# Associations Between Physical Activity, Self-reported Joint Function, and Molecular Biomarkers in Working Age Individuals With Hip and/or Knee Osteoarthritis

Clinical Medicine Insights: Arthritis and Musculoskeletal Disorders
Volume 15: 1–8

DOI: 10.1177/11795441221081063
SAGE

Elin Östlind[1,2], Frida Eek[3], Kjerstin Stigmar[3,4], Anita Sant'Anna[5], Eva Ekvall Hansson[3,4] and André Struglics[6]

[1]Research Group Physiotherapy, Division of Physiotherapy, Department of Health Sciences, Lund University, Lund, Sweden. [2]Dalby Healthcare Center, Region Skåne, Lund, Sweden. [3]Division of Physiotherapy, Department of Health Sciences, Lund University, Lund, Sweden. [4]Skåne University Hospital, Lund, Sweden. [5]Viniam Consulting AB, Halmstad, Sweden. [6]Department of Clinical Sciences, Orthopaedics, Lund University, Lund, Sweden.

## ABSTRACT

**OBJECTIVE:** Previous research has suggested an association between physical activity (PA), joint function, and molecular biomarkers, but more studies are needed. The aim of this study was to explore the associations between PA or self-reported joint function and molecular biomarkers of cartilage and inflammation in individuals with hip and/or knee osteoarthritis (OA). Specific objectives were to explore the correlations between (1) the change over 3 months in self-reported PA/joint function and the change in molecular biomarkers (2) objectively measured PA and molecular biomarkers measured at 3-month follow-up.

**DESIGN:** Working age participants (n = 91) were recruited from a cluster randomized controlled trial. Self-reported PA, joint function, and serum samples were collected at baseline and after 3 months. Serum concentrations of the inflammatory marker C-reactive protein (CRP) and the cartilage markers Alanine-Arginine-Glycine-Serine (ARGS)-aggrecan, cartilage oligomeric matrix protein (COMP), and type II collagen C2C were analyzed by immunoassays. Objectively measured PA (steps/day) was collected during 12 weeks from activity trackers used by 53 participants. Associations were analyzed with Spearman's rank correlation.

**RESULTS:** There was a weak negative correlation between the change in self-reported PA and the change in COMP ($r_s = -0.256$, $P = .040$) but not for the other molecular biomarkers. There were no correlations between the change in self-reported joint function and the change in molecular biomarkers or between the average steps/day and the molecular biomarkers at follow-up ($r_s \leqslant -0.206$, $P \geqslant .06$).

**CONCLUSION:** In general, no or only weak associations were found between PA/joint function and molecular biomarkers. Future research recommends including participants with lower PA, extend the follow-up, and use a design that allows comparisons.

**KEYWORDS:** Knee osteoarthritis, hip osteoarthritis, physical activity, molecular biomarkers

**RECEIVED:** December 1, 2021. **ACCEPTED:** January 28, 2022.

**TYPE:** Original Research

**FUNDING:** The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The underlying cluster randomized controlled trial received funding from the Swedish Research Council (FE). This exploratory project received additional project grants from the Crafoord Foundation (AS), the Swedish Rheumatism Association (AS), the Faculty of Medicine Lund University (AS), Kocks Foundation (AS), and Alfred Österlunds Foundation (AS). The funding sources had no role in the design, collection, and interpretation of the data or the decision to submit for publication.

**DECLARATION OF CONFLICTING INTERESTS:** The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

**CORRESPONDING AUTHOR:** Elin Östlind, Research Group Physiotherapy, Division of Physiotherapy, Department of Health Sciences, Lund University, HSC, Box 157, S-221 00 Lund, Sweden. Email: elin.ostlind@med.lu.se

## Introduction

Osteoarthritis (OA) is a common, multifaceted joint disease driven by biomechanical stress and low-grade inflammatory factors that leads to osteochondral changes in the joint.[1,2] Cartilage reduction is one of the main characteristics of OA.[3,4] Healthy articular cartilage is elastic and can adapt its structure, composition, and metabolism to a wide range of activities.[5-7] In healthy synovial joints, there is a low turnover of the extracellular matrix of the articular cartilage, but in joints affected by OA, homeostasis is disrupted, causing cartilage degradation.[4] In joints with OA, the subchondral bone, synovium, muscles, ligaments, tendons, and adipose tissue are also affected.[1]

Physical activity (PA) is recommended as the non-surgical core treatment for OA of the knee.[8,9] PA has a positive effect both at the local/systemic level and at biomechanical/inflammatory factors that drive the progression of OA.[3] Previous studies have reported that PA can improve physical function, reduce pain, and improve health-related quality of life (HRQoL) in individuals with knee and/or hip OA.[10]

The diagnosis of OA can be clinically determined, and progression is currently based on radiographic and clinical findings. However, molecular biomarkers in blood, urine, and synovial fluid have been proposed to be useful in detecting changes in joint remodeling and progression of disease.[11] Previous research has shown higher levels of cartilage biomarkers in individuals with OA compared with healthy controls, indicating their possible value in the prediction and progression of OA.[11-13] The neoepitope Alanine-Arginine-Glycine-Serine (ARGS)-aggrecan, generated by aggrecanase proteases, and the C2C neoepitope of type II collagen, generated by

collagenase proteases, have shown to be increased in synovial fluid and serum samples from OA and knee-injured patients.[14-18] ARGS-aggrecan and C2C are included on a list of the best known molecular biomarkers for monitoring OA development.[11,19]

