred during followup (Table 2). An increased risk for overall mortality was observed for both female (SMR 1.97, 95% CI 1.93,2.01) and male (SMR 2.07, 95% CI 2.01,2.13) subjects with a diagnosis of RA. For each of the other 5 rheumatic conditions studied, a significantly increased risk of mortality was seen for both females and males. However, for Felty's syndrome and JCA, the number of observed deaths was small and the confidence intervals for the SMR were wide (Table 2). The remainder of the analyses will concentrate on subjects with RA.

Table 3 presents SMR for selected ICD-9 chapters separately by sex. Chapters with small number of deaths are not included. Increased rates of mortality were seen for the majority of ICD chapters in both the female and male cohorts, the exceptions being deaths due to mental disorders, and external causes among males only. Little difference in risk was observed when the analysis was restricted to those 20,875 patients (15,471 female, 5404 male) who had RA recorded as the main diagnosis at their index hospitalization (Table 4A) when compared to those 12,443 subjects (8844 female, 3599 male) who had RA recorded, but were admitted for another reason (Table 4B).

In both females and males, overall mortality risk was highest in the first 5 year period after the index hospitalization. For each subsequent 5 year period, the risk decreased, although a statistically significant increase in overall mortality was seen in each period (Tables 5A, 5B). A similar pattern was seen in the SMR for most of the ICD chapters, although few maintained significance throughout the whole of the followup period. The exceptions to this were deaths due to infectious and parasitic diseases, diseases of the blood, of the skin and subcutaneous tissue, and endocrine disorders, for which the mortality relationship was either maintained or increased in magnitude over the followup period.

Analyses were carried out for individual causes of death where a minimum of 50 deaths had been observed in the followup period (Table 6). SMR for peptic ulcers are also included in order to provide a comparative figure for studies that may be conducted after the introduction of the cyclooxygenase-2-specific nonsteroidal antiinflammatory drugs. Compared to the general population, subjects hospitalized for RA were significantly more likely to have a recorded cause of death due to upper aero-digestive tract malignancies (females only), lung and bronchus malignant cancers, hematopoietic cancers, CAD, stroke, respiratory infections, chronic obstructive pulmonary disease, or renal failure. Conversely, subjects were significantly less likely to have a recorded death due to gastrointestinal (GI) malignancies.

Table 1. Distribution of subjects according to rheumatic condition.

Rheumatic Condition (ICD-9; ICD-10)	Males No. of Patients	Males Person-years at Risk	Males Mean Age at Admission, yrs	Females No. of Patients	Females Person-years at Risk	Females Mean Age at Admission, yrs
Systemic sclerosis (710.1; M34.0–34.9)	168	980	54.5	753	4280	56.9
Sjögren's syndrome (710.2; M35.0)	133	805	55.3	701	4174	59.8
Arthropathies associated with infection (711.0–711.9; M00.0–03.9)	3090	24,938	37.2	1935	14,306	47.0
Rheumatoid arthritis (714.0–714.2; M05.0–06.9)	9003	59,233	60.5	24,315	171,697	63.1
Felty's syndrome (714.1; M05.0)	26	138	67.2	48	292	63.9
Juvenile chronic arthritis (714.3; M08.0–08.9)	499	4396	11.2	747	6619	12.2

Table 2. Standardized mortality ratios (SMR) and 95% confidence intervals (95% CI) for all deaths: by rheumatic condition and sex.

Rheumatic condition (ICD-9; ICD-10)	Males Deaths	Males SMR	Males 95% CI	Females Deaths	Females SMR	Females 95% CI
Systemic sclerosis (710.1; M34.0–34.9)	78	2.70	2.14,3.38	325	3.81	3.41,4.25
Sjögren's syndrome (710.2; M35.0)	38	1.71	1.21,2.35	223	2.01	1.76,2.30
Arthropathies associated with infection (711.0–711.9; M00.0–03.9)	534	1.44	1.32,1.57	530	1.39	1.28,1.52
Rheumatoid arthritis (714.0–714.2; M05.0–06.9)	4406	2.07	2.01,2.13	11,471	1.97	1.93,2.01
Felty's syndrome (714.1; M05.0)	17	2.86	1.67,4.62	28	4.74	3.15,6.88
Juvenile chronic arthritis (714.3; M08.0–08.9)	17	3.39	1.97,5.46	22	5.09	3.19,7.75

DISCUSSION

In summary, an increased risk of mortality, compared to the general population, was seen for all the rheumatic conditions examined. In the RA cohort, overall mortality was heavily "weighted" by an anticipated excess of deaths due to musculoskeletal causes, although these deaths accounted for less than 10% of all deaths in the RA cohort. Most other ICD chapters showed moderate increases in death, with SMR ranging from 1.5 to 4.0. As expected, the increased risk associated with most ICD chapters fell over time, although in females, the risk for deaths caused by infections increased over the 20 year followup period. SMR (1.4–4.0) were seen for specific causes of death including lung cancer, hematopoietic malignancies, CAD, stroke, respiratory infection, chronic obstructive pulmonary disease, and renal failure.

