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The Relationship Between Pain-Related Psychological Factors and Maximal Physical Performance in Low Back Pain: A Systematic Review and Meta-Analysis

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Abstract: Theoretical frameworks explain how pain-related psychological factors may influence the physical performance. In this systematic review and meta-analysis, we evaluated the evidence regarding the relationship between the pain-related psychological factors and the maximal physical performance in patients with low back pain (LBP). Pubmed, Embase, CINAHL and Web of Science databases were searched from inception to May 2022. Cross-sectional or longitudinal studies reporting cross-sectional measures of association between at least one pain-related psychological factor and a quantitatively measured outcome of maximal physical performance in patients with LBP were eligible for inclusion. Thirty-eight studies (n = 2,490; 27 cross-sectional studies, n = 1,647 (66%); 11 longitudinal studies, n = 843 (34%)) were included, with 92% of participants (n = 2,284) having chronic LBP. Results showed that pain-related fear, pain catastrophizing, and anticipated pain were consistently and negatively associated with the maximal physical performance in chronic LBP, whereas pain-self efficacy showed positive correlations. Overall, magnitudes of absolute pooled r-values were small ($r \leq 0.25$), except for anticipated pain, which was moderately associated with maximal physical performance (r = -0.34 to -0.37). Subanalyses and sensitivity analyses yielded similar pooled correlation coefficients. Certainty of evidence using the GRADE recommendations was very low to moderate for pain-related fear, and very low to low for the other pain-related psychological factors.
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***Perspective:** Overall, small pooled correlation coefficients were shown between pain-related psychological factors and maximal physical performance in chronic LBP. Certainty of evidence was very low to low for all pain-related psychological factors other than pain-related fear. Future studies taking into account limitations of the current literature may therefore change these conclusions.*

***Key words:** Low back pain, physical performance, behaviour, psychological factors, systematic review.*

[1]www.paininmotion.be.

Short study description. The premise of maximal physical performance tests is that they are mainly limited by physical constraints. However, various theoretical frameworks explain how pain-related psychological factors may also influence physical functioning and performance. In this systematic review and meta-analysis, we evaluated the available evidence regarding the relationship between pain-related psychological factors and maximal physical performance (e.g., strength) in patients with low back pain. Meta-analyses were performed for the different psychological constructs that could be retrieved (e.g., pain-related fear). In addition, we conducted various pre-defined subanalyses to examine whether associations were dependent on the type of performance test (e.g., strength *vs* endurance) or self-report measure to assess the psychological construct (e.g., TSK *vs* FABQ). Sensitivity analyses were done to assess the influence of personal factors (e.g., sex or age) and pain intensity.

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Low back pain (LBP) poses an enormous health and socioeconomic problem. It has been identified as the leading cause of years lived with disability worldwide, and is one of the most important reasons for sick leave and early retirement.[17,49]

Low back pain is a multidimensional problem that can be influenced by a myriad of factors, including physical, psychological and social aspects.[24] Consequently, this multidimensional nature should be taken into account during assessment in order to evaluate the relative contribution of these aspects for each individual patient. Regarding the physical component, maximal physical performance tests are often used to evaluate muscle strength, muscle endurance, and functional capacity in patients with LBP.[36,73] Although it can be questioned whether improvements in maximal physical performance are necessary to obtain reductions in pain and disability,[74] rehabilitation programs can be individualized and progress can be monitored based on these type of tests, while functional capacity evaluations may also be useful for the prognosis of work participation.[41,59]

The premise of maximal physical performance tests is that they are mainly limited by the physical constraints. However, various theoretical frameworks explain how psychological factors may also influence physical functioning and performance, in particular in pain populations.[8,26,46,90] The fear-avoidance model of pain posits that maladaptive pain-related cognitions (eg, catastrophic thinking) may lead to pain-related fear of movement, and subsequently to avoidance behaviour and deconditioning.[14,90] In addition, individuals with chronic pain and higher levels of pain-related fear typically overpredict the pain intensity they will experience during physical tasks, which in turn may interfere with the performance on these tasks.[14] However, fear and (predicted) pain are not the sole motivators of avoidance behaviour, and some pain-related psychological factors may actually reduce the latter.[52] For example, individuals who are more confident in their ability to perform activities despite their pain (ie, higher pain self-efficacy) or individuals who are more strongly motivated to pursue valued life goals (ie, goal pursuit) are more likely to engage and persist in (feared) activities.[8,83,84] Accordingly, it can be argued that pain-related psychological factors could also influence the achievements on maximal physical performance tests. In this case, results on such tests may rather reflect (pain-related) behaviour instead of true physiological capacity in patients with maladaptive pain-related cognitions, and thus significantly impact the interpretation of performance test outcomes. On the other hand, if pain-related psychological factors and the maximal physical performance are not related, the theoretical underpinning of current models suggesting this relationship may need to be revised.

Despite a long history of empirical research in patients with LBP, the potential interplay between pain-related psychological factors and the physical performance remains unclear, as shown by 2 previous literature reviews.[32,82] However, these reviews did not include meta-analyses,[32,82] and one review was not based on a systematic literature search.[32] Moreover, a significant number of additional studies have been published since. Given the important consequences for the empirical validation of theoretical frameworks and the interpretation of physical performance test results, a systematic review with meta-analysis on this topic is necessary. Therefore, a meta-analytic review was performed to determine whether pain-related psychological factors are associated with the maximal physical performance in patients with LBP.

Methods

Protocol and Registration

This review was performed and reported according to the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-analyses) and PERSiST (implementing Prisma in Exercise, Rehabilitation, Sport medicine and SporTs science) guidelines.[7,57] The review protocol was prospectively registered on PROSPERO (CRD42021227486).

Eligibility Criteria

Participants

Studies including adults (≥18y) with LBP of musculoskeletal origin (including specific LBP; eg, radicular pain) irrespective of the duration of complaints. Studies were excluded when they only included healthy persons or a heterogeneous pain-population without a specific analysis for LBP, when they were performed in a population with a serious underlying non-musculoskeletal disease (eg, multiple sclerosis) or when experimentally induced pain was used.

Type of Studies

Cross-sectional studies or cross-sectional baseline data from studies with a longitudinal design, including randomized controlled trials.