Molecular biomarkers have also been used to show the effect of PA in individuals with OA.[20] A systematic review reported that the concentrations of C-reactive protein (CRP), a marker of inflammation, decreased after exercise.[21] Research has also shown an association between exercise and the promotion of the joint structure protein cartilage oligomeric matrix protein (COMP).[22,23] The relationship between self-reported joint function and molecular serum biomarkers have also been examined where studies reported that higher levels of biomarkers indicated inferior physical function in individuals with knee OA.[24,25]

According to two more recent reviews, exercise seemed to have a small beneficial long-term effect on cartilage breakdown or turnover and inflammation.[20,26] However, the heterogeneity between the studies regarding design and effect was large and the authors acknowledge the need for more research to gain a better understanding.[20,26] Exploratory studies could be useful to better understand the relationships between PA and molecular biomarkers. Of interest is also the relationship between self-reported joint function and systemic molecular biomarkers in individuals with OA, which, to our knowledge, has only been reported in a few previous studies.[24,25]

Therefore, the objective of this study was to further explore these relationships by studying the associations between (I) PA, (II) self-reported joint function, and serum biomarkers of cartilage (ARGS, C2C, and COMP) and inflammation (CRP) in individuals of working age with hip and/or knee OA. Specific objectives were to study the correlation between (1) change (3 months) in self-reported PA and change in molecular biomarkers, (2) change (3 months) in self-reported joint function and change in molecular biomarkers, and (3) objectively measured PA (average steps/day during 12 weeks) and molecular biomarkers at 3-month follow-up.

## Methods

### *Design and setting*

This is a longitudinal study with an exploratory approach. Data were collected from individuals with hip and/knee OA in working age who participated in a cluster randomized controlled trial (C-RCT). Briefly, the 2-armed C-RCT investigated the effect of participating in a patient education program for OA with the addition of self-monitoring PA using a wearable activity tracker (Fitbit Flex 2) for 12 weeks compared with participating in a patient education program alone. The C-RCT is registered in clinical trials (No. NCT03354091). A study describing objectively measured PA and Fitbit adherence for participants in the C-RCT intervention group has been published.[27]

All participants took part in a Supported Osteoarthritis Self-management Program (SOASP), which is recommended as the first-line treatment for patients with hip, knee, and hand OA in Sweden.[28,29] The SOASP in this study included 3 theoretical group sessions about OA, exercise, and self-management. The intervention in the underlying C-RCT consisted of the addition of self-monitoring PA with a wearable activity tracker for 12 weeks. To make it more achievable for the participants, the default activity goal of 10 000 steps per day was changed to 7000. Data for this study were collected just before participation in the SOASP (baseline) and after 3 months.

### *Participants*

Potential participants for the underlying C-RCT and thereby this study were recruited from October 2018 to May 2019 using a repetitive Facebook advertisement. The inclusion criteria were working ⩾ 20 hours per week, aged between 18 and 67 years, being able to understand Swedish in speech and writing, and able to participate in PA. They also had to have access to a smartphone, tablet, or computer to use the Fitbit-app and be able to wear an activity tracker for 12 weeks. Of those who saw the Facebook advertisement and received additional information, 110 individuals registered on the project's website using an electronic identification (ID) service[30] and thus gave their informed consent to participate in this study. Nineteen individuals chose to drop out before the study started. Ninety-one participants were included in this present study (of which 56 were randomized to the intervention group and 35 to the control group in the C-RCT).

### *Measurements and outcomes*

The demographic data of the participants and the self-reported PA/joint function were collected by e-mail at baseline at the same time as participating in the SOASP and at follow-up after 3 months. Height and baseline weight were collected ad hoc after the completion of the study. PA was measured among participants in the intervention group in the C-RCT using the wearable activity tracker Fitbit Flex 2 and therefore collected for 12 weeks from baseline to follow-up.

*Sampling and molecular biomarkers.* Serum samples at baseline for all participants (n = 91) were collected at the health care center in conjunction with participation in one of the group sessions in the SOASP. Participants returned to the health care center after 3 months when samples were collected again from 86 of the participants. All samples were collected in the afternoon (between 03:30 and 05:00 PM). CRP was analyzed at the Clinical Chemistry Department at the Skåne University Hospital in Lund, Sweden, and the other biomarkers were analyzed at the Biomedical Centre (BMC), Faculty of Medicine, Lund University, Sweden.

*ARGS-aggrecan.* ARGS-aggrecan was analyzed using the Meso Scale Discovery (MSD) platform as described.[31] Briefly, serum samples were deglycosylated with chondroitinase ABC and keratanase. MSD microplates were coated with capture antibody (anti-HABR, Invitrogen no. AHP0022; same lot number for all assessments) against the G1 and G2 globular domains of human aggrecan. ARGS-aggrecan was detected using a biotinylated monoclonal antibody against ARGS neoepitope together with sulfo-tagged streptavidin (MSD) and analyzed in a Sector Imager 6000 (MSD). Serum samples were run undiluted in duplicates with a mean (range) coefficient of variation (CV) of 2.5% (0%-10.8%). The inter plate CV for quality control (QC) serum sample was 10.2% (from 5 plates).

*COMP.* Serum COMP levels were quantified with an ELISA-based immunoassay (BioVendor, no. RD194080200) according to the manufacturer's instructions. The same lot number of the BioVendor COMP assay was used in all assessments. The serum samples were run diluted (50×) in duplicates with mean (range) CV of 2.6% (0%-18.4%). Two serum QC samples were run on each plate (total of 9 plates), and the inter plate CVs were 11.2% and 14.4%.

