Neuropathic pain in the IMI-APPROACH knee osteoarthritis cohort: prevalence and phenotyping

Eefje Martine van Helvoort, Paco M J Welsing, Mylène P Jansen, Willem Paul Gielis, Marieke Loef, Margreet Kloppenburg, Francisco Blanco, Ida K Haugen, Francis Berenbaum, Anne-C Bay-Jensen, et al.

RMD Open
Rheumatic & Musculoskeletal Diseases

ORIGINAL RESEARCH

Neuropathic pain in the IMI-APPROACH knee osteoarthritis cohort: prevalence and phenotyping

Eefje Martine van Helvoort ,[1] Paco M J Welsing,[1] Mylène P Jansen ,[1] Willem Paul Gielis ,[2] Marieke Loef ,[3] Margreet Kloppenburg,[3,4] Francisco Blanco,[5] Ida K Haugen ,[6] Francis Berenbaum ,[7,8] Anne-C Bay-Jensen,[9] Christoph Ladel,[10] Agnes Lalande,[11] Jonathan Larkin,[12] John Loughlin,[13] Ali Mobasheri ,[14,15] Harrie Weinans,[16] Floris Lafeber,[1] Niels Eijkelkamp,[17] Simon Mastbergen[1]

To cite: van Helvoort EM, Welsing PMJ, Jansen MP, *et al*. Neuropathic pain in the IMI-APPROACH knee osteoarthritis cohort: prevalence and phenotyping. *RMD Open* 2021;**7**:e002025. doi:10.1136/rmdopen-2021-002025

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/rmdopen-2021-002025).

Received 14 October 2021
Accepted 28 November 2021

For numbered affiliations see end of article.

Correspondence to
Dr Eefje Martine van Helvoort; E.M.vanHelvoort-3@umcutrecht.nl

ABSTRACT

Objectives Osteoarthritis (OA) patients with a neuropathic pain (NP) component may represent a specific phenotype. This study compares joint damage, pain and functional disability between knee OA patients with a likely NP component, and those without a likely NP component.

Methods Baseline data from the Innovative Medicines Initiative Applied Public-Private Research enabling OsteoArthritis Clinical Headway knee OA cohort study were used. Patients with a painDETECT score ≥19 (with likely NP component, n=24) were matched on a 1:2 ratio to patients with a painDETECT score ≤12 (without likely NP component), and similar knee and general pain (Knee Injury and Osteoarthritis Outcome Score pain and Short Form 36 pain). Pain, physical function and radiographic joint damage of multiple joints were determined and compared between OA patients with and without a likely NP component.

Results OA patients with painDETECT scores ≥19 had statistically significant less radiographic joint damage (p≤0.04 for Knee Images Digital Analysis parameters and Kellgren and Lawrence grade), but an impaired physical function (p<0.003 for all tests) compared with patients with a painDETECT score ≤12. In addition, more severe pain was found in joints other than the index knee (p≤0.001 for hips and hands), while joint damage throughout the body was not different.

Conclusions OA patients with a likely NP component, as determined with the painDETECT questionnaire, may represent a specific OA phenotype, where local and overall joint damage is not the main cause of pain and disability. Patients with this NP component will likely not benefit from general pain medication and/or disease-modifying OA drug (DMOAD) therapy. Reserved inclusion of these patients in DMOAD trials is advised in the quest for successful OA treatments.

Trial registration number
The study is registered under clinicaltrials.gov nr: NCT03883568.

Key messages

What is already known about this subject?

- Osteoarthritis (OA) is a heterogeneous disease with multiple causes for similar clinical symptoms.

What does this study add?

- In knee OA patients with a likely neuropathic pain component, local joint damage is not the leading cause for pain and disability.

How might this impact on clinical practice or further developments?

- Patients with a likely neuropathic pain component reflect a specific OA phenotype, most likely not responding to general analgesics or disease-modifying OA drug (DMOAD) therapy.
- These patients need to be identified and offered a more personalised treatment.
- Moreover, reserved inclusion of these patients in DMOAD trials is advised.

INTRODUCTION

Osteoarthritis (OA) is a degenerative joint disease leading to pain, stiffness and loss of function. Despite the increasing prevalence and great burden, there is still no cure. Treatment is focused on relieving symptoms and controlling inflammation if present. Multiple international guidelines recommend the use of topical/oral non-steroidal anti-inflammatory drugs (NSAIDs) in the treatment of OA pain, if non-pharmacological interventions fail.[1–3] However, in a meta-analysis evaluating the analgesic efficacy of NSAIDs and selective cyclo-oxygenase-2 inhibitors in knee OA, an effect size of 0.32 was found,[4] suggesting the effect is limited and/or that at least part of the OA patients does not benefit from this approach sufficiently.

A possible explanation for the limited efficacy of current analgesic drugs is the variety in pathophysiologic mechanisms between different OA patients. OA is considered

a heterogeneous disease, existing of multiple phenotypes, with different causes for similar clinical symptoms including pain.[5] Pain is currently categorised into nociceptive pain resulting from tissue damage; neuropathic pain (NP), involving nerve damage; and nociplastic pain, which is caused by altered nociception without clear evidence of actual tissue damage.[6] OA pain is classically considered a nociceptive pain that arises from joint tissue damage and inflammation. However, an evident relation between the (radiographic) tissue damage with (reported) pain has not been identified.[7] Not all patients respond to general pain medication, such as acetaminophen, NSAIDs, cyclo-oxygenase-2 inhibitors and tramadol.[8–11] Moreover, in a substantial proportion of knee OA patients, pain persists after removing the damaged tissue during total knee arthroplasty (TKA).[12] These observations indicate that the classification of OA pain as purely nociceptive is erroneous.