Outcome Measures

At least one measure of association between a pain-related psychological factor and the outcome on a maximal voluntary physical performance test had to be reported. If only significant measures of association were reported and non-significant associations were only described as such, we contacted the authors of these studies at least 3 times. When we were not able to obtain the results for all associations (ie, also the non-significant ones), this study was excluded in order to avoid positively biased results. To be included, the questionnaires assessing the psychological factors had to pertain to pain-related cognitions or emotions. For example, studies assessing pain anxiety or pain self-efficacy (eg, using the Pain Anxiety Symptoms Scale of Pain Self-Efficacy Questionnaire) were included, whereas studies assessing anxiety or self-efficacy as a general construct not specifically pertaining to pain (eg, using the Hospital Anxiety and Depression Scale or the General Self-Efficacy Scale) were not included. The physical performance test was considered maximal when the test was explicitly described as such, the authors referred to a previous study describing the test as maximal, or when it could be logically inferred from the definition of the test. The performance also had to be assessed quantitatively. Typical examples are endurance tests (eg, maximal holding time in seconds), strength tests (eg, maximal torque) or maximal functional capacity tests (eg, maximal weight lifted for lifting capacity). Studies were excluded when only submaximal performance tests were included, if participants' cognitions were experimentally manipulated, and when the performance was rated via participant self-report or an assessor evaluation (eg, using a Likert scale ranging from "can do the task with ease" to "cannot perform the task at all,"[76] or via a rating of perceived exertion).

Information Sources and Search Strategy

The electronic databases Pubmed, Embase, CINAHL and Web of Science were searched from inception to May 2022. Search terms for LBP, pain-related psychological factors and performance tests were combined (see supplementary appendix A for full strategy). The reference lists of included studies and other relevant papers were manually checked and forward citation tracking in Web of Science was used to find additional relevant papers.

Study Selection

After removal of duplicates via a reference management tool (Endnote, version X9.2), 2 reviewers (T.M. and L.D.B.) independently screened the titles and abstracts of the obtained articles for eligibility. The relevant studies were read in full length to make a decision about the inclusion. In case of disagreement, a decision was made by consensus, and a third reviewer (L.J.) was consulted when necessary.

Risk of Bias

The Quality In Prognosis Studies (QUIPS) tool was used to assess risk of bias.[28] Six domains were assessed and rated as low, moderate or high risk of bias: study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding and statistical analysis, and reporting. Since physical performance can be influenced by personal factors, such as age, sex, and bodyweight,[64] the risk of bias assessment for study confounding was dependent on how many of these potentially confounding factors were taken into account, ie, high (no factors), moderate (one factor), and low (at least 2 factors) risk of bias. For a study to be considered low risk of bias, at least 4/6 domains had to be low risk, including the domains "study confounding" and "statistical analysis and reporting." Risk of bias was assessed independently by 2 authors (T.M. and L.D.B.). In case of disagreement, a third author (L.J.) was consulted to reach consensus. A Kappa-coefficient was calculated for evaluating interrater agreement for risk of bias assessment. Details on procedures for risk of bias assessment can be found in supplementary appendix B.

Data Collection

Two authors (T.M. and L.D.B.) independently extracted the data using a standardized form, and verified the consistency of the extracted data afterwards. The following information was extracted regarding 1) study population: number of included participants, age, sex (% female), pain intensity, LBP-related disability, time since onset of LBP and type of LBP: acute (<6 weeks), subacute (6−12 weeks), chronic (≥12 weeks) or recurrent LBP; 2) pain-related psychological factors: the psychological construct (eg, pain-related fear), the questionnaires used and the scores on the questionnaires and their relevant subscales; 3) maximal physical performance test: the type of task (eg, strength), the involved body region (eg, lower back or extremities), type of outcome (eg, maximal weight lifted), whether and which type of familiarization was performed in preparation of the task, and the type of motivational cues used during the performance task; 4) measures of association between pain-related psychological factors and results on the maximal physical performance tests. Our approach was similar to a recent meta-analysis by Christe *et al*.[11] When only regression analyses were reported, the correlation coefficients were derived from the standardized beta coefficient as described by Peterson and Brown.[62] In case only between-group differences were available, correlation coefficients were calculated according to Jacobs *et al*[35]; 5) confounding factors: we extracted whether the study design or the statistical analysis took into account or adjusted for relevant personal confounders (age, sex, and bodyweight) and pain intensity.

Data Synthesis and Meta-Analysis

Data were analyzed separately for (sub)acute LBP, chronic LBP, and recurrent LBP in remission. The reason for this distinction is that the temporary avoidance of certain activities might be beneficial in case of (sub) acute injury, while this behaviour becomes maladaptive once the tissues have healed and protection is no longer necessary, as is assumed to be the case in chronic nonspecific LBP and recurrent LBP in remission.[30]

A meta-analysis was performed when at least 3 studies were available for a particular analysis. Given the low number of studies including patients with (sub) acute LBP (n = 1)[31] and recurrent LBP in remission (n = 2),[5,6] results for these types of LBP were reported descriptively. For the meta-analyses in the chronic LBP population, we first used a general approach where all the results for the same psychological construct were combined. Four different psychological constructs were retrieved from the studies, ie, pain-related fear, pain catastrophizing, anticipated pain during the performance test and pain self-efficacy. We hypothesized that 1) higher levels of pain-related fear, pain catastrophizing and anticipated pain would be associated with worse physical performance, resulting in *negative* pooled correlation coefficients, whereas 2) higher levels pain self-efficacy would be associated with better physical performance, resulting in *positive* pooled correlation coefficients.

Next, per psychological construct we performed various sub analyses that were based on:

(1) The type of maximal performance test: based on the included studies, 4 categories could be made, ie, muscle strength, muscle endurance, lifting capacity, and functional mobility. The functional mobility category included tasks that were similar to daily life mobility activities (eg, stair climbing or stationary cycling). Since lifting is often perceived to be a harmful activity by patients with LBP,[50] we hypothesized that associations with pain-related psychological factors may be stronger for this task as compared to other tasks. Muscle strength tests were further divided in tests for respectively trunk and extremity muscles, as it could be hypothesized that performances on tasks involving the painful area (ie, the trunk) may be affected to a higher degree by pain-related psychological factors compared to task involving remote areas (ie, the extremities).
(2) The specific questionnaire: separate meta-analyses were performed for the different questionnaires that measure the same psychological construct. Furthermore, when a questionnaire consisted of different subscales, an additional analysis was made for each subscale that assesses a pain-related psychological factor. It has been hypothesized that some questionnaires or subscales may be more strongly related to physical performance, because their items specifically refer to physical activity and exercises (eg, Tampa Scale for Kinesiophobia-Activity Avoidance subscale) whereas others do not (eg, Tampa Scale for Kinesiophobia-Somatic Focus subscale).[69]
(3) The combination of the type of maximal performance test and the specific questionnaire: per questionnaire, subanalyses were performed for specific types of maximal performance tests.

