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Original article

A study of baseline prevalence and cumulative incidence of comorbidity and extra-articular manifestations in RA and their impact on outcome

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Abstract

Objectives. To study the prevalence at diagnosis and cumulative incidence of comorbidity in RA, associations with clinical features and impact on outcome.

Methods. Standard clinical, laboratory and radiological measures of RA, and details of comorbidity and extra-articular features were recorded at baseline and yearly in an inception cohort of 1460 patients with recently diagnosed RA from nine regions in the UK. The General Practice Research Database was used to compare the incidence of common comorbid conditions (International Classification for Disease-10 codes).

Results. Baseline prevalence was 31.6% and 8.6% for all comorbidities and extra-articular features, respectively, and 15-year cumulative incidence was 81% and 53%, respectively. Rates of hypertension [standardized incidence ratio (SIR) = 1.61; 95% CI 1.43, 1.79] and ischaemic heart disease (SIR = 1.60; 95% CI 1.35, 1.84) were raised compared with figures for the general population, as was stroke in females (SIR = 1.34; 95% CI 1.02, 1.77) and chronic obstructive pulmonary disorder in males (SIR = 1.63; 95% CI 1.17, 2.26). Comorbidity was associated with risk of both all-cause and cardiovascular mortality (hazard ratio = 1.09; 95% CI 1.02, 1.17) and increased rates of functional decline over 10 years ($b = 0.011$; 95% CI 0.004, 0.019). Comorbidity was not related to disease activity or structural damage.

Conclusion. Significant comorbidity was present at the outset of RA, increasing with follow-up, mainly in cardiovascular, non-cardiac vascular and respiratory systems. Specific conditions (e.g. hypertension) occurred more frequently than in the general population. Comorbidity was related to mortality and functional decline, and more intensive therapies may need consideration in these patients. As many co-existent conditions are amenable to preventative/therapeutic measures, comorbidity needs earlier detection and management in order to reduce its impact on outcome in RA.

Key words: rheumatoid arthritis, cardiovascular, epidemiology, outcome measures, health economics.

Introduction

Although primarily affecting joints, RA is a systemic condition and the disease process can involve most organ systems, directly or indirectly. Non-articular features like nodules and vasculitis are well-recognized classic extra-articular manifestations (EAMs). Comorbidities are additional medical conditions, and although many are coincidental, others are complications of RA or RA therapies. Others result from common pathophysiological processes that confer higher than expected risks, and include cardiovascular disease (CVD) [1–6], pleuro-pulmonary disease [7, 8], infection [9], osteoporosis [10] and cancer [11].

How important is comorbidity in the routine management of RA? Suggestions that the average RA patient has 1.6 comorbid conditions [1] add considerable complexity to patient care. Current guidelines for the management of early RA include the principles of treating to a low disease activity target based on consistent evidence

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CLINICAL SCIENCE

of the benefits of this approach [12, 13]. Current opinion encourages urgency in controlling RA early using DAS and intensive combination DMARDs because of the so-called window of opportunity and also because clinical remission is now a realistic target. The evidence on which treatment guidelines are based generally excludes patients with major comorbidity, an important issue that we address in this report by distinguishing between baseline prevalence, which gives an overview of comorbidity at first presentation, and cumulative incidence, which may reflect common causal risk factors or treatment effects over time.

Comorbidity and EAMs are associated with worse outcomes, not only increased and premature mortality [2, 3, 14, 15], but also decreased quality of life [16, 17]. The eventual outcome in RA is related to several different factors, including the disease process itself on the locomotor system, but also increasing age. Less well researched is the impact that individual comorbidities may have on RA outcomes, either directly or indirectly as a result of interactions, contraindications or adherence issues with co-prescribed therapies. Many comorbidities are amenable to specific preventative and therapeutic measures, and if detected and managed early, could reduce their possible impact on RA outcomes. As many carry a worse prognosis, intensive therapies and closer monitoring in this patient group may be required.

Few studies have reported on the number and type of comorbidity in patients recruited close to the time of onset of RA, using validated measures to allow comparative analysis. The present study examined the prevalence and cumulative incidence of comorbidity in RA in comparison with general population rates, using both a total count of all comorbidities and a broadly applicable comorbidity index in an inception cohort with up to 22 years follow-up. We have also examined the impact that comorbid conditions may have on the course of RA, as assessed by well-established and valid measures of disease outcome and whether such effects are independent of disease activity.

Patients and methods

One thousand four hundred and sixty consecutive patients diagnosed with RA (within 2 years of onset and before DMARDs) were recruited from 1986 to 1998 in nine UK centres into the Early RA Study (ERAS). Follow-up is still ongoing and this analysis relates to data collected up to June 2009, a total 12 391 patient-years of follow-up (maximum 23 years, median 10 years).

Standard clinical and laboratory assessments were measured at baseline and annually, including the original three-variable DAS (tender and swollen joint counts, ESR), standard practice when ERAS started [18], HAQ, RF, socio-economic status and EAMs as previously described [19]. Hand/feet radiographs were scored using Larsen's method [20]. ACR criteria were not used formally, but all items were recorded as part of the study [21]. The RA-related shared epitope (SE) was based on HLA-DRB1 typing [22]. Cigarette smoking was included from 1992 and collected retrospectively before this, although not in those who had died or moved. All centres followed the UK published framework guidelines for management of RA in the 1990s, which include early use of sequential monotherapy, step-up combination therapy in patients with severe disease and judicious use of steroids. DMARDs were chosen according to physician preference. SSZ and MTX were the most common first and second choices [3], biologics have only been available since 2001.

