Pain descriptors and determinants of pain sensitivity in knee osteoarthritis: a community-based cross-sectional study

Johanna E. Vriezekolk, Yvonne A. S. Peters, Monique A. H. Steegers, Esmeralda N. Blaney Davidson and Cornelia H. M. van den Ende

Abstract

Objectives. The aim was to explore pain characteristics in individuals with knee OA (KOA), to compare pain sensitivity across individuals with KOA, individuals with chronic back pain (CBP) and pain-free individuals (NP) and to examine the relationship between clinical characteristics and pain sensitivity and between pain characteristics and pain sensitivity in KOA.

Methods. We carried out a cross-sectional, community-based online survey. Two data sets were combined, consisting of Dutch individuals ≥40 years of age, who were experiencing chronic knee pain (KOA, n = 445), chronic back pain (CBP, n = 504) or no pain (NP, n = 256). Demographic and clinical characteristics, global health, physical activity/exercise and pain characteristics, including intensity, spreading, duration, quality (short-form McGill pain questionnaire) and sensitivity (pain sensitivity questionnaire), were assessed. Differences between (sub)groups were examined using analyses of variance or \( \chi^2 \) tests. Regression analyses were performed to examine determinants of pain sensitivity in the KOA group.

Results. The quality of pain was most commonly described as aching, tender and tiring-exhausting. Overall, the KOA group had higher levels of pain sensitivity compared with the NP group, but lower levels than the CBP group. Univariately, pain intensity, its variability and spreading, global health, exercise and having co-morbidities were weakly related to pain sensitivity (standardized \( \beta \): 0.12–0.27). Symptom duration was not related to pain sensitivity. Older age, higher levels of continuous pain, lower levels of global health, and exercise contributed uniquely, albeit modestly, to pain sensitivity (\( P < 0.05 \)).

Conclusion. Continuous pain, such as aching and tenderness, in combination with decreased physical activity might be indicative for a subgroup of individuals at risk for pain sensitivity and, ultimately, poor treatment outcomes.

Key words: pain sensitivity, knee OA, quality of pain, determinants

Key messages.
- In knee OA, the quality of pain was most commonly described as aching, tender and tiring-exhausting.
- Less pain sensitivity was reported in knee OA compared with chronic low back pain.
- Continuous pain, but not intermittent pain nor disease duration, was associated with pain sensitivity.

Introduction

In knee OA, pain is a common symptom and typically changes from (unpredictable) intermittent weight-bearing

Correspondence to: Cornelia H. M. van den Ende, Department of Rheumatology, Radboudumc, PO Box 9101, 6500 HB Nijmegen, The Netherlands. E-mail: els.vandenende@radboudumc.nl
pain to more constant chronic pain [1, 2]. Individuals with OA describe the quality of their pain in terms of sharp or stabbing, but also as dull, throbbing, aching [1, 3]. About one-third of them use descriptors such as tingling, burning and numbness, indicative for neuropathic pain. Pain is the primary symptom to seek medical attention, and it leads to functional limitations and a decrease in quality of life [1].

In OA, the biological mechanisms of pain are explained in terms of peripheral sensitization triggered by ongoing nociceptive stimulation (i.e. nociceptors local to the knee have become sensitized during inflammation) and/or central sensitization (i.e. neurological changes in the central nervous system) [4, 5]. Central sensitization can be inferred clinically from the presence of heightened pain sensitivity: allodynia (pain in response to a stimulus that does not normally provoke pain) and hyperalgesia (increased pain in response to a stimulus that normally provokes pain) at and/or outside the primary reported pain site [6]. The phenomenon of heightened pain sensitivity is implicated in the pain experiences of people with OA and is supported by quantitative sensory testing methodology [7].

Research investigating the extent and determinants of pain sensitivity in OA is scarce. Heightened pain sensitivity has been associated with poor health and poor treatment outcomes. In knee OA, heightened pain sensitivity has been related to being female, higher levels of pain intensity, disability and poorer quality of life, but not to radiographic severity [8, 9]. Conflicting results have been found for pain sensitization and its relationship to the duration of OA symptoms, psychological distress and pain catastrophizing, depending on the quantitative sensory testing methodology used (e.g. stimulus modality, tested body site) [8]. Furthermore, a heightened pain sensitivity has been associated with poor prognosis after joint replacement and non-response after physiotherapy [7, 10]. The assessment of both the quality of pain and pain sensitivity can be important to inform clinical decision-making and treatment.

