Associations of Body Mass Index With Pain and the Mediating Role of Inflammatory Biomarkers in People With Hand Osteoarthritis

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Objective. To examine the association of body mass index (BMI) with pain in people with hand osteoarthritis (OA), and explore whether this association, if causal, is mediated by systemic inflammatory biomarkers.

Methods. In 281 Nor-Hand study participants, we estimated associations between BMI and hand pain, as measured by the Australian/Canadian Osteoarthritis Hand Index (AUSCAN; range 0–20) and Numerical Rating Scale (NRS; range 0–10); foot pain, as measured by NRS (range 0–10); knee/hip pain, as measured by the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC; range 0–20); painful total body joint count; and pain sensitization. We fit natural-effects models to estimate natural direct and natural indirect effects of BMI on pain through inflammatory biomarkers.

Results. Each 5-unit increase in BMI was associated with more severe hand pain (on average increased AUSCAN by 0.64 [95% confidence interval (95% CI) 0.23, 1.08]), foot pain (on average increased NRS by 0.65 [95% CI 0.36, 0.92]), knee/hip pain (on average increased WOMAC by 1.31 [95% CI 0.87, 1.73]), generalized pain, and pain sensitization. Mediation analyses suggested that the effects of BMI on hand pain and painful total body joint count were partially mediated by leptin and high-sensitivity C-reactive protein (hsCRP), respectively. Effect sizes for mediation by leptin were larger for the hands than for the lower extremities, and were statistically significant for the hands only.

Conclusion. In people with hand OA, higher BMI is associated with greater pain severity in the hands, feet, and knees/hips. Systemic effects of obesity, measured by leptin, may play a larger mediating role for pain in the hands than in the lower extremities. Low-grade inflammation, measured by hsCRP, may contribute to generalized pain in overweight/obese individuals.

INTRODUCTION

Osteoarthritis (OA) is the most common joint disease, with pain as the primary symptom. Body weight is a potential modifiable risk factor for OA pain (1), and weight loss may reduce pain, mechanical loading, and systemic inflammation in people with knee OA (2). Since mechanical loading caused by obesity does not have the same effects on hand joints as on the weight-bearing joints in the lower extremities, hand joints are well suited to study the possible systemic effects of obesity on pain.

Overweight and obesity induce a low-grade inflammatory state as adipose tissue produces inflammatory biomarkers, which...
may affect pain mechanisms. Cytokines such as interleukin-1β (IL-1β), IL-6, and tumor necrosis factor (TNF) may act directly on nociceptive neurons through their receptors or indirectly through induction of prostaglandin production, which may activate or sensitize nociceptive neurons, leading to increased pain (3). Cytokines are also proposed to be involved in central pain mechanisms (3). A few clinical studies have indicated that cytokines may be involved in the induction of OA pain, but their findings were inconsistent, and the majority of studies were conducted on people with knee OA (3). Some studies, with conflicting results, have investigated associations between adipokines, such as leptin, adiponectin, and resistin, and symptomatic hand OA or hand OA pain (4–6).

Recent reviews have suggested that central pain sensitization, a phenomenon characterized by increased neural signaling in the central nervous system, contributes to chronic OA pain (7,8). Results from a study of persons undergoing bariatric surgery have suggested that reduced pain sensitization can partly explain the observed improvement in knee pain after weight loss (9). Other studies have investigated pain thresholds before and after weight loss or in persons with higher versus lower body mass index (BMI) and showed conflicting results (10–13).

Previous hand OA studies have presented conflicting results on the associations between BMI and symptomatic hand OA or hand pain (5,6,14–20). Only one of those studies investigated whether adipokines can mediate this possible association (6). That study did not examine pain intensity and did not assess mediation by other inflammatory biomarkers (6). We hypothesized that overweight/obesity is associated with joint pain in both the hands and lower extremities as well as pain sensitization, mediated through the inflammatory state that is affected by the overweight/obesity status. Hence, our aim was to examine whether higher BMI is associated with more severe pain and more central pain sensitization in people with hand OA. Further, using a causal inference-based mediation analysis, we explored whether any associations between BMI and pain, if causal, might be mediated by inflammatory biomarkers measured in serum/plasma.