*C2C.* Serum C2C were quantified with an ELISA-based immunoassay (IBEX, no. 60-1001-001) according to the manufacturer's instructions. The same lot number of the C2C IBEX assay was used in all assessments. Serum samples were run diluted (2×) in duplicates with mean (range) CV of 4.1% (0%-16.7%). Two serum QC samples were run on each plate, and the inter plate CVs were 18.6% and 19.4% (from 6 plates).

*CRP.* Serum CRP were quantified on a Cobas platform (Roche Diagnostics; NPU19748) accredited method.

Serum samples were run undiluted in duplicates with mean (range) CV of 7.9% (0%-49.1%).

*Questionnaires.* Participants completed an online questionnaire that was sent to their emails at baseline and at 3-month follow-up. The baseline questionnaire entailed questions about demographics work, self-reported PA, and joint function. The questionnaire at the 3-month follow-up entailed questions about work, activity tracker-usage, self-reported PA, and joint function.

Self-reported joint function was measured with the Knee injury and Osteoarthritis Outcome Score (KOOS) and the Hip disability and Osteoarthritis Outcome Score (HOOS).[32,33] Participants answered KOOS or HOOS depending on their most affected joint. KOOS and HOOS consist of 5 subscales, Pain, Symptoms, Activities of Daily Living (ADL), Sport and Recreation function (Sport/Rec), and knee/hip-related Quality of Life (QoL). Each subscale contains 2 to 17 items and a mean score (0-100) of the items is calculated for each subscale, with 0 indicating extreme symptoms and 100 indicating no symptoms.[34] KOOS and HOOS have shown adequate psychometric properties for populations with OA.[35,36]

The International Physical Activity Questionnaire–Short Form (IPAQ-SF) was used to measure self-reported PA.[37] IPAQ-SF comprises 9 questions concerning time spent in high intensity, moderate intensity, walking, or sitting in the last 7 days. The outcomes of IPAQ-SF are Metabolic Equivalent of Tasks (MET) minutes/week and PA category score (low, moderate, or high).[38] MET-minutes and PA category were calculated for each individual according to the IPAQ-SF protocol. Only MET-minutes were used in the analyzes.

*Objectively measured PA.* Objectively measured PA was collected from participants in the intervention group (n = 56) during 12 weeks using a wearable activity tracker, Fitbit Flex 2. The Fitbit Flex 2 is a commercial accelerometer-based wearable activity tracker that estimates steps taken, distance traveled, and time in different activity levels. The Fitbit Flex has shown good reliability and validity in measuring steps taken.[39] The activity tracker was connected to an app (Fitbit) on the participants' smartphone or tablet, and the participants were asked to monitor their activity once daily. Activity data were transmitted through the Fitbits Web API[40] to our data server. We requested that participants grant us access to their Fitbit accounts through our project website when they received the Fitbit from the researcher who monitored the study (EÖ). The mean daily number of steps for each participant was calculated during the 12-week period.

### *Data analysis*

The raw activity data from the Fitbit was preprocessed using Rstudio Team (2019)[41] and Microsoft Corporation, Microsoft Excel 2018. Baseline demographics and characteristics are presented as mean, standard deviation (SD), or proportions (%). The proportions of participants in different categories in IPAQ-SF at baseline are described. Subsequent statistical analysis was performed using the statistical package IBM SPSS Statistics version 27.[42]

Changes in molecular biomarkers and changes in self-reported joint function and self-reported PA from baseline to follow-up were calculated. Variable distributions were visually and descriptively assessed with histograms and q plots. Outcome scores were descriptively presented as median and interquartile range (IQR) due to skewed distributions.

The correlations between the change in molecular biomarker concentrations and the change in self-reported joint function and PA were evaluated using Spearman's rank correlation, due to the non-normal distribution of the data. For individuals with data from the objective activity tracker (n = 53), the correlation between molecular biomarker concentrations at follow-up and objectively measured PA (average number of steps/day) was evaluated by Spearman's rank correlation.

### *Ethical considerations*

The procedures and methods used in this study were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and

**Table 1.** Baseline characteristics of the participants (n = 91).

| | |
|---|---|
| Women, % (n) | 81.3 (74) |
| Age in years, mean (SD) | 56.0 (5.7) |
| BMI, kg/m$^2$ (SD)[a] | 26.1 (4.1) |
| Married or living with partner, % (n) | 70.0 (63) |
| Children in the household, % (n) | 24.4 (22) |
| Most affected joint, % (n) | |
| Hip | 23.1 (21) |
| Knee | 76.9 (70) |
| Education (postsecondary), % (n) | 66.7 (60) |
| Present level of physical activity compared to before OA, % (n) | |
| More physically active | 13.3 (12) |
| Less physically active | 50.0 (45) |
| Equally physically active | 35.6 (32) |
| IPAQ, categorical, % (n) | |
| Low | 17.3 (14) |
| Moderate | 37.0 (30) |
| High | 45.7 (37) |
| Assigned group in the C-RCT, % (n) | |
| Intervention | 61.5 (56) |
| Control | 38.5 (35) |

Abbreviations: BMI, body mass index; C-RCT, cluster randomized controlled trial; IPAQ, International Physical Activity Questionnaire; OA, osteoarthritis; SD, standard deviation.
[a]BMI were collected for n = 51.

with the Declaration of Helsinki of 1975, as revised in 2000.[43] This study was approved by the Regional Ethics Review Board in Lund, Sweden (Dnr 2017/596, 2018/593 and 2019/00594). All participants received written information about the study and provided their informed consent with an electronic identification service before registering.

