Protocol

REFERENCE NUMBERS:

IRB number: IRB201900693

NCT# : NCT04104477

REDCap Record ID number: 403

1. PROJECT TITLE

Carpometacarpal Osteoarthritis: Towards Identification of Biomechanical, Neuromuscular, and Somatosensory Mechanisms

2. INVESTIGATOR(S):

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3. ABSTRACT:

This study examines carpometacarpal osteoarthritis (CMC OA). We specifically aim to elucidate the biomechanical, neuromuscular, and somatosensory mechanisms that contribute to CMC OA symptoms by using orthopaedic biomechanics and quantitative pain testing. Completion of this study will provide a comprehensive dataset describing how movement strategies (muscle activity and joint posture) as well as experimental and clinical pain differ between individuals with CMC OA and age-matched controls.

4. BACKGROUND:

Over 13 million Americans suffer from symptomatic hand OA.[6] Involvement of the CMC joint at the base of the thumb (Fig. 1) is particularly disabling. Individuals with CMC OA can lose up to 50% of hand function.[2] Current conservative and surgical treatments do not provide the pain relief, strength, and mobility needed to restore both fine and gross motor function.[7] Conservative treatments, such as physical therapy, orthoses, anti-inflammatory drugs, and local steroid injection are effective for short-term pain relief, but offer minimal functional improvements.[8, 9] Surgically treating CMC OA provides long-term pain relief, but has the unintended consequence of limiting mobility and strength.[7] Unlike OA at the hip or knee, total joint arthroplasty is not standard of care for CMC OA.[10] Instead, CMC OA is surgically treated with ligament reconstruction and/or bone excision.[7] This translates into over eight different surgical options.[3] No one surgery has proven superior and there is no consensus on how to choose between the surgical options.[3]

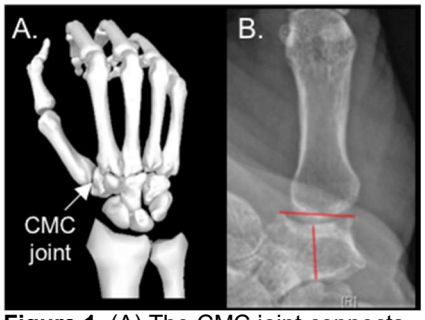

Figure 1. (A) The CMC joint connects the first metacarpal and trapezium. (B) X-ray of mild CMC OA from Ladd et al.[1]

Pain is the primary complaint in individuals seeking treatment for CMC OA. However, even though 33% of postmenopausal women have radiographic evidence of CMC OA,[5] only 5% of all women visit a doctor with painful symptoms.[4] This heterogeneity of pain symptoms suggests there are pain phenotypes in CMC OA, similar to knee OA.[11, 12] Importantly, the experience of pain results from a complex combination of sensory and cognitive processes that do not always clearly align with the underlying disease state.[11, 13, 14] Studies using quantitative sensory testing (QST) to examine pain in CMC OA consistently conclude that CMC OA causes hyperalgesia, or increased sensitivity to painful stimuli.[15-18] However, the mechanisms of hyperalgesia are unclear. Some studies suggest central sensitization changes in the dorsal horn in CMC OA,[15, 17] while other suggest changes in peripheral sensitization occur.[18] Further study is needed to identify the mechanisms of CMC OA pain that should be targeted clinically.

Current treatments focus on modifying joint stability rather than directly addressing pain related symptoms. The focus on joint stability is widely supported by clinical studies theorizing that instability is a predisposing factor in CMC OA.[19-22] A biomechanical study, however, recently challenged this theory by demonstrating that during typical activities joint stability is similar across individuals regardless of disease status.[23] Importantly, this study assessed joint stability during active muscle contraction, whereas clinical studies typically assess joint stability through passive tests. Thus, muscle activity may play a critical role in modulating CMC joint stability and potentially symptom severity. To our knowledge, whether individuals with CMC OA can adapt altered muscle coordination strategies to mitigate symptom severity has not been directly studied.

Clinically, there is a critical need for new treatments that provide long-term pain relief and more effectively restore fine and gross motor function in individuals with CMC OA. As a first step toward addressing this need, the ***contribution of this proposal*** is expected to be improved understanding of how biomechanical, neuromuscular, and somatosensory mechanisms influence symptom severity in adults with CMC OA. This contribution is ***significant*** as it directly addresses the primary barrier preventing the design of new, optimal treatments: the mechanisms that influence the severity of CMC OA have not been fully identified, and therefore cannot be clinically targeted.

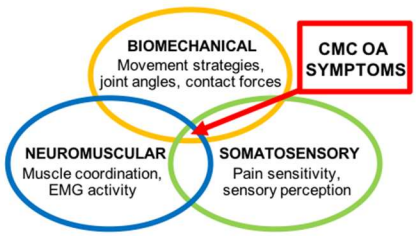

Figure 2. To alleviate CMC OA symptoms, we must understand multiple mechanisms.

