Title	Recovery From a First-Time Lateral Ankle Sprain and the Predictors of Chronic Ankle Instability: A Prospective Cohort Analysis
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ABSTRACT

Background: Impairments in sensorimotor control may underpin the paradigm of "Chronic ankle instability" (CAI) that may develop in the year following an acute lateral ankle sprain (LAS) injury. No prospective analysis is currently available which has sought to identify the mechanisms by which these impairments develop and contribute to long-term outcome following LAS.

Purpose: To identify the sensorimotor deficits predicating CAI outcome following a first-time LAS injury

Study Design: Cohort study

Methods: Eighty-two individuals were recruited after sustaining a first-time LAS injury. Several biomechanical analyses were performed on these individuals completing five movement tasks at three time-points: 1) 2-weeks, 2) 6-months and 3) 12-months following LAS onset. A logistic regression analysis of several 'salient' biomechanical parameters identified from the movement tasks, in addition to scores from the Cumberland Ankle Instability Tool (CAIT) and Foot and Ankle Ability Measure (FAAM) recorded at the 2-week and 6-month time-points, were utilised as predictors of 12-month outcome (CAI or LAS "coper").

Results: 40% of participants who completed the study protocol developed CAI with the remaining 60% being designated as LAS "copers". Preliminary analyses revealed that the deficits exhibited by the CAI group during one of the movement tasks [reach distances and sagittal plane joint positions at the hip, knee and ankle during the Star Excursion Balance Test (SEBT)] and their scores in the activities of daily living subscale of the FAAM at the 6-

month time-point had potential to be predictive of long-term outcome. When entered into the prediction equation, these outcomes correctly classified 84.8% of cases (sensitivity: 75%, specificity 91%; $P < 0.001$).

Conclusion: Poorer dynamic postural control as measured with the SEBT and poorer self-reported function as measured using the activities of daily living subscale of the FAAM 6-months following a first-time LAS are predictive of eventual CAI outcome.

Clinical Relevance: Individuals who exhibit deficits during the SEBT with reduced reach distances and impaired range of motion at the hip, knee and ankle joints, and who report poorer function based on the activities of daily living subscale of the FAAM 6-months following a first-time LAS are more likely to develop CAI.

Key terms: ankle joint [MeSH]; biomechanical phenomena [MeSH]; kinematics [MeSH]; kinetics [MeSH]; postural balance [MeSH]; ankle instability [MeSH].

What is known about the subject: Previous cross-sectional studies have established that individuals with Chronic Ankle Instability exhibit poorer performance during the Star Excursion Balance Test and report poorer function on the basis of the Foot and Ankle Ability Measure.

What this study adds to existing knowledge: Due to its design, this is the first study to establish that some of the deficits that have previously been documented in participants with Chronic Ankle Instability are actually predictive of this outcome when identified earlier in the disease process.

INTRODUCTION

Acute sprain of the ankle joint represents a significant risk for participants of a diverse range of activities, with lateral ankle sprain (LAS) constituting the most prevalent sub-classification of this injury[13]. Despite its high incidence[13], LAS is typically regarded as an innocuous injury that resolves readily with minimal treatment[38].

The inaccuracy of this perception[22] should be of particular pertinence to healthcare practitioners as the first incurrence of LAS is a potential 'gateway' to an array of chronic symptom sequalae in the year following[23-25]. Freeman et al. were the first to propose that this gateway was erected primarily on a foundation of local "articular deafferentation" at the ankle joint; that damage to local sensory receptors following LAS creates a proprioceptive deficit which impairs the central nervous system's ability to accurately position the ankle joint during movement[17-19].

This 'feedback' model of chronicity has since evolved and expanded to included 'feed-forward' mechanisms of sensorimotor control[35,41] and the capability (or indeed, incapability) of the nervous system to exploit motor control degeneracies [8,16,32,34,47,50] in the fulfilment of required movements. Still, it is accepted that anomalous movement patterns are at the crux of the LAS injury paradigm, the chronic symptoms of which are now universally described by the term "Chronic Ankle Instability" (CAI)[9,23-25].

In 2008, Hertel suggested that CAI is belied by a range of motor control deficits which should be evaluated along a continuum of sensorimotor measures[29]. His proposition was that this would accommodate the formulation of a robust theoretical model which could delineate the contributory factors of CAI and on which the basis of its conservative management be developed[23-25,29]. A 'spectrum' of human movement comprises a section of the continuum, and researchers have sought to identify movement pattern anomalies in cohorts with CAI across this spectrum: during static[31,50,54] (ref) and dynamic[26,27,30,37] (ref) postural control assessments, gait[7,11,14,39](ref), and jumping/landing[10,11,48,55](ref) tasks. Consequently, the gateway to CAI is considered to be partially composed of the anomalous movement patterns to which individuals ‘fall victim’ in the year post-injury. This hypothesis is borne out of the existence of a group who exhibit no such movement aberrancy with symptom recurrence[3,52]: LAS ‘copers’. ‘Copers’ represent the ‘polar’ end-point to CAI participants in the LAS injury paradigm[23-25,52]: it has been theorized that they are better able to exploit kinematical degeneracies[21] following LAS in the formulation of movement strategies appropriated to the post-injury composition of their motor apparatus[52], a feat their chronically impaired counterparts are unable to realize. This is evidenced by a number of observational analyses which have identified differences between copers and participants with CAI across the movement spectrum[3,4,54-56](refs).

Importantly however, it is unknown whether the conglomeration of movement patterns that characterise these groups in this spectrum is a manifestation of their outcome or contributed to it. Currently, no prospective analysis tracking an LAS population during their settlement into the dichotomous outcomes of CAI or LAS coper status is available. A collection of exploratory reports from our laboratory were intended to culminate in such an analysis. These reports have documented separate observational evaluations of participants with LAS completing tasks across the spectrum of human movement. Specifically, participants were recruited after sustaining a first-time LAS and required to complete static and dynamic balance assessments, and gait, jumping and landing tasks. Biomechanical evaluations of participants performing each task were completed first within 2-weeks of injury occurrence, and then 6- and 12-months following.

By extracting the most ‘salient’ biomechanical outcomes from these reports, the objective of the current prospective cohort study is to identify which of the anomalies across the movement spectrum exhibited within 2-weeks and 6-months of injury contribute to final outcome (CAI or coper, determined at the 12-month time-point). Our hypothesis was that 12-month outcome is belied by deficits across the spectrum of the movement patterns analysed, that CAI is underpinned not by one anomalous movement pattern during one of the prescribed movements, but a group of movement anomalies in the postural control, jumping/landing and gait tasks combined[29]. We further hypothesise that the self-report rating scales of ankle joint function and disability utilised at each time-point would be of predictive value.

MATERIALS AND METHODS

Study design

1-year cohort study

Participants

Eighty-two participants were recruited at convenience from a University-affiliated hospital emergency department (ED) within two weeks of sustaining an acute first-time LAS injury. All LAS participants were provided with basic advice on applying ice and compression for the week on discharge from the Emergency Department. Activities of daily living were encouraged: participants were instructed to weight-bear and walk within the limits of pain when possible. An additional cohort of twenty non-injured participants was recruited at convenience from the hospital catchment area using posters and flyers to act as a control group. All participants were recreationally active.

Recruitment for the current study was completed between March 1st, 2012 and September 29th, 2013.

Participant demographics for the LAS and control groups are presented in Table 1. Exclusion criteria for participants of the current study are presented in Table 2.

The Human Research Ethics Committee of the university where the study was completed approved this research. All participants signed an informed consent form prior to testing.

<u>Design</u>

As part of this prospective cohort study, LAS participants were required to attend the University biomechanics laboratory at three time-points to complete the same experimental protocol: 1) within 2-weeks of injury (time-point 1), 6-months (+/- 1 week of recruitment) following injury (time-point 2), and then 12-months (+/- 1 week) following injury (time-point 3). At the 12-month time-point, the LAS cohort was stratified into CAI and LAS 'coper' groups [52]. Whether LAS participants sought additional rehabilitative medical services for the treatment of their injury was recorded ("yes" or "no") at time-point 3.

