RMD Open
Rheumatic & Musculoskeletal Diseases

ORIGINAL RESEARCH

Comorbidity burden in the first three years after diagnosis in patients with rheumatoid arthritis, psoriatic arthritis or spondyloarthritis: a general practice registry-based study

Veerle Stouten,[1] Sofia Pazmino ,[1] P Verschueren ,[1,2] Pavlos Mamouris,[3] René Westhovens ,[1,2] Kurt de Vlam,[1] Delphine Bertrand,[1] Kristien Van der Elst,[2] Bert Vaes,[3] Diederik De Cock [1]

To cite: Stouten V, Pazmino S, Verschueren P, *et al*. Comorbidity burden in the first three years after diagnosis in patients with rheumatoid arthritis, psoriatic arthritis or spondyloarthritis: a general practice registry-based study. *RMD Open* 2021;**7**:e001671. doi:10.1136/rmdopen-2021-001671

VS and SP are joint first authors.

Received 21 March 2021
Accepted 4 June 2021

[1]Department of Development and Regeneration, Skeletal Biology and Engineering Research Centre, KU Leuven, Leuven, Belgium
[2]Rheumatology, University Hospitals Leuven, Leuven, Belgium
[3]Department of Public Health and Primary Care, KU Leuven, Leuven, Belgium

Correspondence to
Dr Diederik De Cock;
diederik.decock@kuleuven.be

ABSTRACT

Objectives Rheumatoid arthritis (RA), psoriatic arthritis (PsA) and spondyloarthritis (SpA) are chronic inflammatory rheumatic conditions with high levels of comorbidity requiring additional therapeutic attention. We aimed to compare the 3-year comorbidity incidence and pain medication prescription in patients diagnosed with RA, PsA or SpA versus controls.

Methods Data between 1999 and 2012 were obtained from Intego, a general practitioner (GP) morbidity registry in Flanders, Belgium. Cases were identified by International Classification of Primary Care (ICPC-2) codes representing 'rheumatoid/seropositive arthritis (L88)' or 'musculoskeletal disease other (L99)'. The registered keywords mapped to these ICPC-2 codes were further verified and mapped to a RA/SpA/PsA diagnosis. Controls were matched on age, gender, GP practice and diagnosis date. We analysed the 3-year comorbidity burden in cases and controls, measured by the Rheumatic Diseases Comorbidity Index (RDCI). All electronically GP-prescribed drugs were registered.

Results In total, 738, 229 and 167 patients were included with a diagnosis of RA, SpA or PsA, respectively. Patients with RA or PsA had comparable median RDCI scores at baseline, but higher scores at year 3 compared with controls (RA: p=0.010; PsA: p=0.008). At baseline, depression was more prevalent in PsA patients vs controls (p<0.003). RA patients had a higher 3-year incidence of cardiovascular disease including myocardial infarction than controls (p<0.035). All disease population were given more prescriptions than controls for any pain medication type, even opioids excluding tramadol.

Conclusions This study highlights the increasing comorbidity burden of patients with chronic inflammatory rheumatic conditions, especially for individuals with RA or PsA. The high opioid use in all populations was remarkable.

Key messages

What is already known about this subject?

- Rheumatoid arthritis (RA), spondyloarthritis and psoriatic arthritis (PsA) are among the most common inflammatory rheumatic diseases, and are all associated with a high prevalence of comorbidities, such as cardiovascular diseases, kidney diseases, lung diseases, infections, malignancies, osteoporosis, gastrointestinal diseases and depression

What does this study add?

- Most research on comorbidities has focused on patients with established inflammatory rheumatic diseases. Our study shows that even at disease onset and in the first 3 years of the disease, the burden of comorbidities is substantial compared with a control population, especially for individuals with RA or PsA. All disease population were administered more pain medication prescriptions than controls for any pain medication type, even opioids excluding tramadol. There was also a remarkably high opioid use in all populations.

How might this impact on clinical practice or further developments?

- Rheumatologists should consider management of comorbidities as one of the primary tasks involved in the care of a newly diagnosed patient with an inflammatory rheumatic disease. Collaboration with other healthcare providers including nurses, primary care providers and other specialists is key to optimising a holistic management for every patient.

INTRODUCTION

Chronic inflammatory joint diseases form a heterogeneous group of conditions that cause damage in the locomotor system, loss of function with joint instability or joint ankylosis, in addition persistent inflammation might also

affect other organ systems. Their impact on a patient's life can be significant as they are a common cause of long-term pain, disability and poor quality of life.[1]

Rheumatoid arthritis (RA), spondyloarthritis (SpA) and psoriatic arthritis (PsA) are among the most common inflammatory rheumatic diseases. In recent years, the clinical outcome for patients with these conditions has improved with decreased morbidity and mortality due to earlier diagnosis, better treatment strategies and novel therapeutic options. Patients with these chronic conditions are an increasing part of the global ageing population burdening not only more and more individuals but also the society.[1] Despite improving outcome in terms of disease control, preserved functionality and less structural joint damage, many unmet needs, including the management of comorbidities, still exist in the care for patients with these conditions.[2] RA, PsA and SpA are all associated with a high prevalence of comorbidities, including cardiovascular diseases, kidney diseases, lung diseases, infections, malignancies, osteoporosis, gastrointestinal diseases and depression.[3–9] These comorbidities might negatively affect outcomes like disease activity, physical function and health-related quality of life for the patient.[1 2 10–12]