5. SPECIFIC AIMS:

Individuals with symptomatic thumb carpometacarpal osteoarthritis (**CMC OA**) can lose up to 50% of hand function.[2] Surgical treatments aim to restore function and reduce pain by eliminating instability at the CMC joint. However, there are eight different surgeries commonly used, and no consensus on how to optimally choose between them.[3] Treatment is also challenging because the presentation of symptoms is highly variable.[4] For example, 33% of postmenopausal women have radiographic evidence of thumb CMC OA,[5] yet only 5% of all women visit the doctor with symptoms.[4] Some individuals may employ unique coping mechanisms that prevent development of pain and functional loss, while others may simply use over-the-counter medications to avoid the doctor. Regardless, very little is known about how an individual's symptoms relate to the underlying osteoarthritic disease. My *long-term goal* is to design effective, targeted treatments for individuals with CMC OA. As a critical step toward this goal, the *objective of this proposal* is to elucidate the biomechanical, neuromuscular, and somatosensory mechanisms that occur during aging and contribute to the symptomology of CMC OA. This objective will be accomplished through two aims:

Aim 1. Evaluate how muscle activity, joint kinematics, and CMC joint stability change in the presence of movement-evoked pain. Electromyography (EMG), joint kinematics, CMC joint stability, and movement-evoked pain during three functional tasks will be quantified in adults with end-stage CMC OA, age-matched controls, and young-healthy individuals. We *hypothesize* that greater levels of reported pain during task completion will be associated with increased muscle activity, larger joint angles, and decreased joint stability. Completion of this aim will quantitatively characterize biomechanical and neuromuscular mechanisms that influence CMC OA symptomology.

Aim 2. Quantify the relationship between function, pain symptomology, and disease severity. Hand function, clinical and experimental pain, and disease severity will be measured in adults with end-stage CMC OA, age-matched controls, and young-healthy individuals. We *hypothesize* individuals with CMC OA will demonstrate greater functional deficits and higher experimental pain sensitivity than age-matched controls and young-healthy individuals. Additionally, in individuals with CMC OA, we hypothesize that functional loss will be associated with higher clinical pain, but not necessarily higher disease severity. Completion of this aim will comprehensively and quantitatively characterize the multi-faceted symptomology of CMC OA and provide insights into the somatosensory mechanisms affecting this disease.

6. RESEARCH PLAN:

Sample Size & Justification: A total of 60 subjects will complete the proposed research study: 20 individuals with end-stage CMC OA, 20 age-matched controls, and 20 young-healthy individuals. These subjects will represent the racial and ethnic diversity of the state of Florida. Vulnerable populations including pregnant women and prisoners will be excluded. All subjects will be between the ages of 18 to 90. Specifically, the end-stage CMC OA cohort and age-matched controls will be between the ages of 40 to 90 as CMC OA is most prevalent in older adults. While the young-healthy cohort will be between the ages of 18-39. A power analysis ($\alpha = 0.05$, $1-\beta = 0.80$) to detect 20% differences in pinch strength between groups required 15 individuals per cohort. Due to including a young-healthy cohort and to prevent erroneous inferences to occurs after multiple comparisons, 20 individuals per cohort will be recruited. Note, pinch strength was the only relevant variable for which standard deviations could be consistently estimated from the literature.[23, 36] Thus, an important outcome of this pilot project will be the data necessary to robustly estimate sample sizes for future studies. For reference, prior studies indicate that individuals with early-stage CMC OA have 20-30% less pinch strength than controls.[23, 36]

A summary of inclusion and exclusion criteria are provided below:

Inclusion Criteria:

CMC OA Subjects:

- female between the age of 40 to 90 years
- end-stage CMC OA diagnosed by a board-certified clinician

Age-Matched Control:

- female between the age of 40 to 90 years
- no joint or muscle pain in the hand or wrist

Young-Healthy Subjects:

- female between the age of 18 to 39 years
- no joint or muscle pain in the hand or wrist

Exclusion Criteria:

All Groups:

- Pregnant women; minors (under age 18); mentally disabled; any persons incarcerated, on parole, on probation, or awaiting trial
- Individuals with concomitant musculoskeletal pathologies (other than osteoarthritis) in the hand or wrist, including distal radius fracture, contracture, trigger finger, and carpal tunnel
- Individuals with history of uncontrolled diabetes, rheumatoid arthritis, muscular dysfunction, or neurological disease

Recruitment:

The CMC OA subjects,age-matched control subjects, and young-healthy control subjects will be recruited, as described below:

