



LJMU Research Online

Watson, JA, Ryan, CG, Atkinson, G, Williamson, P, Ellington, D, Whittle, R, Dixon, J and Martin, DJ

Inter-Individual Differences in the Responses to Pain Neuroscience Education in Adults With Chronic Musculoskeletal Pain: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

<http://researchonline.ljmu.ac.uk/id/eprint/16896/>

Article

Citation (please note it is advisable to refer to the publisher's version if you intend to cite from this work)

Watson, JA, Ryan, CG, Atkinson, G, Williamson, P, Ellington, D, Whittle, R, Dixon, J and Martin, DJ (2020) Inter-Individual Differences in the Responses to Pain Neuroscience Education in Adults With Chronic Musculoskeletal Pain: A Systematic Review and Meta-Analysis of Randomized Controlled

LJMU has developed **LJMU Research Online** for users to access the research output of the University more effectively. Copyright © and Moral Rights for the papers on this site are retained by the individual authors and/or other copyright owners. Users may download and/or print one copy of any article(s) in LJMU Research Online to facilitate their private study or for non-commercial research. You may not engage in further distribution of the material or use it for any profit-making activities or any commercial gain.

The version presented here may differ from the published version or from the version of the record. Please see the repository URL above for details on accessing the published version and note that access may require a subscription.

For more information please contact researchonline@ljmu.ac.uk

<http://researchonline.ljmu.ac.uk/>

1 Title Page

2

3 Inter-individual differences in the responses to pain neuroscience education in adults
4 with chronic musculoskeletal pain: A systematic review and meta-analysis of
5 randomised controlled trials.

6

7 Short title: Individual differences in response to pain neuroscience education

8

9 Authors:

10

11 James A Watson BSc (Hons) ¹

12 J.A.Watson@tees.ac.uk

13

14 Cormac G Ryan BSc, MSc, PhD¹

15 C.Ryan@tees.ac.uk

16

17 Greg Atkinson BSc (Hons), PhD¹

18 Greg.Atkinson@tees.ac.uk

19

20 Philip Williamson, BSc (Hons), MSc, PhD³

21 phil.williamson@york.ac.uk

22

23 Dominic Ellington BSc (Hons) ²

24 D.Ellington@tees.ac.uk

25

26 Robbie Whittle BSc (Hons) ²

27 robbie.whittle@nhs.net

28

29 John Dixon BSc, PhD¹

30 John.Dixon@tees.ac.uk

31

32 Denis J Martin BSc. MSc. DPhil¹

33 D.Martin@tees.ac.uk

34

35 ¹School of Health and Life Sciences, Teesside University, Middlesbrough, Tees
36 Valley, TS1 3BX, United Kingdom.

37

38 ²North Tees and Hartlepool NHS Foundation Trust, University Hospital of North
39 Tees, Hardwick Road, Stockton on Tees, Cleveland, TS19 8PE, United Kingdom.

40

41 ³York Trials Unit, Department of Health Sciences, University of York, Heslington,
42 York, YO10 5DD, United Kingdom.

43

44 Corresponding author: James Watson, J.A.Watson@tees.ac.uk

45

46 James Watson

47 School of Health and Life Sciences

48 Teesside University

49 Campus Heart

50 Southfield Rd

51 Middlesbrough

52 TS1 3BX

53

54 Telephone number and fax number not available.

55

56 **Disclosures**

57 This research was funded by Teesside University.

58 The authors have no conflict of interest to declare.

59

60 **Highlights:**

- 61 • Pain neuroscience education (PNE) is a pain management intervention.
- 62 • Little evidence of true individual differences in response to PNE for disability.
- 63 • Findings should be interpreted cautiously due to very wide prediction
64 intervals.
- 65 • Estimating individual differences should be applied to other pain interventions.

66

67 **Abstract**

68

69 Pain neuroscience education (PNE) is an approach used in the management of
70 chronic musculoskeletal pain (CMP). Previous reviews on PNE and other pain
71 interventions, have focussed on mean treatment effects, but in the context of
72 “precision medicine”, any inter-individual differences in treatment response are also
73 important to quantify. If inter-individual differences are present, and predictors
74 identified, PNE could be tailored to certain people for optimising effectiveness. Such
75 heterogeneity can be quantified using recently-formulated approaches for comparing
76 the response variance between the treatment and control groups. Therefore, we

77 conducted a systematic review and meta-analysis on the extracted standard
78 deviations of baseline-to-follow up change to quantify the inter-individual variation in
79 pain, disability and psychosocial outcomes in response to PNE. Electronic databases
80 were searched between 01/01/2002 and 14/06/2018. The review included five
81 randomised controlled trials (n=428) in which disability outcomes were reported.
82 Using a random effects meta-analysis, the pooled SD (95% CI) for control group-
83 adjusted response heterogeneity to PNE was 7.36 units /100 (95% CI: -3.93 to
84 11.12). The 95% prediction interval for this response heterogeneity SD was wide (-
85 10.20 to 14.57 units /100). The control group-adjusted proportion of “responders” in
86 the population who would be estimated to exceed a clinically important change of
87 10/100 ranged from 18-45%. Therefore, when baseline-to-follow up random
88 variability in disability is taken into account (informed by the control arm), there is
89 currently insufficient evidence for the notion of clinically important inter-individual
90 differences in disability responses to PNE in people with CMP. The protocol was
91 published on PROSPERO (CRD42017068436).

92

93 **Perspective**

94 We bring a novel method to pain science for calculating inter-individual differences in
95 response to a treatment. This is conducted within the context of a systematic review
96 and meta-analysis on PNE. We highlight how using erroneous methods for
97 calculating inter-individual differences can drastically change conclusions when
98 compared to appropriate methods.

99 **Key words**

100 Pain, neuroscience, education, Individual response variance

101

102 **Introduction**

103

104 Pain neuroscience education (PNE) is an educational approach used in the
105 management of chronic pain. PNE aims to reconceptualise an individuals'
106 understanding of their pain as less threatening to facilitate rehabilitation²³. Since its
107 inception PNE has become increasingly popular in clinical practice²⁴. Our group
108 recently published a mixed-methods systematic review and meta-analysis on the
109 effectiveness of PNE for adults with chronic musculoskeletal pain (CMP)³⁹.

110 Quantitatively we found no evidence to indicate that PNE results in clinically
111 important changes over control for pain or disability. In contrast we found moderate
112 quality evidence that PNE produces small clinically important changes over control
113 for pain catastrophising and kinesiophobia. Qualitatively we found that achieving
114 some degree of pain reconceptualisation following PNE can enhance peoples' ability
115 to cope with their condition.

116

117 One question that arose during our previous research work was whether PNE may
118 be effective for some types of people, implying that there may be some individual
119 differences in response to PNE³⁹. The quantitative component of our review focused
120 on the mean intervention/treatment effect. This focus on mean intervention effect
121 whilst common in research on pain interventions^{5,15,30} could have obscured important
122 inter-individual differences in response to PNE^{16,41}. Such response heterogeneity is
123 particularly important within the context of precision medicine, an increasingly
124 popular field which encompasses 'tailor-made' therapies based on the person's
125 individual response to a given intervention³¹. This individualised approach to
126 medicine aims to improve the quality of care and reduce costs³³. The potential

127 importance of a tailored approach has been highlighted by some of our previous
128 qualitative work on PNE. The relevance of PNE to the individual (i.e. how tailored the
129 material is to that individual) appears to be an important factor in the success of
130 PNE^{17,18,29,39}. Where PNE was reported to be relevant, people reported greater
131 perceived benefit. The opposite was found where PNE was deemed not
132 relevant^{17,18,29}.

