Principal Investigator/Study Chair: Babak Bazrgari

The assessment of lower back mechanical behavior and spinal loads in veterans with non-specific low back pain: a feasibility study (Protocol # TBD)

Funding Agency: Veteran Health Administration

[July 14th, 2022]

## Abstract

Low back pain (LBP) is strongly associated with opioid consumption among veterans, and improved clinical management of LBP is likely to reduce reliance on opioid among veterans. Up to 60% of patients with an acute episode of non-specific LBP experience either symptom persistence or symptom relapse within one year. This is likely an indication of a failure in addressing the underlying mechanisms of pain or initiation of a new etiology; both may stem from a mismatch between patients and treatments. The overall goal of our research is to develop, validate and implement measures that are relevant to known mechanisms of LBP, which can then be used to holistically gauge the health status of patients' lower backs beyond self-reporting of symptoms. More accurate measurements will help better match of patients with existing treatments or development of more effective new treatments. The specific objective of this study is to generate evidence in support of the feasibility of our methods for 1) the evaluation of relative contribution of lower back tissues to spinal loads, and 2) the investigation of the resultant spinal loads in veterans with non-specific LBP. We have developed a powerful set of tools for the comprehensive assessment of spinal loads and lower back mechanical behavior (MB), that will enable us to examine the existence or development of abnormalities in spinal loads and lower back MB in three groups of veterans with different experiences with non-specific LBP. These groups will include 1) veterans with chronic, non-specific LBP and high level of disability (n=18), 2) veterans with chronic, non-specific LBP and low level of disability (n=18), 3) asymptomatic veterans without a recent history of non-specific LBP (n=18; serving as control group). Successful completion of this feasibility project will pave the way for future studies (merit grant applications) that will verify the role of abnormalities in lower back MB and spinal loads in the clinical presentation of LBP. Such an understanding has the potential to help the affected veterans with disabling non-specific LBP. Specifically, measures of lower back MB and spinal loads can be used not only to identify veterans with mechanical abnormalities in their lower back who are likely to experience LBP in the future, but also to guide novel integrated physical and psychological preventative treatments aimed at improved lower back mechanics. Ultimately, the goal and resultant improvement in clinical outcomes of treatment for non-specific

LBP is to diminish reliance on opioids for the symptom management of particularly veterans with chronic LBP.

**List of Abbreviations**

| | |
|---|---|
| Abaqus/CAE | A finite element software |
| CBOC | community-based outpatient clinic |
| cm | centimeter |
| Co-I | Co-Investigator |
| DMAP | Data management and access plan |
| EMG | Electromyography |
| FE | Finite element |
| Fig | Figure |
| Hz | Hertz |
| ICC | Intra class correlation |
| ID | Identification |
| IRB | Institutional Review Board |
| Kollmorgen, AKM53K | A servomotor model |
| KY | Kentucky |
| L4, L5 | $4^{th}$ and $5^{th}$ lumbar vertebrae |
| LBP | Low back pain |
| Matlab | A computational software |
| MB | Mechanical behavior |
| n | Number of participants |
| Natick, MA | Natick, Massachusetts |
| Optex FA | A laser sensor model |
| PI | Principal Investigator |
| PROMIS | patient-reported outcomes measurement information system |
| Providence, RI | Providence, Rhode Island |
| Radford, VA | Radord, Virginia |
| RFA | Request for application |

| | |
|---|---|
| RMDQ | Roland-Morris Disability Questionnaire |
| S1 | 1st sacrum vertebra |
| Scottsdale, AZ | Scottsdale, Arizona |
| SL | Spinal load |
| VA | Veterans administration |
| VAMC | Veterans administration Medical Center |
| Xsens MTW | A motion sensor model |

# Contents

**Protocol Title: The assessment of lower back mechanical behavior and spinal loads in veterans with non-specific low back pain: a feasibility study**

## 1.0 Study Personnel

- Provide name, contact information, and affiliations/employee status for Study Investigators and research staff: (e.g. John Smith, Principal Investigator, john.smith@va.gov. , Part Time 5/8)

Principal Investigator: Babak Bazrgari, babak.bazrgari@uky.edu, VA part time 5/8

Co-Investigators: Theresa Wolfe, theresa.wolfe@va.gov, VA full time

Coordinator: N/A

Research Assistant/Staff: Clare Tyler, cety222@g.uky.edu, VA WOC

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Research Assistant/Staff: Vanessa Ramirez, vanessa.ramirez@uky.edu, VA WOC

Collaborators: TBD

## 2.0 Introduction

- Provide scientific background and rationale for study.
- Include summary of gaps in current knowledge, relevant data, and how the study will add to existing knowledge.
- Include rationale for including or excluding certain populations – in particular vulnerable populations.

Low back pain (LBP) is a significant human health disorder affecting up to 18% of the world population at any given time.[1-3] In response to a recent national survey, 33% of veterans versus 28% of non-veterans reported an episode of significant LBP in the prior three months.[4] Chronic

LBP, the leading cause of disability globally,[5] reduces quality of life[6] and forces older workers to retire prematurely.[7] Adding to the problem, highly addictive opioids are the most commonly used prescription pain medication among patients with chronic LBP in the U.S., both for veterans[8-10] and non-veterans,[11] and more than half of regular opioid users report LBP.[12] Thus, LBP is a major economic and medical burden on patients and the Veterans Health Administration system.

Symptom persistence or relapse is prevalent in patients with non-specific LBP, with two out of three patients experiencing these symptoms during the year following an episode of non-chronic LBP.[13-16] Such an unsatisfactory clinical outcome for non-specific LBP is likely an indication of an unaddressed or newly developed etiology. While identification of the exact root cause(s) of LBP in these patients will be an important research challenge for years, there are measures that have relevance to some specific causal sources of LBP. These measures can be used for the clinical management of LBP to holistically gauge the health status of patients' lower back more accurately than from the symptom reports alone. One such group of measures relates to the "spinal loads" experienced in daily life. Despite considerable controversies,[17-21] there is strong evidence in the literature to support the plausibility of a causal relationship between spinal loads and LBP. For instance, the association of measures of spinal loads (e.g., net moment at the lower back), and the incidence and prevalence of LBP have been widely reported.[22-26] Further, recent systematic reviews and meta-analyses have provided consistent evidence in support of a prospective association between spinal loads and LBP.[27-29] Finally, animal and human cadaver studies have demonstrated how spinal loads occurring in daily life can activate nociceptor and initiate the inflammatory response, with or without injuries in spinal tissues.[30-32] Therefore, **there is an important research need** for determination of whether measures of spinal loads can be integrated in clinical assessment of patients with non-specific LBP, and to help eliminate the risk of symptom relapse or persistence. Improved and objective assessment of patients' lower back will enable clinicians to better match patients with treatments or develop more personalized novel treatments which will ultimately help improve the clinical outcomes of treatments offered for LBP.