The control group of participants attended the laboratory on a single occasion within 2-weeks of recruitment.

In a series of separate exploratory reports, the control cohort was compared to the LAS cohort at the 2-week and 6-month time-points, and to the CAI and 'coper' groups at the 12-month time-points (refs). A pictorial representation of this experimental design is depicted in the supplementary documents (Figure S1).

The current investigation will use these exploratory reports to identify suitable ('salient') input variables for a regression analysis to predict final outcome (CAI vs coper) at the 2-week and/or 6-month time-points.

A table of operational definitions relevant to the above paragraphs is available in the supplementary documents (Table S1).

The dependent variables for this prospective analysis were divided into three groups: questionnaire, biomechanical and performance.

<u>Dependent variables</u>

Questionnaires

Self-reported ankle instability and ankle joint function were assessed and documented for all participants at each visit to the biomechanics laboratory using the Cumberland Ankle Instability Tool (CAIT) [23,59] and the activities of daily living and sports subscales of the Foot and Ankle Ability Measure (FAAMadl and FAAMsport) [23] respectively. Furthermore, participants' designation as CAI or LAS coper status at time-point 3 was completed on the basis of the CAIT [23-25]: participants with a CAIT score of <24 were designated as having CAI while participants with a CAIT score ≥24 were designated as LAS "copers"[59].

Biomechanical

Following completion of the questionnaires, participants were instrumented with the Codamotion bilateral lower limb gait setup (Charnwood Dynamics Ltd, Leicestershire, UK) which relayed marker data to 3 Codamotion cx1 units during the experimental protocol. The Codamotion setup was fully integrated with two AMTI walkway-embedded force plates (Watertown, MA) and time synchronized for the experimental protocol. This allowed construction of lower limb link-segment model in the Codamotion software for biomechanical (kinematic and kinetic) analyses. Force plate data were integrated with kinematic data using an inverse dynamics procedure to calculate joint moments[58].
Ground reaction force (GRF) and centre of pressure (COP) data were also acquired. A neutral stance trial was used to align each participant with the laboratory coordinate system and to function as a reference position for subsequent kinematic analysis [60]. This was performed for all participants at each visit to the laboratory. A full description of this Codmation setup and link segment model construction with inverse dynamics is published in greater detail elsewhere[40], and is separately reported in the exploratory analyses (refs).

Participants were familiarised with experimental protocols prior to commencement. Following familiarisation, participants attempted (injury and/or ability permitting) to complete a protocol of five movement tasks which were considered to detail comprehensively the spectrum of human movement. The five movement tasks utilised for evaluation were as follows: single-limb stance (SLS) (eyes-open and eyes-closed), the anterior (ANT), posterior-lateral (PL) and posterior-medial (PM) components of the Star Excursion Balance Test (SEBT), a single-leg drop land (DL), a drop vertical jump (DVJ) and gait. All unilateral tasks (SLS, SEBT and DL) were completed on both the limb affected by the initial LAS (designated the 'Involved' limb) and the contralateral limb (designated as the 'Uninvolved' limb). The tasks were completed in the order they are described above. The experimental protocol for each task is described in Table 3. A pictorial representation of the biomechanical dependent variables for each task is available in Figure 1 and definitions of these are presented in Table 4. A thorough description of the biomechanical dependent variables relevant to each task is presented in the supplementary documents (Table S2). Experimental procedures (including data acquisition and management) for each task at each time-point have been previously documented (refs). All tasks were completed in the barefoot condition.

Performance

The performance related dependent variables for this investigation were scores accomplished in an assessment of ankle dorsiflexion range of motion (ROM) (the knee to wall test as described by Denegar et al.[12]), and during the reach attempt for the specified components of the SEBT at each time-point. To determine the ankle dorsiflexion ROM, the mean value (of 2 knee to wall test measures) was calculated separately for each limb at each time-point. Reach distances during the SEBT were averaged across the three completed trials for each participant at each time-point, and normalised to leg length prior to data aggregation and analysis [28].

Data management and statistical analysis

In the exploratory reports of each task at each time-point (refs), dependent variables were calculated separately for every task attempt and averaged across the required number of task repetitions. Group mean profiles were subsequently calculated and compared. In all data analyses, the involved and uninvolved limbs of each group (LAS/CAI vs control/coper) were analysed.

In attempting to identify the predictors at time-point 1 and/or time-point 2 of CAI/coper status (which was confirmed at time-point 3), our approach consisted of a three step process: 1) identify the 'salient' biomechanical dependent variables for regression analysis; 2) prepare these variables for regression (including missing value analysis and dimension reduction); 3) perform regression analysis in a model that also includes questionnaire and performance dependent variables where appropriate. This statistical analysis model for the biomechanical group of dependent variables is described in Table 5.

To complete the first step, we first to extracted the results for the biomechanical dependent variables of the exploratory case-reports from the three time-points (refs). The specifics of this extraction process are detailed in the supplementary documents of this article (Methods S1). The extracted variables are presented for time-point 1 in Figure 2, for time-point 2 in Figure 3 and for time-point 3 in Figure 4. In summary, this process identified twenty-one 'salient' biomechanical dependent variables for the commencement of step 2. These 'salient' biomechanical variables are described in Table 6, and are herein referred to using their tabular numerical value (#1to #21).

Step 2 (preparation of the identified variables for regression) was necessary because a notable proportion of biomechanical data were missing at time-points 1 and 2, and because of the large number of identified salient dependent variables, which was potentially problematic for statistical power in any regression analyses.

Of the participants that attended the laboratory at each time-point, complete datasets were available only for the questionnaire group of dependent variables. With regard to task performance and the biomechanical groups, a frequent occurrence was that participants were unable to complete the prescribed task. These occurrences varied according to each time-point: at time-point 1, injury severity was the primary reason cited predicating an inability to complete a given task, while at time-point 2, task difficulty was alluded to most commonly by participants. Such instances manifested in incomplete data sets, one at the single-subject level (wherein the movement spectrum was only partially evaluated for an individual participant) and the other at the group level (wherein data for a given task was only representative of those participants actually able to complete that task). To accommodate missing data values a multiple imputation procedure was implemented. This served the dual purpose of limiting bias associated with some participants being unable to complete a task (assuming these participants were a random subset of the total cohort) and allowing for dimension reduction procedures to be completed for the salient biomechanical dependent variables. We adopted two pre-requisites for imputation eligibility. At the single-subject level, 60% data availability was required for each participant during all five tasks. At the group level, 60% data availability for a given task was required from the total study cohort. Therefore, if data were unavailable for ≥40% of variables for one participant, that participant was not considered for data imputation and if ≥40% of participants were unable to complete a task, this task (and its associated biomechanical parameters) was not considered.

Based on these criteria, sixteen individuals were removed from analysis at time-point 1 and four were removed from time-point 2. Furthermore, of the total of twenty-one ‘salient’ biomechanical dependent variables, those relating to the DL (3), DVJ (3) and eyes-closed SLS (2) tasks from time-point 1 and eyes-closed SLS (2) from time-point 2 were removed from analysis (Table 6). The methods for imputing missing salient biomechanical dependent variable data are presented in the article supplementary material (Methods S2).

After imputation, the complete data set were subjected to a principal components analysis to reduce their dimensionality. Specifically, the thirteen remaining variables at time-point 1 and the nineteen remaining variables from time-point 2 were considered ‘latent’, and reduced into significant ‘factors’ where possible. This was performed separately for the 2-week and 6-month time-points due to differences in data availability.

Preliminary analyses (scree test and parallel analysis) informed our decision to retain two factors for time-point 1 and three factors for time-point 2. With regards to the PCA for time-point 1, outcome #11 had low communality (<0.3) to both factors and outcome #20 was factorially complex. At time-point 2, outcomes #1 and #16 displayed low communalities to the three factors, and outcome #13 was factorially complex. In both instances these outcomes were removed from the PCA analysis for the relevant time-point, and were considered as separate input variables for the analyses detailed below. Therefore, the thirteen biomechanical variables from time-point 1 were reduced to two factors, with two independent salient outcomes (#11 and #20). For time-point 2, the nineteen biomechanical variables were reduced to three factors and three independent salient outcomes (#1, #13 and #16). The pattern and structure coefficients are presented for these factors in Table 7 for time-points 1 and 2 separately.