Patients with OA who experience pain that is not a pure nociceptive pain but also has neuropathic features could be recognised as a distinct subgroup. Identification of this subgroup, may allow clinicians to improve the management of symptoms of this specific OA phenotype, using distinct treatments focused on this NP component.[6] Moreover, excluding these patients from disease-modifying OA drug (DMOAD) trials may benefit the quest for discovery of tissue structure modifying medication accompanied by analgesic activity as requested by European Medicines Agency (EMA) and Food and Drug Administration (FDA).[13 14]

Although definite NP requires an objective diagnostic test to confirm a lesion or disease of the somatosensory system, questionnaires like the painDETECT, assessing pain characteristics suggestive for NP, show high sensitivity and specificity to distinguish NP from non NP.[15] The painDETECT questionnaire predicts the likelihood of an NP component in patients with chronic low back pain,[16] and has widely been used in OA studies as well. A low score on the painDETECT questionnaire (≤12) means that the presence of an NP component is unlikely (<15%), while a high score (≥19) indicates that the presence of an NP component is likely (>90%).[16]

In general, OA patients with a high painDETECT score (more likely to have an NP component) also have higher scores on other pain questionnaires like Western Ontario McMaster Universities Osteoarthritis Index and Numeric Rating Scales (NRS),[17–23] hampering in this respect selection of patients.

In this study, for the first time, knee OA patients with a likely NP component (as defined by painDETECT score ≥19) and OA patients without a likely NP component (as defined by painDETECT score ≤12) were matched for knee pain levels, to compare differences in clinical characteristics. We hypothesise that knee OA patients with a likely NP component form a specific OA phenotype, without a relation between joint damage and clinical symptoms.

METHODS

Overall study population

Patients were selected from the Innovative Medicines Initiative Applied Public-Private Research enabling OsteoArthritis Clinical Headway (IMI-APPROACH) clinical cohort,[24] a 2-year follow-up study including 297 knee OA patients. The IMI-APPROACH consortium provides a broad database of OA patients and a longitudinal cohort study to combine conventional and new disease markers, to identify different OA phenotypes. The study is being conducted in compliance with the protocol, Good Clinical Practice, the Declaration of Helsinki and the applicable ethical and legal regulatory requirements (for all countries involved). All patients have received oral and written information and provided written informed consent. The present analysis used baseline data.

Identification of patients with and without a likely NP component

The painDETECT questionnaire[16] was used to identify patients with a high likelihood of an NP component. This questionnaire contains nine questions: seven questions to characterise pain, one for the pain course pattern and one for the presence or absence of radiating pain, leading to a final score ranging from −1 to 38. −1 is scored when all seven questions about pain characteristics are answered with 'never', the pain course pattern is 'persistent pain with pain attacks' and no radiation is present. In case of a score ≤12 a NP component is unlikely (<15%), whereas in case of a score ≥19 a NP component is likely (>90%).[16] In-between scores provide doubtful classification and patients with these intermediate scores are therefore left out of the current analyses.

Evaluation of joint pain

Multiple questionnaires were used to evaluate joint pain. The pain subscales of the Knee injury and Osteoarthritis Outcome Score (KOOS)[25] and its equivalent for the hip (Hip disability and Osteoarthritis Outcome Score, HOOS)[26] consist of nine questions for pain, each scored on a 5-point scale. A normalised score is calculated where 0 means maximal pain and 100 means no pain. The Short Form 36 (SF-36) contains 36 questions and measures eight domains of health status, including bodily pain ranging from 0 to 100, where 0 means no pain and 100 mean maximal pain.[27] A NRS for pain[28] was used for both knees, both hips, both hands and the lower back. It consists of an 11 point-scale on which patients score pain from 0 (no pain) to 10 (worst imaginable pain). The Intermittent and Constant OA Pain (ICOAP) questionnaire[29] for knee and hip contains eleven questions, five for constant pain and six for intermittent pain, each question scored on a 5-point scale. A higher total score reflects more pain.

Evaluation of physical function

The Functional Index for Hand OA (FIHOA)[30] comprises ten questions, scored on a 4r-grade scale. Scores range

from 0 (no difficulties) to 30 (maximal difficulties). In addition, two performance-based tests, recommended by OsteoArthritis Research Society International, were used in APPROACH. For the 30s chair-stand test (chair) patients had to stand up completely from a sitting position in the middle of a seat with feet shoulder width apart, flat on the floor, arms crossed at chest, and then sit completely. The result is the number of repetitions completed in thirty seconds. The 40m self-paced walk test (walk) records time in seconds needed to walk as quickly but as safe as possible (regular walking, no running) to a mark 10m away, return, and repeat for a total distance of 40m.

Evaluation of structural joint damage in the index knee

For each patient an index knee was selected based on American College of Rheumatology (ACR) clinical criteria.[31] If both knees fulfilled the criteria, the most painful knee was selected as the index knee. If equal, the right one was selected as the index knee. Standardised semiflexed posterior–anterior weight bearing knee radiographs were taken according to Buckland-Wright.[32] Kellgren and Lawrence (KL) grading was performed by one blinded observer. The intraobserver and interobserver correlation were both previously found to be good (>0.83),[33] and in IMI-APPROACH an intraclass correlation coefficient (ICC) of 0.88 was found (using 10% of the radiographs). Additionally, Knee Images Digital Analysis[34] was performed by one single experienced observer. Minimum Joint Space Width (minJSW) of the index knee (mm), osteophyte area (mm^2) and subchondral bone density (mm Alu Eq.) were used as radiographic parameters. Previous studies demonstrated an ICC of 0.73–0.99 for the different features.[35]

Evaluation of OA grades of other joints

Whole-body low-dose CT was performed to assess concomitant OA or degenerative disc disease (DDD) in case of intervertebral discs. Scans were evaluated using the OsteoArthritis CT (OACT) score, grading all joints on a 0–3 scale. For intervertebral discs, DDD of the two most degenerated levels of each region (cervical, thoracic, lumbal) were scored. Next to grades per joint, the OACT provides a score for total body OA, ranging from 0 to 72 (24 joints with a maximum score of 3 per joint). Kappa values for the intra-observer reliability for individual joints ranged from 0.79 to 0.95, and for inter-observer reliability from 0.48 to 0.95. ICC for the total OA body score ranged from 0.94 to 0.97 for different observers.[36]

Statistical analysis

First, all patients with a painDETECT ≥19 (NP) were matched in a 1:2 ratio to patients with a painDETECT score ≤12 (non-NP), using the MatchIt package from the R statistical package. Subjects were matched using KOOS pain (as a knee specific pain measure) and SF-36 pain (as a general pain score) based on the 'nearest neighbour' principle as well as using a calliper for KOOS pain (as the primary matching criterion) of ten points. These matching variables were chosen because they are known to have a significant relation with painDETECT scores.[17 20–23] Further analyses were performed using IBM SPSS Statistics V.26.0.0.1. Differences between patients with a likely NP component and matched patients without a likely NP component were evaluated using Student's t-tests (for continuous variables), and chi-squared or Fisher's Exact test when assumptions for chi-squared were not met. P<0.05 were considered statistically significant.