In order to perform the meta-analyses, an average correlation coefficient per study was calculated if necessary.[11] For example, if a study reported correlation coefficients between lifting capacity and both the Fear Avoidance Beliefs Questionnaire and Tampa Scale for Kinesiophobia, these correlation coefficients were averaged to obtain a single correlation coefficient to assess the association between the construct pain-related fear and lifting capacity. When a single correlation coefficient was available for each analysis, they were first transformed using a Fisher's z transformation. Meta-analyses were performed using the z-scores, after which an inverse Fisher's z transformation was used to obtain the pooled correlation coefficient and 95% confidence interval (95% CI).[63] Pooled correlation coefficient effect sizes were interpreted as small ($r < 0.30$), moderate ($r = 0.30-0.50$) or strong ($r > 0.50$).[12] A random effects model was used for all meta-analyses. The I^2 statistic was used to describe the percentage of variability in effect estimates due to heterogeneity,[29] and potential outliers or influential cases were assessed according to Viechtbauer *et al*.[87] If present, sensitivity analyses were performed excluding these studies. Publication bias was assessed with funnel plots and Egger's regression when more than 10 studies were included in the meta-analysis.[75] Statistical analyses were performed using R software using the "metaphor" package.

Since the performance on the maximal physical performance tests may be significantly influenced by personal factors, such as age, sex, and bodyweight,[64] we performed sensitivity analyses with only studies that had low risk of bias on the categories "study confounding" (ie, controlling for at least two of these parameters) and "statistical analysis and reporting." To investigate the potential influence of pain intensity, we also performed a sensitivity analysis including studies with low risk of bias on the 2 abovementioned categories, and which statistically controlled for pain intensity.

Certainty of Evidence

Two reviewers (T.M. and L.D.B.) independently assessed the certainty of evidence for the meta-analyses of the general and subanalyses using a modified version of the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) criteria.[10,18,48] We did not downgrade the certainty of evidence for non-RCT designs, as this was not a review about effectiveness of interventions and because non-randomized cross-sectional designs were appropriate for our research question. As such, the initial certainty of evidence was high, and could be downgraded for following reasons: 1) study limitations when >25% (-1 level) or >50% (-2 levels) of participants came from studies with high risk of bias; 2) inconsistency when I^2 was >50% (-1 level); 3) imprecision when the meta-analysis contained <400 participants (-1 level) or <100 participants (-2 levels); 4) publication bias, if present on funnel plots and Egger's regression for meta-analyses including ≥10 studies. We did not downgrade certainty of evidence for indirectness, since our inclusion criteria resulted in satisfaction of this criterion.[27] The certainty of evidence was upgraded if the effect size was moderate or large, ie, absolute value of pooled correlation coefficient >0.30 (+1 level).

Deviations from Protocol

Although we registered all of our subanalyses in the review protocol, we did not mention the specific hypotheses they were based on. Furthermore, we did not mention the sensitivity analyses that were performed.

Results

Study Selection

The search strategy resulted in 7,982 papers. After removing duplicates and screening on title and abstract, the full texts of 220 papers were read. Finally, 38 studies

(36 reports, 2,432 participants) were included in the review. Two reports[16,68] each described two separate studies in different patient samples. A flowchart is shown in Fig 1.

Study Characteristics

The majority of studies (35/38, 92%) included patients with chronic LBP. One study was performed in patients with (sub)acute LBP.[31] Two studies[5,6] reported results on the same cohort of patients with recurrent LBP in remission. Roelofs *et al*[69] partially reanalyzed data from a previous study in patients with chronic LBP that is also included in this review.[91] Therefore, we only included the unique data reported in Roelofs *et al*.[69]

Pain-related fear was assessed in 33 studies,[2-6,15,16,21-23,31,34,39,42-44,54-56,67-72,79,80,85,86,88,91] pain catastrophising in 8 studies,[5,6,16,23,42,54,58,86] anticipated pain in 5 studies,[2,4,16,65,66] and pain self-efficacy in four studies.[37,38,42,54] Regarding the maximal physical performance tests, trunk muscle strength was evaluated in 19 studies,[3,4,16,21-23,34,37-39,42-44,54,56,58,66,80,85] lifting capacity in 12 studies,[16,43,55,65,66,68-72,79,91] functional mobility in 8 studies,[2,43,55,65,69,71,85,88] trunk muscle endurance in 6 studies[5,6,21,56,68,70] and extremity muscle strength in 5 studies.[15,31,34,55,86]

A summary and detailed description of study characteristics are provided in Table 1 and supplementary appendix C, respectively. The specific questionnaires (and their scores) that were used to assess the pain-related psychological factors for each study can also be found in supplementary appendix C. Overall, levels of pain-related psychological factors across the studies that were included in the meta-analyses were similar to clinically relevant scores for patients with LBP (eg, weighted mean TSK-17 score across

