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Prognostic factors for disability and sick leave in patients with sub-acute non-malignant pain: A systematic review and meta-analysis of cohort studies

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Abstract

Objective: Early identification and timely treatment of pain patients at high risk of disability or long-term sick leave is essential to ensure optimal care. Pain researchers typically view prognostic factors for a poor outcome in relation to one specific pain site. This approach, however, is likely to have limited clinical applicability because most pain patients have pain at more than one anatomical location, and pain across different sites might be indicated by similar prognostic factors. This systematic review aims to identify generic prognostic factors for disability and sick leave in sub-acute pain patients.

Eligibility criteria: Cohort studies investigating the prediction of disability or long-term sick leave in adults with a sub-acute pain condition in a primary care setting.

Methods: Pubmed, Embase, CINAHL, and PEDro databases were searched from 16 January 2003 to 16 January 2014. Data were combined using random effects models, and quality of evidence was presented according to the GRADE WG recommendations.

Results: Nineteen studies were included, referring to a total of 6,266 patients suffering from pain in the head, neck, back, and shoulders. Eleven studies were included in the meta-analyses. Four factors were found to be associated with disability at follow-up for at least two different pain complaints. Due to insufficient studies, no generic risk factors for sick leave were identified.

Conclusion: Multiple-site pain, high pain severity, older age, and baseline disability were identified as potential prognostic factors for disability across pain sites. Anxiety and depression were not associated with disability in patients with sub-acute pain, indicating that these factors may not play as large a role as expected in developing disability due to a pain condition. Quality of evidence was low, implying that confidence in the estimates is low. Large prospective prognostic factor studies are needed with sufficient study populations and transparent reporting of all factors examined.

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Strength and limitations of this study

- This systematic review provides new knowledge on risk factors across pain sites, which may help physicians and researchers when initial referral decisions are made.
- The review also provides a solid foundation for planning future high-quality studies on risk factors for poor outcomes in pain patients.
- The protocol for the systematic review was registered beforehand in PROSPERO and reported according to the PRISMA statement, with the quality of the evidence judged as recommended by the GRADE Working Group.
- The review is based primarily on observational cohort studies on prognostic factors and thus the quality of evidence is low.

Key words: Prognostic factors, early detection, pain, disability, sick leave, primary care

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INTRODUCTION

Pain is the most common reason patients consult general practice,[1] and long-term disability and sick leave due to a pain condition are associated with huge negative consequences for the individual and for society.[2] It would be both costly and unnecessary, however, to offer specialized treatment to all patients presenting in primary care with a pain condition; despite its frequency, pain is in most cases a temporary phenomenon.[3] Still, a small group of patients will develop chronic or recurrent pain causing long-term disability and sick leave. It is estimated that approximately 3-10% of patients with acute pain develop a chronic pain condition.[3, 4] Chronic pain conditions are associated with social and family problems, loss of work, and loss of self-esteem and integrity.[5-7] Moreover, chronic pain is often associated with other symptoms or comorbidities like fatigue, concentration and memory problems, sleep disorders, depression, and anxiety.[5] Once pain has become chronic, treatment is complex and difficult.[2] Thus, early identification of pain patients at high risk of developing long-term problems would offer a great opportunity for reducing cost and suffering associated with long-term disability and sick leave because optimal care could be initiated at an early stage.

Most pain research focuses on one specific pain site (e.g., low back or shoulder pain[8, 9]). As a result, prognostic factor research is normally conducted on each site separately.[8] For example, substantial prognostic factor studies on back pain have been carried out, with several systematic reviews reporting prognostic factors for back pain.[10-14] However, this single-site approach limits clinical applicability for the general practitioner because most pain patients have pain at more than one anatomical location.[9, 15] Factors that have predictive value across different pain sites (i.e., generic factors) may exist,[8] but few attempts have been made to explore prognostic factors across pain sites.[8, 16]

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To our knowledge, no systematic review has performed a meta-analysis of prognostic factors across pain sites in patients with sub-acute pain. However, such an analysis would likely assist clinicians in identifying patients at high risk of developing disability, thereby allowing resources to be concentrated on those who are most in need of further attention.

This systematic review was conducted as part of a national Danish '*Health Technology Assessment*'(HTA) aimed to identify possibilities for early identification and timely treatment for pain patients across pain-sites with relevance to a broad range of stakeholders in Denmark.[17] The specific aim of the evidence synthesis was to identify potential factors for the development of long-term disability or sick leave in patients with sub-acute, non-malignant pain in primary care.

METHODS

The review was conducted in accordance with the PRISMA statement[18] on the basis of a predefined protocol available from the International Prospective Register of Systematic Reviews (PROSPERO: CRD42014008914).

Data sources and searches

Studies were identified via a systematic literature search in the following databases: PubMed, Embase, CINAHL, and PEDro. Additional studies were identified through experts and through review of the included studies´ reference lists. The following search terms were used: "Pain," "Prognosis," "Predictor," "Prognostic factor," "Primary Health Care," "General Practice," and "Family Practice"(full search is available on request). As part of the search and selection strategy, according to the HTA protocol, the major outcome was long-term disability (> 3 months) due to a pain condition. A secondary outcome was sick leave, defined as "absence from work" or "return-to-

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work". The search was restricted to identify studies published in English, Danish, Norwegian, or Swedish between 16 January 2003 and 16 January 2014.

Study selection

Studies were eligible for inclusion if they met the following criteria: prospective cohort study (incl. randomized controlled trials), with at least 3 months' follow-up investigating the prediction of long-term disability and/or sick leave in adults (> 18 yrs) with a sub-acute (≤ 3 month) non-malignant pain condition, visiting general practitioners or other primary care facilities. If two or more published studies originated from the same patient population, the study with the longest follow-up period was included. Two reviewers (GHV and MSP) independently assessed abstracts and full-text articles for eligibility, and disagreement was solved by a third reviewer (LØ).

Data extraction and quality assessment

Two review authors (GHV and MSP) independently performed data extraction using a customized data extraction form. To summarize the evidence following the systematic review in the HTA, we applied the "Grading of Recommendations Assessment, Development, and Evaluation" (GRADE) approach for rating quality of evidence (i.e., our confidence in the estimates). [19] Because we anticipated that the evidence base would come from cohort studies the GRADE approach for prognostic factor research[20] was applied. The risk of bias in the individual studies was assessed by two reviewers (GHV and MSP) using the Quality in Prognosis Studies tool (QUIPS).[21] The overall risk of bias for each of the studies was judged as: 1) low if there were a low risk of bias in all key domains, 2) unclear risk of bias if there were an unclear risk of bias for one or more key domains, and 3) high risk of bias if there were a high risk of bias for one or more key domains.[22] Disagreement was resolved by consensus.

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Data synthesis and analysis

If a baseline factor was associated with outcomes at follow-up in two or more studies of different pain sites, it was considered a "possible prognostic" factor and the results were combined and subsequently presented as part of the evidence profile. When data were available in different formats, data from the "fully adjusted" analyses were given preference and included in the meta-analysis. From each cohort study, the "statistical signal" (The "Wald-test"—the ratio between signal and noise) was derived from the effect size and the standard error of the estimate (SE). These were subsequently handled using Fisher's z-transformation.[23] This z-transformation was used to communicate the statistical power for any given association (i.e., correlation) between a given prognostic factor and an outcome. Summary estimates of associations across studies were derived from random effects meta-analysis, anticipating clinical heterogeneity, with modelling allowing for differences in the association from study to study.[24]

Heterogeneity across studies was statistically assessed using the Q-test and quantified by the inconsistency (I^2) index.[25] I^2 represents the percentage of total variation across studies attributable to heterogeneity rather than (statistical) chance.[26] In cases with substantial heterogeneity across studies ($I^2 > 50\%$), the robustness of the results was checked using the "fixed effects" model. A result was considered robust if the point estimate for "fixed effects" was within the confidence interval of "random effects"; as a consequence, the risk of "small-study" bias was considered to be high if the point estimate was outside the confidence estimate. If this was the case, the evidence for the given prognostic factor was downgraded due to inconsistency. Meta-analyses were performed using Review Manager (RevMan) provided by the Cochrane Collaboration.[27] A two-sided P-value of ≤ 0.05 (and 95% confidence interval excluding the null) was considered to be statistically significant in all analyses. For each outcome, we prepared an evidence profile based on the GRADE profiler software.[28]

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RESULTS

Results of the literature search

The search in the selected databases returned a total of 3,533 references. A total of 32 references were identified through the additional search. After removing duplicates, 1,841 references remained. The 1,841 references were screened for eligibility, and 1,641 records were excluded. The remaining 200 articles were read in full-text; of these, 181 articles were excluded because they did not satisfy the inclusion criteria. A full list of excluded studies and the reason for exclusion is available from the authors upon request. A total of 19 studies satisfied the inclusion criteria and were included in the systematic review. However, only 11 were eligible for inclusion in the meta-analysis; the other 8 studies were excluded from the quantitative synthesis due to: 1) inadequate statistical analyses,[3, 29] 2) the factors studied were assessed in only one study,[30-32] or 3) the factors studied were assessed for only one pain site (e.g., only studies on back pain).[33-35] See **Figure 1** for a flow diagram of the included studies.

