Within-person pain variability and mental health in older adults with osteoarthritis: an analysis across six European cohorts

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Running title: *Pain variability and mental health in OA*

Disclosures: *Research funding*: The Indicators for Monitoring COPD and Asthma - Activity and Function in the Elderly in Ulm study (IMCA - ActiFE) was supported by the European Union [No.: 2005121] and the Ministry of Science, Baden-Württemberg. The Italian cohort study is part of the National Research Council Project on Aging (PNR). The Longitudinal Aging Study Amsterdam (LASA) is financially supported by the Dutch Ministry of Health, Welfare and Sports. The Penagrande study was partially supported by the National Fund for Health Research (Fondo de Investigaciones en Salud) of Spain [project numbers FIS PI 05/1898; FIS RETICEF RD06/0013/1013 and FIS PS09/02143]. The Swedish Twin Registry is supported in part by the Swedish Ministry of Higher Education. The Hertfordshire Cohort Study is funded by the Medical Research Council of Great Britain, Arthritis Research UK, the British Heart Foundation and the International Osteoporosis Foundation. The funding sources had no role in the study design, the collection, analysis and interpretation of the data, in the writing of the report and in the decision to submit the article for publication. *Conflicts of interest*: The authors declare that they have no conflicts of interest.

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ABSTRACT

Pain is a key symptom of Osteoarthritis (OA) and has been linked to poor mental health. Pain fluctuates over time within individuals, but a paucity of studies have considered day-to-day fluctuations of joint pain in relation to affective symptoms in older persons with OA. This study investigated the relationship of both pain severity and within-person pain variability with anxiety and depression symptoms in 832 older adults with OA who participated in the European Project on OSteoArthritis (EPOSA): a six-country cohort study. Affective symptoms were examined with the Hospital Anxiety and Depression Scale, pain severity was assessed with the WOMAC/AUSCAN, and intra-individual pain variability was measured using pain calendars assessed at baseline, 6 and 12-18 months. Age-stratified multiple linear regression analyses adjusted for relevant confounders showed that more pain was associated with more affective symptoms in older-old participants (74.1-85 years). Moreover, older-old participants experienced fewer symptoms of anxiety (ratio=.85, 95% CI: .77-.94), depression (ratio=.90, 95% CI: .82-.98) and total affective symptoms (ratio=.87, 95% CI: .79-.94) if their pain fluctuated more. No such association was evident in younger-old participants (65-74.0 years). These findings imply that stable pain levels are more detrimental to mental health than fluctuating pain levels in older persons.

Perspective: *This study showed that more severe and stable joint pain levels were associated with anxiety and depressive symptoms in older persons with OA. These findings emphasize the importance of measuring pain in OA at multiple time-points, as joint pain fluctuations may be an indicator for the presence of affective symptoms.*

KEYWORDS

Osteoarthritis; pain variability; depressive symptoms; anxiety symptoms; older persons.

INTRODUCTION

Osteoarthritis (OA) is the most common form of musculoskeletal disorders worldwide [41] and a leading cause of functional limitations and loss of independence in later life. Chronic pain represents one of the key debilitating symptoms of OA [10]. Moreover, OA - and in particular pain experienced by OA patients - has been linked to an increased risk of affective symptoms, such as depression [5, 6, 20, 29] and anxiety [5, 6, 29]. In turn, affective symptoms may have a detrimental effect on pain perception [5]. A recent systematic review and meta-analysis concluded that around 20% of persons with OA experience depressive and/or anxiety symptoms [35]. More insight is needed in the vicious circle in which pain, depression, and anxiety may continually reinforce each other over time in persons who suffer from OA.

The severity of pain in OA may vary greatly between individuals [11]. Moreover, individuals may experience stable pain levels or fluctuations in pain over time [11, 32]. A fluctuating course requires repeated measurements and is difficult to capture with commonly used instruments such as the Western Ontario and McMaster Universities OA Index (WOMAC) [7] and the Australian/Canadian Hand Osteoarthritis Index (AUSCAN) [8].

The association between variability in pain experience and mental health is bi-directional [18, 21] and has been rarely studied [32]. Schneider et al. [32] showed more day-to-day fluctuations of pain in adult patients with OA or other rheumatic diseases who had higher levels of depressive symptoms. Anxiety symptoms were not predictive of variability in pain scores in their study.

