

# Patient self-reported functioning by pain severity and usual analgesic treatment among older adults with osteoarthritis: Analysis of the 2017 Spanish National Health Survey

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## Research article

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# Abstract

## Background

Osteoarthritis (OA) pain is among the leading causes of disability and social isolation worldwide. Since prevalence is high, particularly in adults aged 65 or older, it represents a significant burden for society and national health systems. The objective of this study was to determine whether patient self-reported functioning in key domains of daily living differs by pain severity and analgesic treatment among older OA patients in Spain.

## Methods

The Spanish National Health Survey (ENSE), a large, nationally representative, cross-sectional general health survey administered by trained interviewers to 23,089 adults, was the data source. Subjects of both sexes aged 65 or older with a self-reported physician diagnosis of OA who completed the survey were analyzed. Patients were cross classified by pain severity (no/mild, moderate or severe) and analgesia (treated or untreated). Assessment of daily living included basic and instrumental activities of daily living and mental, social, and cognitive domains. Scores were re-scaled to a 0%-100% standardized metric (0%: no limitation [independence]; 100%: complete limitation [full dependence]).

## Results

A total of 3,526 (3,389 surveys completed [96.1%]) older adults with OA were analyzed (women 73.3%; age 77.4 [standard deviation {SD}: 7.5]). Adjusted means (95% confidence interval [CI]) scores in domains of functioning showed significant association with pain severity ( $p < 0.001$ ) but not treatment status, except basic and instrumental activities and social functioning, with higher scores in treated patients. Limitations in patients with untreated no/mild pain versus severe treated pain were as follows: in basic activities, 6.5% (5.0–8.0) versus 31.5% (30.1–32.9); in instrumental activities, 9.0% (7.2–10.8) versus 34.1% (32.3–35.8); in mental, 29.1% (27.9–30.3) versus 45.0% (43.9–46.2); in social, 3.0% (0.6–5.4) versus 42.2% (39.9–44.5); and, in cognitive, 10.9% (9.2–12.6) versus 23.4% (21.8–25.1).

## Conclusions

Pain severity was a major driver of functional impairment in all the main domains of functioning analyzed in older OA patients. Regardless of pain severity, treated patients showed poorer functioning in basic, instrumental and social activities versus untreated subjects. Treated patients might have been in later disease stages, which would have affected the results. Existing analgesic treatment strategies do not meet patient needs for adequate pain management.

## Background

Osteoarthritis (OA) is the most prevalent form of arthritis [1]. It is a heterogeneous disease with multiple underlying mechanisms that affects all joint tissues. Age, body mass index and gender as well as mechanical, biochemical, genetic, immunologic and psychopathological features play a role in the development of the disease [2]. Hence, OA is now considered a disease of an organ [2], the joint. OA is often painful and debilitating, and at present it is not possible to predict whether a patient will gradually lose joint function and develop more joint damage requiring a joint replacement [3,4]. The burden of OA is increasing as population aging is advancing and obesity rates are rising. OA has become one of the leading causes of disability and social isolation worldwide [5,6]. Suboptimal pain management is known to have negative effects on the physical and mental well-being of the population as it greatly impacts quality of life, with a commensurate tremendous individual and socioeconomic burden [4–6, 7–9]. Given its vast implications, the United States Food and Drug Administration (FDA) considers OA a serious disease [10]. It is estimated that OA will be the fourth leading cause of disability in 2020 and one of the 25 main causes of disability with the greatest impact on health worldwide [11].

The mechanisms of OA pain are diverse and complex. Biological, psychological and social factors are interconnected and contribute equally to the genesis of OA pain [12, 13]. Psycho-social factors have a key role in the pain perception experience and might play a part in pain exacerbation, spreading and perpetuation that lead to peripheral pain sensitization. The consequences of OA pain include activity limitations and participation restrictions in addition to negative effects on mood, fatigue and sleep [14, 15]. Persistent pain, activity limitations and resulting frustration are known to seriously affect patient quality of life [15]. OA management guidelines recommend a wide variety of core non-pharmacological and pharmacological treatments [6, 8, 16]. However, current pharmacological treatments are ineffective in halting disease progression and are mainly aimed at modifying pain symptoms with debated effectiveness [5, 16].

Despite its well-known social burden, OA has traditionally received moderate interest. Historically, it has been studied as part of a group of rheumatic diseases, not as an independent entity, particularly in the aging population [8, 9]. Prior research sought to demonstrate that individuals with OA are more likely to have functional impairment, measured as the ability to perform basic activities of daily living (BADLs) and instrumental activities of daily living (IADLs) [17–21]. Nevertheless, most of these studies were conducted on selected populations in specific health settings or on waiting lists for joint replacement. Moreover, many of them lacked appropriate control groups or did not involve representative samples of elderly subjects.

Thus, the objective of this study was to determine the level of disability in key domains of the patient functioning in adults 65 years or older with OA pain in Spain, based on the data collected in the 2017 Spanish National Health Survey (ENSE) [22]. Domains of patient functioning included basic and instrumental activities of daily living and mental, cognitive, and social functioning. The impact of OA pain on functioning was analyzed according to pain severity and recent treatment with analgesia.

## Methods

### Study design

This study had a cross-sectional design written according to the STROBE checklist (See supporting information) [23].

## Data source

Data were abstracted from the most recent ENSE survey (from 2017) [22]. The ENSE is funded every five years by the Spanish Ministry of Health and constitutes the main source of information on health perceived by the population residing in Spain. It is highly representative of Spain as a nation according to population geographic density and collects an extensive set of disaggregated aspects of health according to demographic and socioeconomic characteristics. The information was obtained through interviews in homes throughout the country using computer-assisted personal interviews (CAPIs) as a method of information collection after obtaining the informed consent of the individuals surveyed [22]. The 2017 ENSE collected information on a representative sample of 23,089 men and women over 15 years of age in the Spanish population.

## Study population

For this study, a subsample was used comprising survey participants of both sexes aged 65 or older with a self-reported physician diagnosis of OA who completed the survey. The population of people aged 65 or older was selected for this study because, by design, the ENSE only surveys people in this age range for some of the variables that corresponded to the study objectives, specifically basic and instrumental activities of daily living and cognitive functioning. Pain was assessed by pain domain in the Spanish version of the Short Form 36 Health Survey Version 2 (SF-36v2) questionnaire included in the ENSE questionnaires (Question 45, supporting information). To analyze the study objectives, the OA subsample of the ENSE was grouped into six categories. According to the presence of pain in the past 4 weeks, which was assessed according to the mentioned question on pain severity in the past four weeks, said subsample was grouped into three categories: no pain/mild pain (response 1, 2 or 3 to Q45), moderate pain (response 4) and severe pain (response 5 or 6). These were then crossed with the use of analgesic medications in the past two weeks according to the ENSE (Question 87\_2a, supporting information) such that six subgroups were formed based on pain severity in the past four weeks and the use of analgesics in the past two weeks.