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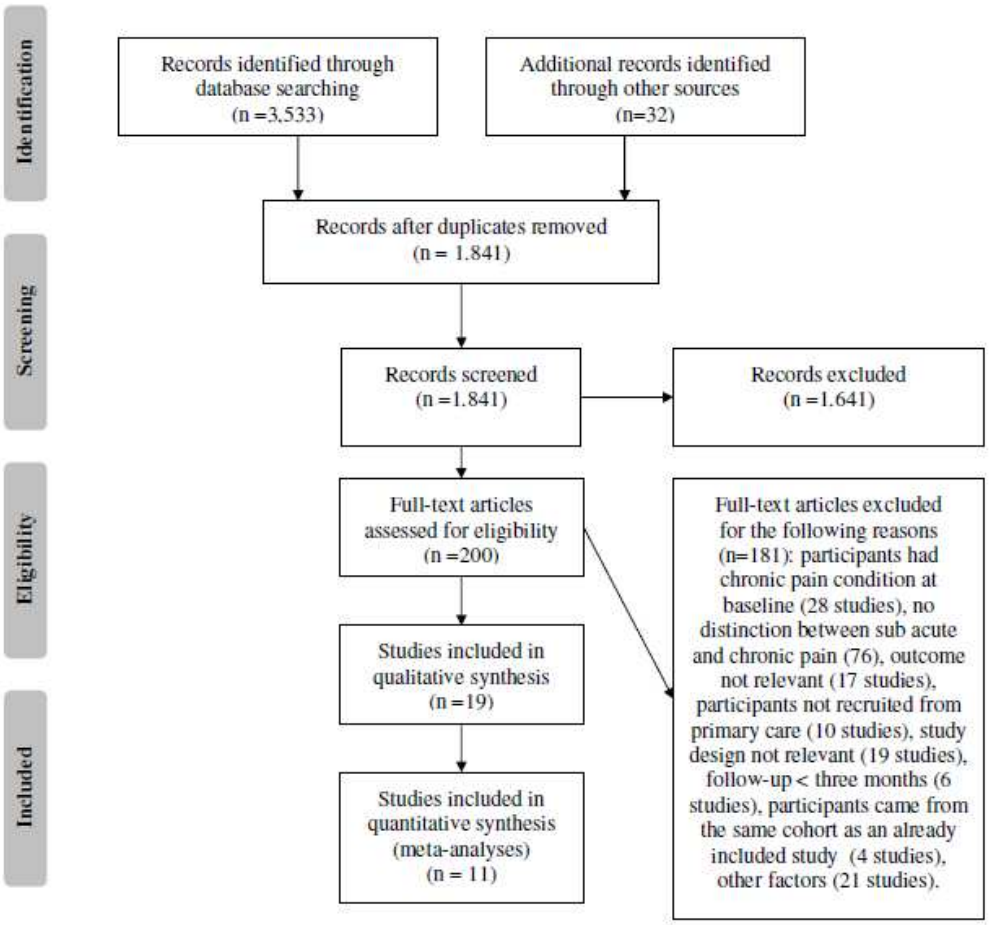

Figure 1: Flow-diagram of the literature search

Included studies

The 19 included studies consisted of 17 cohort studies and two randomized controlled trials. Fourteen of the studies referred to patients with back pain[4, 29-31, 33, 34, 36-43] and one referred to patients with pain in the neck or back.[3] Two studies referred to patients with neck pain,[32, 44], one referred to patients with headache,[45] and one referred to patients with shoulder or back pain.[35] From this last-mentioned study, only the cohort with back pain was included in the synthesis because the cohort with shoulder pain comprised both patients with sub-acute pain and patients with chronic pain.[35] Outcome measures were disability in 16 studies,[3, 4, 29, 33-45] sick leave in three studies,[3, 32, 42] and return-to-work in two studies.[30, 31]

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Characteristics of the 19 included studies are presented in Table 1. The total number of patients included in the 19 studies was 6,266. The median number of patients per study was 184 (range: 56–2,662). In eleven of the studies, more women than men participated. Age was reported in 18 studies, with a median average of 42 years (range: 34–52 years). Pain duration at baseline was reported in eight studies with a median average of 12.6 days (range: 1–27 days). Follow-up period ranged from 3 months to 22 years (with a median of 9 months). Most of the studies recruited patients from general practice.[3, 4, 29, 31-33, 35-38, 40-43, 45] The remaining studies recruited patients from physiotherapy or chiropractor clinics[34, 39, 44] and workers compensation board.[30]

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Table 1: Characteristics of the included studies

Author (publication year)	Country of origin	Participant eligibility criteria	No. of participants at baseline	Age at baseline Mean (SD)	Pain site	Recruitment	Outcome measure	Follow up (months)
Boardman HF. (2006)	UK	Adults > 18 years.	730[A]	52 (18-90)[B]	Head	GP	Disability (Migraine Disability Assessment)	12
Boersma K. (2005)	Sweden	No information	363	47 (10.2)	Back or neck	GP	Disability (Örebro Musculoskeletal Pain Screening Questionnaire) and sick leave (> 15 days)	12
Childs J. (2004)	US	Patients 18 to 60 years; with a primary symptom of LBP, with or without referral into the lower extremity; and an Oswestry Disability Questionnaire (ODQ) score of at least 30%.	131	33.9 (10.9)	LPB	Physiotherapy	Disability (Modified Oswestry Disability Index)	6
Coste J. (2004)	France	Patients > 18 years, self-referring to GP (n: 40) or rheumatologists (n: 7) for a primary complaint of LBP with pain duration < 72 hours and without radiation below the gluteal fold	113	44.3 (13.7)	LBP	GP	Disability (VAS and Roland Morris Disability Questionnaire)	3
Grotle M. (2007)	Norway	Patients 18–60 years; acute LBP of less than 3 weeks duration, with or without radiating pain to the limb; and had not been treated for LBP earlier	123	37.9 (10.1)	LBP	GP	Disability (Roland Morris Disability Questionnaire)	12
Grotle M. (2010)	Norway	Patients consulting GP with non-specific LBP of varying duration and localization	258	46 (9)	LBP	GP	Disability (Roland Morris Disability Questionnaire)	12
Hancock M. (2008)	Australia	Primary complaint of pain in the area between the 12th rib and buttock crease causing moderate pain and moderate disability (measured by adaptations of items 7 and 8 of the SF-36).	240	40.7 (15.6)	LPB	GP	Disability (Roland Morris Disability Questionnaire)	3
Hendrick P. (2013)	New Zealand	Patients aged 18–65 years with an episode of LBP of ≤ 6 weeks, preceded by a minimum period of 3 months during which participants had not sought treatment for LBP, and no other pre-existing conditions that limited their mobility.	101	38.8 (14.6)	LBP	GP, Physiotherapy clinics and newspaper advertisement	Disability (Roland Morris Disability Questionnaire)	3
Heneweer H. (2007)	Holland	Patients aged 21–60 years with sufficient knowledge of the Dutch language to complete the questionnaires.	56	42 (9.2)	LBP	Physiotherapy clinics	Disability (recovery yes/no and sick leave yes/no)	3

[A]: 2,662 patients were included in the study but only 730 respondents are included in the relevant analyses.
[B]: Median (range).

