Thermal hyperalgesia distinguishes those with severe pain and disability in unilateral lateral epicondylalgia

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1 **Thermal hyperalgesia distinguishes those with severe pain and disability in unilateral**

2 **lateral epicondylalgia**

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26 **Abstract**

27 **Objectives** To evaluate if sensory, motor and psychological factors are different in severe

28 lateral epicondylalgia compared to less severe cases and control.

29 **Methods** 164 patients with unilateral lateral epicondylalgia and 62 healthy control

30 participants of comparable age and sex underwent the following testing: quantitative sensory

31 testing (pressure, thermal pain thresholds), pain-free grip, quality of life (EuroQol) and

32 psychological (HADS, Tampa). Cluster analysis classified patients into mild, moderate or

33 severe subgroups using the Patient Rated Tennis Elbow Evaluation (PRTEE). Data were then

34 evaluated to determine differences between control and lateral epicondylalgia subgroups.

35 **Results** Bilateral cold hyperalgesia (affected elbow, standardised mean difference (SMD):

36 1.14, P=0.000; unaffected elbow SMD: 0.94, P=0.000) and unilateral heat hyperalgesia

37 (SMD -1.06, P=0.001) were evident in severe lateral epicondylalgia in comparison to healthy

38 controls. All patient groups regardless of severity demonstrated bilateral and widespread

39 mechanical hyperalgesia relative to controls (P<0.003), however only those with moderate

40 and severe symptoms showed large differences (SMD>0.8) at all sites. Quality of life was

41 significantly poorer in patients with severe symptoms, while anxiety, depression and

42 kinesiophobia did not differ between subgroups.

43 **Discussion** Lateral epicondylalgia patients presenting with severe pain and disability could

44 be distinguished by hypersensitivity to thermal stimuli, notably bilateral cold hyperalgesia.

45 Findings may implicate a combination of central, peripheral and sympathetic nervous system

46 processes and may help explain the poorer outcomes found in this subpopulation.

47 **Keywords / Phrases:** tennis elbow, hyperalgesia, depression, quality of life, kinesiophobia.

48

Introduction

Lateral epicondylalgia (LE) or tennis elbow affects up to 3% of the population with peak incidence occurring between 40-50 years of age.[1, 2] For the majority of sufferers, LE is self-limiting, with an average duration of a typical episode between six months and two years.[3] However, in two recent randomised controlled trials, 10 and 17% of people adopting a wait-and-see policy failed to report successful outcomes after one year.[4, 5] Furthermore, it has been estimated that between 5 and 10% of patients develop chronic symptoms and eventually undergo surgery.[6, 7] High pain and disability at baseline is one of the few consistently reported indicators of poorer long term outcome after conservative[3, 8, 9] and surgical treatment of LE.[10] For this reason, it might be valuable to identify other features that differentiate those individuals with higher pain and disability from those with lesser symptoms.

The relative simplicity of the clinical presentation of LE belies the complexity of its underlying aetiological processes. The mechanisms of pain and disability are likely multifactorial, involving an interaction of local tendon pathophysiological changes, motor impairment, nociceptive system mechanisms[11] and possibly psychological factors.[12] Motor impairment is widespread in the affected upper limb,{Alizadehkhaiyat, 2007 #17}{Coombes, 2011 #1344} with consistent evidence of markedly reduced pain-free grip strength being the strongest feature.[24, 25] Nociceptive system impairments in LE as measured through quantitative sensory testing have identified sensory alterations, but little is known about the distinct patterns of these changes in those who have high levels of pain and disability. A number of studies have shown that bilateral mechanical hyperalgesia exists in LE,[13-15] while a nascent body of research has explored thermal hyperalgesia.[15-18] Recently Ruiz-Ruiz et al[16] reported bilateral thermal hyperalgesia in a group of 16 LE participants, whereas other authors[19] have previously proposed that a subgroup of patients with severe LE exhibit cold

74 hyperalgesia. Cold hyperalgesia is emerging as an important factor in other musculoskeletal

75 disorders such as whiplash associated disorders, with evidence that it can differentiate

76 subgroups and help predict poor recovery over and above that of baseline pain and

77 disability.[20, 21] In addition, Huge et al identified bilateral cold and heat hyperalgesia in acute

78 complex regional pain syndrome (CRPS), and incomplete recovery of cold pain thresholds in

79 chronic CRPS in comparison to healthy controls.[22] There is a growing interest in possible

80 psychological factors being associated with chronic musculoskeletal conditions, for example,

81 fear avoidance has been implicated.[23] Preliminary evidence of higher levels of depression and

82 anxiety, which was correlated with pain and disability, has been identified in a small study of

83 LE (n=16), prompting a need for further evaluation of psychological factors in LE.

84

85 The aim of this cross-sectional study was to identify whether sensory, motor and

86 psychological factors can distinguish the subgroup of LE patients with higher pain and

87 disability from those with lesser symptoms and a healthy control population. Comprehensive

88 analysis might provide novel insights into the pathophysiology of the disease and

89 mechanisms underlying delayed recovery found in patients with high baseline pain.

90

91

92 **Methods**

93

94 **Patients and control participants**

95

96 165 participants with LE meeting the following criteria for a randomised controlled trial[26]

97 were recruited: unilateral elbow pain over the lateral epicondyle for longer than six weeks

98 and aggravated by a combination of palpation, gripping and resisted wrist and/or finger

99 extension. Participants were excluded if they had other upper limb conditions, such as,

100 cervicogenic, radiohumeral or neurological, or experienced recent fractures, corticosteroid

101 injection or physiotherapy treatment. 62 healthy participants between 35 and 70, with no

102 history of LE were recruited such that the control group had a similar proportion of males and

103 females to the overall LE population. Participants were excluded if they experienced

104 concomitant neck or other arm pain that prevented participation in their usual work or

105 recreational activities or necessitated treatment within the past six months. All participants

106 were recruited from the general community through media advertisements. Ethical approval

107 was granted by the institutional review board and informed written consent was obtained

108 from all participants.