The main strengths of this study are its size and the use of routinely collected, population based data. Although this large cohort contained several thousand patients, it was only appropriate, due to small numbers of deaths, to examine cause-specific risks in the RA group. The quality of hospital discharge records in Scotland has been confirmed to be high[16] and it is likely that almost all the relevant hospitalizations have been identified. Moreover, any misclassification of the rheumatic disease diagnoses is likely to have reduced the magnitude of any associations. A disadvantage of using routinely collected data is the lack of information on putative confounding factors such as treatment, disease duration, and lifestyle and environmental factors; in order for such information to be available, alternative research methodologies are required. In addition, the linkage methodology used does not take account of the influence of migration, although it is unlikely that this will cause any substantial bias. Further, as the cohort was made up of subjects hospitalized for their condition, the findings may be less generalizable to patients treated in, say, primary care. However, when the data were examined separately for subjects with RA who were and were not hospitalized

Table 3. Standardized mortality ratios (SMR) and 95% confidence intervals (95% CI) by ICD-9 chapter: subjects with RA.

ICD Chapter* (ICD-9; ICD-10)	Males			Females		
	Observed	SMR	95% CI	Observed	SMR	95% CI
Infectious and parasitic diseases (001–139; A00–B99)	50	4.87	3.62,6.44	122	4.01	3.33,4.79
Neoplasms (140–239; C00–D49)	758	1.32	1.23,1.42	1515	1.21	1.15,1.27
Endocrine, nutritional, and metabolic disease and immunity disorders (240–279; D00–D99)	65	2.80	2.16,3.60	141	2.04	1.72,2.40
Diseases of blood and blood-forming organs (280–289; E50–E99)	21	4.09	2.53,6.29	64	3.59	2.76,4.59
Mental disorders (290–319; F00–F99)	24	0.84	0.54,1.26	156	1.06	0.90,1.24
Diseases of the nervous system and sense organs (320–389; G00–H99)	45	1.71	1.24,2.29	101	1.35	1.10,1.64
Disease of the circulatory system (390–459; 100–199)	2004	2.03	1.94,2.12	5181	1.90	1.84,1.94
Diseases of the respiratory system (460–519; J00–J99)	758	2.94	2.73,3.15	1737	2.37	2.26,2.48
Diseases of the digestive system (520–579; K00–K99)	188	2.79	2.40,3.22	667	3.20	2.96,3.45
Diseases of the genitourinary system (580–629; N00–N99)	106	4.11	3.37,4.98	335	3.63	3.26,4.05
Diseases of the skin and subcutaneous tissue (680–709; L00–L99)	16	8.80	5.02,14.4	72	6.69	5.23,8.43
Diseases of the musculoskeletal system and connective tissue (710–739; M00–M99)	295	59.2	52.7,66.4	1103	28.0	26.4,29.7
External causes (E800–999; W00–Y99)	63	1.19	0.91,1.52	231	1.66	1.46,1.89

* Deaths from January 1, 2000, were coded using ICD-10 and were mapped to the corresponding ICD-9 chapter.

specifically as a consequence of the rheumatic condition, no difference in the magnitude of the relationships was seen. These findings provide modest reassurance that the causes of mortality are similar across patients with different severities of RA. To validate these findings, cause-specific mortality data from primary care and population based studies are vital, but currently are not available. However, a population based study has found patients with RA are at increased risk of a number of comorbid conditions (cardiovascular disease, renal problems, and peptic ulcer) that we found to be overrepresented in terms of mortality, although the comorbid association were of a lesser magnitude[17].

Few studies have been able to examine the more rare rheumatic conditions. In a literature search, no reports were found of mortality in patients diagnosed with arthropathies associated with infection or Felty's syndrome. Only 3 previous studies have followed a cohort of patients diagnosed with JCA into adulthood[9,18,19]. Although these studies observed a combined total of only 9 deaths, in comparison to the 39 deaths in the present study, this was more than 4 times the number of deaths expected. The commonest causes of death in the patients with JCA in our study were musculoskeletal/connective tissue (n = 9), circulatory (n = 8), and respiratory (n = 6).