To date, pain sensitivity has been examined in a selected group of individuals with OA, mostly waiting for elective surgery and examined using an intrusive resource- and time-consuming method, the quantitative sensory testing methodology. The pain sensitivity questionnaire (PSQ) was developed to investigate self-reported pain sensitivity in daily life situations as a supplement or alternative to experimental pain testing [11]. The PSQ has been proved to be a valid and reliable instrument in healthy subjects and in patients with chronic pain, such as back pain [11–15]. PSQ scores were associated with both experimental pain intensity ratings and experimental pain thresholds, and chronic pain patients exhibited significantly elevated PSQ scores compared with healthy controls [12, 14]. A Swedish population study showed a positive relationship between spreading of bodily pain, pain intensity or age and pain sensitivity [16]. Given that heightened pain sensitivity is implicated in knee OA in both conservative and surgical treatment and might impact health outcomes and resources, investigating the role of pain sensitivity in less advanced stages of the disease is warranted.

The objectives of this study were first, to explore the quality of pain in individuals with self-reported knee OA and its association with pain sensitivity; second, to examine the extent to which individuals with self-reported knee OA differ from individuals with chronic back pain and individuals without pain with respect to pain sensitivity; and third, to examine the association between demographic, clinical or pain characteristics and pain sensitivity in individuals with self-reported knee OA. We hypothesized that individuals with knee OA would report lower levels of pain sensitivity than individuals with chronic back pain, because more widespread pain is associated with elevated levels of pain sensitivity [16]. In addition, we hypothesized that in individuals with knee OA, higher levels of pain sensitivity would be related to higher levels of pain intensity and duration and to lower levels of quality of life [16, 17].

Methods
Study design, setting and participants
Two cross-sectional data sets were combined for this study. For the first cross-sectional data set, individuals with knee OA (KOA group) were recruited through The Dutch Knee Panel of the Sint Maartenskliniek, The Netherlands. People with self-reported knee OA or with suspicion of knee OA (defined as experiencing knee pain for most days of the month, over a period of ≥3 months consecutively), living in The Netherlands and ≥40 years of age, are eligible for participation in the panel. Participants in this panel (n = 535) received an invitation to complete an online survey that was administered through a cloud-based electronic data capture platform. Participants were required to answer each question in order to continue through the survey. This study was carried out in April 2019.

For the second cross-sectional data set, individuals with chronic back pain and pain-free individuals were recruited through Dutch media to fill out an anonymous nationwide Dutch online survey on pain (Groot Nationaal Onderzoek Pijn) with a total of >10 840 participants. Participants were required to answer each question in order to continue through the survey. The study was carried out from May 2017 to October 2018. From this study, participants with self-reported chronic back pain (CBP group) were selected based on the following criteria: they experienced back pain [numerical rating scale (NRS) pain > 0] over a period of at ≥3 months consecutively and were ≥40 years of age. Pain-free participants (NP group) were selected if they were ≥40 years of age and reported no pain (NRS pain = 0). Excluded were individuals with acute pain, individuals with other areas of chronic pain (head, abdomen, chest, arms, legs) and individuals who watched a short movie (negative/
Measurements in the KOA group

Demographic and clinical characteristics
Besides, sex, age and BMI, the following clinical characteristics were assessed: duration of knee OA symptoms (<1 year, between 1 and 5 years or >5 years), presence of self-reported OA in other joint groups (yes/no), including the number of other affected joint groups (0–9), use of pain medication (yes/no) and presence of comorbidities. One or more of the following co-morbidities could be selected from a pre-defined list: lung diseases; cardiovascular diseases; stomach, intestinal and liver diseases; cancer; vision problems; hearing problems; dizziness and balance disorders; increased cholesterol; dementia; migraine or chronic headache; depression; anxiety disorders; FM; kidney diseases; diabetes; thyroid problems; RA; osteoporosis; gout; and other.

Pain quality descriptors
The sensory and affective aspects of pain were assessed using the short-form McGill pain questionnaire (SF-MPQ) [18]. The SF-MPQ consists of 15 word descriptions (e.g. throbbing). Participants rated each adjective on an intensity scale ranging from 0, indicating none, to 3, indicating severe, for the pain in the last week. Two sum scores were computed that reflected continuous pain descriptors (six items): throbbing, cramping, gnawing, aching, heavy and tender; and intermittent pain descriptors (four items): shooting, stabbing, sharp and splitting [19]. The SF-MPQ is a valid multidimensional measure to assess pain [20, 21].