Comorbidity indices try to estimate the total comorbidity burden, as not all types of comorbidities impact the patient's health status similarly. The Rheumatic Diseases Comorbidity Index (RDCI) was validated in RA to more accurately evaluate the burden and prognostic impact of overall comorbidity, based on a weighted preselection of relevant comorbidities.[13] This index also has clinical applications in identifying patients with worse prognosis in terms of drug survival, functional status, health-related quality of life, hospitalisation frequency and mortality.[14–16]

Most research in this field has focused on patients with established inflammatory rheumatic diseases. The burden of comorbidities in early disease and its evolution over time is ill understood. Our aim was thus to compare the burden of comorbidity by the RDCI in newly diagnosed patient populations with RA, PsA or SpA vs a control population over 3 years in a general practitioners (GP) setting. Related aims were to investigate the yearly incidence of RA, PsA and SpA in this setting, and the prescription behaviour of pain medication by GPs to these patients.

PATIENTS AND METHODS

Patient population

Data were obtained from the Intego-registry over a 13-year time interval from 1999 to 2012. Intego is an ongoing Flemish, GP-based morbidity registration network hosted at the Academic Centre for General Practice of the KU Leuven, covering 2% of the Flemish general population.[17 18] Before inclusion in Intego, GPs must actively send an application and are evaluated. Their data are benchmarked to the results of all other included GP practices. Only data from GP practices with optimal registration quality are included in Intego. Additionally, external validation is assured by national and international comparisons.

In Intego, all new diagnoses and new drug prescriptions are prospectively and routinely registered, as well as laboratory test results and patient information, using computer-generated keywords internally linked to codes. This collected information is extracted and encrypted from the GPs' personal computers and put in a central database on a yearly basis. Registered data are continuously updated and historically accumulated for each patient. New diagnoses are registered by using a very detailed thesaurus (Medidoc codes) automatically linked to the International Classification of Primary Care (ICPC-2) and International Statistical Classification of Diseases and Related Health Problems 10th Revision.[19 20] Drugs are classified according to the WHO's Anatomical Therapeutic Chemical (ATC) classification system.

Patients classified under the ICPC codes L88 (rheumatoid/seropositive arthritis) and L99 (musculoskeletal disease other) were selected as cases for this study. Experienced rheumatologists (KdV and PV) verified if the keywords from the thesaurus mapped to these codes corresponded to a diagnosis of RA/SpA/PsA. The date of data input of these diagnoses in Intego was considered as 'baseline'. Per case, four controls without an L88 or L99 diagnosis were selected. Controls were first matched with cases on gender, type of GP practice and year of diagnosis. Afterwards, the cases were matched as closely as possible on age, and no control patients could be a control for two or more.

Data analysis

The yearly incidence of RA, PsA or SpA was calculated per 1000 patient years with the yearly contact group (YCG) as denominator. The YCG are all patients visiting an Intego practice at least once in a given year. Yearly incidence rates between 1999 and 2012 were calculated. Incidence trends were analysed using joinpoint regression analysis.[21] These analyses are developed to detect a point in the trend curve where a statistically significant change in trend over time is observed.

The total comorbidity burden was summarised by calculating the Rheumatic Disease Comorbidity Index (RDCI) score at baseline and at 3 years. RDCI ranges from 0 to 9, with 9 being the highest comorbidity burden.[13]

Baseline prevalence and incidence rates of the following types of comorbidities were considered for inclusion in the RDCI: lung disease; cardiovascular disease including myocardial infarction, stroke or other heart condition; hypertension; fracture of the spine/hip/leg; depression; diabetes mellitus; digestive disease including ulcers and stomach disorders; and malignancies. See online supplemental table 1 for a detailed list of ICPC-2 codes selected. The incidence over 3 years of these comorbidities was presented as crude incidence rates per 1000 patient-years, calculated as the number of new cases divided by the total persons-years of persons at risk (not having the

comorbidity at baseline) with a maximum of 3 years of follow-up per person.

Age, gender, systolic/diastolic blood pressure, selected baseline comorbidities and the RDCI scores at baseline and at year 3 were compared between patients with rheumatic conditions and their controls and between baseline and after 3 years, using χ^2 and Mann-Whitney U where appropriate. Crude incidences over 3 years were compared between cases and controls by log rank tests.

Finally, GPs' prescription behaviour for pain medication including glucocorticoids, non-steroidal anti-inflammatory drugs (NSAIDs), opioids, tramadol and paracetamol in the 3 years of follow-up was studied in patients with rheumatic conditions and controls. See appendix 1 for a list of ATC codes used per drug. Polypharmacy was defined as the prescription of five or more different medications in the first 3years of follow-up. To count medication, the first five characters of the ATC codes were used (ATC level 4). Proportions of patients and controls receiving at least 1 prescription of pain medication were compared by χ^2 analysis.

A two-sided p<0.05 was considered statistically significant. These analyses were performed by R Software V.3.3.2.

RESULTS

Over the 13-year study period, 738, 229 and 167 patients were included as RA, SpA or PsA cases, respectively. At inclusion, The RA cohort had a mean age of 58±17 with 67% being women. The SpA cohort had a mean (SD) age of 41[15] with 48% being women. The PsA cohort had a mean (SD) age of 47[13] with 49% being women. Matching was successful, resulting in similar characteristics between each case and control population (table 1).