In this application, forces and deformations experienced in spinal tissues are referred to as spinal loads, and are the result of the active and passive mechanical responses of lower back tissues (i.e., internal forces) to the physical demand of an activity (i.e., external forces), in order to assure spinal equilibrium and stability.[33-35] When performing a physical activity, active (motor or sensory) responses of lower back tissues to the activity demand determine the trunk and pelvic motions. The resultant trunk and pelvic motions in turn determine lumbar posture and passive tissue contribution (due to deformation) to spine equilibrium and stability. Therefore, alterations in active and passive aspects of lower back MB, along with changes in the way a physical activity is performed, alter spine equilibrium and stability, and thus ultimately the spinal loads.

There is a large body of literature, including some from our laboratory, concerning the differences in the way a physical activity is performed between individuals with healthy backs, and those with acute/sub-acute/chronic or experimentally-induced LBP.[36-41] Despite some discrepancies, that are likely driven by the heterogeneity of population with non-specific LBP, abnormalities like larger pelvic contribution to trunk motion, more in-phase and less variable lumbo-pelvic coordination during trunk forward bending and backward return, have been widely reported in patients with non-specific LBP.[36-41] A large contribution of pelvis to trunk motion during forward bending has been suggested to be associated with higher spinal loads.[42] It has been further shown that abnormalities in trunk and pelvic motions, observed in patients with non-specific LBP, linger beyond pain alleviation.[43-45] Consistently, similar abnormalities in trunk

and pelvic motions have been reported in individuals with a history of LBP.[46, 47] Individuals with LBP also demonstrate abnormalities in trunk and pelvic motions during activities of daily living like walking[48, 49] and sit-to-stand.[50, 51] Moreover, correlations between psychological factors and differences in trunk and pelvic motions among LBP patients have also been reported.[45, 52] In this project, we will investigate whether these differences in the way a physical activity is performed in veterans with *different LBP experiences* are associated with potential differences in spinal loads (i.e., Aim 2).

Persistent physical abnormalities (§1.4), which are likely influenced by psychological factors, could potentially lead to adaptive changes in lower back MB. For instance, asymmetric trunk motion and lumbo-pelvic coordination is evident in individuals with unilateral lower limb amputation,[53, 54] and we have observed asymmetries in reflexive and intrinsic stiffness of their lower back.[55] We also have shown a reduction in intrinsic stiffness, and an increased latency of reflexive responses of trunk muscles to unexpected perturbations, following an acute exposure to an awkward working posture.[56, 57] Higher activation of trunk muscles in both static and dynamic tasks in patients with chronic LBP [58-62] has been suggested as a compensatory response of the trunk neuromuscular system to impaired spine stability,[63] a response that is associated with higher spinal loads.[64] Lower back MB directly influence spinal stability, hence, such a compensatory response of the trunk neuromuscular system in patients with chronic LBP is likely an indication of alterations in lower back MB that might have been occurred in the course of transition from acute to chronic LBP. Results of this cross-sectional feasibility project (i.e., Aim 1) will equip us with critical preliminary data for future studies aimed at investigation of the role of changes in lower back MB in transition from acute LBP to chronic disabling LBP.

In summary and considering the strong evidence in support of a causal relationship between spinal loads and LBP, investigation of the role of abnormalities in spinal loads in the clinical presentation of LBP (symptom persistence, relapse, or recurrence), is clearly critical. As a first step toward addressing such an important research gap, we will generate evidence in support of the sensitivity of our methods for capturing potential abnormalities in 1) relative contribution of lower back tissues to spinal loads, and 2) the resultant spinal loads in veterans with different experiences of non-specific LBP. Successful completion of this project will facilitate future longitudinal research to determine the role of abnormalities in spinal loads and lower back MB in clinical presentation of LBP. Ultimately, the outcomes of such research will support integration of measures of lower back mechanics in clinical assessment of veterans with LBP, hence will allow identification of veterans at risk for symptom persistence/relapse due to abnormal spinal loads. Availability of such a capability in clinic will enable clinicians to better match patients with existing physical and psychological treatments or even may lead to development of more effective new treatments. The resultant improvement in clinical outcome of treatment for non-specific LBP is likely to reduce reliance on opioids for management of chronic LBP.

## 3.0 Objectives

- Relevance to VA Mission, Veterans health and or healthcare issues
- Describe the study's purpose, specific aims, or objectives.
- State the hypotheses to be tested. How will the aims or objectives test the hypothesis?

Opioids are the most common prescription pain medications among patients with chronic low back pain (LBP),[11] and more than half of regular opioid users report LBP.[12] Not surprisingly, there is a strong association between opioid consumption and LBP among veterans.[8-10] According to a recent national survey, more than a third of veterans reported an episode of significant LBP in the prior three months.[4] At its chronic stage, LBP is among the top ten reasons for veterans to receive disability compensation.[65] Effective treatment of LBP is hindered by an inability to determine the underlying source of pain for most cases (referred as non-specific LBP). Accordingly, unsatisfactory clinical outcomes for LBP are common for a wide range of treatments, with two out of three patients with LBP experiencing symptom persistence or relapses.

Considering the current level of opioid consumption for LBP relief, it is critical to go beyond patient's report of symptoms for the management of non-specific LBP, and to implement screening tools that can direct us to potential root causes of LBP. One group of such tools relates to measures of forces and deformations in spinal tissues, or the "spinal load", experienced in daily life activities. Extensive evidence relates spinal loads to LBP, yet, treatment-induced changes in spinal loads are not monitored in patients with LBP. Spinal loads are influenced by physical function and psychological characteristics of patient and can change due to treatment-induced alterations in trunk neuro-musculoskeletal behavior and lumbo-pelvic coordination. Therefore, it is important to equip researchers and clinicians with the latest advanced tools that will enable evaluation of spinal loads, and eventually help better match patients with treatments, or even designing more effective interventions that mitigate LBP persistence/relapses due to biomechanical factors.