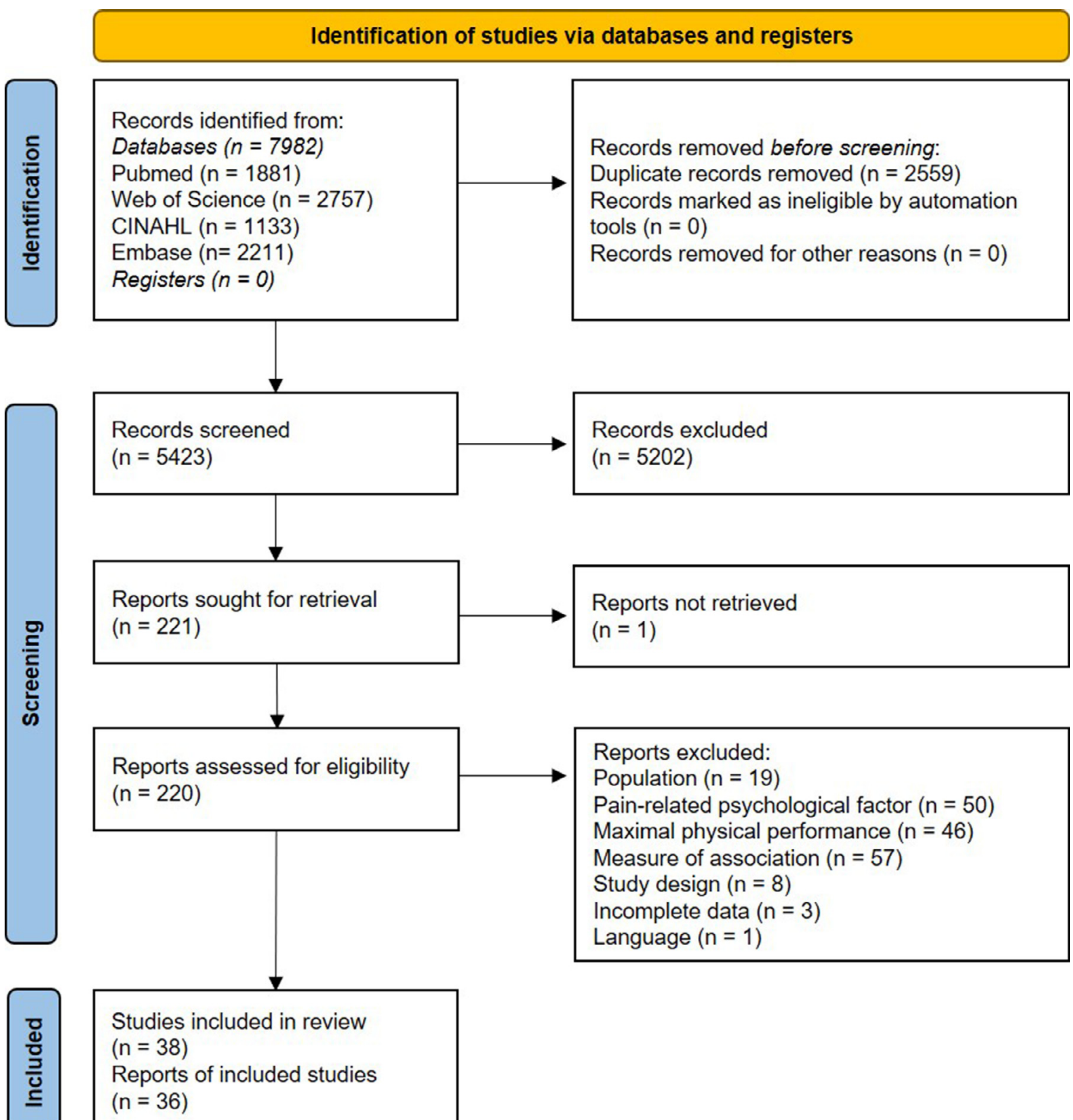

Figure 1. PRISMA flowchart.

Table 1. **Summary of Study Characteristics**

Study	Type of LBP (N)	Maximal Performance Task	Pain-related Psychological Factor
Al-Obaidi *et al*, 2000[4]	Chronic (N = 63)	Trunk muscle strength	Pain-related fear, Anticipated pain
Al-Obaidi *et al*, 2003[2]	Chronic (N = 31)	Functional mobility	Pain-related fear, Anticipated pain
Al-Obaidi *et al*, 2005[3]	Chronic (N = 42)	Trunk muscle strength	Pain-related fear
Applegate *et al*, 2018[5]	Recurrent in remission (N = 24)	Trunk muscle endurance	Pain-related fear, Pain catastrophising, Pain resilience
Applegate *et al*, 2019[6]	Recurrent in remission (N = 24)	Trunk muscle endurance	Pain-related fear, Pain catastrophising, Pain resilience
Crombez *et al*, 1998[15]	Chronic (N = 49)	Extremity muscle strength	Pain-related fear, Anticipated pain
Crombez *et al*, 1999[16] *	Study 1: Chronic (N = 38)	Study 1: Trunk muscle strength	Study 1: Pain-related fear, Anticipated pain
	Study 2: Chronic (N = 31)	Study 2: Lifting capacity	Study 2: Pain-related fear, Pain catastrophising
Demoulin *et al*, 2013[21]	Chronic (N = 50)	Trunk muscle strength and endurance	Pain-related fear
Fehrman *et al*, 2017[22]	Chronic (N = 67)[‡]	Trunk muscle strength	Pain-related fear
Goubert *et al*, 2005[23]	Chronic (N = 84)	Trunk muscle strength	Pain-related fear, Pain catastrophising
Huijnen *et al*, 2010[31]	(Sub)acute (N = 124)	Extremity muscle strength	Pain-related fear
Ishak *et al*, 2017[34]	Chronic (N = 63)	Trunk and extremity muscle strength	Pain-related fear
Kaivanto *et al*, 1995[37]	Chronic (N=105)	Trunk muscle strength	Pain self-efficacy
Keller *et al*, 1999[38]	Chronic (N = 105)	Trunk muscle strength	Pain self-efficacy
Kernan *et al*, 2007[39]	Chronic (N = 63)	Trunk muscle strength, Lifting capacity	Pain-related fear
La Touche *et al*, 2019[42]	Chronic (N = 49)	Trunk muscle strength	Pain-related fear, Pain catastrophising, Pain self-efficacy
Lackner *et al*, 1996[43]	Chronic (N = 85)	Trunk muscle strength, Lifting capacity, Functional mobility	Pain-related fear
Lariviere *et al*, 2003[44]	Chronic (N = 41)	Trunk muscle strength	Pain-related fear
Nieto-Garcia *et al*, 2019[54]	Chronic (N = 30)	Trunk muscle strength	Pain-related fear, Pain catastrophising, Pain self-efficacy
Oesch *et al*, 2012[55]	Chronic (N = 126)	Extremity l muscle strength, Lifting capacity, Functional mobility	Pain-related fear
Pagé *et al*, 2015[56]	Chronic (N = 53)	Trunk muscle strength and endurance	Pain-related fear
Papciak *et al*, 1991[58]	Chronic (N = 186)	Trunk muscle strength	Pain catastrophising
Rainville *et al*, 1992[65]	Chronic (N = 40)	Lifting capacity, Functional mobility	Anticipated pain
Rainville *et al*, 2004[66]	Chronic (N = 70)	Trunk muscle strength, Lifting capacity	Anticipated pain
Reneman *et al*, 2003[67]	Chronic (N = 64)	Lifting capacity	Pain-related fear
Reneman *et al*, 2007[68,*]	Study 1: Chronic (N = 79) Study 2: Chronic (N = 58)	Study 1 and 2: Trunk muscle endurance, Lifting capacity	Study 1 and 2: Pain-related fear
Roelofs *et al*, 2004[69]	Chronic (N = 31)	Lifting capacity, Functional mobility	Pain-related fear
Schiphorst *et al*, 2008[70]	Chronic (N = 92)	Trunk muscle endurance, Lifting capacity	Pain-related fear
Smeets *et al*, 2007[71]	Chronic (N = 221)	Lifting capacity, Functional mobility	Pain-related fear[†]
Soer *et al*, 2006[72]	Chronic (N = 53)	Lifting capacity	Pain-related fear
Thibodeau *et al*, 2013[79]	Chronic (N = 78)	Lifting capacity	Pain-related fear
Thomas *et al*, 2008[80]	Chronic (N = 20)	Trunk muscle strength	Pain-related fear
Verbrugghe *et al*, 2020[85]	Chronic (N =101)	Trunk muscle strength, Functional mobility	Pain-related fear
Verbunt *et al*, 2005[86]	Chronic (N = 25)	Extremity muscle strength	Pain-related fear, Pain catastrophising
Vincent *et al*, 2013[88]	Chronic (N = 55)	Functional mobility	Pain-related fear
Vlaeyen *et al*, 1995[91]	Chronic (N = 33)	Lifting capacity	Pain-related fear

Abbreviation: N, number of participants.
*The papers by Crombez et al (1999)16 and Reneman et al (2007)68 both included results from 2 separate studies on different populations.
†Data for Pain catastrophising could not be retrieved.
‡Data from 67 of 178 participants was included in this review.

studies = 38.1/68 (pooled SD 7.4); see supplementary appendix D).[19,47,89,95]

Risk of Bias and Publication Bias

Results of the risk of bias assessment can be found in Table 2. The Kappa coefficient for inter-rater agreement was 0.76. Risk of bias related to study participation was rated low in only 14 studies (39%)[2-4,21-23,39,55,56,66,67,70,71,85] because the time frame or place of patient recruitment were often not reported. Study attrition was rated low risk of bias, except for 2 studies.[79,91] Regarding study confounding, 18 studies (44%)[5,15,16,21-23,31,37,38, 55,67,68,71,85,86,88] considered at least 2 personal factors in the design or statistical analysis. As a result, 18 studies (44%)[5,15,16,21-23,31,37,38,55,67,68,71,85,86,88] were rated as low risk of bias. No publication bias was present for the four meta-analyses containing ≥10 studies (see supplementary appendix E).

