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Association between risk, duration and cause of hospitalisations in people with rheumatoid arthritis and multimorbidity in the UK Biobank and Scottish Early Rheumatoid Arthritis (SERA) cohorts: Longitudinal observational study

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ABSTRACT

Objectives: To investigate association between presence of multimorbidity in people with established and early rheumatoid arthritis (RA) and risk, duration and cause of hospitalisations.
Design: Longitudinal observational study.
Setting: UK Biobank, population-based cohort recruited between 2006 and 2010, and the Scottish Early Rheumatoid Arthritis (SERA), inception cohort recruited between 2011 and 2015. Both linked to mortality and hospitalisation data.
Participants: 4757 UK Biobank participants self-reporting established RA; 825 SERA participants with early RA meeting the 2010 ACR/EULAR classification criteria. Participants stratified by number of long-term conditions (LTCs) in addition to RA (RA only, RA + 1 LTC and RA + ≥ 2 LTCs) and matched to five non-RA controls.
Main outcome measures: Number and duration of hospitalisations and their causes. Incidence rate ratios (IRR) and 95% confidence intervals (CI) calculated using negative binomial regression models.
Results: Participants with RA + ≥ 2 LTCs experienced higher hospitalisation rates compared to those with RA alone (UK Biobank: IRR 2.10, 95% CI 1.91 to 2.30; SERA: IRR 1.74, 95% CI 1.23 to 2.48). Total duration of hospitalisation in RA + ≥ 2 LTCs was also higher (UK Biobank: IRR 2.48, 95% CI 2.17 to 2.84; SERA: IRR 1.90, 95% CI 1.07 to 3.38) than with RA alone. Rate and total duration of hospitalisations was higher in UK Biobank RA participants than non-RA controls with equivalent number of LTCs. Hospitalisations for respiratory infection were higher in early RA than established RA and were the commonest cause of hospital admission in early RA.
Conclusions: Participants with established or early RA with multimorbidity experienced a higher rate and duration of hospitalisations than those with RA alone and with non-RA matched controls.

Introduction

Rheumatoid Arthritis (RA) is associated with an increased risk of additional long term conditions (LTCs); between 60% and 75% of people with RA exhibit multimorbidity [1–4] - the presence of two or more LTCs - with higher numbers of LTCs reported with increasing age and disease activity [1]. The most common LTCs reported alongside RA include cardiovascular disorders, hypertension, diabetes, gastrointestinal, renal and pulmonary diseases, infections, osteoporosis, tumours and depression [4–6] with cardiovascular disease mortality rates in RA patients being increased by around 50% compared to those without RA [7–9].

High levels of multimorbidity, as seen in people with RA, result in high burden of treatment (that is the workload of self-management e.g. taking medications, attending medical appointments) which may affect patient tolerance, engagement and adherence to treatment [10]. Multimorbidity in RA is also known to be associated with increased mortality, decreased functional status and decreased quality of life [4,11].

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However, little is known about how multimorbidity impacts number and duration of hospitalisations. Those studies that have investigated hospitalisation in RA have focused on the differences between RA patients and the general population, the change in rates of hospitalisation over time and the causes for the hospitalisation or length of hospitalisation following specific procedures [12–14].

This study aims to assess the overall effect of the presence and extent of multimorbidity in people with RA in relation to both the number and the total duration of inpatient hospital stays and to explore the reasons for the hospitalisations by examining data from UK Biobank (a population-based cohort which includes people with established RA), and the national Scottish Early Rheumatoid Arthritis (SERA) inception cohort (a hospital-based cohort which includes people with early RA) and also comparing them to matched controls.

Methods

Study design and data collection

UK Biobank is a longitudinal population-based cohort of 502503 participants, aged 37-73 years in Great Britain [15]. Baseline data on self-reported health and clinical measurements was collected between 2006 and 2010 from recruitment centres in England, Scotland and Wales during nurse led interviews, and subsequently linked to mortality and hospitalisation records by UK Biobank data analysts.

The SERA cohort is a national inception cohort of 1073 patients, aged over 18 years, with newly diagnosed RA or undifferentiated arthritis (UA), recruited from rheumatology departments in 20 hospitals across Scotland between March 2011 and April 2015 [16]. Patients with a new clinical diagnosis of RA or UA, who had at least one swollen joint, were invited to participate. Detailed demographic, clinical, laboratory and radiographic data and biological Biobank samples were collected. Treatment was at the discretion of the treating rheumatologist in line with standard local practice and was recorded in a web-based portal by research nurses at 6 monthly intervals. Data was subsequently linked to mortality and hospitalisation records, with each participant matched by age, sex and postcode to five controls without RA by the electronic Data Research and Innovation Service (eDRIS) team (part of Public Health Scotland).

Participants

In UK Biobank, RA and all LTCs were based on self-report using a questionnaire and nurse-led interview where participants were asked if they had been informed by a doctor that they had any serious illness or disabilities. RA disease duration was calculated using UK Biobank first occurrence data. Participants whose first occurrence of RA was more than two years before their baseline assessment date were selected to ensure that their RA could be considered as *established*. For SERA participants, RA was clinically diagnosed by a rheumatologist and the participants selected additionally met the 2010 ACR/EULAR RA classification criteria at their baseline visit [17]. Information on additional LTCs was obtained from each participant's hospital records by a research nurse.