RESULTS

Patient characteristics

In the whole cohort of 297 knee OA patients, 24 patients (8.2%) scored ≥19 on the painDETECT questionnaire at time of inclusion, whereas 220 patients (74.8%) scored ≤12. Fifty (17.0%) patients had an in-between score (three patients did not have a painDETECT score at baseline). The characteristics of patients with a likely NP component (NP, n=24), and the matched patients without a likely NP component (non-NP, n=48) are shown in table 1. No statistically significant differences were found between groups for demographics or the matching variables (as expected). Characteristics of all patients without a likely NP component, and those with an in-between painDETECT score (13–18) are shown in

Table 1 Participant characteristics

	NP (n=24)	Non-NP (n=48)	P value
Demographics			
Age (years), mean (SD)	64.5 (6.9)	65.7 (7.3)	0.491
BMI, mean (SD)	30.7 (5.9)	29.1 (6.2)	0.295
Female, n (%)	20 (83%)	38 (79%)	0.761*
Matching variables			
KOOS pain, mean (SD)	50.8 (15.1)	49.8 (13.1)	0.777
SF-36 pain, mean (SD)	34.1 (22.8)	39.8 (16.8)	0.285

*Fisher's exact test.
BMI, body mass index; KOOS, Knee injury and Osteoarthritis Outcome Score; non-NP, matched controls; NP, neuropathic pain; SF-36, Short form 36.

Table 2 Radiographic damage in NP and non-NP patients

	NP (n=24)	Non-NP (n=48)	P value
Radiography			
KL grade, n (%)*			**0.003**
0	8 (33.3)	4 (8.3)	
1	8 (33.3)	11 (22.9)	
2	8 (33.3)	19 (39.6)	
3	0 (0)	13 (27.1)	
4	0 (0)	1 (2.1)	
minJSW (mm), mean (SD)	3.0 (1.0)	2.1 (1.4)	0.002
Osteophyte area (mm^2), mean (SD)	12.7 (11.1)	25.5 (19.1)	0.001
Mean subchondral bone density (mm Alu. Eq), mean (SD)	30.1 (4.3)	32.4 (4.7)	0.037

Statistical significant p-values are given in bold.
*Fisher's exact test.
mm Alu Eq.; mm aluminium equivalent.KL grade, Kellgren and Lawrence grade; minJSW, minimum Joint Space Width; NP, neuropathic pain.

online supplemental table 1. These two groups showed statistically significantly different KOOS pain and SF-36 pain scores compared with the NP group.

Differences in radiographic joint damage in patients with and without a likely NP component

Differences in radiographic parameters of the index knee between patients with and without a likely NP component (matched for KOOS and SF-36 pain) are shown in table 2. Patients with a likely NP component have statistically significantly less radiographic damage in their index knee (KL grade p=0.003; minJSW 3.0 vs 2.1, p=0.002; osteophyte area 12.7 vs 25.5, p=0.001; subchondral bone density 30.1 vs 32.4, p=0.037).

Differences in physical function in patients with and without a likely NP component

Differences in physical function between patients with and without a likely NP component are shown in table 3. Patients with a likely NP component have statistically significant worse hand function (FIHOA 12.3 vs 5.3, p<0.001), and perform worse on both performance-based tests (Chair test 7.3 vs 9.7, p<0.001; Walk test 38.1 vs 29.5, p=0.003).

Table 3 Physical function in NP and non-NP patients

	NP (n=24) Mean (SD)	Non-NP (n=48) Mean (SD)	P value
Physical function			
FIHOA	12.3 (6.9)	5.3 (6.3)	**<0.001**
Chair (no standing up)	7.3 (2.2)	9.7 (3.2)	**<0.001**
Walk (s)	38.1 (12.1)	29.5 (8.2)	**0.003**

Statistical significant p-values are given in bold.
FIHOA, Functional Index for Hand OsteoArthritis; NP, neuropathic pain.

Table 4 Pain scores in NP and non-NP patients

	NP (n=24) Mean (SD)	Non-NP (n=48) Mean (SD)	P value
Index knee			
ICOAP knee	13.0 (8.7)	10.5 (9.1)	0.252
NRS index knee	6.3 (2.4)	6.6 (2.2)	0.680
Contralateral knee			
NRS contralateral knee	5.8 (2.5)	4.0 (2.8)	**0.012**
Hips			
HOOS pain	61.0 (24.2)	82.8 (20.9)	**0.001**
ICOAP hip	16.8 (10.1)	6.7 (9.0)	**<0.001**
NRS left hip	4.5 (3.1)	1.9 (2.7)	**0.001**
NRS right hip	5.0 (3.1)	1.5 (2.6)	**<0.001**
Hands			
NRS left hand	6.4 (2.4)	3.9 (3.2)	**0.001**
NRS right hand	6.5 (2.4)	3.7 (3.1)	**<0.001**
Lower back			
NRS lower back	5.6 (3.4)	4.4 (3.2)	0.343

Statistical significant values are given in bold.
HOOS, Hip disability and Osteoarthritis Outcome Score; ICOAP, Intermittent and Constant Osteoarthritis Pain; NP, neuropathic pain; NRS, Numeric Rating Scale.