Incidence

The average incidence of RA was 0.47, of SpA 0.15 and of PsA 0.11 per 1000 person years. Figure 1 presents the yearly incidence per disease. Due to the low number of newly diagnosed SpA and PsA patients per year, only for the RA population a joinpoint regression analysis

Table 1 Characteristics of the cases and controls

Variables	RA	RA control	SpA	SpA control	PsA	PsA control
No of diagnoses	738	2952	229	916	167	668
Demographic/clinical variables						
Mean (SD) age (year)	58 (17)	58 (17)	41 (15)	41 (15)	47 (13)	47(13)
Women n (%)	498 (67)	1992 (67)	111 (48)	444 (48)	82 (49)	328 (49)
Mean (SD) systolic blood pressure (mm Hg)	130 (14)	130 (15)	128 (17)	126 (14)	128 (14)	127(14)
Mean (SD) diastolic blood pressure (mm Hg)	78 (8)	79 (9)	80 (9)	79 (10)	79 (9)	79 (10)
Comorbidity burden						
Median RDCI (0–9) at baseline	1 (2)	1 (2)	0 (1)	0 (1)	1 (2)	0 (2)
Median RDCI (0 to 9) at year 3	**1 (2)***	**1 (2)***	0 (1)	0 (1)	**1 (2)†**	**0 (2)†**
Median change in RDCI over 3 years	**0 (0)***	**0 (0)***	0 (0)	0 (0)	0 (0)	0 (0)
Proportion of RDCI ≥1 at baseline	**58%***	**53%***	36%	34%	**52%†**	**43%†**
Proportion of RDCI ≥1 at year 3	**66%***	**61%***	45%	41%	**61%†**	**48%†**
Change in proportion of RDCI ≥1 over 3 years	8%	8%	7%	9%	5%	8%
Comorbidity types at baseline						
Lung disease n (%)	103 (14)	352 (12)	17 (7)	64 (7)	22 (13)	77 (12)
Cardiovascular disease n (%)	120 (16)	480 (16)	12 (5)	61 (7)	15 (9)	60 (9)
Hypertension n (%)	175 (24)	624 (21)	18 (8)	81 (9)	24 (14)	85 (13)
Fracture of spine/hip/leg n (%)	42 (6)	182 (6)	5 (2)	34 (4)	9 (5)	34 (5)
diabetes mellitus n (%)	72 (10)	263 (9)	7 (3)	39 (4)	11 (7)	38 (6)
Digestive (ulcer or stomach disease) n (%)	128 (17)	460 (16)	36 (16)	107 (12)	30 (18)	96 (14)
Malignancy n (%)	20 (3)	76 (3)	4 (2)	13 (1)	10 (6)	19 (3)
Depression n (%)	93 (13)	357 (12)	19 (8)	72 (8)	**33 (20)†**	**72 (11)†**

cardiovascular disease= (myocardial infarction/stroke/ other cardiovascular); lung disease: predominantly chronic obstructive pulmonary disease and allied conditions.
Statistically significant values are indicated in bold.
*<0.05 difference between RA cases and controls.
†<0.05 difference between PsA cases and controls.
n, number; PsA, psoriatic arthritis; RA, Rheumatoid arthritis; RDCI, Rheumatic Diseases Comorbidity Index; SpA, spondyloarthritis.

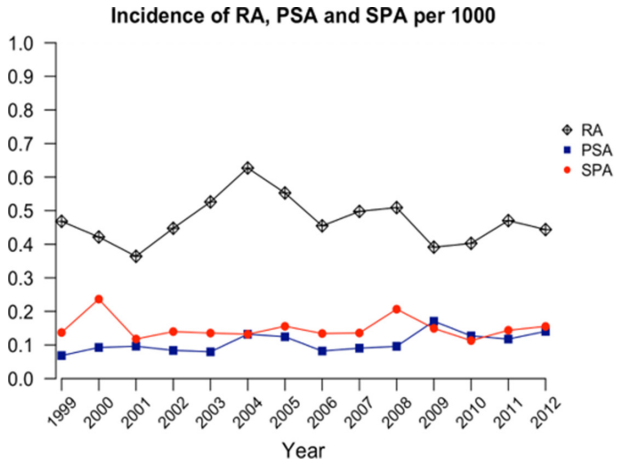

Figure 1 Yearly incidence per disease per 1000 person-years. PSA, psoriatic arthritis; RA, rheumatoid arthritis, SpA, spondyloarthritis.

could be performed. This analysis revealed no diverging trends for incidence of RA over 13 years with an average (95% CI) annual percentage change of 0 (−2.3 to 2.4).

Comorbidities

Median RDCI scores at baseline did not differ for patients with RA (p=0.07), SpA (p=0.76) or PsA (p=0.06), compared with their controls. Patients with SpA had comparable median RDCI-scores at year 3 (p=0.76) to their controls. Patients with RA or PsA had significantly higher RDCI-scores after 3 years than their controls (p=0.01 for RA vs controls; p=0.008 for PsA vs controls; table 1). Accordingly, there were significantly higher proportions of patients with an RDCI ≥1 in the RA and PsA populations, compared with their controls at baseline and at year 3. Figure 2 shows the evolution in RDCI score per disease over the 3 years of follow-up.