**PATIENTS AND METHODS**

**Study design and population.** We used cross-sectional data from the baseline examination of the Nor-Hand study (2016–2017) in the current analyses. The Nor-Hand study is an observational cohort study of people with hand OA. Participants were recruited to the study through the outpatient clinic or a multidisciplinary course organized by the Division of Rheumatology and Research at Diakonhjemmet Hospital. All participants were between 40 and 70 years of age and had hand OA diagnosed by ultrasound and/or clinical examination performed by a rheumatologist. A detailed description of the inclusion and exclusion criteria has been published previously (21). The study has been approved by the Norwegian Regional Committee for Medical and Health Research Ethics (Ref. no: 2014/2057), and all participants provided written informed consent to participate. The study has been registered at ClinicalTrials.gov (identifier: NCT03083548).

**Physical examination.** For all participants, height in a standing position without shoes was measured to the nearest millimeter, and weight in light indoor clothing was measured in kilograms, with accuracy to one decimal place, to calculate the BMI as kg/m². Waist circumference was measured to the nearest millimeter midway between the iliac crest and the lowest rib after the participant took a deep breath and exhaled. We assessed whether participants fulfilled the American College of Rheumatology (ACR) criteria for hand OA and the ACR clinical criteria for knee OA (22,23).

**Pain questionnaires.** Pain in the hands and feet during the last 24 hours was rated on a Numerical Rating Scale (NRS) (range 0–10, where 0 = no pain and 10 = worst imaginable pain). The Australian/Canadian Osteoarthritis Hand Index (AUSCAN) pain subscale (range 0–20) and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale (range 0–20) were used to assess hand pain and knee/hip pain, respectively, during the last 48 hours (24,25). Persistent joint pain during the prior 6 weeks was marked on a homunculus illustrating the neck; the upper, middle, and lower back; and bilateral shoulders, elbows, wrists, hips, knees, and ankles. Pain in at least one joint in each hand, marked on a hand diagram depicting the bilateral distal and proximal interphalangeal, metacarpophalangeal, and thumb base joints, counted as a painful hand in the painful total body joint count (range 0–18). The same homunculus was used to identify the presence of widespread pain for the last 6 weeks, which was defined according to the ACR 1990 criteria as the presence of axial skeletal pain, pain on both the left and right side of the body, and pain both above and below the waist (26). However, in contrast to the definition in the ACR criteria, low back pain was not considered lower segment pain.

**Quantitative sensory testing (QST).** Pressure pain threshold (PPT) was assessed by applying pressure with a digital algometer (FPIX25; Wagner) at mid-portions of the anterior tibialis muscle. The pressure of the algometer was gradually increased by 0.5 kg/second until the participant first reported it to be slightly painful. This examination was performed 3 times with 30-second intervals between the measurements, and the average of the 3 values was used for analyses. Low PPTs, i.e., higher pain sensitivity, at distant nonpainful sites were considered to reflect manifestations of central pain sensitization.

Temporal summation (TS) is another manifestation of central pain sensitization, which can be measured as increased pain ratings after repetitive stimuli (27). TS was assessed with 7 weighted punctuate probes (8–512 mN), which were tapped against the left distal radioulnar joint with increasing weight. The probe that
caused a pain rating of ≥4 on the NRS (or alternatively the 512 mN probe if none of the probes caused a pain intensity rating of ≥4), was tapped 10 times with a rate of once per second at the same site. Pain intensity at the first, fifth, and tenth tap was rated on the NRS. TS was calculated by subtracting the pain rating at the first tap from the pain rating at either the fifth or tenth tap, whichever was higher.

The QST protocol was performed by 2 medical students who were trained according to a detailed predefined protocol. Interassessor reliability was determined by examination of 9 participants by both medical students on the same afternoon. The intraclass correlation coefficient (2-way mixed-effects model, absolute agreement, individual measure) was 0.43 for PPT at the anterior tibialis and 0.56 for TS.