Differences in generalised joint pain between patients with and without a likely NP component

Differences in pain in joints other than the index knee between patients with and without a likely NP component are shown in table 4. As anticipated based on the matching process, ICOAP knee and NRS of the index knee did not differ between groups. In contrast, OA patients with a likely NP component had statistically significantly more pain in the contralateral knee (NRS 5.8 vs 4.0, p=0.012), hips (HOOS 61.0 vs 82.8, p=0.001; ICOAP hip 16.8 vs 6.7, p<0.001; NRS left hip 4.5 vs 1.9, p=0.001; NRS right hip 5.0 vs 1.5, p<0.001) and hands (NRS left hand 6.4 vs 3.9, p=0.001; NRS right hand 6.5 vs 3.7, p<0.001). Also, NRS lower back was higher, although not statistically significant (p=0.343).

Differences in OACT grades of other joints between patients with and without a likely NP component

Differences in OACT grades between patients with and without a likely NP component are shown in table 5. The OACT grade of the index knee in patients with a likely NP component was lower compared with patients without a likely NP component, indicating less joint damage and supporting the data of the standard measurements in table 2. OACT grading of other joints did not differ

Table 5 Osteoarthritis CT grades in NP and non-NP patients

	NP (n=24)	Non-NP (n=48)	P value
OACT grades			
Index knee n (%)			**0.010***
0	7 (29.2)	4 (8.3)	
1	9 (37.5)	10 (20.8)	
2	7 (29.2)	22 (45.8)	
3	1 (4.2)	12 (25.0)	
Contralateral knee n (%)			0.199*
0	4 (16.7)	4 (8.3)	
1	14 (58.3)	20 (41.7)	
2	5 (20.8)	16 (33.3)	
3	1 (4.2)	8 (16.7)	
Index patellofemoral n (%)			0.409
0	6 (25.0)	6 (12.5)	
1	10 (41.7)	18 (37.5)	
2	3 (12.5)	12 (25.0)	
3	5 (20.8)	12 (25.0)	
Contralateral patellofemoral n (%)			0.329
0	7 (14.6)	7 (29.2)	
1	9 (37.5)	15 (31.3)	
2	4 (16.7)	14 (29.2)	
3	4 (16.7)	12 (25.0)	
Left hip n (%)			0.638*
0	16 (66.7)	31 (64.6)	
1	7 (29.2)	16 (33.3)	
2	1 (4.2)	0 (0.0)	
3	0 (0.0)	1 (2.1)	
Right hip n (%)			0.868*
0	14 (58.3)	28 (58.3)	
1	7 (29.2)	16 (33.3)	
2	3 (12.5)	4 (8.3)	
3	0 (0.0)	0 (0.0)	
Left ankle n (%)			0.268*
0	21 (87.5)	33 (68.8)	
1	3 (12.5)	13 (27.1)	
2	0 (0.0)	0 (0.0)	
3	0 (0.0)	0 (0.0)	
Right ankle n (%)			0.420*
0	20 (83.3)	31 (64.6)	
1	4 (16.7)	13 (27.1)	
2	0 (0.0)	2 (4.2)	
3	0 (0.0)	0 (0.0)	
Left acromioclavicular n (%)			0.705*
0	11 (45.8)	16 (33.3)	
1	5 (20.8)	14 (29.2)	
2	2 (8.3)	3 (6.3)	
3	6 (25.0)	15 (31.3)	
Right acromioclavicular n (%)			**0.023**
0	11 (45.8)	7 (14.6)	
1	6 (25.0)	13 (27.1)	
2	1 (4.2)	8 (16.7)	
3	6 (25.0)	20 (41.7)	
Left glenohumeral n (%)			0.480*
0	21 (87.5)	36 (75.0)	
1	2 (8.3)	10 (20.8)	
2	1 (4.2)	1 (2.1)	
3	0 (0.0)	0 (0.0)	
Right glenohumeral n (%)			0.340*
0	19 (79.2)	38 (79.2)	
1	2 (8.3)	8 (16.7)	
2	3 (12.5)	2 (4.2)	
3	0 (0.0)	0 (0.0)	
C1 n (%)			0.786*
0	1 (4.2)	2 (4.2)	
1	5 (20.8)	7 (14.6)	
2	7 (29.2)	11 (22.9)	
3	11 (45.8)	28 (58.3)	
C1 facet n (%)			0.943
0	3 (12.5)	6 (12.5)	
1	5 (20.8)	11 (22.9)	
2	6 (25.0)	9 (18.8)	
3	10 (41.7)	22 (45.8)	
C2 n (%)			0.083
0	6 (25.0)	8 (16.7)	
1	3 (12.5)	12 (25.0)	
2	10 (41.7)	9 (18.8)	
3	5 (20.8)	19 (39.6)	
C2 facet n (%)			0.676
0	8 (33.3)	15 (31.3)	
1	7 (29.2)	9 (18.8)	
2	3 (12.5)	10 (20.8)	
3	6 (25.0)	14 (29.2)	
T1 n (%)			0.422
0	0 (0.0)	0 (0.0)	
1	4 (16.7)	15 (31.3)	
2	10 (41.7)	19 (39.6)	
3	9 (37.5)	14 (29.2)	

Continued

Table 5 Continued

	NP (n=24)	Non-NP (n=48)	P value
T1 facet n (%)			0.705*
0	10 (41.7)	25 (52.1)	
1	8 (33.3)	10 (20.8)	
2	4 (16.7)	8 (16.7)	
3	2 (8.3)	5 (10.4)	
T2 n (%)			0.334*
0	1 (4.2)	1 (2.1)	
1	7 (29.2)	24 (50.0)	
2	11 (45.8)	15 (31.3)	
3	4 (16.7)	8 (16.7)	
T2 facet n (%)			0.916*
0	16 (66.7)	28 (58.3)	
1	5 (20.8)	13 (27.1)	
2	3 (12.5)	6 (12.5)	
3	0 (0.0)	1 (2.1)	
L1 n (%)			**0.042***
0	2 (8.3)	5 (10.4)	
1	2 (8.3)	13 (27.1)	
2	13 (54.2)	11 (22.9)	
3	6 (25.0)	18 (37.5)	
L1 facet n (%)			0.277*
0	14 (58.3)	16 (33.3)	
1	3 (12.5)	12 (25.0)	
2	1 (4.2)	5 (10.4)	
3	5 (20.8)	14 (29.2)	
L2 n (%)			0.772
0	5 (20.8)	15 (31.3)	
1	7 (29.2)	15 (31.3)	
2	8 (33.3)	12 (25.0)	
3	3 (12.5)	5 (10.4)	
L2 facet n (%)			0.357*
0	18 (75.0)	31 (64.6)	
1	5 (20.8)	8 (16.7)	
2	0 (0.0)	3 (6.3)	
3	0 (0.0)	5 (10.4)	
Total body score, mean (SD)	25.4 (8.4)	29.9 (9.0)	**0.044**