At baseline, patients with RA or SpA had a comparable prevalence of any of the eight considered comorbidity types, based on inclusion in the RDCI, as their controls (table 1). Patients with PsA had more often depression than controls at baseline (p<0.003).

After 3 years, the incidence of any of the eight considered comorbidity types did not differ from their controls for patients with SpA and PsA cases. Patients with RA had a higher incidence of cardiovascular disease, including myocardial infarction, than controls (p<0.035). In table 2, number of person-years follow-up, and crude incidence rates expressed as number of cases per 1000 person-years of the eight considered comorbidity types in cases and controls are presented.

Medication

Table 3 presents the pain medication prescribed for patients with rheumatic conditions and for their controls. Patients with any of the three conditions received significantly more prescriptions for all types of pain medications compared with their controls. Approximately 70% of patients with an inflammatory rheumatic condition had been prescribed mild pain medication (here defined as the sum of NSAIDs, tramadol and paracetamol) in the first 3 years after start of the disease. Likewise, polypharmacy was also clearly an issue in patients with an inflammatory rheumatic condition, with 56% (640/1134) of patients having been prescribed five or more different medications in the first 3 years after start of the disease compared with 32% (1471/4536) of the control population The prescription rate of opioids, even when tramadol was not considered, was notably high, ranging up to 15% both in cases and controls. In general, 9% (525/5670) of the total study population had been prescribed an opioid in the first 3 years after start of the disease.

DISCUSSION

In this registry study, we have shown that for patients with RA and PsA, but not for SpA, RDCI scores seem to increase 3 years after diagnosis. At baseline, patients with PsA presented more often with depression than controls, and after 3 years, patients with RA had a higher incidence of cardiovascular comorbidity than controls. Pain medication was more frequently prescribed over 3 years for patients with any of the inflammatory rheumatic diseases compared with controls. Moreover, this study shows yearly incidence rates for RA, PsA and SpA, unique for Belgium.

This study highlights the issue of multimorbidity in patients with musculoskeletal diseases, especially for individuals with RA and PsA. The distribution of the RDCI seems to differ between the rheumatic diseases. This might suggest that the role or composition of comorbidities might be different per disease. The cardiovascular risk is substantial in the RA-population with significantly more cardiovascular comorbidity over time, but also trends towards a higher incidence of hypertension and diabetes. Similar results have been shown in contemporary American and UK cohorts,[22 23] and the relationship between cardiovascular risk and RA has been established previously in other studies.[24] Likewise, the PsA cohort shows a non-statistically significant doubling of the 3-year incidence of cardiovascular disease burden compared with controls. Although numbers are low, this could be related to the adverse body composition associated with this condition that leads to more cardiovascular issues.[25] Depressive symptoms are highly prevalent in both cases and controls. Patients with PsA have more depression at baseline than controls, with 1/5 patients burdened by depressive symptoms, and numerically the incidence of depression was notably higher in this population compared with controls. Depression has already been shown to be more common in PsA.[26 27] The results of our study add evidence that depressive symptoms are present even before disease onset. The mental health needs of this patient population for depression should include early detection and depression management. Numbers of cancer cases were remarkable in our study. The direct relationship between malignancies and inflammatory rheumatic diseases is skewed by the heterogeneity in underlying pathophysiology, treatment options and