Our results confirm those of previous studies in SSc, which have estimated a 3 to 4-fold increase in mortality compared to the general population, and SS, although previous studies suggested the risk is isolated to those with secondary SS.

The roughly 2-fold increase in overall mortality found in the patients with RA in this report is in accord with that found in studies performed in other countries[20-24]. With respect to specific, nonmusculoskeletal, causes of death, our results confirm that subjects with RA generally die from causes similar to the general population, although death is premature. Interestingly, although the risk of mortality for most causes either remained stable or fell over time, the risk of death due to infections (ICD-9 chapter 1) was seen to increase over the 20 year followup period despite the major impact of antibiotics during this time period.

Due to the large size of the cohort, cause-specific mortality could be addressed for the more common causes. With respect to malignancies, this report has shown an increase in the risk of death due to lung cancer and

Table 4A. Standardized mortality ratios (SMR) and 95% confidence intervals (95% CI) by ICD-9 chapter: RA recorded as reason for hospitalization.

ICD Chapter* (ICD-9; ICD-10)	Males			Females		
	Observed	SMR	95% CI	Observed	SMR	95% CI
All causes	2494	1.85	1.77,1.92	6790	1.85	1.80,1.89
Infectious and parasitic diseases (001–139; A00–B99)				84	4.31	3.44,5.34
Neoplasms (140–239; C00–D49)	446	1.20	1.09,1.32	921	1.08	1.01,1.15
Endocrine, nutritional, and metabolic disease and immunity disorders (240–279; D00–D99)				74	1.64	1.29,2.07
Mental disorders (290–319; F00–F99)				65	0.77	0.59,0.98
Disease of the circulatory system (390–459; I00–I99)	1158	1.84	1.73,1.95	2993	1.74	1.68,1.80
Diseases of the respiratory system (460–519; J00–J99)	360	2.27	2.04,2.52	988	2.20	2.07,2.34
Diseases of the digestive system (520–579; K00–K99)	110	2.52	2.07,3.04	400	2.98	2.70,3.29
Diseases of the genitourinary system (580–629; N00–N99)	62	3.99	3.06,5.12	193	3.45	2.98,3.97
Diseases of the musculoskeletal system and connective tissue (710–739; M00–M99)	199	64.1	55.5,73.7	772	31.6	29.4,33.9
External causes (E800–999; W00–Y99)				139	1.59	1.34,1.88

*Deaths from January 1, 2000, were coded using ICD-10 and were mapped to the corresponding ICD-9 chapter.

Table 4B. Standardized mortality ratios (SMR) and 95% confidence intervals (95% CI) by ICD-9 chapter: RA not recorded as reason for hospitalization.

ICD Chapter* (ICD-9; ICD-10)	Males			Females		
	Observed	SMR	95% CI	Observed	SMR	95% CI
All causes	1912	2.47	2.36,2.58	4681	2.18	2.12,2.58
Infectious and parasitic diseases (001–139; A00–B99)				38	3.46	2.45,4.76
Neoplasms (140–239; C00–D49)	312	1.56	1.39,1.74	594	1.49	1.37,1.61
Endocrine, nutritional, and metabolic disease and immunity disorders (240–279; D00–D99)				67	2.77	2.15,3.52
Mental disorders (290–319; F00–F99)				91	1.46	1.17,1.79
Disease of the circulatory system (390–459; I00–I99)	846	2.37	2.22,2.54	2188	2.14	2.05,2.28
Diseases of the respiratory system (460–519; J00–J99)	398	4.01	3.63,4.42	749	2.62	2.44,2.82
Diseases of the digestive system (520–579; K00–K99)	78	3.28	2.59,4.10	267	3.57	3.16,4.03
Diseases of the genitourinary system (580–629; N00–N99)	44	4.31	3.13,5.78	142	3.92	3.30,4.62
Diseases of the musculoskeletal system and connective tissue (710–739; M00–M99)	96	51.3	41.6,62.7	331	22.1	19.8,24.6
External causes (E800–999; W00–Y99)				92	1.78	1.44,2.19

* Deaths from January 1, 2000, were coded using ICD-10 and were mapped to the corresponding ICD-9 chapter.

Table 5A. Standardized mortality ratios (95% confidence intervals) for ICD chapters according to time since hospitalization: male subjects with RA.