133

134 Some researchers²⁷ have attempted to complement the quantification of mean
135 treatment effects with a quantification of how many people in each intervention group
136 change above or below a pre-set threshold, termed sample responder counts.
137 Crucially, this approach does not provide any information about response
138 heterogeneity to a given intervention in the context of precision medicine. In fact,
139 these responder counts lack statistical power and may merely reflect within-subject
140 random variation between timepoints and/or group differences in mean change.
141 Furthermore, the dichotomisation (responder or non-responder) also creates
142 problems adjusting for baseline differences between study groups (comprehensive
143 reviews are available ^{2,32}). These sample responder counts tell us little about
144 whether different people respond to different degrees to the same intervention, which
145 is one of the fundamental questions in precision medicine. Should any inter-
146 individual differences be falsely identified using the above-mentioned methods, any
147 follow-up analysis to explore potential moderators of the intervention effect to explain
148 the individual differences in response are therefore unwarranted^{1,2}. Subsequent
149 follow-up studies on the same participants is a waste of resources, and potentially
150 unethical, if no true inter-individual differences in response exist to explain.

151

152 Inter-individual differences in response can be quantified by comparing the SDs of
153 the baseline-to-follow-up changes between the experimental and control groups^{1,4}.
154 The difference between these SDs represents the SD for individual responses (SD_{ir})
155 which quantifies the individual variability in treatment response *per se*. The SD of the
156 mean change score solely for the intervention group comprises treatment response
157 variance *in addition to* the random variability in measurements between the baseline
158 and follow-up timepoints. The SD of the changes in the control group represents this
159 random variability in measurements between baseline and follow up – the random
160 within-subjects variance component and measurement error.

161

162 Our qualitative analysis highlighted that PNE may be effective for some people but
163 not for others implying that true inter-individual differences in response to PNE may
164 exist which could be explored to facilitate appropriate targeting of PNE to those most
165 likely to benefit³⁹. However, clinically relevant inter-individual response variation
166 should first be conducted using appropriate methodology^{1,2,13,40,41} to confirm the
167 presence of such inter-individual responses. If individual differences are observed,
168 and predictors of individual response are identified, then PNE could be tailored to the
169 individual optimising its effect⁴¹.

170

171 To date, there has been no investigation of ‘true’ individual response variation of the
172 effect of PNE, or indeed any pain management intervention. Therefore, we aimed to
173 conduct a systematic review and meta-analysis of the available research to quantify
174 the ‘true’ inter-individual variation in pain, disability and psychosocial outcomes in
175 response to PNE in adults with CMP.

176

177 **Methods**

178

179 The protocol for the systematic review was published on PROSPERO
180 (CRD42017068436). The analysis of inter-individual differences is presented here in
181 detail to ensure the background and rationale for this novel method within the field of
182 pain is adequately reported. A detailed account of the full review-methods has been
183 published elsewhere³⁹ but a brief summary is provided below.

184 Inclusion and Exclusion Criteria

185

186 *Inclusion criteria*

187

- 188 • Studies including adults (≥ 18 years) who have CMP consistent with the British
189 Pain Society definition (chronic pain, that lasts beyond the time that tissue
190 healing would normally be expected to have occurred, often taken as ≥ 3
191 months)³⁵.
- 192 • RCTs that (i) compared the intervention with no treatment (true control) or
193 usual care (ii) concomitant studies where PNE was delivered in addition to
194 another intervention where that other intervention was received by both
195 groups and (iii) head-to-head studies where PNE was compared to another
196 active intervention.
- 197 • Studies reporting either pain and/or disability and/or psychosocial wellbeing.
- 198 • The SD of the changes for the intervention and control groups must have
199 been included within the publication, have been available from the author
200 upon request, or could be calculated from other information given such as the

201 standard error. This is an additional criterion that was not included in the
202 registered protocol.

203

204 *Exclusion criteria*

205

- 206 • Studies that included participants with non-musculoskeletal pain such as
207 cancer pain, visceral pain or post stroke pain.

208

209

210 Search Strategy

211

212 Pre-identified keywords (Pain AND (Physiology OR Neurophysiology OR
213 Neuroscience OR Biology) AND Education) and index terms were searched across
214 all included databases (The Cochrane Library, AMED, CINAHL Complete,
215 MEDLINE, PsycINFO, PEDro, Scopus, EMBASE, Education Resources Information
216 Centre (ERIC), Web of Science, clinicaltrials.gov, dissertations indexed with
217 ProQuest Dissertations and Theses Global and EThOS) from 2002-25 July 2017,
218 and updated on 14 June 2018.

219

220 After removing duplicates, the title and abstracts were screened by two authors and
221 disagreements were resolved through discussion or a 3rd reviewer. The full-text was
222 obtained for all records that could potentially fit the criteria. Upon reading the full-
223 texts those deemed not to meet the inclusion criteria were rejected. See
224 Supplementary Digital Content 1 for a list of excluded publications and reasons for
225 exclusion.

226

227

228 Deviation from protocol

229

230 In our previous review³⁹ when the SD of change was not reported, and could not be
231 obtained by contacting the authors, it was either calculated from other information
232 given such as standard error, or estimated from the baseline and follow up SDs,
233 according to methods described in the Cochrane handbook¹⁰. Where there was
234 uncertainty regarding the validity of baseline, follow up and change score SDs from
235 included studies we opted not to use this data to inform our calculations to estimate
236 the SD of change scores. Instead, we used a robust data set of individuals with CMP
237 where we were confident in the validity of the baseline, follow up and change score
238 SDs. However, for the current review, given that to calculate the true inter-individual
239 differences in response to an intervention the SD of the mean change score is of
240 central importance¹, it would be inappropriate to estimate the SD of the change or
241 use a robust data set. Thus, an additional criterion for inclusion was created for the
242 current review where the SD of the changes for the intervention and control groups
243 must have been published in the article, available upon request by the author, or
244 could be calculated from other information given, such as the standard error.

245

246 Assessment of methodological quality and data extraction

247

248 Articles selected for critical appraisal were independently assessed by two reviewers
249 using the Cochrane tool for assessing risk of bias⁹. Two reviewers independently
250 extracted the data using JBI-SUMARI³⁶ including details about the interventions,

251 populations, study methods and outcomes of relevance to the review
252 question/objectives. The Grades of Recommendation, Assessment, Development
253 and Evaluation (GRADE) approach⁷ was used to rate the overall quality of
254 quantitative evidence for each outcome. A summary of findings table created using
255 GradePro is presented (Table 1 and 2).

256

257 Meta-analysis

258

259 To contextualise the results for individual response variance we conducted a
260 random-effects meta-analysis for the mean difference in disability across the
261 included studies using a restricted maximum likelihood (REML) model combined with
262 the Knapp-Hartung method. This method uses quantiles of the t distribution to
263 calculate a confidence interval for the average effect instead of the standard normal
264 distribution in the more conventional methods³⁷. The Knapp-Hartung method has
265 been shown to be superior to the DerSimonian-Laird method where there is a small
266 number of studies (<20) and heterogeneity is present¹¹. We then extracted the
267 standard deviation of the changes in disability for both control (C) and PNE (I)
268 groups. The true individual response variance (intervention minus control) was then
269 calculated by $\sqrt{(SD_I^2 - SD_C^2)}$ ¹³. The standard error (SE) for this variance was then
270 calculated using the equation: $SE = \sqrt{[2(SD_I^4/DF_I + SD_C^4/DF_C)]}$, where DF_I and DF_C
271 are the degrees of freedom of the standard deviation in the PNE group and the
272 control groups¹³. A negative value for the individual response variance for the
273 confidence intervals or prediction intervals implies greater variability in the changes
274 in disability in the control versus PNE group.

