Sex- and osteoarthritis-related differences in muscle co-activation during weight-bearing tasks

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Word Count manuscript (excluding abstract): 3685

Word Count Abstract: 300

Running heading: Muscle co-activation and sex in knee OA

Acknowledgements

We want to acknowledge the assistance of professor Iain McInness, Dr John Hunter, Dr John Haughney, Dr Mhairi Brandon, Dr Stefan Siebert, Dr James Dale, Linda Wilson and Marion Flood for

their assistance with participant recruitment. Richard Allan, Sara Marreiros, Diane Dickson for help with data collection. The participants who gave up their valuable time, it is greatly appreciated.

Abstract

Background: Individuals with knee osteoarthritis (OA) demonstrate impairments in muscle function (i.e. muscle weakness, high muscle co-activation believed to have detrimental effects on joint integrity). Women with knee OA exhibit poorer health outcomes than men. Sex and muscle function are known risk factors for knee OA. It is unclear how these risk factors are associated with muscle function in knee OA and the implications for disease aetiology.

Research question: How does sex and knee osteoarthritis disease status relate to muscle function, specifically strength and muscle co-activation, during walking, stair negotiation and sit-to-walk activities.

Methods: A cross-sectional study assessed muscle co-activation in 77 individuals with knee OA (62.5[8.1]yrs; 48/29 women/men) and 18 age-matched controls (62.5[10.4]yrs; 9/9 women/men), during a series of walking, stair ascent and descent and sit-to-walk activities. Muscle strength of the knee extensors and flexors was assessed using maximal voluntary isometric contractions (MVIC). Electromyography was recorded from the vastus lateralis/medalis, rectus femoris, biceps femoris, semitendinosus, medial/lateral gastrocnemius normalised to MVIC. Multiple regression assessed the relationship between sex, disease status, and muscle strength on muscle co-activation.

Results: Individuals with knee OA were weaker than controls, had higher hamstrings-quadriceps and medial-lateral co-activation for specific phases of gait. Women were weaker than men with higher muscle co-activation across all activities. Sex and muscle weakness, but not age or disease status predicted high muscle co-activation.

Significance: High muscle co-activation was associated with female sex and muscle weakness regardless of disease status and age. High muscle co-activation is believed to be a compensatory mechanism for muscle weakness to maintain a certain level of function. High muscle co-activation is also thought to have detrimental effects on cartilage and joint integrity this may explain high muscle

co-activation in women with muscle weakness and contribute to increased risk of incidence and progression of knee OA in women.

Keywords: Knee osteoarthritis; muscle; sex; co-activation; gait;

Introduction

Female sex and muscle weakness are known risk factors for the development of symptomatic knee osteoarthritis (OA) [1]. A meta-analysis of sex-difference in knee OA found reduced prevalence (Risk Ratio [RR] 0.63, 95% CI 0.53-0.75) and incidence (RR 0.55, 95% CI 0.32-0.95) in men, with prevalent knee OA significantly more severe in women (standardised mean difference 0.20, 95% CI 0.11-0.28)[2]. There are several possible explanations for sex differences in individuals with knee OA, including increased joint loading in women as a result of increased weight gain during and following the menopause, and changes in joint angles caused by wider hips, which alters the joint biomechanics [3]. Additionally, differences in sex hormones specifically ovarian hormones effects on joint health and muscle function, although research remains unclear, hormone replacement therapy demonstrates positive effects on knee OA [4]. The increased loading and biomechanical alterations are often accompanied by changes in muscle function such as strength, muscle activation, and co-activation patterns, due to a greater reliance on the active muscle system for support and control, further exacerbated by disease severity [5–7].

Muscle function in individuals with knee OA is extensively studied as a primary underlying cause of functional limitations. Large variations (4-64%) in muscle strength are observed between individuals with knee OA and controls, with no differences in muscle strength between OA disease severity identified [8,9]. Muscle weakness is associated with altered muscle activation patterns, specifically increased amplitude and duration of muscle activation and high muscle co-activation during gait [5]. Certain levels of muscle co-activation are required to stabilise the joint [5,10]. High levels of muscle co-activation are believed to be detrimental to joint integrity potentially increasing joint load, especially when load is focused to a single point rather than distributed across the joint [11]. Several cross-sectional studies have shown elevated muscle co-activation in individuals with knee OA during gait [5], increasing with disease severity [12], while others have found no difference [13]. This could

be a result of methodological differences, whereby Zeni et al. grouped Kellgren and Lawrence grades 2 and 3 together whereas Rutherford et al. kept each grade separately [12,13]. Moreover, muscle co-activation was assessed differently with one study using principal component analysis while the other used the co-activation index equation [12,13]. During other weight-bearing activities of daily living, there remains limited research. Studies exploring activation patterns found elevated muscle co-activation for stair negotiation [10,14], and sit-to-stand [14,15]; moreover the authors [14] demonstrated different co-activation patterns across activities of daily living (gait, stair negotiation, sit-to-walk). These elevated levels of muscle co-activation are believed to have detrimental effects on joint integrity by increasing the joint load, which exacerbates joint damage [5].

Sex differences in muscle weakness are seen with knee OA [16–18]. Previous research comparing normal-weight and obese adults with knee OA found reduced strength (normalised to body mass) in obese women and no difference in men, and while muscle cross-sectional area increased in obese men there was no difference in women [16]. These changes in muscle cross-sectional area are associated with the composition of the muscle determined from magnetic resonance imaging. Obese women had increased intra-muscular fat, reduced muscle fibre tissue and no change in cross-sectional area, while the men had no changes in the amount of muscle tissue but increased intra-muscular fat explaining the increase in cross-sectional area [16,19]. Sex-hormones modulate knee tissue; however, estrogen alone cannot explain the observed sex-differences [20]. The poor prognosis of knee OA in women with muscle strength deficits may be explained by sex-specific relationships between muscle-specific strength and body mass index [16]

The further implications of sex in the relationship between muscle function and knee OA may be able to explain why females are at an increased risk of knee OA. Women with knee OA have been shown to have poorer health outcomes [21], specifically elevated pain levels [22] and impaired physical and

self-reported function [18], compared to men. Reduced muscle function is associated with pain and functional limitations and may, therefore, explain these differences [23,24].