## Assessment of functioning

Assessment of functioning was based of essential functioning of individuals expressed as basic activities of daily living (BADLs), instrumental activities of daily living (IADLs), mental, social, and cognitive functioning. In order to examine the survey participants' limitations (dependency) across these five key dimensions of functioning, ENSE questions on the variables of interest were used. Responses to these questions are on an ordinal Likert scale; however, to harmonize assessments, all types of functioning were re-scaled to a standardized metric of 0%-100% [24], where 0% indicates no limitation and 100% indicates complete limitation in terms of functioning, or complete dependence. In addition, to facilitate interpretation, measures were reorganized into categories according to severity of limitation as described below. These ENSE questions consist of four response levels, where a value of 1 would correspond to complete independence in carrying out the activities studied and a value of 4 would correspond to complete limitation therein. Re-scaling to a metric of 0%-100% was achieved using the following equation [25]: [Observed score – Minimum

score) / Range] x 100. The result is expressed as a percentage of limitation (the range is understood to be the difference obtained by subtracting the minimum possible score from the maximum possible score). Thus, in the case of the score for limitation in basic and instrumental activities of daily living, each having seven items, a score of 7 corresponds to 0% limitation in activity and a score of 28 corresponds to 100% limitation.

A clinical interpretation of the results obtained was performed by analyzing the proportion of persons who, regarding variables for functioning (BADLs, IADLs, cognitive, social, and mental functioning), showed a meaningful or important restriction, limitation or dependency in each type of functioning. This level of restriction not only is significant for the survey participant, but also should be the subject of a health decision intended to result in an improvement in or relief of the dependency represented by this situation, in accordance with the recommendations of the World Health Organization and the World Bank [26]. For BADLs and IADLs, the criterion for interpretation of the Barthel Index was followed, considering meaningful dependency to be severe or complete limitation in functioning: limitation > 60% after adjusting by covariates, since the score correction method was inverted compared to the Barthel Index) [27,28]. For mental functioning, the threshold value for significant mental decline, consistent with mental illness, was > 50%, in accordance with Goldberg et al. [29, 30], also using corrected values for covariates. For the cognitive functioning and social functioning variables, the threshold values for significant limitation were those corresponding to extreme or total deterioration/inability regarding remembering and concentrating, and 100% inability/restriction with regard to social daily activities, respectively.

## Physical functioning: Basic and instrumental activities of daily living

To assess the degree of difficulty in going about activities of daily living, an activity limitation score was calculated for basic and instrumental activities. Limitation in going about basic activities was calculated using responses to Questions 37, 38 and 39 (sub questions a-e), corresponding to Modules K (Physical, sensory, and cognitive limitations) and L (Limitations in going about activities of daily living) of the ENSE survey (**See supporting information**), consisting of activities related to mobility, capacity for getting dressed, continence, eating and bathing and hygiene. Similarly, limitation in instrumental activities was calculated using ENSE Question 42 (sub questions a-g, **see supporting information**) evaluating the survey participants' difficulty in going about activities such as preparing meals, using the telephone, shopping, taking medication, doing light housework, occasionally doing more physically demanding (hard) housework and managing their own money.

## Mental functioning

To assess mental health in the study population, ENSE questions were used according to the methodology of the 12-Item General Health Questionnaire (GHQ-12) [30]. This GHQ-12 Questionnaire was designed by the British scholar Goldberg in 1972 and reflects the mental health status of the survey participants based on the analysis of 12 attributes. The GHQ-12 scale consists of 12 questions with four Likert response levels. The questions used for the analysis of mental health correspond to Block M of the ENSE (Mental health and occupational stress) and comprise Sect. 1–12 of Question 47 (**See supporting information**). They have four response levels from 0 to 3 (from more than usual to much less than usual); these have also been converted

to a 0%-100% metric using the above-mentioned equation. These questions examine decline in mental health as a combination of two dimensions: well-being and coping.

## **Social functioning and cognitive functioning**

Restriction or degree of limitation in going about regular social activities (social functioning) was estimated based on Questions 28b and 29b, corresponding to Module I of the ENSE on restriction of regular activity in the past two weeks. These questions examine the number of days during which individuals limit, both completely or partially, their daily activity or even remain in bed. Regarding cognitive functioning, to measure survey participants' difficulty in remembering and concentrating; Question 38 from Module K of the ENSE was used. This question has four response levels (1–4) corresponding to scores of 1 (no limitation) to 4 (complete limitation). As indicated above, these metrics were also converted to a score of 0%-100%.

## **Statistical analysis**

The statistical analysis included a preliminary analysis of the sample study groups through the preparation of dynamic tables and a descriptive univariate analysis of relevant sociodemographic variables and characteristics related to the study objectives. Prior to any analysis, the rate of response or proportion of people interviewed who had provided a response for the variable to be analyzed was estimated. Missing data were not imputed due to the cross-sectional design of the survey and the fact that the loss of data in the variables studied was always less than 5% of the numbers analyzed (range 0.6%-3.9%). The descriptive analysis included the percentage distribution for categorical variables and measures of central tendency and dispersion for continuous variables, including normality tests. IBM SPSS (Version 26.0, New York, United States; <https://www.ibm.com/analytics/spss-statistics-software>), a software program for statistical processing, was used.

Generalized linear models (GLMs) with normal linear regression and covariates were used with estimation of effects using a factorial model with covariates to analyze scores in functioning domains expressed as a continuous linear metric with a range of 0%-100%. The covariates included in the models were as follows: the survey participant's geographic region of residence, age, sex, marital status, level of education, accidents in the past 12 months, smoking status, alcohol use, level of physical activity, and Functional Comorbidity Index (FCI) [31]. The FCI was used to correct the individual's functioning weighted by the density of comorbidities deemed significant in terms of their impact on the individual's functioning. It was calculated as a count of affirmative responses to the 18 items or comorbidities that comprise it as recommended by its authors, Groll DL et al. [31], and that are included, amongst others, in the ENSE survey questionnaire. The sequential Bonferroni correction was applied to estimate statistical significance in multiple comparisons. GLMs with binary logistic regression and covariates were used with estimation of effects using a factorial model with the covariates to analyze dichotomous responses on severe to total limitation/decline (yes or no) in each domain of functioning by analgesia status in each level of pain severity. Finally, patients were classified according to severity of limitation/restriction into categories of functional limitation for each of the variables analyzed: none/no, mild/low/mild to moderate, moderate/normal and severe to total/high/complete limitation. GLMs with Poisson log linear regression and covariates were used with estimation of effects using a factorial model with covariates to analyze functioning classified into categories of severity of

limitation by analgesia status in each level of pain severity. The main statistical analyses were also replicated in the overall sample split into two samples according to gender.

