Orthopaedic Surgery Trend in Rheumatoid Arthritis – results of the National Registry of Hospitalised Patients (CMBD) over a 17 year period (1999-2015). TREND-AR Study.

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Abstract:

Objective: Analyse the trend of orthopaedic surgery (OS) rates on patients with rheumatoid arthritis.

Methods: Retrospective observational study based on information provided by the Spanish National System of Hospital Data Surveillance. All hospitalisations of patients with RA for Orthopedicic Surgery (total hip arthroplasty -THA-, total knee arthroplasty -TKA-, arthrodesis and upper limb arthroplasty -ULA-) during the period 1999-2015 were analysed. The age-adjusted rate was calculated. Generalised linear models were used for trend analysis.

Results: There were 21,088 OS in patients over 20 with (77.9% women). OS rate adjusted by age was 754.63/100,000 RA-patients*year (women 707.4; men 861.1). Neither an increasing nor decreasing trend noted for the global OS included. However, we noted trend and age interacted, so in the age ranges 20-40 and 40-60 years an annual reduction of 2.69% and 2.97%, respectively was noted. Whereas in the age ranges over 80 and 60-80 years we noted an annual increase of 5.40% and 1.09%, respectively. The average age at time of OS increased 5.5 years during the period analysed. For specific surgeries, a global annual reduction was noted in rates for arthrodesis. In THA, there was an annual reduction in patients under 80 years. In TKA and ULA, there was an annual reduction in patients under 60.

Conclusions. Although the overall OS rate has not changed, there is a decrease in the rate of arthrodesis at all ages, THA in patients under 80 years of age, as well as TKA and ULA in patients under 60 years of age.

Keywords

Orthopaedic Surgery

Rheumatoid Arthritis

Trend

Epidemiology

Conflict of interest

None declared.

Mini abstract

Our aim was to analyse the trend in orthopaedic surgery rates in RA patients over a long period of time. We have noted a drop in surgery rates on patients under 60 and an increase in those over that age.

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Statement of Human and Animal Rights

This article does not contain any studies involving human participants or animals that were performed by the authors. For this type of study, formal consent was therefore not required.

Orthopedic Surgery Trends in Rheumatoid Arthritis – study of the National Registry for Hospitalized Patients (CMBD) over a 17-year period (1999-2015). TREND-AR Study.

INTRODUCTION

Rheumatoid arthritis (RA), a systemic auto-immune disease mainly affecting diarthrodial joints, is one of the most debilitating forms of arthritis and affects approximately 0.5-2% of the world's population. (1). RA is characterised by functional incapacity, joint damage, reduced quality of life and early death. RA is 2 to 4 times more common in women than men (2). In serious or uncontrolled RA, inflammation may lead to irreparable joint damage (1, 3, 4). In terminal stages, the only treatment available for joint damage is surgical replacement of the damaged joint or arthrodesis (5). A recent UK study showed that the accumulated disease burden, based on DAS28 scoring, during the first 5 years post-RA diagnosis predicted the need for major joint surgery. Moreover, the highest surgery incident rates were observed among patients with moderate and high disease activity (3). These findings support the importance of aggressive early treatment emphasized in current RA treatment guidelines. In older RA patient cohorts, over 50% of patients were found to require joint surgery during the course of their disease (6, 7).

RA treatment has progressed significantly in the last 20 years, due to early application and a strategy aimed at achieving disease remission. Advances in the understanding of RA pathogenesis have evolved significantly during this period and have led to the introduction of biological therapies and new strategies in RA management like 'Treat to Target' (T2T) (8), although it is not clear whether this has translated in lower rates of orthopedic surgery (OS). The majority of studies suggest a reduction in OS incidence post-introduction of biological therapies (5, 9-13). However, studies have also been published showing no changes or even an increase in the number of OS (5, 12, 14, 15).

Using data from the national registry of hospitalizations in Spain (CMBD), our aim was to research the likely impact of this new RA treatment paradigm on the

incidence rate and trend of certain OS , such as total hip arthroplasty (THA), total knee arthroplasty (TKA), arthrodesis and upper limb arthroplasty (ULA) in RA patients.