To our knowledge, no study to date has focused on the effect of intra-individual pain variability over time on anxiety and depressive symptoms in persons with OA. The European Project on OSteoArthritis (EPOSA) provides a unique opportunity to examine these associations in older persons with OA from the general population [40]. In this study, we used data of the EPOSA cohort to examine the relationship of both pain severity and within-person pain variability over time with symptoms of anxiety and depression. Presuming that a lack of predictability of pain is detrimental to mental wellbeing [32], it was hypothesized that more

severe pain and greater pain variability over time would be associated with more affective symptoms [5, 20, 32].

METHODS

Study design and participants

The European Project on OSteoArthritis (EPOSA) is a multi-cohort study aimed at investigating the personal and societal consequences of OA and its determinants, using pre-harmonized data from six European population-based cohorts of older adults. Participating countries include Germany, Italy, the Netherlands, Spain, Sweden and the United Kingdom. Detailed information about the EPOSA design, participants and procedures of data collection are described elsewhere [40]. In short, 2942 community-dwelling persons of 65-85 years with and without OA were included. Interviews and clinical assessments took place at baseline and after 12 to 18 months. Furthermore, immediately after the baseline and follow-up interview as well as 6 months after baseline, participants were asked to complete a two-week calendar assessing joint pain. Presence of the three most common forms of OA – knee, hip and hand OA – was assessed with a clinical examination based on the criteria of the American College of Rheumatology [3], which resulted in a total of 889 participants with clinical OA of the knee, hand and/or hip. For the current study, we used data from persons with clinical OA who did not report joint replacements or surgery in the past two weeks at the site of the clinical OA (N=832). All six cohort studies were approved by the Ethical Review Boards of the respective institutions and all participants gave written informed consent prior to the start of the study.

Measurements

Pain severity

Pain severity in the past 48 hours was measured with the WOMAC [7] (knee and hip OA) and AUSCAN [8] (hand OA) pain subscales at baseline and follow-up. These commonly-used

questionnaires assess pain in five daily life situations, rated on a 0 (no pain) to 4 (extreme pain) scale. As the WOMAC and AUSCAN pain subscales are scored on the same scale (score range: 0-20), the raw scores of knee, hip and hand pain were added up, resulting in a total pain severity score (range 0-60). This score was then transformed to a 0-100 scale for comparability to other studies [7].

Pain variability

At baseline and after 6 and 12-18 months, participants completed two-week calendars assessing daily joint pain. On these calendars, participants indicated their amount of joint pain per day, ranging from 0 (no pain) to 10 (extreme pain). In addition, participants were asked to indicate whether they took pain medication, whether they consulted a doctor and whether they had surgery as a result of their joint pain. No information regarding site and context of the joint pain was collected. Participants from Spain did not complete the 6-month calendar. As a measure of individual day-to-day pain variability over a longer time period, the standard deviation (SD) of the scores of all available days of the three calendars was calculated for each participant. The more day-to-day pain variability a person reported, the larger the SD. At least 7 of 14 days of at least one calendar had to be completed by a participant in order to be included in the pain variability analyses.

Affective symptoms

The Hospital Anxiety and Depression Scale (HADS) [44] was used to measure symptoms of anxiety (HADS-A, 7 items) and depression (HADS-D, 7 items) at baseline and follow-up. The HADS is a widely-used, self-rated measure assessing affective symptoms the participant experienced in the past four weeks. The total HADS score (HADS-T) is a general measure of total affective symptoms. Item scores range from 0 (rarely or never) to 3 (mostly or always). Total scores for the subscales range from 0-21, with a score of ≥8 being indicative of the presence of a disorder. Total scores for the combined scale range from 0-42. The HADS

displays good reliability and validity in several medical and general population samples [9] and in people with OA [6].