275

276 The individual response variances and their SEs were meta-analysed using an
277 REML model combined with Knapp-Hartung method. It's important to highlight that
278 the variances are unbiased, whereas the SD is not, and deriving a SE for the SD for
279 individual responses is also problematic. Thus, we synthesised the individual
280 response variances instead of the SDs for individual responses. The point estimate
281 for the pooled individual response variance were derived together with a 95% CI to
282 express its uncertainty. The point estimate and CIs were then square rooted to
283 convert to an SD metric. If the lower limit was negative, the sign was ignored, the
284 square root taken, and the sign re-applied. This approach is consistent with the 'no
285 bound' option in SAS/STAT® software, which permits negative variances (SAS
286 Institute Inc. 2017. SAS/STAT 14.3 User's Guide. Cary, NC: SAS Institute Inc.).

287

288 Using the methods of Swinton et al.³⁴ the proportion of responders in the population
289 of interest within each included RCT was estimated. To estimate this, the observed
290 mean change score and true individual response variance are needed for each RCT.
291 Normal variance is assumed. The total area of any probability distribution is equal to
292 one, thus the estimate of the proportion of response can be obtained by calculating
293 the area of the derived normal distribution that lies beyond the minimally clinically
294 important difference (MCID). An MCID of 10% was used in recent NICE guidelines
295 for back and radicular pain²⁵. The calculation estimating the proportion of response
296 was performed via an online calculator²⁸. The proportion of response was estimated
297 for the intervention and control groups for all RCTs and has been used to
298 demonstrate the difference in results, and thus conclusion that could be made if
299 researchers erroneously ignored the control group data.

300

301 The tau statistic (τ) was used to quantify between-study heterogeneity – a SD that
302 describes the typical variability of the mean effect between studies^{3,8}. A 95%
303 prediction interval was calculated using the tau and the SE for the pooled mean
304 effect to quantify the expected range of true effects in future similar studies¹². Stata
305 (StataCorp. 2019. Stata Statistical Software: Release 16. College Sttion, TX:
306 StataCorp LLC.) was used to conduct all statistical analysis.

307

308 **Results**

309

310 Following removal of duplicates, 12,136 publications were identified (Fig. 1). Fifty-
311 seven full text articles were screened. Forty-nine articles were excluded at this stage.
312 See document, supplementary digital content 1 for a list of excluded publications and
313 reasons for exclusion. Thus, six publications reporting five RCTs were
314 included^{6,19,20,21,26,38}. The included studies encompassed a total of 428 participants (I
315 = 212, C = 216). Table 3 provides further details regarding the studies.

316

317

318 Methodological quality

319

320 Quality scores ranged from 1-6 out of 7 (Table 4). There was a high risk of
321 performance bias due to lack of blinding of participants and personnel (Fig. 2 and 3
322 produced by using RevMan software (Review Manager. Version 5.3. Copenhagen:
323 The Nordic Cochrane Centre. The Cochrane Collaboration, 2014).

324

325

326

327 Study outcomes

328

329 Jackson and Turner¹⁴ recommend only pooling data where the number of studies is
330 ≥ 5 to ensure adequate statistical precision. Disability was the only outcome
331 measured consistently in all five included studies, thus our analysis focused solely
332 on this outcome.

333

334 The pooled mean group difference in pre/post changes in disability (intervention
335 minus control) was -2.26 units /100 (95% CI: -6.49 to 1.97). See Fig. 4. Between
336 study heterogeneity in mean treatment effect was observed ($\tau = 2.49$; 95% CI: 0.48
337 to 4.51). The prediction interval revealed that, were investigators to undertake a
338 future trial, the 95% plausible range for mean disability change versus control would
339 be -11.56 to 7.04 units /100.

340

341 The pooled point estimate for the inter-individual variability in disability change in
342 response to PNE (SD_{IR}) was 7.36 units /100 (95% CI: -3.93 to 11.12). Substantial
343 between-study heterogeneity was observed ($\tau = 6.55$). The 95% prediction interval
344 for true inter-individual responses was -10.20 to 14.57. Appendix 1 provides a step
345 by step guide for the calculations here.

346 Using the methods of Swinton et al.³⁴ we estimated the proportion of responders in
347 the population of interest within each included RCT (Table 5). The threshold
348 reduction in disability for clinical relevance was set at -10/100, in keeping with recent
349 NICE guidelines for back and radicular pain²⁵. These proportions were adjusted for

350 the apparent proportions exceeding this threshold in the comparator groups that
351 were estimated to be due wholly to random variability in the pre to post
352 measurements of disability. It can be seen that these proportions are generally lower
353 than the proportion of participants who exceed the threshold in the intervention
354 groups *per se*.

355

356 **Discussion**

357 We conducted a systematic review and meta-analysis of the literature in order to
358 quantify the control-group adjusted inter-individual variation in pain, disability and
359 psychosocial outcomes in response to PNE in adults with CMP. Several potential
360 studies did not report the SD of the mean change, and this information could not to
361 be obtained upon request meaning our analysis was restricted to disability.

362

363 The inter-individual difference in disability change in response to PNE, as indicated
364 by our SDir of 7.36 /100 units, did not reach our criterion for clinical significance (10
365 /100 units). Therefore, there is insufficient evidence at present for the existence of
366 inter-individual differences in people's response to PNE over and above random
367 within-subjects variability between baseline and follow-up observations. Although this
368 finding, seems at odds with previous qualitative study findings from our group^{17,18,29},
369 that qualitative work focused upon patient experience rather than attempting to
370 objectively quantify inter-individual differences. Considering the upper 95% CI
371 (11.12 /100 units) and wide 95% prediction interval -10.20 to 14.57 of the SDir, any
372 inferences regarding "true" inter-individual responses are unclear. Given the small
373 number of included studies, the wide prediction intervals are unsurprising and this

374 illustrates the importance of statistical power in any analysis of response
375 heterogeneity^{1,2}.

376

377 Therefore, it is apparent that more high quality RCTs are needed that sufficiently
378 report relevant data. We encourage researchers and reviewers of academic journals
379 to ensure that the means and standard deviations of the change scores in all
380 treatment groups are reported. This will provide the information required to include
381 the study within meta-analyses of both individual responses and mean effect of
382 treatment.

383 It is worth highlighting that the very common act of simply looking at the intervention
384 group responses (Table 4) would have falsely led a researcher to think that
385 substantial response heterogeneity was present. This may have led to follow-up
386 analyses to explore potential moderators which may be unwarranted and a waste of
387 resources. Furthermore, any follow-up studies on the same participants may be
388 unethical if there are no true individual differences in response present to explain¹.

389

390 This is the first systematic review and meta-analysis to employ the method of
391 calculating true inter-individual differences in response to an intervention within the
392 pain sciences³⁴. Given the huge global burden of chronic pain, and the limited
393 efficacy of current treatment options for matching peoples' individual responses to
394 treatments, appropriate methodology needs to be applied across the pain field. This
395 will hopefully lead to improved quality of care, reduced costs³³ and ultimately
396 improve the quality of life of people with pain.