ICD Chapter* (ICD-9; ICD-10)	Time Since Hospitalization with RA			
	0–5 yrs	5–10 yrs	10–15 yrs	15–20 yrs
All causes	2.33 (2.24, 2.41)	1.86 (1.76, 1.98)	1.75 (1.16, 1.91)	1.35 (1.13, 1.61)
Infectious and parasitic diseases (001–139; A00–B99)	5.31 (3.53, 7.71)	4.99 (2.73, 8.46)	5.06 (2.18, 10.2)	—
Neoplasms (140–239; C00–D49)	1.54 (1.41, 1.69)	1.14 (0.98, 1.32)	1.01 (0.80, 1.25)	0.84 (0.52, 1.29)
Endocrine, nutritional, and metabolic disease and immunity disorders (240–279; D00–D99)	3.17 (2.25, 4.34)	1.73 (0.86, 3.13)	3.26 (1.63, 5.92)	3.54 (0.95, 9.57)
Disease of the circulatory system (390–459; I00–I99)	2.20 (2.08, 2.33)	1.92 (1.76, 2.09)	1.79 (1.57, 2.04)	1.31 (0.98, 1.72)
Diseases of the respiratory system (460–519; J00–J99)	3.31 (3.02, 3.63)	2.66 (2.29, 3.07)	2.65 (2.15, 3.23)	1.37 (0.79, 2.20)
Diseases of the digestive system (520–579; K00–K99)	3.20 (2.64, 3.85)	2.48 (1.82, 3.32)	1.82 (1.08, 2.90)	3.02 (1.45, 5.64)
Diseases of the genitourinary system (580–629; N00–N99)	5.18 (4.05, 6.54)	3.17 (1.98, 4.82)	2.93 (1.46, 5.32)	1.54 (0.17, 6.28)

* Deaths from January 1, 2000, were coded using ICD-10 and were mapped to the corresponding ICD-9 chapter.

Table 5B. Standardized mortality ratios (95% confidence intervals) for ICD chapters according to time since hospitalization: female subjects with RA.

ICD Chapter* (ICD-9; ICD-10)	Time Since Hospitalization with RA			
	0–5 yrs	5–10 yrs	10–15 yrs	15–20 yrs
All causes	2.09 (2.03, 2.14)	1.95 (1.88, 2.02)	1.75 (1.66, 1.84)	1.50 (1.36, 1.65)
Infectious and parasitic diseases (001–139; A00–B99)	3.68 (2.77, 4.81)	3.88 (2.65, 5.44)	4.55 (2.88, 6.86)	5.54 (2.76, 10.1)
Neoplasms (140–239; C00–D49)	1.34 (1.25, 1.43)	1.15 (1.05, 1.27)	1.00 (0.86, 1.16)	0.72 (0.52, 0.97)
Endocrine, nutritional, and metabolic disease and immunity disorders (240–279; D00–D99)	2.24 (1.78, 2.78)	1.86 (1.30, 2.59)	1.94 (1.17, 3.05)	1.15 (0.31, 3.10)
Diseases of blood and blood-forming organs (280–289; E50–E99)	3.76 (2.62, 5.25)	3.40 (1.98, 5.49)	3.49 (1.59, 6.76)	3.11 (0.62, 9.80)
Diseases of the nervous system and sense organs (320–389; G00–H99)	1.72 (1.32, 2.19)	1.26 (0.83, 1.84)	0.62 (0.25, 1.30)	0.49 (0.05, 1.98)
Disease of the circulatory system (390–459; I00–I99)	1.97 (1.90, 2.04)	1.88 (1.78, 1.98)	1.74 (1.61, 1.88)	1.48 (1.28, 1.71)
Diseases of the respiratory system (460–519; J00–J99)	2.55 (2.39, 2.72)	2.32 (2.12, 2.54)	2.13 (1.87, 2.42)	1.57 (1.21, 2.01)
Diseases of the digestive system (520–579; K00–K99)	3.51 (3.16, 3.88)	3.35 (2.90, 3.86)	2.30 (1.79, 2.90)	1.77 (1.06, 2.78)
Diseases of the genitourinary system (580–629; N00–N99)	3.91 (3.37, 4.51)	3.70 (2.99, 4.52)	2.80 (1.98, 3.86)	2.90 (1.58, 4.91)
Diseases of the skin and subcutaneous tissue (680–709; L00–L99)	7.27 (5.20, 9.93)	6.07 (3.65, 9.54)	5.01 (2.16, 10.1)	9.24 (2.98, 22.5)
External causes (E800–999; W00–Y99)	1.83 (1.54, 2.16)	1.63 (1.25, 2.09)	1.19 (0.75, 1.82)	1.25 (0.54, 2.52)