The purpose of this study was to investigate sex and disease-related differences in muscle function (strength and muscle co-activation) in individuals with and without knee OA. It was hypothesised that muscle co-activation during weight-bearing activities (gait, stair negotiation, sit-to-walk) will be higher in women compared to men, regardless of disease status.

Methods

Participants

Participants were recruited based on sample size calculations of the NEKO study (NCT02314715 www.clinicaltrials.gov). A sample size calculation for this study based on multiple regression with muscle co-activation as the independent variable and four dependent variables (age, sex, strength, disease status), effect size of 0.35, alpha 0.05, and 80% power, resulting in a minimum required sample size of 39. A convenience sample of adults (aged ≥40years) with doctor-diagnosed unilateral/bilateral knee OA, self-reported pain, stiffness lasting <30minutes, were recruited, as well as asymptomatic healthy age-matched controls. The presence of knee OA-related structural change (i.e. joint space narrowing, osteophytes, bone marrow lesions) was confirmed by magnetic resonance imaging (scored based on the Boston Leeds Osteoarthritis Knee Score, data not presented here), and ultrasound (sonographer with 12 years clinical experience, data not presented here). Participant recruitment was through rheumatology clinics; general practitioners; local newspaper adverts; friends and family of individuals with knee OA; the Active Living Database, a Glasgow Caledonian University held database of older adults willing to volunteer for research; and Glasgow Caledonian University staff.

Exclusion criteria were: any other neuromuscular skeletal injury or disease; knee replacement; knee surgery in the past year; steroid injections in the past three months or severe co-morbidity which would interfere with the study. A history of lower limb OA or chronic/stable lower limb pain in the past three months (controls only).

All participants gave written informed consent to participate in the study approved by Glasgow Caledonian University (HLS12/86) and West of Scotland (13/WS/0146) Research Ethics committees and conducted in compliance with the Declaration of Helsinki.

Electromyography

Surface electromyography (EMG) was recorded from the vastus medialis and lateralis (VM, VL); rectus femoris (RF); semitendinosus (ST); biceps femoris (BF): medial and lateral gastrocnemius (MG, LG) of the test leg (Trigno sensors, 99% silver 4 5*1mm bar sensors, fixed inter-electrode distance 10mm, Delsys, Boston USA). The most symptomatic knee based on self-report in individuals with knee OA or a randomly assigned knee in controls defined the test leg. Based on surface electromyography for the non-invasive assessment of muscles recommendations [25], the area was prepared by shaving, lightly abrading and cleaning with alcohol. Isolated contractions assessed EMG recordings for signal quality and noise. The raw signal passed through a Trigno differential amplifier, input impedance 10,000MΩ, common mode rejection ratio >80dB, gain 1,000 with a bandwidth of 20Hz-450Hz and recorded with a 16bit analogue-to-digital converter (PCI-DAS6402/16, Measurement computing corporation, Massachusetts, USA), at a sampling rate of 2400Hz. All EMG and force data were collected in Qualysis Track Manager (version2.7-2.9, Qualysis Motion Capture Systems, Sweden) and processed in Spike2 (version 2.7.10, Cambridge Electronic Design, Ltd, Cambridge, UK).

Measurement of activities of daily living (ADL)

During a single visit, participants performed a series of ADL in the following order: stair ascent and stair descent; walking; and sit-to-walk transitions, followed by muscle strength assessments. The number of trials performed for each activity, as stated below was a pragmatic decision to enable high-quality data while safeguarding against high levels of fatigue.

A four-step instrumented staircase with a Kistler force plate (9286BA, Kistler, Switzerland) embedded into the second step and aligned with a force plate embedded in the walkway assessed stair negotiation. Participants were instructed to ascend the stairs, turn and descend. Three successful trials defined as the entire foot of the test leg landing within the boundaries of both force plates with no apparent signs of targeting the force plate were collected. The use of handrails was permitted if required. Step-over-step (alternate leg on each step) was preferred, and when this was not possible step-by-step (both legs on the same step, with the test leg as the leading leg) was permitted.

Participants performed seven successful (defined above) walking trials at self-selected walking speed. Each trial was within 10% of mean movement time for that task (Brower timing system, Draper, Utah, USA). Walking unaided was prefered; however, due to the lack of a harness, participants were permitted to use walking aids if required.

Participants were seated on a standard armchair (height 48cm) aligned next to the force plate with their back against the chair and the test leg on the force plate. Participants were instructed to stand up, walk 3.6m before turning and returning to the seated position. The use of the chair arm was permitted if required. The transition from sit-to-walk (onset of force to toe-off) from three trials was used for the analysis [26].

For gait and stair negotiation trials, the stance phase was analysed, defined from initial contact (ground reaction force exceeding 20N) to toe-off (ground reaction force subsiding below 20N). The stance phase was compartmentalised into four sub-phases; loading (0-15% of stance); early-stance (15-40%); mid-stance (40-60%); and late-stance (60-100%) with an additional pre-stance phase of 150ms prior to initial contact [27]. Stair negotiation was also compartmentalised into transition (stance phase on the force plate embedded in the floor), and continuous (stance phase on the force plate embedded in the staircase), for ascent and descent.

Muscle strength testing

Participants were seated in the Biodex dynamometer (Biodex 4pro, Biodex Medical Systems Inc, New York, USA), and secured using padded straps across the distal thigh, and waist with their knee and hip flexed at 50^{o} and 90^{o} respectively. 45^{o} and 30^{o} knee flexion is the typical angle for strength testing due to its link between strength and functional performance [28] and least ligamentous strain [29] respectively. However, 50^{o} flexion is the angle at which the greatest force is produced [30–32]. The dynamometer lever arm was attached to the distal shank approximately an inch above the malleolus, aligned to the knee joint axis. Participants were instructed to sit with their arms folded across the chest and extend or flex their knee as forcefully as possible, holding for 3s with 30s rest between contractions. Following a series of incremental warm-up contractions starting from light building to maximal, participants performed a series of 3 maximal voluntary isometric contractions (MVIC's) for the knee flexors and extensors with verbal encouragement provided. For the gastrocnemius, participants were seated with their knee fully extended (participants full extension 0-5^{o}) and foot in anatomical neutral, secured using strapping across the pelvis and thigh with a resistance, applied to the ball of the foot. Following a series of incremental warm-up contractions (as above), participants performed a series of 3 plantarflexion MVIC's lasting 3s with 30s rest, with verbal encouragement. EMG only was recorded during plantarflexion contractions.