**Inflammatory biomarkers.** Plasma was collected in containers with EDTA and was centrifuged immediately (maximum of 30 minutes) after collection. Serum was collected in containers with EDTA and was centrifuged immediately (maximum of 30 minutes) after collection. Serum was analyzed for high-sensitivity C-reactive protein (hsCRP) and matrix metalloproteinase–dependent degradation of C-reactive protein (CRPM). High-sensitivity CRP was measured on an ADVIA 1800 platform using a CardioPhase hsCRP assay (Siemens Medical Solutions) according to the manufacturer’s instructions. The hsCRP measurements were performed in singlet. CRPM measurements were performed in duplicate using a handheld competitive enzyme-linked immunosorbent assay (Nordic Bioscience). Briefly, 96-well streptavidin-coated plates were coated with 0.4 ng/ml of KAFVFPKESDK-biotin and left for 30 minutes at 20°C. After washing, calibrators, controls, and serum samples (diluted 1:4 in incubation buffer) were added, followed by peroxidase-conjugated antibody. The sample/antibody mixture was incubated at 20°C for 60 minutes. Tetramethylbenzidine was added after washing off the plates, incubated at 20°C, and stopped with sulfuric acid after 15 minutes. The colorimetric reaction was measured at 450 nm with reference at 650 nm using SoftMax Pro, version 5 software (Molecular Devices).

Plasma was analyzed for inflammatory biomarkers using a Luminex assay (Bio-Techne) according to the manufacturer’s protocol. The samples were evenly distributed across plates based on the pain severity and BMI of the individuals they were obtained from. The following biomarkers were selected to represent Th1, Th17, and M1 inflammatory responses, based on previously identified associations with obesity and/or OA: IL-1β, IL-1 receptor antagonist (IL-1Ra), IL-4, IL-6, IL-10, IL-12, IL-17, IL-18, IL-21, interferon-γ, TNF, vascular endothelial growth factor, granulocyte–macrophage colony-stimulating factor (GM-CSF), CCL2, CCL3, CCL4, CXCL10, leptin, and resistin. These measurements were performed in singlet. Values below the detection limit were estimated as half of the lower limit of detection or the lowest estimated value, depending on which was the lowest. Biomarkers for which >50% of the values were estimated (CCL3, IL-12, and GM-CSF) were excluded from the statistical analyses. The intraassay and interassay coefficients of variation for leptin were acceptable (4.6% and 12.0%, respectively).

**Potential confounders.** Data regarding age and sex were collected from patient journals. Participants answered questions about potential confounders, such as their highest degree of completed education (7 levels), physical exercise (4 levels, dichotomized into “at least one time weekly” and “less than one time weekly”), sleep (5 levels, from normal sleep to extreme sleep disturbances), smoking (dichotomized into “current regular or occasional smoker” and “previous smoker or non-smoker”), anxiety and depression, measured by the Hospital Anxiety and Depression Scale (HADS; range 0–21) (28), and pain catastrophizing, measured by the Pain Catastrophizing Scale (PCS; range 0–52) (29).

**Statistical analysis.** In all analyses, the inflammatory biomarkers were log-transformed to decrease skewness. First, we wanted to examine whether BMI was associated with inflammatory biomarkers in our data, and linear regression analyses were therefore conducted. In our main analyses, a causal inference-based mediation analysis was performed by fitting natural-effects models to decompose the effect of BMI on pain into a natural indirect effect, which is potentially mediated by an inflammatory biomarker, and a natural direct effect that is not mediated by the biomarker. The natural-effects decomposition is used to formally assess mediation and is estimated based on the counterfactual framework for causal inference (30). The natural-effects model enables a nonparametric (i.e., model-free) decomposition of the effect of an exposure on an outcome. This causal inference-based mediation analysis does not rely on assessing whether the association between levels of exposure and mediators/outcomes reach statistical significance. Rather, it relies on the counterfactual framework to infer whether mediating effects exist. Natural effects were fitted using the imputation-based approach for mediation analysis (31). Estimates for the total, natural direct, and natural indirect effects are presented per SD increase in BMI with corresponding 95% confidence intervals (95% CIs) estimated by the bootstrapping technique.