Pain sensitivity. Pain sensitivity was assessed using the PSQ, which is a self-rating measure for global pain perception based on imagined painful daily life situations [11]. It contains a series of 17 situations in which the severity of the pain is measured on an NRS ranging from 0, indicating not at all painful, to 10, indicating the most imaginable pain [22]. To assess spreading of pain in the most affected knee, the knee pain map was used [23]. Participants were asked, ‘When your knee hurts, where does it hurt?’, and they could indicate the location of painful areas, with a maximum of eight areas.

Health status
Health status was assessed using the EuroQuol-5D-L descriptive system [24]. The standardized EQ-5D-5L measurement maps five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Participants rated their health status for each dimension by choosing one of the five levels: having no problems, having slight problems, having moderate problems, having severe problems and being unable to do/having extreme problems. The individual health levels were summarized into 5-digit code and converted into the Dutch EQ-5D index values [25]. Global health status was assessed with a visual analogue scale (EQ-VAS) ranging from 0, indicating the worst imaginable health, to 100, indicating the best imaginable health. The EQ-5D-L has been validated in several studies [26].

Physical activity
Physical activity was assessed using the brief physical activity assessment (BPAA) [27], an adapted version of the international physical activity questionnaire [28]. This two-item questionnaire assessed whether an individual is (in)sufficiently active by asking how many times they carry out vigorous and moderate physical activities during a week. The BPAA is a valid and reliable instrument in primary care setting for identifying (in)sufficiently active patients [27]. In addition, whether participants exercised (yes/no), and the number of hours of exercise per week (0–1, 2–3, 4–6, 7–10 and >10 h per week) was assessed.

Measurements in the CBP and NP groups only
For the CBP and NP groups, the following data were available: sex, age, BMI, use of pain medication, health status (EQ-5D-L), whether participants exercised and the number of hours of exercise per week, pain intensity (NRS) and pain sensitivity (PSQ).

Statistical analysis
The mean and S.D. and frequencies (percentages) were computed, if appropriate. To explore the sensory and affective pain quality in the KOA group, response options were collated and dichotomized into zero, indicating non-mild intensity, and one, indicating moderate–severe intensity, and subsequently frequencies (percentages) were computed. Differences between (sub)groups were assessed using a series of analyses of variance, followed by Student’s post hoc unpaired t-tests for equal and unequal variance (using Welch’s approximation) for continuous variables, and χ² tests for categorical variables. Low- and high-pain sensitivity subgroups were formed based on the PSQ total score (i.e. median split), to examine the relationships between pain quality descriptors and pain sensitivity in the knee OA group. To compare pain sensitivity scores between KOA, CBP and NP groups, regression analyses adjusted for sex and age were performed. In the KOA group only, univariate and multivariate regression analyses with backward selection (variable selection with Akaike information criterion P < 0.157) were conducted to examine associations of knee OA determinants with pain sensitivity scores. No collinearity (r ≥ 0.70) between determinants was detected. Standardized correlation coefficients <0.2
were considered as no clinically relevant effect, between 0.2 and < 0.5 as a small clinically relevant effect, between 0.5 and < 0.8 as a moderate effect, and ≥ 0.8 as a strong effect [29]. All statistical analyses were performed using STATA (v.13.0; StataCorp, College Station, Texas, USA).

Ethical considerations
This study was conducted in accordance with the Declaration of Helsinki and was approved by the local review committees of the Sint Maartenskliniek, The Netherlands and Radboudumc, The Netherlands. The Dutch medical research ethical committee of Arnhem-Nijmegen waived ethical approval because this study was not subject to the medical research involving the human subjects act (file number 2019-5298). Participants gave written informed consent before completing the surveys.

Results
Participants
A total of 1205 participants were enrolled in this study: 445 individuals with KOA, 504 individuals with CBP, and 256 NP individuals (see Supplementary Fig. S1, available at Rheumatology Advances in Practice online). Except for BMI, the KOA and CBP group differed for all variables (P-values < 0.002). The highest proportion of females was found in the CBP group (83%) and highest mean age in the KOA group (63 years) (see Supplementary Table S1, available at Rheumatology Advances in Practice online).