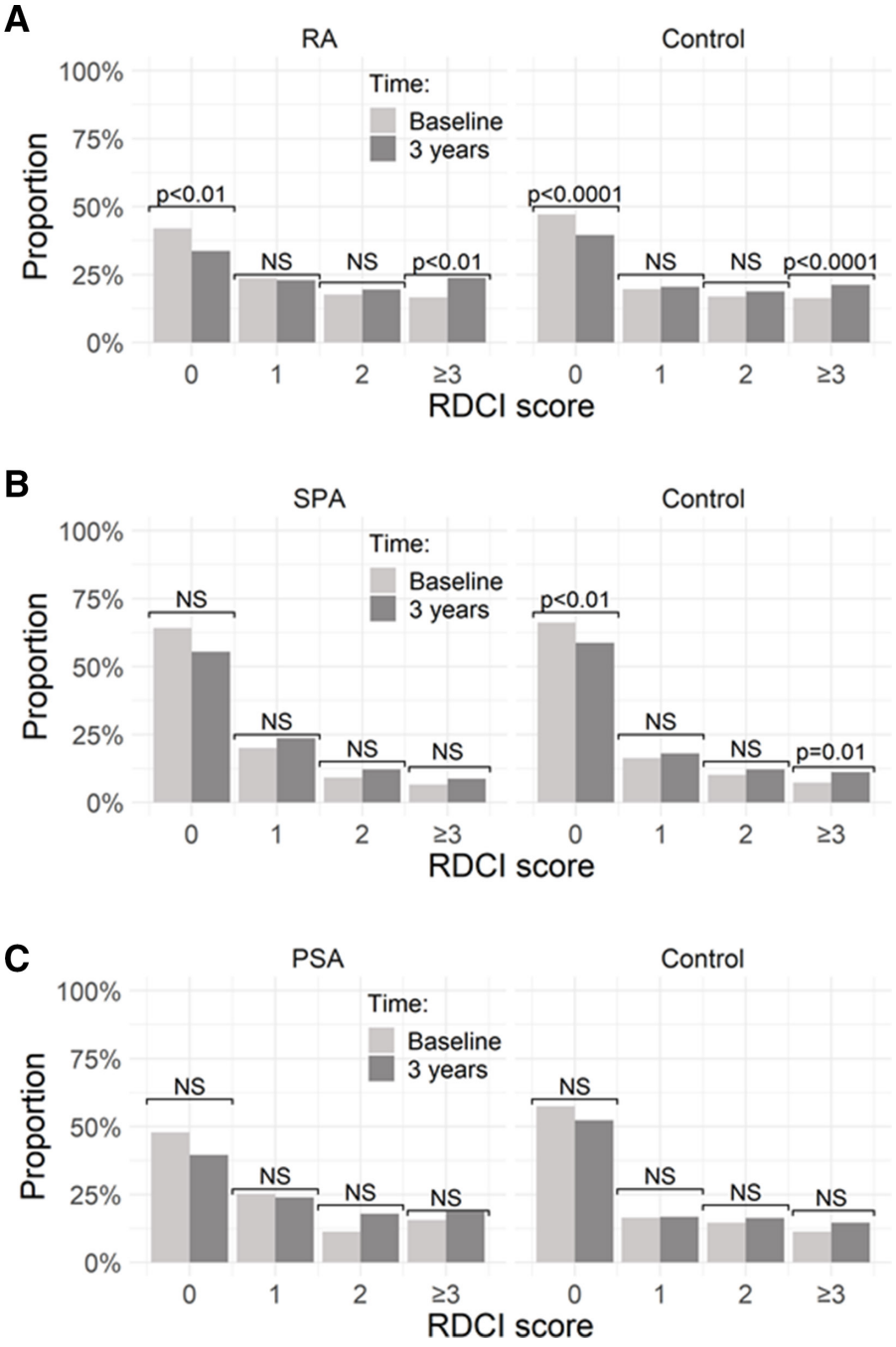

Figure 2 Evolution in RDCI-score for RA (A), SPA (B) and PSA (C) and their controls over the 3-year study period. NS, non-significant; PsA, psoriatic arthritis; RA, rheumatoid arthritis; RDCI, Rheumatic Disease Comorbidity Index; SpA, spondyloarthritis.

cancer types. In our study, malignancy incidence rates were numerically lower for RA, and to a lesser extent for SpA cases, while elevated in PsA cases. This confirms previous findings in PsA.[28] This study is of course limited by a small population with a relatively short follow-up duration in terms of cancer incidence. Literature is not conclusive about the relation between malignancies and inflammatory rheumatic diseases.[29–31]

Pain medication was prescribed frequently to patients with a chronic inflammatory condition in our study. Around 70% of patients were prescribed at least once pain medication consisting of NSAIDs, tramadol or paracetamol, but excluding other opioids. Pain management by these types of medication is prevalent as pain levels remain high even in patients under the sustained clinical control.[32] The prescription rate by GPs of opioids, even with the exclusion of tramadol, was strikingly high both for patients with RA, SpA and PsA, but also for the control population. Our data show that around 9% of this segment of the Belgian population receives at least once over a 3-year period an opioid prescription. This confirms the global opioid pandemic, also present in

Table 2 Person-years and 3-year incidence of the eight considered comorbidity types in patients with rheumatic conditions and controls

Type of comorbidity	Patients at risk (person-years)	No (incidence per 1000 person-years)	Controls at risk (person-years)	No (incidence per 1000 person-years)	P value
RA					
Lung disease	635 (1710.8)	28 (16.37)	2600 (6644.6)	87 (13.09)	0.307
Cardiovascular disease	618 (1644.5)	**40 (24.32)**	2472 (6310.1)	**104 (16.48)**	**0.035**
Hypertension	563 (1482.6)	43 (29.00)	2328 (5806.9)	121 (20.84)	0.059
Fracture of spine/hip/leg	696 (1910.2)	13 (6.81)	2770 (7183.7)	42 (5.85)	0.662
Diabetes mellitus	666 (1779.7)	31 (17.42)	2689 (6891.8)	81 (11.75)	0.058
Digestive (ulcer or stomach problem	610 (1632.6)	24 (14.70)	2492 (6340.3)	80 (12.62)	0.512
Malignancy	718 (1962.5)	16 (8.15)	2876 (7402.4)	95 (12.83)	0.079
Depression	645 (1761.8)	13 (7.38)	2595 (6645.8)	73 (10.98)	0.180
SpA					
Lung disease	212 (569.5)	5 (8.78)	852 (2130.3)	25 (11.74)	0.542
Cardiovascular disease	217 (582.1)	4 (6.87)	855 (2137.8)	14 (6.55)	0.917
Hypertension	211 (568.8)	4 (7.03)	835 (2082.1)	26 (12.49)	0.262
Fracture of spine/hip/leg	226 (612.1)	3 (4.90)	904 (2290.9)	6 (2.62)	0.357
Diabetes mellitus	222 (601.5)	2 (3.33)	877 (2195.7)	16 (7.29)	0.279
Digestive (ulcer or stomach problem)	193 (501.7)	11 (21.93)	809 (2007.9)	33 (16.44)	0.409
Malignancy	225 (609.3)	2 (3.28)	903 (2270.6)	18 (7.93)	0.193
Depression	210 (568.8)	3 (5.27)	844 (2118.4)	14 (6.61)	0.735
PsA					
Lung disease	145 (385.5)	4 (10.38)	591 (1415.3)	19 (13.43)	0.676
Cardiovascular disease	152 (394.2)	8 (20.29)	608 (1457.4)	16 (10.98)	0.133
Hypertension	143 (377.9)	4 (10.58)	583 (1397.2)	15 (10.74)	0.992
Fracture of spine/hip/leg	158(424)	0 (0)	634 (1551.7)	4 (2.58)	0.300
Diabetes mellitus	156(411)	4 (9.73)	630 (1530.9)	11 (7.19)	0.567
Digestive (ulcer or stomach problem)	137 (357.2)	4 (11.2)	572 (1367.5)	14 (10.24)	0.831
Malignancy	157 (412.5)	6 (14.55)	649 (1454.2)	10 (6.88)	0.086
Depression	134 (360.3)	4 (11.1)	596 (1441.7)	9 (6.24)	0.320