CMC OA Subject Recruitment: Subjects with CMC OA will be recruited directly from the hand clinics at the UF Orthopaedics Sports Medicine Institute (OSMI). Specifically, a clinical member of the study team affiliated with the Department of Orthopaedics (e.g., Dr. Wright) will identify individuals who meet the inclusion criteria. These individuals will be asked at the end of their clinic visit if they are interested in learning more about the research study and potentially participating. At this time, the potential participant's contact information (name, e-mail, phone number) and preferred contact method (phone or e-mail) will be recorded. A member of the IRB-approved study team will then reach out to the potential participant by phone or e-mail to discuss the study and answer any questions. If the potential participant expresses interest, he or she will be e-mailed a copy of the informed consent document to review and discuss with their friends and/or family. The study sessions will also be scheduled at this time. Subjects will be consented in-person at the time of their first study session.

Age-Matched Control Subjects and Young-Healthy Subjects: Age-matched control subjects and young-healthy subjects will be recruited using the mechanisms listed below. It should be noted that individuals with CMC OA may also contact the study team via these mechanisms. However, the study team anticipates that these mechanisms will more readily identify age-matched control subjects:

1) Recruitment Flyer – An IRB-approved recruitment flyer will be posted around the University of Florida's campus and the Gainesville community in approved advertising

locations. The flyer will provide potential participants with the information necessary to contact the Study Team by phone and/or e-mail.

2) Website Advertisement – An IRB-approved recruitment message will be posted on the Principal Investigator's Lab Website (https://www.bme.ufl.edu/labs/nichols/get-involved/) The recruitment message will provide potential participants with the information necessary to contact the Study Team by phone and/or e-mail.

3) Word of Mouth – The Principal Investigator and Study Team frequently share results from completed studies through invited talks, guest lectures in undergraduate and graduate courses, and community events. When discussing our human subjects research, one of the most commonly asked questions is whether there are opportunities to become involved as a study participant. Thus, we will share information about the study verbally with interested members of the community. When such verbal conversations take place, we will provide the potential participants with the information necessary to contact the Study Team by phone and/or e-mail. Scheduling and enrollment will occur at least 48 hours after the initial conversation and only after the potential participant has proactively contacted the Study Team.

Initial Contact with Study Team:
When a potential participant contacts the Study Team, we will follow-up with the potential participant by phone or e-mail. During that discussion, we will ask the following questions:

a) Are you a female between 18 and 90 years old?
b) Have you been diagnosed with arthritis in your hand or wrist?
c) Do you currently have muscle or joint pain in the hand or wrist?
d) Have you had any muscle or joint pain in your hand or wrist requiring medical attention or physical therapy in the last 6 months?
e) Are you currently pregnant, mentally disabled, incarcerated, on parole, on probation, or awaiting trial?
f) Do you have any systemic musculoskeletal, neurological, or autoimmune diseases, such as diabetes, rheumatoid arthritis, or stroke?

If a potential participant answers "yes" to question (a) and "no" to questions (b) – (f), then we will proceed with scheduling a study visit as an age-matched control subject.

If a potential participant answers "yes" to question (a) – (b) and "no" to questions (c) – (f), then we will ask the following follow-up question: "What kind of arthritis have you been diagnosed with in your hand or wrist?" If the answer is thumb OA, we will proceed with scheduling a study visit as an CMC OA subject.

Otherwise, the potential participant will be informed that he or she is ineligible to participate.

To facilitate continued communication and follow-up, we will ask the potential participant what his or her preferred method of contact is and will record his or her name, phone number, and e-mail address during these initial conversations. We will use the e-mail address to provide the potential participant with an electronic copy of the informed consent form to review prior to his or her first visit. This copy of the informed consent form will be provided to the subject at least 24 hours prior to their scheduled participation. All research subjects will be consented in-person at the time of their first study session.

Enrollment & Informed Consent:
Prior to experimental data collection, each participant will be given the opportunity to review the informed consent form and study procedures in-person with a member of the study team. This discussion will include information on study purpose and procedures, benefits and risks, who to contact (study team, IRB, etc.), that participation is voluntary and participants can withdraw at any time, HIPAA and confidentiality, as well as cost and compensation. The participant will be given the opportunity to ask questions. After all questions have been answered, the participant will sign the informed consent form, documenting that they provide consent to participant as well as authorization to access their private health information as outlined on the informed consent form.