Data Management

All EMG data was Finite Impulse Response Butterworth 4th Order bandpass filtered at 20-450Hz. Root mean squared amplitude (RMS_{amp}) was calculated for the stance phase and subsequent sub-phases as the RMS_{amp} over the epoch defined above and normalised to MVIC RMS_{amp}. MVIC RMS_{amp} was calculated over a 500ms window, 250ms either side of peak torque for the hamstring and quadriceps, and 250ms either side of peak EMG amplitude for the gastrocnemius. Peak torque defined as the highest torque during the MVIC.

Muscle co-activation was calculated using normalised RMS_{amp} and assessed using the co-activation index (1) [33]. The mean RMS_{amp} was calculated for each time epoch as stated above for each muscle. The number of samples within each epoch varied between individuals. The grand mean was then calculated for each muscle group (flexors, extensors, medial, lateral). For each muscle co-activation pairing, the lower of the two values was *lowerEMGi* and the higher *higherEMGi* to determine muscle co-activation; knee extensors (VL, RF, VM): flexors (ST, BF) and medial (VM, ST, MG): lateral (VL, BF, LG) combinations during all activities.

$$\text{Co-activation index} = \frac{\text{lowerEMGi}}{\text{higherEMGi}} (\text{lowerEMGi} + \text{higherEMGi}) \quad (1)$$

Statistical Analysis

Means and standard deviations, or frequencies were determined. Skewness, kurtosis, and boxplots were obtained to examine the distribution and identify outliers for all variables. Hierarchal sensitivity analysis with 1) all data; 2) extreme outliers (>3x inter-quartile range [IQR]) removed; 3) all outliers (>1.5x IQR) removed; 4) all outliers and device users removed ('minimal data'); 5) minimal data with

1.5x IQR outliers with low MVIC or reported pain during MVIC included. Device users are defined as individuals who used the handrails, chair arm or a walking aid while performing the tasks. Once extreme outliers were removed, some variables became significantly different between individuals with knee OA and controls (data not presented), this did not change when further outliers were removed [34]. The main analysis was run with only extreme (3x IQR) outliers removed. Sensitivity analysis was performed with and without device users for each activity separately; there was no difference in the results between these analyses.

Independent-samples Student's t-test was performed to assess the differences in muscle function between individuals with knee OA and controls, and between sexes. Levene's test was performed to test heteroscedasticity to assess the appropriateness of linear regression, with the exception of mediolateral walking the data did not violate assumptions. Linear regression was performed with muscle co-activation as the dependent variable and sex-adjusted muscle strength, age, sex and disease status (present/absent of knee OA) as independent variables. Sex and disease status were coded as 0/1 (Women/Men, KOA/C). Muscle strength was corrected for sex; the average muscle strength for each sex was calculated and subtracted from muscle strength of the individuals. All statistical analysis was conducted using SPSS (Version 22.0-23.0, Chicago, USA) with alpha set at 0.05. The data was Bonferroni-Holm corrected for multiple comparisons [35,36].

Results

A total of 77 individuals with knee OA and 18 age-matched controls were recruited (Table 1.). MRI was performed on 68 individuals with knee OA, of those 24 had Tri compartmental, 14 medial, 3 lateral, 15 mediolateral OA, and 12 had no knee OA on MRI, however, had been diagnosed as having knee OA. Fifteen people had missing data for stairs tasks only (2 controls 11%, 13 knee OA 17%) due to equipment failure resulting in the inability to move the stairs into position.

Knee OA vs Controls

Individuals with knee OA were weaker than healthy controls for both knee extensors (*P*=0.001 95%CI -0.33, -0.09, Table 1.) and flexors (*P*=0.001 95%CI -0.18, -0.05). Overall there were limited differences in muscle co-activation index between individuals with knee OA and controls, across activities (2/22, 9%). Sensitivity analysis showed device use did not affect the results. Muscle co-activation index was higher in individuals with knee OA for knee flexors-extensors during mid-stance, and mediolateral during early-stance during gait only (Figure 1.).

Men vs women

When participants were grouped together by sex regardless of disease status men (extensors 0.72 [0.23] Nm/kg, flexors 0.43 [0.12] Nm/kg) were stronger than women (extensors 0.57 [0.24] Nm/kg, flexors 0.30 [0.12] Nm/kg) for both extensors (*P*<0.001 95%CI -0.19, -0.08) and flexors (*P*=0.004, 95%CI -0.25, -0.05). Men were stronger than women in individuals with knee OA, there was no difference between men and women for controls (Table 1.).

Muscle co-activation index was higher in women compared to men in individuals with knee OA (Figure 2). The control group women had higher flexor-extensor co-activation index during late stance, and continuous stair negotiation. Overall when grouped by sex regardless of disease status muscle co-activation was higher in women compared to men across all activities except flexor-extensor muscle co-activation index during loading and mediolateral muscle co-activation during sit-to-walk (20/22, 89% significant combinations *P*<0.05, Figure 3.).

Muscle co-activation across sex and disease status

Sex, disease status, age and muscle strength explained 14-36% of the variance in flexor-extensor and 13-21% of mediolateral muscle co-activation index (power 75.4-99.8%). Bonferroni-Holm corrected for multiple comparisons sex, and muscle strength were significant variables within the model (Table 2.). Sex was significant for flexor-extensor walk, sit-to-walk and continuous stair descent only. Muscle weakness was significant for flexor-extensor sit-to-walk, stair descent transition, and mediolateral stair ascent. Mediolateral walking violated the assumption of heteroscedasticity and should be interpreted with caution.

