Factors influencing quality of life in patients with osteoarthritis

analyses from the BISCUITS study

Schepman, Patricia; Robinson, Rebecca; Blakeman, Karin Hygge; Wilhelm, Stefan; Beck, Craig; Hallberg, Sara; Liseth-Hansen, Johan; De Geer, Anna; Rolfson, Ola; Arendt-Nielsen, Lars

Published in:
Scandinavian Journal of Pain

DOI (link to publication from Publisher):
10.1515/sjpain-2021-0213

Publication date:
2023

Document Version
Publisher's PDF, also known as Version of record

Observational Studies

Patricia Schepman, Rebecca Robinson, Karin Hygge Blakeman, Stefan Wilhelm, Craig Beck, Sara Hallberg*, Johan Liseth-Hansen, Anna De Geer, Ola Rolfson and Lars Arendt-Nielsen

Factors influencing quality of life in patients with osteoarthritis: analyses from the BISCUITS study

https://doi.org/10.1515/sjpain-2021-0213
Received December 2, 2021; accepted June 14, 2022;
published online July 6, 2022

Abstract

Objectives: Osteoarthritis can have a profound effect on patients' quality of life. The Burden of Disease and Management of Osteoarthritis and Chronic Low Back Pain: Health Care Utilization and Sick Leave in Sweden, Norway, Finland and Denmark (BISCUITS) study aimed to describe the impact of osteoarthritis on quality of life and determine the association with factors such as pain severity and pharmacological treatment.

Methods: An observational study was performed with a cross-sectional design including patients with a confirmed osteoarthritis diagnosis enrolled in the National Quality Register for Better management of patients with Osteoarthritis (BOA) between 2016 and 2017 in Sweden. Patient-reported information from BOA was linked to administrative data from three national health registers. The impact of osteoarthritis on quality of life was estimated using the EQ-5D-5L and the first developed experienced-based time-trade-off value set for Sweden to calculate the EQ-5D-5L index scores. EQ-5D-3L index scores were also estimated based on a UK hypothetical value set via a crosswalk method. Ordinary least squares regression models were used to analyse the association between quality of life and potential influencing factors.

Results: For the 34,254 patients evaluated, mean EQ-5D-5L index score was 0.792 (SD 0.126). Stratifications showed that the index score varied across different levels of pain severity. Increased pain severity and use of pain-relieving medications remained significantly associated with a lower quality of life index score when controlled for potential confounders. The mean EQ-5D-3L index score was 0.605 (SD 0.192).

Conclusions: This large population-based study from Sweden highlights the substantial impact of osteoarthritis on quality of life amongst different patient groups and that currently available treatment options for osteoarthritis pain do not appropriately address the needs for many osteoarthritis patients.

Keywords: cohort study; EQ-5D-5L; observational data; osteoarthritis; pain severity; real-world data.

Previous presentation of study data at scientific meeting: ISPOR 2020, Virtual, 18-05-2020, https://doi.org/10.1016/j.jval.2020.08.1160.

***Corresponding author: Sara Hallberg**, Quantify Research, Hantverkargatan 8, 112 21 Stockholm, Sweden, Phone: +46 70 306 7110, E-mail: sara.hallberg@quantifyresearch.com
Patricia Schepman, Pfizer Inc., New York, NY, USA
Rebecca Robinson, Eli Lilly & Co., Indianapolis, IN, USA
Karin Hygge Blakeman and Anna De Geer, Pfizer Innovations, Sollentuna, Sweden
Stefan Wilhelm, Eli Lilly International Medical Affairs, Bad Homburg, Germany
Craig Beck, Pfizer Ltd, Tadworth, UK
Johan Liseth-Hansen, Quantify Research, Stockholm, Sweden
Ola Rolfson, University of Gothenburg, Gothenburg, Sweden
Lars Arendt-Nielsen, Department of Health Science and Technology, Center for Neuroplasticity and Pain (CNAP), SMI, School of Medicine, Aalborg University, Aalborg, Denmark; and Department of Medical Gastroenterology (Mech-Sense), Aalborg University Hospital, Aalborg, Denmark

Introduction

Osteoarthritis (OA) is a chronic disease characterized by the deterioration of cartilage and joint inflammation impacting mobility and leading to chronic pain [1]. OA is a major public health problem affecting more than 300 million people worldwide, and it is estimated that one in 10 people over the age of 60 have health issues due to OA [2, 3]. The global prevalence of OA has increased by 30% during the last 10 years and it is described as the fastest growing disability given the aging population and increased rates of obesity [3, 4].

There is considerable evidence from the literature on the negative impact of OA on quality of life (QoL) for affected patients, indicating that this is a major contributor to the

overall disease burden [5–7]. Prior research of population-based QoL studies has concluded that the effect OA have on QoL is one of the largest compared with other chronic conditions [8–10]. Predictive factors for lower QoL in OA patients include pain severity, with a strong link to the disabling effects of OA and decreased QoL [11, 12], and prescribed medication [13, 14]. However, there may be several important mediators such as pain severity and the number of pain locations which affect the association.

Management of OA aims to reduce pain and to improve function. Current treatment guidelines recommend a multimodal pain management approach including non-pharmacologic and pharmacologic therapies [15–17]. Non-pharmacological management includes life-styles alterations and physical exercise while short-term pharmacologic pain treatment consists of paracetamol and nonsteroidal anti-inflammatory drugs (NSAIDs) [16, 18]. Opioids have traditionally been considered an option for OA pain and are still prescribed to patients [19], although their use over longer periods is questioned and no longer recommended by certain guidelines [16, 20]. While joint replacement surgery is considered the end stage option for managing severe OA, it has been shown that one in five patients undergoing total knee arthroplasty continue to have persistent chronic pain. Furthermore, four in five of those who underwent revision surgery continued to have pain at an even higher level [21].