Research Approach:
The proposed human subject research will occur during three sessions. The first session (focused on biomechanics data for Aim 1) will include motion capture, electromyography (EMG), movement-evoked pain testing. This session is expected to last no more than 4-hours. The second session (focused on somatosensory data for Aim 2) will include experimental pain testing, clinical pain testing, and clinical outcome measures. If needed, the clinical outcome measures can be completed in the first session as it is at no risk to the patient or the study. This session is expected to last 2-hours. The third session (medical imaging for Aim 2) will involve recording plain film radiographs. This session is expected to last less than 1-hour. Sessions can be scheduled consecutively on the same day or as separate study visits, based on the subject's schedule and availability. Sessions can also be completed in any order. Detailed descriptions of each session is provided below:

Session I – Biomechanics Testing Session (*Collection of Data for Aim 1*).
Location: All biomechanics testing will occur in Dr. Nichols' Musculoskeletal Biomechanics Laboratory, located in Room 510 of the New Engineering Building (1064 Center Drive, Gainesville, FL 32611). This laboratory is specifically designed for biomechanical testing and human subject experiments. It is a limited-access lab, meaning that only Dr. Nichols' students and collaborators have access. All individuals with access have completed human subjects research training. During testing, only members of the IRB-approved Study Team will be involved in experimental data collection. A sign that reads "Experiment in Progress" will be posted on the door during data collection to ensure subject privacy is maintained.

Testing Procedures: All participants will be asked to wear short sleeve or sleeveless tops during testing. Participants will have the option to wear their own clothing or clothing provided by the lab. Participants will also be given the option to change into clothing in a private changing area after arrival at the lab.

Upon arriving at the Musculoskeletal Biomechanics Lab, participants will be asked to provide basic demographic (age and sex) and anthropometric (height, weight, limb length) data. Following collection of this information, biomechanical data will be collected using skin-marker motion capture, electromyography (EMG), and movement-evoked pain testing.

During testing, participants will be asked to perform range of motion tasks (e.g., circumduction of the CMC joint) as well as strength tasks (e.g., lateral pinch and opposition pinch) at varying effort levels (maximal and sub-maximal). Each task and effort level will be repeated at least twice. Skin-marker motion capture, EMG, and movement-evoked pain data will be collected during each task as described below:

Skin-Marker Motion Capture & Force Sensors
Skin-marker motion capture involves placing reflective markers on palpable boney landmarks, such as the distal radial styloid. These reflective markers are secured to the subject's skin using adhesive tape. Reflective markers will be placed across the hand and arm following the guidelines of the International Society of Biomechanics. Locations of the markers will be recorded during completion of the tasks using a 12-camera Vicon Vero motion capture system. During testing, the forces produced by the thumb will be recorded using custom force sensors. These data will provide a kinematic description of how the thumb, wrist, and arm move during the recorded tasks as well as kinetic data describing the forces produced. These data will also be used in the musculoskeletal simulations to calculate CMC joint contact forces.

Intramuscular and Surface Electromyography (EMG).
EMG uses surface electrodes (adhered to the skin) and/or intramuscular electrodes (fine wire needles inserted into the muscle belly) to measure muscle activity. The thumb is controlled by 9 muscles: 4 extrinsic muscles [*extensor pollicis brevis* (EPB), *extensor pollicis longus* (EPL), *abductor pollicis longus* (APL), and *flexor pollicis longus* (FPL)] that have their muscle bellies located in the forearm and 5 intrinsic muscles [oblique and transverse heads of the *adductor pollicis* (ADPo and ADPt), *abductor pollicis brevis* (APB), *opponens pollicis* (OPP), and *flexor pollicis brevis* (FPB)] that have their muscle bellies located in the hand. These muscles will be recorded using intramuscular EMG. Up to ten additional muscles may be recorded using surface EMG. All intramuscular electrodes will be placed by a trained researcher following standard practice guidelines. Specifically, the insertion site will be cleaned with alcohol and the fine wire needle electrodes will be inserted using a disposable, sterile needle. When the needle is withdrawn, the two fine wire electrodes (roughly the thickness of a human hair) will remain in the muscle belly. Electrode wires will be secured to the skin with tape to prevent unintended removal. All electrodes will be removed at the end of data recording. Ultrasound imaging and muscle stimulation, the standard techniques for ensuring appropriate electrode placement, will be used to verify that the electrodes have been placed in the correct muscles. No more than three insertion attempts will be made for any single muscle. If after three attempts, the electrode cannot be placed, we will not record from that muscle. Subjects will be instructed that they may choose to stop placement of intramuscular electrodes at any time, and reminded of this fact during placement of intramuscular electrodes. All surface electrodes will be placed in accordance to the guidelines established by the European Recommendations for Surface Electromyography (SENIAM) and the International Society of Electrophysiology and Kinesiology (ISEK). Unlike intramuscular electrodes, surface electrodes are adhered to the skin like stickers and record from superficial muscles, such as the ECRL. All EMG signals will be recorded using a Delysis Trigno EMG system, which is synched with the Vicon system to allow simultaneous recording of muscle activity, kinematic data, and kinetic data. The collection of EMG data is important because muscle activity measured *in vivo* will be used to understand whether individuals use different muscles to perform specific activities given their condition (i.e., CMC OA versus age-matched controls).