Discussion

Muscle co-activation was higher in women with knee OA compared to their male counterparts, however, there was no difference between sexes for controls. High muscle co-activation was primarily related to sex rather than disease status, where muscle co-activation was higher in women regardless of whether knee OA was present. There was no difference in muscle co-activation between individuals with knee OA and healthy controls.

Muscle co-activation was higher in women and individuals who were weaker regardless of age and disease status. However, age, sex, disease status and muscle strength only explained a small proportion of variance in muscle co-activation (13-36%). These results may explain why women are at an increased risk of incidence and progression of knee OA, as a result of muscle weakness [16–18], higher muscle activation potentially increasing joint loading [5]. However, there was no difference between sexes in the control group. Additionally, the sex differences for the knee OA group may be explained by unequal group size. While the unequal group size reduced the power for the t-tests, the study was powered based on the more robust regression models.

Muscle weakness and female sex were significant predictors of high muscle co-activation. Muscle co-activation is theorised to be a compensatory mechanism for muscle weakness [5]. Accommodating for the diminishing force-generating capabilities associated with knee OA to maintain a certain level of function and movement activation patterns [37]. Muscle weakness may, therefore, be the contributing factor to high muscle co-activation. High muscle co-activation is thought to increase joint load, with detrimental effects on cartilage and joint integrity [7]. These alterations within the joint as a result of high muscle co-activation within women may also explain why women are at an increased risk of knee replacement [38], and joint space narrowing [39].

Contrary to previous research there was no difference in muscle co-activation between individuals with knee OA and healthy controls. When the normalised muscle activation (supplementary file) is compared to that of the literature, the mean EMG patterns are similar in amplitude and shape. Within our results, large variation between participants can be seen, with the controls demonstrating very similar traces. There are several possible explanations. Firstly we did not grade disease severity; therefore, the participants spanned the spectrum of disease from very early to awaiting joint replacement which may explain the large variation. Additionally, the control group where asymptomatic, however, it is plausible that structural joint disease features of knee OA may have been present. The combination of these two may explain the lack of significant differences between groups. Participants were also permitted to use handrails, chair-arms and walking aids where required. When sensitivity analysis was performed on the results with and without the use of assistive devices the results did not change. This may be due to participants performing the activities with their usual gait patterns, whereas removing assistive devices would have resulted in a more guarded gait pattern.

Muscle co-activation in both the knee OA and control groups in the present study were higher than previously reported [5]. A possible explanation is a difference in signal processing, previous studies using the same equation and normalisation methods used linear envelope to process the data rather

than RMS_{amp}. RMS_{amp} was used because it is believed to be more robust than linear envelope and directly linked to electrical power, having more physiological significance over linear envelope [40]. Additionally, muscle strength including EMG used for normalisation was assessed at 50° flexion the angle at which the greatest force is produced [30–32]. While the previous literature uses 15° 45°, 55°, 90° [13,37,41–44], or do not report the joint angle [27,45–47]. Alternatively, it has been highlighted that asymptomatic individuals may demonstrate knee OA joint damage [48,49], suggesting high muscle co-activation may be associated with joint damage regardless of symptoms. Some studies define knee OA and control groups using Kellgren and Lawrence scores; this approach was not used for the present study which defined controls by the absence of knee OA-related symptoms.

This study has several strengths and limitations. 1. It is a relatively large convenience sample (N=95) with substantial sensitivity analysis performed before and during the statistical analysis. 2. Participants ranged from newly diagnosed to awaiting a joint replacement, covering a spectrum of disease severity. 3. MVC's were performed for the hamstrings and quadriceps, however standardised reference contractions were performed for the gastrocnemius to prevent discomfort to the patients. 4. During stair negotiation and sit-to-walk transitions, participants were permitted to use the handrails, step-by-step stair negotiation style and the chair arm. This showed muscle co-activation during normal daily living, this meant the dynamic movements were not standardised across the entire sample. Sensitivity analysis indicated that this did not affect the results. 5. The muscle co-activation equation used in this study is the equation predominantly adopted in the muscle co-activation literature, however, the output is non-directional meaning it is unclear which muscle group has the higher muscle activation without looking at the raw data. 6. There were differences in the statistical power between the sex and disease analysis, where the sex analysis had greater power (38 males versus 57 females) than the disease analysis (77 individuals with knee OA versus 18 controls). Using post-hoc power analysis, there is potentially only one model where disease status would have reached statistical significance if the disease status had the same level of power as the sex analysis. Therefore, this issue would not have

affected the overall conclusions. 7. Mediolateral walking violated the assumption of heteroscedasticity for the linear regression model and should, therefore, be interpreted with caution. 8. Flexor-extensor and mediolateral muscle co-activation may not be independent of each other due to the use of the same muscles within the calculations.

In conclusion, high muscle co-activation was associated with female sex and muscle weakness regardless of disease status and age. Muscle weakness in women may explain higher muscle co-activation compared to men and potentially contributes to the explanation of the increased risk of incidence and progression of knee OA in women. In contrast to previous research, no statistical difference was found in muscle co-activation between individuals with knee OA and age-matched controls. Further longitudinal research is required to understand the link between muscle co-activation, sex, muscle weakness and the associated risk of incidence and progression of knee OA.