Outcomes

For UK Biobank the total number and total duration of inpatient hospitalisations over the follow-up period was calculated for each participant from the date of baseline assessment to the date of the last hospitalisation in each cohort or, if a participant had died, their date of death. For SERA the total number and total duration of inpatient hospitalisations was calculated for each participant over a two-year period starting from the date of baseline visit or, if a participant had died, until their date of death. The most common reasons for hospitalisation were calculated using the primary ICD-10 code assigned to the final episode of their hospital stay. Hospitalisation reasons were grouped by ICD-10 subchapter and the rate per 1000 patient-years calculated.

Assessment of LTCs at baseline

The list of 42 LTCs considered for both cohorts was based on based on previous literature [18], author experience (FSM) and a UK Biobank prevalence of $\geq$0.1% and have been used in our previous UK Biobank work [4,19–21]. The LTC count, excluding RA, were summed and then categorised into the following groups: RA only (1 LTC in total), RA + 1 LTC (2 LTCs in total) or RA + $\geq$ 2 LTCs (3 or more LTCs in total). For each UK Biobank participant with RA, five age, sex and Townsend quintile matched control participants without RA were identified using nearest neighbour matching and categorised as having No RA & No LTCs, No RA + 1 LTC, No RA + 2 LTCs and No RA + $\geq$ 3 LTCs. For SERA participants, five age, sex and postcode matched participants were identified by the eDRIS team. The prevalence of all LTCs in UK Biobank and SERA were calculated and the 10 most prevalent LTCs were compared between the datasets.

Sociodemographic and lifestyle variables

Both UK Biobank and SERA cohorts collected information on a wide range of demographic and lifestyle factors at baseline assessment. These included age, sex, socioeconomic status (Townsend score for UK Biobank [22], Scottish Index of Multiple Deprivation (SIMD) for SERA [23]), smoking status, alcohol intake, and body mass index (BMI). Age was categorised into bands of 37-49, 50-59 and 60-73 years for UK Biobank. SERA participants were grouped into bands 18-36, 37-49, 50-59, 60-73 and $\geq$ 74 years to reflect the age ranges used in UK Biobank. Sex was a binary categorical variable. Smoking status was categorised into "never" or "current or previous". Alcohol intake was categorised into three groups based on the 2017 Health Survey for England [24]: 0-14 units (low risk), 15-35 units in females and 15-50 units in males (increasing risk) and $>$ 35 units in females and $>$ 50 units in males (higher risk) per week. BMI was categorised into four groups based on WHO BMI guidelines [25]: "underweight $<$ 18.5", "normal weight 18.5-24.9", "overweight 25-29.9" and "obese $\geq$ 30".

Statistical methods

R, version 4.0.3, was used for all statistical analyses in this study [26]. Comparisons between the proportions of individual LTCs in the most prevalent conditions in UK Biobank and SERA were performed using the two-proportions z-test. Negative binomial regression models were used to evaluate the effect of different LTC counts on the number of hospital admissions and the total duration of the admissions in participants with RA using the R MASS package [27]. Additional models were also fitted to compare the participants with RA to controls with varying numbers of LTCs, but without RA.

The models comparing different numbers of LTCs within RA participants for both UK Biobank and SERA were adjusted for age and sex, with participants with RA but no additional LTCs used as the reference group. To assess the differences between the RA and control participants two different approaches were used. For UK Biobank data the participants with RA and participants with no RA but other LTCs were compared to participants with no RA and no other LTCs. Models were adjusted for age and sex. In SERA, data identifying lifestyle factors or the number of LTCs were not available for the age, sex and postcode matched non-RA controls. Therefore, for both UK Biobank and SERA, models comparing all RA participants to all non-RA participants were used to evaluate the differences in the number of hospital admissions and the total duration of the admissions. The baseline assessment date of the matched RA participant was used as the index date and the duration of time over which hospitalisations were observed for each participant was included as an offset in all models.

Patient and public involvement

Those living with RA and/or chronic pain were involved in this research from the outset. Initial discussions on the focus of the research were discussed with members of the ALLIANCE, a Scotland-wide organisation representing those living with LTCs. One patient representative was a co-applicant in the original funding application. On successful receipt of funding, we approached Versus Arthritis in Scotland and sought patient volunteers to convene a patient advisory group to oversee the project. The advisory group met six times over the course of the study. The group discussed the research focus, recruitment and sampling strategies, and emerging findings. Following data collection, the advisory group joined a wider stakeholder group in a series of confirmatory workshops aimed at developing recommendations. The advisory group continues to advise on the study dissemination strategy, including the development of a series of public-facing animations detailing our main findings. Members of the study team attend local RA groups to share findings.