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Table 1(continued): Characteristics of the included studies

Author (publication year)	Country of origin	Participant eligibility criteria	No. of participants at baseline	Age at baseline Mean (SD)	Pain site	Recruitment	Outcome measure	Follow up (months)
Karjalainen K. (2003)	Finland	25 to 60-year-old patients having disabling LBP for the preceding 4 to 12 weeks.	164	44 (8.8)	LBP	GP	Disability (Oswestry Disability Index) and sick leave (1: 0 days, 2: 1–30 days, 3: > 30 days)	12
Leaver AM. (2013)	Australia	Patients aged 18–70 years with a new episode of non-specific neck pain.	181	38.8 (10.7)	Neck	Physiotherapy and chiropractor clinics	Disability (Neck Disability Index)	3
Lonnberg F. (2010)	Denmark	Patients seeking care for the first time regarding an episode of LBP.	78	57[C]	LBP	GP	Disability (Limitations- no further information)	264
Melloh M. (2013)	New Zealand	Patients 18–65 years.	315	34.9 (12.6)	LBP	GP	Disability (Oswestry Disability Index)	6
Schultz IZ. (2004)	Canada	Participants 18–60-year old remaining off work 4–6 weeks post-injury (sub-acute group) or remaining off work 6–12 months after injury (chronic).	253	40.3 (11.4)	LBP	Workers´Compensation Board	Return-to-work status	3
Sieben JM. (2005)	Holland	Patients aged 18–60 years with a new episode of non-specific LBP.	222	No information	LBP	GP	Disability (Graded Chronic Pain Scale)	12
Storheim K. (2005)	Norway	Patients sick listed from a permanent job and receiving between 50% and 100% compensation for non-specific LBP for 8–12 weeks, but with no sick leave due to LBP during a period of 12 weeks before the current sick-listing period; aged between 20 and 60 years.	93	RTW:40.5 (9.8) NRTW: 42.3 (11.7)	LBP	GP and National Insurance Offices	Return-to-work status	12
Swinkels-Meewisse, (2006)	Holland	Patients aged 18–65 years having an episode of nonspecific LBP independent of radiation.	374[D]	42.4 (11.3)	LBP	GP and Physiotherapy clinics	Disability (Roland Morris Disability Questionnaire)	6
Van der Windt DA. (2007)	Holland	Patients 18–65 years with a duration of LBP < 12 weeks at presentation, or exacerbation of mild symptoms of back pain.	171 (Back group)	42.0 (12.0) (back group)	LBP	GP	Disability (Roland Morris Disability Questionnaire)	3
Vos CJ. (2008)	Holland	Patients > 18 years with neck pain < 6 weeks.	187	40.7 (14.1)	Neck	GP	Sick leave (> 7 days)	12

[C]: Median (range)
[D]: 555 Participants are included in the trial, but data regarding disability were available from only 374 of the participants

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Risk of bias within studies

Risk of bias in the included studies was assessed using QUIPS (figure 2). Overall, the agreement between the two assessors (GHV and MSP) on the different aspects of Risk of Bias assessment was 85.5% (weighted Kappa 0.49), which corresponds to a moderate degree of agreement. In all cases, any disagreement between the assessors was settled by consensus discussion. The domain "Study Confounding" carried the highest risk of bias. In this domain, three studies were judged as having high risk of bias, and eleven studies were assessed as having a moderate risk of bias. The high number of studies judged as having a high or moderate risk of bias in this domain was due mainly to insufficient description of the factors that were included in the multivariable analysis. Based on the judgement of the six domains, eleven studies were judged to have low risk of bias,[4, 31, 33-35, 38, 40-44] three studies had moderate risk of bias,[32, 36, 37] and five studies had high risk of bias.[3, 29, 30, 39, 45]

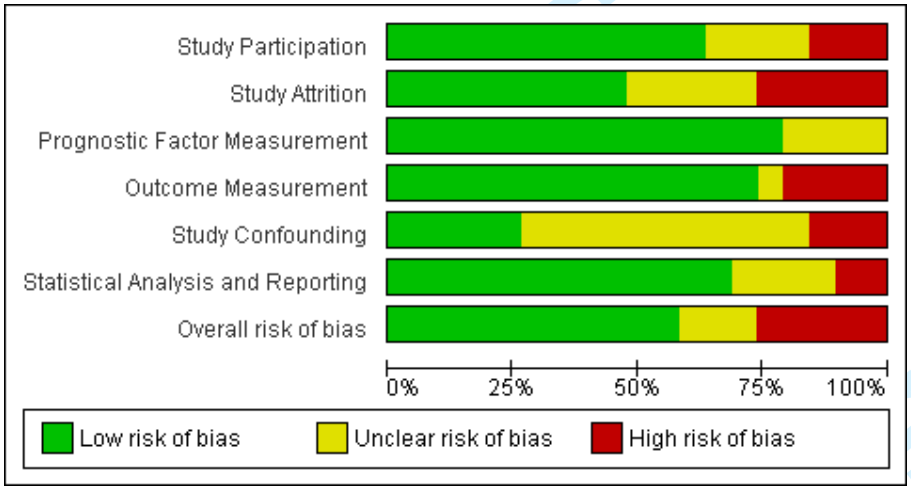

Figure 2: Risk of bias of the six domains in QUIPS

Prognostic factors for disability

Prognostic factors for disability were assessed in 16 studies.[3, 4, 29, 33-45] A total of 81 factors were assessed in the unadjusted analysis (Supplementary Material S1). Of the 81 factors assessed, 53 were included in the multivariable analysis of the primary studies. Of these factors, the following

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eight were assessed in two or more studies and for at least two different pain sites: multiple-site pain, higher baseline pain severity, previous pain episodes, older age, longer baseline pain duration, baseline disability, anxiety, and depression. A total of eleven studies were included in the meta-analysis (figure 3 and 4).[4, 36-45] The association between multiple-pain sites and disability at follow-up was assessed in three studies, including patients with headache,[45] low back pain,[41] and neck pain[44] (figure 3a). The combined estimate showed a statistically significant association between multiple-pain sites at baseline and risk of disability at follow-up ($p = 0.010$). The association between higher pain severity at baseline and disability was assessed in six studies including patients with headache[45] and low back pain[36, 37, 39, 41, 42] (figure 3b). The combined estimate showed a statistically significant association between higher baseline pain severity and disability ($p < 0.001$). This result was, however, not robust when using the "fixed effects" model, so small-study bias is therefore likely. Consequently, the quality of evidence was downgraded due to inconsistency. The association between baseline disability and disability at follow-up was examined in seven studies relating to patients with neck pain[44] and low back pain[37, 39-43] (figure 3c). Baseline disability was associated with a higher risk of disability at follow-up ($p = 0.007$). The association between higher age and the risk of disability was assessed in seven studies concerning patients with neck pain[44] and low back pain[4, 36-38, 41, 42] (figure 3d). A significant association was seen between higher age and risk of disability ($p = 0.04$). A dose-response effect was observed; an increase by 10 years of age was associated with a higher risk of disability than was a one-year increase. No statistical significant associations between disability and previous pain episodes ($p = 0.08$; figure 4a), longer baseline pain duration ($p= 0.12$; figure 4b), anxiety ($p = 0.25$; figure 4c), or depression ($p = 0.14$; figure 4d) were observed.

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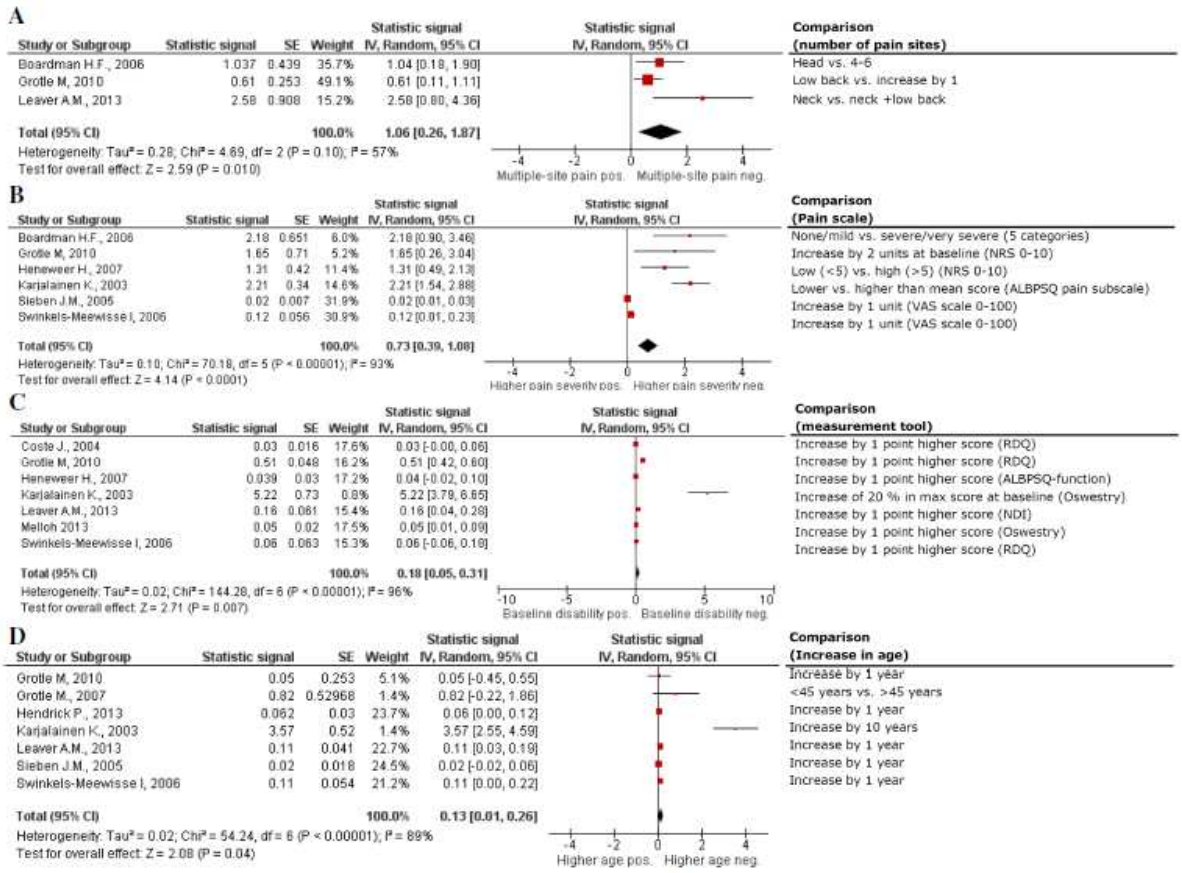

Figure 3: Forest plots of the association between potential prognostic factors and long-term disability in patients with a sub-acute pain condition.