Statistical significant p-values are given in bold.
*Fisher's exact test.
NP, neuropathic pain; OACT, OsteoArthritis CT.

between both groups, except for the right acromioclavicular joint (p=0.023; less damage in NP group), and the worst degenerated intervertebral disc of the lumbal spine (p=0.042; more damage in NP group).

DISCUSSION

In the IMI-APPROACH knee OA cohort 24 patients out of 297 (8%) had a likely NP component. Interestingly, despite similar general knee pain levels (due to matching), patients with a likely NP component had less radiographic damage in their index knee, but a significant more impaired physical function. This might be explained by higher pain scores in joints other than the index knee, although OACT grades of these joints did not statistically significantly differ between patients with and without an NP component. The total body OACT score was even lower in patients with a likely NP component. These data indicate that patients with a likely NP component, determined with the painDETECT questionnaire, represent a specific phenotype, where local and overall joint damage is not the main cause of pain and disability.

Although questionnaires like the painDETECT show high sensitivity and specificity to distinguish NP from non-NP,[15] an objective measurement to show presence of a lesion of the somatosensory system is required, which has not been done within IMI-APPROACH. As a consequence, other pain mechanisms than a pure NP component, such as nociplastic pain or occurrence of central sensitisation may play a role in these patients as well. Although fibromyalgia patients were excluded from inclusion in the IMI-APPROACH cohort, the presence of comorbidities/generalised pain syndromes was only assessed by asking the patients directly at time of inclusion. Objective scoring to determine specific pain syndromes was not used. Therefore, the presence of other pain phenotypes cannot be excluded.

The majority of the patients with a likely NP component (67%) had KL grade of 0 or 1. This raises the question whether these subjects are actually knee OA patients. The patients of the IMI-APPROACH knee OA cohort were included based on the clinical ACR criteria for knee OA. The agreement between these criteria and symptomatic radiographic knee OA is known to be low.[37] The IMI-APPROACH also did use a knee radiograph, taken at a screening visit, for final selection of patients, which was afterwards scored for KL grading performed by one observer blinded for the source of material. In the whole cohort, 47% of patients had a KL grade of 0 or 1 at baseline. The follow-up data of the study are currently being analysed and will demonstrate whether these patients are actual knee OA patients.

In our study, 8% of patients reported a painDETECT score ≥19. The presence of painDETECT scores ≥19 in knee OA patients in other studies ranges from 5% to 67%.[17–22 38 39] In a recently published systematic review, a prevalence of 19% (95% CI 15% to 24%) in patients with hip and knee OA was found, although the prevalence depended on population type: community based 17% (95% CI 11% to 24%), hospital based 25% (95% CI 15% to 36%), RCT patients 15% (95% CI 5% to 26%), end-stage knee OA 16% (95% CI 8% to 26%).[40] In the general population these numbers ranged from 1% to 14%.[41–43]

In our study, patients with a likely NP component showed less radiographic damage compared to patients without a likely NP component that were matched for

KOOS and SF-36 pain. Others compared patients with clinical knee OA with and without an NP component and found no differences in duration of OA symptoms,[44] refuting the argument of NP being simply a symptom of OA progression. Duration of the OA was not assessed in the IMI-APPROACH study, irrespectively, it supports the concept of OA patients with a likely NP component as a specific phenotype, not related to radiographic severity (our data) or duration[44] of disease.

Age, body mass index (BMI) and gender did not differ between patients with and without a likely NP component, confirming results from previous studies.[19 22] However, in other studies OA patients with higher painDETECT scores were younger[44] and had a higher BMI.[18 44] In contrast to our study, these studies included patients with painDETECT scores from 13 to 18 (uncertain result) in their analysis, giving a possible explanation for the different results.

In our study, patients with a likely NP component had a worse self-reported hand function (FIHOA) and worse outcomes on the two performance-based tests compared with patients without a likely NP component. Others also found OA patients with NP-like symptoms had impaired walk and stair climb activity,[21] but no difference in sit-to-stand activity.[17 21] Self-reported joint related function is also diminished in knee OA patients with a likely NP component compared with patients without a likely NP component.[17 18] Possibly, the impaired function is caused by OA pain in other joints. Indeed, more pain was found in the other joints, something that was also found previously.[20] However, joint damage of joints other than the index knee, assessed by OACT grades, did not differ between both groups. The total body score was even lower in patients with a likely NP component compared with patients without a likely NP component. Nevertheless, increased lumbar spine damage in patients with a likely NP component could contribute to the worse results on the two performance-based tests. Although, this does not explain the observed limited hand function. Besides, NRS pain of the lower back did not statistically differ between both groups. In addition to more severe overall pain, other causes for the physical impairment should be considered as well. Psychosocial factors, less physical activity and other comorbidities are factors known to interfere with pain and physical impairment.[45]

In agreement with the above-mentioned finding that in patients with a likely NP component local joint damage is not the main cause of pain (similar pain level but less radiographic joint damage), these findings show that this is the case for other joints as well (more pain but comparable joint damage).

Based on our results, it is possible that the generally found discordance between radiographic damage and pain in OA studies, is explained by the inclusion of patients with an NP component. Online supplemental table 2 shows that the relationships between knee pain and radiographic damage are very small in the whole IMI-APPROACH. Excluding patients with a likely NP component from this cohort, increases the relationships. The relationships increased even more when patients with an in-between painDETECT score (13–18) were also excluded. These data indicate that OA patients with a likely NP component indeed weaken the relationship between joint damage and pain.