Patients and methods

Retrospective populational study based on analysing the administrative data collected by a Basic Minimum Set of Data (CMBD – Spanish acronym) from all hospitals in Spain provided by the Ministry for Health. This database encompasses administrative data (date of admission, hospital, financing system, place of residence and others), demographic data (gender, age, town, region, death while hospitalized), clinical data (personal history and diagnosis on discharge) and procedures (e.g., tests or interventions performed during hospitalization), of all hospitalizations in Spain. This database employs a uniform code for all hospital discharge reports and its completion is compulsory for all hospitals both private and public.

The CMBD uses the clinical codes of the Spanish version of the 9th International Classification of Diseases (ICD-9), includes admission to any national hospital (public or private) and is estimated to cover 99.5% of the Spanish population (16). We have assumed that the remaining population and hospitalization information not included in the study follow the same epidemiological characteristics.

We requested from the Ministry for Health (ICD-9: 714.0- 714.9) data on all hospitalizations in which the primary or secondary diagnosis was RA during the period 1 January 1999 to 31 December 2015. The different OS were identified via their respective codes (ICD-9) involving any procedure position: THA 81.50-81.53, TKA 81.54 -81.55, arthrodesis of upper or lower limb joints 81.20-81.29 and ULA: elbow and shoulder 81.80-81.88 and hands 81.70-81.79. Available administrative, demographic and clinical data were included for each registry. The Charlson index was obtained through the ICD-9 codes, following the methodology recommended by Deyo RA et al (17). The formula used by this methodology is the original (18). In general, the absence of comorbidity corresponds to 0 or 1 point, low comorbidity 2 points and high comorbidity more than 3 points. Age groups were established as follows: 20-39 years. 40-59 years. 60-79 years and over 80 years.

Statistical methods

For the total OS and for each of those included (THA, TKA, ULA, and arthrodesis) crude yearly rates were calculated (/100,000 RA-patients*year) by gender and age group. The numerator of this rate is the number of cases registered at the CMBD and the risk population denominator. The risk population was estimated based on the national census provided by the National Statistics Institute (INE – Spanish acronym) and assumed an RA prevalence of 0.5% (both genders): 0.8% in women and 0.2% in men. This RA prevalence is the same as that estimated in the EPISER study (19).

Adjusted rates using the direct method were also calculated according to age, estimated with a 95% confidence interval (CI 95%) using 2015 as the reference population.

The change in annual rates (linear trend) was analysed via Generalized Linear Models (GLM) with a Poisson distribution or negative binomial distribution in cases of over-dispersion. To assess trends according to age groups, the models include a first-tier level of interaction effect. Estimated rates are presented for models with their corresponding 95% confidence level. Analyses were performed for all samples and strata according to gender.

Quantitative data are described with average and standard deviation. Categorical data are expressed with absolute and relative frequencies. In the univariant analysis, the Chi-squared test was performed for qualitative variables, and the Student-T-test or the Mann-Whitney U test, according to data distribution, in the case of quantitative variables. All tests were considered bilateral, with a significance level of $p<0.05$.

Statistical analysis was performed using IBM SPSS 24.0. Epidat 4.2 and Stata 14 packages.

This study was approved by the Hospital U. Fundación Alcorcón Ethics Research Committee (reference number 17/48).

RESULTS

There were a total of 338,343 RA patient hospitalizations throughout the 17-year study period corresponding to a total of 176,097 patients (117,985 women and 58,112 men). 21,088 (6.62%) involved hospitalizations for OS, 8,709 (2.6%) THA, 9,006 (2.7%) TKA, 1,372 (0.4%) arthrodesis and 2,230 (0.7%) ULA. By gender, 16,432 (77.92%) were women and 4,656 (22.07%) men. The average age was 65.03 (SD 13.26) years. The average stay was 10.97 (SD 12.55) days. The Charlson Index average was 1.26 (SD 0.71); 1.34 (SD 0.84) men and 1.23 (SD 0.66) women ($p<0.001$). A total of 125 (0.6%) died during hospitalization; 38 (0.81%) were men and 87 (0.52%) women ($p=0.079$). Table 1 shows the main characteristics according to OS type.