Potential effect modifiers and confounders

We examined whether age [23, 27] and gender [25, 38] were effect modifiers in the relationship between pain and affective symptoms. The analyses were adjusted for the following confounders: age, gender (if no effect modifier), country, education level (< elementary school, elementary school, vocational/secondary education, or college/university education), smoking [15] (never, former, or current smoker), body mass index (BMI: weight in kg / height in m^2) [26], number of chronic diseases (selected from the seven most common chronic somatic diseases in the older population: chronic non-specific lung disease, cardiovascular disease, disease of peripheral arteries, stroke, diabetes mellitus, cancer and osteoporosis), physical activity (in kcal/day, assessed with the LASA Physical Activity Questionnaire) [34, 36] and use of psychotropic medication (antidepressants, anxiolytics and/or antipsychotics use yes/no) and pain medication (analgesics or anti-inflammatory medication use yes/no) [1428].

Statistical analysis

Descriptive characteristics of the study sample were examined with frequencies / percentages for categorical variables and medians / interquartile ranges (IQRs) for skewed continuous variables. With the exception of age, gender and country, all descriptive statistics were weighted to adjust for differences in the distributions of age and gender across the six samples. Weights were calculated per gender and per five-year age category, using the formula: *W = Nexp / Nobs*, where Nexp is the number of persons in a specific age/gender category in the European population, and Nobs is the number of persons in a specific age/gender category in the cohort [40]. Differences between participants in the analysed sample and persons who dropped out after baseline were examined with chi-square (for dichotomous or categorical variables) or Mann Whitney (continuous variables) tests in non-

response analyses. Cronbach's alphas were calculated for the HADS and the WOMAC/AUSCAN, both at baseline and at follow-up, to evaluate the reliability of the scales in the EPOSA sample.

For pain severity, both cross-sectional and longitudinal multiple linear regression analyses were conducted. For the cross-sectional analysis, the baseline WOMAC/AUSCAN combined pain score was used as predictor and the baseline HADS-A, HADS-D and HADS-T scores as continuous outcome variables. To examine the relationship between pain severity and affective symptoms over time, the baseline WOMAC/AUSCAN combined pain score was used as predictor, the HADS-A, HADS-D and HADS-T scores after 12-18 months, respectively, as outcomes and the respective baseline HADS score as additional covariate to control for baseline levels of affective symptoms.

To study whether intra-individual pain variability over time affects affective symptoms, multiple linear regression analyses were performed with the individual joint pain SDs (calculated from the three pain calendars) as predictor and the three HADS scores at 12-18 months as outcomes. A potential drawback of using the SD of the individual pain scores as a measure of pain variability is that the SD is the same for persons who report the same magnitude of fluctuations, regardless of their mean pain score. For instance, two persons with mean pain levels of 0 and 10, respectively, who experience no pain fluctuations, will both have an SD of 0. For this reason, we adjusted all pain variability analyses for the individual mean joint pain score, calculated from all available joint pain scores on the calendars (similar to the calculation of the SD pain variablility score).

To study possible effect modification by age and gender, an interaction term of the predictor with the potential effect modifier was created. This interaction term was added to the unadjusted analyses. If the p-value of the interaction term was <.10, effect modification was considered to be present and stratified analyses were conducted.

To examine the robustness of the effects, we analyzed two models. In Model 1, we adjusted for country, age and gender (if no effect modifier). In Model 2, we additionally

adjusted for education level, smoking, BMI, number of chronic diseases, physical activity and use of psychotropic and pain medication.

We conducted pre-planned sensitivity analyses for both pain severity and pain variability omitting persons who reported taking psychotropic medications, as these drugs may not only decrease affective symptoms, but also alleviate pain [28].

As the score distribution of all three HADS measures was skewed to the right, the following natural log transformation was conducted on the HADS scores: Ln(1+HADS score). The regression coefficients and confidence intervals (CIs) from the regression analyses were back-transformed to obtain interpretable ratios. These ratios can easily be converted into a percentage of change in the outcome variable (affective symptoms) per one unit change in the predictor (pain). As a one-unit increase/decrease on the pain severity scale of 0-100 is very small, a more meaningful 10-unit increase/decrease [4] was derived by calculating ratio^10. A two-sided p-value of .05 was regarded as statistically significant. All analyses were conducted with SPSS version 22 (SPSS Inc. Chicago, IL, USA).