Associations Between Pain-Related Psychological Factors and Maximal Physical Performance

(Sub)acute Low Back Pain

One study (n = 111)[31] in patients with (sub)acute LBP reported that pain-related fear was not significantly associated with the maximal isometric quadriceps torque when controlling for age, sex and bodyweight (r = -0.16, $P > .05$). However, a significant association was present (r = -0.48, $P < .01$) in a subgroup of patients (n = 30) who overpredicted their pain during the task, while this was not the case for patients who made a correct prediction (r = 0.11, $P > .05$).

Recurrent Low Back Pain in Remission

Two studies reported results on the same cohort of patients with recurrent LBP in remission (n = 24) who performed 2 types of maximal endurance tests for the lumbar extensor muscles.[5,6] In both studies, pain-related fear (-0.28 < r < -0.19), pain catastrophising (-0.09 < r < 0.06) and pain-resilience (-0.36 < r < -0.3) were not significantly associated with muscle endurance (all *P*-values > 0.05). When controlling for trunk mass, pain-related fear was significantly associated with the trunk muscle endurance in one study,[5] but not in the other study,[6] while correlations with pain catastrophising and pain-resilience remained non-significant in both studies (all *P*-values > 0.05).

Chronic Low Back Pain

The results of the meta-analyses and the GRADE certainty of evidence assessment are summarized in Table 3. Forest plots of the meta-analyses are provided in supplementary appendix F.

Pain-related fear

All questionnaires combined. When combining all pain-related fear questionnaires and all types of maximal physical performance tests, a total of 30 studies (n = 1877)[2-4,15,16,21-23,34,39,42-44,54-56,67-72,79,80,85,86,88,91] showed a significant pooled correlation coefficient of -0.11 (95% CI = -0.15, -0.06). Looking at the different types of maximal performance tests separately, the pooled correlation coefficients for trunk muscle strength (15 studies, n = 849),[3,4,16,21-23,34,39,42-44,54,56,80,85] trunk muscle endurance (5 studies, n = 332),[21,56,68,70] lifting capacity (12 studies, n = 983)[16,39,43,55,67,68,70-72,79,91] and functional mobility (8 studies, n = 744)[2,43,55,69-71,85,88] were statistically significant and ranged between -0.08 and -0.22 (all *P*-values <0.03). In contrast, the pooled correlation coefficient for extremity muscle strength (4 studies, n =263) was not significant (r = 0.02; 95% CI = -0.11, 0.14).[15,34,55,86] Certainty of evidence was low to moderate.

Tampa Scale for Kinesiophobia (TSK). Meta-analyses could be performed for the total score on the TSK and for the TSK-Activity Avoidance subscale.

Tampa Scale for Kinesiophobia−Total score: The pooled correlation coefficient for all studies using the TSK-total score (18 studies, n = 1161) was -0.11 (95% CI = -0.17, -0.05).[16,21,23,34,39,42,54,56,67,68,70-72,85,86,88,91] Subanalyses per type of task showed that trunk muscle strength (9 studies, n = 531),[16,21,23,34,39,42,54,56,85] trunk muscle endurance (4 studies, n = 274)[21,56,68,70] and lifting capacity (7 studies, n = 580)[16,39,67,68,70-72] were significantly associated with TSK-total scores (pooled r-range = -0.19 to -0.11, all *P*-values <0.05). Functional mobility (3 studies, n = 377)[71,85,88] was not significantly associated with TSK-Total scores (pooled r = -0.04; 95% CI = -0.14, 0.07). Certainty of evidence was moderate, except for trunk muscle endurance (very low certainty of evidence).

Tampa Scale for Kinesiophobia−Activity Avoidance Subscale: The pooled correlation for three studies (n= 111) was not statistically significant (r = -0.23; 95% CI = -0.56, 0.17). Certainty of evidence was very low.

Fear-Avoidance Beliefs Questionnaire (FABQ). Studies only reported associations for the FABQ-Physical Activity and the FABQ-Work subscale separately, so results are presented accordingly.

Fear-Avoidance Beliefs Questionnaire−Physical Activity subscale: The pooled correlation coefficient of eight studies (n = 391)[2-4,16,39,44,68,72] was -0.11 (95% CI = -0.27, 0.06). Subanalyses per task resulted in non-significant pooled correlation coefficients for trunk muscle strength (5 studies, n = 247; r = -0.13; 95% CI= -0.36, 0.13)[2,3,16,39,44] and lifting capacity (3 studies, n = 144; r = -0.04; 95% CI = -0.21, 0.13).[39,68,72] Certainty of evidence was very low.

Fear-Avoidance Beliefs Questionnaire−Work subscale: The pooled correlation coefficient from eight studies (n = 484)[3,4,16,39,44,55,68,72] was -0.09 (95% CI = -0.18, -0.01). Subanalyses per type of task resulted in non-significant pooled correlation coefficients for trunk muscle