To interpret the results obtained, when statistically significant differences were found between pairs, the magnitude of the difference was calculated by estimating the effect size with Cohen's *d* statistic [32]. Effect size was estimated by dividing the mean difference between groups by the overall standard deviation and was interpreted according to the recommendations of Cohen and Kazis [32, 33]: 0.20–0.50 = small effect size; 0.50–0.80 = moderate effect size; and  $\geq 0.80$  = large effect size.

## Results

A total of 7,023 ENSE records for people 65 years of age or older were analyzed. Of these, 3,526 (96.1% of surveys completed,  $n = 3,389$ ) corresponded to patients with a self-reported physician diagnosis of OA; 50.2% (95% CI: 49.0–51.4). Of these, 40.8% (39.1–42.4) had no pain/mild pain, 34.1% (32.6–35.8) had moderate pain and 25.1% (23.4–26.6) had severe pain. Most of them (70.2% [68.7–71.7]) had been treated with oral analgesics in last two weeks. Table 1 describes the main demographic characteristics of the population analyzed by study group.

Table 1  
Demographic characteristics of the study population.

TOTAL N = 3,389 <sup>a</sup>	No pain/mild pain		Moderate pain		Severe pain		
	N = 1,382 (40.8%)		N = 1,157 (34.1%)		N = 850 (25.1%)		
	Yes	No	Yes	No	Yes	No	
Analgesia within the last two weeks	Yes = 2,380 (70.2%); No = 1,009 (29.8%)	N = 675 (19.9%)	N = 707 (20.9%)	N = 932 (27.5%)	N = 225 (6.6%)	N = 773 (22.8%)	N = 77 (2.3%)
Age (mean, SD) (years)	77.2 (7.7)	76.2 (7.3)	77.7 (7.4)	76.4 (7.3)	78.8 (7.3)	76.8 (7.9)	
Sex (female) (%)	71.7	60.3	78.7	64.8	84.7	68.2	
Marital status (%)	6.9	9.3	7.0	5.2	5.4	7.1	
Single	45.4	47.6	42.8	47.2	38.7	52.9	
Married	44.3	39.8	46.5	43.6	53.7	32.9	
Widowed	1.0	1.4	1.8	1.2	1.3	2.4	
Legally separated	2.4	1.6	1.9	2.8	0.9	3.5	
Divorced							
Level of education (%)	7.1	3.9	5.9	4.4	11.1	12.9	
None	66.7	64.5	71.9	69.2	70.3	62.4	
Primary	17.7	18.7	15.7	14.8	13.5	17.6	
Secondary	2.6	3.8	1.9	4.0	1.9	4.8	
Professional training	5.9	9.2	4.7	7.6	3.2	2.4	
University education							
Sleep interference, %	30.1	31.0	27.0	24.6	16.4	17.6	
No	51.2	52.3	46.5	46.8	36.6	41.2	
As usual	16.2	13.5	22.9	25.4	33.6	31.8	
More than usual	2.5	3.3	3.6	3.2	13.4	9.4	
A lot more than usual							
Smokers (%)	5.0	6.8	4.6	5.6	4.5	3.5	

<sup>a</sup>A total of 3,526 (3,389 completed surveys) individuals were analyzed.

<sup>b</sup>Maximum number of comorbidities 18, minimum 0 (see reference 19 with list of comorbidities deemed significant in terms of their impact on the individual's functioning according to Groll DL et al.; J Clin Epidemiol 2002; 58: 595–602).

TOTAL N = 3,389 <sup>a</sup>	No pain/mild pain		Moderate pain		Severe pain	
	N = 1,382 (40.8%)		N = 1,157 (34.1%)		N = 850 (25.1%)	
Alcohol use (%)	35.3	44.0	28.6	42.8	20.6	31.8
Physical activity (%)	43.6	33.2	58.4	54.0	72.0	76.5
Does not exercise	47.9	56.3	35.0	39.2	23.9	20.0
Exercises on occasion	4.0	5.2	2.5	2.8	1.5	1.2
Exercises several times per month	4.6	5.4	4.2	4.0	2.6	1.2
Exercises several times per week						
Accident in past 12 months (%)	11.5	8.2	14.0	12.4	24.0	16.5
Functional Comorbidity Index (mean, SD) <sup>b</sup> (counts)	3.1 (2.3)	2.5 (2.0)	4.0 (2.3)	3.7 (2.2)	5.4 (2.6)	4.7 (2.3)
<sup>a</sup> A total of 3,526 (3,389 completed surveys) individuals were analyzed.						
<sup>b</sup> Maximum number of comorbidities 18, minimum 0 (see reference 19 with list of comorbidities deemed significant in terms of their impact on the individual's functioning according to Groll DL et al.; J Clin Epidemiol 2002; 58: 595–602).						

#### Basic activities of daily living (BADLs) and instrumental activities of daily living (IADLs)

The functioning of OA patients in BADLs was found to be limited, with an adjusted average (standard deviation), to 15.9% (22.1) in the entire group of OA subjects. It was also found to have a significant association with pain severity ( $p < 0.001$ ): the higher the pain, the higher the limitation in BADLs, regardless of whether patients had been treated with analgesics in the last two weeks (Table 2). Nonetheless, OA patients with treated moderate or severe pain showed significantly higher limitation in BADLs than non-treated patients (Table 2). The magnitude of these differences was small, with effect sizes ranging from 0.19 to 0.34. The analysis by gender (Table 3) replicated the findings observed in the entire group, particularly in OA patients with moderate or severe pain. Meaningful limitation (greater than 60%) in BADLs was also significantly associated with pain severity (but not analgesic intake), with 17% of treated patients and 14% of non-treated patients with such a degree of limitation in the severe pain subgroup (Fig. 1). However, the analysis by category of functional limitation showed significant differences in distribution of degrees of limitation according to pain severity as well as in each subgroup between treated and not treated with analgesics (Fig. 2). Figure 2 shows that, for basic activities, restriction increased as pain severity increases and this restriction was greater in individuals who required analgesia. The main drivers for such findings in BADLs were items exploring the patient's mobility and walking and up/downstairs compared with to other items in the domain ( $p < 0.001$ , Fig. 3).

Table 2

Patient functioning in five key domains in osteoarthritis patients by pain severity and analgesia.