Outcome measures recorded at annual review included drug effects and adverse events, work status and orthopaedic surgery. Comorbidity was based on patient self-report, clinical assessment and medical records, recorded on a standard form, then coded using the International Classification for Disease (ICD)-10 into organ systems (chapters). Individual co-existent conditions were assigned as major or non-major within each system or as EAMs or complications of RA, and with the total number of all comorbidities (NCom) and of major comorbidities (NCom-maj) provided both quantitative and qualitative data [23]. From ICD-10 codes the Charlson comorbidity index (CCI) was calculated, a validated score assigning weights of 1–6 for 18 medical conditions, based on their predictive strength of 1-year mortality in medical inpatients [24]. A modification, the age-adjusted CCI (CCI_A), adds an extra point for each decade of age $>$ 50 years [25]. The weighting of 1 for RA was not applied.

There is no internationally agreed and unifying classification for EAMs, defined as symptoms and signs not directly related to the locomotor system. Published accounts vary according to clinical and pathological criteria. One set includes only severe manifestations [26], others a wider range of features [27]. We included all features, using the broad classification of EAM, but also complications of RA (e.g. CTS) as previously described [23].

ERAS patients were tracked by the UK National Health Service Central Register, which provided copies of death certificates and ICD-10 codes for primary, secondary and contributory causes of death [3]. Comorbidity identified only through death certificates was not included in the analysis to better reflect comorbidity profiles seen in clinics. Orthopaedic interventions were recorded on standard ERAS forms and coded according to the UK Office of Population Censuses and Surveys Classification of Surgical Operations and Procedures (OPCS-4), as previously described [28]. Work disability was defined when a patient reported permanently leaving the paid labour force at least in part due to RA [29]. ERAS received ethical approval from the West Hertfordshire Local Research Ethics Committee and subsequently from the Caldicott Guardian.

Statistical analysis

Statistical analysis was conducted in Stata 11.0 (StataCorp, College Station, TX, USA). Simple descriptive statistics show differences in baseline characteristics across groups defined by the number of comorbid conditions at baseline.

(i) Incidence rates were based on total follow-up: annualized and 15-year cumulative incidence was calculated per 100 patients, reported as percentages.

Directly standardized incidence ratios (SIRs) were calculated for hypertension, ischaemic heart disease (IHD), stroke, chronic obstructive pulmonary disease (COPD) and diabetes using summary data provided by the General Practice Research Database (GPRD), a primary care research databank covering ~7% of the UK population started in 1987 [4]. SIRs were calculated adjusting for age, sex and the GPRD rate for the calendar year in which the comorbidity developed.

(ii) Outcomes: crude and adjusted hazard ratios (HRs) for CCI, CCI_A and NCom as predictors of all-cause mortality, cardiovascular mortality and work disability were estimated using Cox proportional-hazards regression. Fully adjusted estimates included baseline age, sex, social class, smoking, erosions, functional grade, RF, ANA, BMI, ESR, visual analogue scale pain, HAQ, DAS, hypertension, and time to first DMARD and steroid use within the first year. Fully adjusted estimates were based on multiply imputed data because of the small number of cases with no missing data ($n = 565$, 39%). Missing data were mainly due to smoking and HLA-DRB1 status. Multiple imputations were conducted using the ICE package for Stata, which employs imputation by chained equations using a Gibbs-type sampler [30]. Ten imputed datasets were constructed using all covariates adjusted for, plus baseline CCI and the natural logarithm of time to death, work disability and surgery. Sensitivity analysis using complete cases only is also reported.

Mixed-effects regression models allowing for random intercepts and slopes were employed to assess the impact of baseline CCI on HAQ score over time. A piecewise approach was used to account for non-linearity of change in HAQ over time. The model incorporated a random intercept, representing baseline HAQ, and two random slopes representing change between baseline and 1 year and change after 1 year. Separate models were fitted for CCI, CCI_A, NCom and NCom-maj. Interactions between the comorbidity variable and each of the random slopes were included to allow for differences in the rate of change over time. Fully adjusted estimates were calculated as above.

Results

Table 1 shows demographic and baseline clinical and laboratory features, and are typical of early RA cohorts. Four hundred and sixty-two (31.6%) patients already had at least one other medical condition at diagnosis of RA. Including EAMs and RA complications, this increased to 48.3%. Those with comorbidity were older ($P < 0.001$), less likely to be in paid employment ($P < 0.001$) and more likely to come from socially deprived areas ($P = 0.019$). The number of comorbid conditions was not associated with other baseline variables (all $P > 0.05$).

Prevalence and incidence

Baseline prevalence, annualized incidence and 15-year cumulative incidence rates of comorbidities and EAMs

Table 1 Baseline demographic and clinical features by number of comorbidities at baseline ($n = 1460$)