Results

4757 participants in UK Biobank who self-reported having RA were identified as having established RA and were matched with 23785 UK Biobank non-RA controls. 825 participants in SERA were identified as meeting the 2010 ACR/EULAR RA classification criteria. Table 1 shows the lifestyle and demographic characteristics of participants in both the established and newly diagnosed RA cohorts and UK Biobank non-RA controls (lifestyle data for the SERA controls was not available). The median follow-up period from the initial assessment was 12.0 years (Interquartile range (IQR) 11.1-12.6) in UK Biobank (established RA) and 2.0 years (IQR 2.0-2.0) in SERA (newly diagnosed RA). The proportion of females was similar (70.2% for UK Biobank RA participants, 65.2% for SERA RA), as was the median age (61, IQR 55-65 vs 60, IQR 50-68). The number of RA participants who were current or previous smokers in UK Biobank was lower than in SERA (53.3% vs 64.8%), but both were higher than the non-RA controls (46.2%). The proportion of participants who were in the increasing risk or higher risk alcohol groups was higher in UK Biobank controls (30.9%) than in UK Biobank RA participants (23.8%) or SERA (9.8%). The BMI classifications and socioeconomic quintiles were comparable between both datasets. The majority of participants with RA in both UK Biobank and SERA had at least one LTC in addition to RA. However, levels of multimorbidity were higher in UK Biobank with 76.0% of participants with established RA having one or more LTCs in addition to RA compared to 56.0% in the SERA early RA participants. The mean number of LTCs was 2.6 (SD 1.5) in UK Biobank RA participants, 2.0 (SD 1.1) in RA patients in SERA and 1.9 LTCs (SD 1.1) in UK Biobank matched controls with LTCs, but no RA. Total rates of hospitalisation were 254 per 1000 patient-years in UK Biobank RA participants, 256 per 1000 patient-years in RA patients in SERA and 142 per 1000 patient-years in UK Biobank matched controls. Total duration (days) of hospitalisation were 1635 per 1000 patient-years, 1434 per 1000 patient-years and 819 per 1000 patient-years, respectively. Within the LTC groups in both UK Biobank and SERA, the median age, the proportion of deaths and the number and total duration of hospitalisations increased with the number of LTCs.

Prevalence of additional long-term conditions (LTCs)

The prevalence of the top 10 LTCs for UK Biobank and SERA are shown in supplementary Table 1. Eight out of the top 10 LTCs were shared by the UK Biobank RA and non-RA groups and those in SERA. Hypertension was the most prevalent condition in all datasets. However, the proportion of participants with hypertension was significantly higher in the established RA participants in UK Biobank than the early RA participants in SERA (1702, 35.8% vs 175, 21.2%), as were painful conditions (886, 18.6% vs 87, 10.5%), asthma (709, 14.9% vs 70, 8.5%) and dyspepsia (534, 11.2% vs 35, 4.2%). The proportions with thyroid conditions, chronic heart disease, diabetes and depression were not significantly different.

Hospitalisations and number of LTCs in participants with RA

We examined the total number and duration of hospitalisations for participants with RA in the different LTC groupings in UK Biobank and SERA (Fig. 1). In UK Biobank the number of hospitalisations were 35% higher (incidence rate ratio (IRR) 1.35, 95% confidence intervals (CI) 1.22 to 1.49) in participants with RA + 1 LTC (215 per 1000 patient-years) and 2.10 times higher (IRR 2.10, 95% CI 1.91 to 2.30) in those with RA + ≥ 2 LTCs (331 per 1000 patient-years) than in those with RA alone (160 per 1000 patient-years) (Fig. 1a). In SERA, the number of hospitalisations were 74% higher (IRR 1.74, 95% CI 1.23 to 2.48) in those with RA + ≥ 2 LTCs (382 per 1000 patient-years) than those with RA alone (182 per 1000 patient-years) (Fig. 1b). The number of hospitalisations in SERA participants with RA + 1 LTC (252 per 1000 patient-years) were not significantly different to those with RA alone (IRR 1.25, 95% CI 0.88 to 1.78).

The total duration of hospitalisations in UK Biobank was 46% higher (IRR 1.46, 95% CI 1.26 to 1.68) in participants with RA + 1 LTC (1376 days per 1000 patient-years) and 2.48 times higher (IRR 2.48, 95% CI 2.17 to 2.84) in participants with RA + ≥ 2 LTCs (2182 days per 1000 patient-years) than in participants with RA alone (955 days per 1000 patient-years) (Fig. 1c). In SERA the total duration of hospitalisations in participants with RA + ≥ 2 LTCs (2379 days per 1000 patient-years) was 90% higher (IRR 1.90, 95% CI 1.07 to 3.38) than in participants with RA alone (812 days per 1000 patient-years) (Fig. 1d). Duration of hospitalisations in those in SERA with RA + 1 LTC (1495 days per 1000 patient-years) was not significantly different to those with RA alone (IRR 1.42, 95% CI 0.83 to 2.45).

Hospitalisations and number of LTCs in participants with and without RA

The rate of both hospitalisations and total duration of hospitalisations in UK Biobank increased with increasing number of LTCs in RA and non-RA participants relative to the matched participants without RA or any other LTCs (Table 2). However, the rate and duration of hospitalisation was higher in participants with RA than the equivalent non-RA group with the same number of total LTCs. Both the total number of hospitalisations and the duration of hospitalisation were significantly higher in all groups with RA compared to participants with the equivalent number of LTCs, but without RA (supplementary Table 2).

For SERA it was not possible to compare RA and control participants in the same way as for UK Biobank. However, comparing all SERA RA patients to age, sex and postcode matched non-RA participants showed that the total number of hospitalisations was 35% higher (IRR 1.35, 95% CI 1.11 to 1.64) for participants with RA. There was no significant difference in the total duration of hospitalisation (IRR 0.81, 95% CI 0.59 to 1.13). This was lower than for UK Biobank where the total number of hospitalisations was 82% higher (IRR 1.82, 95% CI 1.73 to 1.90) and double (IRR 2.07, 95% CI 1.93 to 2.22) for total duration of hospitalisation for participants with RA compared to non-RA participants.