**The specific objective of this study** is to generate evidence in support of the feasibility of our developed methods for the evaluation of 1) relative contribution of lower back tissues to spinal loads, and 2) the resultant spinal loads experienced during daily activities **in veterans with non-specific LBP**. Results of this feasibility study will enable proper design of our future projects, wherein we will investigate the role of spinal loads experienced in daily life activities in clinical presentation of LBP. We have developed several innovative computational and experimental methods for a comprehensive and personalized assessment of spinal loads. Specifically, the relative mechanical contribution of active and passive lower back tissues to spinal loads is assessed using advanced measures of [*bulk*] lower back mechanical behavior (MB), whereas muscular responses to physical demands of daily activities and the resultant spinal loads are evaluated using our finite element model of human spine. We have used the methods proposed in this application extensively for evaluation of [*bulk*] lower back MB and spinal loads in asymptomatic individuals. This project will demonstrate the sensitivity of our measures for capturing abnormalities in lower back MB and spinal loads in patients with non-specific LBP by completing the following two aims to achieve our objective [*given the feasibility nature of this project and lack of adequate power, no specific hypothesis has been provided*]:

**Aim-1: Feasibility of distinguishing potential differences in lower back MB between veterans with different LBP experiences.** We will characterize lower back MB in three gender-balanced groups of veterans between 20 and 70 years old. These will include veterans with *1) chronic LBP and a Roland-Morris Disability Questionnaire (RMDQ) score of >12 (n=18), 2) chronic LBP and RMDQ score of ≤12 (n=18), 3) no recent history of LBP and currently asymptomatic (n=18), serving as control group).* Participants will be recruited from the population served by the Lexington, KY, VA Medical Center. We will determine passive stiffness of the lower back and its relaxation along with its active intrinsic and reflexive mechanical properties, using our sudden perturbation and stress-relaxations tests. Given the reported differences in trunk neuromuscular behavior and lumbo-pelvic coordination, we expect to see differences in our measures between patient groups targeted for this project.

**Aim-2: Feasibility of distinguishing potential differences in spinal loads between veterans with different LBP experiences.** Trunk muscle forces and the resultant spinal loads will be determined in the same participant groups when they perform common activities of daily living like walking and manual material handling. Considering the causal role of spinal loads, and given the persistence of symptom in patients with chronic LBP, along with the high risk of LBP recurrence in patients with non-chronic LBP and those with a recent history of LBP, we expect differences in spinal loads between patient groups.

**Our long-term goal** is to help uncover the potential role of spinal loads in clinical presentation of LBP by facilitating the assessment of lower back MB and spinal loads in clinics. If such a role is established, our measures can be used to identify veterans at risk for [symptom relapse, or transitioning to disabling chronic LBP] due to biomechanical factors, and can guide novel, integrated physical and psychological treatments aimed at improved lower back mechanics. Ultimately, the resultant improvement in clinical outcome of treatment for non-specific LBP **is likely to reduce reliance on opioid** for management of chronic LBP.

## 4.0 Resources and Personnel

- Include where and by whom the research will be conducted.
- Provide a brief description of each individual's role in the study. Be sure to indicate who will have access to protected health information and who will be involved in recruiting subjects; obtaining informed consent; administering survey/interview procedures; and performing data analysis.
- If applicable provide information on any services that will be performed by contractors including what is being contracted out and with whom.
- If applicable provide information on any Memoranda of Understandings (MOUs) or Data Use Agreements (DUAs) that are being entered into including with whom and for what reason.

Data collection and analyses will be conducted in a designated research space in the Lexington VA Medical Center on Leestown Road, building 27, room #003E. The current research team include Dr. Bazrgari (PI) and Dr. Wolfe (Co-Investigator), Dr. Salt (Research Staff), Clare Tyler (Research Staff), Allison King (Research Staff), Evan Brown (Research Staff), Amy Pohle (Research Staff), and Vanessa Ramirez, PT (Research Staff). Dr. Kryscio (biostatistics) will be included later on for statistical support.

The study will not involve accessing protected health information of participants.

Dr. Bazrgari, PI, will have the overall responsibility and will lead all aspects of the project including protocol implementation, data collection and analyses, computational modeling, results interpretation and dissemination. He will also be responsible for recruiting and training of research personnel who will be assisting with subject recruitment, data collections and analyses.

Dr. Wolfe, Co-Investigator, will provide specific contributions in recruitment, consenting and medical screening of potential participants to assure their overall eligibility (i.e., meeting the primary inclusion/exclusion criteria) for the study.

All Research Staff will assist with screening of potential participants, and will also contribute to experimental studies.

Clare Tyler will assist in subject recruitment, consenting, data collection and data analyses.

Dr. Kryscio will oversee our statistical analyses.

# 5.0 Study Procedures

## 5.1 Study Design

- **Study Design:**Describe experimental design of the study. Include sequential and/or parallel phases of the study, including durations, and explain which interventions are standard of care and which procedures are being done for research purposes.

This is a cross-sectional, observational study to investigate differences in **1)** active and passive aspects of lower back MB and **2)** spinal loads experienced during simulated daily activities between three veteran groups. Each participants will complete one data collection session during which they will complete a number of experiments and surveys.

- **Risk vs Benefit:** Include a description of how anticipated risk will be minimized and include an analysis of risk vs. potential benefit.

The potential risks of this study will be outlined in the informed consent document, and discussed with participants during the screening meeting. While the risk associated with the tasks performed during biomechanical assessment is no more than the risk experienced during daily life, some participants may experience muscle and/or joint soreness associated with the tests that are self-limiting and last a few minutes to a few hours. Mild discomfort may also occur during EMG preparation consisting of mild skin rubbing (with alcohol), possible shaving (with electric clippers), and the removal of adhesive tape holding the electrodes after test completion. The PI have run similar experiments with well over 100 healthy participants and 30 patients with LBP without any adverse incidents. Also, no injuries have been reported from similar measurements in the literature. Participants may feel unpleasant or uncomfortable answering some questions on the self-reported questionnaires. We will ensure participants that their answers are confidential and also inform them that they may choose not to answer any question.