Movement-Evoked Pain.
Movement-evoked pain testing requires subjects to provide a self-reported pain level before, during, and after each task. For this study, we will use the Visual Analog Scale (VAS) to record movement-evoked pain. Movement-evoked pain levels will be used to understand whether differences in pain severity exist between the maximal and sub-maximal effort tasks and to also evaluate how various pain levels affect the movement strategies (i.e., muscle activity recorded via EMG and joint angles recorded via motion capture).

Session II – Somatosensory Testing Session (*Collection of Data for Aim 2*)

Location: Somatosensory testing, which involves quantitative sensory testing (QST) and completion of questionnaires, will be completed in the Pepper Center Institute on Aging in the Clinical Translational Research Building (CTRB) or the Dental Tower. Location will be determined in advance based on availability and scheduling of the equipment necessary for QST. The space and equipment needed for QST is available to Dr. Cruz-Almeida (co-Investigator), who has extensive experience with these study procedures.

Testing Procedure: Through a combination of quantitative testing and self-reported assessments, data on experimental pain, clinical pain, hand function, and disease severity will be reported. Details on the methods used are provided below.

Quantitative Sensory Testing (QST).

QST involves systematically exposing individuals to stimuli in order to detect their pain threshold. Mechanical (i.e., pressure) and thermal stimulation will be used in this study. QST will be performed in standardized sites using anatomical landmarks. All tests will be demonstrated and explained prior to being performed. All participants will be tested on the extremities. For participants with pain, additional standardized testing sites will be chosen to include painful areas. The "TSA Thermal Sensory and Vibratory Sensory Analyzer (Model TSA II, VSA 3000) (Medoc. LTD)" will be used in this study to quantify nerve fiber dysfunction with measurements of vibratory, pinprick and thermal sensory thresholds (warm, cold, heat-induced pain, and cold-induced pain). A hand-held algometer (FDX, Wagner Instruments and/or Algomed, Medoc.LTD) will be used to assess pressure pain sensitivity. Prior to testing we will obtain skin temperature readings at all testing sites by using the DT1001 DermaTemp infrared scanner (Exergen). Similar procedures have been used by us and other investigators in older adults with and without pain.

a. Vibratory Detection Thresholds: Vibratory threshold is tested with a vibratory pin, which presses the measured area with a consistent pressure of 50g. The vibratory sense analysis will be performed using upward-moving stimulus (increasing in intensity until a sensation is perceived). Several vibrations will be given sequentially and the mean end variance will be determined to verify the consistency of the test.

b. Tactile Detection Thresholds: Thresholds for light touch will be assessed with von Frey monofilaments, using two ascending and two descending stimulus series, according to the method of limits. Detection threshold at each test site will be determined by the obtaining the geometric mean across these four test series.

c. Thermal Detection Thresholds, Pain Thresholds and Temporal Summation: Following a brief introduction familiarizing each subject with the procedure, several trials will be performed for each sensory modality and a mean threshold will be calculated. For threshold determination we will use a "reaction time-inclusive" method, the method of limits, consisting of continuously changing intensities of stimuli halted automatically by the subject at the moment that the requested sensation is perceived. The following thresholds will be evaluated using the TSA II: (1) cool sensation; (2) warm sensation; (3) cold pain; and (4) heat pain. Subjects will also be asked to rate the painful sensation. Temporal summation of heat pain may be assessed by administering brief repetitive suprathreshold heat stimuli to the hand.

d. Allodynia and Temporal Summation: Dynamic mechanical allodynia will be investigated using a soft brush and lightly brushing the skin of the hands and feet as well as any reported painful areas. If pain is evoked in the test area, the participant will be asked to rate the intensity of the pain. If an allodynic area is detected, temporal summation will be evoked by repetitively tapping the skin of the allodynic area with von Frey hairs (100g) at 1

Hz for 10 seconds. If temporal summation is evoked in the allodynic test area the participant will be asked to rate the intensity of the pain.

e. Punctate Pain Testing and Temporal Summation: We will apply punctate mechanical stimuli to the test sites with a series of weighted probes. Probes of different weights will be applied to participants' skin to determine the level that produces slight discomfort or pain. Two measures are obtained: 1) Pain threshold is determined by applying probes of different weights in ascending and descending sequences and participants are asked to tell the examiner which probes produce pain; 2) A weighted probe is applied either once or several times in a row and participants are asked to rate the pain they experience from the probe. In addition, a standardized plastic MediPin commonly used in neurological examinations will be applied to testing areas and participants will be asked to rate the intensity of any pain that is experienced.

f. Pressure Pain Thresholds: Pressure is delivered by a hand-held algometer (spring-controlled device delivering calibrated pressure via a flat 10mm diameter rubber tip). Pressure is delivered at an approximate rate of 1 kg/sec. Participants respond when they first feel pain, at which time the pressure is removed.