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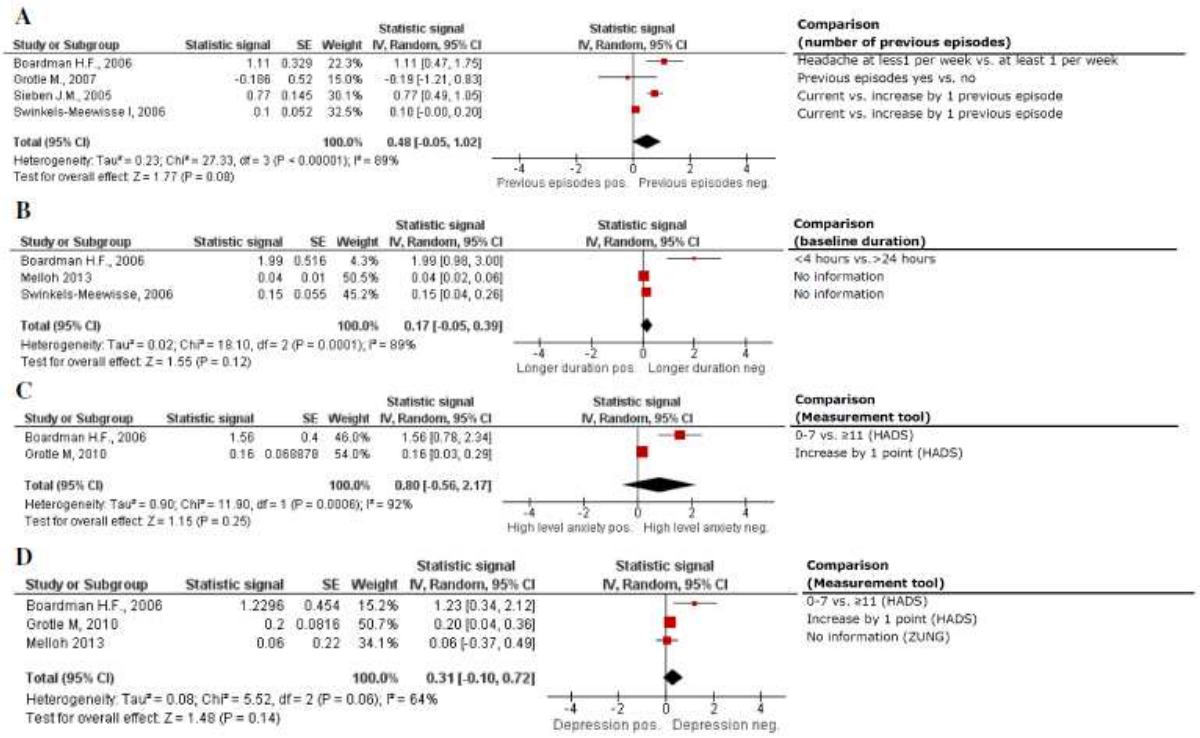

Figure 4: Forest plots of the association between potential prognostic factors and long-term disability in patients with a sub-acute pain condition.

Quality of evidence for the risk of developing disability

The quality of evidence for the potential prognostic factors for the risk of developing disability is presented in table 2. All the included studies in the meta-analysis were phase 1 studies, which are characterized as predictive modelling studies or explanatory studies conducted to generate a hypothesis.[20] Thus, the quality of evidence was low as a starting point. Reasons for up- or down-grading the quality of evidence for the given prognostic factor are described below in table 2. The quality of evidence was graded as either low or very low and thus the validity of the results is low.

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Table 2: GRADE evidence profile of the potential prognostic factors for long-term disability in patients with a sub-acute pain condition.

Prognostic factors (no. of studies)	Phase	Quality assessment						Summary of findings		
		Limitations	Inconsistency	Indirectness	Imprecision	Publication bias	Other considerations	No. of participants included in the analyzes	Estimated "Effect size"	Overall quality
Multiple-site pain [41, 45, 46] (3)	1	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected [A]		1,164	0.07 (0.02;0.13) p=0.01	Low ⊕⊕⊖⊖
High baseline pain severity [37, 39, 41, 42, 45, 47] (6)	1	Serious limitation (-1)	Serious inconsistency [B] (-1)	No serious indirectness	No serious imprecision	Detected [C] (-1)	Dose-respons effect detected (+1)	1,711	0.04 (0.02;0.06) p<0.0001	Very low ⊕⊖⊖⊖
Baseline disability [37, 39-44] (7)	1	No serious limitations	No serious inconsistency [I]	No serious indirectness	No serious imprecision	Undetected [A]		1,263	0.01 (0.00;0.02) p=0.007	Low ⊕⊕⊖⊖
Older age [4, 37, 38, 41, 42, 44, 47] (7)	1	No serious limitations	No serious inconsistency [F]	No serious indirectness	No serious imprecision	Detected (-1)[G]	Dose-respons effect detected (+1)	1,296	0.01 (0.00;0.02) p=0.04	Low ⊕⊕⊖⊖
longer pain duration [37, 43, 45] (3)	1	Serious limitations (-1)	No serious inconsistency	No serious indirectness	No serious imprecision	Detected (-1)[H]		1,236	0.01 (0.00;0.03) p=0.12	Very low ⊕⊖⊖⊖
Previous episodes [4, 37, 45, 47] (4)	1	Serious limitation (-1)	No serious inconsistency [D]	No serious indirectness	Serious imprecision (-1)	Detected [E] (-1)		1,353	0.03 (0.00;0.06) p=0.08	Very low ⊕⊖⊖⊖
Anxiety [41, 45] (2)	1	Serious limitations (-1)	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected [A]		988	0.07 (-0.05;0.18) p=0.25	Very low ⊕⊖⊖⊖
Depression [41, 43, 45] (3)	1	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected [A]		1,157	0.02 (-0.01;0.05) p= 0.14	Low ⊕⊕⊖⊖

A: The association between the prognostic factor and disability is assessed only in the trials included in the meta-analyses.
B: Results of the meta-analyses were not robust when using the "fixed-effects" model.
C: Nine studies assessed the association between high baseline pain and disability at follow-up, but only six studies reported the results in the adjusted analyses.
D: Inconsistency in the results between the study by Boardman et al. and the study by Swinkels-Mewisse et al. can be explained by differences in the reporting of previous episodes. In the study by Swinkels et al., the participants could have experienced pain once 10 years ago, whereas Bordman looks at pain episodes one or more times per. week.
E: Nine studies reported previous pain episodes in the unadjusted analyses, but only seven studies included the results in the adjusted analyses.
F: Karjalainen et al. reported the association between an increase in age by 10 years and disability, whereas the other studies reported the association between age and disability by an increase of one year.
G: Nine studies reported the association between age and disability, but only seven studies included the results in the adjusted analyses.
H: The association between baseline pain duration and disability was reported in the unadjusted analyses in five studies, but only three studies included the results in the adjusted analyses.
I: In the study by Karjalainen et al., the association between baseline disability and disability at follow-up was reported by an increase by 20 % in max score at baseline, whereas the other studies reported an increase by 1 point. This difference could be a plausible reason for the inconsistency between the results.