Table 2. Risk of Bias

Study	Study Participation	Study Attrition	Prognostic Factor Measurement	Outcome Measurement	Study Confounding	Statistical Analysis and Reporting	Overall Risk of Bias
Al-Obaidi *et al*, 2000[4]	L	L	L	L	H	L	H
Al-Obaidi *et al*, 2003[2]	L	L	L	L	H	L	H
Al-Obaidi *et al*, 2005[3]	L	L	L	L	H	L	H
Applegate *et al*, 2018[5]	M	L	L	L	L	L	L
Applegate *et al*, 2019[6]	M	L	L	L	M	L	H
Crombez *et al*, 1998[15]	H	L	L	L	L	L	L
Crombez *et al*, 1999[16]	H	L	L	L	L	L	L
Demoulin *et al*, 2013[21]	L	L	L	L	L	L	L
Fehrman *et al*, 2017[22]	L	L	L	L	L	L	L
Goubert *et al*, 2005[23]	L	L	L	L	L	L	L
Huijnen *et al*, 2010[31]	M	L	L	L	L	L	L
Ishak *et al*, 2017[34]	M	L	L	L	H	L	H
Kaivanto *et al*, 1995[37]	H	L	M	L	L	L	L
Keller *et al*, 1999[38]	M	L	L	L	L	L	L
Kernan *et al*, 2007[39]	L	L	L	L	M	L	H
La Touche *et al*, 2019[42]	M	L	L	L	H	L	H
Lackner *et al*, 1996[43]	M	L	H	L	H	M	H
Lariviere *et al*, 2003[44]	M	L	L	L	M	L	H
Nieto-Garcia *et al*, 2019[54]	M	L	L	L	H	L	H
Oesch *et al*, 2012[55]	L	L	L	L	L	L	L
Pagé *et al*, 2015[56]	L	L	L	L	H	L	H
Papciak *et al*, 1991[58]	M	L	L	L	H	L	H
Rainville *et al*, 1992[65]	M	L	L	L	H	L	H
Rainville *et al*, 2004[66]	L	L	L	L	H	L	H
Reneman *et al*, 2003[67]	L	L	L	L	L	L	L
Reneman *et al*, 2007[68]	H	L	L	L	L	L	L
Roelofs *et al*, 2004[69]	M	L	L	L	H	L	H
Schiphorst *et al*, 2008[70]	L	L	L	L	M	L	H
Smeets *et al*, 2007[71]	L	L	L	L	L	L	L
Soer *et al*, 2006[72]	M	L	L	L	M	L	H
Thibodeau *et al*, 2013[79]	H	M	L	L	M	L	H
Thomas *et al*, 2008[80]	M	L	M	L	M	M	H
Verbrugghe *et al*, 2020[85]	L	L	L	L	L	L	L
Verbunt *et al*, 2005[86]	M	L	L	L	L	L	L
Vincent *et al*, 2013[88]	M	L	L	L	L	L	L
Vlaeyen *et al*, 1995[91]	H	M	L	L	H	M	H
% Low RoB	39%	94%	92%	100%	44%	92%	44%
% Moderate RoB	44%	6%	5%	0%	20%	8%	-
% High RoB	17%	0%	3%	0%	36%	0%	56%

Abbreviations: L, Low risk of bias; M, moderate risk of bias; H, high risk of bias; RoB, risk of bias.

Table 3. **Meta-analyses of Associations between Pain-related Factors and Maximal Physical Performance in Chronic Low Back Pain**

	Studies (n)	Participants (n)	Pooled r	95% CI	I^2 (%)	GRADE
Pain-related fear						
All questionnaires combined						
All studies	30	1877	−0.11	−0.15, −0.06	0	Moderate[a]
Muscle strength						
Trunk	15	849	−0.12	−0.19, −0.05	0.02	Low[b]
Extremities	4	263	0.02	−0.11, 0.14	3.19	Moderate[d]
Trunk muscle endurance	5	332	−0.22	−0.32, −0.12	0	Low[a,d]
Lifting capacity	12	983	−0.12	−0.20, −0.03	37.78	Moderate[a]
Functional mobility	8	744	−0.08	−0.15, −0.01	0	Moderate[a]
Tampa Scale for kinesiophobia						
Tampa Scale for Kinesiophobia − Total score						
All studies	18	1161	−0.11	−0.17, −0.05	0.02	Moderate[a]
Muscle strength						
Trunk	9	531	−0.11	−0.22, −0.006	30.42	Moderate[a]
Trunk muscle endurance	4	274	−0.19	−0.30, −0.07	0	Very low[b,d]
Lifting capacity	7	580	−0.19	−0.27, −0.11	0.06	Moderate[a]
Functional mobility	3	377	−0.04	−0.14, 0.07	0.02	Moderate[d]
Tampa Scale for Kinesiophobia − Activity Avoidance subscale						
All studies	3	111	−0.23	−0.56, 0.17	76.38	Very low[b,c,d]
Fear-Avoidance Beliefs Questionnaire						
Fear-Avoidance Beliefs Questionnaire − Physical Activity subscale						
All studies	8	391	−0.11	−0.27, 0.06	62.43	Very low[b,c,d]
Muscle strength						
Trunk	5	247	−0.13	−0.36, 0.13	73.96	Very low[b,c,d]
Lifting capacity	3	144	−0.04	−0.21, 0.13	0	Very low[b,c,d]
Fear-Avoidance Beliefs Questionnaire − Work subscale						
All studies	8	484	−0.09	−0.18, −0.01	0	Low[b]
Muscle strength						
Trunk	4	205	−0.13	−0.27, 0.01	0	Very low[b,d]
Lifting capacity	4	270	−0.11	−0.27, 0.04	34.12	Low[a,d]
Pain Anxiety Symptoms Scale						
All studies	3	129	−0.16	−0.49, 0.21	71.2	Very low[b,c,d]
Pain catastrophising						
All questionnaires combined						
All studies	6	405	−0.18	−0.27, −0.08	0	Low[b]
Muscle strength						
Trunk	4	349	−0.15	−0.26, −0.05	0	Low[b]
Pain Catastrophising Scale						
All studies	4	194	−0.18	−0.32, −0.04	0.01	Low[a,d]
Muscle strength						
Trunk	3	163	−0.13	−0.29, 0.02	0	Low[a,d]
*Pain self-efficacy**						
All questionnaires combined						
All studies	4	289	0.22	0.10, 0.33	0.02	Low[a,d]
Anticipated pain						
All questionnaires combined						
All studies**	5	244	−0.51	−0.77, −0.09	92.4	Very low[b,c,d,e]
Muscle strength						
Trunk	3	171	−0.37	−0.50, −0.23	0	Low[b,d,e]

*All studies for Pain self-efficacy used a trunk strength performance test.
**When removing one influential case, the pooled r = -0.34 (95% CI = -0.45, -0.21) with I^2 = 0% (GRADE= Low).GRADE:
aSerious study limitations, >25% of participants from studies with high risk of bias (-1).
bVery serious study limitations, >50% of participants from studies with high risk of bias (-2).
cInconsistency, I^2> 50% (-1).
dImprecision, n <400 (-1).
eModerate or large effect size, absolute value of pooled correlation coefficient >0.30 (+1).

strength (4 studies, n = 205; r = -0.13; 95% CI = -0.27, 0.01) and for lifting capacity (4 studies, n = 270; r = -0.11, 95% CI = -0.27, 0.04).[39,55,68,72] Certainty of evidence was low to very low.

Pain anxiety symptoms scale. The pooled correlation coefficient from three studies (n = 129)[16,79,80] was not significant (r = -0.16; 95% CI = -0.49, 0.21). Certainty of evidence was very low.