We further assessed mediated interaction, that is, whether BMI and the inflammatory biomarker interact in their effects on the pain outcomes, whenever estimates of indirect effects suggest that mediation by the inflammatory biomarker is present. Sensitivity analyses were performed per SD increase in waist circumference to assess the relationship between abdominal obesity and pain. The potential mediating role of leptin was analyzed.
RESULTS

Participant characteristics and inflammatory biomarkers. The Nor-Hand study includes 300 participants, of whom 19 had missing plasma/serum samples. Characteristics of the 281 participants who were included are listed in Table 1. The participants demonstrated a wide range of pain intensity in the hands, feet, and knees/hips, with the highest pain intensity in the hands. Ninety-five (34%) of the participants were overweight, and 60 (21%) were obese. Higher BMI was associated with higher levels of 6 of the inflammatory biomarkers, namely, TNF, IL-6, IL-1Ra, resistin, leptin, and hsCRP (data not shown).

BMI and pain outcomes. Participants with a higher BMI reported more severe pain in their hands, feet, and knees/hips, as well as a higher painful total body joint count during the prior 6 weeks (total effects in Table 2). Further, participants with a higher BMI had more central pain sensitization (i.e., lower PPTs at the anterior tibialis muscle and greater TS) (Table 3). The odds of widespread pain were higher in participants with a higher BMI, such that for every 5-unit increase in BMI, widespread pain experience increased by 54% (total effects odds ratio 1.54 [95% CI 1.17, 1.96] in the parsimonious model).

Mediating role of inflammatory biomarkers. In these exploratory analyses, estimates of the natural indirect effects suggested that the effect of BMI on hand pain was partially mediated through plasma levels of leptin. Effect sizes for mediation by leptin were larger for hand pain than for pain in the lower extremities and for painful total body joint count, and reached statistical significance for hand pain only (Table 2 and Supplementary Figure 1, available on the Arthritis & Rheumatology website at http://onlinelibrary.wiley.com/doi/10.1002/art.42056). The effects of BMI on measures of central pain sensitization did not appear to be mediated through leptin (Table 3). Similar results were found after additional adjustment for other potential confounders in the comprehensive model (Supplementary Table 1, available on the Arthritis & Rheumatology website at http://onlinelibrary.wiley.com/doi/10.1002/art.42056).

A borderline statistically significant mediating effect of hsCRP was found on the effect of BMI on the painful total body joint count in the parsimonious model, whereas the mediating effect in the comprehensive model was statistically significant (Supplementary Table 2, available on the Arthritis & Rheumatology website at http://onlinelibrary.wiley.com/doi/10.1002/art.42056).

Table 1. Characteristics of the study population (n = 281)*

| Characteristic                              | n   | Mean ± SD (range)       |
|---------------------------------------------|-----|-------------------------|
| Age, median (IQR) years                     | 61  | 57–66                   |
| Sex, no. (%) women                          | 249 |                         |
| Fulfilled ACR hand OA criteria, no. (%)     | 261 | 93                      |
| Fulfilled ACR clinical knee OA criteria, no. (%) | 172 | 63                      |
| Body mass index, mean ± SD kg/m²            | 26.5| 5.0                     |
| Waist circumference, mean ± SD cm          | 88.8| 13.1                    |
| AUSCAN hand pain, mean ± SD (range 0–20)   | 8.1 | 4.0                     |
| NRS hand pain, mean ± SD (range 0–10)      | 3.8 | 2.3                     |
| NRS foot pain, median (IQR) (range 0–10)   | 2   | (0–4)                   |
| WOMAC knee/hip pain, median (IQR)          | 4.5 | (1.0–8.5)               |
| Painful total body joint count, median (IQR)| 4   | (2–8)                   |
| Presence of widespread pain, no. (%)       | 99  | (35.2)                  |
| PPT at the anterior tibialis muscle, mean ± SD kg/cm² | 5.5 | 2.6                     |
| Temporal summation, median (IQR)            | 1   | (0–2)                   |
| Leptin, median (IQR) µg/liter               | 12.8| (5.6–24.4)              |
| hsCRP, median (IQR) mg/liter                | 1.5 | (0.8–4.1)               |
| Physical exercise at least 1 time weekly, no. (%) | 192 | (70)                   |
| University or other higher education, no. (%) | 163 | (58)                   |
| Moderate to extreme sleep disturbances, no. (%) | 113 | (40)                   |
| Current regular or occasional smoker, no. (%) | 44  | (16)                   |
| HADS total score, median (IQR) (range 0–42) | 6   | (3–10)                  |
| PCS total score, median (IQR) (range 0–52) | 9   | (5–15)                  |