Prognostic factors for long-term sick leave or return-to-work

Three of the included studies had long-term sick leave as an outcome[3, 32, 42]. Two of the studies, referring to patients with pain in the neck[32] and back,[42] respectively, had performed multivariable analysis. The follow-up period was three months in both studies. Long-term sick leave was defined as sick leave for more than 30 days in one study[42] and more than 7 days in the other.[32] Baseline

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disability was the only potential prognostic factor that was assessed in both studies. In the study by Karjalainen et al., however, the results were described only as being "non-significant."[42] Thus, it was not possible to present the results in a meta-analysis. In the study by Karjalainen and colleagues, factors like blue-collar work and long-term sick leave at baseline were associated with an increased risk of long-term sick leave at follow-up in patients with sub-acute back pain. Vos and colleagues found that factors like previous pain episodes, a follow-up appointment scheduled with a GP, and the GP's referring the patient to treatment and baseline disability all were associated with an increased risk of long-term sick leave among patients with acute neck pain[32]. Two studies described "return-to-work" as an outcome.[30, 31] Follow-up was 3 [30] and 12 months,[31] respectively. Both studies related to patients with back pain, so potential generic factors could not be extracted.

DISCUSSION

Four potential generic prognostic factors for developing disability following a sub-acute pain condition were identified. Risk factors across different pain sites included multiple-site pain, higher pain severity, higher age, and baseline disability. Previous pain episodes, pain duration at baseline, anxiety, and depression were not associated with the risk of disability at follow-up. Due to the limited number of studies, it was not possible to identify potential generic risk factors for long-term sick leave or return-to-work. Quality of evidence was low or very, low implying that confidence in the estimate is low.

Comparison with other studies or reviews

Despite sparse literature in this field, there is some evidence to support our findings. In concurrence with our findings, a previous review reported factors such as multiple-site pain, higher pain severity, higher age, and baseline disability as being potential prognostic factors for a poor outcome in patients with musculoskeletal pain.[8] A strong association between the number of pain sites and

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disability also was demonstrated in a previous cross-sectional study.[9] Furthermore, a recent systematic review found some evidence suggesting that the number of somatic symptoms and baseline severity of the condition influenced the future course in patients with medically unexplained symptoms.[48] Thus, despite the low quality of evidence of the results, we find it reasonable to believe that the factors indentified in our systematic review may act as central prognostic factors for the development of disability across pain sites. Therefore, future research should address confirming the role of these factors.

Interestingly, our review found that anxiety and depression at baseline were not associated with disability at follow-up. These findings are controversial because psychosocial factors also known as "yellow flags" are widely accepted as being key factors in the transition from acute to chronic pain conditions [49]. "Yellow flags" include depression, anxiety, catastrophic thoughts, and pain-related fear of movement/fear avoidance among others.[50, 51] Several national and international guidelines recommend that clinicians screen for the presence of these factors in the early phase[52-54]. In addition, several well-established screening tools for the risk of chronicity are based on the presence of these factors (e.g., the Orebro Musculoskeletal Pain Questionnaire,[55] the Fear-Avoidance Health Beliefs Questionnaire,[56] and the STarT Back Screening Tool[57]). Most studies, however, have not included pain duration at baseline when the importance of "yellow flags" was assessed.[16] A plausible explanation for the apparent discrepancy between our results and the widely accepted "yellow flags," therefore, could be the inclusion criteria in our review regarding short pain duration at baseline. It is likely that factors like anxiety and depression are of greater importance once pain has become chronic. Another explanation for the discrepancy could be that our review focuses on risk factors for future disability and sick leave and not on risk factors for developing a chronic pain condition. Nonetheless, future research should address and clarify the role "yellow-flag" factors play in the various phases of pain.

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Strength and limitations

It is considered a strength in our systematic review that we followed a rigorous protocol (registered in PROSPERO) prespecifying all the outcomes and analyses; our adherence to the protocol likely strengthens the credibility of the evidence synthesis. Meta-analysis of the association between the identified prognostic factors and the outcome was conducted; i.e., combining results from studies addressing different groups of patients may be controversial. The purpose of our review, however, was to identify prognostic factors of importance across pain sites, and a meta-analysis was well suited for this purpose. We reported our findings as recommend by the PRISMA statement[18] and judged the quality of the evidence based on the recommendations from the GRADE Working group. We believe that the GRADE framework applied to prognostic factor research was valuable for assessing and transparently reporting the quality of the evidence of the possible prognostic factors. To our knowledge, this is the first time GRADE has been used in the evaluation of prognostic studies.

Limitations regarding the interpretation of the results from this study should be taken into consideration. A total of 14 of the 19 included studies in our review referred to patients with back pain. The high number of studies concerning patients with back pain may affect the external validity of the results to patients with pain at other sites. However, the vast majority of pain patients visiting general practice suffer from back pain, and the large number of studies on back pain included in the present review therefore reflects the distribution of patients seen in general practice.[58] Future studies assessing prognostic factors for non-spinal pain are needed. Another limitation of this review was the risk of selective reporting of primary study results. Our review was based primarily on observational cohort studies on prognostic factors (Phase 1 studies). Such studies harbour a high risk that non-significant findings are not reported or only included in the first (unadjusted) part of

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the analysis. Any non-reporting of non-significant results invites a risk that the findings in the meta-analysis were overestimated. We attempted to account for such bias due to selective outcome reporting by listing all the studies that examined a specific prognostic factor in the unadjusted analysis. If a factor was investigated in eight studies, for example, but included only in the adjusted analysis of five, the quality of the evidence was downgraded.

Implications for clinical practice

No high-quality evidence was provided for any of the potential prognostic factors; therefore, no definite clinical conclusion can be made about how to identify patients at high risk of long-term disability or sick leave at an early stage in general practice. However, the empirical evidence illustrates what kind of prognostic factor research would be relevant to pursue in order to increase value and reduce waste in prognostic factor research on long-term disability among patients with sub-acute non-malignant pain.[59] It appears that multiple-site pain, high-baseline pain severity, older age, and baseline disability are associated with future disability across pain sites in sub-acute pain patients. Therefore, it may be helpful for GPs to have these factors in mind in clinical decision making.

Implications for future research on prognostic factors

Correctable weaknesses in biomedical and public health research studies can produce misleading results and waste valuable resources.[60] During the preparation of this review, it became clear that the current literature in this field falls short on a number of counts. As suggested by Ioannidis et al.,[60] this area of research also has weaknesses, such as selective reporting of results; lack of prespecified defined prognostic factors to be assessed; inadequate description of methods; inadequate or poor quality of statistical analysis; failure to distinguish between prognostic factors among patients with acute, sub-acute, and chronic pain; and lack of published studies on patients

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suffering from non-spinal pain. We suspect most of these limitations can be related to the absence of detailed written protocols and poor documentation of research in general.[60-63]

Although good research ideas often yield unanticipated but valuable results, much research fails to effect worthwhile achievements. As long as the way in which research projects are prioritized for research is transparent and warranted, the disappointments should not be deemed wasteful; they are simply an inevitable feature of the way science works.[59] In order to gain further knowledge on which factors are central prognostic factors (sub-acute phase), future studies should take into account baseline pain duration at the time patients are enrolled. Future studies on prognostic factors in chronic pain should be conducted as large, prospective, registered, and protocol-based prognostic factor studies with sufficient study populations and transparent reporting of all factors studied. Once sufficient knowledge on risk factors has been obtained, documentation of effective treatment for high-risk pain patients is needed. Further, the effect of offering stratified care to pain patients based on their risk profiles should be tested in randomized controlled trials.[64]

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Conflicts of interest: None. Dr. Christensen declares, however, that he is involved in many health-care initiatives and research that could benefit from a wide uptake of this publication (including Cochrane, OMERACT, and the GRADE Working Group).

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FIGURE LEGENDS

Figure 1: Flow diagram of the literature search

Table 1: Characteristics of the included studies

Figure 2: Risk of bias of the six domains in QUIPS

Figure 3: Forest plots of the association between potential prognostic factors and long-term disability in patients with a sub-acute pain condition

Figure 4: Forest plots of the association between potential prognostic factors and long-term disability in patients with a sub-acute pain condition

Table 2: GRADE evidence profile of the potential prognostic factors for long-term disability in patients with a sub-acute pain condition

Supplementary Material

Supplementary Material S1: Potential prognostic factors for disability assessed in the included studies. A plus sign indicates a statistically significant association between the given factor and the outcome. A minus sign indicates a non-significant association.

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Supplementary material

Supplementary Material S1: Potential prognostic factors for disability assessed in the included studies. A plus sign indicates a statistically significant association between the given factor and the outcome. A minus sign indicates a non-significant association.