397

398 **Limitations**

399

400 Only five studies were eligible for this review which meant that we could only analyse
401 disability data and the inter-individual differences in response to PNE for other
402 outcomes are unknown. Six studies that were otherwise eligible, were excluded
403 because they did not report the appropriate data needed to conduct an inter-
404 individual differences meta-analysis and this data was not available upon email
405 request. We have no reason to believe that authors would withhold this data and
406 thus assume these studies are missing at random. Only studies published in English
407 were eligible for inclusion as no facility for translation was available. Thus, important
408 data from non-English studies may have been missed.

409

410 The nature of the comparison group will influence the calculation of the inter-
411 individual difference. In the case of usual care comparisons and other intervention
412 comparisons, if these have inherent variability in response within them, beyond
413 random variability (noise) of a true no intervention control, this may mask the degree
414 of interindividual variability seen within the PNE (intervention of interest) group.
415 Thus, this could have influenced the findings. Nevertheless, in the case of
416 intervention vs usual care, if there are true individual differences in the responses to
417 the novel component(s) of the intervention under study, then this should, in theory,
418 manifest itself in a larger change variance in the intervention group vs the usual care
419 group.

420

421 **Conclusion**

422

423 This is the first study to investigate “true” inter-individual differences in response
424 within the field of pain. By this, we mean a quantification of response heterogeneity
425 that takes into account the individual differences in baseline to follow-up change that
426 can be observed in the comparator groups, and are attributable to random fluctuation
427 in pain scores over time. Our findings provide little evidence at present of “true”
428 variation in peoples’ response to PNE regarding disability, but the evidence is very
429 uncertain. Furthermore, given the wide 95% confidence and prediction intervals any
430 inferences made regarding true individual variation in peoples’ response to PNE are
431 unclear. Moreover, given the small number of studies included in the analysis further
432 work is warranted before firm conclusions can be drawn. Therefore, the data
433 currently available does not allow us to clearly identify if individual differences in
434 disability occur for people with CMP following PNE. We would recommend against
435 studies exploring which factors may explain which people will benefit from PNE until
436 such time as the existence of inter-individual differences has been confirmed using
437 appropriate methodology and we would extend this recommendation to all pain
438 interventions.

439

440 **Acknowledgements**

441 This research was funded through Teesside University.

442 The authors have no conflict of interests to declare.

443 **References:**

- 444 1. Atkinson G, Batterham AM: True and false interindividual differences in the
445 physiological response to an intervention. *Exp Physiol* 100:577-588, 2015

- 446 2. Atkinson G, Williamson P, Batterham AM: Issues in the determination of
447 “responders” and “non-responders” in physiological research. *Physiol* 2019
- 448 3. Borenstein M, Higgins JP, Hedges LV, Rothstein HR: Basics of meta-analysis:
449 I2 is not an absolute measure of heterogeneity. *Res Synth Methods*. 8(1):5-
450 18, 2017
- 451 4. Cortés Martínez J, González Alastrué JA, Medina MN, Vogler M, Vilaró
452 Pacheco M, Elmore M, Senn SJ, Campbell MJ, Cobo Valeri E: Does evidence
453 support the high expectations placed in precision medicine? A bibliographic
454 review. *F1000Res* 7:1-11, 2018
- 455 5. Furlan AD, Sandoval JA, Mailis-Gagnon A, Tunks E: Opioids for chronic
456 noncancer pain: a meta-analysis of effectiveness and side
457 effects. *CMAJ* 174:1589-1594, 2006
- 458 6. Gallagher L, McAuley J, Moseley, GL: A randomized-controlled trial of using a
459 book of metaphors to reconceptualize pain and decrease catastrophizing in
460 people with chronic pain. *Clin J Pain* 29:20-5, 2013
- 461 7. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P,
462 Schünemann HJ: GRADE: An emerging consensus on rating quality of
463 evidence and strength of recommendations. *BMJ* 336:924-926, 2008
- 464 8. Higgins JPT: Commentary: heterogeneity in meta-analysis should be
465 expected and appropriately quantified. *Int J Epidemiol* 37:1158–1160, 2008
- 466 9. Higgins JP, Altman DG, Sterne JA: Chapter 8: Assessing risk of bias in
467 included studies. In: Higgins JP, Green S, editor(s). *Cochrane Handbook for*
468 *Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011).
469 The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.
470 [Accessed 26/06/2018].

- 471 10. Higgins JPT, Deeks JJ, Altman DG (editors). Chapter 16: Special topics in
472 statistics. In: Higgins JPT, Green S (editors), Cochrane Handbook for
473 Systematic Reviews of Interventions Version 5.1.0 (updated March 2011).
474 The Cochrane Collaboration, 2011. Available from
475 www.handbook.cochrane.org. [Accessed 26/06/2018].
- 476 11. IntHout J, Ioannidis JP, Borm GF: The Hartung-Knapp-Sidik-Jonkman method
477 for random effects meta-analysis is straightforward and considerably
478 outperforms the standard DerSimonian-Laird method. *BMC Med. Res.*
479 *Methodol.* 14(1):25, 2014
- 480 12. IntHout J, Ioannidis JP, Rovers MM, Goeman JJ: Plea for routinely
481 presenting prediction intervals in meta-analyses. *BMJ Open* 6:e010247, 2016
- 482 13. Hopkins W: Individual responses made easy. *J Appl Physiol* 118:1444–1446,
483 2015
- 484 14. Jackson D, Turner R: Power analysis for random-effects meta-analysis. *Res*
485 *Synth Methods* 8:290-302, 2017
- 486 15. Kamper SJ, Apeldoorn AT, Chiarotto A, Smeets RJE, Ostelo RWJG,
487 Guzman J, Van Tulder MW: Multidisciplinary biopsychosocial rehabilitation for
488 chronic low back pain: Cochrane systematic review and meta-
489 analysis. *BMJ* 350:p.h444, 2015
- 490 16. King NA, Hopkins M, Caudwell P, Stubbs RJ, Blundell JE: Individual variability
491 following 12 weeks of supervised exercise: identification and characterization
492 of compensation for exercise induced weight loss. *Int J Obes* 32: 177–184,
493 2008
- 494 17. King R, Robinson V, Ryan CG, Martin DJ: An exploration of the extent and
495 nature of reconceptualisation of pain following pain neurophysiology

- 496 education: A qualitative study of experiences of people with chronic
497 musculoskeletal pain. *Patient Educ Couns* 99:1389-93, 2016
- 498 18. King R, Robinson V, Elliot-Button HL, Watson JA, Ryan CG, Martin DJ: Pain
499 reconceptualisation after Pain Neurophysiology Education in Adults with
500 Chronic Low Back Pain: A Qualitative Study. *Pain Res Treat* 1-10, 2018
- 501 19. Louw A, Diener I, Landers MR, Puentedura EJ: Preoperative pain
502 neuroscience education for lumbar radiculopathy: a multicenter randomized
503 controlled trial with 1-year follow-up. *Spine* 39:1449-57, 2014
- 504 20. Louw A, Diener I, Landers MR, Zimney K, Puentedura EJ: Three-year follow-
505 up of a randomized controlled trial comparing preoperative neuroscience
506 education for patients undergoing surgery for lumbar radiculopathy. *J Spine*
507 *Surg* 2:289, 2016
- 508 21. Malfliet A, Kregel J, Meeus M, Roussel N, Danneels L, Cagnie B, Dolphens
509 M, Nijs J: Blended-Learning Pain Neuroscience Education for People With
510 Chronic Spinal Pain: Randomized Controlled Multicenter Trial. *Phys Ther*
511 98:357-68, 2018
- 512 22. Moher D, Liberati A, Tetzlaff J, Altman DG: Preferred reporting items for
513 systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern*
514 *Med* 151:264-269, 2009
- 515 23. Moseley GL. Reconceptualising pain according to modern pain science. *Phys*
516 *Ther Rev* 12:169-178, 2007
- 517 24. Moseley GL, Butler DS. Fifteen years of explaining pain: the past, present,
518 and future. *J Pain* 16:807-13, 2015
- 519 25. National Institute for Health and Clinical Excellence (NICE). Low back pain
520 and sciatica in over 16s: Assessment and management draft. (NICE guideline