The impact of OA on QoL can have far reaching and complex effects on people's lives [11, 22] and assessing predictors of QoL is important for understanding the effect of disease progression and pharmacological treatment in OA patients [7]. Furthermore, disease management can be better targeted with knowledge of the differential burden amongst OA subpopulations. The BISCUITS (Burden of Disease and Management of Chronic Low Back Pain and Osteoarthritis) study is a cross-sectional case-control cohort study of real-world observational data which aims to describe the multi-dimensional burden of OA and describe its many contributing factors. The aim of the present study was to describe the impact of OA on QoL and its association with potential predictive factors such as pain severity and pharmacological treatment, using Swedish national health registry data.

Methods

Study population

This study consisted of an observational cross-sectional cohort study of adult (≥18 years) OA patients based on their first registration ("index date") in a self-management program in Sweden from January 1, 2016 to December 31, 2017. The study was a part of The Burden of Disease and Management of Osteoarthritis and Chronic Low Back Pain: Healthcare Utilization and Sick Leave in Sweden, Norway, Finland and Denmark (BISCUITS), an observational cohort study linking longitudinal healthcare and socioeconomic registers in the Nordics, which has been described in detail elsewhere [submitted/if accepted: reference to "sjpain-2021-0212"]. Individuals with a primary diagnosis of malignant cancer (ICD10: C00-C43; C45-C97) during the three years before index date were excluded from the study, focusing on non-malignant pain in accordance with other analyses within the BISCUITS study.

Data sources and study measures

This study used data from the National Quality Register for Better Management of Patients with Osteoarthritis (BOA) [23], with data on over 139,000 patients who have been referred to a nationwide self-management program after confirmed OA diagnosis. The register has been described in detail elsewhere [23]. Information from the BOA register include QoL (measured as EQ-5D-5L and EQ-5D-3L via crosswalk method), perceived pain variables and demographic variables (age, sex, body mass index [BMI], smoking, weekly physical activity). For further details, see appendixS1, online supplement. Since pain is strongly associated with OA outcomes, including QoL, results were stratified by self-reported pain severity using Numeric Rating Scale.

Additional data was retrieved from three national registers and linked together by the Swedish National Board of Health and Welfare using unique personal identifiers [24–27]. Information on hospitalizations and outpatient physician specialist visits was collected from the National Patient Register and the Swedish Prescribed Drug Register provided data on pain relief medication (Table 1) filled at pharmacies for the complete observable period for each patient. Opioid use was estimated as dispensed oral morphine equivalents (OMEQ) (see appendixS2, online supplement). These national registers are mandatory to report to with a high degree of coverage [24, 25]. Socioeconomic variables were provided by Statistics Sweden's Longitudinal integrated database for health insurance and labour market studies.

Statistical analysis

Continuous variables were presented with means and standard deviations (SDs), and categorical variables were shown as frequencies with percentages. To analyse the association between QoL and potential influencing factors, a cross-sectional ordinary least squares (OLS) regression model with robust standard errors was used. An OLS model was chosen as it is recommended as a simple and valid approach and may be less biased than alternative models [28]. The dependent variable was EQ-5D-5L and the independent variable of interest was the continuous pain intensity score. There were four OLS models that included different sets of covariates. Model 1 was unadjusted, with pain intensity as the only independent variable. In the other models 2–4, potential confounding factors (demographics, drug utilization and other pain severity measures) were added sequentially to evaluate whether these covariates had an impact on the effect of pain intensity on EQ-5D-5L. All tests were two-tailed and an alpha

Table 1: Pain relief medication – ATC-codes and definitions.

Medication	ATC-code	Definitions
Opioids	N02A	Non-persistent opioid users: <4,500 OMEQ Persistent opioid use: ≥4,500 OMEQ Persistent high opioid use: ≥8,100 OMEQ Measured 1 year pre-index
Other analgesics and antipyretics	N02B	Active treatment: Supply of filled prescription lasting over the index date
Nonsteroidal anti-inflammatory drugs (NSAIDs)	M01A	Long-term NSAIDs user: ≥2 NSAIDs prescriptions measured 3 months pre-index Active treatment: Supply of filled prescription lasting over the index date
Topical products for joint and muscular pain	M02A	Active treatment: Supply of filled prescription lasting over the index date
Tricyclic antidepressants	N06AA	
Serotonin-norepinephrine reuptake inhibitors	N06AX	
Gabapentin and pregabalin (anti-epileptics)	N03AX12, N03AX16	

ATC, anatomical therapeutic chemical; OMEQ, oral morphine equivalents; NSAIDs, nonsteroidal anti-inflammatory drugs.

value of 0.05 was employed as the cut-off for statistical significance. All data management and statistical analyses were performed using RStudio v1.3 (RStudio Team, PBC, Boston, MA) and Stata version 16 (StataCorp, College Station, US).

Results

Characteristics

In total, 34,254 patients with OA during 2016 and 2017 were included in the study (Table 2). Most patients had moderate (40.0%) or severe (40.0%) pain relative to no/mild pain (20.0%). The mean age at time of registration in BOA was 67 years and 68% of the patients were female. Of those below 65 years of age (43% of total study sample), 80% were employed and the mean disposable income was 28,096 euro per year. Overall, 17% of the patient were educated beyond secondary school level. These socioeconomic variables decreased with increasing pain severity.

The Elixhauser comorbidity index was 0.48 overall, and varied with pain severity, from 0.36 (SD 0.83) in no/mild pain patients to 0.54 (SD 1.05) in severe pain patients. In terms of depressive episodes and anxiety disorders, 3% of both no/mild and moderate pain groups were affected, compared to 5% of those reporting severe pain. An overall mean BMI of 28 was relatively stable across pain groups, but current smoking rates in the severe pain group were double (11%) compared to no/mild pain (6%). More patients with severe pain (27%) reported zero minutes of physical activity per week compared to patients with no/mild (22%) and moderate pain (24%).