## Results

Of the 91 participants in this study, 90 (99%) responded to the questionnaire at baseline and 89 (98%) responded to the questionnaire at follow-up. Fifty-six participants used an activity tracker, but 3 individuals in the intervention group had technical issues and lacked data; objectively measured PA was therefore collected from 53 individuals. The majority (82.5%) of the participants were classified as highly or moderately physically active at baseline according to IPAQ-SF. The baseline characteristics of the participants are presented in Table 1. Outcomes at baseline and follow-up and change between the measurements are presented in Table 2.

### *Correlation between change in self-reported joint function or PA and change in molecular biomarkers*

No significant correlations ($r_s = -0.105$ to $0.206$, $P \geq .06$) were found between the change in self-reported joint function and the change in molecular biomarkers (Table 3). A weak negative correlation ($r_s = -0.256$, $P = .040$) was found between the change in self-reported PA and the change in COMP but not for the other molecular biomarkers (Table 3).

### *Correlation between objectively measured PA and molecular biomarkers*

Individuals with activity tracker data (n = 53) walked on average 10 730 steps per day during the 12-week period. No correlations were found between steps per day and molecular biomarkers (Table 4).

## Discussion

In this study, we examined the associations between joint function/PA and molecular biomarkers in individuals with hip and/or knee OA. Except for a weak negative correlation between the change in self-reported PA and the change in COMP, we did not find any correlations between change in joint function/PA and change in molecular biomarkers. We also did not find any correlation between steps/day and molecular biomarkers measured at follow-up. The general results of our study are consistent with the results of a systematic review investigating the impact of exercise on molecular biomarkers.[26] A meta-analysis within the review showed an association between exercise and CRP and C2C, but the associations were not statistically significant.[26] In another systematic review, a statistically significant association between exercise and decrease in CRP level was reported, but a simultaneous reduction in body mass index (BMI) was the most important factor for a reduction in CRP.[21] However, in our study, the average BMI was 26 at baseline, indicating a close to normal BMI.[44] ARGS-aggrecan and PA has also been evaluated in a OA-population.[45] That study showed that serum ARGS-aggrecan has a low sensitivity to PA which is in line with the results in this study, but the measurements were only collected for 24 hours.

We did find a weak negative correlation between the change in self-reported PA and the change in serum COMP concentration, indicating that an increase in PA was associated with a reduction in COMP levels. This finding may be due to multiple comparisons causing a type 1 error. However, the result is in line with the result of a previous randomized controlled pilot study.[46] In that study, a reduction in serum-COMP (admittedly another COMP assay) was observed in the intervention group after 10 weeks of exercise. It has been suggested that COMP levels induced by a mechanical stimulus such as exercise could have a higher correlation with markers of OA progression such as self-reported function than COMP levels at

**Table 2.** Outcomes at baseline and follow-up and change between baseline and 3-month follow-up.

| | BASELINE | | FOLLOW-UP | | CHANGE | |
|---|---|---|---|---|---|---|
| | N | MEDIAN (IQR) | N | MEDIAN (IQR) | N | MEDIAN (IQR) |
| Molecular biomarkers | | | | | | |
| CRP (µg/mL) | 91 | 1.30 (0.56–2.95) | 86 | 1.35 (0.62–3.04) | 86 | −0.02 (−0.50 to 0.50) |
| ARGS-aggrecan (pmol/mL) | 91 | 0.15 (0.12–0.17) | 86 | 0.15 (0.12–0.17) | 86 | 0.01 (−0.02 to 0.02) |
| COMP (ng/mL)[a] | 91 | 800 (544–1051) | 85 | 798 (576–1095) | 85 | 11 (−109 to 134) |
| C2C (ng/mL) | 91 | 194 (153–239) | 86 | 214 (164–254) | 86 | 2 (−20 to 36) |
| HOOS/KOOS | | | | | | |
| Pain | 88 | 61.1 (41.7–75.0) | 87 | 66.7 (47.5–80.6) | 87 | 5.55 (−2.8 to 15.0) |
| Symptoms | 88 | 54.3 (35.7–67.9) | 88 | 53.6 (42.9–71.4) | 88 | 7.1 (−4.6 to 14.3) |
| ADL | 90 | 72.1 (52.6–86.8) | 88 | 76.7 (61.8–86.8) | 88 | 1.5 (−6.8 to 8.8) |
| Sport/Recreation | 87 | 30.0 (10.0–50.0) | 87 | 30.0 (10.0-55.0) | 84 | 0.0 (−11.9 to 10.0) |
| QoL | 90 | 43.8 (29.7–56.3) | 88 | 43.8 (31.3–61.5) | 88 | 0.0 (−6.3 to 12.5) |
| IPAQ-SF | | | | | | |
| MET-minutes/week | 81 | 2337 (1395–4626) | 78 | 2876 (1538–4334) | 70 | 588 (−817 to 1677) |

Abbreviations: ADL, activities of daily living; ARGS, neoepitope of aggrecan; C2C, collagen type II cleavage; COMP, cartilage oligomeric matrix protein; CRP, C-reactive protein; HOOS, Hip disability and Osteoarthritis Outcome Score; IPAQ-SF, International Physical Activity Questionnaire–Short Form; IQR, interquartile range (Q1-Q3); KOOS, Knee injury and Osteoarthritis Outcome Score; MET, metabolic equivalent of tasks; QoL, hip/knee-related quality of life.
[a]n = 85 for COMP follow-up due to one value below the lower limit of detection.