- 521 NG59). Available at:
522 www.nice.org.uk/guidance/ng59/documents/draftguideline. Accessed October
523 1, 2018
- 524 26. Pires D, Cruz EB, Caeiro C. Aquatic exercise and pain neurophysiology
525 education versus aquatic exercise alone for patients with chronic low back
526 pain: a randomized controlled trial. *Clin Rehabil* 29:538-47, 2015
- 527 27. Pires D, Caeiro C, Cruz EB. Individual patient responder analysis of the
528 effectiveness of a pain neuroscience education programme in chronic low
529 back pain. In *IFOMPT Conference 2016*.
- 530 28. Rice University: *Online Statistics Education: A Multimedia Course of Study*.
531 2019. Available at: http://onlinestatbook.com/2/calculators/normal_dist.html
532 (Accessed: 02/09/2019).
- 533 29. Robinson V, King R, Ryan CG, Martin DJ: A qualitative exploration of people's
534 experiences of pain neurophysiological education for chronic pain: The
535 importance of relevance for the individual. *Man Ther* 22:56-61, 2016
- 536 30. Searle A, Spink M, Ho A, Chuter V: Exercise interventions for the treatment of
537 chronic low back pain: a systematic review and meta-analysis of randomised
538 controlled trials. *Clin Rehabil* 29:1155-1167, 2015
- 539 31. Senn S, Rolfe K, Julious SA: Investigating variability in patient response to
540 treatment—a case study from a replicate cross-over study. *Stat Methods Med
541 Res* 20:657–666, 2011
- 542 32. Snapinn SM, Jiang Q: Responder analyses and the assessment of a clinically
543 relevant treatment effect. *Trials* 8:31-37, 2007
- 544 33. Spear BB, Heath-Chiozzi M, Huff J: Clinical applications of pharmacogenetics.
545 *Trends Mol Med* 7:201–204, 2001

- 546 34. Swinton PA, Hemingway BS, Saunders B, Gualano B, Dolan E: A statistical
547 framework to interpret individual response to intervention: paving the way for
548 personalised nutrition and exercise prescription. *Frontiers in nutrition* 5:41,
549 2018;
- 550 35. The British Pain Society. Guidelines for Pain Management Programmes for
551 adults - An evidence-based review prepared on behalf of the British Pain
552 Society. 2nd Ed. The British Pain Society. London: The British Pain Society;
553 2013.
554 https://www.britishpainsociety.org/static/uploads/resources/files/pmp2013_main_FINAL_v6.pdf. Accessed October 1, 2018.
- 556 36. The Joanna Briggs Institute (JBI). The System for the Unified Management,
557 Assessment and Review of Information (SUMARI) is the Joanna Briggs
558 Institute's premier software for the systematic review of literature. JBI
559 SUMARI. <https://www.jbisumari.org>. 2017. Accessed October 1, 2018.
- 560 37. van Aert RC, Jackson D: A new justification of the Hartung-Knapp method for
561 random-effects meta-analysis based on weighted least squares
562 regression. *Res Synth Methods*. 2019
- 563 38. van Ittersum MW, Wilgen CP, Schans CP, Lambrecht L, Groothoff JW, Nijs J:
564 Written pain neuroscience education in fibromyalgia: A multicenter
565 randomized controlled trial. *Pain Pract* 14:689-700, 2014
- 566 39. Watson JA, Ryan CG, Cooper L, Ellington D, Whittle R, Lavender M, Dixon J,
567 Atkinson G, Cooper K, Martin DJ: Pain neuroscience education for adults with
568 chronic musculoskeletal pain: a mixed-methods systematic review and meta-
569 analysis. *J Pain* 2019

570 40. Williamson PJ, Atkinson G, Batterham AM: Inter-individual responses of
571 maximal oxygen uptake to exercise training: a critical review. *Sports Med*
572 47:1501-1513, 2017

573 41. Williamson PJ, Atkinson G, Batterham AM: Inter-individual differences in
574 weight change following exercise interventions: a systematic review and
575 meta-analysis of randomized controlled trials. *Obes Rev* 19:960-975, 2018

576 42. Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL,
577 Tugwell P, Campbell SM, Abeles M, Clark P, Fam AG: The American College
578 of Rheumatology 1990 criteria for the classification of fibromyalgia: report of
579 the Multicenter Criteria Committee. *Arthritis Rheum* 33:160-72, 1990

580
581
582
583
584
585
586
587
588
589
590
591
592
593
594

Table 1 Summary of findings:						
PNE compared to control for treatment of adults with chronic musculoskeletal pain						
Patient or population: treatment of adults with chronic musculoskeletal pain Setting: Intervention: PNE Comparison: control						
Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with control	Risk with PNE				
Change in disability score in the short term. (ST Disability) assessed with: Validated measure of disability converted to percentage Scale from: 0 to 100 (worse)	The mean change in disability score in the short term. was -8.63 units	mean 2.26 units lower (6.49 lower to 1.97 higher)	-	428 (5 RCTs)	⊕○○○ VERY LOW a,b,c,d,e,f,g,h	PNE may reduce/have little to no effect on change in disability score in the short term. but the evidence is very uncertain.
<p>*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).</p> <p>CI: Confidence interval</p> <p>GRADE Working Group grades of evidence High certainty: We are very confident that the true effect lies close to that of the estimate of the effect Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect</p>						

595 **Explanations**

- 596 a. A large proportion of the weight came from a study where there was concern over selection bias, performance bias, attrition bias,
 597 reporting bias and other bias. There was concern with most studies over performance bias which whilst normal of these types of studies may
 598 still impact the results.
 599 b. Some variation is size of the effect, however the difference between studies does not reach a clinically meaningful difference
 600 c. Good overlap of the confidence intervals.
 601 d. I-Squared above 50%
 602 e. Tau-Squared higher than point estimate.
 603 f. Sample of chronic musculoskeletal pain comparing PNE against control using an appropriate outcome measure.
 604 g. Has over 400 participants but imprecise due to prediction interval including null effect and clinically important benefit.
 605 h. A comprehensive search was conducted on electronic databases and trials registries. References lists and citing articles of included studies
 606 were searched to identify any further articles.
 607

608 *Table 1 Legend: Summary of findings, PNE compared to control for treatment of*
 609 *adults with chronic musculoskeletal pain*