Overall, 84% of the study sample reported lasting pain (defined as daily and always), which was most common among those in the severe pain group (95% compared to 57% with no/mild pain). A similar pattern of increased percentage across the pain severity groups was found for having more than one joint affected (no/mild: 52% – severe: 68%), overall pain intensity (2.36–7.64), and walking difficulty due to pain (55–92%). Across all three pain severity groups, the joint with most pain in our population was the knee (62–68%).

Within the study population, 19% had used opioids within the year prior to index date. Of these, 3.7% were classified as persistent or persistent high opioid users, having dispensed ≥4,500 OMEQ of opioids in the year before index date. Of the non-persistent opioid users (<4,500 OMEQ of opioids in the pre-index year), 11% reported no/mild pain, 36% moderate and 52% severe pain. This skewed distribution was also seen for persistent opioid users as 66% reported severe pain and 8% no/mild pain. Of the included patients, 1% had filled at least two NSAID prescriptions in the first quarter prior to the index date and were defined as long-term NSAID users. A higher share of patients with severe pain (2.3%) were long-term NSAID users compared to patients with no/mild pain (0.5%).

Quality of life (QoL)

Across this study sample of patients with OA, the mean EQ-5D-5L index score was 0.792 (SD 0.126) (Figure 1 and Table 3). The impact of pain severity on QoL was demonstrated by a drop in mean EQ-5D-5L index score of 0.170 between patients who reported no/mild vs. severe pain. The mean EQ-5D-3L index score, created via a crosswalk method, was 0.605 (SD 0.192).

The impact of pain severity on each of the five subdimensions of EQ-5D-5L is shown in Figure 2. Almost all OA patients reported problems in the subdimension pain/discomfort and more patients with higher levels of pain severity reported problems as well as worse intensity of

Table 2: Study population characteristics for all and by pain severity category.

	All		No/Mild pain		Moderate pain		Severe pain	
	No/mean	%/SD	No/mean	%/SD	No/mean	%/SD	No/mean	%/SD
Number of individuals	34,254	100%	6,548	19%	13,733	40%	13,824	40%
Age	66.81	9.68	66.86	9.55	67.46	9.65	66.10	9.71
Sex								
Females	23,441	68.4%	4,225	64.5%	9,449	68.8%	9,655	69.8%
Males	10,813	31.6%	2,323	35.5%	4,284	31.2%	4,169	30.2%
BMI	28.08	4.90	26.94	4.40	27.88	4.78	28.83	5.12
Smoking								
Never smoked	17,089	49.9%	3,594	54.9%	6,882	50.1%	6,533	47.3%
Stopped smoke before index	14,060	41.0%	2,557	39.1%	5,768	42.0%	5,682	41.1%
Smoke regularly	2,892	8.4%	358	5.5%	998	7.3%	1,525	11.0%
Comorbidity profile								
Elixhauser comorbidity index	0.48	0.97	0.36	0.83	0.47	0.94	0.54	1.05
Depressive episodes	1,362	4.0%	204	3.1%	498	3.6%	653	4.7%
Anxiety disorders	1,428	4.2%	210	3.2%	504	3.7%	710	5.1%
Medication profile								
Non-persistent opioid users	5,129	15.0%	580	8.9%	1,845	13.4%	2,683	19.4%
Persistent opioid users[a]	436	1.3%	35	0.5%	112	0.8%	286	2.1%
Persistent high opioid users[a]	810	2.4%	57	0.9%	222	1.6%	527	3.8%
Long-term NSAIDs users[b]	475	1.4%	30	0.5%	123	0.9%	318	2.3%
Self-reported pain[c]								
Recurrent pain	5,416	15.8%	2,814	43.0%	1,863	13.6%	716	5.2%
Lasting pain	28,657	83.7%	3,680	56.2%	11,795	85.9%	13,081	94.6%
Pain intensity (continuous 0–10)	5.66	2.27	2.20	0.90	5.11	0.77	7.86	0.96
Number of pain locations								
1	12,886	37.6%	3,157	48.2%	5,186	37.8%	4,461	32.3%
2–4	19,273	56.3%	3,262	49.8%	7,836	57.1%	8,110	58.7%
5+	2,095	6.1%	129	2.0%	711	5.2%	1,253	9.1%
Joint with most pain								
Hip	10,607	31.0%	1,766	27.0%	4,185	30.5%	4,616	33.4%
Knee	21,956	64.1%	4,448	67.9%	8,874	64.6%	8,543	61.8%
Hand	1,639	4.8%	324	4.9%	658	4.8%	639	4.6%
Walking difficulty due to pain								
No	7,354	21.5%	2,973	45.4%	2,942	21.4%	1,404	10.2%
Yes	26,549	77.5%	3,496	53.4%	10,648	77.5%	12,297	89.0%
Physical activity per week								
0 min	8,544	24.9%	1,429	21.8%	3,305	24.1%	3,775	27.3%
1–60 min	13,028	38.0%	2,291	35.0%	5,314	38.7%	5,376	38.9%
60–150 min	7,079	20.7%	1,550	23.7%	2,916	21.2%	2,583	18.7%
>150 min	5,407	15.8%	1,244	19.0%	2,117	15.4%	2,018	14.6%
Highest attained level of education								
<upper secondary school	10,236	29.9%	1,486	22.7%	4,147	30.2%	4,552	32.9%
Upper secondary school	13,296	38.8%	2,325	35.5%	5,304	38.6%	5,611	40.6%
>upper secondary school	4,870	14.2%	1,108	16.9%	1,957	14.3%	1,788	12.9%
First stage tertiary education (bachelor)	3,326	9.7%	878	13.4%	1,352	9.8%	1,079	7.8%
First stage tertiary education (master)	2,161	6.3%	627	9.6%	839	6.1%	687	5.0%
Second stage tertiary education (PhD)	231	0.7%	101	1.5%	78	0.6%	52	0.4%
Working age population (18–65 years)	14,693	42.9%	2,770	42.3%	5,444	39.6%	6,438	46.6%
Employment (in working age population)								
Not employed	2,912	19.8%	400	14.4%	1,005	18.4%	1,499	23.2%
Employed	11,781	80.0%	2,370	85.4%	4,439	81.4%	4,939	76.5%
Disposable income (in working age population)	28,096	25,303	30,509	22,106	29,106	33,179	26,167	17,530