These four potential biomechanical predictors for time-point 1 (two factors + two independent salient outcomes) and six potential predictors for time-point 2 (three factors +

three independent salient outcomes), in addition to the questionnaire and performance groups of dependent variables, were then subjected to preliminary univariate statistical analysis to evaluate their potential value in two separate prediction models for each time-point (2-week and 6-month). Specifically, the correlation of questionnaire scores, SEBT reach distance performances, ankle dorsiflexion ROM and the salient biomechanical dependent variables (following PCA) to outcome at the 12-month time-point was evaluated using Pearson's r. This was performed separately for the 2-week and 6-month time-points to identify the likely 'predictors' of CAI or coper status following initial LAS. Variables were entered into a direct logistic model provided their correlation to outcome was significant at the level of $p < 0.05$. No adjustment was made to the p-value to accommodate multiplicity at this stage to guard against the potential exclusion of important variables for the regression model.

All statistical analyses were performed with IBM SPSS Statistics 20 (IBM Ireland Ltd, Dublin, Ireland).

RESULTS

Follow-up and rehabilitation

Seventy-one of the original 82 injured participants completed the 6-month follow-up, with 70 participants completing the 1-year follow-up; these final seventy were included in the prospective analysis. Of the final seventy, 28 (40%) were designated as having CAI with 42 (60%) being designated as LAS "copers" (Figure S1). Twenty-eight (40%) of these participants did not seek rehabilitative medical services while forty-two (60%) did. Univariate statistical analyses revealed no significant trends between rehabilitation and outcome (CAI/coper) ($r = 0.11$; $p = 0.372$).

Preliminary univariate statistics and regression

Following preliminary correlation analysis, no potential predictors at the two-week time-point were identified. However, six potential predictors were identified at the 6-month time-point [CAIT and FAAMadl scores; reach distances in the ANT and PL directions of the SEBT (involved limb); Factor 1 and salient parameter #16]. Results of preliminary correlation analyses for time-points 1 and 2 are presented in the article supplementary documents (Tables S3 and S4 respectively). Descriptive statistics for the six potential predictors at time-point 2 are presented in Table 8.

These potential predictors were entered into a direct logistic regression model in a hierarchical fashion, whereby clinically accessible measures (questionnaire scores and SEBT reach distances) were entered first, followed by the salient biomechanical variables. Thus, one logistic regression analysis was completed for the predictors identified at the six-month time-point. CAIT score, ANT reach distance and salient parameter #16 were then removed sequentially from the model using a backward elimination technique because they displayed low beta weights in the model despite significant correlation to outcome (likely indicating shared predictive power taken up by the remaining predictor variables due to correlation[43]). The regression analysis was then repeated with the remaining predictors (FAAMadl score, PL reach distance score and factor 1).

The model was statistically significant after the first block of variables were entered, χ (2, N = 68) = 21.75, $p < 0.001$, explaining between 28.1% (Cox and Snell R square) and 38.4% (Nagelkerke R squared) of the variance in outcome, and correctly classifying 81.8% of cases. When the final variable (factor 1) was entered into the model, the explained variance increased to between 34.7% and 47.5%, and correctly classified 84.8% of cases. The sensitivity and specificity of the final model was 75% and 91% respectively. Factor 1 was the strongest predictor of outcome, with an odds ratio of 2.48. Reflection of the structure and pattern coefficients for this factor revealed that it represented salient biomechanical parameters #3 to #12 inclusive (involved limb: sagittal plane joint positions at the hip, knee and ankle in the PL and PM directions, and at the knee and ankle for the ANT direction; uninvolved limb: sagittal plane joint positions at the knee in the PL and PM directions). Therefore, this indicates that participants who exhibited less flexion and dorsiflexion displacement (bilaterally) during specified directions of the SEBT at the 6-month time-point were over twice as likely to be CAI participants[43].

Due to the potential value these measures possess for clinicians, separate specificity and sensitivity analyses were completed for several of the predictors identified via the preliminary correlation analysis (CAIT, FAAMadl scores; ANT and PL reach distances). These analyses revealed cut-off scores of 18 for the CAIT (sensitivity: 0.929; specificity: 0.375), 94.05% for the FAAMadl (sensitivity: 0.93; specificity: 0.63), and 59.34% (sensitivity: 0.71; specificity: 0.63) and 91.35% (sensitivity: 0.69; specificity: 0.71) of leg length for the ANT and PL directions of the SEBT respectively.

The results from the preliminary correlation and subsequent regression analyses with multiple imputation were largely consistent with those from a complete case analysis. The results from the complete cases analysis are presented in this article's supplementary material (Results S1).

DISCUSSION

The ankle sprain literature is replete with studies which have sought to identify the movement patterns that characterise and thus predicate the CAI condition[1,2, 3-6 , 8,9,13]. The use of LAS copers in these case-control analyses[3,4,54-56](refs) is a recent development which has afforded superior statistical validity to the deductions made compared to those of a more traditional framework using non-injured controls; it is envisaged that because CAI and LAS coper participants have a shared injury exposure, any discrepancies in their movement strategies are more likely to be representative of coping or non-coping mechanisms for long-term injury outcome[52,54,55]. Unfortunately, the observational design of these studies has meant that the deductions made regarding the true coping mechanisms of LAS remain speculative. While a number of longitudinal studies have identified several risk factors for the first instance of ankle sprain[15,46,57], no such research is available evaluating the mechanisms that predispose an individual to a dichotomous post-LAS outcome of CAI or coper status. Herein lies the novelty of our research as, to our knowledge, this is the first prospective analysis of a population recruited after they incurred a first-time LAS and which has tracked this 12-month divergence.

LAS can be considered the ‘gateway’ to these dichotomous states, and findings from this study have identified that a number of variables at the 6-month time-point following injury are directly predictive of 12-month outcome. Inconsistencies in the literature concerning the ‘bona-fide’ CAI-defining movement deficits[36] compelled us to use a series of exploratory analyses of this LAS cohort (refs) to inform our choice of dependent variables for the subsequent regression analyses. Our hypothesis was that the ‘salient’ biomechanical outcomes identified via this process would represent a conglomeration of deficits across a spectrum of human movement in the CAI group[29]. Contrary to our primary hypothesis, the deficits exhibited were generally isolated to only one part of this spectrum (a measure of dynamic postural control: the SEBT task).

The SEBT is both a rehabilitative and objective balance assessment tool popularised in the clinical setting due to its excellent reliability and validity in injury risk and performance assessment[28]. One of the many advantages of this test is that it can be modelled on an assessment hierarchy[22]: simple documentation of the reach distance achieved by the participant (which in itself has great clinical value[44]) can be advanced using instrumented biomechanical acquisition methods in the research setting to discern the movement patterns belying the reach performance achieved. Such methods have been shown to advance the discriminatory ability of the SEBT[45], and have revealed that the ANT, PL and PM reach components best consummate overall SEBT performance, reducing the redundancies associated with evaluating all eight of its original reach directions[30]. As such, a number of investigations in the CAI literature have documented differences in both reach distance performance and its underlying movement compared to non-injured controls[26,27,30,45] and LAS copers[45]. Indeed the inclusion of salient biomechanical outcomes relating to the SEBT in the current investigation was based on a persistent observation of deficits in hip, knee and ankle ROM in the sagittal plane in the LAS group 2-weeks and 6-months following injury onset (compared to non-injured controls), and in the CAI group at the 12-month time-point (compared to LAS copers and controls)(refs). PCA was utilised to reduce the dimensionality of the salient biomechanical outcomes, and in retrospect it is unsurprising that this dimension reduction procedure grouped the SEBT-based salient outcomes together (factor 1), because they are likely to be highly correlated[43]. Factor 1 represented sagittal plane joint positions for both the involved (ANT: knee, ankle; PL/PM: hip, knee and ankle) and uninvolved (PL/PM: knee) limbs. Due to the positive correlation of factor 1 to the aforementioned sagittal plane motions during the SEBT (Table 7), and in light of the negative mean value for the CAI group for this outcome (Table 8), we can deduce that the odds that participants had CAI at the final evaluation increased the likelihood that they displayed a reduction in sagittal plane ROM at these joints during the SEBT at the 6-month time-point. Not only does this contradict the notion that the limb contra-lateral to the side of injury is ‘uninvolved’, but also implicates proximal joints (hip/knee) in the coping mechanisms of LAS.

