exploratory analysis showed that BMI was no associated with any pain outcomes.

Conclusions: MetS is associated with more hand pain in hand OA, partly mediated by anxiety- depression. MetS also increased the risk of OA pain nonspecifically related to hands suggesting a higher susceptibility to joint pain in general in patients with MetS.

Association between metabolic syndrome and pain in hand osteoarthritis according to various measurement tools*

	Unadjusted model	Adjusted for age, sex, KL total sum score	Adjusted for age, sex, KL total sum score and HAD
AUSCAN Pain subscore ≥ 20	1.59 (1.03; 2.46) °	1.51 (0.97; 2.37)	1.40 (0.89; 2.21)
AIMS 2 pain score ≥ 33	1.89 (1.21; 2.95) °	1.90 (1.20; 3.01) °	1.70 (1.06; 2.74) °
VAS at rest ≥ 15	1.39 (0.90; 2.15)	1.39 (0.89; 2.17)	1.30 (0.82; 2.04)
VAS at activity ≥ 44	1.64 (1.06; 2.54) °	1.63 (1.04; 2.56) °	1.48 (0.94; 2.35)
Number of painful joints ≥3	1.38 (0.88; 2.17)	1.38 (0.87; 2.20)	1.32 (0.83; 2.12)

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°Statistically significant; *Data are OR (95% CI) given for Mets+ versus Mets-.

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CHRONIC EROSIVE HAND OSTEOARTHRITIS PATIENTS HAVE HIGHER RISK TO EXPERIENCE SEVERE PAIN THAN TREATED RHEUMATOID ARTHRITIS PATIENTS: A COMPARATIVE STUDY BETWEEN DIGICOD AND ESPOIR COHORTS

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Purpose (the aim of the study): Nowadays, hand osteoarthritis (HOA) is considered as a less severe disease with a better functional prognosis and a lower global burden than rheumatoid arthritis (RA). This paradigm may no longer be true considering the efficacy of biologics and targeted therapies in RA compared to the weak efficacy of therapies in the most severe form of HOA, namely erosive HOA (EHOA).

We aimed to compare the burdens of established EHOA and RA. The objectives were 1) to compare pain and functional impairment and 2) the prevalence of comorbidities and of cardiometabolic diseases (CMD).

Methods: This study involved EHOA patients, defined by at least 1 erosive joint according to the Verbruggen score from inclusion visit of DIGital Cohort Osteoarthritis Design (DIGICOD), a French cohort of symptomatic HOA (mean duration of disease of the all cohort 12.6 ± 9.6 years.). RA patients fulfilling ACR/EULAR 2010 criteria at the 10th year visit were selected from the ESPOIR cohort (*Étude et Suivi des Polyarthrites Indifférenciées Récentes*), a French cohort of early RA.

For our first objective, the outcomes were pain intensity at rest or mobilization (0-100mm visual analogical scale (VAS) ≥ 40/100), fatigue (VAS fatigue ≥ median), function (normalized (0-100) scores of Health assessment questionnaire (HAQ) for RA, and AUStralian CANadian Osteoarthritis Hand (AUSCAN) function for EHOA ≥ median)). For the second objectives, we assessed the risk to have ≥ 2 comorbidities (among CMD, cancer, hematologic malignancies, fracture) or at least 1 CMD (among high blood pressure, diabetes, dyslipidemia, myocardial infarction and stroke). We compared the outcomes between EHOA and RA using logistic regression models. We performed a univariate analysis and multivariate analyses, adjusted by age, sex, body mass index and socio-educational level for the 2 objectives. Additionally, for our first objective, we adjusted also by the number of comorbidities as a relevant covariate. Odds ratios (OR) and their 95% confidence intervals (CIs) were reported (EHOA versus RA).

Results: We selected 138 patients with EHOA and 379 with RA. The median [interquartile] age for EHOA patients was 67.3 [64.3; 72.2] years vs 48.6 [39.9; 55.6] years for RA patients ($p < 0.001$). The disease duration, at the evaluation time, was 13.5 [7.0; 20.0] for EHOA and 10.5 years [10.3; 10.7] for RA patients. RA was anti-citrullinated protein antibodies (ACPA) positive for 56% of patients and in remission for 61% (DAS28 CRP < 2.6). RA patients received methotrexate (82%), biologics (37%) and corticosteroids (25%) while 20% of EHOA patients received oral non-steroidal anti-inflammatory drugs.

The number of painful joints in the hands was higher for EHOA than RA patients (4.0 [2.0;8.8] vs 0.0 [0.0;3.0], $p < 0.001$).

In the adjusted analysis, the risk of experiencing pain exceeding 40/100 was found to be three times higher in EHOA than in RA (OR = 3.13 95% CI [1.74 to 5.68] $p < 0.001$). There was also higher risk to have a functional impairment with score above the median (OR = 2.27 CI 95% [1.26 to 4.17], $p = 0.007$) in EHOA patients compared to RA (Figure 1). There was no difference for pain at rest and for VAS fatigue.