[a]Persistent opioid use – defined as annual OMEQ pre-index: 4,500–8,100. Persistent high opioid use – defined as annual OMEQ pre-index: >8,100. [b]Long-term NSAID use – defined as ≥2 NSAIDs prescriptions within three months post-index. [c]Self-reported pain: Either stated as Recurrent or as Lasting pain(defined as "daily and always"). OMEQ, oral morphine equivalents measured within one-year post-index, see appendixS2 in the online supplement; SD, standard deviation; BMI, body mass index; NSAIDs, nonsteroidal anti-inflammatory drugs.

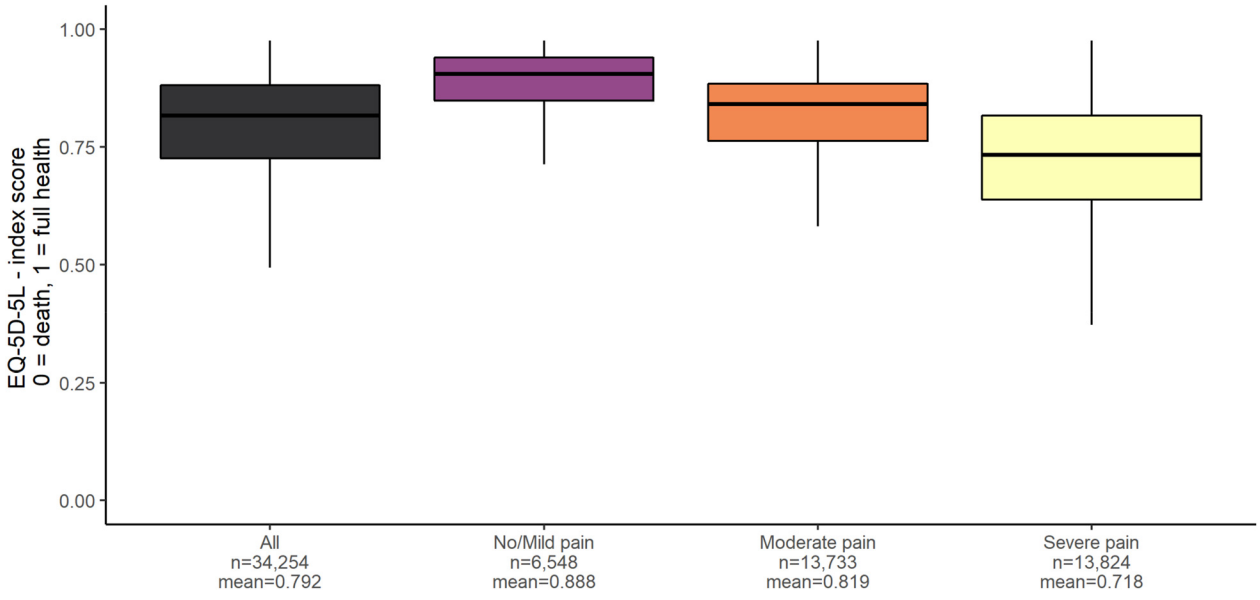

Figure 1: Boxplot figure of EQ-5D-5L (mean, distribution) for all and by pain severity.

Table 3: EQ-5D index scores, for all and by pain severity.

	Mean	Standard deviation	Minimum	1st quartile	4th quartile	Maximum
EQ-5D-5L index score – *Experienced-based value set*						
All	0.792	0.126	0.243	0.726	0.881	0.975
No/Mild pain	0.888	0.076	0.408	0.849	0.939	0.975
Moderate pain	0.819	0.094	0.243	0.762	0.884	0.975
Severe pain	0.718	0.131	0.243	0.637	0.817	0.975
EQ-5D-3L index score – *Hypothetical value set*						
All	0.605	0.192	−0.594	0.531	0.735	1.000
No/Mild pain	0.743	0.112	−0.163	0.691	0.836	1.000
Moderate pain	0.654	0.130	−0.594	0.612	0.735	1.000
Severe pain	0.491	0.209	−0.511	0.336	0.654	1.000

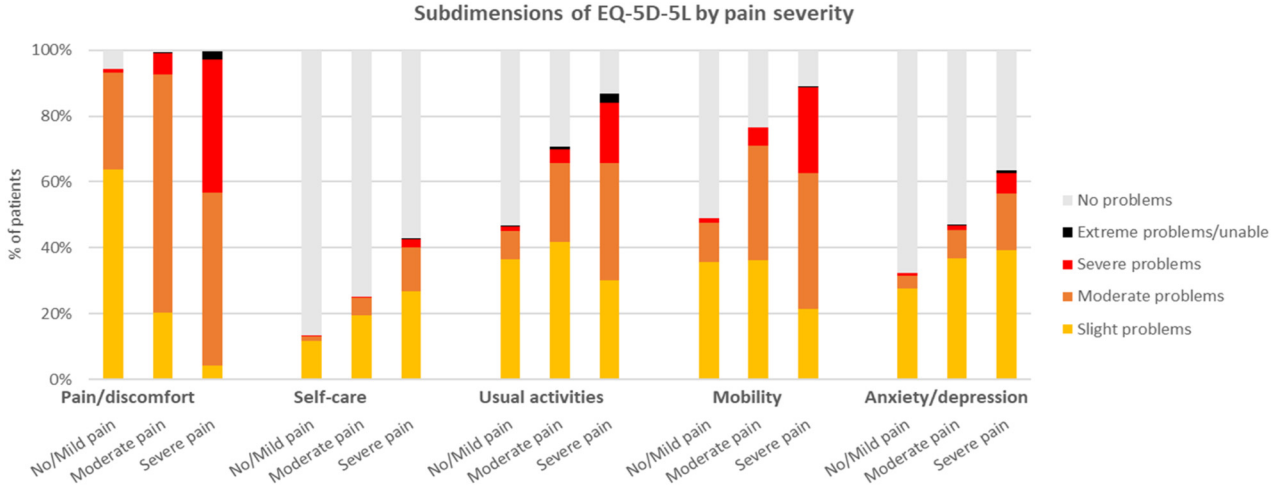

Figure 2: Percentage of people reporting subdimensions of EQ-5D-5L by pain severity.

problems, a pattern that could be seen in all subdimensions. For example, 12% of patients with no/mild pain had moderate or worse problems performing usual activities while the corresponding proportion within the group of severe pain patients was 56%.