Funding

No funding was received for the work carried out as part of this article

Conflicts of interest

The authors have no conflicts of interest to declare with the work presented in this article

Author contributions

Conception and design of the Study: **Smith, Steultjens, Woodburn**

Acquisition of data: **Smith,**

Analysis and interpretation of data: **Smith, Steultjens**

Drafting of the article and revising it critically for important content: **Smith, Steultjens, Woodburn**

Final approval of the version to be submitted: **Smith, Steultjens, Woodburn.**

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Tables

Table 1. Patient demographics and activities of daily living data presented as means (SD)

	Knee OA				Controls				Knee OA vs Control
	Men (N=29)	**Women** (N=48)	**All** (N=77)	**P (95% CI)**	**Men** (N=9)	**Women** (N=9)	**All** (N=18)	**P (95% CI)**	**P (95% CI)**
Age, years	61.80 (8.35)	62.96 (7.98)	62.5 (8.1)	0.545 (-2.64, 4.97)	66.31 (9.98)	58.71 (9.80)	62.5 (10.4)	0.123 (-17.49, 2.29)	0.996 (-5.40, 5.42)
Height, m	1.76 (0.07)	1.60 (0.07)	1.66 (0.11)	**<0.001** (-19.05, -12.12)	1.70 (0.06)	1.64 (0.04)	1.67 (0.06)	0.020 (-11.24, -1.10)	0.495 (-4.95, 2.42)
Body mass, kg	92.18 (16.68)	75.08 (18.16)	81.5 (19.4)	**<0.001** (-25.36, -8.85)	72.29 (9.00)	63.56 (9.86)	67.9 (10.2)	0.067 (-18.17, 0.70)	**<0.001** (7.03, 20.15)
BMI, kg/m^2	29.80 (4.96)	29.19 (6.63)	29.4 (6.0)	0.650 (-3.26, 2.04)	24.88 (2.75)	23.69 (4.46)	24.3 (3.6)	0.506 (-4.89, 2.51)	**<0.001** (2.92, 7.36)
Duration of symptoms, years	9.83 (10.37)	8.82 (8.44)	9.3 (9.2)	0.643 (-5.32, 3.31)	-	-	-	-	-
Quadriceps Peak Torque, Nm/kg	0.68 (0.17)	0.52 (0.23)	0.58 (0.23)	**0.002** (-0.27, -0.06)	0.80 (0.36)	0.78 (0.15)	0.79 (0.26)	0.881 (-0.29, 0.25)	**0.001** (-0.33, -0.09)
Hamstrings Peak Torque, Nm/kg	0.41 (0.10)	0.28 (0.12)	0.33 (0.13)	**<0.001** (-0.19, -0.08)	0.49 (0.18)	0.39 (0.11)	0.44 (0.15)	0.170 (-0.25, 0.05)	**0.001** (-0.18, -0.05)
Activities of Daily Living									
Walk Speed, m/s	1.08 (0.15)	1.04 (0.15)	1.05 (0.15)	0.314 (-0.12, 0.04)	1.18 (0.16)	1.28 (0.17)	1.23 (0.17)	0.225 (-0.67, 0.27)	**<0.001** (-0.26, -0.10)
Walking stick use, yes (%) #	1 (1%)	1 (1%)	2 (3%)	-	0	0	0	-	-
Chairarm use, Yes (%) #	18 (62%)	35 (73%)	53 (69%)	-	6 (67%)	6 (67%)	12 (67%)	-	-
Stairs walking style (Knee OA=64 [men=24, women=40] Controls =16 [men=7, women=9])									
Ascent, SOS (%) #	24 (100%)	35 (88%)	59 (92%)	-	7 (100%)	9 (100%)	16 (100%)	-	-
Ascent, SBS (%) #	0	5 (12%)	5 (8%)	-	0	0	0	-	-
Descent SOS (%) #	23 (96%)	32 (80%)	55 (86%)	-	7 (100%)	9 (100%)	16 (100%)	-	-
Descent, SBS (%) #	1 (4%)	8 (20%)	9 (14%)	-	0	0	0	-	-
Handrail use, Yes (%) #	4 (16%)	22 (55%)	26 (41%)	-	1 (14%)	0	1 (6%)	-	-

OA – osteoarthritis; 95% CI – 95% confidence interval; SOS – step-over-step; SBS – step-by-step; # number(percentage). **Bold** indicated Bonferroni-Holm significant differences

Table 2. Results of regression analysis of muscle co-activation during activities of daily living

	Hamstrings:quadriceps walk			Medial:lateral walk[a]		
	B Coeff	SE	P	B Coeff	SE	P
Age	0.651	0.272	0.019	-0.114	0.480	0.812
Sex	-17.924	4.702	**<0.001#**	-19.630	8.349	0.021
Disease status	3.590	5.892	0.544	-4.668	10.723	0.664
Quads PT	-26.965	10.432	0.012	-60.123	18.373	0.002
	R^2=0.242, P=<0.001* PWR=0.830			**R^2=0.182, P=0.002* PWR=0.696**		
	Hamstrings:quadriceps sit-to-walk			Medial:lateral sit-to-walk		
	B Coeff	SE	P	B Coeff	SE	P
Age	1.402	0.307	**<0.001#**	0.290	0.409	0.480
Sex	-14.596	5.337	0.008	-11.300	7.131	0.117
Disease status	12.569	6.854	0.070	10.611	9.123	0.248
Quads PT	-49.369	11.743	**<0.001#**	-49.446	15.770	0.002
	R^2=0.362, P=<0.001* PWR=0.997			**R^2=0.131, P=0.018* PWR=0.702**		
	Hamstrings:quadriceps SUT			Medial:lateral SUT		
	B Coeff	SE	P	B Coeff	SE	P
Age	0.498	0.270	**0.069**	0.112	0.406	0.783
Sex	-19.026	4.613	**<0.001**	-19.407	7.045	0.008
Disease status	4.607	5.809	**0.430**	2.932	8.793	0.740
Quads PT	-36.028	10.330	**0.001**	-53.913	15.353	**0.001#**
	R^2=0.314, P=<0.001* PWR=0.923			**R^2=0.234, P=0.001* PWR=0.680**		
	Hamstrings:quadriceps SUC			Medial:lateral SUC		
	B Coeff	SE	P	B Coeff	SE	P
Age	0.250	0.527	0.698	0.038	0.405	0.925
Sex	-22.753	8.613	0.010	-13.707	7.031	0.055
Disease status	6.939	10.837	0.524	19.321	8.775	0.031
Quads PT	-38.959	18.920	0.043	-58.569	15.322	**<0.001#**
	R^2=0.137, P=0.037* PWR=0.715			**R^2=0.213, P=0.002* PWR=0.668**		
	Hamstrings:quadriceps SDC			Medial:lateral SDC		
	B Coeff	SE	P	B Coeff	SE	P
Age	0.604	0.353	0.091	0.116	0.323	0.721
Sex	-17.192	6.032	0.006	-10.054	5.610	0.078
Disease status	7.508	7.595	0.326	3.872	7.002	0.582
Quads PT	-41.938	13.321	0.002	-39.801	12.226	0.002
	R^2=0.230, P=0.001* PWR=0.663			**R^2=0.172, P=0.011* PWR=0.700**		
	Hamstrings:quadriceps SDT			Medial:lateral SDT		
	B Coeff	**SE**	**P**	**B Coeff**	**SE**	**P**
Age	0.653	0.424	0.128	0.488	0.456	0.289
Sex	-24.265	7.199	**0.001#**	-17.056	7.902	0.034
Disease status	1.160	9.147	0.899	-0.130	9.906	0.990
Quads PT	-67.537	15.610	**<0.001#**	-54.768	17.012	0.002
	R^2=0.335, P=<0.001* PWR=0.961			**R^2=0.206, P=0.003* PWR=0.696**		