610

Table 2 Summary of findings:				
Do inter-individual differences in disability change in response to PNE exist in adults with chronic musculoskeletal pain?				
Patient or population: treatment of adults with chronic musculoskeletal pain Setting: Intervention: PNE Comparison: control				
Outcomes	Estimated absolute inter-individual difference in response (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
Inter-individual variability in disability change in the short term. SD _{IR} assessed with: Validated measure of disability converted to percentage Scale from: 0 to 100 (worse)	mean 7.36 units (3.93 lower to 11.12 higher)	428 (5 RCTs)	⊕○○○ VERY LOW a,b,c,d,e,f,g	Little evidence of “true” variation in peoples’ response to PNE for disability, but the evidence is very uncertain.
CI: Confidence interval				
GRADE Working Group grades of evidence High certainty: We are very confident that the true difference in response lies close to that of the estimate of the difference in response Moderate certainty: We are moderately confident in the difference in response estimate: The true difference in response is likely to be close to the estimate of the difference in response, but there is a possibility that it is substantially different Low certainty: Our confidence in the difference in response estimate is limited: The true difference in response may be substantially different from the estimate of the difference in response Very low certainty: We have very little confidence in the difference in response estimate: The true difference in response is likely to be substantially different from the estimate of difference in response				

611 **Explanations**

- 612 a. A large proportion of the weight came from a study where there was concern over selection bias, performance bias, attrition bias,
 613 reporting bias and other bias. There was concern with most studies over performance bias which whilst normal of these types of studies may
 614 still impact the results.
 615 b. Some variation in size of the effect, however the difference between studies does not reach a clinically meaningful difference
 616 c. Good overlap of the confidence intervals.
 617 d. Tau-Squared higher than point estimate.
 618 e. Sample of chronic musculoskeletal pain comparing PNE against control using an appropriate outcome measure.
 619 f. While the analysis includes over 400 participants this lack precision due to the very wide prediction interval including both a clinically
 620 important positive effect and clinically important negative effect.
 621 g. No evidence of publication bias. Sample sizes ranged from 62-120. A comprehensive search was conducted on electronic databases and
 622 trials registries. References lists and citing articles of included studies were searched to identify any further articles.
 623

624 *Table 2 Legend: Summary of findings, Do inter-individual differences in disability*
 625 *change in response to PNE exist in adults with chronic musculoskeletal pain?*

626

627

Table 3 Characteristics of included studies

Study	Methods	Sample size (baseline)/ gender/ mean age in years	Participants	Intervention(s)	Duration of educational intervention	Control	Authors conclusions/notes	Setting/country
van Ittersum et al. 2013 ³⁸	RCT	N = 105 7% M 46.7	Fibromyalgia diagnosed according to The American College of Rheumatology 1990 criteria ⁴² . 18-65 years of age. Baseline pain as mean % = 71.5% Duration of pain in mean months = unknown	Written PNE + 1 phone call for motivation/questions +/- 2x phone calls/emails for further clarification/questions	Unknown	Written Relaxation exercises + 1 phone call for motivation/questions +/- 2x phone calls/emails for further clarification/questions	Written PNE alone is not effective for changing the impact of the illness on daily life, pain catastrophising, or illness perceptions in fibromyalgia patients.	Specialised centres for chronic pain and chronic fatigue. Belgium.
Gallagher, McAuley	RCT	N = 79 39% M	18-75 years of age with pain that had	80-page booklet divided into 11 sections -	Unknown	80-page booklet divided into 11	Written material using metaphors to explain key	Unknown Unknown

and Moseley 2013 ₆		43.5	<p>been sufficient to disrupt their activities of daily living for more than the previous 3 months.</p> <p>Baseline pain as mean % = 65%</p> <p>Duration of pain in mean (SD) months = 28 (19.5)</p>	Metaphors and stories to help understand the biology of pain		sections - Advice about managing pain (The back book and Manage your pain)	biological concepts increased knowledge of pain biology and decreased catastrophic thought processes about pain and injury when compared to material that presented biopsychosocial advice for pain management.	
Pires, Cruz and Caeiro, 2015 ₂₆	RCT	N = 62 35% M 51	<p>Low back pain >3 months duration +/- leg pain. 18-65 years of age.</p> <p>Baseline pain as mean % = 42.9%</p> <p>Duration of pain in mean (SD) months = unknown</p>	<p>2x 1.5h Group PNE. 12 sessions of aquatic exercise over 6 weeks. 30-50m each session.</p>	<p>PNE 3h Control 3h</p>	<p>12 sessions of aquatic exercise over 6 weeks. 30-50m each session.</p>	<p>PNE is a clinically effective addition to aquatic exercise. The addition of PNE resulted in statistically significant reduction in pain intensity at 3-month follow up. No statistically significant differences were found for pain intensity at 6 weeks follow up or functional disability at either follow up.</p>	<p>Outpatient clinic. Portugal</p>
Louw et al. 2014/16 _{19,20}	RCT	N = 67 46% M	Patients with lumbar	0.5h individual PNE.	PNE 0.5h	Lumbar surgery alone + usual care	Providing a single PNE session to patients prior to lumbar	7 Clinical sites in the US.

		49.6	radiculopathy, scheduled for lumbar surgery. 18-65 years of age. Baseline pain as mean % = 48.4% Duration of pain in mean (SD) months = 3 (7.5)	PNE booklet "your nerves are having back surgery" & Lumbar surgery + usual care	Control 0		surgery results in significant reduction in healthcare costs 3-years after LS.	
Malfliet et al. 2018 ²¹	RCT	N = 120 39.2% M 39.8	Non-specific chronic spinal pain (neck and lower back) at least 3 days a week for at least 3 months since the first symptoms. 18-65 years of age Baseline pain as mean % = 50.65	3 PNE sessions 1. 0.5-1h group (maximum of 6 patients). Information booklet provided at the end. 2. ~0.63h home-based online e-learning module containing 3 explanatory videos and	PNE 1.88h Control 1.88h	3 biomedical education sessions 1. 0.5-1h group (maximum of 6 patients). Information booklet provided at the end. 2. ~0.63h Home-based online e-learning module containing 3 explanatory videos	PNE, and not neck/back school education, is able to improve kinesiophobia, beliefs regarding the negative impact of the illness on quality of life and functional capacity, and beliefs regarding the chronicity of pain and the time scale of illness symptoms. However, none of the educational programs of this study were able to decrease the participants perceived disability due to pain. Nevertheless, as kinesiophobia is generally	University hospitals in Ghent and Brussels, Belgium.

			Duration of pain in mean (SD) months = 82 (143.25)	<p>questions about pain.</p> <p>3. 0.5 Individual education. Focus on patients' personal needs following difficulties with session 2. Focus on the application of knowledge to participants life.</p>		<p>3. 0.5 Individual. Focus on patients' personal needs following difficulties with session 2. Focus on the application of knowledge to participants life.</p>	<p>considered to be a strong predictor and mediator of chronic pain, PNE is preferred as the educational approach for people with non-specific chronic spinal pain.</p>	
--	--	--	--	---	--	--	---	--

630
631
632
633

Table 3 Legend: Randomized controlled trial, RCT. Male,

634 *Table 3 Legend: Characteristics of included studies. PNE, Pain neuroscience education. SD, Standard deviation. RCT,*

635 *Randomised controlled trial*

636
637

Table 4 Critical appraisal of quantitative studies

Study	Score /7	Percentage
Gallager 2013 ⁶	5	71%
Louw 2014/16 ^{19,20}	3	43%
Malfliet 2018 ²¹	6	86%
Pires 2015 ²⁶	3	43%
van Ittersum 2013 ³⁸	1	14%

638 *Figure 4 Legend: Forest plot of PNE versus control in the short term; primary*
639 *outcome disability mean difference.*