Clinical Pain & Psychological Measure.

Clinical pain will be assessed through questionnaires, including the Graded Chronic Pain Scale (GCPS), pain experience questionnaire (OPTIMIZE Pain Experience FITT), a comprehensive pain history (OPTIMIZE Health History), SF-36 - Short Form Health Survey, Brief Pain Inventory, PainDetect and the Australian Canadian OA Hand Index (AUSCAN). Psychological measures will also be assessed using the PROMIS Anxiety and Depression short forms, Center for Epidemiologic Studies Depression Scale (CES-D), Beck Depressive Inventory (BDI), Perceived Stress Scale (PSS), Montreal Cognitive Assessment (MoCA), Coping Strategies Questionnaire – Revised (CSQ-R), Satisfaction with Life Scale (SWLS), the Revised Life Orientation Test (LOT-R), and the Positive and Negative Affect Sale (PANAS).

Together, these assessments will provide insights into each subject's clinical pain experience. Specifically, the GCPS yields a "Characteristic Pain Intensity" score and an overall "Disability" score providing insight into global pain severity and pain-related interference over the past 6 months. The comprehensive pain history provides an index measure of important pain domains associated with biological aging ad functioning. These domains are frequency, intensity, time (duration) and total pain sites. The AUSCAN assesses disease-related pain and is specifically designed for hand OA. The PROMIS Anxiety and Depression short forms, CES_D, and BDI screen for symptoms of mood disturbance and has been extensively validated in chronic pain populations such as OA. The MoCA evaluates different types of cognitive abilities. The CSQ-R uses a pool of items that reflect coping strategies frequently reported by patients and proven to be important in the management of pain. The LOT-R measures how optimistic or pessimistic people feel about the future which has been shown to correlate with people's health, work performance, and educational attainment. The PANAS will report how individuals generally feel with positive affect reflecting enthusiasm and negative affect reflecting distress. Subject's response to questions regarding risk of suicide will be reviewed immediately after the study. If a subject or potential subject indicates suicidal thoughts or wishes, the principal investigator of the study, Dr. Nichols, and a representative the UF Psychology Clinic, Dr. Dawn Bowers (or their appropriate designees), will be informed. In the unexpected event that Dr. Bowers, nor their designees are available, the Alachua Country Crisis Center will be contacted. The clinical pain metrics will be primary outcome variables of the study. The psychological measures will be used as possible covariates and support future studies that more comprehensively include

psychological measures. Subjects will be given ample time to complete all questionnaires and provided with the opportunity to ask questions about any and all measures. The questionnaires can be completed by the subject in any session (Session I or Session II) as needed.

Functional Outcome Measures.
Participants will perform range of motion (thumb only) and strength (pinch and grip) tests as well as the Jebsen Hand Function test, which includes seven timed activities to evaluate fine and gross motor function. Participants will also complete the Disability of arm, shoulder, hand (DASH) score, a widely used functional outcome measure for the upper limb. Together, these measures were chosen to provide insights into strength, range of motion, as well as fine and gross motor function.

Session III – Medical Imaging Session (*Collection of Data for Aim 2*)
Location: Plain film radiographs will be collected at the Orthopaedic Sports Medicine Institute (OSMI) located at 3450 Hull Road.

Testing Procedure: Plain film radiographs will be acquired to assess disease severity. Acquisition methods will be similar to those used for clinic patients:

Plain Film Radiographs.
For each subject, radiographs will be acquired from two views: anteriorposterior (Robert view) and lateral view. For the CMC OA subjects, if the x-ray views required for this study have been acquired as part of a standard clinical visit in the last 1 month, new x-rays will not be acquired as part of the study. Instead, x-rays will be obtained from the subject's medical record, following informed consent and approval. A certified UF Health technician will acquire the films. According to RadiologyInfo.org, an information service sponsored by the Radiological Society of North America (RSNA) and the American College of Radiology (ACR), an x-ray of an extremity (such as the hand or foot) has an approximate radiation dose of 0.001 mSv, which is equivalent to approximately 3 hours of natural background radiation (https://www.radiologyinfo.org/en/info.cfm?pg=safety-xray). Given that this study will require two x-rays, we estimate the approximate radiation dose as 0.002 mSv, or the equivalent of 6 hours of natural background radiation. The radiographs will be used to classify the presence of CMC OA using the Eaton classification method and the Hand OA Index. The control subjects will be recruited based on lack of pain and disability. These asymptomatic subjects may have evidence of CMC joint degeneration, which will be an important covariate in the analyses. The severity of CMC OA within the CMC OA participants will also be important for analyzing the experimental and clinical pain as well as functional measures in the context of disease severity.