TOTAL N = 3,389*	No pain/mild pain		Moderate pain		Severe pain	
	N = 1,382 (40.8%)		N = 1,157 (34.1%)		N = 850 (25.1%)	
Domain of functioning (%)	Analgesia within the last two weeks; Yes = 2,380 (70.2%); No = 1,009 (29.8%)					
Range: 0% (no limitation) – 100% (complete limitation)	Yes	No	Yes	No	Yes	No
	N = 675 (19.9%)	N = 707 (20.9%)	N = 932 (27.5%)	N = 225 (6.6%)	N = 773 (22.8%)	N = 77 (2.3%)
Basic activities of daily living	10.2 <sup>†</sup> (8.6–11.7)	6.1 (4.7–7.5)	15.9 <sup>†,\$\$\$</sup> (14.6–17.2)	11.6 <sup>\$\$\$</sup> (9.1–14.1)	31.5 <sup>†,\$\$\$,\$\$\$</sup> (30.1–32.9)	24.0 <sup>\$\$\$,\$\$\$</sup> (19.7–28.2)
Instrumental activities of daily living	13.6 <sup>‡</sup> (11.7–15.4)	8.3 (6.6–10.0)	20.5 <sup>†,\$\$\$</sup> (18.9–22.1)	14.2 <sup>\$\$</sup> (11.2–17.2)	34.1 <sup>†,\$\$\$,\$\$\$</sup> (32.3–35.8)	23.4 <sup>\$\$\$,\$\$\$</sup> (18.2–28.5)
Mental functioning	29.8 (28.6–31.1)	28.8 (27.7–30.0)	34.4 <sup>\$\$\$</sup> (33.4–35.5)	33.6 <sup>\$\$\$</sup> (31.6–35.7)	44.7 <sup>\$\$\$,\$\$\$</sup> (43.6–45.9)	41.8 <sup>\$\$\$,\$\$\$</sup> (38.3–45.3)
Social functioning	6.7 <sup>*</sup> (4.2–9.1)	2.7 (0.5–5.0)	19.4 <sup>*,\$\$\$</sup> (17.4–21.5)	14.8 <sup>\$\$\$</sup> (10.8–18.8)	42.2 <sup>*,\$\$\$,\$\$\$</sup> (40.0–44.5)	31.5 <sup>\$\$\$,\$\$\$</sup> (24.7–38.4)
Cognitive functioning	14.7 <sup>†</sup> (13.0–16.4)	10.5 (8.9–12.1)	18.2 <sup>§</sup> (16.7–19.6)	16.4 <sup>\$\$</sup> (13.5–19.2)	23.4 <sup>\$\$\$,\$\$\$</sup> (21.8–25.0)	20.0 <sup>\$\$</sup> (15.1–24.9)

\*A total of 3,526 (3,389 completed surveys) individuals were analyzed.

‡ = p &lt; 0.001;

† = p &lt; 0.01;

\* = p &lt; 0.05 analgesia versus no analgesia within pain severity subgroup;

\$\$\$ = p &lt; 0.001;

\$\$ = p &lt; 0.01;

§ = p &lt; 0.05 versus no pain/mild pain within analgesic treatment subgroup;

\$\$\$\$ = p &lt; 0.001;

\$\$ = p &lt; 0.01;

<b>TOTAL N = 3,389*</b>	<b>No pain/mild pain</b>	<b>Moderate pain</b>	<b>Severe pain</b>
	<b>N = 1,382 (40.8%)</b>	<b>N = 1,157 (34.1%)</b>	<b>N = 850 (25.1%)</b>
§ = p < 0.05 versus moderate pain within analgesic treatment subgroup; not significant when not specified.			
Values expressed as mean (95% CI) adjusted with covariates (see Methods section for a list of covariates included in the GLM model).			

Table 3

Patient functioning in five key domains in osteoarthritis patients by pain severity, analgesia and gender.

<b>Women (n = 2,584; 73.3%)</b>	<b>Analgesia within the last two weeks; Yes = 1,884 (72.9%); No = 700 (27.1%)</b>					
Domain of functioning (%)	No pain/mild pain		Moderate pain		Severe pain	
Range: 0% (no limitation) to 100% (complete limitation)	Yes	No	Yes	No	Yes	No
	N = 487 (18.9%)	N = 480 (18.6%)	N = 738 (28.6%)	N = 162 (6.3%)	N = 659 (25.5%)	N = 58 (2.2%)
Basic activities of daily living	10.9* (9.0-12.7)	7.1 (5.2-9.0)	15.8 <sup>\$\$\$</sup> (14.3-17.3)	12.1 <sup>\$</sup> (8.9-15.3)	31.1 <sup>†,\$\$\$,\$\$\$</sup> (29.5-32.7)	21.2 <sup>\$\$\$,\$</sup> (15.8-26.5)
Instrumental activities of daily living	15.1* (12.9-17.4)	10.3 (8.1-12.6)	20.8 <sup>\$\$</sup> (19.0-22.6)	16.0 (12.1-19.9)	34.4 <sup>†,\$\$\$,\$\$\$</sup> (32.5-36.4)	20.9 <sup>\$</sup> (14.5-27.4)
Mental functioning	30.4 (28.9-31.9)	30.0 (28.5-31.5)	34.9 <sup>\$\$</sup> (33.7-36.1)	33.6 <sup>\$</sup> (31.0-36.2)	44.5 <sup>\$\$\$,\$\$\$</sup> (43.3-45.8)	40.5 <sup>\$\$\$,\$</sup> (36.2-44.8)
Social functioning	6.6 (3.7-9.6)	3.3 (0.3-6.3)	19.3 <sup>\$\$\$</sup> (16.9-21.7)	14.9 <sup>\$\$</sup> (9.7-20.1)	42.5 <sup>\$\$\$,\$\$\$</sup> (39.9-45.0)	31.8 <sup>\$\$\$,\$\$\$</sup> (23.2-40.4)
Cognitive functioning	14.8 (12.7-16.8)	11.3 (9.3-13.4)	17.9 (16.3-19.6)	16.7 (13.1-20.3)	22.8 <sup>\$\$\$,\$\$</sup> (21.0-24.6)	16.7 (10.7-22.6)
<b>Men (n = 942, 26.7%)</b>	<b>Analgesia within the last two weeks; Yes = 511 (54.2%); No = 431 (45.8%)</b>					
Domain of functioning (%)	No pain/mild pain		Moderate pain		Severe pain	
Range: 0% (no limitation) to 100% (complete limitation)	Yes	No	Yes	No	Yes	No
	N = 192 (20.4%)	N = 316 (33.6%)	N = 200 (21.2%)	N = 88 (9.3%)	N = 119 (12.6%)	N = 27 (2.9%)
Basic activities of daily living	8.3 (5.7-10.8)	4.6 (2.6-6.5)	16.3 <sup>\$\$\$</sup> (13.8-18.8)	10.6 <sup>\$</sup> (6.8-14.4)	33.7 <sup>\$\$\$,\$\$\$</sup> (30.4-36.9)	30.0 <sup>\$\$\$,\$\$\$</sup> (23.2-36.8)
Instrumental activities of daily living	9.7 (6.6-12.7)	5.3 (3.0-7.7)	19.4 <sup>*,\$\$\$</sup> (16.4-22.3)	11.0 (6.5-15.4)	32.0 <sup>\$\$\$,\$\$\$</sup> (28.1-35.8)	28.6 <sup>\$\$\$,\$\$</sup> (20.5-36.6)