Description of sample of individuals with knee OA
Table 1 shows the demographic and clinical characteristics of the KOA sample. The majority of the individuals were female (75%), with a mean age of 63 years (s.d. = 8.8) and mean BMI of 27.9 kg/m² (s.d. = 4.8). Forty per cent of the participants were overweight; 29% were obese. Fifty-six per cent of the participants had KOA symptoms for > 5 years; 57% indicated that they had OA in other joint groups than the knee, with an average of 2.7 (s.d. = 1.8) other affected joint groups. The majority (72%) of the participants reported co-morbidities (mean = 2.3, s.d. = 1.5). The most common co-morbidities reported were cardiovascular diseases (20.0%), hearing-impairment problems (20.0%) and elevated cholesterol (19.6%).

Pain descriptors and their relationship to pain sensitivity in knee OA
Mean continuous pain was 1.16 (s.d. = 0.7), and mean intermittent pain was 1.17 (s.d. = 0.8). The three pain quality descriptors that were most frequently rated as moderate to severe were aching, tenderness and tiring–exhausting (Fig. 1). Generally, the high pain sensitivity subgroup had higher mean intensity scores on pain descriptors compared with the low pain sensitivity subgroup.

| Characteristic | Total n = 445 |
|----------------|--------------|
| Female, n (%)  | 333 (75)     |
| Age, mean (s.d.), years | 63.0 (8.8) |
| BMI, mean (s.d.), kg/m²  | 27.9 (4.8) |
| Health status, mean (s.d.), EQ5D-5L index score (0-1) | 0.7 (0.1) |
| Health status, mean (s.d.), EQ5D-5L VAS (0-100) | 69.6 (15.2) |
| Pain intensity, mean (s.d.), NRS (0–10) | 4.5 (2.3) |
| Continuous pain, mean (s.d.), SF-MPQ (0–3) | 1.16 (0.7) |
| Intermittent pain, mean (s.d.), SF-MPQ (0–3) | 1.17 (0.8) |
| Number of painful areas in the knee (1–8), mean (s.d.) | 2.6 (1.5) |
| Duration of KOA symptoms, n (%) | |
| <1 year | 31 (7) |
| 1–5 years | 163 (37) |
| >5 years | 251 (56) |
| Presence of OA in other joint groups, n (%) | 253 (57) |
| Number of other joint groups affected by OA (0–9), mean (s.d.) | 2.7 (1.8) |
| Pain medication, n (%) | 177 (40) |
| Exercise, n (%) | 271 (61) |
| 0–3 h | 178 (66) |
| 4–10 h | 88 (33) |
| >10 h | 5 (2) |
| Insufficiently physical active (BPAA), n (%) | 212 (48) |
| Presence of co-morbidities, n (%) | 320 (72) |
| Number of co-morbidities, mean (s.d.) | 2.3 (1.5) |

BPAA: brief physical activity assessment; KOA: knee OA, NRS: numerical rating scale; SF-MPQ: short-form McGill pain questionnaire; VAS: visual analogue scale.

Table 1 Characteristics of individuals with self-reported knee OA
Extent of pain sensitivity across the three groups (KOA, CBP and NP)

Table 2 shows the mean (s.d.) pain sensitivity scores across the three groups. Adjusted for age and sex, higher PSQ minor scores were found for the CBP group compared with the KOA group \((P = 0.007)\). Lower scores were found for the NP group compared with the KOA and CBP groups \((P\text{-values} < 0.0001)\).

Associations of determinants with pain sensitivity scores in the KOA group

Overall, pain sensitivity was weakly associated with pain intensity, continuous pain, intermittent pain, number of painful areas in the most affected knee, presence and number of OA in other joint groups, number of co-morbidities, exercise and global health. In addition, pain sensitivity was weakly associated with female sex, having co-morbidities and being insufficiently active, depending on the PSQ score used (see Supplementary Table S2, available at Rheumatology Advances in Practice online).

Discussion

In this cross-sectional study, the quality of pain was most commonly described as aching, tender and tiring–exhausting by individuals with self-reported knee OA. Furthermore, the intensity of pain quality descriptors was consistently higher in the subgroup of individuals with higher levels of pain sensitivity compared with the subgroup with lower levels of pain sensitivity. Overall, individuals with knee OA reported higher levels of pain sensitivity compared with pain-free individuals, but lower
levels than individuals with chronic back pain. Older age, higher levels of (continuous) pain and lower levels of global health uniquely contributed to higher levels of pain sensitivity, whereas exercise was uniquely related to lower levels of pain sensitivity. These findings confirm our hypotheses, in part.