* IQR = interquartile range; ACR = American College of Rheumatology; OA = osteoarthritis; AUSCAN = Australian/Canadian Osteoarthritis Hand Index; NRS = Numerical Rating Scale; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; PPT = pressure pain threshold; hsCRP = high-sensitivity C-reactive protein; HADS = Hospital Anxiety and Depression Scale; PCS = Pain Catastrophizing Scale.

† Data were missing for 9 participants.
‡ Data were missing for 1 participant.
¶ Data were missing for 5 participants.
® Data were missing for 4 participants.
Table 2. Estimates of the total effect of a 5-unit increase in BMI on pain and the corresponding natural direct effects and natural indirect effects mediated by plasma levels of leptin

|                          | AUSCAN hand pain (range 0–20) | NRS hand pain (range 0–10) | NRS foot pain (range 0–10) | WOMAC knee/hip pain (range 0–20) | Painful total body joint count (range 0–18) |
|--------------------------|--------------------------------|----------------------------|--------------------------|----------------------------------|---------------------------------------------|
| **Total effect**          | 0.64 (0.23, 1.08)†             | 0.46 (0.20, 0.72)†         | 0.65 (0.36, 0.92)†         | 1.31 (0.87, 1.73)†               | 1.15 (0.68, 1.60)†                         |
| **Direct effect**         | 0.26 (–0.34, 0.85)             | 0.24 (–0.09, 0.56)         | 0.57 (0.13, 0.96)†         | 1.13 (0.52, 1.75)†               | 0.87 (0.25, 1.47)†                         |
| **Indirect effect**       | 0.39 (0.02, 0.78)              | 0.22 (–0.00, 0.44)         | 0.09 (–0.14, 0.34)         | 0.18 (–0.23, 0.56)               | 0.28 (–0.11, 0.66)                         |

* The effect estimates (95% confidence intervals) shown in the table represent the estimated average change in the pain outcomes per SD (5.0 kg/m²) increase in body mass index (BMI). Analyses were adjusted for age, sex, and education. AUSCAN = Australian/Canadian Osteoarthritis Hand Index; NRS = Numerical Rating Scale; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.
† Significant.

Table 3. Estimates of the total effect of a 5-unit increase in BMI on pain sensitization and the corresponding natural direct and natural indirect effects mediated by plasma levels of leptin

|                          | PPT at the anterior tibialis | Temporal summation of pain |
|--------------------------|-----------------------------|----------------------------|
| **Total effect**          | –0.38 (–0.64, –0.12)†       | 0.27 (0.09, 0.45)†         |
| **Direct effect**         | –0.34 (–0.70, 0.01)         | 0.23 (0.02, 0.45)†         |
| **Indirect effect**       | –0.04 (–0.31, 0.24)         | 0.04 (–0.10, 0.18)         |

* The effect estimates (95% confidence intervals) shown in the table represent the estimated average change in the pain sensitization outcomes per SD (5.0 kg/m²) increase in body mass index (BMI). Analyses were adjusted for age, sex, and education. PPT = pressure pain threshold.
† Significant.

Weak and not statistically significant mediating effects of hsCRP were found on the effects of BMI on pain in the hands, feet, and knees/hips. Estimates of natural indirect effects suggested that none of the inflammatory biomarkers mediated the association between BMI and the presence of widespread pain, although small effect sizes were observed for hsCRP and leptin (natural indirect effect odds ratio 1.08 [95% CI 0.96, 1.19] and 1.12 [95% CI 0.90, 1.40], respectively, in the parsimonious model).

Natural indirect effect estimates for the other inflammatory biomarkers measured in plasma/serum did not suggest a mediating role in the effect of BMI on pain outcomes (data not shown).