109

110

111 **Measures**

112

113 *Pressure pain threshold*

114 Pressure pain thresholds (PPT) were measured using a digital algometer (Somedic AB,

115 Farsta, Sweden) with probe size of $1cm^2$, applied at a rate of 40 kPa/s until the first sensation

116 of pain was perceived. PPT were measured bilaterally at the lateral epicondyle and C6-C7

117 facet joints and over the left tibialis anterior muscle. These sites have been previously

118 evaluated in LE, demonstrating substantial intra-rater repeatability (ICC>0.89).[27]

119

120 *Thermal pain thresholds*

121 Heat (HPT) and cold (CPT) pain thresholds were measured bilaterally over the lateral elbow

122 using the Thermotest system (Somedic AB, Farsta, Sweden).[17] Previous studies have

123 confirmed the reliability of these measures (ICC>0.86).[15] From a baseline temperature of

124 30°C, the thermode was increased or decreased at a rate of 1°C/s until the first sensation of

125 pain was perceived, or until maximum and minimum cut-out temperatures of 50°C and 5°C

126 were reached.

127

128 *Pain-free grip*

129 Pain-free grip (PFG) is well established as a highly reliable (ICC>.97) and convenient

130 clinical assessment tool, which correlates more strongly with disability and perceived

131 improvement than maximal grip strength in LE populations.[28-30] It was measured using a

132 digital grip dynamometer with variable handle position (MIE, Medical Research, UK). The

133 participant was positioned in supine with the tested elbow in relaxed extension and forearm in

134 pronation, such that the palm of the hand faced down on the plinth.[26] They were instructed to

135 squeeze the dynamometer handle at a consistent rate and to stop the instant pain was

136 experienced.

137

138 *Pain, disability and quality of life*

139 The patient rated tennis elbow evaluation (PRTEE) was used to quantify pain and functional

140 disability in LE.[31] The PRTEE has been validated in a MRI-confirmed LE population and

141 demonstrated good reliability and sensitivity to change.[31] Responses were scored on 11-point

142 Likert scales with pain and disability subscales contributing equally to the total score, ranging

143 from 0 (no pain or functional disability) to 100 (worst imaginable pain with a very significant

144 functional disability).[31] Participants were asked to rate the level of pain currently experienced

145 at rest and the worst level of pain experienced during the past week on 100mm visual

146 analogue scales (VAS) with the following endpoints: no pain (0mm) and worst pain

147 imaginable pain (100mm). Their level of function during the past week was also rated on a

148   100mm VAS with endpoints: no function (0mm) and full function (100mm). Substantial test-

149   retest reliability has been demonstrated for these two VAS measures (ICC 0.89, 0.85).[32]

150

151   The EuroQol EQ-5D instrument was used to measure health-related quality of life.[33]

152   Responses to five questions regarding different health dimensions were used to generate an

153   index, ranging from 0 to 1, with 1 representing perfect health, by applying predefined scoring

154   weights.[34]

155

156   *Psychological factors*

157   The Hospital Anxiety and Depression Scale (HADS) was measured in all participants to

158   quantify the two most common forms of psychological disturbances - anxiety and

159   depression.[35] It comprised questions rated on four point scales, with anxiety and depression

160   subscales contributing equally to the total score, ranging from 0 to 42, with greater scores

161   indicating greater anxiety and depression. The degree of kinesiophobia, also known as fear of

162   movement or injury,[36] was assessed in the LE participants with the shortened Tampa Scale

163   for Kinesiophobia (TSK-11). Each of the 11 items were scored on four point Likert scales

164   giving a total score ranging from 11 to 44, with higher scores indicating greater

165   kinesiophobia.

166

167   **Procedure**

168

169   Following completion of relevant questionnaires, testing was performed in the following

170   sequence: PFG, PPT, HPT, CPT. The same examiner (BKC) performed all tests, without

171   knowledge of PRTEE total scores or clustering. Tests were performed in triplicate starting on

172   the unaffected or left side in LE or control participants respectively, with twenty second

173 intervals. Mean values were used in analyses. In order to determine the reliability of

174 quantitative sensory testing, they were measured twice in the first 46 participants with LE,

175 separated by a one week interval in which their condition was assumed to be stable.

176

177

178 **Statistical analysis**

179

180 Cluster analysis (based on the K-means algorithm) of the PRTEE scores was performed using

181 SPSS 19 (IBM, Somers, New York, USA) to classify LE participants into three subgroups.

182 This procedure, previously used in studies of other musculoskeletal conditions (e.g., whiplash

183 associated disorders[37]) attempts to identify homogenous groups of cases based on selected

184 characteristics. Following the formation of clusters, analysis of variance (ANOVA) was

185 performed for each continuous outcome in order to compare the three LE groups and the

186 control group. To account for any potential influence of hand dominance, the control group

187 was randomly allocated a "matched affected arm" with an equivalent proportion of dominant

188 sided arms as that observed in the LE group.[38, 39] *Sex* (between-subject) and *Side* (within-

189 subject) factors were included in the ANOVA model along with *Group* (between-subject).

190 Where significant side by group interactions were present, follow-up univariate ANOVA was

191 performed separately for affected and unaffected sides. Pairwise comparisons of interest

192 (simple effects) were followed up with Bonferroni post-hoc tests. Significance was

193 nominated a-priori at $P<0.01$. To enable comparison of effect sizes, standardised mean

194 differences (SMD) were calculated by dividing mean differences (MD) relative to the control

195 group (extracted from SPSS) by the pooled standard deviation (SD). SMD scores greater

196 than 0.8 were interpreted as a strong effect.[40] Categorical outcomes were compared between

197 groups using Chi-squared analysis. Intra-class correlation coefficients (ICC) and their 95%

198 confidence intervals (CI) were calculated using an ICC(3,1) model as a measure of test-retest

199 reliability.

200

201 **Results**

202 Analysis was performed using data from 62 healthy controls and 164/165 patients with LE,

203 owing to one missing PRTEE questionnaire. Cluster analysis identified three subgroups

204 within the LE population based on total PRTEE scores (Figure 1). The clusters, referred to

205 herein as mild, moderate and severe LE, showed an expected incremental increase in mean

206 total PRTEE, supported by a similar increase in worst/resting pain and decrease in function as

207 measured using VAS (P<0.01). Injury duration was not found to differ between LE

208 subgroups, with the average duration being 25 weeks (range six weeks to four years). Levels

209 of anxiety, depression and kinesiophobia were also not significantly different between LE

210 subgroups. No other demographic differences were found between LE and control groups,

211 including gender, age, body mass index, manual occupation or participation in sports

212 involving gripping.