The average age (of all OS) increased by 5.5 years during this 17-year study period, from 61.8 years (SD 13.8) in 1999 to 67.3 years (SD 12.8) in 2015 ($p<0.05$). Figure 1 shows the evolution of average age for the different surgeries.

The age-adjusted rate of OS total was 754.63/100,000 RA-patients*year (95%CI 713.15 to 798.04) during the study period, being greater in men (861.18; 95%CI 761.85 to 970.97) than in women (707.49; 95%CI 663.57 to 753.72). The crude and adjusted rates per year are shown in table 2 (Figures 1 and 2 of the Supplementary Material section show the results by gender).

Neither an increasing nor decreasing trend in the global rate of OS was observed (IRR 1.002; 95%CI 0.991 to 1.014) during the study period (Figure 2). However, we did find a statistically significant correlation with age. Thus, by age strata, the results were as follows: in the over 80 and 60-80 year groups, an annual increase of 5.40% (IRR 1.054; 95%CI 1.04 to 1.068) in the former and 1.1% (IRR 1.011; 95%CI 1.003 to 1.019) in the latter were recorded. In the age strata 20-40 years and 40-60 years, an annual decrease was observed of 2.69 % (IRR 0.973; 95%CI 0.99 to 1.017) and 2.97% (IRR 0.973; 95%CI 0.962 to 0.979), respectively. (Table 3) (Figure 2).

Hip arthroplasty:

Regarding hip arthroplasty in women, there was a non-significant annual age-adjusted rate reduction of 0.69% (IRR 0.993; 95%CI 0.98 to 1.006), whereas in men there was a non-significant annual increase of 0.42% (IRR 1.004 95%CI 0.994 to 1.014). By age strata, we observed an annual reduction of 2.05% in the 20-40 year range (IRR

0.979; 95%CI0.966 to 0.997), an annual reduction of 3.55% (IRR 0.964; 95%CI 0.955 to 0.974) in the 40-60 year range, and an annual reduction of 0.98% (IRR 0.99; 95%CI 0.981 to 0.999) in the 60-80 year range. Lastly, in patients over 80 there was an annual increase of 4.64% (IRR 1.046; 95%CI 1.031 to 1.062); (Table 3) (Figure 3) (Figures 1 and 2 of the Supplementary Material section show results by gender).

Knee arthroplasty:

Annual age-adjusted rates by age for knee prostheses in men increased 1.51% (IRR 1.015; 95%CI 1.004 to 1.027) while in women there was a non-significant increase of 0.65% (IRR 1.006; 95%CI 0.993 to 1.02). By age range it was noted that in the 20-40 age range there was an annual reduction of 3.79% (IRR 0.962; 95%CI 0.946 to 0.979), in the 40-60 age range the annual reduction was 2.86% (IRR 0.971; CI95% 0.961 to 0.982), in the 60-80 age range there was an annual increase of 2.56% (IRR 1.026; 95%CI 1.018 to 1.034) and in the over 80s age range an annual increase of 6.75% (IRR 1.067; 95%CI 1.043 to 1.092); (Table 3 and Figure 3) (Figures 1 and 2 of the Supplementary Material section show the results by gender)

Arthrodesis

Annual age-adjusted rates by age for arthrodesis dropped 2.89% (IRR 0.971; 95%CI 0.944 to 0.999) in men and 3.04 % (IRR 0.97; 95%CI 0.957 to 0.983) in women; (Table 3 and Figure 3) (Figures 1 and 2 of the Supplementary Material section show the results by gender).

Upper limb arthroplasty:

In the annual age-adjusted rates by age for upper limb prosthesis there was an increase of 1.58% (IRR 1.016; 95%CI 1.001 to 1.031) in women, while in men there was a non-significant increase of 1.78% (IRR 1.018; 95%CI 0.989 to 1.047). By age strata, it we observed a non-significant annual reduction of 1.57% (IRR 0.984; 95%CI 0.954-1.015) in the 20-40 year range, a non-significant annual reduction of 1.05 (IRR 0.989;

95%CI 0.968 to 1.011) in the 40-60 year range, an annual increase of 3.29% (IRR 1.033; 95%CI 1.019 to 1.048) in the 60-80 year range, and an annual increase of 0.68% (IRR 1.107; 95%CI 1.063 to 1.153) in the over-80s age range; (Table 3 and Figure 3) (Figures 1 and 2 of the Supplementary Material section show the results by gender).