Sensitivity analyses. Participants with a larger waist circumference reported more pain. Estimates of the total effects per SD (13.1 cm) increase in waist circumference on pain, and the estimated natural direct and natural indirect effects of plasma levels of leptin were of similar magnitude as the estimates reported for BMI (Supplementary Table 3, available on the Arthritis & Rheumatology website at http://onlinelibrary.wiley.com/doi/10.1002/art.42056). The effect of waist circumference on painful body joint count was partially mediated through hsCRP, although it was only borderline statistically significant in the parsimonious model (data not shown).

In sex-stratified mediation analyses, similar estimates for the total effects, natural direct effects, and natural indirect effects of plasma levels of leptin were observed in women as in the main analyses (data not shown). Weak and not statistically significant associations between BMI and pain were observed in men (n = 32). Due to the small number of men in the study, natural direct and natural indirect effects were not estimated for men separately.

**DISCUSSION**

In the Nor-Hand study, participants with a higher BMI reported greater pain severity in their hands, feet, and knees/hips, a higher painful total body joint count, a more frequent presence of widespread pain, and more central pain sensitization. If these associations express a causal effect of BMI on pain, our analyses suggest that leptin and hsCRP might play a role of mediators on hand pain and painful total body joint count, respectively. Effect sizes for mediation by leptin were larger for the hands than for the lower extremities.

As expected, due to increased loading of joints in the lower extremities, a higher BMI was associated with more pain in the feet and knees/hips. Interestingly, a higher BMI was also related to greater pain severity in the hands, although the strength of association was modest. A difference of 1 point on the NRS for pain is the minimal clinically important difference (32). According to our model, 2 persons would need to have a difference of ~10 units in their BMI to have a clinically meaningful difference in hand pain. Positive associations between BMI and hand pain have been shown in previous cross-sectional studies (5,15,18), whereas longitudinal studies have not been able to demonstrate that baseline BMI or changes in BMI are associated with pain outcomes (16,17). The lack of significant associations in longitudinal studies may be related to small changes in exposure and/or outcome.

Our results suggest that plasma levels of leptin may partially mediate the association between BMI and hand pain. Leptin is an adipokine mainly secreted by adipose tissue, with proinflammatory effects. Findings from previous studies are inconsistent with regard to the association between leptin and pain, which may be due to the inclusion of BMI as a covariate in most, but not all, studies. Since BMI and leptin are highly correlated, collinearity may be a problem in these analyses. In contrast to our
findings, a small pilot study suggested a negative association between serum leptin levels and hand pain in people with hand OA (5). In the Third National Health and Nutrition Examination Survey cohort, no differences in serum leptin levels between people with symptomatic hand OA, those with asymptomatic hand OA, and those without hand OA were found (4). A recent cross-sectional study, however, found a positive association between serum leptin levels and symptomatic hand OA, and the relationship between adiposity and symptomatic hand OA was partially mediated by leptin (6). Conflicting results have been found in people with knee and hip OA with regard to the association between serum/plasma levels of leptin or leptin/adiponectin ratio and pain (33–36). Higher leptin levels were associated with a higher self-reported intensity of general body pain in the Women’s Health Initiative (37).

Several mechanisms for how leptin may influence pain and pain sensitivity have been proposed. Leptin may contribute to the development of allodynia by stimulating the production of pronociceptive factors in macrophages (38). Further, leptin has been shown to modulate and exert structural changes in microglia (39), and microglia are increasingly recognized as important for the induction and maintenance of chronic pain (40). Glial cell dysfunction in the peripheral and central nervous system may cause chronic pain (40). A preclinical study has suggested that leptin may decrease pain thresholds in mice (41). However, this finding is not supported by our results, as we found no mediating effect of leptin on the association between BMI and pain sensitization. Our results are consistent with the findings of 2 other studies demonstrating no correlation between pain thresholds and leptin in patients with fibromyalgia or obese individuals (12,42). The lack of a mediating effect in our study may be related to the modest reliability of the QST. Furthermore, assessment of sensitization should preferably include various pain mechanisms (e.g., pain thresholds, tolerance thresholds, temporal and spatial summation, and conditioned pain modulation), and several different modalities (e.g., mechanical, electrical, and chemical stimuli) (43). In the present study, we assessed only PPTs and mechanical TS summation due to feasibility reasons.