Predictors of EQ-5D-5L

The results from the OLS regressions are presented in Table 4, displaying the associations between the included covariates and the EQ-5D-5L index score for the four models. The regression coefficient for pain severity was robust across the models, even with an increasing number of covariates. The adjusted R^2 estimates increased as covariates were added to model, from 0.32 to 0.42 for the main model. When all factors were considered (model 4), the five main categorical factors that were associated with worsening QoL as shown by the EQ-5D-5L index scores were, in order of largest to smallest coefficient size: having walking difficulty due to pain, dispensed over 8100 OMEQ, dispensed between 4,500 and 8,100 OMEQ, having five or more pain locations and having an active treatment with serotonin-norepinephrine reuptake inhibitors (SNRIs) ($p<0.05$ for all). Of the four non-categorical covariates in the model, pain intensity had a large impact on the index score. One unit increase in the pain intensity scale being associated with a 0.025 decrease of the EQ-5D-5L index score. Having an additional disease category in the Elixhauser comorbidity index implied on average a 0.004 decrease of the EQ-5D-5L index score, while each additional year in age increased the score with 0.001.

Discussion

This observational cross-sectional study of 34,254 patients with OA estimated the impact of the multidimensional aspects of the disease on QoL using the EQ-5D-5L. To our knowledge, this is one of the largest studies to date with EQ-5D-5L measures for OA patients.

A regional Swedish registry data study utilizing both primary and secondary care data found that one in four adults over 45 years old had physician-diagnosed OA [29]. Given the implications of this for the sheer number of affected patients, it is important to acknowledge the between patient variation and identify groups with OA that are disproportionally affected. Apart from presenting stratified QoL measures by pain severity, we reviewed the predictive ability of several pain characteristics and pharmacological treatment on QoL. It is known that the use of prescription medication rises when the severity of pain increases [30] and most patients classified as opioid- or long-term NSAID users in this study reported severe pain.

An association between prescribed medication and lower QoL for OA patients has been found in two recent studies [13, 14]. However, the methodology of those studies did not allow the results to be controlled for certain important possible mediators such as pain severity and the number of pain locations. In our study we were able to adjust for these covariates in an OLS model and active treatment with pain-relieving medications remained predictive of a lower EQ-5D-5L index score. However, the method of the study does not allow causality to be attributed to the results. Covariates capturing aspects of non-pharmacological treatment such as physical activity and lower BMI were on the contrary predictive of a higher QoL.

This study employs the first experience-based time-trade-off (TTO) value set available to calculate the EQ-5D-5L index score, meaning that patients with direct experience of the condition have valued their own health. This implies that the estimates used in the value set become more patient-centric rather than utilizing a societal view. As the study uses this more recent version of the EQ-5D questionnaire in conjunction with a newly developed value set to calculate the index score, there are currently no comparable EQ-5D-5L estimates in the literature to contrast our findings with. We therefore also generated EQ-5D-3L index scores via a crosswalk method [31] to allow for comparisons with estimates for the general population using the same UK hypothetical-based TTO value set [32]. The mean EQ-5D-3L index score of 0.61 is lower than the general Swedish population norm of 0.80 for ages 60–69 years (0.84 for all ages) [33]. Previous studies aiming to assess the predictive power of EQ-5D-3L for work ability have suggested a cut-off of 0.6 as for having sufficient capacity to be able to work [34, 35]. The study population mean is just above this cut-off, while patients with severe pain are well below, with a mean EQ-5D-3L of 0.49.

The observed inverse associations between pain severity and QoL seen in our study are consistent with previous results from several countries [6, 13, 14, 36–40]. Patients with moderate and severe pain were more likely to report walking difficulty and problems in the functional subdimensions of the EQ-5D (self-care, daily activities, and mobility) compared to patients with no/mild pain. These findings indicate that pain is a major contributing factor to the functional limitations associated with OA, as previously seen in other studies [14, 38].

Table 4: OLS models comparing impact of factors on EQ-5D-5L index score.