Data security protections: To protect confidentiality, data on paper will be kept in locked filing cabinets and will be identifiable only by unique study ID numbers. Identifying participant information will be kept separate from other study-related materials. Computer files will be kept in password-protected computers with access restricted to the members of the study team who will use this information to recruit participants or obtain follow-up data. Computer files will also be backed up on a VA designated network location as well as on a VA-approved encrypted hard drive which will be used primarily for transfer of computer files between PI's VA and UK labs. No electronic data will contain participants' identifying information. Only study personnel who are approved by

Institutional Review Board will have access to the lab wherein all study equipment and materials are housed.

Emotional distress or sadness in completing self-report measures: In the event that answering any study questions elicits emotional distress or sadness, study personnel will assist participants to access counseling services through their primary care provider.

Biomechanical assessment: Risks of muscle strain and soreness during our proposed experimental tasks is considered low, as the movement associated with these tests is self-selected pace. Risks of skin irritation from the EMG electrodes will be minimized by asking the subjects if they are aware of any allergies or susceptibility to rashes. Research clinicians and biomechanical personnel conducting the tests will monitor participants closely and stop the testing procedure if safety is or is potentially compromised. Testing will also be terminated by participants or at the participant's request.

We have implemented all of the proposed biomechanical methods in this application in our earlier studies of asymptomatic individuals (see Research Approach). However, the proposed sudden perturbation and stress-relaxation tests will be done on patients with LBP for the first time in our lab. Similar tests on patients with LBP have been reported in the literature,[70-72] therefore, we do not expect failure in the conduct of the proposed tests. It is of note that our perturbation testing device has several redundant safety measures. Participants hold a safety switch, which must be depressed to activate testing equipment. Testing is immediately discontinued due to electrical power loss if the participant releases the safety switch. Participants will be instructed to release the switch and de-activate testing equipment if they experience discomfort during the perturbation. The perturbation test has a limit stop switch that cuts all power to the motor if the motor rotates more than 60 degrees past its normal range, limiting accidental perturbation to approximately 2cm. A manual emergency power switch is located on the front of the frame, reachable both by participants and study personnel, with additional power switches on the electrical power box and within the computer software that controls the motor. Finally during the stress-relaxation test, the participant's leg will be raised using a slow speed (3 deg/second) actuator which can be stopped immediately at subject's request.

Direct benefits to the subjects are minimal; in particular, there are no immediate health benefits of participating in the proposed study. A potential indirect benefit is further the understanding of LBP for patient veterans.

LBP is a significant health problem and is strongly associated with opioid use among veterans.[3-6] Despite decades of intensive research efforts, LBP persistence, recurrence, and transition from the acute to chronic stage is not managed effectively for majority of patients.[14-17] This clinical challenge arises, in part, because of the inability to determine the etiology of symptom (i.e., patients with non-specific LBP). The objective of this feasibility project is to verify the sensitivity of our biomechanical outcome measures for capturing potential differences in lower back mechanics between veterans with different LBP experiences. Successful completion of this project will warrant conduct of larger projects (i.e., using merit grant mechanism) to verify the role of lower back biomechanical abnormalities in LBP presentation. Given technological advances that have made biomechanical assessment more accessible, screening patients with non-specific LBP for biomechanical abnormalities can help reduce the possibility of symptom persistence and relapse due to excessive force and deformation experienced in spinal tissues. Improvement in clinical outcomes of treatment for non-specific LBP will diminish

reliance on opioids for the symptom management of particularly veterans with chronic LBP.

- **Patient Population:** Provide description of the study population (delineate all categories of subjects – patients, providers, family members, employees, etc.). Include anticipated enrollment numbers. How many participants.samples per group studies? Justify the sample size to obtain power for statistical analysis.

We will conduct a cross-sectional study involving three groups of research participants with and without LBP:

Group-1: Veterans with chronic, non-specific LBP and a Roland-Morris Disability Questionnaire (RMDQ) score of >12 (gender-balanced, n1=18)

Group-2: Veterans with chronic, non-specific LBP and a RMDQ score of ≤12 (gender-balanced, n2=18)]

Group-3: Asymptomatic veterans with no recent history of LBP (gender-balanced, n3=18)

Sample size justification: The purpose of this SPiRE project is to generate the required data for effect size calculation of future merit grants. In the absence of preliminary data from veterans with LBP, we calculated a sample size using effect sizes estimated from our earlier investigations of back-healthy individuals as well as reports of relevant measures in the literature. Based on our earlier studies of asymptomatic individuals,[56, 57, 66] a sample size of 10 would have a power of >80% for detection of significant ($p = 0.05$) differences in the proposed measures of lower back MB following acute exposure to awkward working posture. Further, using results in the literature,[67-69] a sample size (i.e., sum of two groups) of 18 was estimated to detect reported significant effect sizes between individuals with and without LBP with 80% power. Therefore, a sample size of 18 for each group is selected to facilitate sample size calculation and power analyses for our future merit grant applications while maximizing our chances of discovering potential differences in lower back MB and spinal loads between groups.

- **Vulnerable Populations:** As applicable, provide information on any added protections for vulnerable populations.

Not Applicable

- **Data and Specimen Banking:** If applicable include information on data and specimen banking.

Not Applicable

## 5.2 Recruitment Methods

- State how many subjects will be needed.
- Describe when, where, how and by whom potential subjects will be identified and recruited.
- Describe materials that will be used to recruit subjects, e.g., advertisements. Include materials as an appendix or separate attachment.

- Describe any payments to subjects, including the amount, timing (at the end of the study or pro-rated for partial study participation), method (e.g., cash, check, gift card), and whether subjects will experience a delay in receiving the payment.

We will recruit 54 gender-balanced veterans in the following three groups: 1) with chronic, non-specific LBP and a Roland-Morris Disability Questionnaire (RMDQ) score of >12 (n=18), 2) with chronic, non-specific LBP and a RMDQ score of ≤12 (n=18), 3) asymptomatic and no a recent history of non-specific LBP (n=18; serving as control group)

Participants will primarily be recruited from veteran populations receiving treatments at the Lexington VA Medical Center in Lexington, KY. This center has two facilities and several community-based clinics in the surrounding areas, and serves a population of more than 92,000 veterans. Veteran population in our local communities who do not receive care at the Lexington VA Medical Center will also be recruited. Dr. Wolfe (Co-I) from the Department of Physical Medicine and Rehabilitation, with assistance from Vanessa Ramirez (Clinical Research Assistant), will lead our patient recruitment efforts.