We found that the association between BMI and painful total body joint count may be partially mediated by hsCRP. There was also a tendency toward a mediating effect of hsCRP on the association between BMI and the presence of widespread pain, although it was not statistically significant. These results may suggest that low-grade inflammation in overweight/obese individuals, reflected by increased levels of hsCRP, contribute to more generalized pain. It is well-known that overweight and obese individuals are more likely to have elevated CRP levels compared with persons of normal weight (44), and this is consistent with our results. Our results are also consistent with those of a meta-analysis that found a significant correlation between levels of hsCRP and joint pain (45). However, the meta-analysis included mainly studies on knee and hip OA, and only one study of OA in several joints. In contrast to these results, associations between BMI and pain in the hands, feet, and knees/hips were not mediated through hsCRP in our study. Our result may be due to involvement of other joints and/or fibromyalgia-like symptoms in the painful total body joint count. CRP levels above the reference value have been found in fibromyalgia patients (46).

Except for leptin and hsCRP, the inflammatory biomarkers in serum/plasma did not seem to mediate the association between BMI and pain, although there is increasing evidence that cytokines like IL-1β, IL-6, and TNF play a role in the development of chronic pain (47). Future studies should explore whether combinations of inflammatory biomarkers, rather than one biomarker alone, influence pain to a larger extent than what we found for the individual inflammatory biomarkers.

There are some limitations to this study that should be considered. Due to the cross-sectional study design, we cannot answer questions about causality, and reverse causation cannot be excluded. Longitudinal studies are needed to confirm the mediating role of inflammatory biomarkers on pain. We made the assumption that the exposure preceded the mediator, and that the mediator preceded the outcome. The first of these assumptions is based on the fact that adipose tissue produces inflammatory adipokines and obesity is associated with a low-grade inflammatory state (48). Longitudinal studies have suggested that a higher BMI predicts development of chronic pain (49). We cannot exclude the possibility that pain might also influence BMI through, e.g., a more sedentary lifestyle, but we consider this to be less likely for hand pain. Although we adjusted for several potential confounders, residual confounding by unmeasured variables may be present. This may have led to biased results. Furthermore, we have no information about the use of analgesics on the same day participants answered pain questionnaires and underwent QST. The interassessor reliability of the QST was moderate. The reliability could possibly have been improved by the inclusion of more participants in the exercise, more extensive training of the examiners, and increased emphasis on the cooperation, focus, and concentration of the participants in the QST protocol.

The generalizability of the results may be limited, since OA patients from secondary care may have more pain than patients seeking primary care. However, we did not require participants to fulfill the ACR hand OA criteria or a certain level of pain at inclusion, so that participants with a wide range of symptoms could be included in our study. This may increase the generalizability of the results to people with milder disease severity. We have limited information about OA in joints other than the hands and knees. Joint pain and biomarker levels may fluctuate throughout the day. All blood samples were collected between 4:00 PM and 9:00 PM, and it was thus not feasible to draw fasting blood samples. This may have introduced variation, although the variation between fasting and postprandial adipokine levels is usually small (50). Our relatively
small sample size (n = 281) contributed to a lack of sufficient precision in the CIs, so that CIs for some of the mediating effects slightly overlapped with the null despite sizable effect sizes. Because a lot of inflammatory biomarkers were tested, false-positive results cannot be ruled out, especially for hsCRP.

In conclusion, our results support a relationship between increased BMI and pain severity in both the hands and the lower extremities in a population with hand OA. Effect sizes for mediation by leptin were larger for the hands than for the lower extremities, which may suggest that the systemic effects of obesity on pain are more important in the hands than in the lower extremities, where the biomechanical effects of obesity may play a more important role. Most of the inflammatory biomarkers assessed in this study did not mediate the relationship between BMI and pain, suggesting that there are more specific pathways by which specific mediators may contribute to pain or that systemic low-grade inflammation mediates the relationship to a lesser extent than what we hypothesized. Despite modest strengths of associations, our results suggest that weight loss may be a strategy to prevent or treat pain in people with hand OA, which should be further explored in future studies.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Gløersen had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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ADDITIONAL DISCLOSURES

Authors Thudium and Bay-Jensen are employees of Nordic Bioscience A/S.

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