OLS models	Outcome: EQ-5D-5L index score							
	Model 1		Model 2		Model 3		Model 4	
	CE	SE	CE	SE	CE	SE	CE	SE
Constant	0.969	0.001	0.949	0.008	0.953	0.008	0.945	0.008
Pain intensity (continuous)	−0.031	0.000	−0.029	0.000	−0.025	0.000	−0.024	0.000
Age (continuous)			0.001	0.000	0.001	0.000	0.001	0.000
Male (ref: female)			−0.014	0.001	−0.014	0.001	−0.016	0.001
Employment status (ref: employed)								
– Not employed			−0.012	0.003	−0.012	0.003	−0.012	0.003
– Disability pension			−0.041	0.003	−0.034	0.003	−0.026	0.003
– Retired (>66 years of age)			0.003[a]	0.002	0.003[a]	0.002	0.003[a]	0.002
Highest attained level of education (ref: <Upper secondary education)								
– Upper secondary education			0.006	0.001	0.007	0.001	0.006	0.001
– >Upper secondary education			0.005	0.001	0.005	0.001	0.004	0.001
Elixhauser comorbidity index (continuous)			−0.007	0.001	−0.006	0.001	−0.004	0.001
BMI (continuous)			−0.002	0.000	−0.002	0.000	−0.001	0.000
Weekly physical activity (ref: nothing)								
– Between 1 and 60 min			0.013	0.001	0.011	0.001	0.011	0.001
– Between 60 and 150 min			0.025	0.002	0.021	0.002	0.020	0.002
– More than 150 min			0.032	0.002	0.026	0.002	0.025	0.002
Smoking (ref: never smoked)								
– Stopped before index			−0.001[a]	0.001	0.000[a]	0.001	0.001[a]	0.001
– Smoke regularly			−0.020	0.002	−0.018	0.002	−0.014	0.002
Number of pain locations (ref: one)								
– Two to four pain locations					−0.013	0.001	−0.012	0.001
– Five or more pain locations					−0.046	0.003	−0.043	0.003
Joint with most pain (ref: hip)								
– Most pain in knee					0.014	0.001	0.011	0.001
– Most pain in hand					0.004[a]	0.003	0.001[a]	0.003
Walking difficulty due to pain (ref: no)					−0.061	0.001	−0.059	0.001
Active treatment with NSAIDs (ref: no)							−0.008	0.001
Active treatment with other analgesics (ref: no)							−0.016	0.001
Active treatment with TCA (ref: no)							−0.015[a]	0.006
Active treatment with topical products (ref: no)							−0.019	0.005
Active treatment with SNRI (ref: no)							−0.032	0.004
Active treatment with anti-epileptics (ref: no)							−0.021	0.006
Opioid use (ref: no opioid use)								
– Non-persistent opioid use							−0.028	0.002
– Persistent opioid use							−0.050	0.006
– Persistent high opioid use							−0.052	0.007
Adjusted R^2		0.32		0.36		0.40		0.42

[a]Non-significant at p-value ≥0.05. All other p-values <0.05. Non-persistent opioid use – defined as annual OMEQ pre-index: 1–4,499. Persistent high opioid use – defined as annual OMEQ pre-index: >8,100. Persistent opioid use – defined as annual OMEQ pre-index: 4,500–8,100. Active treatment – defined as prescription covering index date. OLS, ordinary least squares; CE, coefficient; SE, standard error; BMI, body mass index; OMEQ, oral morphine equivalents; NSAIDs, nonsteroidal anti-inflammatory drugs; TCAs, tricyclic antidepressants; SNRIs, serotonin-norepinephrine reuptake inhibitors; anti-epileptics, Gabapentin and Pregabalin. For ATC-codes, see Table 1.

A systematic review of patients' experience of living with OA found that pain severity and its impact on functional capability were two key factors in the attitude the patient had towards the condition. Other studies exploring personal living experiences with OA, and how it affects the person's life at many levels, have found a desire of patients with OA to remain active and independent [41–43] denoting the importance of retaining the functional capability of OA patients.

Demographic characteristics of the OA patients varied with pain severity classification. Generally, in comparison to patients with no/mild pain, patients with severe pain had lower socioeconomic status in terms of higher unemployment rate, lower income, and lower level of

education. These descriptive results also showed that patients with severe pain had higher BMI and lower physical activity. These lifestyle factors and common social determinants of health have been found to have a negative impact on the QoL of OA patients [7, 36]. Furthermore, OA patients have been shown to have more comorbidities [44]. This is important from a treatment perspective as comorbidities may present contraindications to pharmacological treatment. This study shows that patients with higher pain severity have more comorbidities but also that OA patients with more comorbidities have a lower QoL.

Strengths/limitations

The major strength of this study is the large study population with a rich data set linking various data sources with information on patients treated in a real-world setting. This study utilizes a combination of survey-based data for patient-reported outcomes on pain and QoL, and administrative data which are known to have a high degree of completeness since reporting on health care visits and prescriptions used in this study is mandatory in Sweden.

However, there are some limitations that should be addressed. Patients in the BOA register are not necessarily representative of all Swedish OA patients. All BOA register patients are a part of self-management program after confirmed OA diagnosis and this group may be different to the OA patients not included in the self-management program. For instance, patients in the BOA register had achieved a higher level of education compared to the general population [45], despite a known association between OA and lower educational level [46, 47]. Furthermore, as the study only captured prescribed medication, exclusion of over-the-counter drugs may have led to an underestimation of NSAID usage in our results. Also, information on what condition the medications were prescribed for was not available. Lastly, this was a cross-sectional study and as such, the correlational nature of this research makes it unable to attribute any causality to the results.

Conclusions

In conclusion, this large population-based study on Swedish national health registry data describes the humanistic burden of OA in terms of its impact on QoL. The QoL of OA patients decreased considerably with increased pain severity. When controlling for potential confounders, pain severity and current pharmacological treatment with NSAIDs and opioids remained as independent explanatory factors for lower QoL in OA patients.

Acknowledgments: Christoph Varenhorst, Emilie Toresson Grip and Anders Gustavsson are acknowledged for their contributions to the study.
Research funding: This study was sponsored by Pfizer and Eli Lilly & Company. Center for Neuroplasticity and Pain (CNAP) is supported by the Danish National Research Foundation (DNRF121).
Author contributions: All authors have accepted responsibility for the entire content of this manuscript and approved its submission.
Competing interests: Sara Hallberg and Johan Liseth Hansen are employees at Quantify Research, who were paid consultants to Pfizer and Eli Lilly & Company in connection with this research and the development of this manuscript. Rebecca Robinson and Stefan Wilhelm are employees and stockholder of Eli Lilly. Patricia Schepman, Karin Hygge Blakeman, Anna De Geer, and Craig Beck are employees at Pfizer with stock and/or stock options. Lars Arendt-Nielsen was a paid contractor to Pfizer and Eli Lilly & Company in connection with this study. Ola Rolfson is an employee of the Swedish Arthroplasty Register which received funding from Pfizer and Eli Lilly and Company to conduct this study. Medical writing support was provided by Sara Hallberg at Quantify Research and was funded by Pfizer and Eli Lilly & Company.
Informed consent: Individual informed consent was not required for this study and was therefore not collected.
Ethical approval: This study complied with all relevant national regulations, institutional policies and is in accordance with the tenets of the Helsinki Declaration (as amended in 2013). Ethical approval was granted for this work on September 12, 2018 (registration number: 2018/1634-31/2) from the ethical review board in Stockholm, Sweden.