Causes of hospitalisation

The main causes of hospitalisation for UK Biobank and SERA participants were assessed and are shown in supplementary Table 3a–c and are summarised in Table 3. For UK Biobank participants with RA only and RA + 1 LTC, the commonest causes of admission were due to inflammatory polyarthropathies (mainly M05 and M06 RA ICD-10 codes) and osteoarthritis (M15-M19 ICD-10 codes), whilst those with RA + ≥ 2 LTCs were admitted predominantly due to heart disease (combined I20-I25 and I30-I52 ICD-10 sub-chapters), osteoarthritis and symptoms and signs involving the circulatory and respiratory systems (R00-R09 ICD-10

Table 1
Baseline demographic and lifestyle characteristics by LTC group for UK Biobank and SERA participants.

	UK Biobank with RA				SERA				UK Biobank non-RA				
	RA only	**RA + 1 LTC**	**RA + ≥ 2 LTCs**	**Total**	**RA only**	**RA + 1 LTC**	**RA + ≥ 2 LTCs**	**Total**	**No RA & No LTC**	**No RA + 1 LTC**	**No RA + 2 LTCs**	**No RA + ≥ 3 LTCs**	**Total**
Total participants	1141 (24.0)	1448 (30.4)	2168 (45.6)	4757 (100)	363 (44.0)	235 (28.5)	227 (27.5)	825 (100)	7337 (30.8)	7852 (33.0)	4873 (20.5)	3723 (15.7)	23785 (100)
Sex													
Male	324 (28.4)	452 (31.2)	643 (29.7)	1419 (29.8)	128 (35.3)	84 (35.7)	75 (33.0)	287 (34.8)	2153 (29.3)	2334 (29.7)	1520 (31.2)	1088 (29.2)	7095 (29.8)
Female	817 (71.6)	996 (68.8)	1525 (70.3)	3338 (70.2)	235 (64.7)	151 (64.3)	152 (67.0)	538 (65.2)	5184 (70.7)	5518 (70.3)	3353 (68.8)	2635 (70.8)	16690 (70.2)
Age at baseline													
Median age	59 (52-63)	61 (55-65)	62 (57-66)	61 (55-65)	53 (46-63)	61 (51-69)	66 (59-72)	60 (50-68)	59 (52-63)	61 (55-65)	62 (57-66)	63 (59-66)	61 (55-65)
18-36					40 (11.0)	15 (6.4)	7 (3.1)	62 (7.5)					
37-49	212 (18.6)	171 (11.8)	162 (7.5)	545 (11.5)	90 (24.8)	37 (15.7)	15 (6.6)	142 (17.2)	1336 (18.2)	837 (10.7)	375 (7.7)	177 (4.8)	2725 (11.5)
50-59	397 (34.8)	462 (31.9)	623 (28.7)	1482 (31.2)	117 (32.2)	58 (24.7)	39 (17.2)	214 (25.9)	2642 (36.0)	2551 (32.5)	1314 (27.0)	903 (24.3)	7410 (31.2)
60-73	532 (46.6)	815 (56.3)	1383 (63.8)	2730 (57.4)	95 (26.2)	86 (36.6)	122 (53.7)	303 (36.7)	3359 (45.8)	4464 (56.9)	3184 (65.3)	2643 (71.0)	13650 (57.4)
74+					21 (5.8)	39 (16.6)	44 (19.4)	104 (12.6)					
Smoking status													
Current or previous	537 (47.1)	752 (51.9)	1248 (57.6)	2537 (53.3)	234 (64.5)	152 (64.7)	149 (65.6)	535 (64.8)	3068 (41.8)	3546 (45.2)	2379 (48.8)	1990 (53.5)	10983 (46.2)
Never	604 (52.9)	696 (48.1)	920 (42.4)	2220 (46.7)	129 (35.5)	83 (35.3)	78 (34.4)	290 (35.2)	4269 (58.2)	4306 (54.8)	2494 (51.2)	1733 (46.5)	12802 (53.8)
Alcohol intake													
Low risk	838 (73.4)	1090 (75.3)	1699 (78.4)	3627 (76.2)	328 (90.4)	204 (86.8)	212 (93.4)	744 (90.2)	4902 (66.8)	5353 (68.2)	3394 (69.6)	2787 (74.9)	16436 (69.1)
Increasing risk	246 (21.6)	299 (20.6)	389 (17.9)	934 (19.6)	33 (9.1)	30 (12.8)	15 (6.6)	78 (9.5)	2097 (28.6)	2121 (27.0)	1223 (25.1)	746 (20.0)	6187 (26.0)
Higher risk	57 (5.0)	59 (4.1)	80 (3.7)	196 (4.1)	2 (0.6)	1 (0.4)	0 (0)	3 (0.4)	338 (4.6)	378 (4.8)	256 (5.3)	190 (5.1)	1162 (4.9)
BMI													
Underweight	16 (1.4)	16 (1.1)	12 (0.6)	44 (0.9)	9 (2.5)	2 (0.9)	2 (0.9)	13 (1.6)	53 (0.7)	47 (0.6)	21 (0.4)	15 (0.4)	136 (0.6)
Normal weight	400 (35.1)	420 (29.0)	501 (23.1)	1321 (27.8)	127 (35.0)	62 (26.4)	50 (22.0)	239 (29.0)	3103 (42.3)	2659 (33.9)	1330 (27.3)	743 (20.0)	7835 (32.9)
Overweight	498 (43.6)	622 (43.0)	787 (36.3)	1907 (40.1)	130 (35.8)	87 (37.0)	82 (36.1)	299 (36.2)	2963 (40.4)	3360 (42.8)	2037 (41.8)	1411 (37.9)	9771 (41.1)
Obese	227 (19.9)	390 (26.9)	868 (40.0)	1485 (31.2)	97 (26.7)	84 (35.7)	93 (41.0)	274 (33.2)	1218 (16.6)	1786 (22.7)	1485 (30.5)	1554 (41.7)	6043 (25.4)
Social deprivation quintiles (1 = least deprived; 5 = most deprived)													
1	242 (21.2)	277 (19.1)	322 (14.9)	841 (17.7)	62 (17.1)	34 (14.5)	40 (17.6)	136 (16.5)	1388 (18.9)	1432 (18.2)	870 (17.9)	515 (13.8)	4205 (17.7)
2	203 (17.8)	267 (18.4)	371 (17.1)	841 (17.7)	86 (23.7)	49 (20.9)	46 (20.3)	181 (21.9)	1417 (19.3)	1399 (17.8)	823 (16.9)	566 (15.2)	4205 (17.7)
3	263 (23.0)	301 (20.8)	388 (17.9)	952 (20.0)	69 (19.0)	38 (16.2)	48 (21.1)	155 (18.8)	1501 (20.5)	1658 (21.1)	956 (19.6)	645 (17.3)	4760 (20.0)
4	228 (20.0)	302 (20.9)	449 (20.7)	979 (20.6)	67 (18.5)	61 (26.0)	50 (22.0)	178 (21.6)	1480 (20.2)	1634 (20.8)	1004 (20.6)	777 (20.9)	4895 (20.6)
5	205 (18.0)	301 (20.8)	638 (29.4)	1144 (24.0)	79 (21.8)	53 (22.6)	43 (18.9)	175 (21.2)	1551 (21.1)	1729 (22.0)	1220 (25.0)	1220 (32.8)	5720 (24.0)