Recruitment will be done between months 6 and 18 of the project period. During this period, PI and Co-I will meet providers that see patients with LBP to seek their assistance in identification of patients with LBP. This will include, but not limited to, primary care physicians, physical therapist, chiropractors, acupuncturists, and etc., to inform them about the study and target patient population. These providers will be asked to inform their potentially eligible patients about our study and give them our IRB approved recruitment flyer. In addition to posting flyers in these clinics, we will have one of our research staff to be present in select days to provide more information to the interested patients. We will also distribute our study flyers to local institutions that serve Veterans. The distribution of study flyers will also include the use of listservs that will be sent to Veterans who are studying at the University of Kentucky.

The recruitment flyer describes the main inclusion/exclusion criteria, contact information of the PI, location and duration of experiments and the amount of compensation.

Participants will be compensated for their time and efforts in participating in the study for a total of $40.

## 5.3 Informed Consent Procedures

- Indicate if informed consent will be obtained and/or if you are requesting a waiver of informed consent or waiver of documentation of informed consent. If the research involves multiple phases, specify for which phases of the research the waiver(s) is being requested and/or the informed consent will be sought.

- Describe who will be obtaining informed consent, if applicable, and any circumstances that may need to be addressed (e.g. subjects with impaired decision making ability and the use of a legally authorized representative, etc.)

- If applicable, indicate how local site study personnel will be trained regarding human subjects protections requirements and how to obtain and document informed consent.

This project requires written documentation of informed consent from all study participants. Approval of the informed consent document, the study protocol, and recruitment materials will be obtained before data collection begins. During the informed consent process, research personnel will explain the handling of data and personal health information and guide potential participants through the study consent form. Additionally, study staff will explain the study requirements and provide a study flow chart and information sheet to the potential participant. This will include an explanation of the interview time commitments and biomechanical assessments, potential risks of participation, potential benefits of participation, what to do if an adverse event occurs, and the option for discontinuation of study participation. Participants will be informed that they may choose to stop participating in the study at any stage. Once informed consent is administered, both the participant and research personnel will sign and date the consent form. A copy of the consent form will be provided to the participant.

Finally, all study personnel will have up-to-date training in human subject's protection and study procedures.

## 5.4 Inclusion/Exclusion Criteria

- Describe the criteria that determine who will be included in or excluded from the study.

| **Inclusion/Exclusion Criteria** | | | |
|---|---|---|---|
| | Group-1 | Group-2 | Group-3 |
| Current condition | Non-specific LBP | Non-specific LBP | Asymptomatic |
| LBP Experience | Chronic* | Chronic* | No recent history |
| RMDQ score | >12 | ≤12 | N/A |
| Pain severity (0-9) | ≥2 | ≥2 | N/A |
| Inclusion criteria | • Age between 21 and 70 years old<br>• Body mass index between 18 and 32 | | |
| Exclusion criteria | • Any spinal surgery *[e.g., spinal fusion surgery*]<br>• Any abnormalities in lower extremity joints due to disease or injury that would likely affects lower back mechanics [*e.g., lower limb amputation or peripheral arterial disease*]<br>• Any safety concern [*e.g., pregnancy*]<br>• Any medical condition for which we can't determine the impact of our experimental procedures. [*e.g., we don't know whether our measurement instrument will affect pacemakers.*]<br>• Inability to read or verbally comprehend English<br>• Unwilling or unable to comply with study protocol<br>• Retention of legal advice or an open / pending legal case related to | | |

| | LBP |
|---|---|
| • *Definition recommended by the NIH task force on research standards for chronic LBP will be used: a pain in the lower back on more than half of days over the past 6 months*. | |

Eligibility of participants will be determined in a two-step screening procedure involving an initial brief screening followed by an on-site screening. The brief screening will be done over phone for participants who contact the study personnel via information given in the flyer or it will be done in the clinic by the research staff who will be present in clinic for participant recruitment. During the brief screening an overview of study objectives and procedures will be provided, and the following provisional eligibility criteria will be verified:

- Age between 21 and 70 years
- Body mass index between 18 and 32, calculated using self-report of weight and height
- Current, a recent history, or no recent history of LBP
- Any spinal surgery *[e.g., spinal fusion surgery*]
- Any abnormalities in lower extremity joints due to disease or injury that would likely affects lower back mechanics [*e.g., lower limb amputation or peripheral arterial disease*]
- Any safety concern [*e.g., pregnancy*]
- Any medical condition for which we can't determine the impact of our experimental procedures. [*e.g., we don't know whether our measurement instrument will affect pacemakers*.]
- Inability to read or verbally comprehend English
- Retention of legal advice or an open / pending legal case related to LBP

Those who are provisionally eligible and still interested will then complete an on-site screening, consisting of informed consent process and final eligibility screening. Dr. Wolfe (Co-I) will oversee the on-site screening. Dr. Bazrgari (PI) together with Dr. Wolfe (Co-I) will then review the results of each screening and decide about the eligibility of the participants. Participants deemed eligible will be scheduled for the data collection which can also take place immediately after eligibility determination. The study will be conducted in a newly developed lab for studies of the human musculoskeletal biomechanics that will be directed by Dr. Bazrgari.

## 5.5 Study Evaluations

- Describe all evaluations to be conducted (including screening; tests/questionnaires that will be administered; any procedures that subjects will be required to complete) and data collection methods. Include materials as an appendix or separate attachment.