Statistically significant values are indicated in bold.
RA, Rheumatoid arthritis; PsA, psoriatic arthritis; SpA, spondyloarthritis.;

Europe.[33 34] Furthermore, as our data only registers electronical prescriptions by GPs, this is likely to be an underestimation of the true prescription proportion.

A first strength of our study is that we used data of the Intego registry which embodies 2.3% of the Flemish population. It is representative of the Flemish population in terms of age and sex. Moreover, quality controls are in place before GP practices are accepted. Further external validation has been performed by means of national and international comparisons.[17] Intego also offers an opportunity to compare cases with controls. However, medication registration is not complete as shown by previous analyses,[35] because only electronic prescriptions by a GP are registered. However, as the same is true for cases and controls, this bias should be balanced in the different populations. Moreover, the longitudinal data from an extensive period enabled us to investigate disease incidences, trends in comorbidity incidence in a newly diagnosed population, which goes beyond the typical cross-sectional nature and study population of many studies. Rheumatologists are responsible for diagnosing rheumatic diseases; thus, some heterogeneity might exist of course in coding practices as input of data is done in this case by GPs. Therefore, two experienced rheumatologists have explored the keywords registered by the GPs and mapped to IPCP-2 codes L88 and L99 to further validate the diagnoses. Given the Belgian healthcare system, we expect that the recording of comorbidities via a GP

Table 3 Prevalent medication use after 3-year follow-up in RA, SpA and PsA patients versus controls

Pain medication	RA	RA control	SpA	SpA control	PsA	PsA control
No of patients	738	2952	229	916	167	668
Glucocorticoids	241 (33%)	348 (12%)	29 (13%)	70 (8%)	47 (28%)	67 (10%)
NSAIDs	455 (62%)	1156 (39%)	161 (70%)	340 (37%)	114 (68%)	267 (40%)
Opioids*	109 (15%)	263 (9%)	31 (14%)	53 (6%)	24 (14%)	45 (7%)
Tramadol	87 (12%)	150 (5%)	22 (10%)	28 (3%)	16 (10%)	26 (4%)
Paracetamol	233 (32%)	598 (20%)	63 (28%)	165 (18%)	51 (31%)	141 (21%)
Total pain medication	506 (69%)	1409 (48%)	172 (75%)	407 (44%)	121 (72%)	309 (46%)
Polypharmacy	448 (61%)	1057 (36%)	94 (41%)	209 (23%)	98 (59%)	205 (31%)

Total pain medication is the sum of NSAIDs, tramadol and paracetamol. Polypharmacy was defined as the prescription of ≥5 different medications in the first 3 years of follow-up.
*Excluding tramadol. All analgesics were prescribed significantly more often in cases than controls.
NSAIDs, non-steroidal anti-inflammatory drug; PsA, psoriatic arthritis; RA, Rheumatoid arthritis; SpA, spondyloarthritis.

registry is outperforming recording by rheumatologists. A final strength is the use of the RDCI, a comorbidity index specific for rheumatic diseases, compared with other widely used generic comorbidity indices as the Charlson and the Functional Comorbidity index.[13 16 36] However, the RDCI is not validated specifically for PsA or SpA, and it does not cover all disease specific comorbidities including obesity or metabolic syndrome.

This study also has limitations. Intego is a registry without systematic monitoring of data registration. Crude incidence rates or prescription rates could be influenced by the quality of registration. For example, some comorbidities might be missing as patients do not necessarily frequent the same GP in Belgium. However, we tried to limit this bias by selecting a case–control design. Study samples for PsA and SpA are limited in comparison with larger registries and unprecise initial diagnostic coding might also be partly responsible for this in contrast to RA. The relatively low number of PsA and SpA cases might also affect the identification of rare comorbidities. Several different types of bias are inherent in a registry study of chronic diseases. The prevalence of some comorbidities might be overestimated by diagnostic bias. Patients with a chronic rheumatic condition could be screened more intensively for comorbidities which are more prevalent than in a control population. Reporting bias could also occur as patients might be diagnosed more frequently with comorbidities known to be associated with the specific inflammatory pathology. Additionally, we did not match cases and controls on follow-up time in the study, which could also affect this reporting bias. However, to minimise this bias, we restricted ourselves to a 3-year follow-up time.