(*continued on next page*)

Table 1 (*continued*)

	UK Biobank with RA				SERA				UK Biobank non-RA			
	RA only	RA + 1 LTC	RA + ≥ 2 LTCs	Total	RA only	RA + 1 LTC	RA + ≥ 2 LTCs	Total	No RA & No LTC	No RA + 1 LTC	No RA + 2 LTCs	No RA + ≥ 3 LTCs	Total
Deaths	24 (2.1)	55 (3.8)	161 (7.4)	240 (5.0)	1 (0.3)	6 (2.6)	9 (4.0)	16 (1.9)	92 (1.3)	217 (2.8)	161 (3.3)	217 (5.8)	687 (2.9)
Hospitalisations													
Number per 1000 person-years	160	215	331	254	182	252	382	256	81	119	173	274	142
Total duration (days) per 1000 person-years	955	1376	2182	1635	812	1495	2379	1434	406	655	1005	1765	819
Follow-up, years	12.0 (11.2-12.6)	12.0 (11.1-12.6)	12.0 (11.1-12.6)	12.0 (11.1-12.6)	2.0 (2.0-2.0)	2.0 (2.0-2.0)	2.0 (2.0-2.0)	2.0 (2.0-2.0)	11.8 (11.1-12.5)	11.8 (11.1-12.5)	11.8 (11.1-12.5)	11.7 (11.0-12.4)	11.8 (11.1-12.5)

Data are number (%) or median (IQR) unless otherwise indicated.

codes). In SERA, those with RA only were predominantly admitted for heart disease, their inflammatory polyarthropathies (mainly M05 and M06 RA ICD-10 codes) and respiratory infections (combined J09-J18 and J20-J22 ICD-10 subchapters), with admissions for RA + 1 LTC dominated by respiratory disease and infections (combined J09-I18, J20-I22 and J40-J47, J80-84 and J90-94), whilst those with RA + ≥ 2 LTCs were predominantly admitted due to respiratory disease and infections (combined J09-J18, J20-J22 and J40-J47 ICD-10 codes) and heart disease (combined I20-I25 and I30-I52 ICD-10 sub-chapters), as well as their inflammatory polyarthropathies. Across all SERA RA groups, respiratory infections (J09-J18 and J20-J22 sub-chapters combined) were a more common cause of hospitalisation than RA. In both UK Biobank and SERA, the rate of admissions per 1000 patient-years due to inflammatory polyarthropathies were not significantly different between RA only, RA + 1 LTC and RA + ≥ 2 LTCs groups, whereas the number of admissions due to chronic lower respiratory disease, respiratory infections and heart disease were significantly higher in the RA + ≥ 2 groups. Additionally, in all SERA LTC groups the rate of admissions due to respiratory infections were more than three times that of the corresponding UK Biobank RA group.