Table 4. **Sensitivity Analyses Including Studies Controlling for Personal Factors**

	Studies (n)	Participants (n)	Pooled r	95% CI	I^2 (%)	Absolute Δ Pooled r With General Analysis
Pain-related fear						
All questionnaires combined						
All studies	14	1048	−0.11	−0.17; −0.05	0	0.01
Muscle strength						
Trunk	5	340	−0.12	−0.23; −0.01	0.05	0
Extremities	3	200	−0.002	−0.21; 0.20	40.1	0.02
Lifting capacity	6	579	−0.15	−0.25; −0.05	24.08	0.03
Functional mobility	4	503	−0.08	−0.16; 0.01	0.01	0
Tampa Scale for Kinesiophobia − Total score						
All studies	10	748	−0.10	−0.17; −0.02	0.01	0.01
Muscle strength						
Trunk	4	273	−0.10	−0.22; 0.02	0.01	0.01
Lifting capacity	4	395	−0.21	−0.36; −0.04	52.93	0.02
Functional mobility	3	377	−0.04	−0.14; 0.07	0.02	0
Fear-Avoidance Beliefs Questionnaire − Work subscale						
All studies	3	222	−0.11	−0.25; 0.03	11.97	0.02
Pain Catastrophising						
All questionnaires combined						
All studies	3	140	−0.25	−0.40; −0.08	0	0.07

The sensitivity analysis only includes studies that controlled for at least two of the following personal factors: age, sex and bodyweight-related measures.
Absolute Δ pooled r = the absolute difference between the pooled r of the general analysis (including all studies) and the pooled r of the sensitivity analysis.

Pain catastrophising

All questionnaires combined. Six studies (n = 405)[16,23,42,54,58,86] investigated the association between the pain catastrophising and the maximal physical performance. This resulted in a significant pooled correlation coefficient of -0.18 (95% CI = -0.27, -0.08). Four studies (n = 349)[23,42,54,58] evaluated trunk muscle strength, resulting in a significant pooled correlation coefficient of -0.15 (95% CI = -0.26, -0.05). Certainty of evidence was low.

Pain catastrophising scale. The pooled correlation coefficient of four studies (n = 194)[16,23,42,54] was -0.18 (95% CI = -0.32, -0.04). Three of these studies (n = 163)[23,42,54] investigated the relation with trunk muscle strength, which resulted in a non-significant pooled correlation coefficient of -0.13 (95% CI= -0.29, 0.02). Certainty of evidence was low.

Pain self-efficacy

Four studies (n = 289)[37,38,42,54] assessed the associations between pain self-efficacy and trunk muscle strength, resulting in a significant pooled correlation coefficient of 0.22 (95% CI = 0.10, 0.33). Certainty of evidence was low.

Anticipated pain

In 5 studies (n = 244),[2,4,16,65,66] participants were asked before the task to rate the LBP intensity they expected to feel during the actual test. The pooled correlation coefficient was -0.51 (95% CI = -0.77, -0.09). One study (n = 33, r = -0.91)[2] was considered an influential case (eg, based on large externally studentized residuals and Cook's distance),[87] which was also reflected in the wide 95% CI and a very large I^2-statistic of 92.4%. Removing this study confirmed its important influence, since removal resulted in a clearly smaller pooled correlation coefficient (4 studies, n = 211)[4,16,65,66] of -0.34 (95% CI= -0.45, -0.21) and an I^2-statistic of 0%. Three studies (n = 171),[4,16,66] not including the influential case, evaluated trunk muscle strength and this resulted in a pooled correlation coefficient of -0.37 (95% CI = -0.50, -0.23). Certainty of evidence was low to very low.

Sensitivity Analyses

We repeated the same meta-analyses as described above (ie, general analyses), but only with studies that had a low risk of bias on "study confounding" and "statistical analysis and reporting." Fourteen studies (37%, n = 1,048) that were conducted in a chronic LBP population could be included,[15,16,21-23,37,55,67-69,71,85,86,88] which resulted in 11 separate sensitivity analyses for either pain-related fear of pain catastrophising (Table 4, forest plots are provided in supplementary appendix G). The results of the sensitivity analyses were very similar to the results from the general analyses. All pooled correlation coefficients were small (absolute r-values ≤ 0.25) and the absolute differences between pooled correlations of the general and sensitivity analyses were very small (ie, differences in pooled r-values < 0.05), except for pain-catastrophising (general analysis pooled r = -0.18, sensitivity analysis pooled r = -0.25).

Nine studies (24%, n = 802)[16,23,31,55,67,68,71,85] with low risk of bias on "study confounding" and "statistical analysis" additionally controlled for pain intensity (Table 5, forest plots are provided in supplementary appendix H). Sensitivity analyses including these studies could only be performed for the psychological factor pain-related

Table 5. **Sensitivity Analyses Including Studies Controlling for Personal Factors and Pain Intensity**

	Studies (n)	Participants (n)	Pooled r	95% CI	I^2 (%)	Absolute Δ Pooled r With General Analysis
Pain-related fear						
All questionnaires combined						
All studies	9	802	−0.12	−0.19; −0.05	0.02	0
Muscle strength						
Trunk	3	223	−0.12	−0.25; 0.01	0.05	0
Lifting capacity*	6	579	−0.15	−0.25; −0.05	24.08	0.03
Functional mobility	3	322	−0.10	−0.19; −0.01	0	0.02
Tampa Scale for Kinesiophobia − Total score						
All studies	7	618	−0.13	−0.21; −0.05	0.01	0.02
Muscle strength						
Trunk	3	223	−0.12	−0.25; 0.01	0	0.01
Lifting capacity*	4	395	−0.21	−0.36; −0.04	52.93	0.02
Fear-Avoidance Beliefs Questionnaire − Work subscale						
All studies*	3	222	−0.11	−0.25; 0.03	11.97	0.02

The sensitivity analysis only includes studies that controlled for pain intensity and at least two of the following personal factors: age, sex and either bodyweight or body mass index.
Absolute Δ pooled r= the absolute difference between the pooled r of the general analysis (including all studies) and the pooled r of the sensitivity analysis.
*Studies controlling for pain intensity and personal factors were the same as the studies in the sensitivity analyses for studies controlling for personal factors.

fear. Again, pooled correlation coefficients were very similar to those of the general analysis, with differences in pooled r-values < 0.05.

Since the results of the sensitivity analyses did not change the conclusions of the general analyses, certainty of evidence was not further downgraded.

Discussion

We performed a systematic review and meta-analysis to investigate the associations between the pain-related psychological factors and the maximal physical performance tests in patients with LBP. Very few studies were available for patients with (sub)acute LBP and recurrent LBP in remission, so it is difficult to draw conclusions for these populations. Regarding chronic LBP, higher levels of pain-related fear, pain catastrophising and anticipated pain were associated with worse maximal physical performance, whereas higher levels of pain self-efficacy were associated with a better physical performance. However, all pooled correlation coefficients were small and the majority ranged between 0.10 and 0.20, when expressed in absolute values. There was one exception, where anticipated pain was moderately associated with maximal physical performance. Overall, the certainty of evidence was low to moderate for pain-related fear when all questionnaires were combined and for the TSK-total score. For the other analyses, the certainty of evidence was low or very low.