Variable	Total	None	1	>1	Missing, %
Age, mean (S.D.), years	55.34 (14.61)	52.74 (14.74)	59.97 (12.92)	62.88 (11.77)	0
Male, *n* (%)	491 (33.6)	334 (33.5)	99 (32.1)	58 (37.7)	0
Low education, *n* (%)	519 (36.3)	374 (38.4)	93 (30.5)	52 (34.2)	2
Low social class, *n* (%)	512 (42.3)	332 (41.7)	114 (41.9)	66 (46.2)	17
Socially deprived area, *n* (%)	602 (48.6)	391 (48.2)	139 (49.3)	72 (49.7)	15
Working, *n* (%)	645 (46.3)	500 (53.3)	105 (34.7)	41 (26.8)	5
Past/current smoker, *n* (%)	199 (21.9)	141 (23.6)	41 (19.7)	17 (16.7)	38
BMI, mean (S.D.)	25.55 (4.49)	25.47 (4.44)	25.77 (4.32)	25.68 (5.08)	14
Erosions, *n* (%)	366 (25.6)	254 (26.1)	80 (26.4)	31 (20.7)	2
HLA-DRSE, *n* (%)	672 (70.3)	465 (71.3)	141 (69.1)	66 (66.0)	35
HAQ, mean (S.D.)	1.15 (0.77)	1.14 (0.77)	1.19 (0.75)	1.15 (0.81)	0
VAS pain, mean (S.D.)	45.85 (27.77)	45.49 (28.52)	46.77 (25.55)	46.29 (27.26)	1
DAS, mean (S.D.)	4.22 (1.63)	4.20 (1.59)	4.27 (1.67)	4.25 (1.74)	1
Swollen joints, median (IQR)	15 (19)	15 (19)	15 (20)	12 (20)	0
Tender joints, median (IQR)	10 (12)	10 (12)	10 (14)	8 (14)	0
ESR, median (IQR)	38 (44)	36 (45)	40 (43)	40 (37)	0
RF^+, *n* (%)	1056 (73.1)	725 (73.4)	220 (72.6)	111 (72.1)	1
ANA^+, *n* (%)	381 (30.7)	254 (30.2)	74 (27.9)	53 (39.0)	15
RA onset-first visit, mean (S.D.), months	8.17 (6.08)	7.98 (6.01)	8.32 (5.97)	8.42 (6.34)	0
DMARD start <3 months, *n* (%)	840 (57.5)	418 (56.6)	222 (59.8)	200 (57.0)	0
MTX use ever, *n* (%)	599 (41.0)	330 (44.7)	144 (38.8)	125 (35.6)	0
Steroids use in first year, *n* (%)	285 (19.5)	148 (20.1)	62 (16.7)	75 (21.4)	0

HLA-DRSE: HLA-DR shared epitope; VAS: visual analogue scale; IQR: interquartile range.

TABLE 2 Incidence, baseline prevalence and 15-year cumulative incidence of comorbid conditions in ERAS

Condition	CCI score	*n*	Annualized incidence, %	95% CI	Baseline prevalence, %	95% CI	15-year cumulative incidence, %	95% CI
Total comorbidity		907	12.1	11.3, 12.9	31.6	29.6, 34.4	80.7	76.8, 84.3
CCI >0		591	6.1	5.6, 6.6	17.5	15.7, 19.6	53.7	49.7, 57.9
Neoplasms								
Solid tumours	2	118	1.0	0.8, 1.2	1.5	1.0, 2.3	14.2	11.1, 18.1
Haematolgical cancers	2	18	0.1	0.6, 1.6	0.1	0.0, 0.5	3.0	1.6, 5.7
Endocrine, nutritional and metabolic								
Thyroid disease		91	0.8	6.5, 9.8	3.8	2.9, 4.9	10.1	7.6, 13.5
Diabetes	1	76	0.6	4.8, 7.5	2.5	1.8, 3.4	8.5	6.4, 11.4
Mental and behavioural								
Psychiatric disorder		90	0.7	0.6, 0.9	2.5	1.8, 3.4	9.7	7.3, 12.9
Dementia	1	10	<0.1	0.0, 0.3	0.0	0.0, 0.3	0.9	0.5, 1.8
Nervous system		16	0.1	0.1, 0.2	0.2	0.1, 0.6	2.4	1.1, 4.9
Parkinson's disease		10	0.1	0.0, 0.1	0.0	0.0, 0.3	1.5	0.6, 3.5
Eye disease		80	0.6	0.5, 0.8	0.1	0.5, 0.8	10	7.3, 13.5
Circulatory system								
Cardiovascular		246	2.1	1.9, 2.4	5.1	4.1, 6.4	27.5	23.6, 31.9
IHD	1	202	1.7	1.5, 1.9	4.5	3.5, 5.7	20.8	17.7, 24.6
Congestive heart failure	1	65	0.5	0.4, 0.7	0.7	0.4, 1.4	9.6	7.0, 13.0
Non-cardiac vascular		344	3.1	2.8, 3.4	8.4	7.1, 10.0	44.3	39.2, 49.9
Peripheral vascular disease	1	37	0.2	0.1, 0.3	0.4	0.2, 0.9	5.9	3.8, 9.2
Hypertension		298	2.7	2.4, 3.0	7.9	6.7, 9.5	37.9	33.0, 43.2
Stroke	1	72	0.6	0.5, 0.8	0.3	0.1, 0.8	10.1	7.4, 13.7
Thrombo-embolic disease		19	0.2	0.1, 0.3	0.1	0.0, 0.5	4.1	2.3, 7.4
Deep vein thrombosis		22	0.2	0.1, 0.3	0.3	0.1, 0.7	3.5	2.0, 6.2
Respiratory system								
Respiratory disease		241	2.1	1.8, 2.4	7.5	6.3, 9.0	25.4	21.6, 29.7
Asthma		85	0.7	0.6, 0.9	3.0	2.3, 4.0	8.7	6.5, 11.6
COPD	1	55	0.4	0.3, 0.5	2.1	1.4, 2.9	5.0	3.7, 6.8
Digestive system								
Gastrointestinal disease		103	0.9	0.7, 1.1	2.8	2.1, 3.8	10.3	8.0, 13.2
Peptic ulcer disease	1	62	0.5	0.4, 0.6	1.9	1.3, 2.8	6.7	4.7, 9.6
Mild liver disease	1	6	<0.1	0.0, 0.3	0.0	0.0, 0.3	0.1	0.0, 0.2
Moderate or severe liver disease	3	0	0.0	0.0, 0.3	0.0	0.0, 0.3	0.0	0.0, 0.3
Skin and s.c. tissue								
Psoriasis		37	0.3	0.2, 0.4	1.8	1.2, 2.6	4.0	2.5, 6.4
Musculoskeletal and connective tissue								
OA and spinal degeneration		249	2.2	1.9, 2.5	7.3	6.0, 8.7	30.4	26.0, 35.4
Genitourinary system								
Chronic renal damage	2	34	0.3	0.2, 0.4	0.4	0.2, 0.9	4.6	3.0, 7.0

are presented in Tables 2 and 3. SIRs were calculated for the more common individual conditions with adequate numbers for analysis using data provided by the GPRD (Table 4).