213 The severe LE cluster contained the smallest number of patients (n=27), of which 59.3%

214 were female. These patients were characterised by substantial worst pain levels (mean ± SD:

215 78.1 ± 16.2) and notable resting pain levels (21.8mm ± 12.5mm). Their health-related quality

216 of life (0.59 ± 0.16) was significantly poorer, and the majority (66.7%) reported sleep

217 disturbances due to their elbow condition. The mild LE cluster (n=53) contained a smaller

218 proportion (28.3%) of females and was characterised by moderate worst pain levels (50.6 ±

219 18.2), minimal pain at rest (6.5 ± 13.8mm), higher quality of life (0.77 ± 0.15) and lower

220 prevalence (32.1%) of sleep disturbance, though the latter was not statistically different to the

221 severe group (P = 0.011). The moderate LE cluster comprised the largest number of patients

222   (n=84), displaying intermediary characteristics for pain, quality of life and other clinical

223   variables (Table 1).

224   Substantial test-retest reliability (ICC>0.80)[41] was found for all quantitative sensory measures

225   over a one week period (PPT elbow 0.80, PPT neck 0.84, PPT tibia 0.83, HPT 0.86, CPT

226   0.84). Moderate (ICC 0.79) and substantial (ICC 0.89) reliability was found for PFG testing

227   of the affected and unaffected arms respectively.

228   *Thermal pain threshold*

229   Analysis of pain thresholds to cold stimuli revealed significant main effects for both side

230   (P<0.001) and group (P=0.002) but no interaction effect (P=0.195) (Figure 2). Post hoc

231   analysis revealed only the severe LE group demonstrated significantly reduced thresholds to

232   cold pain compared to controls, evident at both the affected (MD 6.7**°**C, 99% CI 1.6 to

233   11.8**°**C, P<0.001, SMD 1.14) and unaffected elbow (MD 4.4**°**C, 99% CI 0.3 to 8.5**°**C,

234   P=0.004, SMD 0.94).

235   Pain thresholds to heat stimuli demonstrated a significant interaction between side and group

236   (P=0.005). No differences were found for the unaffected elbow between controls and any of

237   the LE groups (P=0.172). In contrast, significant differences were found between groups for

238   the affected elbow (P=0.004) (Figure 2). Post-hoc analysis revealed only the severe LE group

239   demonstrated significantly lower HPT on the affected side in comparison to controls (MD -

240   3.0**°**C, 99% CI -0.5 to -5.5**°**C, SMD -1.06).

241   *Pressure pain threshold*

242   A significant interaction between side and group was found for PPT at the elbow (P<0.001).

243   All three LE groups demonstrated significantly lower thresholds in comparison to controls

244   (P<0.01), with differences being greater on the affected (MD -251.5KPa, 99% CI -302.1,-

245 200.8, SMD -1.92, P<0.001) than unaffected elbow (MD -131.4KPa, 99% CI -184.0,-78.8,

246 SMD -0.97, P<0.001) (Figure 3). In the affected arm, progressively lower thresholds were

247 seen with increasing pain and disability, with the differences between the severe and mild LE

248 subgroups being statistically significant (P=0.005). PPT at the neck was significantly lower

249 than controls, for all LE groups (MD -114.4kPa, 99% CI -163.8,-64.9, SMD -0.90, P<0.001).

250 Similarly, PPT at the remote tibial site was significantly lower than controls for all LE groups

251 (MD -102.6kPa, 99% CI -158.1,-47.1, SMD -0.84, P<0.001). There were no differences

252 between mild, moderate and severe LE groups for PPT at either the neck or tibia

253 *Pain-free grip*

254 A significant three-way interaction between side, group and gender was evident for PFG

255 (P<0.001). The affected arm of all three LE groups was significantly weaker than controls

256 (P<0.001) (Figure 4). Differences were significantly (P<0.001) greater in males (MD -303N,

257 99% CI -334.3,-271.7, SMD -5.00) than females (MD -177.1N, 99% CI -198.9,-155.4, SMD

258 -4.85), but proportionally (MD/control mean) they were similar (males 75.6% and females

259 73.4%), which is largely a function of greater normal strength in males.[42] Analysis of the

260 unaffected arm, revealed no differences between controls and any of the LE groups for either

261 gender.

262 **Discussion**

263 LE patients could be clustered into subgroups according to self-rated levels of pain and

264 disability, supported by incremental differences in corresponding pain and function VAS

265 measures. This study is the first to show that the presence of thermal hyperalgesia in

266 comparison to healthy controls is a distinguishing feature in LE patients with severe pain and

267 disability. Specifically, hyperalgesia to both hot and cold were demonstrated at the affected

268 elbow, while cold hyperalgesia was also evident at the unaffected elbow. Previous

269 investigation of the thermal sensory profile of LE has revealed inconsistent findings, ranging

270 from bilateral deficits in HPT,[16] to no differences in HPT,[17, 43] or reduction of HPT in the area

271 of pain referral.[18] Elevated CPT was found in patients with unilateral LE compared to the

272 unaffected arm[17] and to healthy controls,[15, 16] however only in the most recent study by Ruiz-

273 Ruiz et al were the differences statistically significant. It is highly likely that these studies

274 were either underpowered (the largest number of LE patients examined was 16) or did not

275 comprise sufficient numbers of patients with severe LE. Our findings confirm the suspicions

276 of Smith and colleagues that cold hyperalgesia exists in a subgroup of patients with LE.[19]

277

278 The presence of thermal hyperalgesia in severe cases of LE might provide an insight into the

279 possible underlying neurophysiological basis of a condition understood to be musculoskeletal

280 in nature. That cold hyperalgesia was bilaterally present in severe cases of unilateral LE lends

281 support to a central mechanism being involved in these cases.[13-15, 44] Interestingly, there are

282 similarities with CRPS 1 of the upper limb, where cold hyperalgesia has been associated with

283 both peripheral sensitisation of C-fibres and central disinhibition of nociceptive pathways

284 secondary to A-delta fibre degeneration.[22] Others[19] have proposed that cold hyperalgesia in

285 LE may be dependent upon a sympathetic noradrenergic mechanism, based on their findings

286 of selective improvement in CPT following guanethedine but not a control block in LE

287 patients. They postulated that the presence of cold hyperalgesia may be a useful clinical

288 indicator of the likely benefit of a sympathetic block, however this requires further research.