Whether these deficits in ROM at the hip and knee joints originate from restrictions at the distal ankle magnifying proximally, or from central motor control mechanisms deserves consideration. Deficits in ankle dorsiflexion ROM as determined using the knee to wall test have been shown to impair reach performance in the ANT direction of the SEBT[33], yet in the current study, this performance measure (the knee to wall test) yielded no significant correlation to outcome at any of the time-points. Therefore, it is likely that the observed sagittal plane ROM deficits are a manifestation not of structural or morphological ‘blocks’ at the ankle, but of spinal and/or supraspinal alterations in motor control mechanisms following the initial LAS[15,29]. The presence of static and dynamic postural control deficits in LAS participants both within 2-weeks (refs) and 6-months (refs) following injury incurrence lend to this hypothesis, implicating centrally mediated sensorimotor control changes[29]. These findings were consistent with the 12-month data, wherein many of the deficits exhibited earlier in the disease process persisted in CAI participants (refs). While a recent systematic review and meta-analysis has determined that there is a subsidence of the bilateral deficits that initially affect individuals with an acute LAS as they proceed to CAI, the pooled outcomes in that study were generally limited to observational reports of stabilometric measures acquired during static postural control tasks[53]. Findings from the current investigation imply that individuals with CAI do indeed exhibit deficits in postural control, some of which are bilateral in nature (as factor 1 represented sagittal plane knee motion on the uninvolved limb). Therefore, based on the current findings it is likely that centrally mediated (spinal and/or supraspinal) mechanisms of sensorimotor control are implicated in the development of chronicity following an initial, first-time acute LAS[29]. This is of clinical importance, as rehabilitation programmes must be thus designed with the bilateral nature of these deficits in mind.

While the salient outcomes from the higher level measures of sensorimotor function (the DL and DVJ tasks in the current study) did not contribute to the prediction equation, it is worth noting that the outcome relating to hip flexion moment following ground contact would have had some predictive value if entered into the regression equation independently (recall that it was removed because it did not explain any additional variance when included in the model with the other salient, performance and questionnaire dependent variables). We were surprised by this ‘redundancy’ and the lack of significant independent contributors for outcome for the variables from the dynamic movement tasks. However, their lack of contribution to prediction is partly elucidated in lieu of the fact that as part of the data imputation procedures, some of the ‘salient’ biomechanical outcomes relating to these tasks were removed entirely due to excessive ‘missingness’. Indeed the variables relating to the eyes-closed variant of the SLS task could not even be considered at either time-point for regression due to data ‘missingness’, with the DL and DVJ tasks similarly oriented at time-point 1. We would offer that these components of the movement spectrum are likely to be useful in the assessment of LAS and CAI populations but due to problems with task completion and data ‘missingness’, this is not reflected in the current study. This is evidenced by the fact that findings from the exploratory reports, wherein findings were simply presented for the data that were available, identified deficits which were persistent across time-points [namely, increased hip-ankle coupling during SLS (ref), and increased hip flexion during the DL (ref) and DVJ (ref) tasks].

That deficits in hip joint control seemed to be a continuous theme in both the exploratory reports (refs) and in the final regression analysis of the current study is an interesting finding. Reflection of the forest plots used to extract the salient biomechanical outcomes illustrates this, whereby at the 12-month time-point, the hip was the predominant lower extremity joint at which biomechanical deficits manifested in the CAI group (compared to copers and controls). It is plausible that the aforementioned alterations in central motor control mechanisms involve increasing weighted dominance on hip-joint movement strategies to fulfil postural control (both static and dynamic)(refs) and jumping/landing tasks(refs). Thus, hip joint stability and the strength or activation of its supporting musculature is likely to be a central characteristic of the coping mechanisms exhibited by CAI or coper participants, directly affecting global movement mechanics and foot positioning [20]. This may be due to the extensive musculature at the disposal of this joint for performing the required movements[1], which is recruited immediately following injury to compensate for ankle joint dysfunction, but may become redundant during recovery if it persists. Individuals with CAI have previously been shown to exhibit altered hip muscle activation onsets and patterns [5], with reduced strength of the hip abductors on their involved limb also evident [20], lending to this hypothesis. Weakness or changes in activation patterns in a key stabilizing muscle groups such as at the hip or ankle has the potential to produce deviations in joint motion which can subsequently alter stability [6]. Because the hip joint is appropriate for correcting large deviations of the body's centre of mass and the ankle is more suited to the 'fine-tuning' of postural control [42,49], we speculate that in maintaining reliance on hip-dominant movement strategies which begin following LAS incurrence, individuals who develop CAI do so partly because of this persistence.

As such, we believe that rehabilitation following LAS should incorporate the full spectrum of human movement and should contextually encourage the appropriate use of hip-based and/or ankle based static and dynamic movement strategies. The current research cannot confirm the potential efficacy of such an approach, however, but may inform future intervention studies of LAS populations. The most recent currently available systematic review and meta-analysis on the topic of rehabilitation efficacy for CAI based on twenty randomized controlled trials has identified that more evidence is required in this area[51]. We believe that the "limited to moderate" efficacy of training programs for CAI treatment compared to controls[51] would be advanced using a structured approach that that includes 1) the entire movement spectrum; 2) both the injured limb and the contralateral limb; 3)hip- and ankle- based static and dynamic movement tasks, for the reasons we have alluded to above. This can only be confirmed with an appropriately designed intervention study however.

That our secondary hypothesis was confirmed by the results of the current study should be of particular interest to clinicians: the predictive value of the self-report questionnaires and the ANT and PL reach directions of the SEBT are likely to be of significant value to them. Utilising the cut-off scores for these outcomes (in particular, the FAAMadl and PL reach direction due to their contribution to the prediction equation) should be incorporated in a goal-oriented rehabilitation programme design, and could be used to give an indication of the likelihood that a patient will (or will not) develop CAI. With regards to the questionnaires, these findings substantiate the recommendations of recent consensus statements[9,23-25] to use the CAIT and FAAMadl to both quantify the extent of the CAI associated disability and functional deficits, and as an objective means to track recovery. Note however, that these measures, and the identified salient biomechanical outcomes, were only predictive at the 6-month time-point.

In many ways it is unfortunate that no predictors emerged at the 2-week time-point in the current study, as this is the time that clinicians are most likely to encounter their patients and have the ability to implement preventive measures, prior to the onset of chronic sequalae. It is likely that the 2-week window of eligibility for assessment undermined the homogeneity of our sample at this time-point, thus increasing the chance of sampling error: whether a patient came to our lab for assessment the day after LAS incurrence probably had serious implications for the extent of their disability compared to if they attended thirteen days after, for example. This must be recognised as a serious limitation of the current study. However, due to the high prevalence of LAS, the difficulty in actually recruiting patients with a first-time LAS would have been compounded further if we were only able to assess them in a pre-determined 24-hour interval, thus threatening the feasibility of the study. A further limitation of this research is that because the LAS cohort were recruited after the initial injury, it is unknown as to whether the deficits identified either in the exploratory research reports (refs) or in this prospective analysis preceded or were caused by the first instance of LAS.

In conclusion, this analysis has identified several clinically accessible and biomechanical outcomes which have predictive capacity of long term outcome, 6-months following a first-time LAS injury. These findings have implications for clinicians, who can use the reported cut-off scores in goal-oriented rehabilitation programs and to assess the risk a given patient has for developing CAI, and for researchers, who should attempt to develop rehabilitation programs on the basis of the biomechanical deficits identified.