The presence or not of NCom and CCI over time is shown in Fig. 1, demonstrating the linear increase in cumulative incidence of comorbidity. RA patients have, on average, 0.9 comorbidities at baseline (95% CI 0.8, 1.0), increasing to 1.8 (95% CI 1.6, 1.9) and 2.3 (95% CI 2.1, 2.5) after 5 and 10 years, respectively. Fig. 2 shows the actual numbers of comorbid conditions and CCI accumulated over time, stratified by age and gender. At baseline, comorbidity was more prevalent in males compared with age-matched females, though the gap narrowed with increasing age. The increasing incidence of comorbidity in females over time meant that by 10 years this was greater than in age-matched males for those with an onset age of $\geqslant$40 years.

The most common baseline comorbidity was hypertension, and SIR was high, at 1.61 (95% CI 1.43, 1.79), greater for females than males. Although the prevalence of IHD was relatively low at baseline (4%), the 15-year cumulative incidence was 17%, 60% higher than expected (SIR = 1.60; 95% CI 1.35, 1.84) and slightly higher for males than females. This is consistent with previous reports that RA is an independent risk factor for CVD, and that individuals who have had RA for several years have around a two-fold higher risk for CVD compared with

Table 3 Incidence, baseline prevalence and 15-year cumulative incidence of extra-articular conditions and complications of RA in ERAS

Condition	*n*	Annualized incidence, %	95% CI	Baseline prevalence, %	95% CI	15-year cumulative incidence, %	95% CI
Extra-articular features	709	8.6	8.0, 9.3	23.0	20.9, 25.2	64.1	59.9, 68.3
Nodules	458	4.6	4.2, 5.0	10.6	9.1, 12.3	46.9	42.5, 51.6
SS	177	1.5	1.3, 1.7	4.3	3.4, 5.5	19.0	15.8, 22.8
RP	145	1.2	1.0, 1.4	6.3	5.1, 7.6	12.0	10.0, 14.4
Cutaneous/ocular vasculitis	54	0.4	0.3, 0.5	1.0	0.6, 1.7	6.2	4.4, 8.8
Malaise/fatigue	45	0.4	0.4, 0.5	2.3	1.7, 3.3	3.4	2.5, 4.5
Pleural involvement	21	0.2	0.1, 0.3	0.5	0.2, 1.0	2.4	1.3, 4.4
RA-ILD	42	0.3	0.2, 0.4	1.0	0.6, 1.7	3.9	2.8, 5.5
Systemic vasculitis	25	0.2	0.1, 0.3	0.5	0.3, 1.1	3.4	1.9, 5.9
FS	8	0.1	0.0, 0.2	0.3	0.1, 0.7	0.8	0.4, 2.0
Neuromyopathies	7	0.1	0.0, 0.2	0.0	0.0, 0.3	1.6	0.6, 4.5
Complications of RA	233	2.0	1.8, 2.3	3.2	2.4, 4.3	35.4	30.3, 41.2
Osteoporosis	95	0.8	0.6, 1.0	1.5	1.0, 2.3	15.1	11.6, 19.5
CTS	91	0.8	0.6, 1.0	2.7	2.0, 3.7	9.9	7.6, 12.8
Osteoporotic fracture	91	0.7	0.6, 0.9	0.8	0.5, 1.4	15.7	11.9, 20.5
Cervical spine subluxation	26	0.2	0.1, 0.3	0.3	0.1, 0.8	3.9	2.3, 6.6
Anaemia chronic disease	27	0.2	0.1, 0.3	0.3	0.1, 0.8	3.5	2.1, 5.7
Chronic leg ulcers	21	0.2	0.1, 0.3	0.2	0.1, 0.6	3.6	1.9, 6.6

Table 4 Standardized incidence ratio for common comorbid conditions

Condition	Observed	Expected	SIR	95% CI
Hypertension				
Male	82	61.8	1.33*	1.07, 1.65
Female	216	122.9	1.76*	1.54, 2.01
IHD				
Male	84	45.9	1.83*	1.48, 2.27
Female	86	60.4	1.42*	1.15, 1.76
Stroke				
Male	22	23.5	0.94	0.62, 1.42
Female	50	37.3	1.34*	1.02, 1.77
COPD				
Male	56	18.8	1.63*	1.17, 2.26
Female	79	25.6	0.76	0.49, 1.18
Diabetes				
Male	30	26.0	1.16	0.81, 1.65
Female	46	37.3	1.23	0.93, 1.65

*$P < 0.05$.

non-RA persons after taking account of most traditional risk factors [31]. There was a small but non-significant increase in the incidence of stroke (SIR = 1.19; 95% CI 0.92, 1.47), significant for females but not males.

The 15-year cumulative incidence of respiratory disorders was 25%, with asthma and COPD accounting for more than half of incident cases. The overall SIR showed a small, but non-significant increase in the incidence of COPD (SIR = 1.15; 95% CI 0.84, 1.45) due to a significantly increased incidence in males.

Almost a quarter of patients had one or more EAMs at baseline, with a 15-year cumulative incidence of approximately two-thirds. Nodules accounted for almost half of baseline EAMs and two-thirds of cumulative incidence. Complications were uncommon at baseline (3%), but the 15-year cumulative incidence was 30%, with CTS, osteoporosis and osteoporotic fracture the most common.