**Table 3.** Correlation (Spearman's Rho) between change in self-reported joint function/PA and change in molecular biomarkers.

| | CRP $R_S$ | *P* | ARGS-aggrecan | *P* | COMP $R_S$ | *P* | C2C $R_S$ | *P* |
|---|---|---|---|---|---|---|---|---|
| KOOS/HOOS (n = 83) | | | | | | | | |
| Pain | 0.016 | .886 | 0.096 | .389 | −0.037 | .744 | −0.095 | .391 |
| Symptoms | −0.050 | .654 | 0.026 | .812 | 0.111 | .318 | 0.141 | .201 |
| ADL | 0.104 | .347 | 0.051 | .648 | 0.071 | .521 | 0.112 | .310 |
| Sport/Rec | 0.057 | .618 | −0.003 | .978 | −0.006 | .955 | −0.105 | .356 |
| QoL | 0.206 | .060 | 0.171 | .120 | 0.032 | .777 | −0.100 | .366 |
| IPAQ-SF (n = 65) | | | | | | | | |
| MET-minutes/week | 0.107 | .390 | −0.083 | .508 | −0.256 | .040 | −0.089 | .475 |

Abbreviations: ADL, activities of daily living; ARGS, neoepitope of aggrecan; C2C, collagen type II cleavage; COMP, cartilage oligomeric matrix protein; CRP, C-reactive protein; HOOS, Hip disability and Osteoarthritis Outcome Score; IPAQ-SF, International Physical Activity Questionnaire–Short Form; KOOS, Knee injury and Osteoarthritis Outcome Score; MET, metabolic equivalent of tasks; PA, physical activity; QoL, knee/hip-related quality of life.

**Table 4.** Correlation (Spearman's Rho) between the average number of steps per day for 12 weeks and molecular biomarkers at 3-month follow-up (n = 51).

| | CRP $R_S$ | *P* | ARGS-aggrecan | *P* | COMP $R_S$ | *P* | C2C $R_S$ | *P* |
|---|---|---|---|---|---|---|---|---|
| Steps/day | 0.034 | .811 | −0.163 | .254 | 0.024 | .865 | 0.113 | .430 |

Abbreviations: ARGS, neoepitope of aggrecan; C2C, collagen type II cleavage; COMP, cartilage oligomeric matrix protein; CRP, C-reactive protein.

rest.[22] Erhart-Hledik et al[22] hypothesized that OA progression (cartilage thinning 5 years later) would be more easily detected with a mechanical stimulus such as walking. In our study, the correlation could have been stronger if participants had engaged in PA before serum sampling.

No correlations between joint function and molecular biomarkers were found in this study which is in line with previous studies examining the relations between COMP and self-reported joint function or CRP and self-reported function.[24,25] The relation between synovial fluid ARGS-aggrecan and self-reported joint function (KOOS) has been examined in a study that showed a decrease in ARGS-aggrecan concentrations for patients with worsening in the KOOS subscale *pain*.[47]

We would like to recognize two reasons why, in general, no associations were found in the present study. The median changes in the outcomes between baseline and follow-up were close to zero or relatively small (except for self-reported PA) which could be one potential reason for the lack of associations. In addition, the changes in KOOS/HOOS subscales were at most 7.1 (*symptoms*) which are just below the cutoff point for a clinically significant difference (8–10) and the minimal detectable change (⩾20) for older individuals in KOOS.[32,36] The changes in self-reported PA are consistent with a previous study in participants with knee OA, although the level of PA was higher in this study.[48] In addition, participants were already more physically active compared with other populations with hip and/or knee OA and had a better joint function as measured with HOOS/KOOS[36] which limits the possibility of detecting a change in the measured outcomes.

We believe that molecular biomarkers could be clinically useful in a population with OA. They could serve as an indicator of OA progression or as a marker of cartilage and/or entire joint quality.[25] Previous research has reported a U-shaped relationship between PA and OA progression where both underloading and overloading are detrimental to the OA joint.[49,50] Finding the optimal dose of PA for each individual may be a challenge for the clinician. In the SOASP in Sweden, the acceptable pain model is used to guide the clinician and patient in deciding the optimal dose of exercise.[28,51] According to the model, pain during exercise should not exceed 5 on a scale between 0 and 10 and any increase in pain during exercise should be normalized after 24 hour. However, pain tolerance and experience are different for each individual and an objectively measured marker of OA progression could be helpful in deciding the optimal load for individuals with OA.

### *Strengths and limitations*

This study has several strengths. It explores a relatively new and important area of research, and both self-reported and objectively measured PA are used. To our knowledge, the association between objectively measured PA and molecular biomarkers in individuals with OA is mainly unexplored. There was also a fairly large number of participants and a limited amount of missing data. With the current sample size, we had sufficient power (80%, alpha level 0.05) to detect week/moderate correlations ($r_s > 0.3$).