In each data collection session, participants will first be instrumented with sensors to enable measurement of kinematics and muscle activity, similar to procedures we used in our earlier studies.[70-73] Specifically, wireless inertial measurement units (Xsens MTW, Xsens Technologies, Enschede, Netherlands)[74] will be used to measure rotations of the thorax and pelvis, and surface EMG electrodes will be used to measure the activity of erector spinae, rectus abdominus, internal and external obliques. Participants will then be asked to stand on a force plate and perform a forward bending and backward return test.[38, 72, 75] Participants will be instructed to bend from an upright standing posture to their maximum comfortable forward bending posture and then return to the upright posture at a self-selected pace. Participants will then be instructed to perform the following activities of daily life at a self-selected pace: walking on level[76, 77] surfaces, sit-to-stand and stand-to-sit motions,[79] and lowering and lifting a 10 lb load to their knee height.[80] These activities have been selected because they represent basic

but repetitive activities of daily life, and we have successfully used them in our earlier investigation of spinal loads among asymptomatic non-veterans, as well as persons with unilateral lower limb amputation. Finally, sudden perturbation followed by stress-relaxation tests will be conducted as in earlier studies and as explained below. Each of the above tests will take less than 5 minutes, and we will provide break periods between each set of tests to minimize fatigue and discomfort.

In preparation for future projects, we will also administer the following questionnaires that are relevant to LBP experience during the data collection session: 1) comprehensive health status using the PROMIS-29 questionnaire[81] ([*all participants*]), 2) survey of habitual physical activity[82] (all participants), 3) the short version of Copenhagen Psychosocial questionnaire concerning work and non-work-related factors[83] (all participants), [*4) the minimum data set recommended by the NIH task force on research standards for chronic LBP (only veterans with LBP)*], 5) pain intensity using a numerical rating scale[84] (only veterans with LBP), 6) LBP-related disability using the 24-item Roland Morris Disability Questionnaire[85] (only veterans with LBP), 7) the fear-avoidance beliefs questionnaire[86] (only veterans with LBP), pain catastrophizing scale questionnaire (only veterans with LBP), and pain self-efficacy questionnaire (only veterans with LBP). Total time for the entire data collection session, including the instrumentation time, is estimated to be less than 3 hours.

*Characterization of lower back MB:* Sudden perturbation and stress-relaxation tests will be used to characterize [*bulk*] active and passive aspects of lower back MB. Sudden perturbation tests will be conducted in a displacement-control manner that we have developed, which provides separate quantification of both active reflexive and intrinsic stiffness of the lower back.[71, 73] Here, intrinsic stiffness refers to aspects of lower back MBs that are quantified during the reflex delay period (i.e., between perturbation onset and reflexive muscle response), and which incorporate both passive and active contributions of lower back tissues. However, the passive contribution of tissues to intrinsic stiffness in upright standing posture (i.e., the position used in our experimental setting) is minimal;[87] therefore, intrinsic stiffness primarily reflects the contribution of background muscle activities.

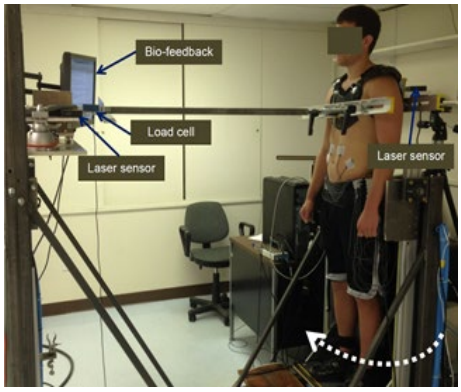

**Figure 1.** Setup for the trunk perturbation and stress-relaxation tests.

During the sudden perturbation test, participants will stand in a metal frame that restrains the pelvis and lower limbs [*to isolate the lower back response*] (**Fig. 1**). Horizontal position perturbations, generated by a servomotor (Kollmorgen AKM53K, Radford, VA, USA), are transmitted to the trunk (T8) via a rigid harness-rod system. A one-minute sequence of anteroposterior trunk displacements (± 5 mm) is induced with a pseudo-random set of delays between each. The driving force during the perturbations will be measured using an in-line load cell (Interface SM2000, Scottsdale, AZ, USA) located next to the motor, whereas the resulting kinematics (small displacements with high accelerations) will be measured using two laser displacement sensors (Optex FA, Kyoto, Japan), with one targeting the back of the harness at the T8 level, and the other targeting the load cell.

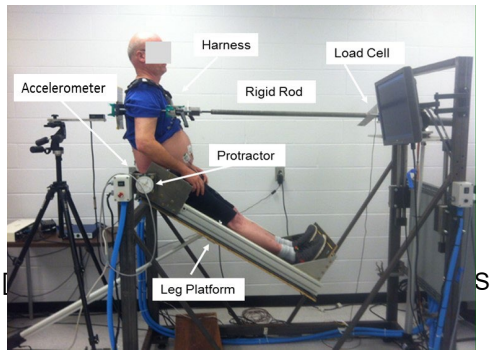

**Figure 2.** Setup for the trunk stress-relaxation tests.

The sudden perturbation frame is designed so that trunk flexion can be achieved by raising the participant's legs/pelvis using an actuator (**Fig. 2**); rotation of the lower body is about the L5-S1 while the trunk is kept upright. Accordingly, the stress-relaxation tests will be conducted in the same setup used for the perturbation tests, by

rotating the participant's legs around his/her lower back using an actuated platform.[70, 88] The lower extremities and the pelvis of participants will be constrained to the platform and the thorax position will be fixed (**Fig. 2**). Therefore, the amount of lumbar flexion will be the same as the amount of platform rotation. During stress-relaxation tests, we will specifically rotate the leg platform to the extent that it generates 70% of the lumbar flexion angle that can be achieved during a trunk forward bending and backward return activity, as described in §2.6. This posture will be maintained for 4 minutes, during which trunk resistance (via load cell) will be measured. We have extensively used the methods proposed here in our earlier studies of asymptomatic individuals [56, 57, 70, 88] and persons with unilateral lower limb amputation.[55] Our sudden perturbation and stress-relaxation tests yield excellent within-day (ICC>0.85) and moderate-high between-day (ICC=0.5-0.8) reproducibility of measures of lower back MB.[66]