Consistent with previous research [3, 30, 31], OA pain was characterized as a mix of continuous pain and intermittent pain. It has been suggested that pain characteristics might change as OA progresses from early to late stages [5]. We found no relationship between pain quality descriptors and symptom duration in our KOA group. A previous study showed that patients after a total knee/hip replacement used similar pain descriptors for persistent pain to OA individuals without knee/hip replacement OA [32], which suggests that the quality of pain does not differ whether pain arises from nociceptive processes (i.e. activation of nociceptors owing to real or threatened damage to non-neural tissue) or neuroplastic processes (i.e. no clear evidence of real or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain).

Unfortunately, the questionnaire used in the present study to assess pain descriptors did not include neuropathic features of pain (e.g. tingling, burning), limiting further investigation of possible changes of the quality aspects of pain. Recent prevalence estimates of neuropathic pain varies between 20 and 48% across different knee OA populations, suggesting that neuropathic pain quality descriptors might be unrelated to OA progression [33]. Future longitudinal studies (e.g. cohort studies, ecological momentary assessment studies) can provide a better understanding of changes in temporal (intermittent vs continuous) and quality characteristics of OA pain [3, 31].

Compared with pain-free individuals and consistent with previous research [11, 12, 14], individuals with self-reported knee OA reported higher levels of pain sensitivity as measured with the PSQ, but lower levels of pain sensitivity compared with individuals with CBP. Research and clinical observations suggest that widespread pain and pain present in multiple body regions are an indication of central sensitization [16, 34–36]. People with regional pain (e.g. low back pain) and people with widespread pain (e.g. FM) have demonstrated higher levels of pain sensitivity than people with localized pain (e.g. knee OA) [16, 36]. Our study supports these findings. Likewise, we found a relationship between the number of painful areas of the affected knee and the presence of OA in other joint groups with higher levels of pain sensitivity in the KOA group. These clinical signs might help to identify individuals with knee OA at risk for poor treatment outcomes [37].

In our multivariate model of pain sensitivity in KOA, only older age, higher levels of (continuous) pain and lower levels of global health uniquely contributed to higher levels of pain sensitivity, whereas exercise was uniquely related to lower levels of pain sensitivity. Their contribution was modest; the explained variance in pain sensitivity scores varied between 9 and 12%. Notably, female sex was inconsistently related to pain sensitivity, depending on the PSQ score. Moreover, female sex was no longer related to higher levels of pain sensitivity when accounting for, among other factors, age and pain. Contrary to our findings, few studies have demonstrated that women with knee OA exhibit heightened pain sensitivity and greater widespread pain in response to experimental pain stimuli relative to men [9, 38, 39]. It is plausible that sex differences in pain processes are more easily detected using experimental pain stimuli than patient-reported measures. We found a small significant, albeit not clinically relevant, relationship between exercise and lower levels of pain sensitivity. There is low evidence suggesting that exercise can increase pain threshold and, in turn, decrease pain sensitivity [40, 41]. Strong methodological studies are needed to confirm or refute the effectiveness of exercise training to buffer the negative effects of pain sensitivity.

Contrary to our expectations, symptom duration was not related to pain sensitivity. Previous research also found no relationship between symptom duration and pain sensitivity in knee OA [42, 43]. In a large multicentre

### Table 3: Multivariate model of demographic and clinical determinants with pain sensitivity scores in the knee OA group

| Parameter                              | PSQ total |             | PSQ minor |             |
|----------------------------------------|-----------|-------------|-----------|-------------|
|                                        | B         | 95% CI      | β         | B           | 95% CI      | β         |
| Female sex                             | –         | –           | –         | 0.29        | –0.05, 0.62 | 0.08      |
| Age, years                             | 0.03      | 0.01, 0.04  | 0.15      | 0.03        | 0.01, 0.04  | 0.15      |
| Obese, >30 kg/m²                       | –         | –           | –         | –0.28       | –0.61, 0.04 | –0.08     |
| Global health, VAS (0–10)a             | –0.01     | –0.02, –0.00| –0.12     | –0.01       | –0.02, –0.00| –0.11     |
| Continuous pain, MPQ (0–3)             | 0.44      | 0.21, 0.67  | 0.19      | 0.57        | 0.33, 0.81  | 0.22      |
| Number of painful areas in the knee (1–8) | 0.09     | –0.01, 0.19 | 0.08      | –          | –          | –         |
| Presence of OA in other joint groups   | 0.21      | –0.07, 0.50 | 0.07      | 0.30        | –0.00, 0.60 | 0.09      |
| Exercise (yes)                         | –         | –           | –         | –0.32       | –0.62, 0.01 | –0.09     |