Discussion

Our study demonstrates that multimorbidity in people with RA is common across two datasets encompassing both established RA (UK Biobank) and newly diagnosed (early) RA (SERA), with additional LTCs more prevalent in the established RA cohort. We have shown that in both UK Biobank and SERA, those with two or more additional LTCs were hospitalised more often and spent longer in hospital than participants with only RA. The data also suggest that the association of LTCs with hospitalisation rates and duration is higher in established RA than early RA. Furthermore, we found that people with established RA are hospitalised more often and spend longer in hospital than people without RA with the equivalent number of LTCs. In both UK Biobank and SERA, RA was a principal cause of hospitalisation in those without additional LTCs and whilst rates of admission due to RA were similar across LTC groups, rates of admission due to other causes were higher in those with more LTCs. Additionally, admissions due to respiratory infections were a main cause of hospitalisation in all the SERA early RA LTC groups and were more than three times as common than in the corresponding UK Biobank RA group. In contrast, a prevalent cause of hospitalisation in the established RA plus LTC groups was osteoarthritis, with the majority being for joint replacements.

To the best of our knowledge, this study is the first to investigate the effect of multimorbidity on the number and total duration of hospitalisations in people with established and early RA. Prevalence of multimorbidity in those with RA was in line with what has previously been reported for UK Biobank, but slightly lower in SERA [1–4]. It may be that additional LTCs are still to develop in SERA participants due to this being a younger inception cohort, such that the condition itself or treatments used for RA have not yet impacted, or, as has been previously reported, that conditions such as hypertension and depression may be underdiagnosed in early RA when the clinical focus is on controlling RA disease activity [28,29]. The most common LTCs in addition to RA in each cohort were similar and are consistent with LTCs previously described in RA [2,3,6,30] and are also shared by the non-RA UK Biobank participants.

Previously it has been reported in a population-based cohort that those with RA experience higher rates of hospitalisation (IRR 1.51, 95% CI 1.42 to 1.59) than the general population [12]. Our analysis is in agreement, with hospitalisations in UK Biobank RA participants being 82% higher (IRR 1.82, 95% CI 1.73 to 1.90) compared to age, sex and Townsend quintile matched non-RA participants and in SERA participants being 35% higher (IRR 1.35, 95% CI 1.11 to 1.64) compared to age, sex and postcode matched participants without RA. Additionally, a study of 2535 patients with established RA reported an increase in the