Women (n = 2,584; 73.3%)	Analgesia within the last two weeks; Yes = 1,884 (72.9%); No = 700 (27.1%)					
Mental functioning	28.3 (26.2–30.5)	27.0 (25.3–28.7)	32.8 <sup>§§</sup> (30.7–34.9)	33.7 <sup>§§</sup> (30.5–36.9)	45.8 <sup>§§§,§§§</sup> (43.0–48.6)	44.5 <sup>§§§,§§</sup> (38.8–50.3)
Social functioning	6.7 (2.6–10.8)	1.8 (0.0–5.0)	19.9 <sup>§§§</sup> (15.9–23.9)	14.7 <sup>§§</sup> (8.6–20.7)	41.0 <sup>§§§,§§§</sup> (35.8–46.2)	31.0 <sup>§§§</sup> (20.0–41.9)
Cognitive functioning	14.5 (11.4–17.6)	9.2 (6.8–11.6)	19.0 (15.9–22.1)	15.9 (11.3–20.5)	26.9 <sup>§§§,§§§</sup> (22.9–30.9)	27.2 <sup>§§§,§</sup> (18.8–35.5)
‡ = p < 0.001;						
† = p < 0.01;						
* = p < 0.05 analgesia versus no analgesia within pain severity subgroup;						
§§§ = p < 0.001;						
§§ = p < 0.01;						
§ = p < 0.05 versus no pain/mild pain within analgesic treatment subgroup;						
§§§ = p < 0.001;						
§§ = p < 0.01;						
§ = p < 0.05 versus moderate pain within analgesic treatment subgroup; not significant when not specified.						
Values expressed as mean (95% CI) corrected for covariates (see Methods section for a list of covariates included in the model).						

Adjusted mean functioning in IADLs was found to be slightly higher than in BADLs, being 19.1% (25.8) in the entire group of OA subjects. It was again also found to exhibit a significant association with pain severity ( $p < 0.001$ ) regardless of analgesic treatment (Table 2). Likewise, OA patients with treated moderate or severe pain showed significantly higher limitation in IADLs than non-treated OA patients (Table 2). The magnitude of these differences was small to moderate, with effect sizes ranging from 0.20 to 0.44. The analysis by gender (Table 3) replicated the findings observed in the entire group, mainly in OA patients with severe pain. Meaningful limitation (greater than 60%) in IADLs was also significantly associated with pain severity, but not analgesic intake, with 21% of treated patients and 12% of non-treated patients with such a degree of limitation in the severe pain subgroup (Fig. 1). However, the analysis by category of functional limitation again showed significant differences in distribution of degrees of limitation according to pain severity as well as in each subgroup between treated and not treated with analgesics (Fig. 2). This figure shows that, for instrumental activities, restriction increased as pain severity increases and this restriction was greater in

individuals who required analgesia. The main driver for such findings in IADLs was the item exploring the patient's ability to do hard housekeeping compared to the other items in the domain ( $p < 0.001$ , Fig. 3b).

#### Mental functioning

Adjusted mean limitation in mental functioning was even higher than in physical activities; it was found to be 34.7% (17.4) in the entire OA group and to have a significant linear association with pain severity ( $p < 0.001$ , Table 2). Limitation in this key domain was found to be not significantly different by analgesic treatment status (Table 2). The analysis by gender (Table 3) replicated the findings observed in the entire group. Meaningful limitation (greater than 50%) in mental decline was also significantly associated with pain severity (but not analgesic intake), with 38% of treated patients and 34% of untreated patients with such a degree of limitation in the severe pain subgroup (Fig. 1). However, the analysis by category of this functional limitation showed significant differences in the distribution of degrees of limitation according to pain severity, but not between those treated and those untreated with analgesics (Fig. 2). Figure 2 shows that, for mental functioning, decline increased as pain severity increased, regardless of analgesic treatment.

#### Social functioning

Adjusted mean limitation in social functioning was found to be 18.2% (35.4) overall. It was also found to have a significant association with pain severity ( $p < 0.001$ ), regardless of whether patients were treated with analgesics (Table 2). Nonetheless, treated OA patients showed significantly higher restriction of social activity than non-treated OA patients in all three subgroups by pain severity (Table 2). However, the magnitude of these differences was again small, with effect sizes ranging from 0.11 to 0.30. The analysis by gender (Table 3) replicated the findings observed in the entire group. Meaningful limitation (100% restriction of social activity) was also significantly associated with pain severity (but not analgesic intake, except for OA subjects with mild pain,  $p = 0.006$ ), with 32% of treated patients and 25% of non-treated patients with such a degree of limitation in the severe pain subgroup (Fig. 1). The analysis by category of functional limitation showed significant differences in the distribution of degrees of limitation according to pain severity, but only a trend toward statistical significance by analgesic status (Fig. 2). Figure 2 also shows that, for social functioning, restriction increased as pain severity increased, regardless of analgesic treatment.

#### Cognitive functioning

Adjusted mean limitation in cognitive functioning was 16.8% (23.3) for OA patients, but also with a significant association with pain severity ( $p < 0.001$ , Table 2). Only OA patients with treated mild pain showed significantly greater cognitive deterioration than non-treated OA patients (Table 2), with a negligible effect size of 0.18. The analysis by gender (Table 3) replicated the findings observed in the entire group. Meaningful limitation (severe to total inability with regard to remembering and concentrating) was also significantly associated with pain severity (but not analgesic intake, except for OA subjects with mild pain,  $p = 0.038$ ), with 17% of treated patients and 11% of non-treated patients with such a degree of limitation in the severe pain subgroup (Fig. 1). The analysis by category of functional limitation showed significant differences in the distribution of degrees of limitation according to pain severity, but not by analgesic status (Fig. 2). Figure 2 also shows that, for cognitive functioning, deterioration increased as pain severity increased, regardless of analgesic treatment.

## Discussion

This study was conducted with the objective of determining whether patient self-reported functioning in key domains of daily living differs by pain severity and analgesic treatment among older adults with OA in Spain. To do this, the data from the latest available ENSE survey were used [22]; this could be considered a strength of this study due to the large size of the sample analyzed and its nationwide representability, despite the fact that data capture was based on persons surveyed. Nonetheless, self-rated OA severity and other outcomes, including pain, function, productivity, and costs in both United States and European populations suggest that self-reporting of OA severity provides an accurate and tangible assessment of patients' perceptions of their disease [15,34,35]. Another strength of using the ENSE survey was that the self-reported prevalence of OA was more or less the same as the physician-based Spanish prevalence study of rheumatologic diseases (the EPISER study) conducted recently by the Spanish Association of Rheumatology [36]; the prevalence of OA in persons aged 40 or older was 29.4% in the EPISER study versus 29.8% in the ENSE survey in the same age group. In the analysis included here, a large sample comprising a total of 3,389 OA patients aged 65 or older was analyzed, given that the ENSE only examines the variables that were objective of this study in that age group. However, while analysis was restricted to this population, it is ultimately the population that is most representative of osteoarthritis; 67.4% of patients with self-reported OA in Spain are 65 years of age or older, and the figure is similar to that seen in the EPISER study [22, 36]. Also, the study analyzed up to five different key domains of patient functioning in daily life; that too could be considered as a strength of this study as, to the best of our knowledge, there are no existing similar studies in the Spanish population.