* Deaths from January 1, 2000, were coded using ICD-10 and were mapped to the corresponding ICD-9 chapter.

hematopoietic malignancies, and a decrease of deaths due to GI tract malignancies. Previous results reported from this cohort showed similar findings for the incidence of these malignancies[13]. Several previous studies have highlighted the increase in deaths due to disorders of the circulatory system, confirmed by results from this study, with most risks being concentrated in the more commonly observed cardiac causes[20,23,25]. Moreover, this study has been able to show that there is a similar magnitude of increase in risk from deaths due to cerebrovascular causes, in particular

Table 6. Standardized mortality ratios (SMR) and 95% confidence intervals (95% CI) by individual causes of death: subjects with RA.

ICD Code* (ICD-9; ICD-10)	Males			Females		
	Observed	SMR	95% CI	Observed	SMR	95% CI
Upper aero-digestive tract malignancies (140–150, 161; C00–C14, C15, C32)	47	0.92	0.67, 1.22	78	1.37	1.08, 1.71
Gastrointestinal tract malignancies (151–154; C16–C20)	97	0.82	0.66, 0.998	179	0.81	0.70, 0.94
Lung and bronchus cancers (162; C33–C34)	318	1.36	1.21, 1.52	428	1.61	1.46, 1.77
Breast malignancy (174; C50)				209	1.10	0.96, 1.26
Hematopoietic malignancies (200–209; C81–C96)	68	1.82	1.41, 2.31	152	1.97	1.67, 2.31
Coronary artery disease (410, 414; 121–122, 125)	1248	1.63	1.54, 1.72	2624	1.95	1.87, 2.02
Stroke (431, 434, 436; 161, 164, 166)	295	1.36	1.21, 1.52	1164	1.73	1.63, 1.83
Respiratory infection (481, 485–487; J10–J12, J18)	317	1.92	1.72, 2.15	1064	2.42	2.28, 2.57
COPD (491, 496; J42, J44)	249	1.79	1.57, 2.03	382	2.12	1.91, 2.34
Peptic ulcer (533; K27)	10	4.03	1.93, 7.53	24	4.23	2.71, 6.32
Renal failure (584–586; N17–N19)	75	3.13	2.46, 3.93	195	3.49	3.02, 4.01

* Deaths from January 1, 2000, were coded using ICD-10 and were mapped to the corresponding ICD-9 chapter. COPD chronic obstructive pulmonary disease.

strokes. Confirming the increase in deaths due to infection, this study shows a 2-fold increase in infections specific to the respiratory system in addition to the 4-fold increase for deaths recorded under "infectious and parasitic disease" (ICD-9 chapter 1).

Vascular biologists are beginning to believe that all atherosclerosis is related to inflammation, reflecting pathogenetic mechanisms similar to RA[26]. Simple inactivity imposed by painful joints may be a major contributor in RA. However, synovial inflammation may affect endothelial dysfunction as well, as suggested by the association of elevated C-reactive protein with both preclinical atheroma and the severity of established RA[27].

There is also increasing recognition that patients with RA are at increased risk of cardiovascular disease. Studies from both the UK[28] and the US[29] have suggested that this risk does not appear to be due to increased levels of classic cardiac risk factors (e.g., cholesterol, high blood pressure), although a higher proportion of patients with RA smoke compared to the general population[30].

A recent study has shown no improvement in RA mortality over the last 4 decades[31]. This study confirms these results with data for the last 20 years emphasizing that RA still considerably shortens life expectancy. Specifically, we have shown that the SMR associated with cardiovascular disease fall with time since hospitalization, suggesting that RA disease activity may be one of the risk factors for increased deaths due to this cause. By contrast, the risk of infection, either due to RA itself or as a consequence of medication, was shown to increase with disease duration, a phenomenon observed in previous studies.

In summary, this study supports previous results suggesting that rheumatic conditions have an adverse effect on life expectancy. Specifically in patients with RA the results have confirmed increases in deaths due to infections, respiratory disease, GI disease, and circulatory disease. However, due to the large size of the cohorts examined in this study we have been able to show increased risk of mortality related to specific causes of death such as lung cancers, hematopoietic malignancies, renal failure, and respiratory infections. Population studies requiring primary data collection are required to extend knowledge about the underlying mechanisms of altered risk of death in patients with rheumatic conditions.

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