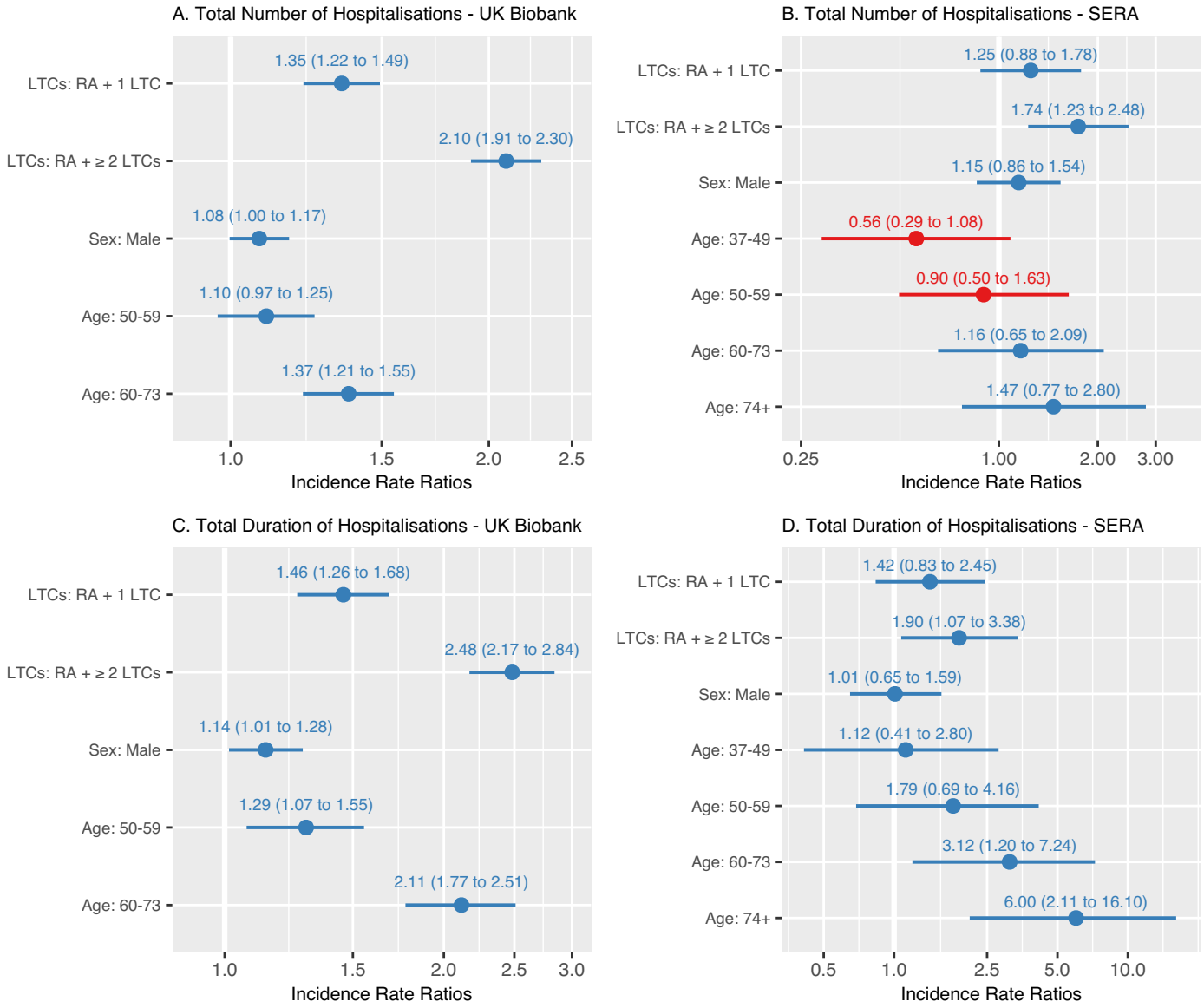

Fig. 1. Forest plots showing the incidence rate ratio (IRR) and 95% confidence intervals of the covariates for the total number and total duration of hospitalisations using negative binomial models. For each covariate the reference groups are: LTC, RA only; Sex, Female; Age, UK Biobank: 37-49, SERA: 18-36. (A) Total number of hospitalisations in UK Biobank. (B) Total number of hospitalisations in SERA. (C) Total duration of hospitalisations in UK Biobank. (D) Total duration of hospitalisations in SERA. Blue dots and lines indicate positive association and red dots and lines negative association relative to the reference group. Data are plotted on log scale.

Table 2
Incidence Rate Ratio of number of hospitalisations and total duration of hospitalisation in RA and non-RA participants in UK Biobank.

	Total number of LTCs	LTC Group	IRR (95% CI)
Number of hospitalisations	**0**	**No RA & No LTC**	1
	1	**No RA + 1 LTC**	1.46 (1.39 to 1.54)
		RA only	2.03 (1.85 to 2.22)
	2	**No RA + 2 LTCs**	2.04 (1.93 to 2.15)
		RA + 1 LTC	2.71 (2.49 to 2.94)
	≥ 3	**No RA + ≥ 3 LTCs**	3.37 (3.18 to 3.57)
		RA + ≥ 2 LTCs	4.20 (3.92 to 4.50)
Duration of hospitalisations	**0**	**No RA & No LTC**	1
	1	**No RA + 1 LTC**	1.59 (1.48 to 1.71)
		RA only	2.42 (2.12 to 2.77)
	2	**No RA + 2 LTCs**	2.23 (2.06 to 2.42)
		RA + 1 LTC	3.48 (3.08 to 3.93)
	≥ 3	**No RA + ≥ 3 LTCs**	4.36 (4.00 to 4.75)
		RA + ≥ 2 LTCs	5.97 (5.39 to 6.63)

Models adjusted for age and sex. Reference group = No RA & No LTCs.

Table 3
Summary of the causes of hospitalisation in UK Biobank and SERA RA participants.

		UK Biobank RA			SERA	
	RA only	**RA + 1 LTC**	**RA + ≥ 2 LTCs**	**RA only**	**RA + 1 LTC**	**RA + ≥ 2 LTCs**
1	Inflammatory polyarthropathies	Osteoarthritis	Heart disease	Heart disease	Respiratory disease	Heart disease
2	Osteoarthritis	Inflammatory polyarthropathies	Osteoarthritis	Respiratory infections	Respiratory infections	Respiratory infections
3	Complications of surgical and medical care, not elsewhere classified	Heart disease	Symptoms and signs involving the circulatory and respiratory systems	Inflammatory polyarthropathies	Inflammatory polyarthropathies	Respiratory disease
4	Symptoms and signs involving the circulatory and respiratory systems	Symptoms and signs involving the circulatory and respiratory systems	Inflammatory polyarthropathies	Symptoms and signs involving the circulatory and respiratory systems	Symptoms and signs involving the digestive system and abdomen	Inflammatory polyarthropathies
5	Respiratory infections	Complications of surgical and medical care, not elsewhere classified	Respiratory infections	Symptoms and signs involving the digestive system and abdomen	Infectious arthropathies	Osteoarthritis

proportion of RA patients with at least one admission to a hospital with increasing number of LTCs [31]. Our study adds to this research, showing that not only do the number of hospitalisations increase but also that the total duration of these hospitalisations increases with increasing LTC count in both established and early RA. Furthermore, we have shown in UK Biobank, that the rates and duration of hospitalisation are higher in participants with RA than in those with the equivalent number of LTCs but no RA, suggesting that both the presence of RA and the number of LTCs are important.

As expected, a common reason for hospitalisation in those with RA (with and without other LTCs) was for inflammatory arthritis and the rates were similar between LTC groups within the established and early RA cohorts. RA was a predominant reason for hospitalisation in those without any other LTCs, however, as the number of LTCs increased in participants with RA, other causes became more prevalent. In established RA participants in UK Biobank, osteoarthritis was listed as one of the top two reasons for hospitalisation in all LTC groups, which presumably reflects the age of the cohort (also reported commonly as cause for hospitalisation in non-RA participants in UK Biobank, albeit at slightly lower prevalence rates) and likely due to joint damage from longstanding RA, which is usually coded as osteoarthritis, and which can itself lead to the development of secondary osteoarthritis. In the early RA participants in SERA, osteoarthritis is also one of the commonly reported causes of hospitalisation in all groups, although overall prevalence rates per 1000 patient-years were slightly lower than those for established RA, presumably reflecting the shorter RA duration and therefore time to accrue damage, despite being of similar age.