Some limitations should also be acknowledged. The observational design of this study hinders the ability to demonstrate causality. A randomized controlled study design with physically inactive participants would probably have had greater possibilities of detecting an eventual causal association with a more apparent difference between the groups. Furthermore, participants are probably not representative for the entire population with OA in the hip or knee. Compared with a large cohort with hip and/or knee OA in Sweden, the participants in this study were younger and had a higher proportion of women and participants with postsecondary education.[52] Furthermore, the method of recruiting participants with an advertisement on Facebook and self-registration was effective, but probably resulted in a selection bias where a majority of the participants already were engaged in PA. Consequently, and as mentioned previously, there was probably little room for improvement or change in self-reported outcomes for the participants in this study. Another limitation is that we did not collect relevant variables such as weight/height, smoking, use of non-steroidal anti-inflammatory drugs, or recent PA at baseline. Weight/height was collected ad hoc but almost half of the participants did not respond and the data that were collected might be affected by recollection bias. Also, we did not control for potential factors that could affect molecular biomarkers such as age, sex, BMI, smoking, recent PA, or the use of non-steroidal anti-inflammatory drugs. However, potential confounding would probably have less effect on the association between changes in the measures over time than if cross-sectional associations were evaluated.

In conclusion, a weak negative correlation was found between the change in self-reported PA and the change in the molecular biomarker COMP, but not for any of the other variables in this exploratory study. These results are consistent with the results of previous studies but could also be explained by the characteristics of the participants and the small changes from baseline to follow-up. Due to the limitations and the exploratory nature of this study, we imply that no definitive conclusions can be drawn on the basis of the results in this study. Molecular biomarkers may be clinically useful, but more research is needed to further explore the potential association between PA/joint function and molecular biomarkers. We suggest that future research include participants with lower levels of physical activity at baseline and/or longer follow-up times.

## Acknowledgements

We thank the operational manager of the health care center for providing the premises used in the SOASP and serum sampling. We also thank the assistant nurses for helping with the serum sampling. Mina Davoudi contributed excellent technical

assistance in analyzing the molecular biomarkers which we thank her for. Last but not least, we thank the participants who contributed to this study.

## Author Contributions

All authors contributed to conceptualizing and designing the study. EÖ recruited participants, managed the intervention in the C-RCT, and collected the data. AS'A analyzed the data from the activity trackers. EÖ and AS handled and analyzed the serum samples. All authors contributed to the analysis and writing the manuscript, and all authors read and approved the final manuscript.

## ORCID iDs

Elin Östlind https://orcid.org/0000-0001-9725-1786
André Struglics https://orcid.org/0000-0003-4289-1393