Clearly, in OA patients with a likely NP component, joint damage itself is not the driving factor of pain and loss of function. This implies that pain and physical function are less likely to improve after TKA in this specific group. In general, about 20% of TKA is not successful.[46] Indeed, multiple studies found that OA patients with a likely NP component were twice as likely to experience pain after TKA than those without a likely NP component.[47–49] This effect may also interfere in case of DMOAD trials where the combination of tissue structure modification and pain control is needed (as requested by EMA and FDA[13 14]).

Obviously, the small number of patients with a NP component (n=24) is a clear limitation of this study. The main objectives of the IMI-APPROACH cohort study did not include evaluation of an NP component, therefore, the current analysis should be considered as post-hoc analysis with limited power. Nevertheless, the results are important to consider in patient selection of future OA clinical trials and further research to characterise this specific group is warranted.

In conclusion, this study shows that OA patients with a likely NP component possibly reflect an OA phenotype where local tissue damage is not the leading cause for pain and physical impairment. As a consequence, the general one-size fits all approach, focused on treatment of nociceptive pain (resulting from tissue damage), might be inappropriate in this specific patient group. Therefore, it is advised to use the painDETECT questionnaire, or an alternative measure to assess NP. Identifying these OA patients and offering them a more personalised treatment[6 15] as well as excluding them from DMOAD trials could increase successes.

Author affiliations
[1]Rheumatology & Clinical Immunology, UMC Utrecht, Utrecht University, Utrecht, The Netherlands
[2]Orthopedics, UMC Utrecht, Utrecht University, Utrecht, The Netherlands
[3]Rheumatology, Leiden University Medical Center, Leiden, The Netherlands
[4]Epidemiology, Leiden University Medical Center, Leiden, The Netherlands
[5]Servicio de Reumatologia, INIBIC-Hospital Universitario A Coruña, A Coruña, Spain
[6]Department of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway
[7]Rheumatology, Sorbonne Université, Paris, France
[8]INSERM, Paris, France
[9]Nordic Bioscience, Herlev, Denmark
[10]BioBone BV, Amsterdam, The Netherlands
[11]Institut de Recherches Internationales Servier, Suresnes, France
[12]GlaxoSmithKline USA, Philadelphia, Pennsylvania, USA
[13]Musculoskeletal Research Group, Newcastle University, Newcastle upon Tyne, UK
[14]Research Unit of Medical Imaging, Physics and Technology, University of Oulu, Oulu, Finland
[15]Regenerative Medicine, State Research Institute Centre for Innovative Medicine, Vilnius, Lithuania
[16]Orthopedics, UMC Utrecht, University Utrecht, Utrecht, The Netherlands

[17]Center for Translational Immunology, UMC Utrecht, Utrecht University, Utrecht, The Netherlands

Twitter Ali Mobasheri @Ali_Mobasheri

Acknowledgements We thank M. Melief for performing the KIDA analysis on all radiographs.

Contributors EMvH acted as guarantor. EMvH, PMJW, MPJ, WPG, ML, MK, FBI, IKH, FBe, NE and SM contributed to the conception and design of the study, or acquisition of data, or analysis and interpretation of data. EMvH, PMWJ, MPJ, MK, FL, NE and SM contributed to drafting the article or revising it critically for important intellectual content. All authors gave final approval of the version to be submitted.

Funding This work was supported by the Innovative Medicines Initiative Joint Undertaking under Grant Agreement no 115770, resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in kind contribution. See www.imi.europe.eu and www.approachproject.eu.

Disclaimer This communication reflects the views of the authors and neither IMI nor the European Union and EFPIA are liable for any use that may be made of the information contained herein. See www.approachproject.eu.

Competing interests The IMI-APPROACH project received a grant from Innovative Medicines Institute, grant agreement 115770. Outside the submitted work: EMvH has nothing to disclose; PMJW has nothing to disclose; MPJ has nothing to disclose; WPG has nothing to disclose; ML has nothing to disclose; MK reports grants from IMI-APPROACH, grants from Dutch Arthritis Association, during the conduct of the study; other from GlaxoSmithKline, Pfizer, Merck-Serono, Kiniksa, Abbvie, outside the submitted work; FBI reports grants from Gebro Pharma, grants from BIOIBERICA, grants from AB Science, grants from Abbvie, grants from Ablynx N.V., grants from Amgen, grants from Archigen Biotech, grants from Boehringer, grants from Bristol-Myers, grants from Celgene, grants from Eli Lilly and Company, grants from F. Hoffmann- La Roche., grants from Galapagos, grants from Gedeon, grants from Genentech, grants from Gideal Sciences, NC, grants from Glaxosmithkline, grants from Hospira, grants from INC Research UK, grants from Inventiv Health Clinical, grants from Janssen, grants from Lilly, grants from Nichi-IKO Pharmaceutical, grants from Novartis, grants from ONO Pharma, grants from Pfizer, grants from Pharmaceutical Research, grants from Regeneron, grants from Roche, grants from SA UCB Pharma, grants from Sanofi, grants from TRB Chemedica, grants from UCB Biosciences, outside the submitted work; In addition, FB has a patent Molecular block-matching method for gel image analysis issued, a patent Targeting A Specific Receptor On Cells With A Specific Compound For Use In The Treatment And/Or The Prevention Of Osteoarthritis And Rheumatoid Arthritis pending, a patent Genetic markers for osteoarthritis issued, a patent Method for the diagnosis of osteoarthritis issued, a patent Genetic markers for osteoarthritis pending, a patent Method for the diagnosing Arthrosis pending, a patent Method for diagnosing Arthrosis pending, a patent Method for the diagnosis of osteoarthritis pending, and a patent Anti-connexin compounds for use in the prevention and/or treatment of degenerative joint diseases. pending; IKH reports personal fees from AbbVie, grants from Pfizer, outside the submitted work; FBe reports personal fees from Boehringer, Bone Therapeutics, Expanscience, Galapagos, Gilead, GSK, Merck Sereno, MSD, Nordic, Novartis, Pfizer, Regulaxis, Roche, Sandoz, Sanofi, Servier, UCB, Peptinov, TRB Chemedica, 4P Pharma; A-CB-J reports non-financial support from Nordic Bioscience, personal fees from Nordic Bioscience, during the conduct of the study; CHL reports other from Merck KGaA, during the conduct of the study; AL is employee of Institut de Recherches Internationales Servier; JLa reports personal fees and other from GlaxoSmithKline, outside the submitted work; JLo has nothing to disclose; AM has nothing to disclose; HHW has nothing to disclose; FL has nothing to disclose; NE has nothing to disclose; SM has nothing to disclose.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by Medisch ethische toetsingscommisscie van het UMC UtrechtID nr. 17/440. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. In order to gain and govern access to the central IMI-APPROACH databases, tranSMART and XNAT, access has to be approved by the IMI-APPROACH Steering Committee.