As OA is a heterogeneous disease, several limitations of this study are to be pointed out. First, it lacks detailed data with regard to OA location; second, it lacks data regarding whether OA affects a single joint or several joints; third, it lacks a radiographic assessment scale; and fourth, it lacks data about the relationship between OA and other comorbidities and their relationship to the functional impairment found. Moreover, it must be taken into account that the survey collected information on pharmacological analgesic treatment of OA in a generic fashion (treated or not treated with usual analgesics in the last two weeks), but lacked detailed information on active substances, doses, etc., as well as information regarding non-pharmacological treatment (which is central to OA treatment). Those data were not reported in the survey; moreover, the data in the survey are self-reported by survey participants rather than drawn from medical databases or directly from medical personnel. Furthermore, although the size of the sample analyzed was large, some subgroups of patients (particularly OA subjects with untreated severe pain) could be under-represented in the study.

Regarding the comparability of this analysis, a similar study was conducted by Stamm et al. in Austria [21]. That study focused on activities of daily living alone; however, it did analyze the impact of pain. Our study of functional capacity found that these patients have a considerable degree of limitation in carrying out both basic and instrumental activities of daily living, mainly those with severe pain. Mobility (walking and up/downstairs) and hard housekeeping were the specific activities most seriously impacted by OA pain and accounted for the most weight (around 17–23% per item) in the total scores for BADLs and IADLs, respectively, when compared with other items in such domains. In addition, patients with OA experienced restriction and decline in other essential functions such as cognition, social functioning and mental health. In all these domains of functioning, a significant association was found between pain severity and impairment, such that the higher the pain, the higher the impairment, regardless of treatment status; this points to an increased need for external care. All OA patients with severe pain in the ENSE survey declared they were

dependent to some degree of external caregiver care for both BADLs and IADLs. In addition, OA subjects treated with common analgesics showed significantly higher impairment in BADLs, IADLs, and social functioning, particularly subjects with moderate or severe pain; limitation of social functioning was as high as 42% compared with 32% in the group of patients not treated with analgesia. The study by Stamm et al. [21] also found a significant association between pain severity and impact thereof on both BADLs and IADLs in older adults with OA among other disorders. The European Project on OsteoArthritis (EPOSA study), aimed at investigating the consequences of the most common forms of OA in older adults using data from six European countries, including Spain [37], found that clinical OA, present in one or two sites (hip and knee), or in two or three sites (hip, knee, and hand), increased the risk of social isolation, cognitive impairment and worse walking and physical activity [38, 39]. These findings are consistent with our analysis, particularly in the moderate to severe pain group, although the EPOSA study did not analyze whether the presence of pain interferes with activities of daily living [40]. Likewise, more severe and stable joint pain levels were found to be associated with anxiety and depressive symptoms in older persons with OA [41]; this is fairly consistent with the impairment in mental functioning found in the analysis of older Spanish subjects with OA included in the 2017 ENSE survey. Research aiming to demonstrate that individuals with OA are more likely to experience impairment in their ability to perform activities of daily living has been seen previously, but in selected populations and mainly on patients with OA in specific health settings or on waiting lists for joint replacement [17–20]. Recently, persistent opioid users were found to be more likely than non-users to report limitations in IADLs and physical, social, and cognitive functioning in follow-up [42]. Our analysis is also consistent with data regarding poorer patient functioning in BADLs, IADLs, and social functioning in subjects using analgesic drugs, although the ENSE survey was not able to identify active substances in analgesic agents used by patients. Given the nature of this study, not allowing to see a cause–effect relationship, it is possible that treated patients had more severe joint destruction; it is also possible that treated patients had developed a phenomena of secondary central sensitization to pain, due to a failure to achieve optimal pain management, perhaps because they had partially responded or not responded to conventional analgesic therapies, and other psychopathological reasons. Although not evaluated in this survey, frailty, defined as a geriatric syndrome that involves loss of functioning and is a prognostic factor for disability [43], might have been present in a significant percentage of these patients, given the impairment observed in activities of daily living and mental function, which might have been correlated with low physical activity, overall weakness, exhaustion and overall slowness [43].

The gender analysis showed similar findings. Due to limitations in sample sizes, differences did not reach statistical significance in some comparisons; regardless, our analysis failed to find significant differences between treated and untreated patients within the subset of patients with meaningful limitation (the most impaired category) in each of the key domains of functioning analyzed in this study, although this subset was larger in treated subgroups. Nonetheless, the association between pain severity and percentage of OA patients with significant limitation was present in each of the domains of functioning evaluated, with significantly more subjects with meaningful restriction in the severe pain category subgroup. Also, clinical OA was associated with frailty and pre-frailty in older adults in European countries [37].

The prevalence and burden of OA is growing as both population aging and obesity rates rise; this means that the viability of joint replacement programs will be at risk by 2030. Unmet needs exist regarding not only

disease progression modifiers but also pain management. Hence, this disease merits more attention, not only from medical researchers, but also from healthcare policymakers, who must work towards coordinating a holistic approach that includes comprehensive OA treatment and adequate pain management. In conclusion, in a representative nationwide sample in Spain, in patients aged 65 years and older with treated moderate to severe OA pain, said pain was associated with a substantial impact on their functioning in five key domains of patient functioning. Pain severity was the major determinant of disability, and all other study variables decreased as pain severity increased, regardless of the analgesia approach pursued.

## Abbreviations

BADLs

basic activities of daily living

CAPI

computer-assisted personal interview

CI

confidence interval

ENSE

Spanish National Health Survey

FCI

Functional Comorbidity Index

FDA

United States Food and Drug Administration

GHQ-12

12-Item General Health Questionnaire

GLM

generalized linear model

IADLs

instrumental activities of daily living

OA

osteoarthritis

SD

standard deviation

SF-36v2

Short Form 36 Health Survey Version 2

## Declarations

**Ethics approval and consent to participate:** The analysis carried out in this study used aggregate data available in the public domain only, thus, de-identification was guaranteed to prevent anyone's personal identity from being revealed. Therefore, studies such as this one are exempt from IRB review and from classification by the Spanish Agency of Medicines and Medical Devices according to current regulations for post-authorization observational studies

(<https://www.aemps.gob.es/investigacionClinica/medicamentos/estudiosPostautorizacion.htm#norEstatal>). The confidentiality of the records (anonymous and dissociated) was respected according to the existing Spanish Law on Personal Data Protection (Law 15/1999, of 13 December 1999, on Personal Data Protection). Individuals included in the ENSE survey participated voluntarily and gave their personal consent prior to their participation in the survey (see details on survey implementation at: <https://www.msbs.gob.es/estadEstudios/estadisticas/encuestaNacional/encuesta2017.htm>).