## REFERENCES

1. Robinson WH, Lepus CM, Wang Q, et al. Low-grade inflammation as a key mediator of the pathogenesis of osteoarthritis. *Nat Rev Rheumatol*. 2016;12:580-592. doi:10.1038/nrrheum.2016.136.
2. Vincent TL. Mechanoflammation in osteoarthritis pathogenesis. *Semin Arthritis Rheum*. 2019;49:S36-S38. doi:10.1016/j.semarthrit.2019.09.018.
3. Griffin TM, Guilak F. The role of mechanical loading in the onset and progression of osteoarthritis. *Exerc Sport Sci Rev*. 2005;33:195-200. doi:10.1097/00003677-200510000-00008.
4. Loeser RF, Goldring SR, Scanzello CR, Goldring MB. Osteoarthritis: a disease of the joint as an organ. *Arthritis Rheum*. 2012;64:1697-1707. doi:10.1002/art.34453.
5. Nia HT, Bozchalooi IS, Li Y, et al. High-bandwidth AFM-based rheology reveals that cartilage is most sensitive to high loading rates at early stages of impairment. *Biophys J*. 2013;104:1529-1537. doi:10.1016/j.bpj.2013.02.048.
6. Mündermann A, Klenk C, Billich C, et al. Changes in cartilage biomarker levels during a transcontinental multistage footrace over 4486 km. *Am J Sports Med*. 2017;45:2630-2636. doi:10.1177/0363546517712945.
7. Cattano NM, Driban JB, Cameron KL, Sitler MR. Impact of physical activity and mechanical loading on biomarkers typically used in osteoarthritis assessment: current concepts and knowledge gaps. *Ther Adv Musculoskelet Dis*. 2017;9:11-21. doi:10.1177/1759720x16670613.
8. Bannuru RR, Osani MC, Vaysbrot EE, et al. OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. *Osteoarthritis Cartilage*. 2019;27:1578-1589. doi:10.1016/j.joca.2019.06.011.
9. Fernandes L, Hagen KB, Bijlsma JW, et al. EULAR recommendations for the non-pharmacological core management of hip and knee osteoarthritis. *Ann Rheum Dis*. 2013;72:1125-1135. doi:10.1136/annrheumdis-2012-202745.
10. Kraus VB, Sprow K, Powell KE, et al. Effects of physical activity in knee and hip osteoarthritis: a systematic umbrella review. *Med Sci Sports Exerc*. 2019;51:1324-1339. doi:10.1249/mss.0000000000001944.
11. Lotz M, Martel-Pelletier J, Christiansen C, et al. Republished: value of biomarkers in osteoarthritis: current status and perspectives. *Postgrad Med J*. 2014;90:171-178. doi:10.1136/postgradmedj-2013-203726rep.
12. van Spil WE, DeGroot J, Lems WF, Oostveen JC, Lafeber FP. Serum and urinary biochemical markers for knee and hip-osteoarthritis: a systematic review applying the consensus BIPED criteria. *Osteoarthritis Cartilage*. 2010;18:605-612. doi:10.1016/j.joca.2010.01.012.
13. Valdes AM, Meulenbelt I, Chassaing E, et al. Large scale meta-analysis of urinary C-terminal telopeptide, serum cartilage oligomeric protein and matrix metalloprotease degraded type II collagen and their role in prevalence, incidence and progression of osteoarthritis. *Osteoarthritis Cartilage*. 2014;22:683-689. doi:10.1016/j.joca.2014.02.007.
14. Larsson S, Lohmander LS, Struglics A. Synovial fluid level of aggrecan ARGS fragments is a more sensitive marker of joint disease than glycosaminoglycan or aggrecan levels: a cross-sectional study. *Arthritis Res Ther*. 2009;11:R92. doi:10.1186/ar2735.
15. Germaschewski FM, Matheny CJ, Larkin J, et al. Quantitation of ARGS aggrecan fragments in synovial fluid, serum and urine from osteoarthritis patients. *Osteoarthritis Cartilage*. 2014;22:690-697. doi:10.1016/j.joca.2014.02.930.
16. Struglics A, Larsson S, Kumahashi N, Frobell R, Lohmander LS. Changes in cytokines and aggrecan ARGS neoepitope in synovial fluid and serum and in C-terminal crosslinking telopeptide of type II collagen and N-terminal cross-linking telopeptide of type I collagen in urine over five years after anterior cruciate ligament rupture: an exploratory analysis in the knee anterior cruciate ligament, nonsurgical versus surgical treatment trial. *Arthritis Rheumatol*. 2015;67:1816-1825. doi:10.1002/art.39146.
17. Kumahashi N, Swärd P, Larsson S, Lohmander LS, Frobell R, Struglics A. Type II collagen C2C epitope in human synovial fluid and serum after knee injury—associations with molecular and structural markers of injury. *Osteoarthritis Cartilage*. 2015;23:1506-1512. doi:10.1016/j.joca.2015.04.022.
18. Cahue S, Sharma L, Dunlop D, et al. The ratio of type II collagen breakdown to synthesis and its relationship with the progression of knee osteoarthritis. *Osteoarthritis Cartilage*. 2007;15:819-823. doi:10.1016/j.joca.2007.01.016.
19. Hunter DJ, Nevitt M, Losina E, Kraus V. Biomarkers for osteoarthritis: current position and steps towards further validation. *Best Pract Res Clin Rheumatol*. 2014;28:61-71. doi:10.1016/j.berh.2014.01.007.
20. Bjerre-Bastos JJ, Karsdal MA, Boesen M, et al. The acute and long-term impact of physical activity on biochemical markers and MRI measures in osteoarthritis—perspectives for clinical osteoarthritis research. *Transl Sports Med*. 2020;3:384-394.
21. Fedewa MV, Hathaway ED, Ward-Ritacco CL. Effect of exercise training on C reactive protein: a systematic review and meta-analysis of randomised and non-randomised controlled trials. *Br J Sports Med*. 2017;51:670-676. doi:10.1136/bjsports-2016-095999.
22. Erhart-Hledik JC, Favre J, Asay JL, et al. A relationship between mechanically-induced changes in serum cartilage oligomeric matrix protein (COMP) and changes in cartilage thickness after 5 years. *Osteoarthritis Cartilage*. 2012;20:1309-1315. doi:10.1016/j.joca.2012.07.018.
23. Bjerre-Bastos JJ, Nielsen HB, Andersen JR, et al. A biomarker perspective on the acute effect of exercise with and without impact on joint tissue turnover: an exploratory randomized cross-over study. *Eur J Appl Physiol*. 2021;121:2799-2809. doi:10.1007/s00421-021-04751-z.
24. Penninx BWJH, Abbas H, Ambrosius W, et al. Inflammatory markers and physical function among older adults with knee osteoarthritis. *J Rheumatol*. 2004;31:2027-2031.
25. Cattano NM, Driban JB, Barbe MF, Tierney R, Amin M, Sitler MR. Physical activity levels and quality of life relate to collagen turnover and inflammation changes after running. *J Orthop Res*. 2017;35:612-617. doi:10.1002/jor.23250.
26. Bricca A, Struglics A, Larsson S, Steultjens M, Juhl CB, Roos EM. Impact of exercise therapy on molecular biomarkers related to cartilage and inflammation in individuals at risk of, or with established, knee osteoarthritis: a systematic review and meta-analysis of randomized controlled trials. *Arthritis Care Res (Hoboken)*. 2019;71:1504-1515. doi:10.1002/acr.23786.
27. Östlind E, Sant'Anna A, Eek F, Stigmar K, Ekvall Hansson E. Physical activity patterns, adherence to using a wearable activity tracker during a 12-week period and correlation between self-reported function and physical activity in working age individuals with hip and/or knee osteoarthritis. *BMC Musculoskelet Disord*. 2021;22:450. doi:10.1186/s12891-021-04338-x.
28. Thorstensson CA, Garellick G, Rystedt H, Dahlberg LE. Better management of patients with osteoarthritis: development and nationwide implementation of an evidence-based supported osteoarthritis self-management programme. *Musculoskeletal Care*. 2015;13:67-75. doi:10.1002/msc.1085.
29. Jönsson T, Eek F, Dell'Isola A, Dahlberg LE, Ekvall Hansson E. The Better Management of Patients with Osteoarthritis Program: outcomes after evidence-based education and exercise delivered nationwide in Sweden. *PLoS ONE*. 2019;14:e0222657. doi:10.1371/journal.pone.0222657.
30. BankID. https://www.bankid.com/en/. Accessed June 4, 2021.
31. Larsson S, Lohmander LS, Struglics A. An ARGS-aggrecan assay for analysis in blood and synovial fluid. *Osteoarthritis Cartilage*. 2014;22:242-249. doi:10.1016/j.joca.2013.12.010.
32. Roos EM, Lohmander LS. The Knee injury and Osteoarthritis Outcome Score (KOOS): from joint injury to osteoarthritis. *Health Qual Life Outcomes*. 2003;1:64-64. doi:10.1186/1477-7525-1-64.
33. Nilsdotter AK, Lohmander LS, Klässbo M, Roos EM. Hip disability and osteoarthritis outcome score (HOOS)—validity and responsiveness in total hip replacement. *BMC Musculoskelet Disord*. 2003;4:10. doi:10.1186/1471-2474-4-10.
34. KOOS/HOOS manuals. http://www.koos.nu. Accessed October 13, 2021.
35. Thorborg K, Roos EM, Bartels EM, Petersen J, Hölmich P. Validity, reliability and responsiveness of patient-reported outcome questionnaires when assessing hip and groin disability: a systematic review. *Br J Sports Med*. 2010;44:1186-1196. doi:10.1136/bjsm.2009.060889.
36. Collins NJ, Prinsen CAC, Christensen R, Bartels EM, Terwee CB, Roos EM. Knee Injury and Osteoarthritis Outcome Score (KOOS): systematic review and meta-analysis of measurement properties. *Osteoarthritis Cartilage*. 2016;24:1317-1329. doi:10.1016/j.joca.2016.03.010.