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LAS	82	54	28	22.78	21.89 to 23.67	76.6	73.66 to 79.54	1.72	1.70 to 1.74
Control	20	15	5	22.53	21.77 to 23.28	71.55	66.46 to 76.64	1.75	1.71 to .178

Abbreviations: CI = Confidence Interval; LAS = Lateral Ankle Sprain

2. No other severe lower extremity injury in the last 6 months	2. No severe lower extremity injury in the last 6 months
3. No history of ankle fracture	
4. No previous history of major lower limb surgery	
5. No history of neurological disease, vestibular or visual disturbance or any other pathology that would impair their motor performance	

Abbreviations: LAS = lateral ankle sprain

Table 3. Experimental protocol for the five movement tasks, including the events analysed and the number of trials acquired.

Task	Conditions	Protocol	Event(s) analysed
SLS (●)	Eyes-open Eyes-closed	Hands on hips Unilateral stance position. 20-seconds Refs	Duration of SLS
SEBT (▲)	ANT PL PM	<u>Start position:</u> Hands on hips Bilateral stance <u>Task performance:</u> Unilateral stance Use non stance limb to reach in specified direction Return to start position Refs	<u>Kinematics</u>: Point of maximu <u>Kinetics</u>: duration of unilatera <u>Reach distance:</u> ANT, PL and directions.
DL (■)		<u>Start position:</u> Standing atop a 40cm platform with the test limb flexed at the knee <u>Task performance:</u> Drop forward onto the force plate, landing on the test limb. Maintain position of unilateral stance x 3-5 sec. Refs	<u>Kinematics</u>: 200ms pre-groun 200ms post-ground contact <u>Kinetics:</u> Ground contact to 2 ground contact
DVJ (x)		<u>Start position:</u> Bilateral stance atop a 40cm platform with hands on hips <u>Task performance:</u> Drop forward onto the two adjacent force plates (landing with both feet simultaneously) and immediately execute a maximal vertical jump. Return to ground in position of bilateral stance Refs	<u>Kinematics</u>: 200ms pre-groun 200ms post-ground contact fo second landings. <u>Kinetics:</u> Ground contact to 2 ground contact for first and se landings
Gait (▬)		Walk across a 10m walkway at a self-determined speed. Only 'clean' gait cycles were saved, and were defined by the participant landing with one foot in each force plate for each trial. Refs	<u>Kinematics</u>: 200ms pre heel-s to 200ms post heel-strike/toe- <u>Kinetics</u>: heel-strike/toe-off to heel-strike/toe-off

Table 4. Definitions of the acquired biomechanical dependent variables relative to this study

Variable	Abbreviation used	Relevant task(s)	Definition
Kinematic		SLS, SEBT, DL, DVJ, Gait	Concerns the details of movement: linear displacement and/or angular displacement of the lower limb joints (hip/knee/ankle).
Kinetic		DL, DVJ, Gait	Refer to the forces that cause movement such as the ground reaction forces, jo moments and joint powers. Joint moments were calculated for the hip, knee a ankle.
Adjusted coefficient of multiple determination	ACMD	SLS	A calculation that conceptualises the similarity between waveform data, the output of which is a discrete number between 0 (where there is no similarity between two waveforms) and 1 (where the waveforms have an identical shape This allows for the conceptualisation of 'coupling' patterns between two joint wherein greater 'coupling' is indicated by greater waveform similarity.
Centre of pressure	COP	SLS, SEBT	A bivariate distribution, jointly defined by the AP and ML coordinates which time series define the COP path of the stance limb relative to the origin of the force platform.
Fractal dimension (FD)	FD	SLS, SEBT	A calculation that determines the complexity of the COP path trajectory by describing its shape using a discrete value between 1 (minimal complexity; straight line) and 2 (significant complexity; line the piles up in the plane). W it has yet to be determined whether there exists a linear relationship between postural control ability and the FD of the combined AP and ML COP path, a lower FD has been linked with a reduced capacity to avail of the supporting b
Ground reaction force	GRF	DL, DVJ	The force exerted by the ground on a body in contact with it.
Rate of force development	RFD	DVJ	The peak vertical ground reaction force normalised to bodyweight divided by time from ground contact with the force plate to the peak vertical ground reac force.

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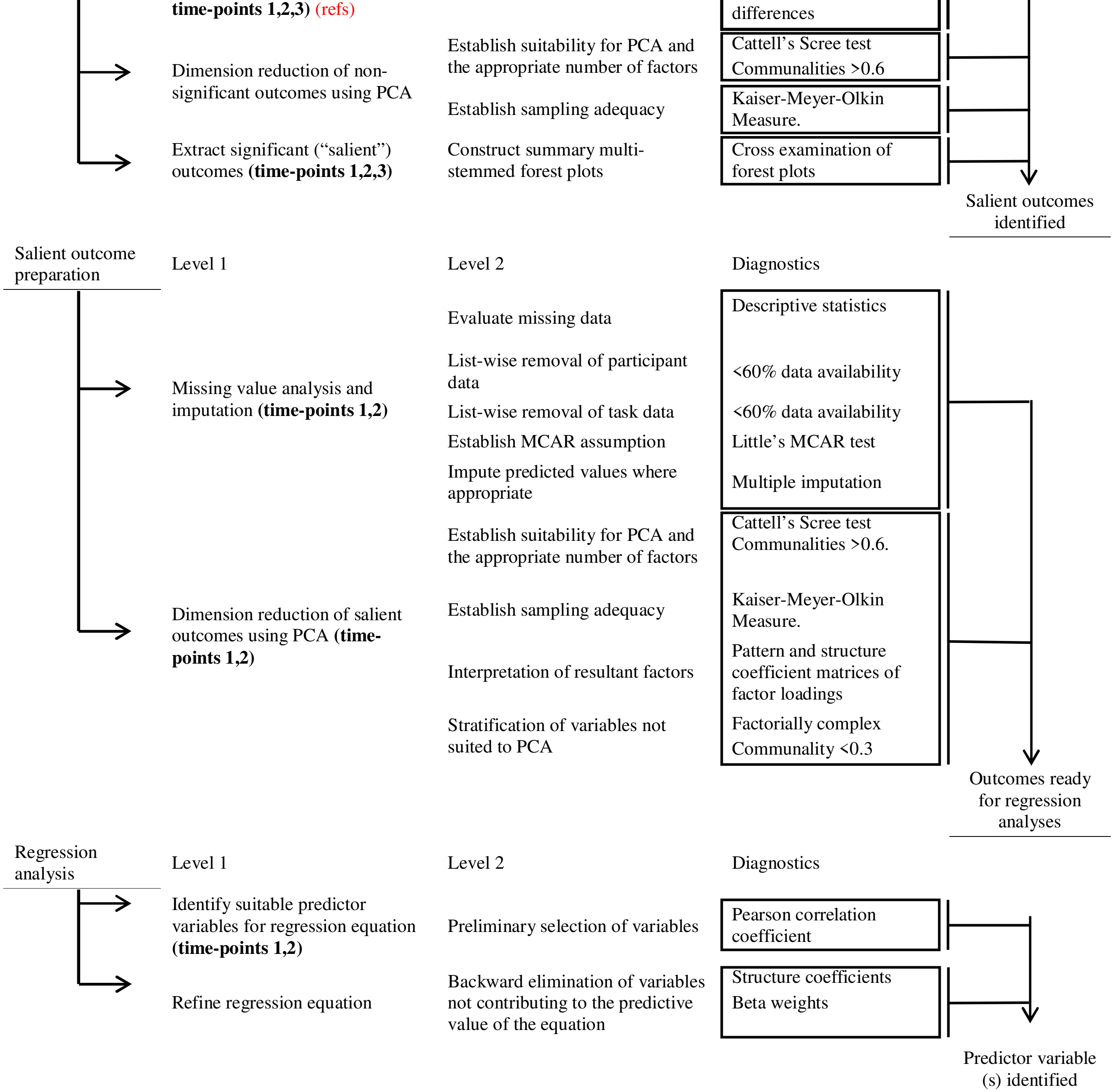


Abbreviations: CAI = Chronic Ankle Instability; LAS = Lateral Ankle Sprain; PCA = Principal Components Analysis; MCAR = Missing Completely at Random.