DISCUSSION

A long period of time was analysed in this national level study (1999-2015), enabling us to research trends in certain OS in RA patients throughout Spain. The demographic characteristics (age and sex) of the sample were as expected. The initial hypothesis of our study was to assess whether the introduction of new therapeutic strategies in treating RA patients, in tandem with strict disease controls and the use of biological therapies during the last 20 years, had made a favorable impact on OS rates. Based on our analysis, the answer is probably affirmative. Although the overall OS rate has not changed, the data supporting this conclusion is reflected in the global reduction in arthrodesis rates, measuring approximately 3% a year in both men and women. In addition, a reduction in THA in the under- duction in TKA and ULA rates in the under-60s and an average age increase of 5.5 years of when OS were performed in 1999 in relation to 2015. Furthermore, these results contrast with others from the 1980s, in which an important increase in OS was observed in the general population (20-23).

In our study we found that in the under-60s age strata there was a reduced trend in all OS rates (THA, TKA, arthrodesis, ULA). Moreover, this reduction in THA was also observed in the 60-80 year range. This trend may reflect observations by different studies on the reduction in the use of healthcare resources in RA patients during the last 20 years. This was observed chiefly in the topic analysed in this paper, namely OS (5, 10, 24-28) and the number of hospitalizations (29, 30). Nevertheless, the apparent association with the introduction of T2T and biological treatments is weak (31). Although we can confirm the time association with this trend, our study design does not allow us to establish any direct link with the introduction of strategies of strict disease activity controls or the use of biological therapies, since these variables were not included in our database. In our study, however, we noticed that surgery rates for

TKA and ULA in patients over 60, and for THA in those over 80 continued to rise. This probably reflects the fact that these procedures are established treatments for hip and knee arthrosis. Furthermore, the global rates for the entire population have increased considerably since the beginning of the 1980s in many countries with aging populations (20-23). Despite advances in medical treatment, overall population aging, among other causes, means there is a growing number of elderly RA patients with degenerative joint damage secondary to RA. These patients typically undergo a larger number of age-related surgeries to preserve their function and quality of life (28). Nevertheless, another analysis that examined 345,000 hospitalizations, as well as 18,000 deceased RA patients, not only determined the average age of hospitalized patients, but also that the age at death was around 5 years greater during this same time period.

As with other studies (32), of the 4 surgeries analysed in our study, only arthrodesis showed a global reduction trend in both men and women. In part, the reason for this decrease in arthrodesis rates stems from the fact that this particular surgical technique for joint replacement has improved substantially during the last 20 years. Currently, elbow, ankle, shoulder and other arthroplasties are routinely performed, rather than arthrodesis of these joints.

In recent decades, RA patients seem to have received more positive prognoses. This improvement may reflect both early diagnosis and correct treatment, as opposed to any changes in the aggressive characteristics of this disease (33). In fact, some variables and non-modifiable sociodemographic factors separately associated with OS remain similar to those identified previously. Unlike those reported on in other papers (6, 28, 33-36), the men with RA in our study had an older crude and age-adjusted rate than women. This may reflect a difference in the attention paid to male and female patients, with the former group typically demanding less. Another possible explanation is that the RA prevalence estimation of 0.2% in men in Spain (19) is too low.

OS in RA patients can be considered a disease treatment failure marker. In prospective follow-up studies of patients with recent RA onset, the prevalence of OS during disease progression was 17% over a 5-year follow-up period (37) and 48% during a 16-year follow-up period (38). These prospective studies were performed in

the era prior to the availability of biological therapies. This situation has very likely undergone a considerable improvement.

Our study has both strengths and limitations, and its main strength lies in the large sample size over a longer period of time together with a standardised methodology maintained throughout the study period. We believe the duration of the study period coupled with the exhaustive data from the CMBD provide sufficient internal validity, which in quantitative terms, can be observed in the constant frequency detected each year. This is also true of its qualitative aspects and in its identification of age groups at greater risk.