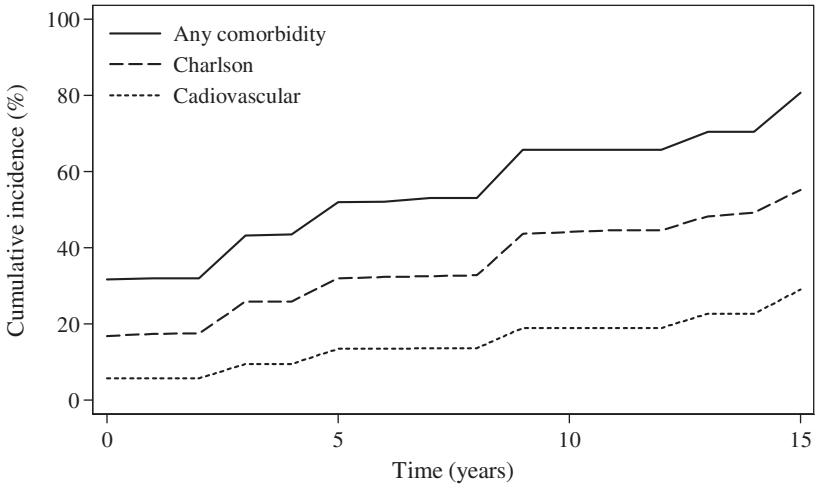
Comorbidity and RA outcomes

Mortality

Median survival from diagnosis was 17, 13 and 11 years for individuals with a CCI of 0, 1 or >1, respectively. Cox proportional-hazards regression revealed a significant relationship between baseline CCI, CCI_A, NCom and NCom-maj with mortality risk (Table 5). A one unit increase in CCI and CCI_A was related to increased mortality risk of 63% and 78%, respectively. Each additional comorbid condition increased the risk of death by 24% and each additional major comorbidity by 52%. The effect was attenuated but remained significant when adjusted for baseline characteristics. The adjusted estimate is based on multiply imputed data due to missing covariates. Results of complete case analyses were of similar magnitude [$n = 565$; $HR_{CCI} = 1.30$ (95% CI 1.03, 1.65); $HR_{CCIA} = 1.24$ (95% CI 1.00, 1.54); $HR_{NCom} = 1.18$ (95% CI 1.05, 1.34); $HR_{NCom\text{-}maj} = 1.27$ (95% CI 0.93, 1.74)].

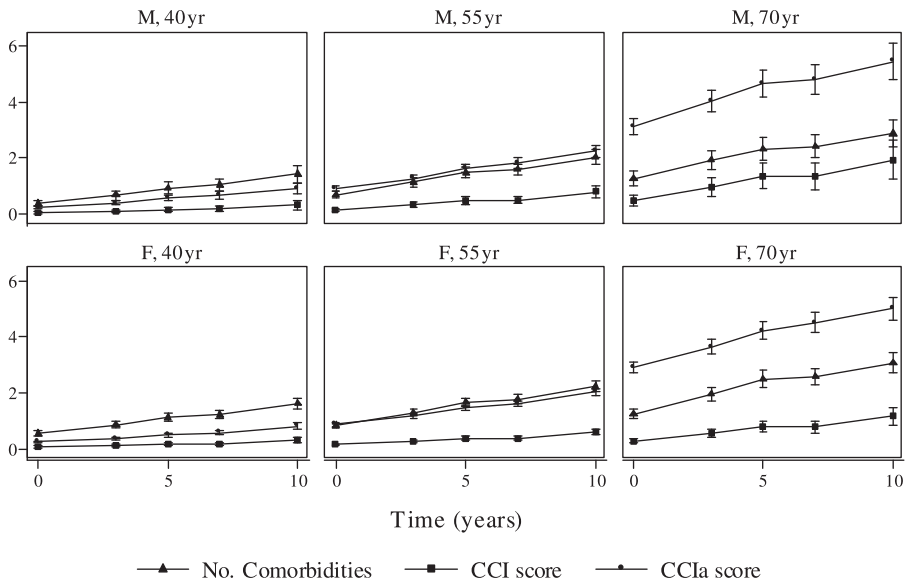
Restricting analysis to cardiovascular deaths also revealed a significant association with comorbidity. Increased baseline CCI, CCI_A and NCom were related to an increased risk of cardiovascular mortality of 79%, 49% and 49%, respectively (Table 5), and NCom-maj with a 170% increased risk. Again, the effect persisted after adjustment for multiply imputed baseline characteristics,

Fig. 1 A 15-year cumulative incidence (per 100) of the total number of all comorbid medical conditions, Charlson comorbidity and cardiovascular comorbidity.



Number at risk				
Any comorbidity	1460	688	309	75
Charlson	1460	854	480	86
Cadiovascular	1460	1098	674	194

Fig. 2 Number of comorbidities over time.



Figures are the expected number of all comorbidities, CCI score and CCI_A score over 10 years in the ERAS cohort, with 95% CIs, stratified by age [roughly mean (1 S.D.)] and sex.

and were of a similar magnitude when restricted to a complete case analysis [$n = 565$; $HR_{CCI} = 1.44$ (95% CI 1.16, 1.78); $HR_{CCIA} = 1.23$ (95% CI 1.02, 1.49); $HR_{NCom} = 1.25$ (95% CI 1.12, 1.39); $HR_{NCom\text{-}maj} = 1.86$ (95% CI 1.41, 2.45)]. The effects of CCI, CCI_A, NCom and NCom-maj on cardiovascular mortality were fully accounted for by prevalent cardiovascular comorbidity at baseline. The effect remained for all-cause mortality.

Impact of comorbidity on work disability and function

Of the 645 patients in paid employment at baseline, 65 (44%) of the 148 with a baseline CCI $\geqslant 1$ stopped working because of RA compared with 164 (33%) of the

497 patients with a baseline CCI score of 0. Cox proportional-hazards regression indicated a non-significant trend for comorbidity being related to work cessation due to RA (Table 5). The effect was similar and remained non-significant after adjustment for multiply imputed baseline characteristics.