For comorbidities, the proportions of EHOA patients with ≥ 2 comorbidities were higher than RA patients (37.7% vs 27.5%). However, considering the age disparity between the groups, we conducted a stratified analysis. In the age range of 50 to 70 years, 30% of EHOA patients had at least two comorbidities compared to 47% in RA patients.

In adjusted analysis, the risk to have ≥ 2 comorbidities was 4 times lower in EHOA than in RA patients (OR = 0.25 CI 95% [0.13 to 0.48]; $p < 0.001$) while there was no difference for CMD risk.

Conclusions: After more than 10 years of disease duration, EHOA is associated with more pain and more functional impairment but less comorbidities than RA. This study highlights the significant unmet need for effective therapies EHOA.

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DETERMINATION OF AN EPIGENETIC POLYGENIC RISK SCORE TO PREDICT RECOVERY FROM PAIN FOLLOWING SURGICAL INTERVENTION FOR LUMBAR SPINAL STENOSIS DUE TO SPINE OSTEOARTHRITIS

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Purpose (the aim of the study): One in five adults over 65 experiences symptomatic lumbar spinal stenosis (LSS), in large part as a consequence of facet joint osteoarthritis (OA). Despite a growing rate of spine surgery and awareness of clinical prognostic factors, a large proportion of patients continue to experience persistent pain after surgery, and our ability to predict who will benefit and who will fail to respond to surgery remains poor. Approximately one-third of patients have minimal change in their pain after surgery, creating a costly unmet need to identify patient biometrics that correlate with successful surgical outcomes. The purpose of this study was to identify preoperative serum epigenetic markers that are predictive of 1-year postoperative recovery from pain following surgery for symptomatic LSS due to spine facet osteoarthritis (S-FOA).

Methods: We used a case-control approach to look for epigenetic signatures in bio-banked blood from patients that had either a super response (> 70% improvement in pain score) or non-response (< 30% improvement) to surgery, as determined by self-reported pain at baseline and 12 months post-surgery. The patient subgroup was selected from participants in the Longitudinal Evaluation in the Arthritis Program, Osteoarthritis (LEAP-OA): Surgical Prognostic Factors study. Pre-surgery blood samples from 40 age- and sex-matched surgical spine OA patients were used in our analysis: 23 super-responders and 17 non-responders. Whole cell genomic DNA was isolated and the TruSeq Methyl Capture

EPIC kit (Illumina) was used to generate libraries for reduced representation bisulphite sequencing (RRBS-sq). Multiplex sequencing was performed with the Highoutput 300 bp kit (Illumina) on the NexSeq550 sequencer. Sequencing data was quality controlled using FastP, and mapped to reference human genome sequence using Bismark. X and Y chromosome data were filtered out and CpGs (DNA methylation sites) within gene promoters with at least 10-fold coverage in all patients were selected for downstream analysis. DNA methylation status was determined at 24,500 gene promoters in all patient samples. β-values were determined as the ratio of methylated to total reads (β = methylated/(methylated + unmethylated)) averaged across all CpGs (DNA methylation sites) within a gene promoter region (defined as 2kb upstream, 1 kb downstream of transcript start site). Genes with significant differences in promoter methylation status between responders and non-responders were determined using Limma in R. The integrated pathway database pathDIP was used to identify biologically relevant pathways among differentially methylated genes that had > 1.5-fold differences in β-scores, comparing super-responders versus non-responders. Lasso logistic penalized regression was carried out using the R package 'glmnet' to identify candidate epigenetic polygenic risk scores (E-PRS) predictive of 12-month pain response.

Results: We identified 210 differentially methylated candidate gene promoters (with nominal uncorrected p-value < 0.01) in super-responders relative to non-responders. Thirty-four of these candidate promoters had greater than 1.5-fold difference in methylation status in super- vs. non-responders, and, based on a literature search, twelve of these were associated with inflammatory or neurological processes or diseases. Focussing on the 34 genes that had > 1.5-fold differences in methylation status, we performed a preliminary pathway enrichment analysis based on negatively and positively differentially methylated promoters. We identified 38 and 14 pathways respectively. Enriched pathways included inflammatory and neuronal signaling. Using lasso penalized logistic regression, a very high degree of accuracy in differentiating pain response was achieved with candidate E-PRSs dependent on as few as 6 (AUC=0.957, accuracy 90.0%) or 11 (AUC=0.990, accuracy 92.5%) genes. In comparison, a model including only typical pre-operative clinical factors performed less well (77.5% accuracy).

Conclusions: We have identified an epigenetic biosignature associated with recovery/non-recovery from pain following surgery for LSS due to facet OA. Using this biosignature, we have determined a biologically plausible candidate E-PRS that may enable a personalized/precision medicine approach to accurately identify spine OA patients that are likely to benefit from surgery. Currently, our ongoing efforts are focussed on further validating the E-PRS's predictive ability in a larger cohort.

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THE RELATIVE IMPORTANCE OF STRUCTURAL CHANGES OF RADIOGRAPHIC OSTEOARTHRITIS AND PAIN IN MULTIPLE SITES: THE JOHNSTON COUNTY OSTEOARTHRITIS PROJECT

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Purpose (the aim of the study): To determine the relative associations of structural burden (multiple joint site radiographic osteoarthritis (rOA)) and pain burden (i.e., pain, aching, and stiffness score) on function, fatigue, and pain behavior in a diverse community-based sample.