*Lower scores represent worse health status. Significant coefficients are in bold, P < 0.05. B: regression coefficient; β: standardized regression coefficient; MPQ: McGill pain questionnaire; PSQ: pain sensitivity questionnaire.*
Pain descriptors and sensitivity in knee OA

cohort study of >2000 persons with or at risk of knee OA, it was found that symptom duration and radiographic severity of OA were not related to pain sensitivity using quantitative sensory testing parameters, mechanical temporal summation and pressure pain thresholds [42]. They suggested that hypersensitivity of the central nervous system is in fact a trait; that is, related to an individual’s vulnerability to sensitization rather than being induced by peripheral nociceptive input from OA pathology. To date, there are limited data to suggest that there is a genetic predisposition in certain susceptible individuals to autonomous pain amplification [44].

Our findings should be interpreted in the context of study limitations. First, the cross-sectional design of the study does not allow for causal or predictive inferences. Second, the diagnosis of knee OA was self-reported and not validated clinically. However, the accuracy of self-reported OA is acceptable (sensitivity of 0.75 and specificity of 0.89) for large-scale studies [45]. Third, the measurement properties of the current PSQ are still suboptimal [46]. We followed the recommendation of the original authors of the PSQ to use only the total score and minor subscale score to assess pain sensitivity; however, a very strong correlation between the two scores ($r > 0.93$) was observed, indicating redundancy. In addition, a post hoc explorative factor analysis showed a one-factor structure, with several poorly discriminating items loading on two factors. The validity of the PSQ has been questioned by others, referring, for instance, to the inability to distinguish widespread pain sensitivity or to distinguish between patients with or without central sensitization, limiting the value for clinical practice [46]. Fourth, individuals with knee OA were from a different sample enrolled at a different time than those with chronic back pain or no pain, which hampers comparisons because the subgroups are not from the same source population. Nevertheless, our findings regarding the extent of pain sensitivity across subgroups were consistent with previous research [12, 36]. Fifth, we did not assess psychological factors that might play an important role in the development of pain sensitivity in knee OA. Last, our findings might not generalize to individuals with knee OA in clinical settings. Although we found similar relationships for heightened pain sensitivity with indices of pain intensity and pain distribution to previous research in clinical settings [47, 48], the predictive value of these pain characteristics for pain sensitivity and the relevance for clinical practice warrant further investigation [37].

Future longitudinal studies are needed that cover biological, clinical and psychosocial factors to identify participants at risk for central sensitization and to inform decision-making and treatment.

In conclusion, the majority of Dutch individuals with self-reported knee OA described the quality of their pain in terms of aching, tender and tiring–exhausting. They exhibited higher levels of pain sensitivity compared with pain-free individuals, but lower levels than individuals with chronic back pain. Older age, higher levels of continuous pain, lower levels of global health, and exercise uniquely contributed, albeit modestly, to pain sensitivity. It is noteworthy that symptom duration was not related to pain sensitivity, suggesting that only some individuals with knee OA are prone to manifestations of central sensitization. Continuous pain, such as aching and tenderness, in combination with decreased physical activity might be indicative for a subgroup of individuals with knee OA at risk for pain sensitivity and, ultimately, poor treatment outcomes.

Funding: No specific funding was received from any bodies in the public, commercial or not-for-profit sectors to carry out the work described in this article.

Disclosure statement: The authors have declared no conflicts of interest.

Data availability statement

Part of the data is collected through a large Dutch nationwide survey (‘Het Groot Nationaal Onderzoek Pijn’). The authors do not own these data and hence are not permitted to share the data in the original form. Data collected through the Dutch Knee panel will be shared on reasonable request to the corresponding author.

Supplementary data

Supplementary data are available at Rheumatology Advances in Practice online.

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