289 It is becoming clear that to reconcile such findings from different studies requires further

290 research.

291

292 Apart from the likely central implications of bilateral cold hyperalgesia, the finding of heat

293 hyperalgesia further adds to our understanding of the local neurophysiological mechanisms in

294 LE. Heat hyperalgesia has been linked with peripheral sensitisation of C-fibres.[45] Peripheral

295 sensitisation commonly occurs when nociceptors are exposed to inflammation or damaged

296 tissue, however other changes in the immediate tissue environment, including the

297 concentration of neurotransmitters, growth factors, hormones and neuropeptides, can act on

298 the nociceptors.[46] Histological evidence suggests LE is characterised by an absence of

299 inflammatory mediators but high local concentrations of the excitatory neurotransmitter

300 glutamate[47] and presence of neuropeptides, Substance P and CGRP, at the origin of extensor

301 carpi radialis brevis.[48] It is tempting to speculate that in LE where there is likely no ongoing

302 tissue inflammation, the observed heat sensitivity might reflect centrally driven neurogenic

303 inflammation, for which Substance P and CGRP have been implicated.

304

305 Health-related quality of life in our LE population was comparable to a previous study by

306 Struijs et al.[49] Notably, patients with severe LE demonstrated significantly poorer quality of

307 life than those with lower pain and disability. In addition, sleep disturbance was present in

308 the majority (66.7%) of patients with severe LE, while only 32.1% of those with mild LE,

309 however our study may have been underpowered to detect an effect on sleep. Sleep

310 disturbance is increasingly recognised as a common symptom in chronic pain and may be

311 associated with a number of negative physical and psychological effects, including lowered

312 PPT and depression.[50]

313

314 In agreement with previous research,[13, 15, 51] mechanical hyperalgesia was found in the LE

315 population at all evaluated sites and across all levels of pain and disability. A similar pattern

316 of clinical presentation, involving spread of pain sensitivity to areas with no demonstrable

317 pathology, is found in other musculoskeletal conditions and is thought to reflect a

318 commonality of central sensitisation to their pathophysiology.[45] In comparison to controls,

319 large differences (SMD>0.8) were only evident at the symptomatic elbow in the mild LE

320 group, while moderate and severe LE groups displayed large differences at all evaluated sites.

321 This suggests that the transition from local to widespread hyperalgesia may be associated

322 with increased severity (i.e., greater levels of pain and disability).

323

324 Investigation of the role of psychological factors in patients with LE has received limited

325 attention. We found no difference in levels of anxiety and depression between LE groups or

326 controls, which contrasts to the findings of Alizadehkhaiyat et al (2007), which reported

327 significantly higher levels in 16 patients with LE compared to controls.[12] Interestingly, our

328 HADS scores were much lower, even in the most severe LE group, despite displaying

329 comparable levels of pain and disability. Varied inclusion criteria (patients with a minimum

330 three month duration of LE were recruited from an orthopaedic upper limb clinic) may

331 potentially account for study differences. Likewise, we did not detect any difference in fear of

332 movement between different levels of severity of LE. Our data lead us to postulate that levels

333 of anxiety, depression and fear of movement are relatively less important features that

334 distinguish severe from non-severe LE than are thermal hyperalgesia, quality of life and sleep

335 disturbances.

336

337 This cross-sectional study of 164 patients with LE and 62 healthy controls provides valuable

338 groundwork toward understanding the relationships of sensory, motor and psychological

339 factors to an individual's pain and disability. However, there are some caveats and limitations

340 that the reader needs to consider. First, the cross-sectional design limits any inferences

341 regarding causal relationships between the various factors, and longitudinal studies are

342 needed to assess their therapeutic and prognostic implications. Second, results may not be

343 generalised to LE patients who have other concomitant musculoskeletal disorders. Third,

344   potential bias cannot be discounted, as the examiner was not blind to the control group,

345   however the examiner was not aware of PRTEE clustered subgroups. Finally, multiple

346   comparisons were conducted, a danger of which is finding statistically significant differences

347   by chance. To reduce this possibility we set an a-priori p value of 0.01. Of further note, the

348   proportion of females in the severe group was twice that of the mild LE group. Whilst not

349   statistically significant, the potential influence of gender on observed findings cannot be fully

350   ruled out.

351

352   In conclusion, this study provides evidence of thermal hyperalgesia in patients with severe

353   LE in comparison to healthy controls. It lends support to LE representing a complex

354   pathophysiology involving peripheral sensitisation, central sensitisation and sympathetic

355   mechanisms. Improved understanding of these physiological mechanisms may provide

356   insight into why patients with higher initial pain demonstrate a poorer long term outcome.

357   Further study is needed to identify optimal treatment strategies for the subgroup of patients

358   with severe symptoms to improve pain, disability and quality of life outcomes.

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Table Captions

Table 1: Demographic and clinical characteristics for the control group and lateral

epicondylalgia clusters based on pain and disability scores.

Footnote:

Results are expressed as mean ± standard deviation or count (%). Significant (P<0.01)

differences between mild-moderate[1], mild-severe[2] and moderate-severe[3] groups. PRTEE

Patient Rated Tennis Elbow Evaluation (pain and disability); VAS visual analogue scale

(mm); EQ-5D EuroQol (Health-related Quality of Life); TSK-11 Tampa Scale of

Kinesiophobia; HADS Hospital Anxiety and Depression Scale.

Table 2: Quantitative sensory and grip force tests for control group and lateral epicondylalgia

clusters based on pain and disability scores.

Footnote:

Results are expressed as mean and standard deviations (SD) for affected (AFF) and

unaffected (UN) sides as estimated by repeated measures ANOVA adjusting for gender.

*Significantly (P<0.01) different to control group. Standardised mean differences (SMD)

were estimated by dividing mean differences from controls by the pooled SD. Positive SMD

represent increased sensitivity in the LE group. †SMD of large effect size (>0.8).. CPT Cold

pain threshold (^{0}C); HPT Heat pain threshold (^{0}C); PPT Pressure pain threshold (Kpa); PFG

Pain-free grip (N).

512 **Figure Captions**

513 **Figure 1.** Lateral epicondylalgia (LE) clusters based on Patient Rated Tennis Elbow

514 Evaluation (PRTEE) total scores. The box around the mean scores represents their standard

515 deviations, while the whiskers refer to minimum and maximum scores.