RESULTS

Characteristics of the study population can be found in **Table 1**. Over two-thirds of the participants were female (70.2%) and the median age was 74.0 years. Of the 832 participants in the present analyses, 67.0% had OA at one site, 26.6% at two sites and 6.5% at all three sites. The median range of fluctuations in joint pain within one calendar (two weeks) was 3 points (IQR 2-4, range 0-10) for the baseline pain calendar and 2 (IQR 1-4, range 0-10) for the 6 and 12-18 months pain calendars.

Cronbachs alphas of the HADS-A, D and T at baseline and follow-up varied between .736 and .859, indicating good reliability of the scale. Similarly, the reliability of the WOMAC/AUSCAN pain severity scale was also good (Cronbach's alpha .891 and .908 for the baseline and follow-up scales, respectively).

In non-response analyses for pain variability, participants in the analyzed sample were compared to persons who dropped out of the study or did not complete at least 7 days on at least one pain calendar (N=69). At baseline, 85.2% of the participants completed ≥7 days of the calendar. At 6 months, 57.7% completed ≥7 days (Spain not taken into account) and at 12-18 months, 58.5% completed ≥7 days. At baseline, non-responders to the pain calendar were older (p<.001) and had more depressive symptoms (p=.019), compared to participants who did complete at least 7 days. At 6 months, persons who dropped out or did not complete the calendar were older (p=.029), lower educated (p=.009), had more anxiety (p<.001) and depressive symptoms (p=.001), more severe pain (p=.043), more chronic diseases (p=.044) and higher BMI (p=.047). At 12-18 months, this pattern was similar, with the addition that non-responders were more often female (p=.022) and did not have a higher BMI compared to the responders to the calendar.

---Insert Table 1 about here---

Pain severity

Cross-sectional analyses: In the cross-sectional baseline analyses, gender was not an effect modifier. However, age was a significant effect modifier for anxiety (p<.001) and total affective symptoms (p=.002), but not for depressive symptoms (p=.22). Therefore, analyses were stratified at the median age (74.0 years) for anxiety and total affective symptoms and analyses for depressive symptoms were conducted in the group as a whole (see **Table 2**). The regression analyses showed that, adjusted for relevant confounders, greater pain severity was associated with more anxiety (*ratio*=1.011, p<.001) and total affective symptoms (*ratio*=1.007, p=.011) in persons over 74 years ('older old'), but not in persons between 65 and 74 years ('younger old'; *ratio*=1.002, p=.43 and *ratio*=1.004, p=.12, respectively). In the total group, more severe pain was associated with more depressive symptoms (*ratio*=1.006, p=.001). Accordingly, a 10-unit increase in pain severity corresponded to a 11.6% increase in

anxiety symptoms and a 7.2% increase in total affective symptoms in persons >74 years, and with a 6.2% increase in depressive symptoms in the total group.

Longitudinal analyses: Contrary to the cross-sectional analyses, age was not an effect modifier in the longitudinal analyses of pain severity. However, sex was a significant effect modifier for anxiety and total affective symptoms (*p*=.002 and .021, respectively; HADS-D: *p*=.21). Hence, analyses for anxiety and total affective symptoms were conducted separately for males and females and analyses for depressive symptoms were conducted in the total group (see Table 2). Adjusted for confounding, more severe pain at baseline was associated with more affective symptoms at follow-up in males (*ratio*=1.009, *p*=.022) but not in females (*ratio*=0.99, *p*=.78). In the total group, more severe pain at baseline was associated with more depressive symptoms at follow-up (*ratio*=1.006, *p*=.002). In accordance, a 10-unit increase in baseline pain severity corresponded to a 9.4% increase in total affective symptoms at follow-up in males and a 6.2% increase in depressive symptoms in the total group.

Sensitivity analyses: the sensitivity analyses without persons who use psychotropic medications (N=178) did not change any of the conclusions (data not shown but available on request from the author).

---Insert Table 2 about here---

Pain variability

Table 3 displays the results of the pain variability analyses. Gender was not a significant effect modifier. However, age was a significant effect modifier for all three HADS outcomes (HADS-A: *p*=.002; HADS-D: *p*=.004; HADS-T: *p*=.001). Therefore, all analyses were conducted separately for the two age groups, again stratified at the median age. Greater pain variability over 12-18 months was significantly associated with lower anxiety (*ratio*=.85, *p*=.002), depressive (*ratio*=.90, *p*=.018) and total affective symptoms (*ratio*=.87, *p*=.002) after

12-18 months in the older-old participants. In accordance, a 1-unit increase in pain variability was associated with a 15% lower anxiety score, a 10% lower depression score and a 13% lower affective symptoms score in persons with OA over 74 years. No statistically significant associations between pain variability and affective symptoms were observed in participants between 65 and 74 years of age.