*Estimation of spinal loads:* The computational strategy that will be used to estimate spinal loads is our non-linear finite element (FE) model of the spine that, accounting for passive contribution of lower back tissues, can estimate the required muscle forces to complete a particular task using an optimization-based iterative procedure.[89] This advanced kinematics-driven FE model can provide a more nuanced approach to revealing the foundations of spinal loads in relation to LBP, and addresses several important shortcomings of existing models. For instance, geometrical nonlinearities have been included in our model by representing the spine as a set of flexible beam elements that mimic intervertebral discs and rigid elements that mimic the thorax and lumbar vertebrae (**Fig. 3**). Material nonlinearities are also considered in our model by incorporation of intervertebral disc stiffness using nonlinear axial compression-strain relationships, along with moment-rotation relationships in the sagittal/coronal/transverse planes that have been obtained from earlier numerical and experimental studies of lumbar spine motion segments.[90-92]

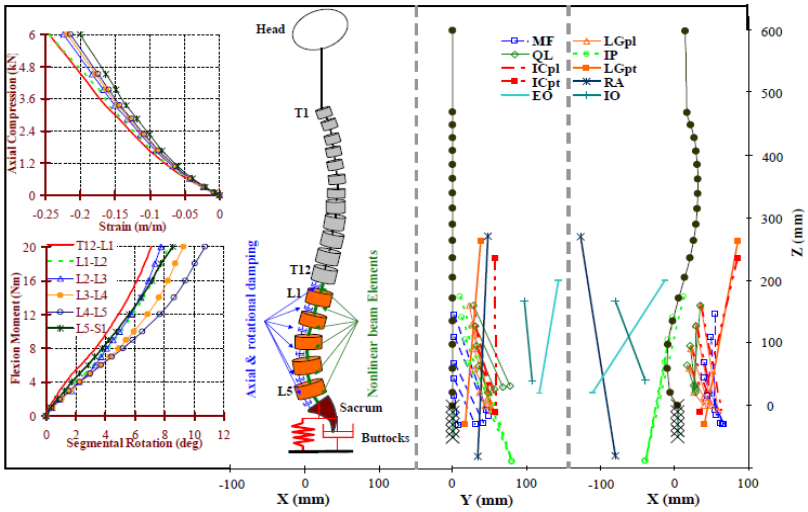


**Figure 3.** FE model of the trunk. Spine geometry and material properties (left), and lateral/sagittal views of muscle architecture (right).

Other modeling approaches generally predict trunk muscle forces on the basis of satisfying equilibrium at only one spinal level (i.e., often at the L4-L5 or L5-S1),[64, 93, 94] and therefore result in the prediction of muscle forces that violate equilibrium requirements at other spinal levels.[95] In our improved model, muscle forces are estimated such that equilibrium requirements are satisfied across the entire lumbar spine. Our model also includes a detailed trunk muscle architecture (**Fig. 3**), wherein muscle wrapping around underlying tissues is considered.[96] The muscle architecture in our computational model includes 56 muscles (**Fig. 3**); 46 muscles connecting the lumbar vertebrae to the pelvis (i.e., local muscles), and 10 muscles connecting the thoracic spine/rib cage to the pelvis (i.e., global muscles). To determine the required muscle forces for the satisfaction of equilibrium across the entire lumbar spine, segmental kinematics in the lumbar region are required. Since only whole-body level kinematics data are available from experimental measurements, a heuristic optimization procedure will be used with our model to determine a set of segmental kinematics in the lumbar region (i.e., from L1 to L5), such that the corresponding set of predicted muscle forces minimize a cost function.[97] The cost function that will be used for this heuristic optimization procedure will be the sum of squared muscle stress

across all 56 lower back muscles. We have recently published a detailed description of this procedure in Journal of Biomechanics.[97] Predictions of lumbar segmental kinematics from this model provide good-excellent agreement with those from image-based measurements.[97] The associated muscle forces with the optimal local kinematics will then be used to determine spinal loads at all lumbar levels. This heuristic optimization procedure was developed in Matlab (The MathWorks Inc., Natick, MA, version 7.13), and FE simulations will be conducted in Abaqus/CAE (Version 2018, Dassault Systemes Simulia, Providence, RI).

We have used our FE computational model extensively to study occupational risk factors for LBP, including manual material handling,[35, 98] trunk motion at different velocities,[89] whole body vibration,[99] impact,[100] and sudden loading/unloading.[101, 102] The bio-fidelity of our model-based predictions of trunk muscle forces and spinal loads has been demonstrated both in static and dynamic situations. More specifically, good-to-excellent correlations were found between model predictions and measured trunk muscle activity (R>0.7),[101] with measured ground reaction forces (R>0.8),[89] and with measured trunk resistance to sudden loading (R>0.8 unpublished data from[103]). In an ongoing collaboration with Walter-Reed National Military Medical Center, we are using our model to estimate spinal loads in service members with and without unilateral lower limb amputation while they performed activities similar to those proposed in this project.[76-79]

*Data analyses- Aim-1:* From the perturbation tests, we will obtain three outcome measures: reflex latency (t), intrinsic stiffness ($K_{IN}$), and maximum reflexive force ($F_{REF}$). Latency of reflexive responses of trunk muscles will be estimated using a system identification approach and by relating muscle activity to trunk displacement.[71] Intrinsic stiffness will be estimated using a system identification procedure, and by relating trunk kinematics with trunk kinetics, respectively, from displacement sensors and load cell obtained during the latency period.[73] To obtain the maximum reflexive force, the reflexive responses of lower back will be estimated by subtracting the intrinsic response from the measured trunk response (i.e., reaction force from load cell) over a time window between the end of latency period and 150 msec post perturbation.[57] From the stress-relaxation test, we will obtain the average passive stiffness ($K_p$) and viscoelastic relaxation (R) of lower back tissues as shown in **Figure 4**.[70, 88]

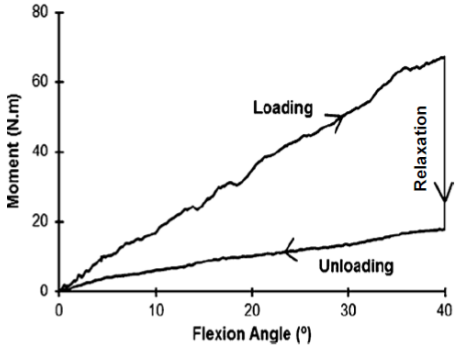


**Figure 4.** The slope of loading side and the moment drop on the relaxation sides of curve denote respectively average passive stiffness ($K_{ave}$) and viscoelastic relaxation (R). Adopted from ref #66.