[a] – violates assumption of heteroscedasticity; Quads PT – quadriceps peak torque; SUT – stairs ascent transition; SUC – stair ascent continuous; SDC – stair descent continous; SDT – stair descent transition; β Coeff – beta standardised regression coefficient; SE – standard error; * uncorrected significant P≤0.05, # significant Bonferroni-Holm corrected terms

Figure legends

Figure 1. Muscle co-activation of the A) hamstrings:quadriceps B) medial:lateral across different activities for knee OA (Black) and controls (Spotted). Significant differences between knee OA and controls * Holm-Bonferroni corrected significant values.

Figure 2. Muscle co-activation of the hamstrings:quadriceps (A-B), medial:lateral (C-D) for individuals with osteoarthritis (A-C) and controls (B-D) for women (Black) and men (spotted). Significant sex differences * Holm-Bonferroni corrected significant values.

Figure 3. Muscle co-activation of the A) hamstrings:quadriceps B) medial:lateral across different activities for women (Black) and men (Spotted) combined regardless of disease activity. Significant sex differences * Holm-Bonferroni corrected significant values.

Figures

Figure 1.

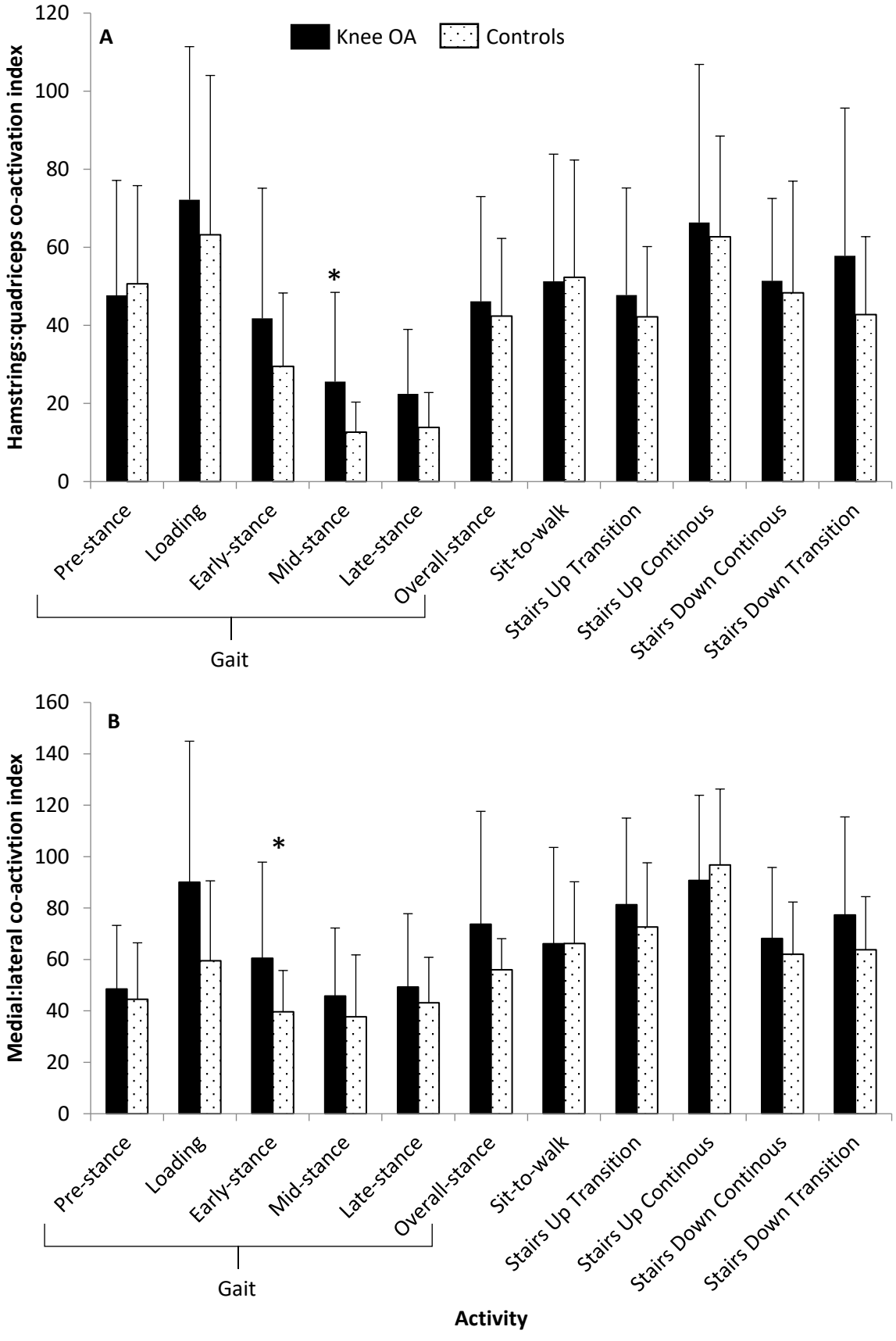
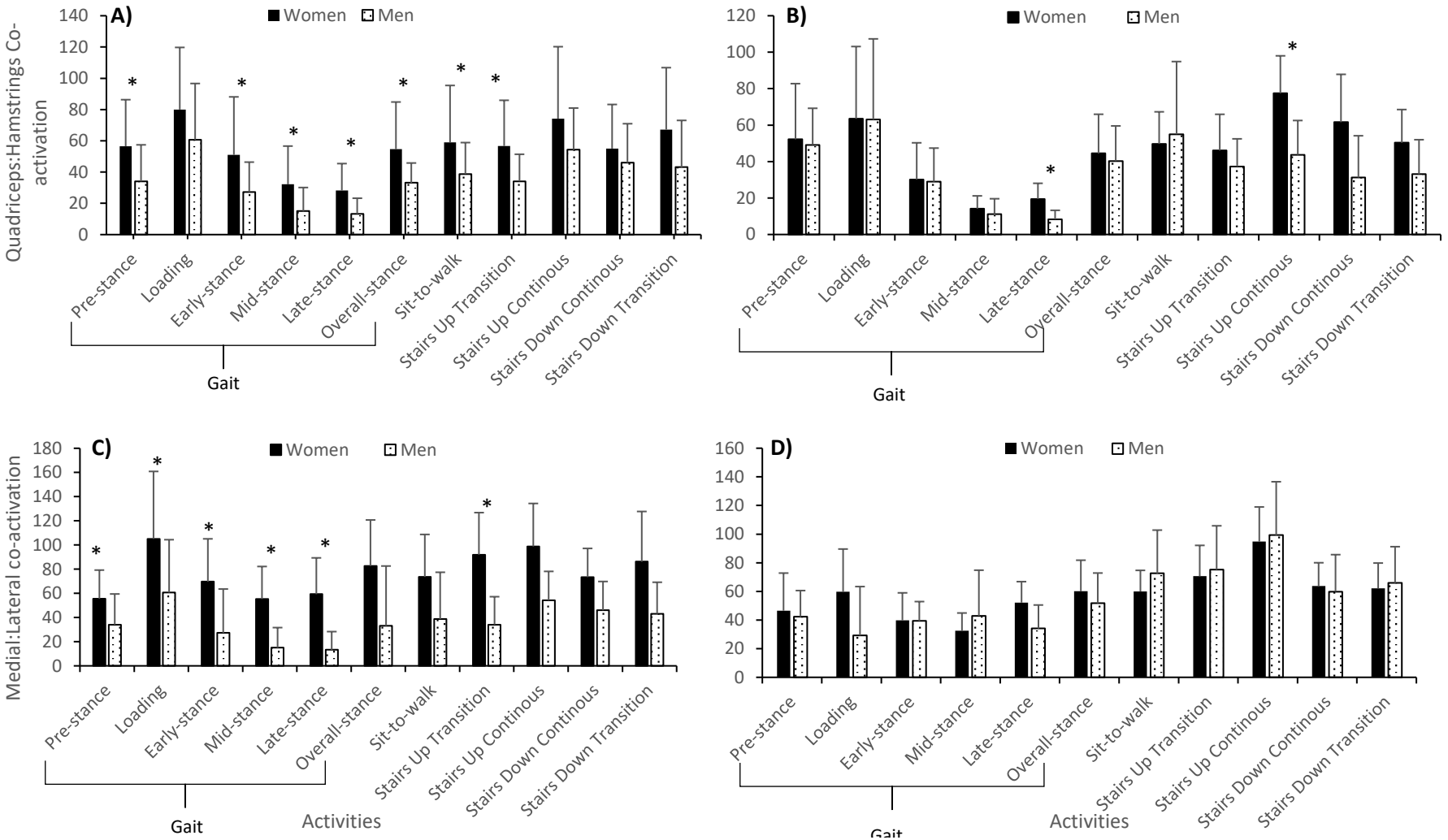


Figure 2.