Sensitivity analyses: the sensitivity analyses without persons who use psychotropic medications (N=178) did not change any of the conclusions (data not shown but available on request from the author).

---Insert Table 3 about here---

DISCUSSION

Pain is a common and debilitating symptom of OA that can have substantial consequences for daily life. The present study investigated whether pain severity and pain fluctuations over time in older persons with OA from the general European population were associated with symptoms of anxiety and depression. The results demonstrated that more severe pain was associated with more depressive symptoms. In addition, higher pain severity in persons over 74 years ('older-old persons') was associated with more anxiety and total affective symptoms. Over time, depressive symptoms became worse when pain severity increased. In males, total affective symptoms increased with increasing pain severity. Previous studies have also indicated that pain severity is related to symptoms of anxiety and depression (refs 4-6). The results from the EPOSA study strenghten these findings by demonstrating the association in a large sample of community-dwelling people with OA from multiple countries.

Day-to-day pain variability was assessed with three two-week pain calendars over a time course of 12-18 monhts. The calendars showed substantial individual day-to-day fluctuations of pain levels. Contrary to our expectations, more fluctuations in joint pain were associated

with less anxiety, depressive and total affective symptoms in the older-old persons. In the younger-old participants (65-74 years), pain variability was not significantly associated with affective symptoms.

Similar to the study by Schneider et al. [32], we expected to find more affective symptoms in persons with more fluctuating pain levels, possibly because of lack of control over and predictability of pain episodes. However, we found the opposite pattern. There are some differences between our study and Schneider's study that may explain this discrepancy. For instance, the study by Schneider recruited patients with OA and other rheumatic diseases from clinics, whereas we investigated a population-based sample with (clinical) OA. Furthermore, Schneider et al. assessed pain in general, whereas we specifically asked about joint pain. Finally, the sample size of the study by Schneider was substantially smaller (N=300) than the sample size of the present study (N=832).

An explanation for the observed pain variability results might be that more predictable, stable and chronic pain levels activate feelings of hopelessness and lack of perspective [37]. In addition, persons who also have 'good days' may be better able to withstand the 'bad days', in contrast to persons who have the same, chronic pain level every day. The latter group may also experience more interference with daily life functioning. Furthermore, evidence suggests that maladaptive plastic brain changes occur in persons with chronic pain, that do not occur in person with more acute pain. These changes may alter pain perception and are related to depression [13, 16].

The negative association between pain variability and affective symptoms was observed in the age group over 74 years only. The cross-sectional pain severity analyses showed a similar pattern. Older persons may have fewer effective coping strategies due to more morbidity and/or frailty, compared to younger persons [17, 19, 31]. In attempting to explain this age difference further, we looked at differences in pain and affective symptoms between these two age groups in our sample. The older-old group did not experience more severe or more fluctuating pain levels, but did report more depressive and total affective symptoms

than their younger-old counterparts. This finding may reflect the mutually reinforcing effect of pain and affective symptoms in the older age group [5, 43]. Our age-stratified results are in contrast with the study by Sanders et al., who found that older age did not influence the relationship between pain and depression [31]. However, the study by Sanders et al. was conducted with older persons from the general population; not in a specific OA sample.

As the minimally important difference (MID) in HADS scores has rarely been studied, it is difficult to draw conclusions about whether the observed association between pain severity and variability and affective symptoms is clinically meaningful. One study involving patients with moderate to severe chronic obstructive pulmonary disease showed that the MID for their study sample was 1.5 points [30]. this MID can be taken as an example for the EPOSA study, but it should be kept in mind that the COPD sample differed from the EPOSA sample in multiple ways. As we calculated ratios in our paper, it depends on the baseline HADS score whether a change is clinically meaningful. Our analyses showed that a reduction in pain severity or variability was associated with up to 15% lower HADS scores. Hence, for higher baseline HADS scores, this change is clinically meaningful. One could argue that this change is especially relevant for persons with higher baseline HADS scores, as they experience the most affective symptoms.