We should highlight the limitations of our research: this was a retrospective observational study, which prevented us from establishing any causal relationships based on the results obtained. Moreover, even though the CMBD provided information on a hospital network encompassing over 99% of the Spanish population, some OS may have eluded the capture area provided by the public hospital discharge registry. In addition, there may have been some coding disparities and/or problems. There is also the possibility of OS cases in RA patients in which RA has not correctly coded, which would result in an underestimation of our findings. Another important limitation is that the Spanish National Hospital (CMBD) hospitalization discharge database does not include any data related to patients' exact treatment. regimens

To summarize, we observed a global reduction trend for arthrodesis in THA in subjects under 80, and in TKA and ULA in subjects under 60 among RA patients in Spain. Likewise, we noted an increase in the average age at OS of 5.5 years during the period studied.

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Table 1: Description of the patients with RA who underwent an orthopaedic surgery, between 1999 and 2015.

	All OS	THA	TKA	AA	ULA
N (% of all hospitalisations)	21,088 (6.2)	8,709 (2.6)	9,006 (2.7)	1,372 (0.4)	2,230 (0.7)
Women (%)	16,432 (100)	6,545 (39.83)	7,117 (43.31)	1,118 (6.8)	1,846 (11.23)
Men (%)	4,656 (100)	2,164 (46.80)	1,889 (40.57)	254 (5.46)	384 (8.25)
Mean Age (SD)	65.02 (13.26)	66.57 (14.78)	65.97 (10.90)	55.90 (13.12)	59.93 (12.50)
Mean ALHS (SD)	10.97 (12.55)	13.48 (13.50)	10.73 (11.20)	6.69 (18.60)	4.54 (4.69)
Mean Charlson Index (SD)	1.26 (0.71)	1.33 (0.80)	1.25 (0.60)	1.08 (0.50)	1.13 (0.70)
In-hospital Exitus (%)	125 (0.60)	104 (1.20)	20 (0.20)	1 (0)	1 (0)

OS: Orthopaedic surgery; THA: Total Hip Arthroplasty; TKA: Total Knee Arthroplasty; AA: arthrodesis; ULA: Upper Limb Arthroplasty

Table 2: Crude and adjusted incidence per OS type in both genders.

		Number of OS				Crude IR/100,000 RA-patients*year				Age adjusted IR / 100.000 RA-patients*year			
Year	RA Population	THA	TKA	AA	ULA	THA	TKA	AA	ULA	THA	TKA	AA	ULA
1999	154,688	382	372	75	76	246.95	240.48	48.48	49.13	263.33	251.60	50.28	51.30
2000	156,458	507	395	81	85	324.05	252.46	51.77	54.33	347.22	262.29	54.99	56.96
2001	158,163	469	443	87	98	296.53	280.09	55.01	61.96	312.09	294.14	56.91	64.66
2002	164,981	539	497	84	128	326.70	301.25	50.92	77.58	359.93	323.87	54.92	83.67
2003	168,509	480	437	125	129	284.85	259.33	74.18	76.55	316.23	279.72	81.36	83.23
2004	171,559	465	493	90	132	271.04	287.36	52.46	76.94	301.18	309.22	57.13	84.16
2005	175,149	541	537	73	127	308.88	306.60	41.68	72.51	341.34	333.80	45.46	78.94
2006	178,059	543	576	79	159	304.96	323.49	44.37	89.30	339.29	347.07	48.32	96.81
2007	181,634	546	551	86	123	300.60	303.36	47.35	67.72	332.72	329.42	50.29	73.27
2008	184,555	500	559	86	128	270.92	302.89	46.60	69.36	297.44	328.53	49.97	74.76
2009	185,995	493	539	76	156	265.06	289.79	40.86	83.87	288.31	311.85	42.91	90.01
2010	186,762	516	527	86	155	276.29	282.18	46.05	82.99	298.56	300.76	48.75	87.88
2011	187,416	510	567	60	135	272.12	302.54	32.01	72.03	289.66	319.44	33.61	75.87
2012	187,508	547	564	56	132	291.72	300.79	29.87	70.40	306.70	314.00	30.72	72.96
2013	186,853	560	597	70	141	299.70	319.50	37.46	75.46	309.67	328.44	38.34	77.60
2014	186,298	554	698	87	167	297.37	374.67	46.70	89.64	301.62	379.66	47.16	90.81
2015	186,069	559	654	71	159	300.43	351.48	38.16	85.45	300.43	351.49	38.16	85.45