Methods: Data were from participants in the Johnston County OA Project (JoCoOA) who completed the baseline (2013-15) and follow-up (2017-18) visits. At eleven joint sites (bilateral hands, hips, knees, ankles, feet, and lumbosacral spine), rOA burden was defined using the number of affected joints (1 point for each, range 0 to 11, **Figure 1**), while pain burden was defined using a sum of the pain score (0-3, none-severe) at each joint (total score range 0-33). The outcomes of interest were change in four Patient Reported Outcomes Measurement Information System (PROMIS) scores (i.e., Physical Function, Fatigue, Pain Interference, and Pain Behavior).

We pre-specified cut-offs of rOA in ≥3 joint sites (high rOA, reflecting more involvement than one site bilaterally) and pain score of ≥6 (high pain, indicating two sites with severe pain or more widespread mild or moderate pain) to define 4 burden groups: low pain/low rOA, low pain/high rOA, high pain/low rOA, and high pain/high rOA (**Figure 1**).

Associations between baseline features and 4-level burden groups were assessed using multivariable, generalized logistic regression (for nominal categories) to estimate adjusted odds ratios (OR) and 95% confidence intervals (CI). For each PROMIS scale, linear regression model was used to examine the association between burden groups and T-score change from baseline to follow-up. Each model was adjusted for age, sex, race, education, baseline participant characteristics (age, body mass index (BMI), Charlson Comorbidity Index, PROMIS depression and anxiety scores), baseline value of the corresponding score, and follow-up time.

Results: Individuals with data available for analyses (n=445, 69% women, 33% Black, 12% with < high school education) had a mean age of 70 ± 7 years and mean BMI of 31 ± 7 kg/m^2 at baseline. Overall PROMIS-Physical Function scores declined (worsened) by about 1 point (mean -1.6 [SD 7.3]) over the 3.5 ± 1 year follow-up. For the other scores where higher scores indicate poorer outcomes, all worsened slightly (from 0.5 to 0.9 points) over time.

The cohort was distributed across the four burden groups as follows: low pain/low rOA (reference, 30%), low pain/high rOA (39%), high pain/low rOA (10%), and high pain/high rOA (21%, **Figure 1**). Older individuals were more likely to have higher rOA burden but not more pain, while those with higher BMI had increased odds of both greater rOA and pain burden. Higher baseline anxiety, but not depression, was also associated with more rOA and pain burden (**Table 1**).

Over 3.5 years, individuals with high pain had clinically meaningfully worse PROMIS scores (2 to 5 points worse) regardless of rOA burden. The sum of joint sites with pain/aching/stiffness was statistically significantly associated with poorer scores (by 2 to 4 points) on all four PROMIS scales, while number of joint sites with rOA was not. Additionally, an increase in pain sites, but not in rOA sites, was modestly but statistically significantly associated with worsening PROMIS scores (**Table 2**).

Conclusions: The presence of pain in multiple body sites was more strongly associated with important outcomes of physical function, fatigue, pain interference and pain behavior than was the burden of structural rOA in this diverse, population-based cohort. It is essential to consider the body burden of OA in relation to important clinical outcomes, regardless of the particular index joint of interest.

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LIPOSOMAL INTRA-ARTICULAR GEL PROVIDES COMPONENTS FOR ULTRA-LOW FRICTION IN THE SYNOVIAL JOINT, THUS IMPROVING CLINICAL AND FUNCTIONAL OUTCOMES OF PATIENTS WITH OSTEOARTHRITIS

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Purpose (the aim of the study): Pathological changes related to OA development induce destructive structural alterations in the joint tissues, subsequently resulting in significant impairment of movement quality within. Finally, impaired joint movement quality substantially contribute to deterioration of OA patient's quality of life, as well as further progression of the disease. Intra-articular therapies based on agents that aims to improve the joint movement quality, like hyaluronic acid (HA) are recognized as one of the most clinically efficient, with strong scientific base justifying their use as therapeutics counteracting OA symptoms and finally delaying total joint replacement. However, HA even though being the major component of synovial fluid, it is not the sole molecule responsible for joint lubrication and elimination of friction between cartilaginous surfaces. Detailed research from cartilage surface mechanics prove the existence of a distinctive link between HA and phospholipids (in a form of liposomes) that further interplays with lubricin located on the cartilage surface, in order to provide physiologically correct, frictionless movement in the joint (Fig.1.). The purpose of this prospective, open-label clinical trial was to investigate if the therapy based on intra-articular injection of a gel composed of HA and liposomes is clinically effective in patients with mild to moderate OA.

Methods: Lipotris™ medical device is a combination of HA (molecular weight: 1.2-2.2 MDa, concentration: 22 mg/mL) and liposomes created from 1-palmitoyl-2-oleoyl-phosphatidylcholine (POPC) (0.8 mg/mL). 50 patients with knee OA (Kellgren-Lawrence Classification grade 2 or 3)