516 **Figure 2:** Mean differences in heat pain thresholds (HPT, ^{0}C) and cold pain thresholds

517 (CPT, ^{0}C) and 99% confidence intervals (CI) for lateral epicondylalgia (LE) clusters

518 compared to the control group. Negative values represent increased sensitivity to heat and

519 cold.

520 **Figure 3:** Mean differences in pressure pain thresholds (Kpa) and 99% confidence intervals

521 (CI) for lateral epicondylalgia (LE) clusters compared to control group at each site (elbow,

522 neck, tibia).

523 **Figure 4:** Mean differences in pain-free grip (N) and 99% confidence intervals (CI) for

524 lateral epicondylalgia (LE) clusters compared to control group.

525

Figure 1
Common.Links.ClickHereToDownloadHighResolutionImage

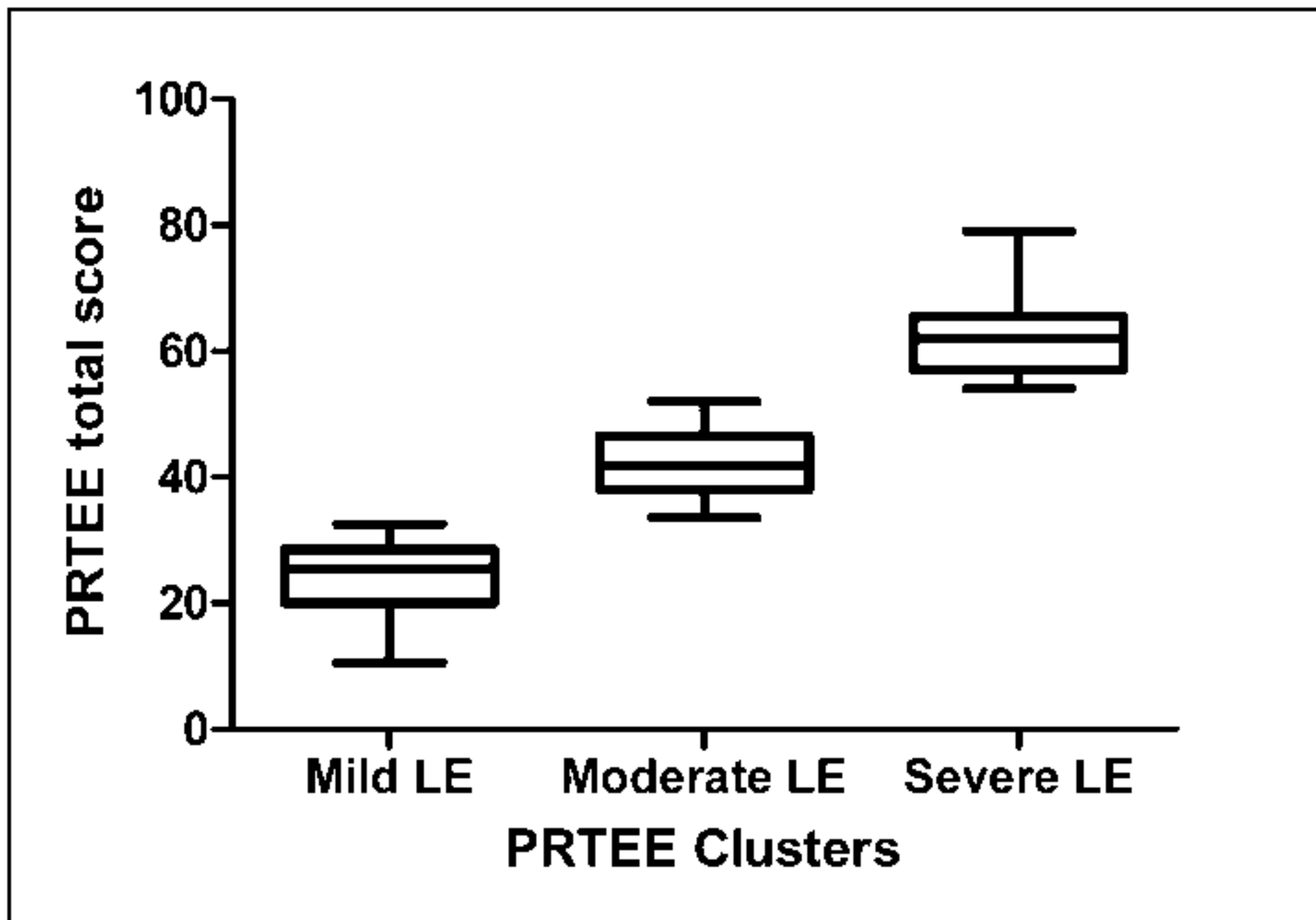Figure 2
Common.Links.ClickHereToDownloadHighResolutionImage