HAQ progression followed a J-shaped curve, initially decreasing over the first year of disease and then increasing in a linear fashion, as previously described [19]. Piecewise mixed-effects regression models were used to assess the impact of comorbidity on baseline HAQ, as well as the change in HAQ between baseline and 1 year, and the rate of HAQ progression between 1 and 10 years (Table 6). The unconditional model indicated that, on average, baseline HAQ was 1.12 (S.D. 0.62) and HAQ decreased by −0.29 (S.D. 0.08) over the first year before increasing in a linear manner by ∼0.05 U per year (S.D. 0.01).

The impact of comorbidity, whether assessed by CCI, CCI_A, NCom and NCom-maj, on HAQ was broadly the same. At baseline, CCI_A and NCom were associated significantly with worse HAQ for the unadjusted analysis, but not after adjustment for baseline characteristics. There was no significant impact of CCI, CCI_A or NCom on the change in HAQ between baseline and 1 year, but all three were associated with increased rates of HAQ progression between 1 and 10 years follow-up. Since the parameter estimates may be difficult to interpret, Fig. 3 plots the estimated HAQ trajectories for patients with a CCI_A score of 0, 1 or 2 at baseline.

Impact of comorbidity on disease activity and structural damage (radiological and *orthopaedic surgery)*

The impact of comorbidity measures on DAS, remission status (DAS <1.6) and Larsen score at baseline and over time was examined using mixed-effects regression models. There was no indication that baseline CCI was related to either baseline DAS, remission status or

TABLE 5 Cox regression estimates for impact of comorbidity on mortality and work disability

	Crude		Adjusted[a]	
	HR	95% CI	HR	95% CI
All-cause mortality				
CCI_A	1.78	1.69, 1.89	1.23	1.09, 1.39
CCI	1.63	1.44, 1.85	1.29	1.13, 1.48
NCom	1.24	1.16, 1.33	1.09	1.02, 1.17
NCom-maj	1.52	1.29, 1.79	1.09	0.92, 1.30
Cardiovascular mortality				
CCI_A	1.49	1.41, 1.59	1.32	1.17, 1.49
CCI	1.79	1.59, 2.04	1.55	1.36, 1.77
NCom	1.44	1.35, 1.53	1.30	1.22, 1.40
NCom-maj	2.70	2.28, 3.20	2.12	1.78, 2.54
Work disability				
CCI_A	1.14	0.98, 1.33	0.95	0.73, 1.23
CCI	1.33	0.98, 1.81	1.32	0.95, 1.82
NCom	1.11	0.96, 1.29	1.07	0.91, 1.25
NCom-maj	1.37	0.98, 1.90	1.18	0.83, 1.67

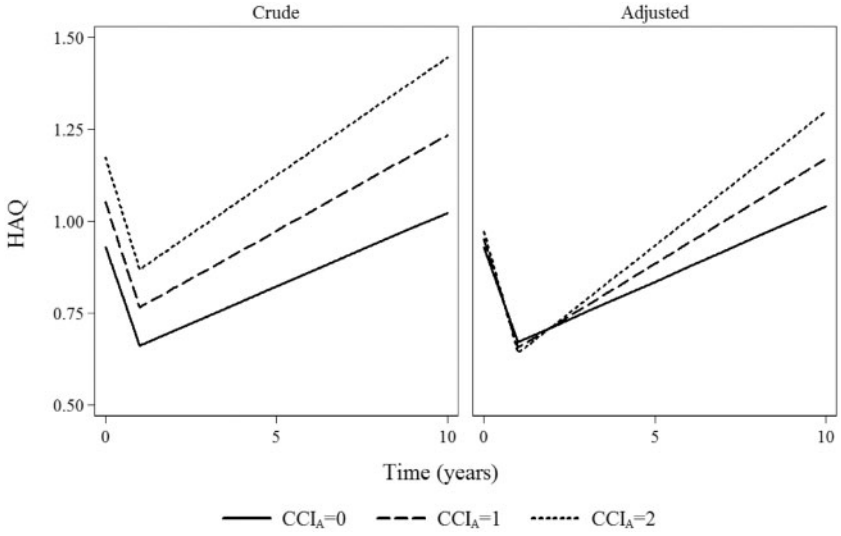
[a]Multiply imputed estimate, adjusted for age, sex, social class, smoking status, presence of erosions at baseline, steroid use within the first year, time of initiation of first DMARD, functional grade, ANA positivity, BMI, RF positivity, ESR, VAS, HAQ and DAS all at baseline visit.

TABLE 6 Impact of comorbidity on HAQ at baseline, change in HAQ between baseline and 1 year, and rate of change in HAQ between 1 and 10 years

	Crude		Adjusted[a]	
	b	95% CI	b	95% CI
Difference in baseline HAQ				
CCI_A	0.122	0.096, 0.149	0.021	−0.003, 0.046
CCI	0.053	−0.019, 0.125	−0.013	−0.059, 0.035
NCom	0.039	0.005, 0.072	−0.013	−0.034, 0.009
Difference in change between baseline and 1 year				
CCI_A	−0.019	−0.038, 0.000	−0.036	−0.059, −0.013
CCI	0.013	−0.036, 0.063	0.005	−0.057, 0.066
NCom	0.029	0.006, 0.052	0.022	−0.006, 0.051
Difference in rate of change between 1 and 10 years				
CCI_A	0.012	0.007, 0.016	0.016	0.010, 0.022
CCI	0.015	0.004, 0.027	0.022	0.006, 0.038
NCom	0.008	0.003, 0.013	0.011	0.004, 0.019

[a]Multiply imputed estimate, adjusted for age, sex, social class, smoking status, presence of erosions at baseline, steroid use within first year, time of initiation of first DMARD, functional grade, ANA positivity, BMI, RF positivity, ESR, VAS, HAQ and DAS all at baseline visit.