References

1. Haq I, Murphy E, Dacre J. Osteoarthritis. Postgrad Med 2003; 79:377–83.
2. World Health Organization. The burden of musculoskeletal conditions at the start of the millennium a report of a WHO scientific group. Geneva: World Health Organization; 2003.
3. Safiri S, Kolahi A-A, Smith E, Hill C, Bettampadi D, Mansournia MA, et al. Global, regional and national burden of osteoarthritis 1990–2017: a systematic analysis of the Global Burden of Disease Study 2017. Ann Rheum Dis 2020;79:819.

4. O'Neill TW, McCabe PS, McBeth J. Update on the epidemiology, risk factors and disease outcomes of osteoarthritis. Best Pract Res Clin Rheumatol 2018;32:312–26.
5. Xie F, Kovic B, Jin X, He X, Wang M, Silvestre C. Economic and humanistic burden of osteoarthritis: a systematic review of large sample studies. Pharmacoeconomics 2016;34:1087–100.
6. Dibonaventura M, Gupta S, McDonald M, Sadosky A. Evaluating the health and economic impact of osteoarthritis pain in the workforce: results from the National Health and Wellness Survey. BMC Muscoskel Disord 2011;12:83.
7. Vitaloni M, Botto-van Bemden A, Sciortino Contreras RM, Scotton D, Bibas M, Quintero M, et al. Global management of patients with knee osteoarthritis begins with quality of life assessment: a systematic review. BMC Muscoskel Disord 2019;20:493.
8. Hopman WM, Harrison MB, Coo H, Friedberg E, Buchanan M, VanDenKerkhof EG. Associations between chronic disease, age and physical and mental health status. Chron Dis Can 2009;29: 108–16.
9. Prior JA, Jordan KP, Kadam UT. Variations in patient-reported physical health between cardiac and musculoskeletal diseases: systematic review and meta-analysis of population-based studies. Health Qual Life Outcome 2015;13:71.
10. Sánchez-Iriso E, Errea Rodríguez M, Cabasés Hita JM. Valuing health using EQ-5D: the impact of chronic diseases on the stock of health. Health Econ 2019;28:1402–17.
11. Montero A, Mulero J-F, Tornero C, Guitart J, Serrano M. Pain, disability and health-related quality of life in osteoarthritis—joint matters: an observational, multi-specialty trans-national follow-up study. Clin Rheumatol 2016;35:2293–305.
12. García-Pérez L, Ramos-García V, Serrano-Aguilar P, Pais-Brito JL, Aciego de Mendoza M, Martín-Fernández J, et al. EQ-5D-5L utilities per health states in Spanish population with knee or hip osteoarthritis. Health Qual Life Outcome 2019;17:164.
13. Conaghan PG, Doane MJ, Jaffe DH, Dragon E, Abraham L, Viktrup L, et al. Are pain severity and current pharmacotherapies associated with quality of life, work productivity, and healthcare utilisation for people with osteoarthritis in five large European countries? Clin Exp Rheumatol 2020;39:819–28.
14. Jackson J, Iyer R, Mellor J, Wei W. The burden of pain associated with osteoarthritis in the hip or knee from the patient's perspective: a multinational cross-sectional study. Adv Ther 2020;37:3985–99.
15. Kloppenburg M, Kroon FP, Blanco FJ, Doherty M, Dziedzic KS, Greibrokk E, et al. 2018 Update of the EULAR recommendations for the management of hand osteoarthritis. Ann Rheum Dis 2019; 78:16–24.
16. Kolasinski SL, Neogi T, Hochberg MC, Oatis C, Guyatt G, Block J, et al. 2019 American college of rheumatology/arthritis foundation guideline for the management of osteoarthritis of the hand, hip, and knee. Arthritis Care Res 2020;72:149–62.
17. Osteoarthritis: care and management. London: National Institute for Health and Care Excellence (NICE); 2020. (NICE Clinical Guidelines, No. 177). Available from: https://www.nice.org.uk/guidance/cg177.
18. Socialstyrelsen. Nationella riktlinjer för rörelseorganens sjukdomar – Reumatoid artrit, axial spondylartrit, psoriasisartrit, artros och osteoporos – Stöd för styrning och ledning 2021. Stockholm: Socialstyrelsen; 2021. Available from: https://www.socialstyrelsen.se/kunskapsstod-och-regler/regler-och-riktlinjer/nationella-riktlinjer/riktlinjer-och-utvarderingar/rorelseorganens-sjukdomar/.
19. DeMik DE, Bedard NA, Dowdle SB, Burnett RA, McHugh MA, Callaghan JJ. Are we still prescribing opioids for osteoarthritis? J Arthroplasty 2017;32:3578–82.e1.
20. Bannuru RR, Osani MC, Vaysbrot EE, Arden NK, Bennell K, Bierma-Zeinstra SMA, et al. OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. Osteoarthritis Cartilage 2019;27:1578–89.
21. Rice DA, Kluger MT, McNair PJ, Lewis GN, Somogyi AA, Borotkanics R, et al. Persistent postoperative pain after total knee arthroplasty: a prospective cohort study of potential risk factors. Br J Anaesth 2018;121:804–12.
22. Lee Y, Lee S-H, Lim S, Baek S, Ha I-H. Mental health and quality of life of patients with osteoarthritis pain: the sixth Korea National Health and Nutrition Examination Survey (2013–2015). PLoS One 2020;15:17.
23. Thorstensson CA, Garellick G, Rystedt H, Dahlberg LE. Better management of patients with osteoarthritis: development and nationwide implementation of an evidence-based supported osteoarthritis self-management programme. Muscoskel Care 2015;13:67–75.
24. Ludvigsson JF, Almqvist C, Bonamy A-KE, Ljung R, Michaëlsson K, Neovius M, et al. Registers of the Swedish total population and their use in medical research. Eur J Epidemiol 2016;31:125–36.
25. Ludvigsson JF, Andersson E, Ekbom A, Feychting M, Kim J-L, Reuterwall C, et al. External review and validation of the Swedish national inpatient register. BMC Publ Health 2011;11:450.
26. Wallerstedt SM, Wettermark B, Hoffmann M. The first decade with the Swedish prescribed drug register – a systematic review of the output in the scientific literature. Basic Clin Pharmacol Toxicol 2016;119:464–9.
27. Wettermark B, Hammar N, Fored CM, Leimanis A, Otterblad Olausson P, Bergman U, et al. The new Swedish prescribed drug register–opportunities for pharmacoepidemiological research and experience from the first six months. Pharmacoepidemiol Drug Saf 2007;16:726–35.
28. Pullenayegum EM, Tarride JE, Xie F, Goeree R, Gerstein HC, O'Reilly D. Analysis of health utility data when some subjects attain the upper bound of 1: are Tobit and CLAD models appropriate? Value Health: J Int Soc Pharmacoecon Outcomes Res 2010;13:487–94.
29. Turkiewicz A, Petersson IF, Björk J, Hawker G, Dahlberg LE, Lohmander LS, et al. Current and future impact of osteoarthritis on health care: a population-based study with projections to year 2032. Osteoarthritis Cartilage 2014;22:1826–32.
30. Kingsbury SR, Gross HJ, Isherwood G, Conaghan PG. Osteoarthritis in Europe: impact on health status, work productivity and use of pharmacotherapies in five European countries. Rheumatology (Oxford, England) 2014;53: 937–47.
31. van Hout B, Janssen MF, Feng Y-S, Kohlmann T, Busschbach J, Golicki D, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. Value Health 2012;15: 708–15.
32. Dolan P. Modeling valuations for EuroQol health states. Med Care 1997;35:1095–108.
33. Burström K, Johannesson M, Diderichsen F. Swedish population health-related quality of life using the EQ-5D. Qual Life Res: Int J Qual Life Aspects Treat, Care Rehabil 2001;10: 621–35.