Figure 2

Figure 3
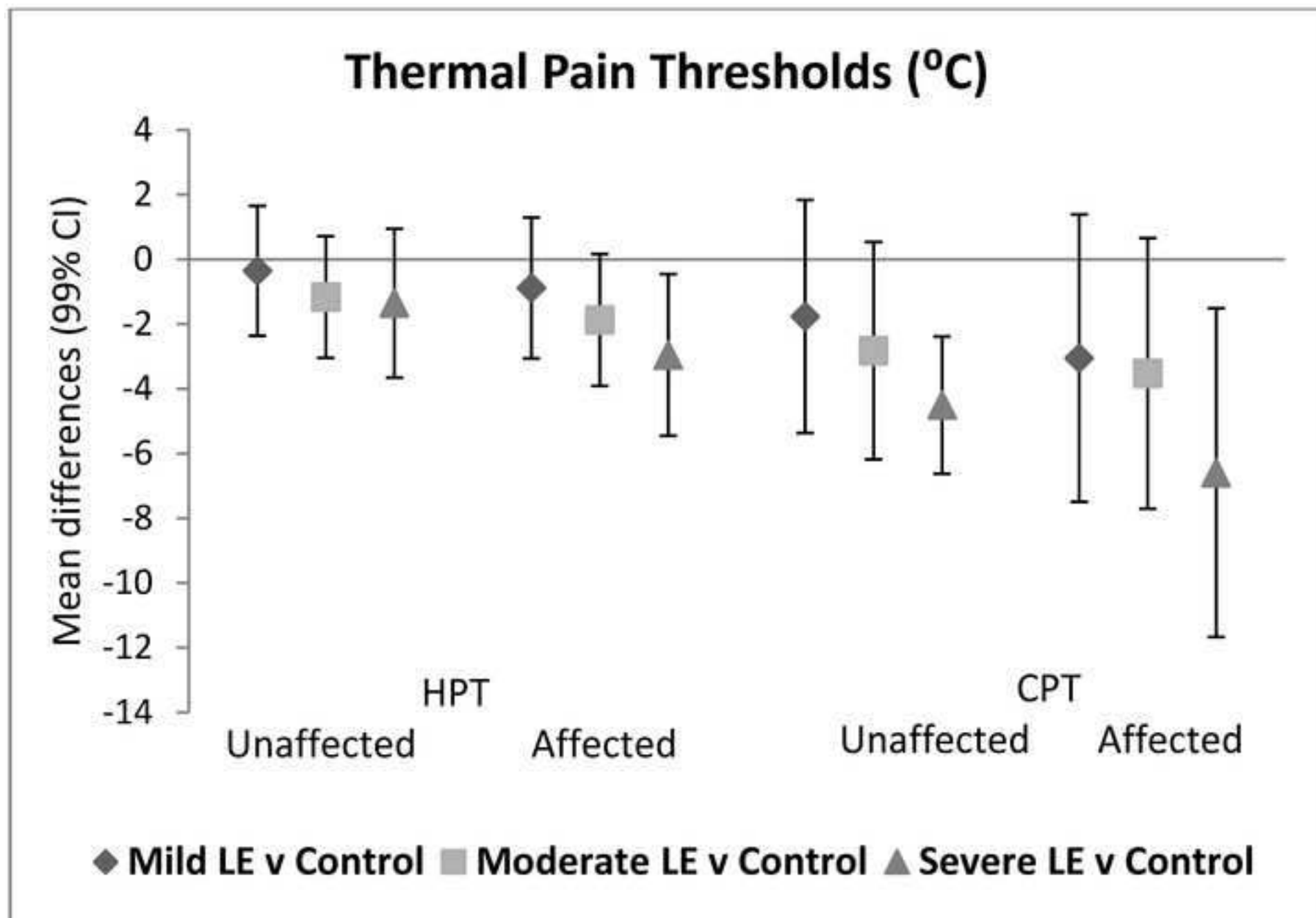Common.Links.ClickHereToDownloadHighResolutionImage

Pressure Pain Threshold (Kpa)

Mean differences (99% CI)