ORCID iDs
Eefje Martine van Helvoort http://orcid.org/0000-0003-3540-4892
Mylène P Jansen http://orcid.org/0000-0003-1929-6350
Willem Paul Gielis http://orcid.org/0000-0003-0540-4808
Marieke Loef http://orcid.org/0000-0003-4301-8350
Ida K Haugen http://orcid.org/0000-0001-7810-2216
Francis Berenbaum http://orcid.org/0000-0001-8252-7815
Ali Mobasheri http://orcid.org/0000-0001-6261-1286

REFERENCES

1 Bruyère O, Honvo G, Veronese N, *et al*. An updated algorithm recommendation for the management of knee osteoarthritis from the European Society for clinical and economic aspects of osteoporosis, osteoarthritis and musculoskeletal diseases (ESCEO). *Semin Arthritis Rheum* 2019;49:337–50.
2 Bannuru RR, Osani MC, Vaysbrot EE, *et al*. OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. *Osteoarthritis Cartilage* 2019;27:1578–89.
3 Kloppenburg M, Kroon FP, Blanco FJ, *et al*. 2018 update of the EULAR recommendations for the management of hand osteoarthritis. *Ann Rheum Dis* 2019;78:16–24.
4 Bjordal JM, Ljunggren AE, Klovning A, *et al*. Non-Steroidal anti-inflammatory drugs, including cyclo-oxygenase-2 inhibitors, in osteoarthritic knee pain: meta-analysis of randomised placebo controlled trials. *BMJ* 2004;329:1317.
5 Bijlsma JWJ, Berenbaum F, Lafeber FPJG. Osteoarthritis: an update with relevance for clinical practice. *Lancet* 2011;377:2115–26.
6 Thakur M, Dickenson AH, Baron R. Osteoarthritis pain: nociceptive or neuropathic? *Nat Rev Rheumatol* 2014;10:374–80.
7 Bedson J, Croft PR. The discordance between clinical and radiographic knee osteoarthritis: a systematic search and summary of the literature. *BMC Musculoskelet Disord* 2008;9:116.
8 Towheed TE, Judd MJ, Hochberg MC, *et al*. Acetaminophen for osteoarthritis. *Cochrane Database Syst Rev* 2003:Cd004257.
9 Toupin April K, Bisaillon J, Welch V, *et al*. Tramadol for osteoarthritis. *Cochrane Database Syst Rev* 2019;5:Cd005522.
10 Puljak L, Marin A, Vrdoljak D, *et al*. Celecoxib for osteoarthritis. *Cochrane Database Syst Rev* 2017;5:Cd009865.
11 da Costa BR, Reichenbach S, Keller N, *et al*. Effectiveness of non-steroidal anti-inflammatory drugs for the treatment of pain in knee and hip osteoarthritis: a network meta-analysis. *Lancet* 2017;390:e21–33.
12 Wylde V, Beswick A, Bruce J, *et al*. Chronic pain after total knee arthroplasty. *EFORT Open Rev* 2018;3:461–70.
13 Food and Drug Administration. *Osteoarthritis: structural endpoints for the development of drugs, devices, and biological products for treatment. guidance for industry*. Rockville: U.S. Department of Health and Human Services, 2018.
14 Committee for medicinal products for human use (CHMP). *Guideline on clinical investigation of medicinal products used in the treatment of osteoarthritis*. London: European Medicines Agency, 2010.
15 Colloca L, Ludman T, Bouhassira D, *et al*. Neuropathic pain. *Nat Rev Dis Primers* 2017;3:17002.
16 Freynhagen R, Baron R, Gockel U, *et al*. painDETECT: a new screening questionnaire to identify neuropathic components in patients with back pain. *Curr Med Res Opin* 2006;22:1911–20.
17 Aşkın A, Özkan A, Tosun A, *et al*. Quality of life and functional capacity are adversely affected in osteoarthritis patients with neuropathic pain. *Kaohsiung J Med Sci* 2017;33:152–8.
18 Blikman T, Rienstra W, van Raay JJAM, *et al*. Neuropathic-like symptoms and the association with joint-specific function and quality of life in patients with hip and knee osteoarthritis. *PLoS One* 2018;13:e0199165.
19 Golob M, Marković I, Zovko N, *et al*. Do we pay enough attention to neuropathic pain in knee osteoarthritis patients? *Acta Clin Croat* 2018;57:16–21.
20 Hochman JR, Gagliese L, Davis AM, *et al*. Neuropathic pain symptoms in a community knee oa cohort. *Osteoarthritis Cartilage* 2011;19:647–54.
21 Moss P, Benson HAE, Will R, *et al*. Patients with knee osteoarthritis who score highly on the PainDETECT questionnaire present with multimodality hyperalgesia, increased pain, and impaired physical function. *Clin J Pain* 2018;34:15–21.
22 Ohtori S, Orita S, Yamashita M, *et al*. Existence of a neuropathic pain component in patients with osteoarthritis of the knee. *Yonsei Med J* 2012;53:801–5.
23 Polat CS, Doğan A, Sezgin Özcan D, *et al*. Is there a possible neuropathic pain component in knee osteoarthritis? *Arch Rheumatol* 2017;32:333–8.