	Eyes	Kinetic	#2. COP fractal dimension	×	63%	×	47%
SEBT	ANT	Kinematic	#3. Knee flex	✓	6%	✓	3%
			#4. Ankle d/f	✓	6%	✓	3%
			#5. Hip flex	✓	6%	✓	3%
	PL		#6. Knee flex	✓	6%	✓	3%
			#7. Ankle d/f	✓	6%	✓	3%
			#8. Knee flex	✓	4%	✓	3%
	PM		#9. Hip flex	✓	6%	✓	3%
			#10. Knee flex	✓	6%	✓	3%
			#11. Ankle d/f	✓	6%	✓	3%
			#12. Knee flexion	✓	4%	✓	3%
	PL	Kinetic:	#13. COP fractal dimension	✓	6%	✓	3%
DL		Kinematic	#14. Hip flexion (max pre-initial contact)	×	73%	✓	24%
			#15. Hip flexion (max pre-initial contact)	×	50%	✓	24%
		Kinetic	#16. Hip flexion moment (max post-initial contact)	×	73%	✓	24%
DVJ	Part 1	Kinematic	#17. Hip flexion (max pre-initial contact)	×	54%	✓	27%
		Kinetic	**18. Hip flexion moment (max post-initial contact)**	×	54%	✓	27%
	Part2		**#19. Hip flexion moment (max post-initial contact)**	×	54%	✓	27%
Gait		Kinematic	#20. Hip extension (max pre toe-off)	✓	6%	✓	3%
			#21. Ankle inversion (max pre toe-off)	✓	6%	✓	3%

✓= eligible for multiple imputation (≥40% data unavailability); × = not eligible for multiple imputation (≥40% data unavailability). Bold text indicates that the variable relates to the 'uninvolved' limb. Abbreviations: SLS = single-limb stance; SEBT = Star Excursion Balance Test; DL = single-leg drop land; DVJ = drop vertical jump; ANT/PL/PM = anterior/posterior-lateral/posterior-

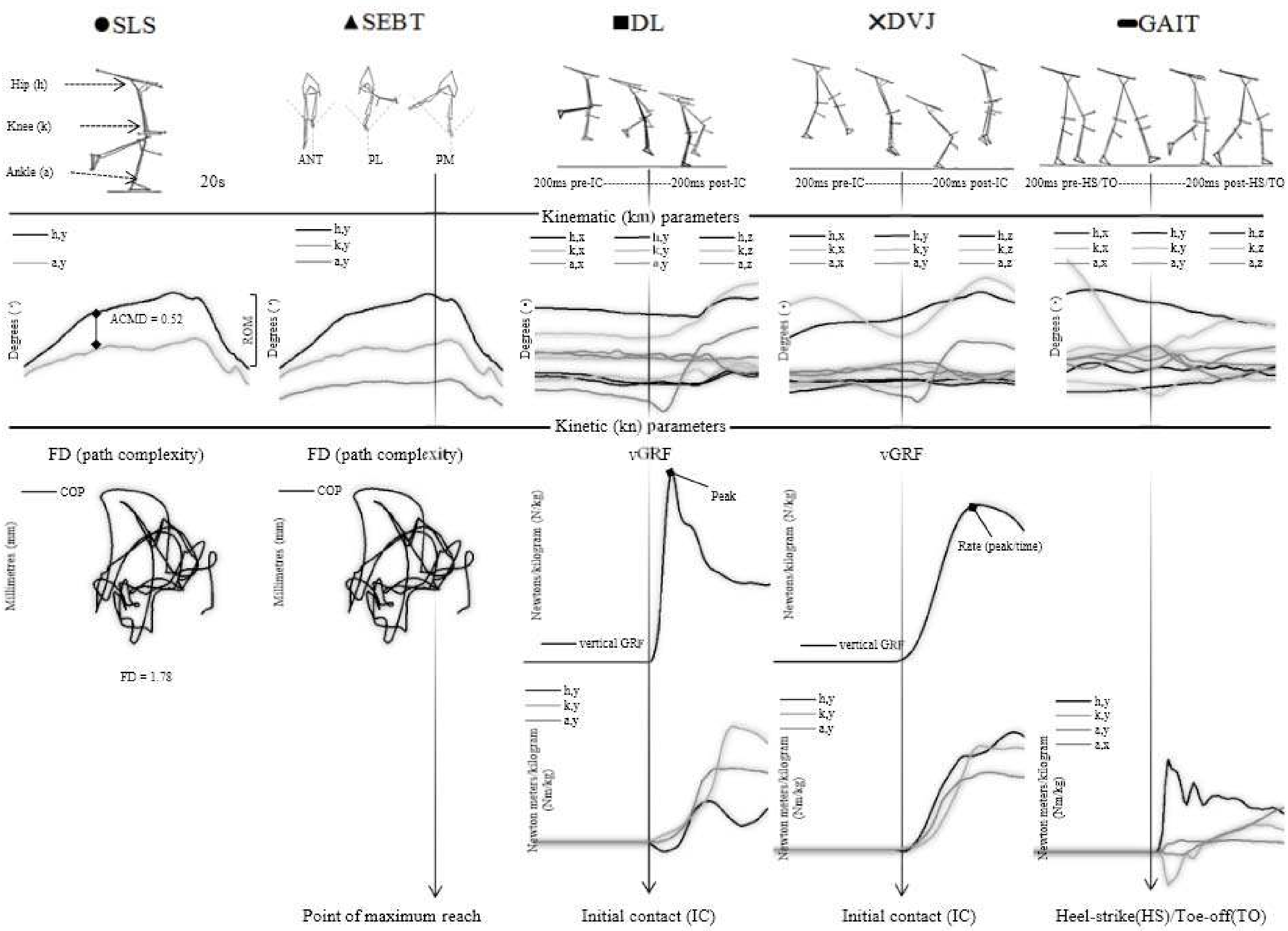
Table 7. Pattern and structure matrices for the principal components analysis of the prominent biomechanical variables at the 2-