In conclusion, this study has reported incidence rates and the burden of comorbidity for patients recently diagnosed with a chronic inflammatory condition. Rheumatologists should consider management of comorbidities as one of the primary tasks involved in the care of a patient. Collaboration with other healthcare providers including nurses, primary care providers and other specialists is key to optimising a holistic management for every patient. Therefore, developing, implementing and evaluating common standardised programmes to detect, manage and prevent comorbidities in daily clinical practice is needed, especially as the comorbidity burden seems to increase and an effect on the healthcare system becomes apparent.[37 38] Although some evidence-based guidelines and recommendations on comorbidity management to advance the care of patients with a chronic inflammatory condition exist, many questions remain unanswered.[39 40]

Twitter Sofia Pazmino @sophie_33pl and Diederik De Cock @DiederikDeCock

Acknowledgements We would like to thank all GPs and patients from INTEGO.

Contributors VS, SP and DDC planned the analysis, PV analysed the data, VS, SP and DDC drafted the manuscript; all authors revised and approved the manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The Intego procedures were approved by the ethical review board of the KULeuven Faculty of Medicine (no. ML 1723) and by the Belgian Privacy Commission (no. SCSZG/13/079).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data may be obtained from a third party (https://intego.be) and are not publicly available.

ORCID iDs
Sofia Pazmino http://orcid.org/0000-0001-8579-6914
P Verschueren http://orcid.org/0000-0002-0340-3580
René Westhovens http://orcid.org/0000-0002-3432-3073
Diederik De Cock http://orcid.org/0000-0002-5656-6236

REFERENCES

1 Sebbag E, Felten R, Sagez F, *et al*. The world-wide burden of musculoskeletal diseases: a systematic analysis of the world Health organization burden of diseases database. *Ann Rheum Dis* 2019;78:844–8.