	Prognostic factor	**Boardman**	**Boersma**	**Childs**	**Coste**	**Grotle, 2007**	**Grotle, 2010**	**Hancock**	**Hendrick,**	**Heneweer**	**Karjalainen**	**Leaver**	**Lonnberg**	**Melloh**	**Sieben**	**Swinkels-Meewisse**	**Van der Windt**
	Pain site	**Head**	**Back or neck**	**LBP**	**LBP**	**LBP**	**LBP**	**LBP**	**LBP**	**LBP**	**LBP**	**Neck**	**LBP**	**LBP**	**LBP**	**LBP**	**LBP**
Socio demo-graphic	**Age**				÷	÷	÷		+ [a]		+	+	÷	÷	÷ [a]	+ [a]	
	Gender				÷	÷	÷				÷	+	÷	÷		÷ [a]	
	BMI										+	+		+			
	Smoking					÷								÷			
	Alcohol	÷ [a]												÷			
	Caffeine	÷ [a]															
	Civil status															÷ [a]	
	Origin				÷												
	Education					÷	+				÷	÷		÷	÷ [a]	÷ [a]	
	Social class						÷										
Pain	**Baseline intensity**	+ [a]			÷		+			+	+	÷		+	+ [a]	+ [a]	
	Baseline duration	+ [a]										+	÷	÷		+ [a]	
	Previous episodes	+ [a]			÷	÷						÷	÷		+ [a]	+ [a]	
	Associated symptoms	+ [a]															
	Duration of previous episodes													+			
	Permanent pain at nigth				÷												
	Pain increased by coughing				+												
	Pain increased by back movement				÷												
	Pain worse when standing				÷												
	Pain worse when lying down				+												
	Pain on passive movements				÷												
	Pain radiation					÷	+				÷		÷			+ [a]	
	Neurological signs					÷							÷				
	Onset (sudden)															÷ [a]	
	Sensory pain													+			
	Affective pain													+			
	Multiple-pain sites	+ [a]					+					+					
	Bothersomeness						+										

a: Only adjusted estimates presented

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Supplementary Material S1 (continued): Potential prognostic factors for disability assessed in the included studies. A plus sign indicates a statistically significant association between the given factor and the outcome. A minus sign indicates a non-significant association.

	Prognostic factor	Boardman	Boersma	Childs	Coste	Grotle, 2007	Grotle, 2010	Hancock	Hendrick	Heneweer	Karjalainen	Leaver	Lonnberg	Melloh	Sieben	Swinkels-Meewisse	Van der Windt
	Pain site	Head	Back or neck	LBP	LBP	LBP	LBP	LBP	LBP	LBP	LBP	Neck	LBP	LBP	LBP	LBP	LBP
Functional status at baseline	Forward lumbar bending (ROM[b])					÷							÷				
	Scoliosis												÷				
	Disability				+		+			÷ [a]	+	+		÷		÷ [a]	
	Physical activity								÷					÷		+ [a]	
	Participation																
	General health				+				÷ [a]		÷	+					
	Limitations physical				÷									+			
	Disability days last month					+											
Work related	Employed at baseline				÷		+					+					
	Changed work status											÷					
	Physically demanding work				÷						÷		÷	+			
	Job unsatisfaction				÷	÷	÷				÷			+			
	Resigned attitude towards the job													+			
	Uncertainty													÷			
	Organization													÷			
	Interruptions													÷			
	Concentration													÷			
	Time pressure													÷			
	Ergonomics													÷			
	Emotions (job related)													÷			
	Resources (job related)													÷			
	Social support at work													+			
	Compensation status				+							÷					
	Job difficulty				÷												
	Pain onset at work												+				
	Sick leave due to pain						+				÷		÷	÷			
	Past sick leave for pain											+					

a: Only adjusted estimates presented

b: Range of motion

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Supplementary Material S1 (continued): Potential prognostic factors for disability assessed in the included studies. A plus sign indicates a statistically significant association between the given factor and the outcome. A minus sign indicates a non-significant association.

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	Pain site	**Head**	**Back or neck**	**LBP**	**LBP**	**LBP**	**LBP**	**LBP**	**LBP**	**LBP**	**LBP**	**Neck**	**LBP**	**LBP**	**LBP**	**LBP**	**LBP**
Psychological	Psychiatric disorder				÷												
	Anxiety	+ [a]					+										
	Depression	+ [a]					+							+			
	Emotional distress					+											÷ [a]
	Fear of pain						+										
	Fear of movement									÷						+ [a]	
	Fear avoidance		?			÷	+		÷ [a]	÷ [a]							÷ [a]
	Coping						÷			÷							
	Catastrophising						+							+			÷ [a]
	Somatisation													+			÷ [a]
	Perceived risk of not recovering										+						
	Expectation regarding the effectiveness of treatment										÷						
	Social functioning				÷												
	Vitality				÷												
	Physical problems				÷												
	Mental health				÷							+		+			
Other	Prescription of bed rest				÷												
	Prescription of sick leave				÷												
	Recruitment group					÷	÷										
	Sleeping/relaxation medication					÷											
	Pain medication					÷						+					
	Prior low back surgery				÷												
	Other co morbidity				÷												
	"Clinical prediction rule"			+				+									
	ALBPSQ* / CPG[d]				+		+			÷ [a]							

a: Only adjusted estimates presented

c: GP, chiropractor or physiotherapist.

d: Acute low back screening questionnaire.

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5-6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6-7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Not relevant
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9-10
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	12-13
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	14
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	16-17
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	16-17
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	18
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Not relevant
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	19-20
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	21
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	22-23
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	23

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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Prognostic Factors for Disability and Sick Leave in Patients with Sub-acute Non-malignant Pain: A systematic review and meta-analysis of cohort studies

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Keywords:	Prognostic factors, Early detection, Pain

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Prognostic factors for disability and sick leave in patients with sub-acute non-malignant pain: A systematic review and meta-analysis of cohort studies

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Abstract

Objective: Early identification and timely treatment of pain patients at high risk of disability or long-term sick leave is essential to ensure optimal care. Pain researchers typically view prognostic factors for a poor outcome in relation to one specific pain site. This approach, however, is likely to have limited clinical applicability because most pain patients have pain at more than one anatomical location, and pain across different sites might be indicated by similar prognostic factors. This systematic review aims to identify generic prognostic factors for disability and sick leave in sub-acute pain patients.

Eligibility criteria: Cohort studies investigating the prediction of disability or long-term sick leave in adults with a sub-acute pain condition in a primary care setting.

Methods: Pubmed, Embase, CINAHL, and PEDro databases were searched from 16 January 2003 to 16 January 2014. Data were combined using random effects models, and quality of evidence was presented according to the GRADE WG recommendations.

Results: Nineteen studies were included, referring to a total of 6,266 patients suffering from pain in the head, neck, back, and shoulders. Eleven studies were included in the meta-analyses. Four factors were found to be associated with disability at follow-up for at least two different pain complaints. Due to insufficient studies, no generic risk factors for sick leave were identified.

Conclusion: Multiple-site pain, high pain severity, older age, and baseline disability were identified as potential prognostic factors for disability across pain sites. Anxiety and depression were not associated with disability in patients with sub-acute pain, indicating that these factors may not play as large a role as expected in developing disability due to a pain condition. Quality of evidence was low, implying that confidence in the estimates is low. Large prospective prognostic factor studies are needed with sufficient study populations and transparent reporting of all factors examined.

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Strength and limitations of this study

- This systematic review provides new knowledge on risk factors across pain sites, which may help physicians and researchers when initial referral decisions are made.
- The review also provides a solid foundation for planning future high-quality studies on risk factors for poor outcomes in pain patients.
- The protocol for the systematic review was registered beforehand in PROSPERO and reported according to the PRISMA statement, with the quality of the evidence judged as recommended by the GRADE Working Group.
- The review is based primarily on observational cohort studies on prognostic factors and thus the quality of evidence is low.

Key words: Prognostic factors, early detection, pain, disability, sick leave, primary care

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INTRODUCTION

Pain is the most common reason patients consult general practice,[1] and long-term disability and sick leave due to a pain condition are associated with huge negative consequences for the individual and for society.[2] It would be both costly and unnecessary, however, to offer specialized treatment to all patients presenting in primary care with a pain condition; despite its frequency, pain is in most cases a temporary phenomenon.[3] Still, a small group of patients will develop chronic or recurrent pain causing long-term disability and sick leave. It is estimated that approximately 3-10% of patients with acute pain develop a chronic pain condition.[3, 4] Chronic pain conditions are associated with social and family problems, loss of work, and loss of self-esteem and integrity.[5-7] Moreover, chronic pain is often associated with other symptoms or comorbidities like fatigue, concentration and memory problems, sleep disorders, depression, and anxiety.[5] Once pain has become chronic, treatment is complex and difficult.[2] Thus, early identification of pain patients at high risk of developing long-term problems would offer a great opportunity for reducing cost and suffering associated with long-term disability and sick leave because optimal care could be initiated at an early stage.