Participants will be given the option during the informed consent process to consent to photographs, videos, and/or audio recordings. If the individual does not consent, photographs, videos, and/or audio recordings will not be collected. The primary purpose of collecting photographs, videos and/or audio recordings is to aid in analysis and interpretation of data. If consent is given, these items may also be used for educational purposes at the University of Florida or in presentations and publications beyond the University of Florida. Collected photographs and video recordings will only be used in ways approved by the subject. In all presentations and publications, identifiable features (defined as unique tattoos or skin markings and/or any aspect of the subject's face) will be removed from displayed images.

Data Storage

Research data collected from the human subjects will include skin marker motion capture data, EMG, movement-evoked pain measures, QST data, clinical pain and psychological measures, function outcome scores, and radiographs. Data will be used only for research purposes. Only the subject's age, sex, and a subject specific code will be documented with the data. The information linking the subject specific code to private health information will be stored securely in a locked cabinet within Dr. Nichols' laboratory and/or electronically on a HIPAA compliant, password-protected server at the University of Florida. Only IRB approved research personnel will have access to identifiable research data. Analysis of research data will be completed on password protected computers. All identifying information will be removed from digital radiographs prior to publication, presentation at conferences, or discussion of the images with persons other than those listed as study personnel. HIPPA compliance will be strictly maintained.

Additionally, the names, visit numbers, and MRNs of each study subject will be included with the digital radiographs on the University of Florida PACs system, as required by the University for auditing purposes. Only trained personnel will retrieve digital radiographs of subjects from the database, as they are required to do so as part of their normal job duties.

All research personnel will complete annual training for human subject protection and HIPAA/confidentiality in compliance with University of Florida guidelines.

7. Possible Discomforts and Risks:

Most of the experimental procedures involved in this study have no greater than minimal risks. However, intramuscular electromyography (EMG), which involves insertion of fine wire needle electrodes, poses slightly more than minimal risk. All procedures are described below:

Activities Performed During Motion Capture. Participation in the motion capture study should not cause pain or discomfort beyond what is experienced in routine, daily life or a standard clinical evaluation during a visit to the doctor. Nonetheless, we will exclude research subjects who are unwilling or unable to perform the activities to ensure that it poses no substantial additional risk or causes no substantial pain to our subjects.

Skin-Marker Motion Analysis. Skin-marker motion analysis poses minimal risk to subjects. Reflective markers are secured to the skin using adhesive tape. Removing this tape may cause mild discomfort or skin irritation (i.e., redness). This discomfort is similar to that experienced when removing a bandaid.

EMG. Surface EMG poses minimal risk. The only known health risk is mild discomfort or skin irritation (i.e., redness) associated with removal of the surface electrodes. Rare, but possible risks of intramuscular (or fine wire) EMG include inflammation, infection, bleeding, and/or fainting. Damage to nerve or blood vessels form the wire is also possible, although rare. Mild discomfort associated with placement of the intramuscular EMG electrode is possible. We will minimize risks by having only trained research staff insert intramuscular electrodes. Ultrasound guidance will also be utilized to assist with needle placement around sensitive anatomy. Additionally, subjects will be given the option of stopping needle insertion at any time. Subjects will be fully compensated for the biomechanics session, even if they choose to stop EMG needle insertion prior to all electrodes being placed.

Quantitative Sensory Testing. QST is generally considered safe. However, participants will experience some pain or discomfort. Due to the pressure pain procedure (mechanical stimuli), there is a slight chance that a bruise may form as a result of the pressure pain procedure. Also, some patients may experience after-sensations after application of pressure stimuli to their symptomatic thumb, though this is expected to be brief in duration. Also, this risk is diminished

by applying brief stimuli well below the participant's tolerance level. Due to the thermal stimulation procedure, there is a slight change of burning the skin. However, this risk is diminished by carefully monitoring the stimuli levels. The risk of burn injury as a result of overheating contact thermode due to technical malfunction is very unlikely because the subject: (1) is free to withdraw from the thermode; (2) has the option to stop the stimulus at any point. In addition, the stimulator incorporates automatic safety features that do not depend on actions of the investigator or subject: (3) a safe range (max 520C) is programmed into the system preventing accidental use of potentially harmful temperature set-points; (4) the software continuously monitors thermode temperature and automatically interrupts thermode contact with the skin when the process value exceeds the set-point by >1.00 C.