34. Forsbrand MH, Grahn B, Hill JC, Petersson IF, Post Sennehed C, Stigmar K. Can the STarT back tool predict health-related quality of life and work ability after an acute/subacute episode with back or neck pain? A psychometric validation study in primary care. BMJ Open 2018;8:e021748.
35. Hansson E, Hansson T, Jonsson R. Predictors for work ability and disability in men and women with low-back or neck problems. Euro Spine J: Off Publ Euro Spine Soc, Eur Spinal Deformity Soc, Euro Sect Cervical Spine Res Soc 2006;15:780–93.
36. Alkan BM, Fidan F, Tosun A, Ardıçoğlu O. Quality of life and self-reported disability in patients with knee osteoarthritis. Mod Rheumatol 2014;24:166–71.
37. Bindawas SM, Vennu V, Alfhadel S, Al-Otaibi AD, Binnasser AS. Knee pain and health-related quality of life among older patients with different knee osteoarthritis severity in Saudi Arabia. PLoS One 2018;13:e0196150.
38. Neogi T. The epidemiology and impact of pain in osteoarthritis. Osteoarthritis Cartilage 2013;21:1145–53.
39. Sadosky AB, Bushmakin AG, Cappelleri JC, Lionberger DR. Relationship between patient-reported disease severity in osteoarthritis and self-reported pain, function and work productivity. Arthritis Res Ther 2010;12:R162.
40. Zambon S, Siviero P, Denkinger M, Limongi F, Victoria Castell M, van der Pas S, et al. Role of osteoarthritis, comorbidity, and pain in determining functional limitations in older populations: European project on osteoarthritis. Arthritis Care Res 2016;68: 801–10.
41. Hall M, Migay AM, Persad T, Smith J, Yoshida K, Kennedy D, et al. Individuals' experience of living with osteoarthritis of the knee and perceptions of total knee arthroplasty. Physiother Theor Pract 2008;24:167–81.
42. Kee CC. Living with osteoarthritis: insiders' views. Appl Nurs Res: ANR 1998;11:19–26.
43. Parsons GE, Godfrey H, Jester RF. Living with severe osteoarthritis while awaiting hip and knee joint replacement surgery. Muscoskel Care 2009;7:121–35.
44. Swain S, Sarmanova A, Coupland C, Doherty M, Zhang W. Comorbidities in osteoarthritis: a systematic review and meta-analysis of observational studies. Arthritis Care Res 2020;72: 991–1000.
45. Gustafsson K, Kvist J, Eriksson M, Dahlberg LE, Rolfson O. Socioeconomic status of patients in a Swedish national self-management program for osteoarthritis compared with the general population-a descriptive observational study. BMC Muscoskel Disord 2020;21:10.
46. Knight JB, Callahan LF, Luong ML, Shreffler J, Schoster B, Renner JB, et al. The association of disability and pain with individual and community socioeconomic status in people with hip osteoarthritis. Open Rheumatol J 2011;5: 51–8.
47. Reyes C, Garcia-Gil M, Elorza JM, Mendez-Boo L, Hermosilla E, Javaid MK, et al. Socio-economic status and the risk of developing hand, hip or knee osteoarthritis: a region-wide ecological study. Osteoarthritis Cartilage 2015;23:1323–9.

Supplementary Material: The online version of this article offers supplementary material (https://doi.org/10.1515/sjpain-2021-0213).