OS: Orthopaedic surgery; RA: Rheumatoid Arthritis; THA: Total Hip Arthroplasty; TKA: Total Knee Arthroplasty; AA: arthrodesis; ULA: Upper Limb Arthroplasty

Table 3: Orthopaedic surgery trend (THA, TKA, AA and ULA), by gender, age ranges and surgery type.

		Annual Trend (%)	IRR	95% CI		p-value
All OS	**Men**	0.74	1,007	0,998	1,017	0,137
	Women	0.17	1,002	0,990	1,014	0,781
	20-40 years	-2,69	0,973	0,959	0,987	<0.001
	40-60 years	-2,97	0,970	0,962	0,979	<0.001
	60-80 years	1.09	1,011	1,003	1,019	0,007
	>80 years	5,40	1,054	1,040	1,068	<0.001
THA	**Men**	0,42	1,004	0,994	1,014	0,412
	Women	-0,69	0,993	0,980	1,006	0,288
	20-40 years	-2,05	0,979	0,962	0,997	0,024
	40-60 years	-3,55	0,964	0,955	0,974	<0.001
	60-80 years	-0,99	0,990	0,981	0,999	0,028
	>80 years	4,64	1,046	1,031	1,062	<0.001
TKA	**Men**	1,51	1,015	1,004	1,027	0,01
	Women	0,65	1,006	0,993	1,020	0,352
	20-40 years	-3,79	0,962	0,946	0,979	<0.001
	40-60 years	-2,86	0,971	0,961	0,982	<0.001
	60-80 years	2,56	1,026	1,018	1,034	<0.001
	>80 years	6,75	1,067	1,043	1,092	<0.001
AA	**Men**	-2,89	0,971	0,944	0,999	0,045
	Women	-3,04	0,970	0,957	0,983	<0.001
ULA	**Men**	1,78	1,018	0,989	1,047	0,223
	Women	1,58	1,016	1,001	1,031	0,034
	20-40 years	-1,57	0,984	0,954	1,015	0,315
	40-60 years	-1,06	0,989	0,968	1,011	0,333
	60-80 years	3,30	1,033	1,019	1,048	<0.001
	>80 years	10,68	1,107	1,063	1,153	<0.001

IRR: Incidence Rate Ratio. OS: Orthopaedic surgery; RA: Rheumatoid Arthritis; THA: Total Hip Arthroplasty; TKA: Total Knee Arthroplasty; AA: arthrodesis; ULA: Upper Limb Arthroplasty