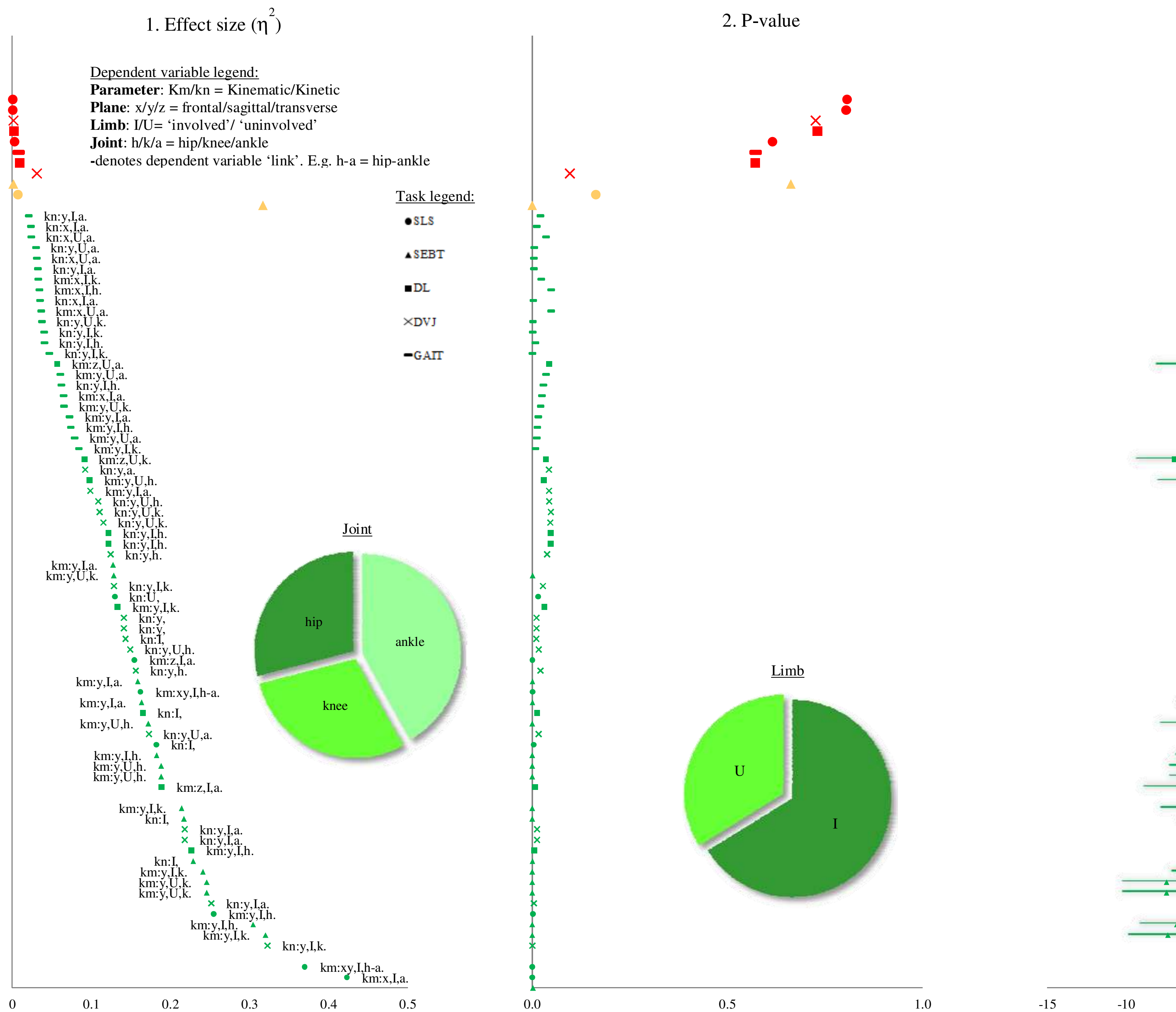
	Variable #	Pattern coefficients			Structure coefficients	
		Factor 1	Factor 2		Factor 1	Factor 2
2-week	10	**.933**	-.005		**.933**	.025
	4	**.870**	.087		**.873**	.115
	6	**.867**	.174		**.872**	.201
	9	**.844**	-.041		**.843**	-.014
	3	**.833**	.044		**.834**	.071
	7	**.822**	.144		**.827**	.170
	5	**.780**	.195		**.786**	.220
	8	**.692**	-.101		**.689**	-.079
	12	**.664**	-.112		**.660**	-.090
	13	**.638**	-.430		**.625**	-.409
	1	.127	**.821**		.153	**.825**
	21	.003	**.748**		.027	**.748**
		Factor 1	Factor 2	Factor 3	Factor 1	Factor 2
6-month	10	**.927**	-.038	.088	**.925**	-.076
	5	**.922**	.127	-.024	**.920**	.115
	9	**.894**	.073	.107	**.893**	-.060
	3	**.893**	.098	-.040	**.893**	.090
	6	**.886**	-.078	-.152	**.889**	.031
	4	**.845**	.078	-.098	**.847**	.085
	12	**.844**	.118	-.044	**.844**	.112
	8	**.812**	.074	.008	**.810**	.056
	11	**.722**	-.223	.422	**.712**	-.337
	7	**.496**	-.335	-.104	**.507**	-.320
	15	.117	**.934**	.032	.098	**.924**
	14	.081	**.867**	-.050	.066	**.877**
	20	-.005	**.784**	.089	.005	**.822**
	17	.007	**.737**	-.366	-.023	**.764**
	18	-.044	.054	**.980**	-.080	-.175
	19	-.092	.040	**.935**	-.126	-.177
	21	.050	-.068	**.587**	.031	-.207

	CAI		Coper	
	Mean	SD	Mean	SD
CAIT (/30)	20.33	5.59	23.17	5.12
FAAMadl (%)	89.32	9.21	97.15	4.01
ANT (%LL)	59.09	4.01	61.98	5.75
PL (%LL)	86.81	11.58	94.51	10.27
Factor 1	-0.54	1.26	0.31	0.65
#16 (Nm/kg)	0.55	1.10	0.12	0.55

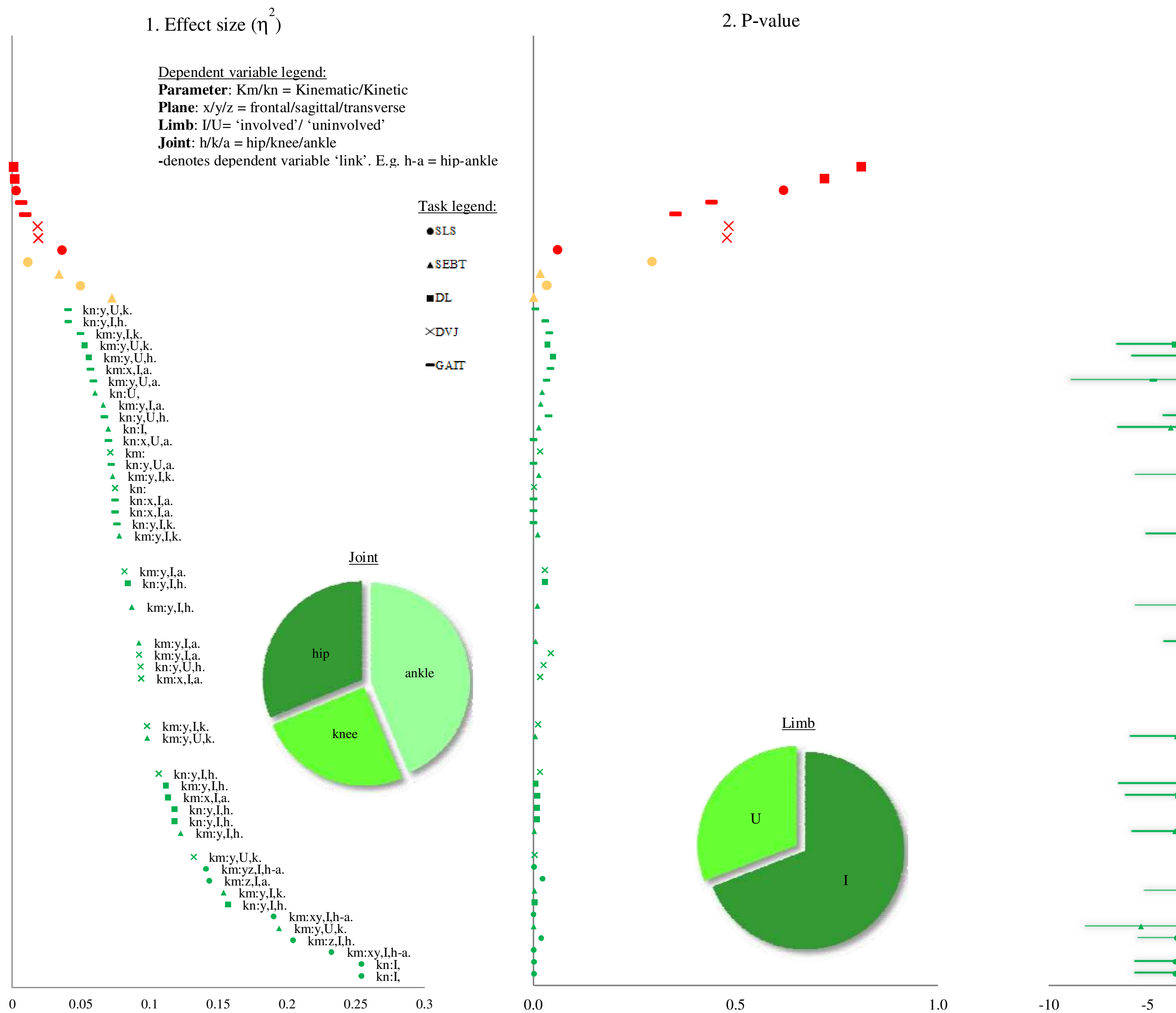
Abbreviations: CAIT = Cumberland Ankle Instability Tool; FAAMadl = Activities of Daily Living subscale of the Foot and Ankle Ability Measure; ANT/PL/PM = anterior/posterior-lateral/posterior-medial directional components of the Star Excursion Balance Test; %LL = percentage of limb length.