*Data analyses-Aim-2:* Outputs of FE simulations of daily activities will include forces in 56 trunk muscles and spinal loads at all lumbar spine levels.[98, 99, 102] These outputs will be estimated for each instance of each simulated activity described in §2.6. To facilitate quantitative comparison, and considering that maximum spinal load at each instant often occurs at the lowermost level of the lumbar spine, we will extract the maximum spinal load experienced at the L5-S1 level during each activity. The measure of spinal load for each participant will then be calculated as follows for statistical analyses: $SL = norm\left(\sum_{activity=1}^{5} SL_{activity}\right)$ wherein *norm* denotes the magnitude of vector summation and $SL_{activity}$ denotes the maximum spinal load under each activity.

## 5.6 Statistical Analysis

- What statistical test will be done?
- Provide sample size determination and analysis (include anticipated rate of screen failures, study discontinuations, lost to follow-up etc.).
- Describe how, where and by whom the data will be analyzed.

For each measure (i.e., reflexive latency, intrinsic stiffness, reflexive force, passive stiffness, and stress relaxation from Aim 1, along with the spinal load, *SL*, from Aim 2), we will run a univariate analysis of variance to verify potential differences between study groups (i.e., independent factor: participant group with five levels). A significant ANOVA will be followed with post-hoc pairwise comparison using Bonferroni's procedures. Prior to these analyses, parametric assumptions will be evaluated. As needed, data transformations will be used, or a non-parametric approach will be employed.

The statistical analyses will be led by the PI will be overseen by Dr. Kryscio

## 5.7 Withdrawal of Subjects

- Describe any anticipated circumstances under which subjects will be withdrawn from the research without their consent.
- Describe the consequences of a subject's decision to withdraw from the research and the procedures for orderly termination of participation by the subject (e.g., the subject contacting the investigator for an end-of-study visit).

Except for the noted exclusion criteria, there is no other anticipated circumstances for subject withdrawal.

Participants will complete a screening session upon completion of the consenting procedure and then will participate in one data collection session if determined eligible. Since it is most likely that the screening and data collection take place in the same visit, there is no specific procedure for withdrawal from the study but to inform the research personnel that they are no longer willing to complete the study.

## 5.8 Expected Results

- Based on literature and hypothesis, what can be expected?
- Alternative Hypothesis if main hypothesis is not confirmed.

This is a feasibility project and doesn't involve a specific hypothesis (per SPiRE mechanism guidelines). The followings are, however, our expected findings: Given the reported differences in physical performance between individuals with and without LBP, we expect differences in spinal loads experienced during daily activity between these groups. Considering the high rate of LBP recurrence, we specifically expect those with LBP (or a recent history LBP) to experience larger spinal loads. Furthermore, we expect differences in lower back MB between veterans with chronic and non-chronic LBP. These differences will support future longitudinal research to verify whether they are developed during transition to chronic LBP. Therefore,

successful completion of this feasibility project will pave the way for future studies (merit grant applications) that will verify the role of abnormalities in lower back MB and spinal loads in the clinical presentation of LBP. Such an understanding has the potential to help the affected veterans, particularly those with disabling non-specific LBP.

## 6.0 Reporting

- Include procedures for reporting unanticipated problems, serious adverse events, and protocol deviations.

Reporting for this study will include an annual report to the VA IRB, regulatory and sponsoring agencies at a minimum, with appropriate updates and reports in the event of unanticipated adverse event(s). This project represents no more than minimal risk as they involve activities participants do during daily life. Further, we do not anticipate moderate, severe, life-threatening or fatal adverse events. The PI is responsible for reporting adverse events to the research team and to the IRB. Mild adverse events will be reported within 10 working days of the occurrence; moderate, severe, life-threatening or fatal adverse events will be reported within 48 hours of the occurrence.

## 7.0 Privacy and Confidentiality

- **Data Collection:** List sources/procedures for which data will be collected, transmitted, stored, maintained and/or shared.
- Describe whether the study will use or disclose subjects' Protected Health Information (PHI).
- Describe the steps that will be taken to secure the data (e.g., training, authorization of access, password protection, encryption, physical controls, Certificates of Confidentiality, and separation of identifiers and data)

Research material obtained for biomechanical assessment during proposed biomechanical tests includes non-invasive measures of muscle activity (EMG), kinetics and kinematics. Patient health-related data such as psychological characteristics, pain, disability, medication use, and health care utilization will be obtained by in-person interviews, self-reporting questionnaires, and/or examinations. All data used for this project will be obtained only after receiving written informed consent from the participant.

We will not collect any PHI

To protect confidentiality, data on paper will be kept in locked filing cabinets and will be identifiable only by unique study ID numbers. Identifying participant information will be kept separate from other study-related materials. Computer files will be kept on a password-protected computer with access restricted to the members of the study team who will use this information to recruit participants or obtain follow-up data. Backups of computer files will be saved on a VA-designated network space as well as on a VA-approved encrypted hard drive. The latter will primarily be used for the transfer of computer files between the PI's lab at VA and University of Kentucky. No electronic data

will contain participants' identifying information. Only study personnel who are approved by Institutional Review Board will have access to the lab wherein all study equipment and materials are housed.

## 8.0 Communication Plan

- Include plan for ensuring all required local site approvals are obtained and notifying the Director of any facility where the research in being conducted but the facility is not engaged.
- Include plan for keeping all engaged sites informed of changes to the protocol, informed consent, and HIPAA authorization
- Include plan for informing local sites of any Serious Adverse Events, Unanticipated Problems, or interim results that may impact conduct of the study.
- Include plan for ensuring the study is conducted according to the IRB-approved protocol.
- Include plan for notifying all local facility directors and LSIs when a multi-site study reaches the point that it no longer requires engagement of the local facility (e.g., all subsequent follow-up of subjects will be performed by the PI from another facility).

This project is a single site project wherein a single group of researchers (PI, Co-I, and research staff) performs all recruitments, screening, data collection and analysis. Any potential changes to the protocol will be discussed during weekly lab meetings. Considering the above described reporting, research personnel will be trained to recognize, respond to, and record adverse events when they occur or immediately after they occur to insure the safety of the human subjects; and to report adverse events to the PI in a timely manner to insure compliance with institutional policies on human subject protection. Research assistants engaged in data collection will contact the PI as soon as an adverse event occurs.

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