2 Baillet A, Gossec L, Carmona L, *et al*. Points to consider for reporting, screening for and preventing selected comorbidities in chronic inflammatory rheumatic diseases in daily practice: a EULAR initiative. *Ann Rheum Dis* 2016;75:965–73.
3 Moltó A, Dougados M. Comorbidities in spondyloarthritis including psoriatic arthritis. *Best Pract Res Clin Rheumatol* 2018;32:390–400.
4 Shah K, Paris M, Mellars L, *et al*. Real-world burden of comorbidities in US patients with psoriatic arthritis. *RMD Open* 2017;3:e000588.
5 Moltó A, Etcheto A, van der Heijde D, *et al*. Prevalence of comorbidities and evaluation of their screening in spondyloarthritis: results of the International cross-sectional ASAS-COMOSPA study. *Ann Rheum Dis* 2016;75:1016–23.
6 Haque N, Lories RJ, de Vlam K. Comorbidities associated with psoriatic arthritis compared with Non-psoriatic spondyloarthritis: a cross-sectional study. *J Rheumatol* 2016;43:376–82.
7 Dougados M, Soubrier M, Antunez A, *et al*. Prevalence of comorbidities in rheumatoid arthritis and evaluation of their monitoring: results of an international, cross-sectional study (COMORA). *Ann Rheum Dis* 2014;73:62–8.
8 Michaud K, Wolfe F. Comorbidities in rheumatoid arthritis. *Best Pract Res Clin Rheumatol* 2007;21:885–906.
9 Blake T, Gullick NJ, Hutchinson CE, *et al*. Psoriatic disease and body composition: a systematic review and narrative synthesis. *PLoS One* 2020;15:e0237598.
10 Bavière W, Deprez X, Houvenagel E, *et al*. Association between comorbidities and quality of life in psoriatic arthritis: results from a multicentric cross-sectional study. *J Rheumatol* 2020;47:369–76.
11 Nikiphorou E, Ramiro S, van der Heijde D, *et al*. Association of comorbidities in spondyloarthritis with poor function, work disability, and quality of life: results from the assessment of spondyloarthritis International Society comorbidities in spondyloarthritis study. *Arthritis Care Res* 2018;70:1257–62.
12 Stouten V, Westhovens R, De Cock D, *et al*. Having a co-morbidity predicts worse outcome in early rheumatoid arthritis despite intensive treatment: a post hoc evaluation of the pragmatic randomized controlled CareRA trial. *Rheumatology* 2021. doi:10.1093/rheumatology/keaa841. [Epub ahead of print: 12 Jan 2021].
13 England BR, Sayles H, Mikuls TR, *et al*. Validation of the rheumatic disease comorbidity index. *Arthritis Care Res* 2015;67:865–72.
14 Biggioggero M, Mesina F, Favalli EG. The use of rheumatic disease comorbidity index for predicting clinical response and retention rate in a cohort of rheumatoid arthritis patients receiving tumor necrosis factor alpha inhibitors. *Biomed Res Int* 2019;2019:6107217
15 Iannone F, Salaffi F, Fornaro M, *et al*. Influence of baseline modified rheumatic disease comorbidity index (mRDCI) on drug survival and effectiveness of biological treatment in patients affected with rheumatoid arthritis, spondyloarthritis and psoriatic arthritis in real-world settings. *Eur J Clin Invest* 2018;48:e13013.
16 Putrik P, Ramiro S, Lie E, *et al*. Deriving common comorbidity indices from the MedDRA classification and exploring their performance on key outcomes in patients with rheumatoid arthritis. *Rheumatology* 2018;57:548–54.
17 Truyers C, Goderis G, Dewitte H, *et al*. The Intego database: background, methods and basic results of a Flemish general practice-based continuous morbidity registration project. *BMC Med Inform Decis Mak* 2014;14:48.
18 Bartholomeeusen S, Kim C-Y, Mertens R, *et al*. The denominator in general practice, a new approach from the Intego database. *Fam Pract* 2005;22:442–7.
19 Soler J-K, Okkes I, Wood M, *et al*. The coming of age of ICPC: celebrating the 21st birthday of the International classification of primary care. *Fam Pract* 2008;25:312–7.
20 Brämer GR. International statistical classification of diseases and related health problems. tenth revision. *World Health Stat Q* 1988;41:32–6.
21 Kim H-J, Fay MP, Feuer EJ, *et al*. Permutation tests for joinpoint regression with applications to cancer rates. *Stat Med* 2000;19:335–51.
22 Bandyopadhyay D, Banerjee U, Hajra A. Trends of cardiac complications in patients with rheumatoid arthritis: analysis of the United States national inpatient sample; 2005-2014. *Curr Probl Cardiol* 2019;100455.
23 Norton S, Koduri G, Nikiphorou E, *et al*. A study of baseline prevalence and cumulative incidence of comorbidity and extra-articular manifestations in RA and their impact on outcome. *Rheumatology* 2013;52:99–110.
24 Buleu F, Sirbu E, Caraba A, *et al*. Heart involvement in inflammatory rheumatic diseases: a systematic literature review. *Medicina* 2019;55:249.
25 Ferguson LD, Linge J, Dahlqvist Leinhard O. Psoriatic arthritis is associated with adverse body composition predictive of greater coronary heart disease and type 2 diabetes propensity - a cross-sectional study. *Rheumatology* 2020.
26 Lukmanji A, Basmadjian RB, Vallerand IA, *et al*. Risk of depression in patients with psoriatic disease: a systematic review and meta-analysis. *J Cutan Med Surg* 2021;25:1203475420977477.
27 Fragoulis GE, Evangelatos G, Tentolouris N, *et al*. Higher depression rates and similar cardiovascular comorbidity in psoriatic arthritis compared with rheumatoid arthritis and diabetes mellitus. *Ther Adv Musculoskelet Dis* 2020;12:1759720X20976975.
28 Westhovens I, Lories RJ, Westhovens R, *et al*. Anti-Tnf therapy and malignancy in spondyloarthritis in the Leuven spondyloarthritis biologics cohort (BIOSPAR). *Clin Exp Rheumatol* 2014;32:71–6.
29 Vaengebjerg S, Skov L, Egeberg A. Incidence, and risk of cancer in patients with psoriasis and psoriatic arthritis: a systematic review and meta-analysis. *JAMA Dermatol* 2020;156:421–9.
30 Karmacharya P, Shahukhal R, Ogdie A. Risk of malignancy in spondyloarthritis: a systematic review. *Rheum Dis Clin North Am* 2020;46:463–511.
31 De Cock D, Hyrich K. Malignancy and rheumatoid arthritis: epidemiology, risk factors and management. *Best Pract Res Clin Rheumatol* 2018;32:869–86.
32 Van der Elst K, Verschueren P, De Cock D, *et al*. One in five patients with rapidly and persistently controlled early rheumatoid arthritis report poor well-being after 1 year of treatment. *RMD Open* 2020;6:e001146.
33 Wertheimer G, Mathieson S, Maher CG, *et al*. The prevalence of opioid analgesic use in people with chronic noncancer pain: systematic review and meta-analysis of observational studies. *Pain Med* 2021;22:506–17.
34 Jani M, Dixon WG. Opioids are not just an American problem. *BMJ* 2017;359:j5514.
35 Vaes B, Ruelens C, Saikali S, *et al*. Estimating the prevalence of diabetes mellitus and thyroid disorders using medication data in Flanders, Belgium. *Eur J Public Health* 2018;28:193–8.
36 Nikiphorou E, de Lusignan S, Mallen C, *et al*. Prognostic value of comorbidity indices and lung diseases in early rheumatoid arthritis: a UK population-based study. *Rheumatology* 2020;59:1296–305.
37 Nikiphorou E, Norton S, Carpenter L, *et al*. Secular changes in clinical features at presentation of rheumatoid arthritis: increase in comorbidity but improved inflammatory states. *Arthritis Care Res* 2017;69:21–7.
38 Nikiphorou E, Morris S, Dixey J, *et al*. The effect of disease severity and comorbidity on length of stay for orthopedic surgery in rheumatoid arthritis: results from 2 UK inception cohorts, 1986-2012. *J Rheumatol* 2015;42:778–85.
39 Kvien TK, Balsa A, Betteridge N, *et al*. Considerations for improving quality of care of patients with rheumatoid arthritis and associated comorbidities. *RMD Open* 2020;6:e001211.
40 Agca R, Heslinga SC, Rollefstad S, *et al*. EULAR recommendations for cardiovascular disease risk management in patients with rheumatoid arthritis and other forms of inflammatory joint disorders: 2015/2016 update. *Ann Rheum Dis* 2017;76:17–28.