24 van Helvoort EM, van Spil WE, Jansen MP, *et al*. Cohort profile: the applied public-private research enabling osteoarthritis clinical Headway (IMI-APPROACH) study: a 2-year, European, cohort study to describe, validate and predict phenotypes of osteoarthritis using clinical, imaging and biochemical markers. *BMJ Open* 2020;10:e035101.
25 Roos EM, Roos HP, Lohmander LS, *et al*. Knee Injury and Osteoarthritis Outcome Score (KOOS)--development of a self-administered outcome measure. *J Orthop Sports Phys Ther* 1998;28:88–96.
26 Nilsdotter AK, Lohmander LS, Klässbo M, *et al*. Hip disability and osteoarthritis outcome score (HOOS)--validity and responsiveness in total hip replacement. *BMC Musculoskelet Disord* 2003;4:10.
27 Ware JE. Sf-36 health survey update. *Spine* 2000;25:3130–9.
28 Downie WW, Leatham PA, Rhind VM, *et al*. Studies with pain rating scales. *Ann Rheum Dis* 1978;37:378–81.
29 Hawker GA, Davis AM, French MR, *et al*. Development and preliminary psychometric testing of a new OA pain measure--an OARSI/OMERACT initiative. *Osteoarthritis Cartilage* 2008;16:409–14.
30 Dreiser RL, Maheu E, Guillou GB, *et al*. Validation of an algofunctional index for osteoarthritis of the hand. *Rev Rhum Engl Ed* 1995;62:43s–53.
31 Altman R, Asch E, Bloch D, *et al*. Development of criteria for the classification and reporting of osteoarthritis. classification of osteoarthritis of the knee. diagnostic and therapeutic criteria Committee of the American rheumatism association. *Arthritis Rheum* 1986;29:1039–49.
32 Buckland-Wright JC, Ward RJ, Peterfy C, *et al*. Reproducibility of the semiflexed (metatarsophalangeal) radiographic knee position and automated measurements of medial tibiofemoral joint space width in a multicenter clinical trial of knee osteoarthritis. *J Rheumatol* 2004;31:1588–97.
33 Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. *Ann Rheum Dis* 1957;16:494–502.
34 Marijnissen ACA, Vincken KL, Vos PAJM, *et al*. Knee images digital analysis (KIDA): a novel method to quantify individual radiographic features of knee osteoarthritis in detail. *Osteoarthritis Cartilage* 2008;16:234–43.
35 Kinds MB, Marijnissen ACA, Vincken KL, *et al*. Evaluation of separate quantitative radiographic features adds to the prediction of incident radiographic osteoarthritis in individuals with recent onset of knee pain: 5-year follow-up in the check cohort. *Osteoarthritis Cartilage* 2012;20:548–56.
36 Gielis WP, Weinans H, Nap FJ, *et al*. Scoring osteoarthritis reliably in large joints and the spine using whole-body CT: osteoarthritis computed Tomography-Score (OACT-Score). *J Pers Med* 2020;11. doi:10.3390/jpm11010005. [Epub ahead of print: 22 12 2020].
37 Peat G, Thomas E, Duncan R, *et al*. Clinical classification criteria for knee osteoarthritis: performance in the general population and primary care. *Ann Rheum Dis* 2006;65:1363–7.
38 Power JD, Perruccio AV, Gandhi R, *et al*. Neuropathic pain in end-stage hip and knee osteoarthritis: differential associations with patient-reported pain at rest and pain on activity. *Osteoarthritis Cartilage* 2018;26:363–9.
39 Hochman JR, Davis AM, Elkayam J, *et al*. Neuropathic pain symptoms on the modified painDETECT correlate with signs of central sensitization in knee osteoarthritis. *Osteoarthritis Cartilage* 2013;21:1236–42.
40 Zolio L, Lim KY, McKenzie JE, *et al*. Systematic review and meta-analysis of the prevalence of neuropathic-like pain and/or pain sensitization in people with knee and hip osteoarthritis. *Osteoarthritis Cartilage* 2021;29:1096–116.
41 DiBonaventura MD, Sadosky A, Concialdi K, *et al*. The prevalence of probable neuropathic pain in the US: results from a multimodal general-population health survey. *J Pain Res* 2017;10:2525–38.
42 Fernandes GS, Valdes AM, Walsh DA, *et al*. Neuropathic-like knee pain and associated risk factors: a cross-sectional study in a UK community sample. *Arthritis Res Ther* 2018;20:215.
43 Inoue S, Taguchi T, Yamashita T, *et al*. The prevalence and impact of chronic neuropathic pain on daily and social life: a nationwide study in a Japanese population. *Eur J Pain* 2017;21:727–37.
44 Terry EL, Booker SQ, Cardoso JS, *et al*. Neuropathic-Like pain symptoms in a community-dwelling sample with or at risk for knee osteoarthritis. *Pain Med* 2020;21:125–37.
45 Geenen R, Overman CL, Christensen R, *et al*. EULAR recommendations for the health professional's approach to pain management in inflammatory arthritis and osteoarthritis. *Ann Rheum Dis* 2018;77:797–807.
46 Gunaratne R, Pratt DN, Banda J, *et al*. Patient Dissatisfaction following total knee arthroplasty: a systematic review of the literature. *J Arthroplasty* 2017;32:3854–60.
47 Wluka AE, Yan MK, Lim KY, *et al*. Does preoperative neuropathic-like pain and central sensitisation affect the post-operative outcome of knee joint replacement for osteoarthritis? A systematic review and meta analysis. *Osteoarthritis Cartilage* 2020;28:1403–11.
48 Soni A, Wanigasekera V, Mezue M, *et al*. Central sensitization in knee osteoarthritis: relating presurgical brainstem neuroimaging and PainDETECT-Based patient stratification to arthroplasty outcome. *Arthritis Rheumatol* 2019;71:550–60.
49 Kurien T, Arendt-Nielsen L, Petersen KK, *et al*. Preoperative neuropathic pain-like symptoms and central pain mechanisms in knee osteoarthritis predicts poor outcome 6 months after total knee replacement surgery. *J Pain* 2018;19:1329–41.