Fig. 3 Estimated unadjusted and adjusted HAQ trajectories by baseline CCI_A score from a piecewise mixed-effects model; adjustment is for multiply imputed baseline clinical and demographic characteristics.



Larsen score, or to change in either variable over time or to orthopaedic surgery using Cox proportional-hazards regression.

Discussion

This study has quantified the extent and type of co-existent medical conditions in RA patients on conventional therapies of the 1990s and showed that nearly half of patients had at least one co-existent medical condition at diagnosis of RA, including EAMs. This increased with follow-up. The cumulative incidence over 15 years for any major comorbid medical condition was 81%. For conditions in the Charlson index this was 53%, for EAMs 65% and for complications of RA 35%. These results provide a background for planning service provision for RA in terms of case complexity, more intensive and preventative measures for co-existent conditions, potential interactions between RA and non-RA drugs and comorbidity, and the need for combined clinics. We estimated that ~40% had a co-existent condition that was either amenable to preventive measures or had the potential to pose problems with RA therapies.

Regardless of the definitions used, most studies report substantial comorbidity in RA patients. The prevalence of 31.6% at diagnosis is comparable to that of a Dutch RA inception cohort that observed at least one comorbid condition in 27% over 6 years ($n = 186$), 66% before the onset of RA. The most frequently reported were cardiovascular 29%, respiratory 18% and dermatological 11% [32]. The UK-based British Society for Rheumatology biologics register reported point prevalence figures of at least one comorbidity in 58% of RA patients before the initiation of biologics [33]. Although these results are not directly comparable due to differences in study design, notably more severe and longer-standing disease, the rank ordering of the most common comorbidities was similar.

The increased risk of CVD compared with the general population confirms previous reports [2–6]. The SIR for non-fatal IHD of 1.60 compared with the GPRD supports the consensus that RA is an independent risk factor for CVD. It has even been suggested that IHD could be considered an extra-articular manifestation of RA [34]. Stroke risk was increased in females only, similar to the 1.5 relative risk reported in an all-female cohort [31] and 1.32 in a Danish nationwide RA study (1.41 for atrial fibrillation) [35]. Other reports on stroke risk in RA have been inconsistent, an area for further research [36].

Although several studies have confirmed excess cardiovascular mortality in established RA, there are few studies in early RA. Some have suggested that cardiovascular risk increases only after 5–7 years from the development of RA [1, 32, 37], in contrast to other studies including this cohort that have demonstrated early mortality due to CVD [3, 38].

The current World Health Organization definition of CVD includes vascular diseases of brain and blood vessels as well as heart diseases, the world's leading killer [39]. The cumulative incidence of these conditions and others amenable to preventative measures was high in this cohort and included cardio ($n = 246$), cerebro ($n = 72$) and peripheral vascular ($n = 37$) diseases, hypertension ($n = 298$), osteoporosis ($n = 95$), fracture ($n = 91$, hip = 39, vertebral = 11), NSAID-related peptic ulceration ($n = 62$) and gastrointestinal haemorrhage and/or perforation ($n = 38$), and NSAID-related renal disease ($n = 6$). More widespread use of preventive measures may be reflected in incidence figures in future cohorts. Hypertension

remains the most important modifiable risk and it is widely recognized that even modest improvement in blood pressure in the general population leads to substantial reductions in cardiovascular mortality. A systemic review reported prevalence rates of hypertension in RA of 52–73% [40], one explanation being widespread use of NSAIDs and oral steroids, although some DMARDs may be partly responsible [41].

The 15-year cumulative incidence for diabetes was 8.5% (95% CI 6.4, 11.4). Literature reviews on RA and diabetes vary, most showing no increase. A more recent meta-analysis of 15 case–control studies reported increased prevalence of diabetes mellitus in RA (OR 1.74, 95% CI 2.2, 2.50) [42]. It has been reported that the prevalence of the metabolic syndrome is high in RA, present in one-third in early RA and 42% in long-standing RA [43].

Pleuro-pulmonary conditions were common in this cohort, including an increased incidence of COPD in males (SIR = 1.63). The 15-year cumulative incidence of interstitial lung disease in RA (RA-ILD) was 3.9%, compared with a 6.3% 20-year cumulative incidence reported by Bongartz *et al*. [7] in a US population-based cohort. Of those with RA-ILD, half already had the diagnosis at baseline or developed it within 3 years [8]. We have previously shown that RA-ILD carries a substantial mortality risk (6% of all deaths in RA) [3].

Limited numbers and diagnostic details of individual conditions and malignancies prevent comparisons with population rates. Some are important to clinicians because they may affect treatment decisions, for example RA-ILD ($n = 42$), bronchiectasis ($n = 31$), cardiac arrhythmias ($n = 39$), chronic hepatic ($n = 7$) and kidney damage (chronic kidney disease stages II–IV) ($n = 34$), depression ($n = 68$) and anxiety ($n = 15$). The combined 15-year cumulative incidence of solid and lympho-proliferative malignancies was 17.2%. We have previously reported excess cancer mortality in this cohort, particularly for lymphomas [3].

Comparisons of EAMs with other reports are limited by variations in criteria and study design (few inception cohorts). Two US studies reported EAMs in 40.6% and 47.5% over a median 11.8 years and mean 3.9 years follow-up, respectively [44, 45]. The higher 15-year cumulative incidence in our study of 64.1% was most likely due to longer follow-up and wider inclusion criteria. There are few reports on complications of RA. In this study the 15-year cumulative incidence was 35.4%. This has important implications for the need for more intensive therapies for RA itself as well as preventative measures, e.g. bone protection to prevent fracture.