**Consent for publication:** The manuscript has been read and approved by all authors who also meet the requirements for authorship. All of them agreed to submit the manuscript for publication, and that decision pertains solely to all authors.

**Availability of data and material:** Data and analysis are available upon request.

**Competing interests:** This work has not received any funding and the authors declare that they have no conflicts of interest with respect to this study. The analysis was conducted by Natalia Llopart and Sofia García to obtain their master's degree in Health Assessment and Market Access at Universidad Carlos III, Madrid, Spain, under the direction of Javier Rejas, Associate Professor for said master's degree. Javier Rejas is also employed at Pfizer, SLU, Alcobendas (Madrid), Spain. Francisco Castro is a rheumatologist at Centro Médico Teknon and Hospital Universitari Sagrat Cor in Barcelona, Spain, and participated in the preparation of the manuscript and interpretation of the findings.

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**Authors' contributions:** Each author agrees that the manuscript represents honest work. The manuscript was prepared jointly by all authors, and all of them had the right to review, comment on, and approve the manuscript prior to submission. The data reported within the manuscript are not proprietary to any of the authors. Javier Rejas was responsible for the study concept. Natalia Llopart, Sofia García, Javier Rejas, and Francisco Castro were responsible for data analysis, data abstraction, and data interpretation.

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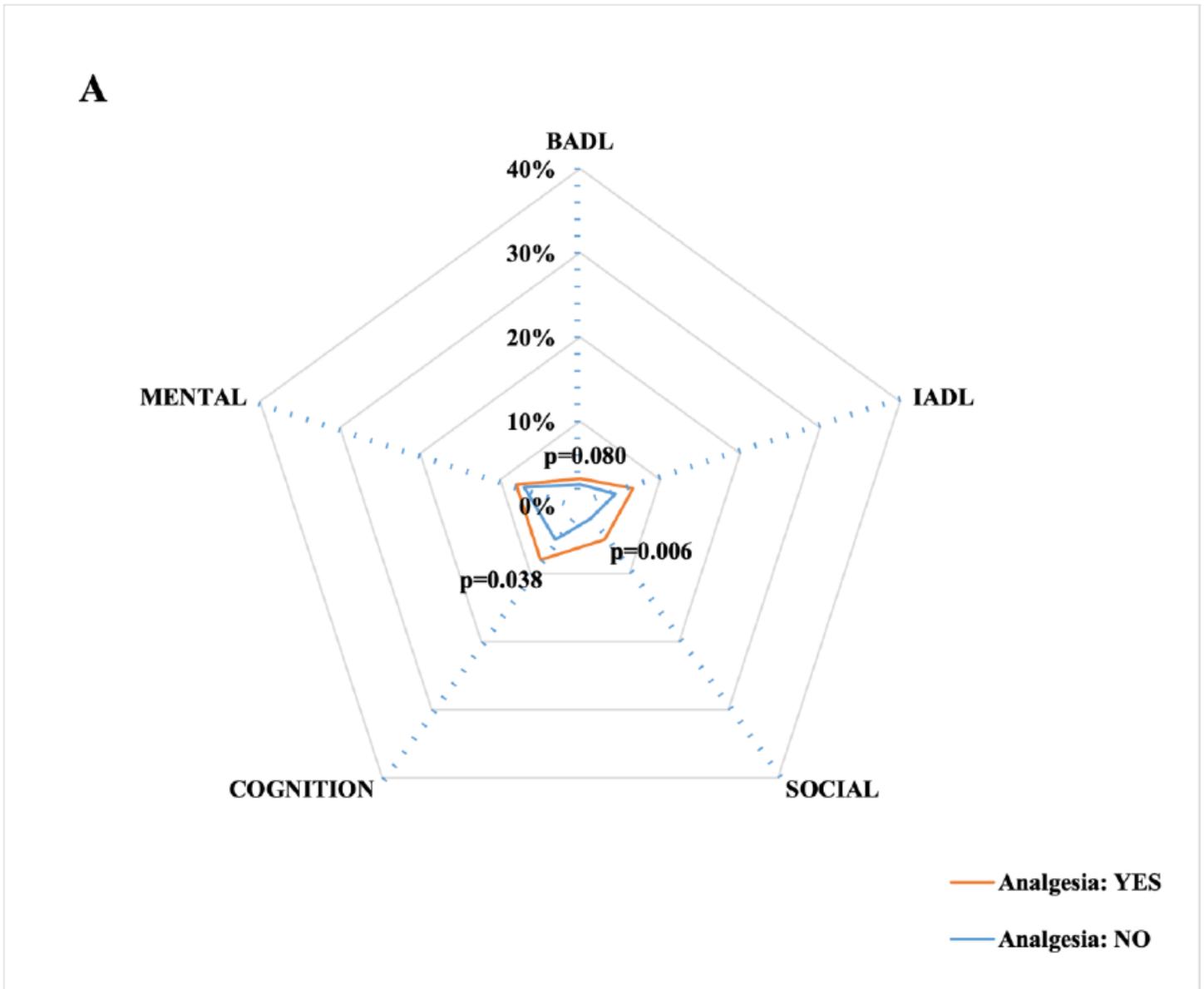
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## Figures



**Figure 1**

Adjusted prevalence of osteoarthritis patients with functional limitation by pain severity and analgesia use. Graph A = No pain/Mild pain; Graph B = Moderate pain; Graph C = Severe pain. BADLs = Basic activities of daily living; IADLs = Instrumental activities of daily living. See text for cut-off value for meaningful limitation in each domain of functioning.