Elbow — Unaffected / Affected
Neck — Unaffected / Affected
Tibia

◆ Mild LE v Control   ■ Moderate LE v Control   ▲ Severe LE v Control
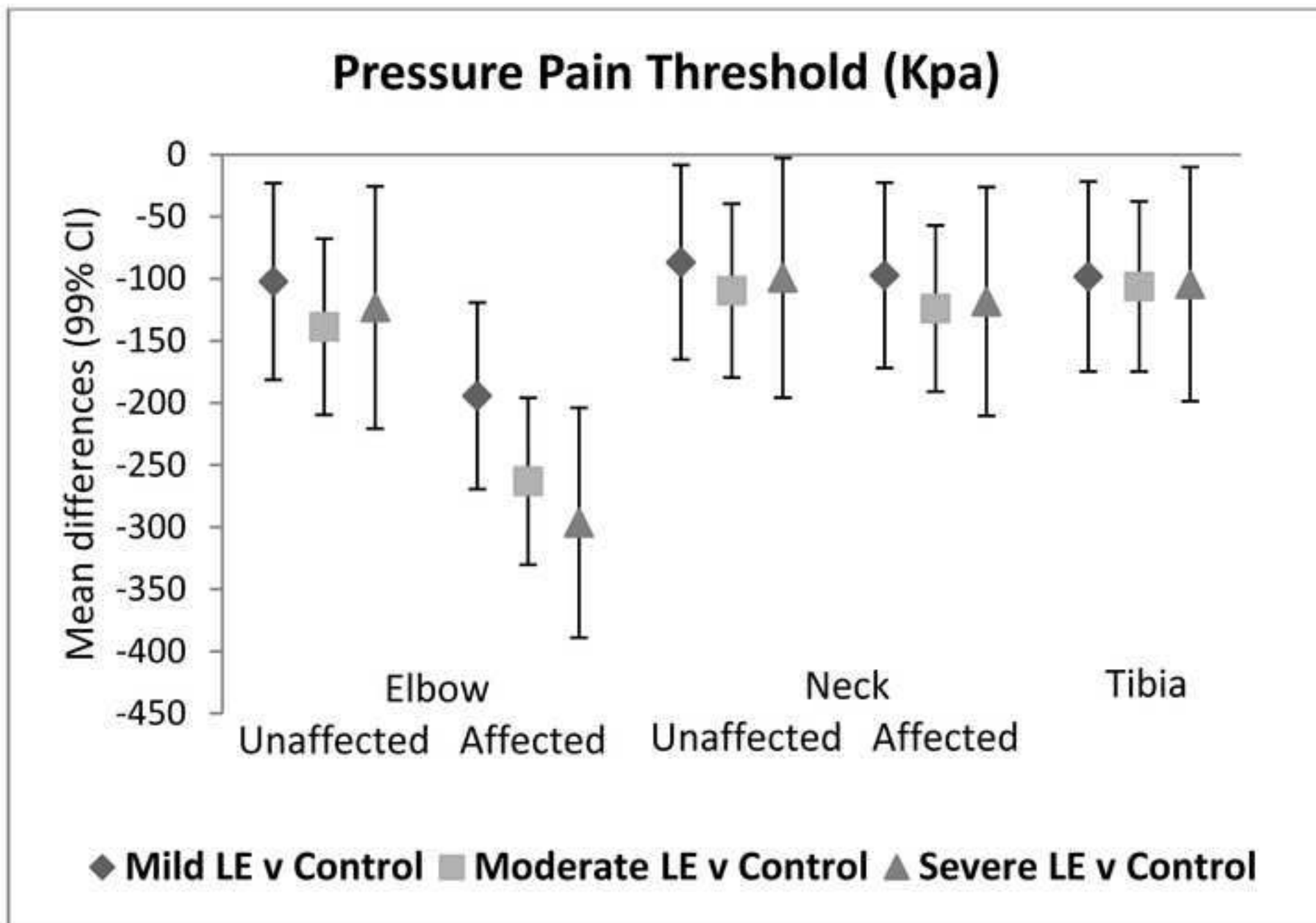
Figure 4
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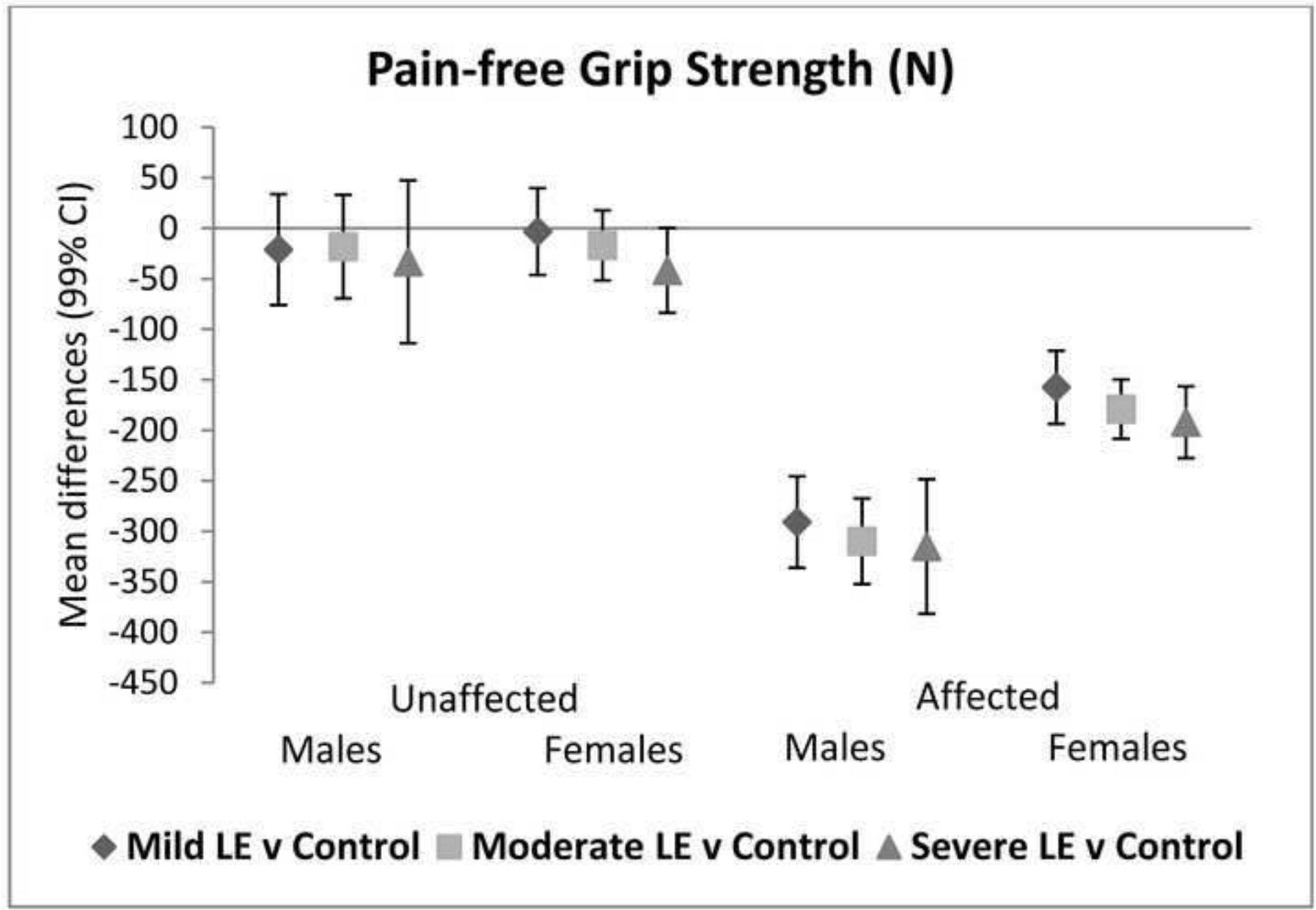
Pain-free Grip Strength (N)

Table 1

Table 1: Demographic and clinical characteristics for the control group and lateral epicondylalgia clusters based on pain and disability scores.

	Control n=62	Lateral Epicondylalgia All n=164	Mild n=53	Moderate n=84	Severe n=27	Sig <0.01
Age (years)	49.6 ± 8.7	49.6 ± 9.0	50.4 ± 9.5	48.8 ± 9.2	51.4 ± 8.8	
Female	28 (45.2)	63 (38.4)	15 (28.3)	32 (38.1)	16 (59.3)	
Post-menopausal	14 (50)	24 (38.1)	5 (33.3)	10 (31.3)	9 (56.3)	
Body mass index	25.4 ± 4.7	26.5 ± 5.1	26.1 ± 5.1	26.3 ± 4.6	27.1 ± 4.7	
Manual occupation	12 (19.4)	41 (24.8)	11 (20.8)	24 (28.6)	6 (22.2)	
Gripping sport	14 (22.6)	58 (35.2)	18 (34.0)	31 (36.9)	9 (33.3)	
Duration (weeks)	-	24.8 ± 30.8	26.6 ± 32.8	19.7 ± 30.2	32.3 ± 30.1	
PRTEE	-	40.1 ± 14.1	24.0 ± 6.0	42.0 ± 5.2	62.6 ± 5.7	[1,2,3]
Resting pain (VAS)	-	11.0 ± 14.1	6.5 ± 13.8	10.9 ± 12.8	21.8 ± 12.5	[2,3]
Worst pain (VAS)	-	61.9 ± 19.3	50.6 ± 18.2	62.4 ± 16.5	78.1 ± 16.2	[1,2,3]
Function (VAS)	-	68.6 ± 21.8	80.9 ± 21.1	65.8 ± 20.2	58.9 ± 20.3	[1,3]
EQ-5D	-	0.74 ± 0.10	0.77 ± 0.15	0.74 ± 0.09	0.59 ± 0.16	[2,3]
Sleep disturbance	-	75 (45.5)	17 (32.1)	39 (46.4)	18 (66.7)	
TSK-11	-	24.3 ± 5.1	23.4 ± 5.1	24.5 ± 4.6	25.1 ± 4.7	
HADS	6.4 ± 3.9	6.5 ± 3.9	6.1 ± 4.4	6.5 ± 4.6	7.5 ± 4.2	

Results are expressed as mean ± standard deviation or count (%). Significant (P<0.01) differences between mild-moderate[1], mild-severe[2] and moderate-severe[3] groups. PRTEE Patient Rated Tennis Elbow Evaluation (pain and disability); VAS visual analogue scale (mm); EQ-5D EuroQol (Health-related Quality of Life); TSK-11 Tampa Scale of Kinesiophobia; HADS Hospital Anxiety and Depression Scale.