This study has found that comorbidity impacts on mortality, functional and work disability, but not on structural damage or disease activity. Baseline comorbidity using CCI, CCI_A, NCom and NCom-maj was associated with all-cause mortality and this remained after adjustment for other variables including disease activity. This is comparable to two cross-sectional studies that reported associations between CCI and mortality in RA [14, 15]. We found that baseline comorbidity was also related to cardiovascular mortality.

Baseline comorbidity was also related to functional disability, as shown by worsening HAQ, consistent with reports on established RA [46], one of which showed that physical disability became worse with increasing levels of CCI_A, irrespective of disease activity in 380 RA patients [47]. After adjustment for demographic and clinical characteristics, comorbidity in our cohort was not related to baseline HAQ, or HAQ progression between baseline and 1 year, but was between 1 and 10 years. There was a trend for patients in paid employment at baseline and with comorbidity to have an increased risk of RA-related work disability over time, but this was not significant. Comorbidity was not associated with radiological progression, confirming another report [32], or with disease activity and orthopaedic surgery.

Physical function is one of the most important needs for RA patients, and our finding that HAQ was related to factors other than disease or treatment effects, namely comorbidity, highlights the multifactorial nature of disability, which needs to be recognized in both clinical practice and research settings. Impaired physical function due to disease activity is potentially reversible with therapy, but may not be from other causes. This has an impact on the interpretation of disability in RA, not just for individually tailored treatment targets, but also in a wider realm, since clinical trials recruit younger and healthier subjects. The HAQ from clinical trials is used in cost-effectiveness modelling, which does not necessarily reflect true-to-life clinical practice. Improvement in HAQ is an important aspect in assessments of evidence of the efficacy of new drugs in RA required by health commissioners and the National Institute of Clinical Excellence (NICE). The results of this study support the view that current measures of physical function reflect a combination of aspects of a patient's health and raise concerns about their use in measures of disease severity without taking into account aspects like comorbidity.

A limitation of this study was ascertainment of comorbidity, as case-finding approaches are liable to under-reporting compared with systematic screening. From death certificates, we suspect some under-reporting in patients who died of chronic conditions not recorded at recent and last visits. To assess for this possible bias, all analyses were repeated, including all conditions listed on death certificates. The findings did not change substantially, although obviously incidence rates were increased, especially for conditions that were common causes of death, e.g. IHD, stroke, pulmonary diseases.

The disadvantage of using CCI weighting is that although one of few validated tools, it was based on hospital inpatients with more severe types of comorbidity than seen in rheumatology clinics, and validated only to predict mortality, not other RA outcomes like function. It does not include the common comorbidities and EAMs seen in rheumatology clinics and known to affect outcome like osteoporotic fracture and depression. For this reason we have also used a simple count of comorbid conditions. Comorbidity data did not always include the exact date or severity of each coexistent condition (e.g. level of raised

blood pressure). ERAS started before the Index of Coexistent Diseases was validated for severity of comorbidity [48], which would have provided very useful additional assessment of the impact of comorbidity on RA. Although ERAS recorded RA therapies, it did not collect routinely all non-RA medications, a surrogate marker for comorbidity. It was not possible to examine in detail possible reasons for therapeutic decisions being delayed or affected by comorbidity. The most common in clinical practice is the presence of lung disease and the initiation of MTX and biologics.

Downwardly biased expected rates of comorbidity have been reported in musculoskeletal conditions from the GPRD database [49], and if so could generalize to other chronic conditions. SIRs presented in this study would therefore be inflated, and comparative figures reported here need careful interpretation and confirmation by further studies.

The strengths of this study include analysis of a large inception cohort designed to address outcomes in real-life settings and in patients on conventional therapeutic schedules over prolonged follow-up. Most clinical trials are short lasting, include patients with high disease activity only and exclude patients with major comorbidities. The findings may not fully reflect outcomes seen in normal clinics. As a follow-up to this study we intend to examine predictive factors for prevalent comorbidity and for incident cardiovascular comorbidity and mortality.

A recent systemic review of the incidence and prevalence of RA revealed consistent shifts toward a more elderly age of onset [50]. With increasing ageing populations this will translate in clinical practice to new RA patients with greater and more complex comorbidity. Reports have shown that CVD and depression in RA significantly affect annual health care costs as well as specific RA-related utilization patterns [51]. In conjunction with the results from our study, these are important facts for service providers who are developing care models for ageing populations.

More evidence is needed on how to manage comorbidities in RA. A good example is malignancy, since many of the drugs used in RA are immunosuppressives and often claimed to increase the risk of malignancy [52]. Comorbidity not only adds challenges to treatment, but also increases the complexity of patient care, as well as adding to the economic burden of disease. In most studies the costs of disease do not seem to be uniformly distributed among the RA population, and this skewing reflects the substantially higher costs incurred by a subset of RA patients [53].

Functional decline in RA is multifactorial and at least in part related to comorbidity. Many comorbidities are amenable to preventive and therapeutic measures, and in order to reduce the impact that they may have on outcome in RA, they need to be detected and managed at early stages, especially cardiovascular risk and respiratory conditions. A recent study identified factors that contributed to the high incidence of lower respiratory tract infections in RA, and specific measures to address these produced a 4-fold reduction in both admissions and case fatality [54]. The focus of health care should not be on one specific disease only, but should include other organ pathology, complications and functional status [55]. The single-disease framework by which most health care and research is configured has been challenged by a recent report showing that most patients with a long-term disorder are multi-morbid [56]. A holistic approach is needed, and a model similar to a diabetic annual review should be incorporated in addition to the regular routine clinics for disease control and treatment adjustment. This should include screening for comorbidity, since we have demonstrated an impact on outcome.

Rheumatology key messages

- Conditions more common in RA than in the general population included cardiovascular and respiratory conditions and stroke.
- Comorbidity in RA was related to increased mortality and poorer function but not inflammatory activity.
- Annual review of RA patients should include comorbidity screening.

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