Beyond RA and osteoarthritis, the other common causes for hospitalisation were largely similar for LTC groups for the established RA and non-RA cohorts in UK Biobank. In contrast, in the newly diagnosed RA participants in SERA, admissions due to respiratory diseases and infections were the most common reasons for hospitalisation, with high rates per 1000 patient-years, in all LTC groups, especially those with RA + ≥ 2 LTCs. These high rates and differences between RA cohorts may reflect that those with early RA are more likely to be receiving more corticosteroids and starting intensive immunosuppressive medications as part of the "treat-to-target" treatment strategy to control their active inflammatory disease in early RA, predisposing them to respiratory infections. Many studies have reported increased infections associated with corticosteroids but not with stable doses of disease modifying antirheumatic drugs [32,33], while it appears that serious infections associated with the latter may occur mainly in the first 6 months of their initiation [34]. Participants with established RA in UK Biobank are less likely to have active inflammatory joint disease, more likely to be on stable immunosuppressant therapies and less likely to be receiving corticosteroids.

Recent work by Gil-Conesa et al has shown that while hospitalisations due to RA itself have decreased over time, hospitalisations of patients with RA due to other causes have increased [13]. In addition, Kuo et al have found that RA is independently associated with a higher risk of preventable hospitalisation [35]. The causes identified included the higher prevalence of comorbidities and the influence of medications; it has been suggested that improved management of RA may influence hospitalisation risk and that risk could be reduced by incorporating comorbidity screening and preventive measures, such as vaccination, into the routine care of RA patients, which may differ in early and established RA. The reasons for the longer duration of hospitalisations in UK Biobank RA participants compared to the non-RA participants are not immediately clear. Factors known to contribute to prolonged hospital stays include pre-admission functional status, discharge destination and levels of caregiver support [36,37]. It is important that these are investigated as prolonged hospital stays increase the risk of falls, infection, morbidity and mortality, as well as incurring increased healthcare costs [37–39].

Our study has several key strengths: We have used two independent datasets encompassing both established and early RA, allowing comparison between these; UK Biobank is a large population-based study with several thousand participants self-reporting RA encompassing three countries within the UK and SERA is a large dedicated Scottish RA inception cohort dataset. Both include details of participant demographic and lifestyle factors, which allowed us to adjust for potential confounding variables. Unlike many previous studies that have investigated LTCs and outcomes in RA, we had linkage to national datasets and were not limited to specific insurance or claims databases.

Our study also has limitations. UK Biobank is not fully representative of the general population with participants being healthier and more affluent [40]. The UK Biobank dataset is also limited by self-reporting of RA and LTCs; however recent studies have shown that self-report is a reliable method for reporting RA [41]. Additionally, UK Biobank results are supported by the results from the SERA dataset analysis, which whilst being an inception cohort and significantly smaller in participant numbers and numbers of LTCs than UK Biobank, has participants whose RA and LTCs have been clinically diagnosed. In SERA data identifying the number of LTCs in control participants was not available, which has meant it has not been possible to replicate all UK Biobank analyses in SERA. However, the analysis carried out comparing the number of hospitalisations in RA participants to those in the controls is comparable to what has been published in the literature. It is possible that participants could have developed further LTCs following baseline assessment in both SERA and UK Biobank. However, taking account of new LTC development was not the aim of this paper. Additionally, considering the relationship between baseline LTCs and health-related outcomes has been done in this way before [4,19,20,42]. In the UK Biobank analyses it is feasible that some LTCs may have occurred due to the presence of RA, however it is not possible to be sure of causality and therefore we cannot take account for this in the analysis.

Conclusion

Our findings highlight the importance of considering multimorbidity as a factor in risk stratification of people with RA, due to higher associated risk of hospitalisation events and longer duration of hospitalisation. Our findings have indicated similarities and important differences between reasons for hospitalisation in established and early RA that have implications for healthcare providers, particularly respiratory infections in those with early RA and additional LTCs. Further work is required to understand fully the mechanisms underpinning these findings.

Ethics statement

This use of UK Biobank data was covered by the generic ethics approval for UK Biobank studies from the NHS National Research Ethics Service (16/NW/0274). The SERA study was approved by the West of Scotland Research Ethics Committee 4 (reference 10/S0704/20) and all participants gave written informed consent.

Data availability statement

The UK Biobank data used in this study are available by application to UK Biobank. SERA data are available upon reasonable request. Access to data is subject to approval by the Scottish Early Rheumatoid Arthritis Inception Cohort and UK Biobank Data Access Committee.

Authors contributions

BDJ, FSM, SM, SS and BIN conceived this study. FRM, PM and RM analysed the data. FRM, BDJ, FSM, PM, JC, SM, RM, SS, BIN substantially contributed to design, interpretation, and discussion of all analyses. FRM wrote the first draft of this manuscript. FRM, BDJ, FSM, PM, JC, SM, RM, SS, BIN edited, reviewed, and commented on each version of the manuscript and approved the final submission.

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Declaration of Competing Interest

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; SS has received research grants from Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly and UCB, consultancy fees from AbbVie, Eli Lily and UCB, honoraria from AbbVie, Biogen, GSK and UCB, and support for attending meetings from UCB. No other relationships or activities that could appear to have influenced the submitted work.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.semarthrit.2022.152130.

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