A)
Women
Men
Quadriceps:Hamstrings Co-activation
140
120
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80
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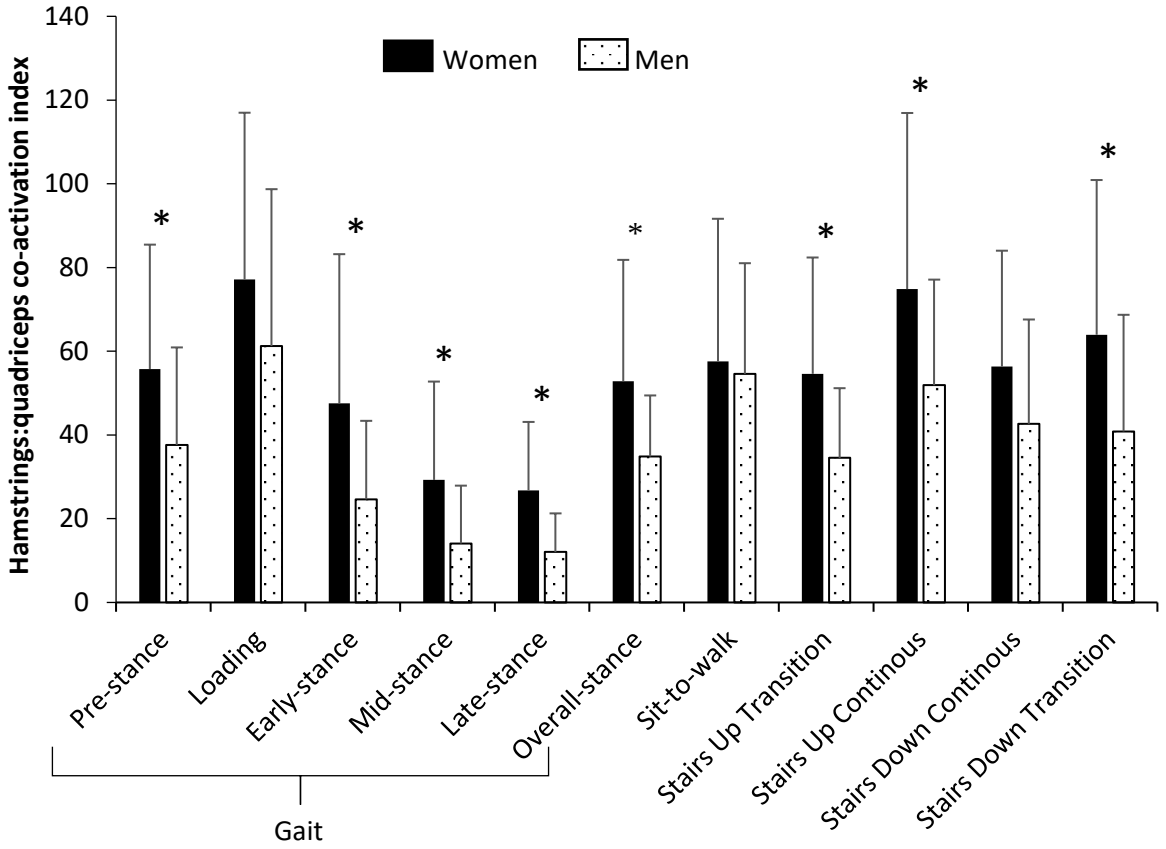
20
0
Pre-stance
Loading
Early-stance
Mid-stance
Late-stance
Overall-stance
Sit-to-walk
Stairs Up Transition
Stairs Up Continous
Stairs Down Continous
Stairs Down Transition
Gait
B)
Women
Men
120
100
80
60
40
20
0
Pre-stance
Loading
Early-stance
Mid-stance
Late-stance
Overall-stance
Sit-to-walk
Stairs Up Transition
Stairs Up Continous
Stairs Down Continous
Stairs Down Transition
Gait
C)
Women
Men
Medial:Lateral co-activation
180
160
140
120
100
80
60
40
20
0
Pre-stance
Loading
Early-stance
Mid-stance
Late-stance
Overall-stance
Sit-to-walk
Stairs Up Transition
Stairs Up Continous
Stairs Down Continous
Stairs Down Transition
Gait
Activities
D)
Women
Men
160
140
120
100
80
60
40
20
0
Pre-stance
Loading
Early-stance
Mid-stance
Late-stance
Overall-stance
Sit-to-walk
Stairs Up Transition
Stairs Up Continous
Stairs Down Continous
Stairs Down Transition
Gait
Activities

Figure 3.


Hamstrings:quadriceps co-activation index
Women
Men
140
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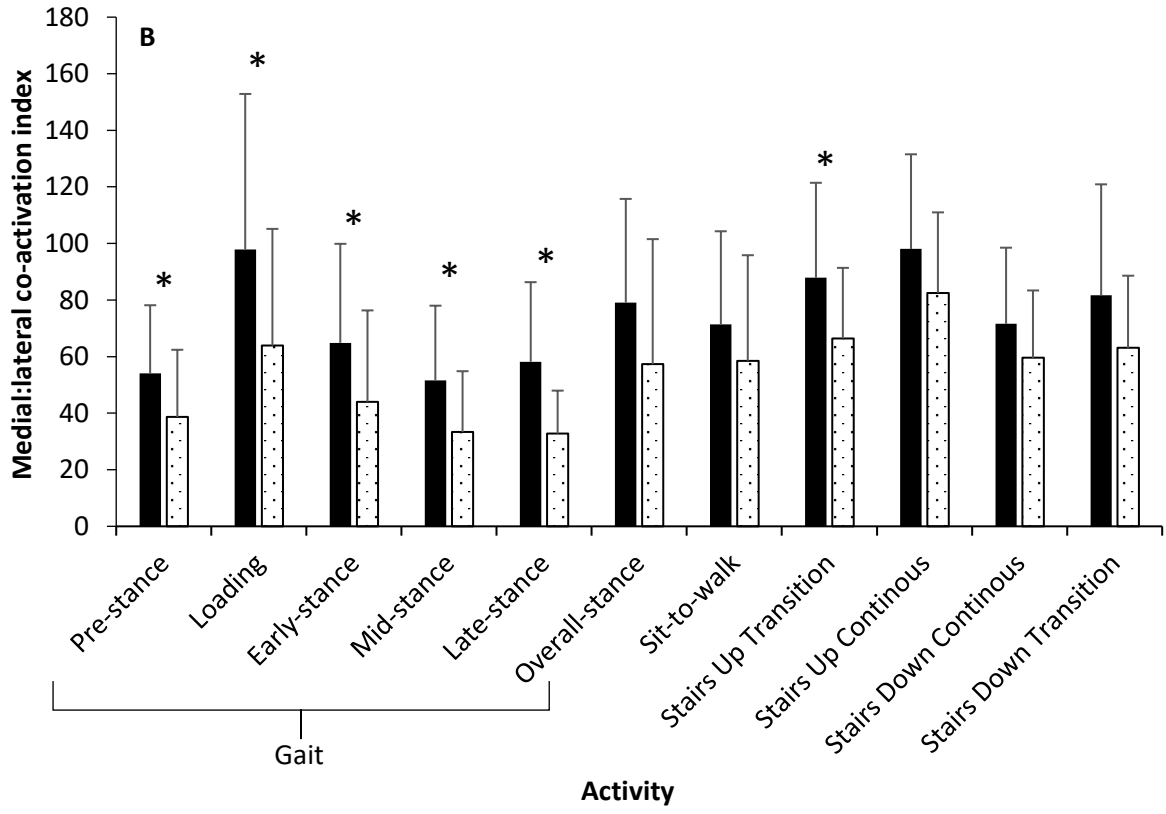
Pre-stance
Loading
Early-stance
Mid-stance
Late-stance
Overall-stance
Sit-to-walk
Stairs Up Transition
Stairs Up Continous
Stairs Down Continous
Stairs Down Transition
Gait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Medial:lateral co-activation index
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Pre-stance
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Late-stance
Overall-stance
Sit-to-walk
Stairs Up Transition
Stairs Up Continous
Stairs Down Continous
Stairs Down Transition
Gait
Activity