640

641

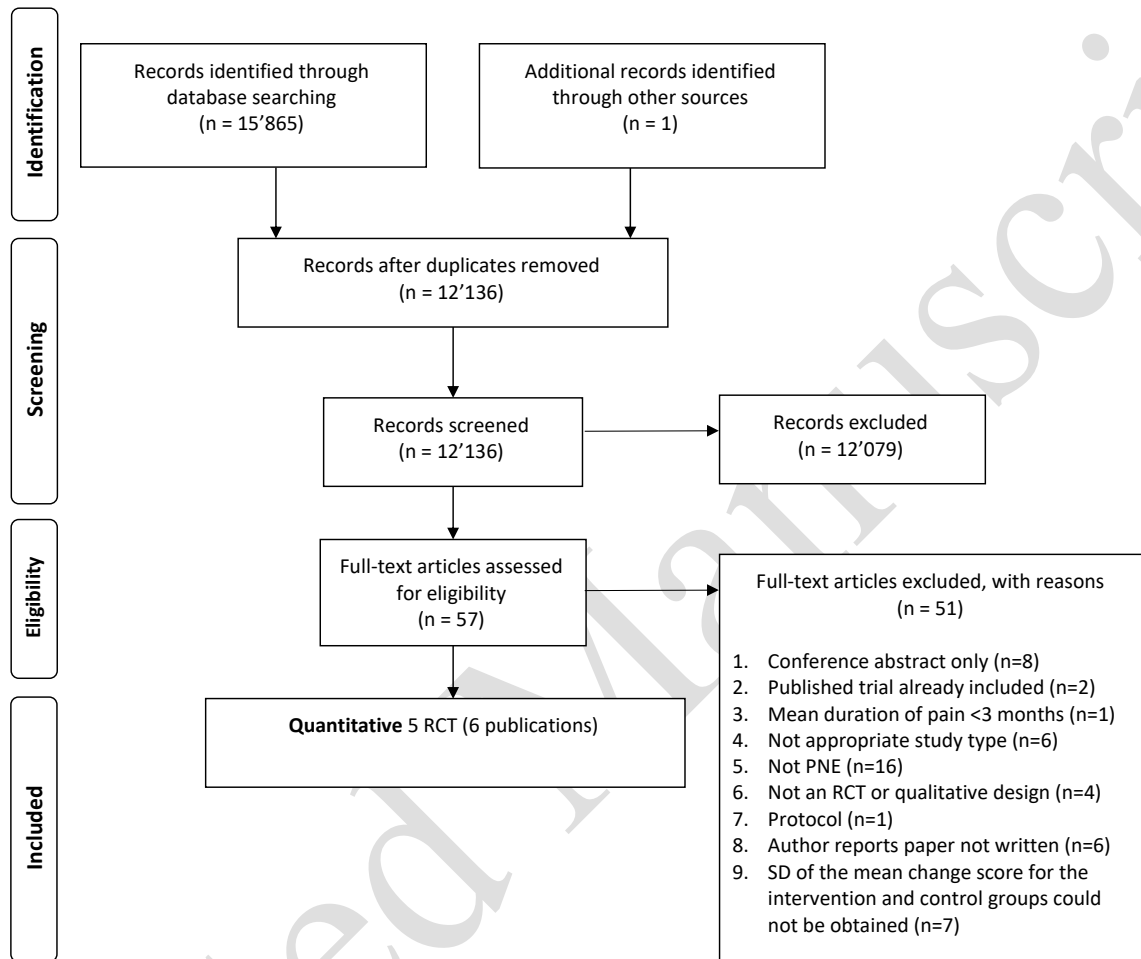
642 Table 5: Proportions of responders.

Study	Mean Change (PNE)	SD (PNE)	% responders (PNE)	Mean change (Con)	SD (Con)	% Responders (Con)	Mean treatment effect (PNE-Con)	SD for true Ind diffs	% Responders based on SDir ³⁴
van Ittersum et al. 2013 ³⁸	0.7	4.2	0	0.3	2.9	0	0.4	3.0	0
Pires, Cruz and Caeiro, 2015 ²⁶	-11.1	15.8	53	-7.7	10.6	41	-3.4	11.7	29
Louw et al. 2014/16 ^{19,20}	-12.0	18.5	54	-11.1	13.8	53	-0.9	12.3	23
Malfliet et al. 2018 ²¹	-1.1	13.8	26	1.6	11.2	15	-2.7	8.1	18
Gallagher, McAuley and Moseley 2013 ⁶	-36	17	94	-27.0	15.0	87	-9.0	8	45

643 *Table 5 Legend: Proportions of responders. PNE, Pain neuroscience education.*

644 *Con, Control. SD, Standard deviation. SDir, Standard deviation for individual*

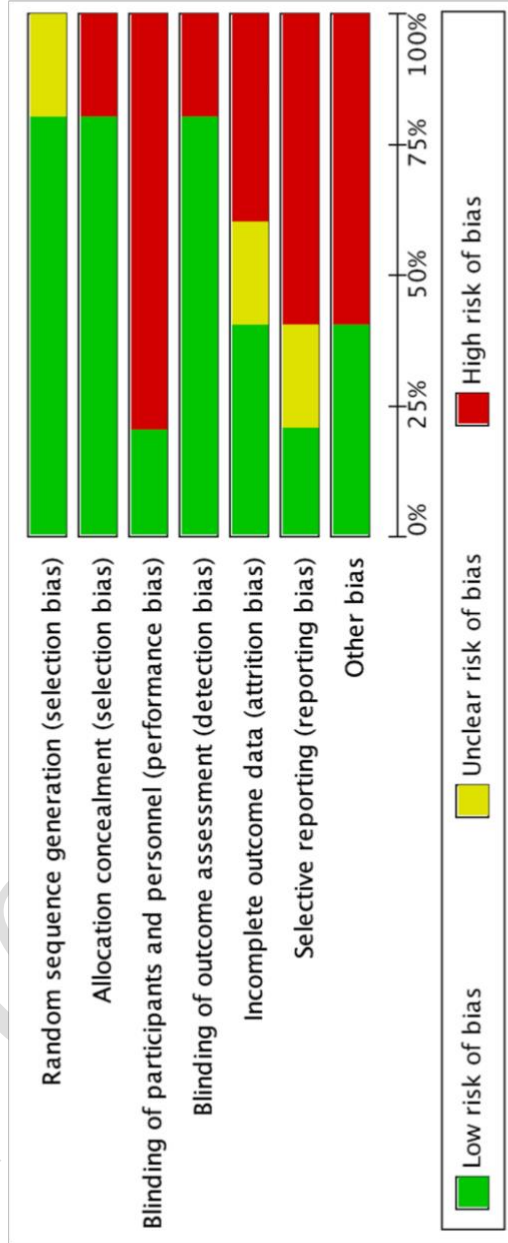
645 *responses.*



646

647 *Figure 1 Legend: PRISMA flow diagram of search and study selection process.*