There is also a minor risk of psychological discomfort due to QST. The prospect of being subjected to painful stimulation in an unfamiliar location, surrounded by unfamiliar investigators and equipment that may look intimidating may lead to anxiety. We try to minimize this anxiety by thoroughly explaining all procedures and taking the time to answer all questions the participant might have. We make sure that ample time is scheduled for the first session, so the participant does not feel rushed and has time to get to know the lab environment and investigators. In addition, we allow the participant to experience a few sample stimuli before deciding whether or not to go ahead with the actual testing. Our tests always start with a few non-nociceptive stimuli before the temperature rises gradually. In spite of these measures we cannot completely rule out that some participants may feel some anxiety during the first session. However, based upon experience in other studies using similar protocols, we are confident that most subjects will not experience psychological stress during the second and subsequent sessions, when they have become familiar with the experimental setting.

Clinical Pain, Psychological, and Function Measures: The questionnaires and functional tasks proposed in this study are considered minimal risk. Some individuals may feel unconformable with some questions. Notably, the PROMIS short for screening for anxiety and depression may indicate that a research subject is anxious or depressed. These forms will be scored prior to the completion of the session. An elevated score, meaning an individual is anxious and/or depressed will be handled by contacting one of the clinical co-Investigators (Sibille or Wright) and obtaining the appropriate referrals.

Radiation Exposure. There is an extremely small chance that research subjects will be more susceptible to developing cancer because of increased exposure to radiation experienced during the radiographs required for this study. However, the risk due to exposing the hand, a distal segment that is not close to vital organs, to the radiation from an x-ray is extremely low. The Food and Drug Administration (FDA) Guidelines for Research Subjects sets an estimated dose equivalent (EDE) limit of 3 rem for a single session and no more than 5 rem annually. The total EDE associated with participation in this study is estimated to be less than 2 mrem (note the difference in units). This is less than 1 percent of the amount of background radiation that the average person in the United States receives each year (annual background radiation estimated to be 0.36 rem).

Additional Protections Against Risk:

The study design provides several measures to minimize the potential risks to subjects:

Minimizing Risks to Privacy by Protecting Confidentiality: The collected PHI includes, age and biological sex. This information will only be identifiable by a subject specific code. A document linking the subject specific code to the name of the subject will be stored securely in a locked cabinet within Dr. Nichols' laboratory and/or electronically on a password-protected

server in the University of Florida. Only IRB approved research personnel will have access to identifiable research data.

Minimizing Risks by Using Qualified Study Personnel

We will also protect subjects by having appropriately trained personnel perform/oversee the necessary procedures. The radiographs will be acquired at UF Health in a manner identical to that used on patients, such that privacy and safety will be ensured. Trained and qualified technicians employed by the University of Florida will obtain all scans.

Motion analysis and EMG testing (Session I biomechanics testing) will take place in Dr. Nichols Musculoskeletal Biomechanical Laboratory in the J. Crayton Pruitt Family Department of Biomedical Engineering. Only trained members of the research team will operate the motion capture and EMG systems. Dr. Nichols has received training on insertion of fine wire EMG electrodes through the Gait & Clinical Movement Analysis short course. This training fulfills the classroom training requirements for clinicians and researchers in California, the state with the strictest fine wire EMG electrode laws. All fine wire needle electrodes will be placed following best practices to ensure safety and sterility.

The experimental pain procedures (Session II somatosensory testing) described in this application are widely used and safe. While they produce pain, risks to the subjects are minimal, because:

1) the pain is transient in nature, and generally subsides immediately after the procedure;
2) subjects are instructed that they may stop any procedure at any time with no adverse consequences; and
3) the level of pain experienced by subjects is below their tolerance level.

Dr. Cruz-Almeida, who has extensive experience with experimental pain testing, and Dr. Sibille, who has extensive experience with clinical pain testing, will ensure all pain testing is completed in a safe and appropriate manner. Risks will also be minimized by adhering to our exclusion criteria, and the study physician (Dr. Wright, co-mentor) will have full discretion to exclude participants for whom they feel there is excessive risk for participation.

8. POSSIBLE BENEFITS:

There are no direct benefits to subjects for participating in this study. However, the knowledge gained from this study will benefit society by providing new information regarding the mechanisms underlying CMC OA pain and disability.

The contribution of this proposal is expected to be improved understanding of how biomechanical, neuromuscular, and somatosensory mechanisms influence symptom severity in adults with CMC OA. This contribution is important as it directly addresses the primary barrier preventing the design of new, optimal treatments: the mechanisms that influence the severity of CMC OA have not been fully identified, and therefore cannot be clinically targeted. The data collected from this study will also form the foundation for future work on CMC OA phenotypes. Thus, this study will enable future design and development of effective, targeted treatment for CMC OA.

9. CONFLICT OF INTEREST:

The investigators do not have any conflicts of interest

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