Most pain research focuses on one specific pain site (e.g., low back or shoulder pain[8, 9]). As a result, prognostic factor research is normally conducted on each site separately.[8] For example, substantial prognostic factor studies on back pain have been carried out, with several systematic reviews reporting prognostic factors for back pain.[10-14] However, this single-site approach limits clinical applicability for the general practitioner because most pain patients have pain at more than one anatomical location.[9, 15] Factors that have predictive value across different pain sites (i.e., generic factors) may exist,[8] but few attempts have been made to explore prognostic factors across pain sites.[8, 16]

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To our knowledge, no systematic review has performed a meta-analysis of prognostic factors across pain sites in patients with sub-acute pain. However, such an analysis would likely assist clinicians in identifying patients at high risk of developing disability, thereby allowing resources to be concentrated on those who are most in need of further attention.

This systematic review was conducted as part of a national Danish '*Health Technology Assessment*'(HTA) aimed to identify possibilities for early identification and timely treatment for pain patients across pain-sites with relevance to a broad range of stakeholders in Denmark.[17] The specific aim of the evidence synthesis was to identify potential factors for the development of long-term disability or sick leave in patients with sub-acute, non-malignant pain in primary care.

METHODS

The review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[18] on the basis of a predefined protocol available from the International Prospective Register of Systematic Reviews (PROSPERO: CRD42014008914).

Data sources and searches

Studies were identified via a systematic literature search in the following databases: PubMed, Embase, CINAHL, and PEDro. Additional studies were identified through experts and through review of the included studies´ reference lists. The following search terms were used: "Pain," "Prognosis," "Predictor," "Prognostic factor," "Primary Health Care," "General Practice," and "Family Practice." The search string tailored for PubMed database is presented below:

Search((("Pain"[Mesh]) OR "Chronic Pain "[Mesh] OR "persistent pain")) AND (("Prognosis" [Mesh]) OR "Outcome Assessment (Health Care)" [Mesh] OR predict* OR prognost* AND

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((English[lang] OR Danish[lang] OR Norwegian[lang] OR Swedish[lang] AND adult[Mesh]))) AND (((“Primary Health Care” [Mesh]) OR “General Practice” [Mesh]) OR “Family Practice” [Mesh] OR GP OR “primary care”). Filters: Published in the last 10 years; English; Danish; Norwegian; Swedish; Adult: 19+years. (full search is available on request). As part of the search and selection strategy, according to the HTA protocol, the major outcome was long-term disability (> 3 months) due to a pain condition. A secondary outcome was sick leave, defined as “absence from work” or “return-to-work”. The search was restricted to identify studies published in English, Danish, Norwegian, or Swedish between 16 January 2003 and 16 January 2014.

Study selection

Studies were eligible for inclusion if they met the following criteria: prospective cohort study (incl. randomized controlled trials), with at least 3 months' follow-up investigating the prediction of long-term disability and/or sick leave in adults (> 18 yrs) with a sub-acute (≤ 3 month) non-malignant pain condition, visiting general practitioners or other primary care facilities. Non-malignant pain condition" was defined as pain conditions of non-cancer origin. If two or more published studies originated from the same patient population, the study with the longest follow-up period was included. Two reviewers (GHV and MSP) independently assessed abstracts and full-text articles for eligibility, and disagreement was solved by a third reviewer (LØ).

Data extraction and quality assessment

Two review authors (GHV and MSP) independently performed data extraction using a customized data extraction form. To summarize the evidence following the systematic review in the HTA, we applied the "Grading of Recommendations Assessment, Development, and Evaluation" (GRADE) approach for rating quality of evidence (i.e., our confidence in the estimates). [19] Because we anticipated that the evidence base would come from cohort studies the GRADE approach for

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prognostic factor research[20] was applied. The risk of bias in the individual studies was assessed by two reviewers (GHV and MSP) using the Quality in Prognosis Studies tool (QUIPS).[21] The overall risk of bias for each of the studies was judged as: 1) low if there were a low risk of bias in all key domains, 2) unclear risk of bias if there were an unclear risk of bias for one or more key domains, and 3) high risk of bias if there were a high risk of bias for one or more key domains.[22] Disagreement was resolved by consensus. Publication bias was explored by funnel plots.

Data synthesis and analysis

If a baseline factor was associated with outcomes at follow-up in two or more studies of different pain sites, it was considered a "possible prognostic" factor and the results were combined and subsequently presented as part of the evidence profile. When data were available in different formats, data from the "fully adjusted" analyses were given preference and included in the meta-analysis. The studies in the meta-analyses were heterogenic regarding statistical methods. Hence, it was not possible directly to compare the results from the original studies. In order to assed the statistical power between a prognostic factor and outcome Fishers z-transformation was used. From each cohort study, the "statistical signal" (The "Wald-test"—the ratio between signal and noise) was derived from the effect size and the standard error of the estimate (SE). These were subsequently handled using Fisher's z-transformation.[23] This z-transformation was used to communicate the statistical power for any given association (i.e., correlation) between a given prognostic factor and an outcome. In one study the outcome was "absence of disability" as opposed to "disability". Thus the effect estimate (HR: 0.97) was reversed (HR: 1.03) before transformed into logscale and entered in RevMan.[24]

Summary estimates of associations across studies were derived from random effects meta-analysis, anticipating clinical heterogeneity, with modelling allowing for differences in the association from study to study.[25]

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Heterogeneity across studies was statistically assessed using the Q-test and quantified by the inconsistency (I^2) index.[26] I^2 represents the percentage of total variation across studies attributable to heterogeneity rather than (statistical) chance.[27] In cases with substantial heterogeneity across studies ($I^2 > 50\%$), the robustness of the results was checked using the "fixed effects" model. A result was considered robust if the point estimate for "fixed effects" was within the confidence interval of "random effects"; as a consequence, the risk of "small-study" bias was considered to be high if the point estimate was outside the confidence estimate. If this was the case, the evidence for the given prognostic factor was downgraded due to inconsistency. In order to explore the robustness of the pooled estimates sensitivity analyses were conducted in cases were three or more studies in the meta-analysis had similar effect value. Meta-analyses were performed using Review Manager (RevMan) provided by the Cochrane Collaboration.[28] A two-sided P-value of ≤ 0.05 (and 95% confidence interval excluding the null) was considered to be statistically significant in all analyses. For each outcome, we prepared an evidence profile based on the GRADE profiler software.[29]

RESULTS

Results of the literature search

The search in the selected databases returned a total of 3,533 references. A total of 32 references were identified through the additional search. After removing duplicates, 1,841 references remained. The 1,841 references were screened for eligibility, and 1,641 records were excluded. The remaining 200 articles were read in full-text; of these, 181 articles were excluded because they did not satisfy the inclusion criteria. A full list of excluded studies and the reason for exclusion is available from the authors upon request. A total of 19 studies satisfied the inclusion criteria and were included in the systematic review. However, only 11 were eligible for inclusion in the meta-analysis; the other 8 studies were excluded from the quantitative synthesis due to: 1) inadequate statistical analyses,[3, 30] 2) the factors studied were assessed in only one study,[31-33] or 3) the factors

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studied were assessed for only one pain site (e.g., only studies on back pain).[34-36] See **Figure 1** for a flow diagram of the included studies.

Figure 1: Flow-diagram of the literature search

Included studies

The 19 included studies consisted of 17 cohort studies and two randomized controlled trials. Fourteen of the studies referred to patients with back pain[4, 24, 30-32, 34, 35, 37-43] and one referred to patients with pain in the neck or back.[3] Two studies referred to patients with neck pain,[33, 44], one referred to patients with headache,[45] and one referred to patients with shoulder or back pain.[36] From this last-mentioned study, only the cohort with back pain was included in the synthesis because the cohort with shoulder pain comprised both patients with sub-acute pain and patients with chronic pain.[36] Outcome measures were disability in 16 studies,[3, 4, 24, 30, 34-45] sick leave in three studies,[3, 33, 42] and return-to-work in two studies.[31, 32]

Characteristics of the 19 included studies are presented in Table 1. The total number of patients included in the 19 studies was 6,266. The median number of patients per study was 184 (range: 56–2,662). In eleven of the studies, more women than men participated. Age was reported in 18 studies, with a median average of 42 years (range: 34–52 years). Pain duration at baseline was reported in eight studies with a median average of 12.6 days (range: 1–27 days). Follow-up period ranged from 3 months to 22 years (with a median of 9 months). Most of the studies recruited patients from general practice.[3, 4, 24, 30, 32-34, 36-39, 41-43, 45] The remaining studies recruited patients from physiotherapy or chiropractor clinics[35, 40, 44] and workers compensation board.[31]

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Table 1: Characteristics of the included studies

[A]: 2,662 patients were included in the study but only 730 respondents are included in the relevant analyses.