This study combines several strengths. First, EPOSA is a large study with a pre-harmonized dataset including prospective cohort data from persons with OA from six European countries. Presence of OA was determined with standardized assessments methods. The study samples were drawn from the general population, which means that we have data from persons with OA ranging from mild to severe and from persons who did and did not receive care for their OA. This study characteristic increases the generalizability of our results. Because of the large dataset, we were able to adjust for many relevant confounders and examine effect modification. Another asset is that we analyzed day-to-day pain variability with multiple joint pain calendars over a large time range, which is a novel and

promising way of analyzing pain in OA. To our knowledge, no other study has focused on the effect of pain variability over time on anxiety and depressive symptoms in persons with OA.

This study also has some limitations. First, we did not ask the participants about other types of pain that they may have had at the same time as their joint pain, so we were not able to adjust for this potentially important confounder. Second, the pain calendar at 12-18 months was completed after the HADS interview, whereas we defined the HADS as our dependent variable. However, the time frame between these measurements was rather short (1 day to two weeks), as the calendar was started the day after the interview. Leaving the third pain calendar out would not only reduce the power of our analyses, but would also mean that the HADS would be measured six months after the last pain calendar, which is a much longer time frame. Third, the information from the pain calendar was not specific enough to determine the site and context of the joint pain. Fourth, the calendars were filled out by hand, without electronic time stamps. Although this paper-and-pen method is preferred by part of the older population, it is prone to 'backfilling' which could potentially harm data quality.

A potential methodological issue is the use of the SD of all available joint pain scores as a measure of pain variability. We combined pain scores from the three calendars that were relatively far apart in time. Correlations between pain variability scores of each calendar were moderate in strength (Spearman's rho: .409 - .571, all $p<.001$), indicating that the three time points are not dissimilar. Moreover, individual SD scores may suffer from relatively low reliability [42]. This potential issue is more pronounced if the number of observations is low. In most cases, the SD was calculated from 3*14=42 observations. Potentially, this number is not sufficient to reach high reliability, which may have led to an underestimation of the results. Future research should examine whether the use of more observations can create a more reliable pain variability score.

The nonresponse analyses revealed that the persons with the highest pain and affective symptom levels were lost to follow-up, which may have attenuated our results. Previous

research, however, indicates that this loss of follow-up data is not likely to be problematic [39]. Finally, despite the longitudinal design, it is still difficult to draw firm conclusions about the causality of pain severity / variability and affective symptoms. Previous research suggests that the relationship may even be bidirectional [5, 33].

The evidence from this study suggests that persons with OA experience substantial day-to-day fluctuations of pain levels. This result is in accordance with another study that also observed that changes in pain were associated with changes in mood in persons with OA [2, 22]. These results emphasize the importance of measuring pain variability in persons with OA, as it may shed a different light on experienced pain and its consequences, compared to measuring pain at only one time-point [2].

At the moment, treatment for depression and anxiety in persons with OA is suboptimal [1, 43]. Pain, anxiety and depression are risk factors for further functional decline in OA [12] and the disease burden increases if a person experiences affective symptoms [24]. Future research should focus on finding effective interventions for reducing (the burden of) chronic pain to improve mental wellbeing in older persons with OA.

In conclusion, the present study showed that more severe and stable joint pain levels are associated with more symptoms of anxiety and depression in persons over 74 years of age who suffer from OA. Due to the fluctuating nature of joint pain in OA, assessing pain severity at only one time-point is not enough to capture the whole story. Therefore, it is important to assess the chronicity of the pain in OA, as it may be an indicator for the presence of anxiety and/or depressive symptoms.