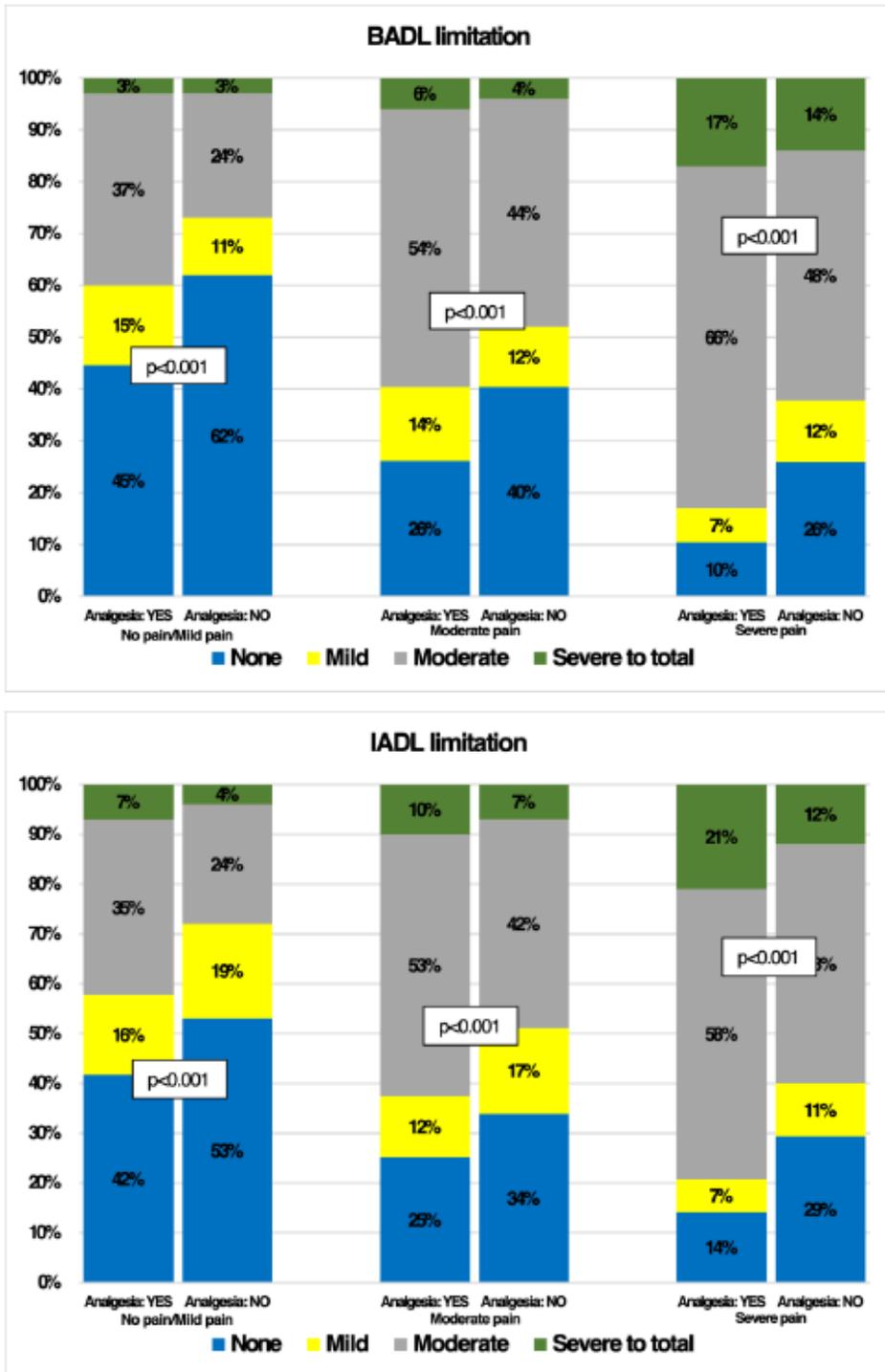


Figure 2

Distribution of functional limitation categories in patients with osteoarthritis by pain severity and analgesia use. p values adjusted by covariates. BADLs = Basic activities of daily living; IADLs = Instrumental activities of daily living.

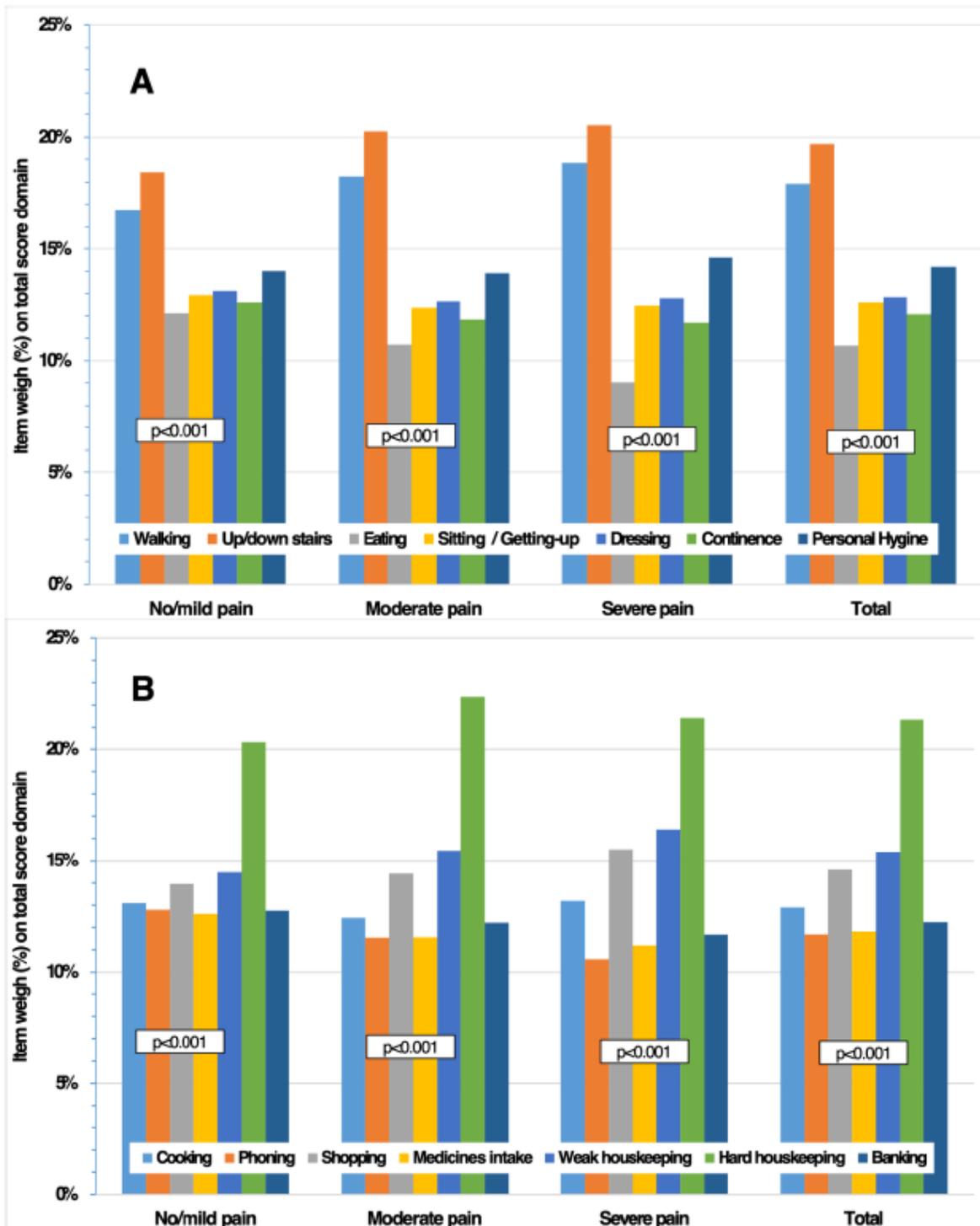


Figure 3

Item weights in total score for domains of physical functioning: BADLs = Basic activities of daily living (Graph A); IADLs = Instrumental activities of daily living (Graph B).

## Supplementary Files

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