Two previous reviews concluded that there was conflicting evidence regarding the relationships between the psychological factors and the physical performance in patients with LBP.[32,82] However, these reviews did not perform a meta-analysis and also included psychological factors that do not specifically pertain to pain-related cognitions or emotions (eg, general self-efficacy). Moreover, Van Abbema *et al*[82] only included studies investigating functional capacity, while Huijnen *et al*[32] also included submaximal performance tests. In addition, a significant number of studies have been available since previous reviews were published. Therefore, by specifically focusing on pain-related psychological factors and the maximal physical performance, the current systematic review with meta-analysis significantly extends our knowledge regarding the relationship between these parameters in patients with LBP.

We conducted several subanalyses and sensitivity analyses to investigate the impact of study heterogeneity and the potential influence of personal factors and pain intensity. Overall, the magnitudes of pooled correlation coefficients of subanalyses and sensitivity analyses were similar to those obtained from the general analyses that included all types of maximal performance tests and questionnaires per psychological construct. The tests included in the subanalyses regarding the functional mobility category (eg, stair climbing, bicycle ergometer) may be more variable compared to the other types of performance tests (eg, trunk strength). In this respect, it should also be noted that we included walking tests at maximal speed in this category, since (maximal) walking tests have been shown to be valid measures of (maximal) performance in patients with LBP.[36] However, despite the apparent variability in test characteristics, meta-analyses regarding functional mobility had very low I^2-values (0%−0.02%), showing there was negligible variability in the reported correlation coefficients. While this consistency in results of the subanalyses and sensitivity analyses adds to the robustness of our findings, certainty of evidence for some subanalyses was (very) low, which warrants for cautious interpretation. In addition, none of the studies included physical activity levels of participants in their analyses, so it was not possible to perform a sensitivity analysis with studies taking this parameter into account.

In contrast to our hypothesis, lifting capacity was not associated more strongly with pain-related psychological factors as compared to most other tasks, despite the fact that patients with LBP typically perceive lifting as more harmful than other activities.[45,50] A potential reason may be that patients were allowed to perform the lifting tasks in their habitual way in all of the included studies. Consequently, they could use their idiosyncratic safety behaviours to reduce their fear for the expected outcome (eg, "I keep my back straight to prevent my disc from popping out."). Disallowing these safety behaviours typically increases fear,[53] so under these conditions pain-related psychological factors may influence physical performance to a higher degree.

Although it has been hypothesized that pain-related psychological factors may have an important influence on physical performance,[8,25,46,90] this was not supported by the small pooled correlation coefficients in our review. However, contextual factors deemed essential in this relationship may not have been properly accounted for in the included studies, which may explain this discrepancy, and which should be considered as a limitation of the current literature.

First, most studies used generic questionnaires (eg, TSK) that only provide a general evaluation of a psychological construct, without questioning a person's beliefs regarding a specific task. For example, the TSK activity avoidance subscale only refers to fear for "exercises" and "being active." However, some patients with LBP may not have a general fear of movement and actually consider exercises to be beneficial for their back, while they do believe that lifting objects or performing strenuous activities might be harmful. As such, the performance during a particular task may be better predicted by task-specific psychological assessments instead of generic questionnaires. Evidence emerging from studies investigating the relationships between task-specific pain-related (psychological) factors and movement behaviour (eg, range of motion) supports this view.[40,50,92-94] In this context, it is interesting that anticipated pain intensity during the performance task was the only psychological factor that showed a moderate association with the actual performance. Clearly, this may be due to the psychological construct itself, but it may also indicate that task-specific pain-related psychological factors are stronger associated with the maximal physical performance than the generic measures.

Second, it has been well-established that motivation can influence physical performance.[51,78] However, only 4 studies (11%) explicitly mentioned that participants were verbally encouraged during the performance task[4,22,23,44] and none of the studies assessed the participants' motivation. In addition, none of the included studies (except one)[72] mentioned the actual reasons why participants stopped a test. Consequently, it is not known whether performances were limited by pain, physical exertion or other reasons. Notwithstanding, the behaviour of patients experiencing pain should be considered in the context of goal pursuit, a pivotal concept within various motivational frameworks.[14,83,84] During a physical performance task, a patient may be faced with two competing goals, ie, performing well on the task versus avoiding pain. When a good performance is considered more important than the avoidance of pain, a person may persist despite the fear for pain and perform better than someone who prioritizes pain control. As such, interindividual differences in motivation may potentially moderate the relationships between pain-related psychological factors and physical performance.[77,81]

Finally, task familiarization prior to the maximal performance test was only reported in 12 studies (32%),[5,6,15,21-23,31,34,37,38,44,58] and studies reporting familiarization either did not describe the familiarization procedures or used inconsistent methods. For example, both the intensity (maximal vs submaximal trials) or number of repetitions (single vs multiple familiarization trials) differed between studies. Since prior exposure to a task and the methods used for this exposure might influence patients' expectations and subsequent task performance,[13,52] the heterogeneity of familiarization procedures of the studies included in this review should be considered as a limitation.

Given the importance for the empirical validation of theoretical frameworks and the interpretation of outcomes on physical performance tests, future studies should take the abovementioned limitations of the current literature into account. It may be recommended to refrain from using only general questionnaires for assessing pain-related psychological factors, as they only showed small associations with maximal physical performance. This is in line with results from similar studies conducted in other chronic musculoskeletal conditions, such as knee osteoarthritis,[1,9] femoroacetabular impingement[60] or whiplash associated disorders.[61] In addition, several recent systematic reviews reported associations of similar magnitude between the psychological factors measured with generic questionnaires and movement behaviour (eg, range of motion) in patients with LBP[11,33] and peripheral joint conditions.[20] Instead, current theoretical models recommend to take contextual parameters into consideration and to identify a person's beliefs and motivation related to the task, in order to better understand an individual's behaviour and physical performance.[14,84] Preliminary evidence from the current review and from studies investigating the relationships between the psychological factors and the spinal movement behaviour support this task-specific and person-centered approach.[40,50,94]

In summary, we performed a meta-analytic review to assess whether pain-related psychological factors are associated with maximal physical performance in patients with LBP. Our results showed that it is difficult to draw conclusions for (sub) acute and recurrent LBP due to the small number of available studies. Regarding chronic LBP, higher levels of pain-related fear, pain catastrophizing and anticipated pain were associated with a worse maximal physical performance, while higher levels of pain self-efficacy were associated with better maximal physical performance. All pooled correlation coefficients were small, except for anticipated pain, which was moderately associated with the maximal physical performance. Certainty of evidence was very low to moderate for pain-related fear, and very low to low for the other pain-related psychological factors.

Authors' contribution

TM, LDB, LJ and **NG:** Study design and conceptualization. All authors: Acquisition, analysis and interpretation of data. **TM** and **LDB:** Manuscript draft. All authors; Critical revision of the manuscript.

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Supplementary data

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