ACKNOWLEDGEMENTS

We are very grateful to all participants of the EPOSA study for their valued contributions. The EPOSA research group: Germany: T. Nikolaus† (Principal Investigator), M. Denkinger, R. Peter, F. Herbolsheimer; Italy: S. Maggi (Principal Investigator), S. Zambon, F. Limongi; M. Noale, P. Siviero; the Netherlands (coordinating center): D.J.H. Deeg (Principal Investigator),

S. van der Pas, N.M. van Schoor, L.A. Schaap, E.J. Timmermans, P. Lips; Spain: Á. Otero (Principal Investigator), M.V. Castell, M. Sanchez-Martinez; Sweden: N.L. Pedersen (Principal Investigator); United Kingdom: E.M. Dennison (Principal Investigator), C. Cooper, M.H. Edwards. The Indicators for Monitoring COPD and Asthma - Activity and Function in the Elderly in Ulm study (IMCA - ActiFE) was supported by the European Union (No.: 2005121) and the Ministry of Science, Baden-Württemberg. The Italian cohort study is part of the National Research Council Project on Aging (PNR). The Longitudinal Aging Study Amsterdam (LASA) is financially supported by the Dutch Ministry of Health, Welfare and Sports. The Penagrande study was partially supported by the National Fund for Health Research (Fondo de Investigaciones en Salud) of Spain (project numbers FIS PI 05/1898; FIS RETICEF RD06/0013/1013 and FIS PS09/02143). The Swedish Twin Registry is supported in part by the Swedish Ministry of Higher Education. The Hertfordshire Cohort Study is funded by the Medical Research Council of Great Britain, Arthritis Research UK, the British Heart Foundation and the International Osteoporosis Foundation.

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Table 1. Characteristics* of the EPOSA participants with clinical OA of the knee, hip, and/or hand.

	Total group		**Younger old (65-74.0 yrs.)**		**Older old (74.1-85 yrs.)**	
Presence of clinical OA:	N=832		N=450		N=382	
Knee OA		523 (63.3)		266 (59.3)		257 (70.2)
Hip OA		162 (19.7)		93 (21.1)		69 (18.2)
Hand OA		468 (56.3)		263 (58.8)		205 (54.8)
Country:	N=832		N=450		N=382	
Germany		76 (9.1)		47 (10.4)		29 (7.6)
Italy		185 (22.2)		109 (24.2)		76 (19.9)
Netherlands		132 (15.9)		53 (11.8)		79 (20.7)
Spain		173 (20.8)		76 (16.9)		97 (25.4)
Sweden		157 (18.9)		115 (25.6)		42 (11.0)
United Kingdom		109 (13.1)		50 (11.1)		59 (15.4)
Gender:	N=832		N=450		N=382	
Females		548 (70.2)		322 (71.6)		262 (68.6)
Males		248 (29.8)		128 (28.4)		120 (31.4)
Age	N=832	74.0 [70.0–78.0]	N=450	70.7 [68.0-72.0]	N=382	78.0 [76.0-81.0]
Education level:	N=831		N=449		N=382	
Elementary school not completed		127 (15.6)		50 (11.3)		77 (21.0)
Elementary school completed		307 (37.3)		152 (34.7)		155 (40.4)
Vocational or general secondary education		263 (31.4)		161 (35.3)		102 (26.4)
College or university education		134 (15.8)		86 (18.7)		48 (12.2)
Smoking:	N=828		N=449		N=379	
Never		445 (55.0)		239 (53.2)		206 (57.2)
Current		46 (5.9)		34 (8.3)		12 (3.0)
Former		337 (39.1)		176 (38.5)		161 (39.8)
Body mass index (kg/m^2)	N=810	27.8 [24.8-31.2]	N=441	27.5 [24.6-30.9]	N=369	28.2 [25.2-31.3]
Number of chronic diseases	N=824	1 [0-2]	N=445	1 [0-2]	N=379	1 [1-2]

Physical activity (kcal/day)	N=798	686 [428–1058]	N=437	749 [494-1176]	N=361	597 [349-940]
Use of psychotropic medication	N=832	178 (21.7)	N=450	82 (17.5)	N=382	96 (27.1)
Use of analgesic/anti-inflammatory medication	N=831	265 (31.6)	N=449	143 (30.5)	N=382	122 (32.9)
Pain severity (WOMAC / AUSCAN)**						
Baseline	N=823	15.0 [10.0-25.0]	N=447	15.0 [8.3-23.3]	N=376	16.7 [10.0-26.7]
Follow-up	N=646	15.0 [6.7-26.7]	N=367	13.4 [5.0-25.0]	N=279	16.7[6.7-28.3]
Pain variability (from Pain Calendar) ***	N=762	1.3 [0.9-1.9]	N=428	1.3 [0.9-1.8]	N=334	1.3 [0.9-1.9]
HADS						
Baseline:	N=802		N=437		N=365	
HADS-A		5 [3-9]		6 [3-9]		5 [3-8]
HADS-D		4 [2-7]		4 [1-6]		5 [2-7]
HADS-T		10 [5-15]		9 [5-15]		10 [6-15]
Follow-up:	N=650		N=370		N=280	
HADS-A		5 [2-7]		4 [2-8]		5 [2-7]
HADS-D		3 [1-6]		3 [1-6]		4 [2-7]
HADS-T		8 [4-13]		8 [4-13]		9 [5-14]