Table 2

Table 2: Quantitative sensory and grip force tests for control group and lateral epicondylalgia clusters based on pain and disability scores.

Variable	Side	Control n=62	Lateral Epicondylalgia All n=164	Mild n=53		Moderate n=84		Severe n=27	
		mean ± SD	mean ± SD	mean ± SD	SMD	mean ± SD	SMD	mean ± SD	SMD
CPT	AFF	7.6 ± 6.1	11.8 ± 6.4	10.6 ± 6.6	0.52	11.4 ± 6.4	0.60	13.7 ± 5.7 *	1.12 †
	UN	7.1 ± 4.6	10.2 ± 5.1	8.9 ± 5.1	0.37	10.3 ± 4.6	0.59	11.2 ± 4.7 *	0.95 †
HPT	AFF	44.5 ± 3.1	42.6 ± 3.1	43.3 ± 2.9	0.31	42.5 ± 2.7	0.65	41.8 ± 3.1 *	1.03 †
	UN	44.3 ± 2.5	43.2 ± 2.82	43.6 ± 2.9	0.13	43.0 ± 2.7	0.43	43.2 ± 2.6	0.51
PPT Elbow	AFF	513.3 ± 128.3	261.1 ± 139.6	305 ± 141.2 *	1.52 †	246.6 ± 131.1 *	2.06 †	227.1 ± 129.9 *	2.32 †
	UN	499.5 ± 135.4	367.5 ± 130.6	382 ± 149.2 *	0.76	354.2 ± 138.4 *	1.03 †	394.7 ± 136.7 *	0.91 †
PPT Neck	AFF	403.8 ± 127.6	282.1 ± 134.5	294.2 ± 140.5 *	0.77	271.6 ± 130.1 *	0.98 †	300.3 ± 128.9 *	0.93 †
	UN	396.2 ± 133.1	287.6 ± 130.6	295.1 ± 147.1 *	0.65	277.3 ± 136.6 *	0.83 †	310.9 ± 135.1 *	0.75
PPT Tibia	Left	517.6 ± 130.7	407.4 ± 133.2	401.2 ± 144.1 *	0.76	405.9 ± 133.8 *	0.82 †	438.7 ± 132.0 *	0.80 †
PFG *Males*	AFF	400.6 ± 81.9	97.4 ± 79.4	109.9 ± 71.3 *	3.80 †	90.8 ± 77.0 *	3.90 †	85.6 ± 94.6 *	3.45 †
	UN	387.5 ± 99.2	367.6 ± 90.9	366.5 ± 86.6	0.22	369.4 ± 93.5	0.19	354.4 ± 114.8	0.30
PFG *Females*	AFF	241.3 ± 52.8	64.2 ± 62.8	84 ± 66.2 *	2.60 †	62.4 ± 56.8 *	3.29 †	49.3 ± 45.7 *	3.99 †
	UN	226.4 ± 62.2	206.5 ± 66.6	223.2 ± 78.6	0.04	209.5 ± 67.8	0.26	184.9 ± 54.6	0.73

Results are expressed as mean and standard deviations (SD) for affected (AFF) and unaffected (UN) sides as estimated by repeated measures ANOVA adjusting for gender. *Significantly ($P<0.01$) different to control group. Standardised mean differences (SMD) were estimated by dividing mean differences from controls by the pooled SD. Positive SMD represent increased sensitivity in the LE group. †SMD of large effect size (>0.8).. CPT Cold pain threshold (^{0}C); HPT Heat pain threshold (^{0}C); PPT Pressure pain threshold (Kpa); PFG Pain-free grip (N).

The Clinical Journal of Pain

Thermal hyperalgesia distinguishes those with severe pain and disability in unilateral lateral epicondylalgia
--Manuscript Draft--

Manuscript Number:	CJP-D-11-00238R1
Full Title:	Thermal hyperalgesia distinguishes those with severe pain and disability in unilateral lateral epicondylalgia
Article Type:	Original Article
Keywords:	Tennis elbow; hyperalgesia; depression; quality of life; kinesiophobia.
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Abstract:	Objectives To evaluate if sensory, motor and psychological factors are different in severe lateral epicondylalgia compared to less severe cases and control. Methods 164 patients with unilateral lateral epicondylalgia and 62 healthy control participants of comparable age and sex underwent the following testing: quantitative sensory testing (pressure, thermal pain thresholds), pain-free grip, quality of life (EuroQol) and psychological (HADS, Tampa). Cluster analysis classified patients into mild, moderate or severe subgroups using the Patient Rated Tennis Elbow Evaluation (PRTEE). Data were then evaluated to determine differences between control and lateral epicondylalgia subgroups. Results Bilateral cold hyperalgesia (affected elbow, standardised mean difference (SMD): 1.14, P=0.000; unaffected elbow SMD: 0.94, P=0.000) and unilateral heat hyperalgesia (SMD -1.06, P=0.001) were evident in severe lateral epicondylalgia in comparison to healthy controls. All patient groups regardless of severity demonstrated bilateral and widespread mechanical hyperalgesia relative to controls (P<0.003), however only those with moderate and severe symptoms showed large differences (SMD>0.8) at all sites. Quality of life was significantly poorer in patients with severe symptoms, while anxiety, depression and kinesiophobia did not differ between subgroups. Discussion Lateral epicondylalgia patients presenting with severe pain and disability could be distinguished by hypersensitivity to thermal stimuli, notably bilateral cold hyperalgesia. Findings might implicate a combination of central, peripheral and sympathetic nervous system processes and may help explain the poorer outcomes found in this subpopulation.