Figure 1. Pictorial representation of the five movement tasks, their dependent variables and the events analysed for each

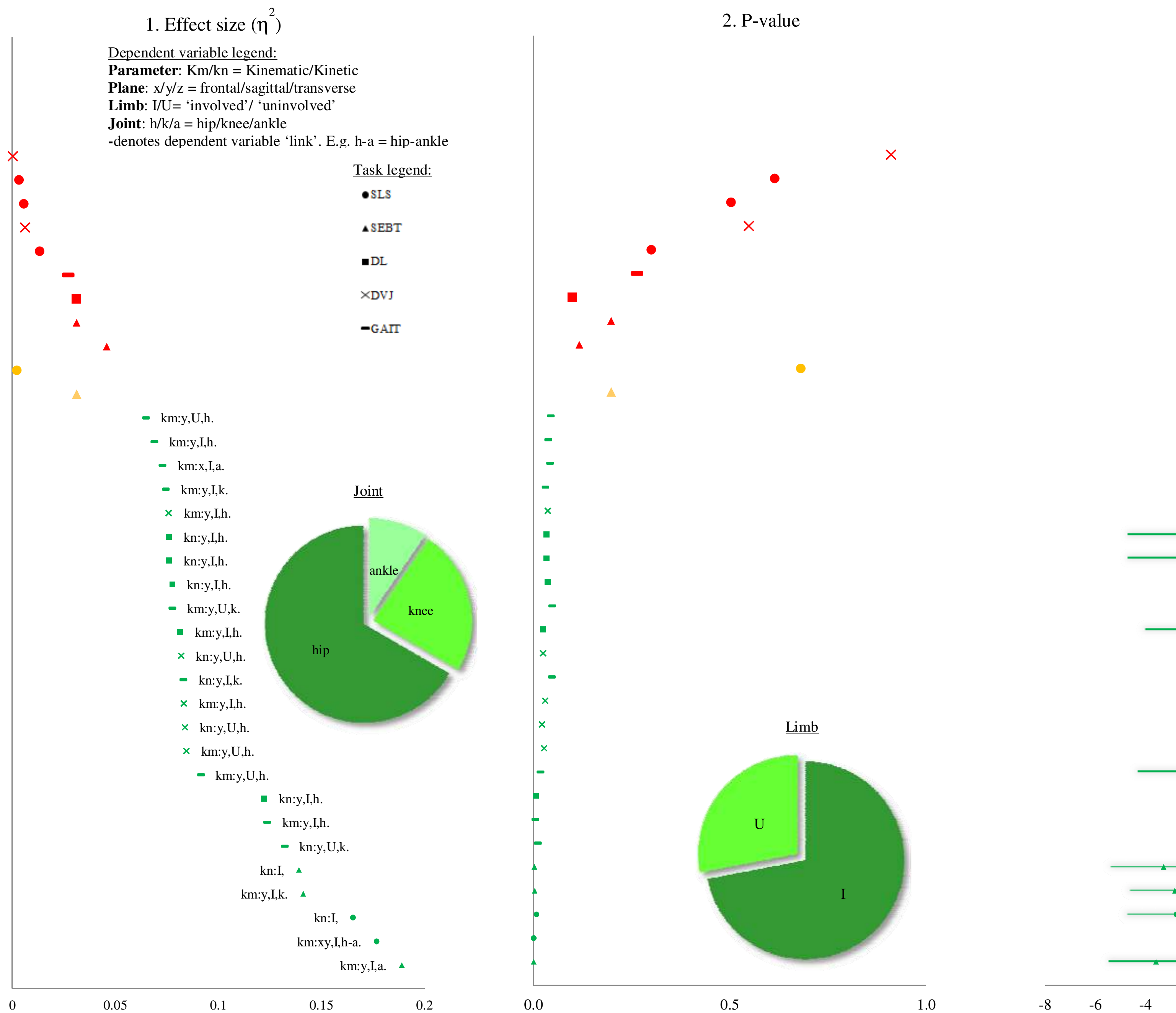



1. Effect size (η^2)
2. P-value
Dependent variable legend:
Parameter: Km/kn = Kinematic/Kinetic
Plane: x/y/z = frontal/sagittal/transverse
Limb: I/U= 'involved'/ 'uninvolved'
Joint: h/k/a = hip/knee/ankle
-denotes dependent variable 'link'. E.g. h-a = hip-ankle
Task legend:
SLS
SEBT
DL
DVJ
GAIT
Joint
hip
knee
ankle
Limb
U
I
0
0.1
0.2
0.3
0.4
0.5
0.0
0.5
1.0
-15
-10

variables relating to joint extension/plantarflexion moments are positive and flexion/dorislfexion moments negative.
Abbreviations: SLS = Single limb Stance; SEBT = Star Excursion Balance Test; DL = Single-leg Drop Land; DVJ = Drop Vertical Jump; U = Uninvolved; I = Involved; LAS = Lateral Ankle Sprain; PCA = Principal Components Analysis.


1. Effect size (η2)
2. P-value
Dependent variable legend:
Parameter: Km/kn = Kinematic/Kinetic
Plane: x/y/z = frontal/sagittal/transverse
Limb: I/U= 'involved'/ 'uninvolved'
Joint: h/k/a = hip/knee/ankle
-denotes dependent variable 'link'. E.g. h-a = hip-ankle
Task legend:
SLS
SEBT
DL
DVJ
GAIT
kn:y,U,k.
kn:y,I,h.
km:y,I,k.
km:y,U,k.
km:y,U,h.
km:x,I,a.
km:y,U,a.
kn:U,
km:y,I,a.
kn:y,U,h.
kn:I,
kn:x,U,a.
km:
kn:y,U,a.
km:y,I,k.
kn:
kn:x,I,a.
kn:x,I,a.
kn:y,I,k.
km:y,I,k.
km:y,I,a.
kn:y,I,h.
km:y,I,h.
km:y,I,a.
km:y,I,a.
kn:y,U,h.
km:x,I,a.
km:y,I,k.
km:y,U,k.
kn:y,I,h.
km:y,I,h.
km:x,I,a.
kn:y,I,h.
kn:y,I,h.
km:y,I,h.
km:y,U,k.
km:yz,I,h-a.
km:z,I,a.
km:y,I,k.
kn:y,I,h.
km:xy,I,h-a.
km:y,U,k.
km:z,I,h.
km:xy,I,h-a.
kn:I,
kn:I,
Joint
hip
ankle
knee
Limb
U
I
0
0.05
0.1
0.15
0.2
0.25
0.3
0.0
0.5
1.0
-10
-5

variables relating to joint extension/plantarflexion moments are positive and flexion/dorislfexion moments negative.
Abbreviations: SLS = Single limb Stance; SEBT = Star Excursion Balance Test; DL = Single-leg Drop Land; DVJ = Drop Vertical Jump; U = Uninvolved; I = Involved; LAS = Lateral Ankle Sprain; PCA = Principal Components Analysis.



1. Effect size (η²)
Dependent variable legend:
Parameter: Km/kn = Kinematic/Kinetic
Plane: x/y/z = frontal/sagittal/transverse
Limb: I/U= 'involved'/ 'uninvolved'
Joint: h/k/a = hip/knee/ankle
-denotes dependent variable 'link'. E.g. h-a = hip-ankle
Task legend:
SLS
SEBT
DL
DVJ
GAIT
km:y,U,h.
km:y,I,h.
km:x,I,a.
km:y,I,k.
km:y,I,h.
kn:y,I,h.
kn:y,I,h.
kn:y,I,h.
km:y,U,k.
km:y,I,h.
kn:y,U,h.
kn:y,I,k.
km:y,I,h.
kn:y,U,h.
km:y,U,h.
km:y,U,h.
kn:y,I,h.
km:y,I,h.
kn:y,U,k.
kn:I,
km:y,I,k.
kn:I,
km:xy,I,h-a.
km:y,I,a.
Joint
ankle
knee
hip
0
0.05
0.1
0.15
0.2
2. P-value
Limb
U
I
0.0
0.5
1.0
-8
-6
-4

Abbreviations: SLS = Single limb Stance; SEBT = Star Excursion Balance Test; DL = Single-leg Drop Land; DVJ = Drop Vertical Jump; U = Uninvolved; I = Involved; CAI = Chronic Ankle Instability; PCA = Principal Components Analysis.