Values column are displayed as N (%) or as median [IQR]. * With exception of age, gender and country, descriptive statistics are weighted; the N is unweighted. ** Score range: 0-100. *** Pain variability displayed in individual standard deviation units. OA: osteoarthritis; HADS-A/D/T: Hospital Anxiety and Depression Scale –Anxiety/Depression/Total scale score. WOMAC: Western Ontario McMasters Universities Osteoarthritis Index; AUSCAN: Australian / Canadian hand Osteoarthritis Index.

Table 2. Cross-sectional and longitudinal associations between pain severity and affective symptoms, analyzed with multiple linear regression analysis, displayed as ratio per 10-point difference/change in WOMAC/AUSCAN pain severity (95% CI).

Cross-sectional	**Total group**		***Younger old (65.0-74.0 yrs.)***		***Older old (74.1-85 yrs.)***	
	Model 1[a]	**Model 2[b]**	**Model 1[a]**	**Model 2[b]**	**Model 1[a]**	**Model 2[b]**
HADS-A			1.04 (.99, 1.09)	1.02 (.97, 1.07)	1.14*** (1.08, 1.21)	1.12*** (1.05, 1.19)
HADS-D	1.08*** (1.05, 1.13)	1.06** (1.02, 1.11)				
HADS-T			1.06* (1.01, 1.12)	1.04 (.99 1.09)	1.12*** (1.06, 1.17)	1.07* (1.02, 1.13)
Longitudinal	**Total group**		***Females***		***Males***	
	Model 1[a]	**Model 2[b]**	**Model 1[a]**	**Model 2[b]**	**Model 1[a]**	**Model 2[b]**
HADS-A			.97 (.93, 1.01)	.98 (.94, 1.02)	1.10* (1.02, 1.20)	1.08 (1.00, 1.17)
HADS-D	1.06** (1.02, 1.09)	1.06** (1.02, 1.09)				
HADS-T			.99 (.95, 1.03)	.99 (.95, 1.04)	1.09* (1.02, 1.17)	1.09* (1.01, 1.17)

Model 1: adjusted for sex, age and country. [b] Model 2: additionally adjusted for education level, smoking, BMI, chronic diseases, physical activity and use of psychotropic and pain medication. HADS-A/D/T: Hospital Anxiety and Depression Scale – Anxiety/Depression/Total scale. *p<.05; ** p<.01; *** p<.001.

Table 3. Longitudinal associations between pain variability and affective symptoms in persons with OA, analyzed with multiple linear regression analysis, displayed as ratio (95% CI).

	Younger old (65.0-74.0 yrs.)		Older old (74.1-85 yrs.)	
	Model 1[a]	**Model 2[b]**	**Model 1[a]**	**Model 2[b]**
HADS-A	1.07 (.97, 1.18)	1.07 (.97, 1.18)	.86** (.77, .95)	.85** (.77, .94)
HADS-D	1.02 (.94, 1.11)	1.02 (.94, 1.12)	.91 (.83, 1.00)	.90* (.82, .98)
HADS-T	1.01 (.92, 1.10)	1.04 (.95, 1.15)	.90* (.82, .98)	.87** (.79, .94)

Pain variability measured with individual SDs of joint pain scores on a maximum of 3 pain calendars. Model 1: adjusted for sex, age and country. [b] Model 2: additionally adjusted for education level, smoking, BMI, chronic diseases, physical activity and use of psychotropic and pain medication. HADS-A/D/T: Hospital Anxiety and Depression Scale – Anxiety/Depression/Total scale. *p<.05; ** p<.01.