37. Craig CL, Marshall AL, Sjostrom M, et al. International physical activity questionnaire: 12-country reliability and validity. *Med Sci Sports Exerc*. 2003;35:1381-1395. doi:10.1249/01.Mss.0000078924.61453.Fb.
38. The IPAQ_Group. IPAQ_scoring protocol. https://docs.google.com/viewer?a=v&pid=sites&srcid=ZGVmYXVsdGRvbWFpbnx0aGVpcGFxfGd4OjE0NDgxMDk3NDU1YWRlZTM. Accessed June 4, 2021.
39. Burton E, Hill KD, Lautenschlager NT, et al. Reliability and validity of two fitness tracker devices in the laboratory and home environment for older community-dwelling people. *BMC Geriatr*. 2018;18:103. doi:10.1186/s12877-018-0793-4.
40. Fitbit. Fitbit Web API. https://dev.fitbit.com/build/reference/web-api/. Accessed March 9, 2022.
41. R Studio Team. *RStudio: Integrated Development for R*. Boston, MA: RStudio, Inc.
42. IBM Corp. *Released 2020. IBM SPSS Statistics for Windows*, version 27.0. Armonk, NY: IBM Corp. https://www.ibm.com/products/spss-statistics. Published 2020. Accessed June 4, 2021.
43. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA*. 2013;310:2191-2194. doi:10.1001/jama.2013.281053.
44. Body mass index—BMI. https://www.euro.who.int/en/health-topics/disease-prevention/nutrition/a-healthy-lifestyle/body-mass-index-bmi. Accessed October 13, 2021.
45. Bjerre-Bastos JJ. Evaluation of serum ARGS neoepitope as an osteoarthritis biomarker using a standardized model for exercise-induced cartilage extra cellular matrix turnover. *Osteoarthr Cartil Open*. 2020;2:100060. doi:10.1016/j.ocarto.2020.100060.
46. Hunt MA, Pollock CL, Kraus VB, et al. Relationships amongst osteoarthritis biomarkers, dynamic knee joint load, and exercise: results from a randomized controlled pilot study. *BMC Musculoskelet Disord*. 2013;14:115. doi:10.1186/1471-2474-14-115.
47. Larsson S, Englund M, Struglics A, Lohmander LS. The association between changes in synovial fluid levels of ARGS-aggrecan fragments, progression of radiographic osteoarthritis and self-reported outcomes: a cohort study. *Osteoarthritis Cartilage*. 2012;20:388-395. doi:10.1016/j.joca.2012.02.001.
48. Gay C, Guiguet-Auclair C, Coste N, et al. Limited effect of a self-management exercise program added to spa therapy for increasing physical activity in patients with knee osteoarthritis: a quasi-randomized controlled trial. *Ann Phys Rehabil Med*. 2020;63:181-188. doi:10.1016/j.rehab.2019.10.006.
49. Dore DA, Winzenberg TM, Ding C, et al. The association between objectively measured physical activity and knee structural change using MRI. *Ann Rheum Dis*. 2013;72:1170-1175. doi:10.1136/annrheumdis-2012-201691.
50. Voinier D, Neogi T, Stefanik JJ, et al. Using cumulative load to explain how body mass index and daily walking relate to worsening knee cartilage damage over two years: the MOST study. *Arthritis Rheumatol (Hoboken, NJ)*. 2020;72:957-965. doi:10.1002/art.41181.
51. Thomeé R. A comprehensive treatment approach for patellofemoral pain syndrome in young women. *Phys Ther*. 1997;77:1690-1703. doi:10.1093/ptj/77.12.1690.
52. Dell'Isola A, Jönsson T, Nero H, Eek F, Dahlberg L. Factors associated with the outcome of a first-line intervention for patients with hip or knee osteoarthritis or both: data from the BOA register. *Phys Ther*. 2020;100:1771-1781. doi:10.1093/ptj/pzaa113.