648 *(Adapted from Moher et al.22).*



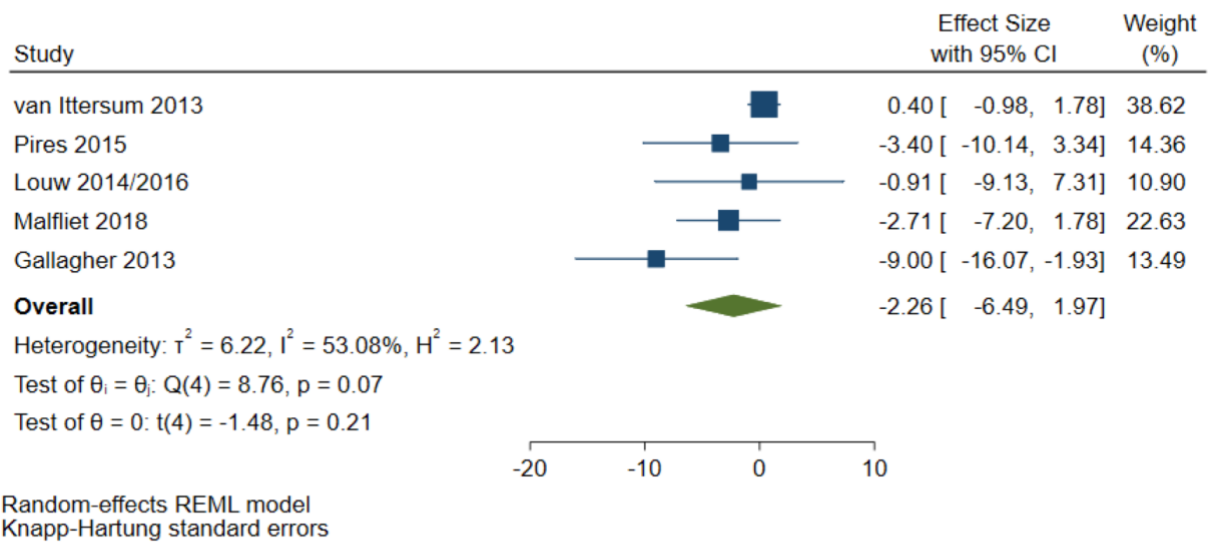
649

650 *Figure 2 Legend: Risk of bias graph.*

651

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Gallagher 2013	+	+	+	+	+	-	-
Louw 2014/16	+	+	-	+	?	-	-
Malfliet 2018	+	+	-	+	+	+	+
Pires 2015	+	+	-	-	-	?	+
van Ittersum 2013	?	-	-	+	-	-	-

654 *Figure 3 Legend: Risk of bias summary*



656

657 *Figure 4 Legend: Forest plot of PNE versus control in the short term; mean*
 658 *difference of disability between groups.*

659

660

661

662

663

664

665

666

667

668

Supplementary Appendix 1 - Calculations for inter-individual differences meta-analysis

Step 1

We extracted the standard deviation (SD) of the changes in disability for both control (C) and PNE (I) groups.

Study	SDC	Mean I
van Ittersum	2.9	0.7
Gallagher	15	-36
Pires	10.6	-11.1
Louw	13.79	-12
Malfliet	11.15	-1.1

Step 2

The true individual response variance (intervention minus control) was then calculated by $\sqrt{(SD_I^2 - SD_C^2)}$ (Hopkins, 2015).

Study	IR_Variance	SDI	SDC
van Ittersum	9.23	4.2	2.9
Gallagher	64	17	15
Pires	137.28	15.8	10.6
Louw	152.09	18.5	13.79
Malfliet	65.84	13.79	11.15

Step 3

The standard error (SE) for this variance was then calculated using the equation:

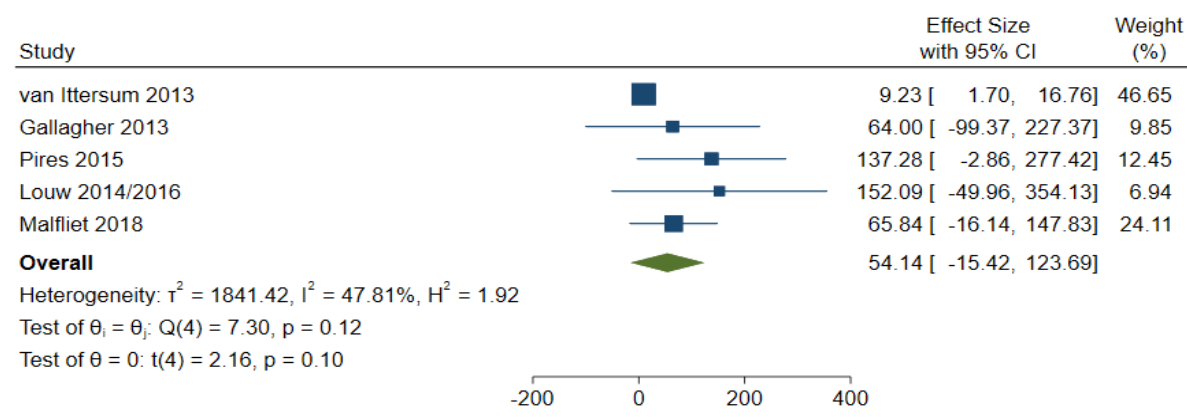
$SE = \sqrt{2[(SD_I^2/DF_I + SD_C^2/DF_C)]}$, where DF_I and DF_C are the degrees of freedom of the standard deviation in the PNE group and the control groups (Hopkins, 2015).

Study	IR_Variance	SE	SDI	SDC	n I	n C
van Ittersum	9.23	3.83949378	4.2	2.9	53	52
Gallagher	64	83.3522758	17	15	40	39
Pires	137.28	71.5013373	15.8	10.6	30	32
Louw	152.09	103.087047	18.5	13.79	29	33
Malfliet	65.84	41.8303551	13.79	11.15	60	60

Step 4

The individual response variances and their SEs were meta-analysed using an REML model combined with Knapp-Hartung method. It's important to highlight that the variances are unbiased, whereas the SD is not, and deriving a SE for the SD for individual responses is also problematic. Thus, we synthesised the individual response variances instead of the SDs for individual responses. The point estimate for the pooled individual response variance were derived together with a 95% CI to express its uncertainty.

Forest plot of **Variance** Meta-analysis for estimating individual differences in response:



Random-effects REML model
 Knapp-Hartung standard errors

Step 5

The point estimate and CIs were then square rooted to convert to an SD metric. If the lower limit was negative, the sign was ignored, the square root taken, and the sign re-applied. This approach is consistent with the 'no bound' option in SAS/STAT® software, which permits negative variances (SAS Institute Inc. 2017. SAS/STAT 14.3 User's Guide. Cary, NC: SAS Institute Inc.).

	As variance	SD without sign	As SD with sign re-applied
Total point estimate	54.14		7.35798886
Lower CI	-	3.92683078	-3.9268308
Upper CI	123.69		11.1216006

Steps to calculate the prediction interval for the inter-individual differences point estimate

$PI = \text{pooled estimate} \pm t_{(n-2)} \times \text{SQRT}(SE^2 + \tau^2)$

Pooled Est 54.14

3.182 is the two-tailed t value for n-2 degrees of freedom = 3 degrees of freedom, and P=0.05. See: <http://www.ttable.org/student-t-value-calculator.html>

$t_{(n-2)} =$ 3.182
 SE= 25.0508232
 $SE^2 =$ 627.543743 (From STATA)
 $\tau^2 =$ 1841.4235

$(SE^2 + \tau^2) =$ 2468.96724
 $\text{SQRT}(SE^2 + \tau^2) =$ 49.6887034

PI = Pooled est +/- $t_{(n-2)}$ x $\text{SQRT}(SE^2 + \tau^2)$
 PI = 54.14 +/- 3.182 x 49.6887034
 PI = 3.182 +/- 158.109454

PI Upper = 212.249454

PI Lower = -103.96945

Square root the above values to convert from variance to SD to get to the PI for the SDir:

PI Upper = 14.5687836

PI Lower = -10.196541