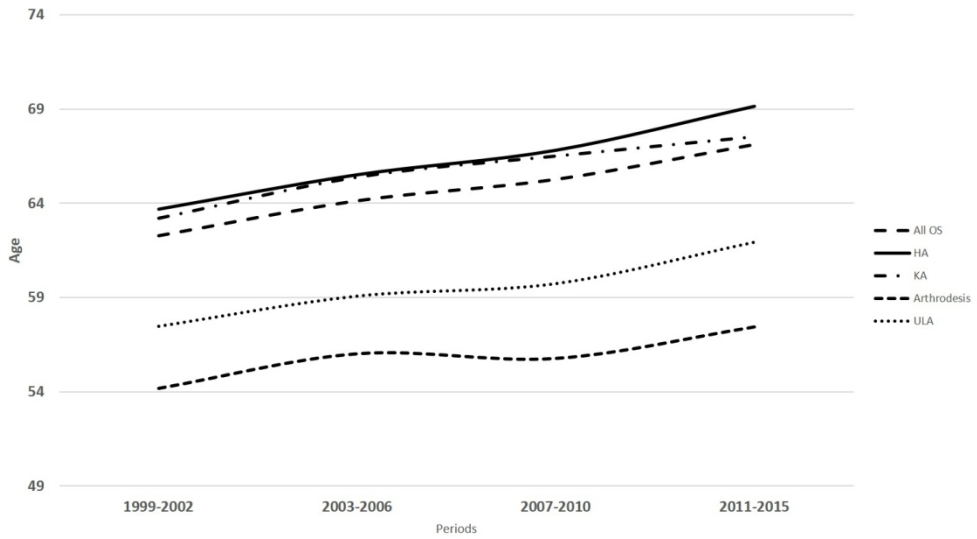

Figure 1: Evolution of average age between 1999-2015, globally and per surgery type.

261x145mm (150 x 150 DPI)

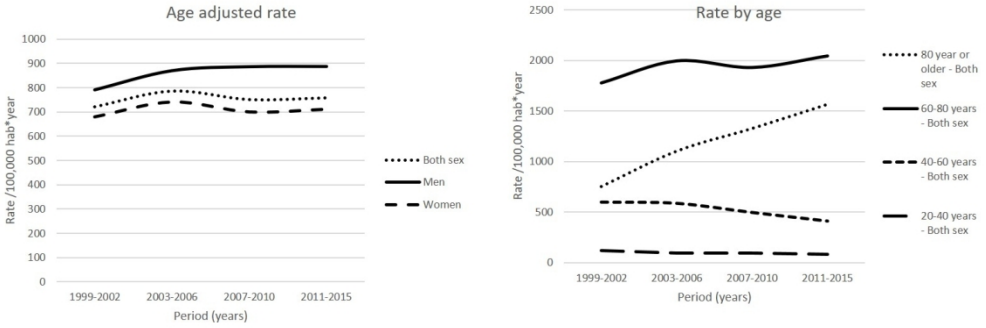

Figure 2: Trend of global orthopaedic surgery and by age ranges

269x94mm (150 x 150 DPI)

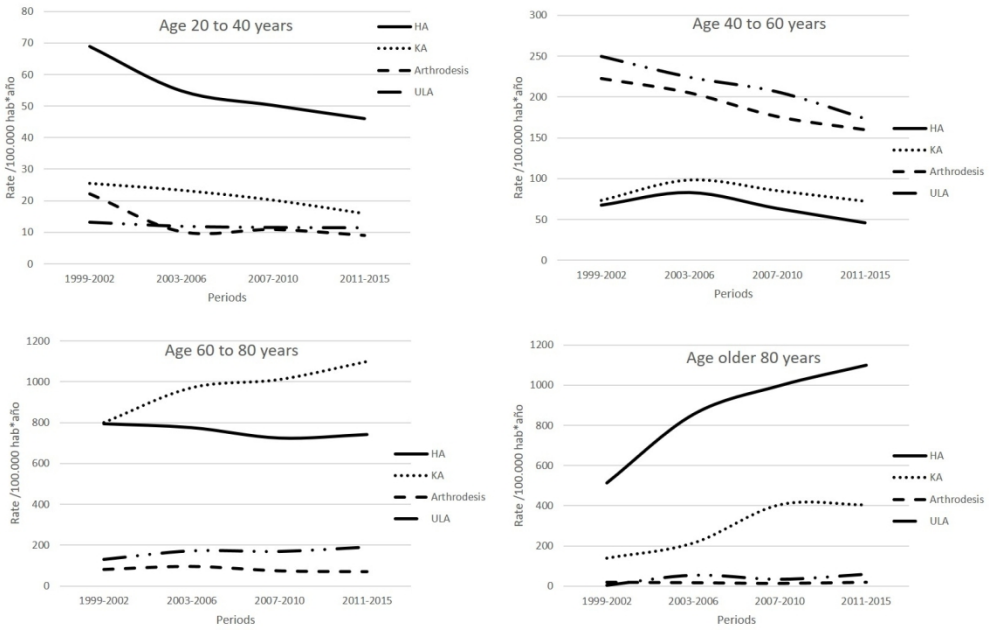

Figure 3: Trend of rates per age range and surgery type.

274x178mm (150 x 150 DPI)