Author (publication year)	Country of origin	Participant eligibility criteria	No. of participants at baseline	Age at baseline Mean (SD)	Pain site	Recruitment	Outcome measure	Follow up (months)
Boardman HF. (2006)	UK	Adults > 18 years.	730[A]	52 (18-90)[B]	Head	GP[D]	Disability (Migraine Disability Assessment)	12
Boersma K. (2005)	Sweden	No information	363	47 (10.2)	Back or neck	GP[D]	Disability (Örebro Musculoskeletal Pain Screening Questionnaire) and sick leave (> 15 days)	12
Childs J. (2004)	US	Patients 18 to 60 years; with a primary symptom of LBP, with or without referral into the lower extremity; and an Oswestry Disability Questionnaire (ODQ) score of at least 30%.	131	33.9 (10.9)	LPB[C]	Physiotherapy	Disability (Modified Oswestry Disability Index)	6
Coste J. (2004)	France	Patients > 18 years, self-referring to GP (n: 40) or rheumatologists (n: 7) for a primary complaint of LBP with pain duration < 72 hours and without radiation below the gluteal fold	113	44.3 (13.7)	LBP[C]	GP[D]	Disability (VAS and Roland Morris Disability Questionnaire)	3
Grotle M. (2007)	Norway	Patients 18–60 years; acute LBP of less than 3 weeks duration, with or without radiating pain to the limb; and had not been treated for LBP earlier	123	37.9 (10.1)	LBP[C]	GP[D]	Disability (Roland Morris Disability Questionnaire)	12
Grotle M. (2010)	Norway	Patients consulting GP with non-specific LBP of varying duration and localization	258	46 (9)	LBP[C]	GP[D]	Disability (Roland Morris Disability Questionnaire)	12
Hancock M. (2008)	Australia	Primary complaint of pain in the area between the 12th rib and buttock crease causing moderate pain and moderate disability (measured by adaptations of items 7 and 8 of the SF-36).	240	40.7 (15.6)	LPB[C]	GP[D]	Disability (Roland Morris Disability Questionnaire)	3
Hendrick P. (2013)	New Zealand	Patients aged 18–65 years with an episode of LBP of ≤ 6 weeks, preceded by a minimum period of 3 months during which participants had not sought treatment for LBP, and no other pre-existing conditions that limited their mobility.	101	38.8 (14.6)	LBP[C]	GP[D], Physiotherapy clinics and newspaper advertisement	Disability (Roland Morris Disability Questionnaire)	3
Heneweer H. (2007)	Holland	Patients aged 21–60 years with sufficient knowledge of the Dutch language to complete the questionnaires.	56	42 (9.2)	LBP[C]	Physiotherapy clinics	Disability (recovery yes/no and sick leave yes/no)	3

[B]: Median (range).
[C]: Low back pain
[D]: General practitione

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Table 1(continued): Characteristics of the included studies

Author (publication year)	Country of origin	Participant eligibility criteria	No. of participants at baseline	Age at baseline Mean (SD)	Pain site	Recruitment	Outcome measure	Follow up (months)
Karjalainen K. (2003)	Finland	25 to 60-year-old patients having disabling LBP for the preceding 4 to 12 weeks.	164	44 (8.8)	LBP[C]	GP[D]	Disability (Oswestry Disability Index) and sick leave (1: 0 days, 2: 1–30 days, 3: > 30 days)	12
Leaver AM. (2013)	Australia	Patients aged 18–70 years with a new episode of non-specific neck pain.	181	38.8 (10.7)	Neck	Physiotherapy and chiropractor clinics	Disability (Neck Disability Index)	3
Lonnberg F. (2010)	Denmark	Patients seeking care for the first time regarding an episode of LBP.	78	57[E]	LBP[C]	GP[D]	Disability (Limitations- no further information)	264
Melloh M. (2013)	New Zealand	Patients 18–65 years.	315	34.9 (12.6)	LBP[C]	GP[D]	Disability (Oswestry Disability Index)	6
Schultz IZ. (2004)	Canada	Participants 18–60-year old remaining off work 4–6 weeks post-injury (sub-acute group) or remaining off work 6–12 months after injury (chronic).	253	40.3 (11.4)	LBP[C]	Workers´Compensation Board	Return-to-work status	3
Sieben JM. (2005)	Holland	Patients aged 18–60 years with a new episode of non-specific LBP.	222	No information	LBP[C]	GP[D]	Disability (Graded Chronic Pain Scale)	12
Storheim K. (2005)	Norway	Patients sick listed from a permanent job and receiving between 50% and 100% compensation for non-specific LBP for 8–12 weeks, but with no sick leave due to LBP during a period of 12 weeks before the current sick-listing period; aged between 20 and 60 years.	93	RTW:40.5 (9.8) NRTW: 42.3 (11.7)	LBP[C]	GP[D] and National Insurance Offices	Return-to-work status	12
Swinkels-Meewisse, (2006)	Holland	Patients aged 18–65 years having an episode of nonspecific LBP independent of radiation.	374[F]	42.4 (11.3)	LBP[C]	GP[D] and Physiotherapy clinics	Disability (Roland Morris Disability Questionnaire)	6
Van der Windt DA. (2007)	Holland	Patients 18–65 years with a duration of LBP < 12 weeks at presentation, or exacerbation of mild symptoms of back pain.	171 (Back group)	42.0 (12.0) (back group)	LBP[C]	GP[D]	Disability (Roland Morris Disability Questionnaire)	3
Vos CJ. (2008)	Holland	Patients > 18 years with neck pain < 6 weeks.	187	40.7 (14.1)	Neck	GP[D]	Sick leave (> 7 days)	12

[E]: Median (range)
[F]: 555 Participants are included in the trial, but data regarding disability were available from only 374 of the participants

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Risk of bias within studies

Risk of bias in the included studies was assessed using QUIPS (figure 2). Overall, the agreement between the two assessors (GHV and MSP) on the different aspects of Risk of Bias assessment was 85.5% (weighted Kappa 0.49), which corresponds to a moderate degree of agreement. In all cases, any disagreement between the assessors was settled by consensus discussion. The domain "Study Confounding" carried the highest risk of bias. In this domain, three studies were judged as having high risk of bias, and eleven studies were assessed as having a moderate risk of bias. The high number of studies judged as having a high or moderate risk of bias in this domain was due mainly to insufficient description of the factors that were included in the multivariable analysis. Based on the judgement of the six domains, eleven studies were judged to have low risk of bias,[4, 24, 32, 34-36, 39, 41-44] three studies had moderate risk of bias,[33, 37, 38] and five studies had high risk of bias.[3, 30, 31, 40, 45] Publication bias was assessed by funnel plots for all eight prognostic factors. No obvious asymmetry was found (Supplementary Material S2).

Figure 2: Risk of bias of the six domains in QUIPS

Prognostic factors for disability

Prognostic factors for disability were assessed in 16 studies.[3, 4, 24, 30, 34-45] A total of 81 factors were assessed in the unadjusted analysis (Supplementary Material S1). Of the 81 factors assessed, 53 were included in the multivariable analysis of the primary studies. Of these factors, the following eight were assessed in two or more studies and for at least two different pain sites: multiple-site pain, higher baseline pain severity, previous pain episodes, older age, longer baseline pain duration, baseline disability, anxiety, and depression. A total of eleven studies were included in the meta-analysis (figure 3 and 4).[4, 24, 37-45] The association between multiple-pain sites and disability at follow-up was assessed in three studies, including patients with headache,[45] low back pain,[41] and

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neck pain[44] (figure 3a). The combined estimate showed a statistically significant association between multiple-pain sites at baseline and risk of disability at follow-up (p = 0.010). The test for heterogeneity was I^2 =57%. However, "fixed effects" did not change the result significantly.

The association between higher pain severity at baseline and disability was assessed in six studies including patients with headache[45] and low back pain[37, 38, 40-42] (figure 3b). The combined estimate showed a statistically significant association between higher baseline pain severity and disability (p < 0.001). I^2 was 93% and the result was not robust when using the "fixed effects" model, so small-study bias is therefore likely. Consequently, the quality of evidence was downgraded due to inconsistency. The association between baseline disability and disability at follow-up was examined in seven studies relating to patients with neck pain[44] and low back pain[24, 38, 40-43] (figure 3c). Baseline disability was associated with a higher risk of disability at follow-up (p = 0.007). I^2 was 96%. The "fixed effects" model did not change the result significantly.The association between higher age and the risk of disability was assessed in seven studies concerning patients with neck pain[44] and low back pain[4, 37-39, 41, 42] (figure 3d). A significant association was seen between higher age and risk of disability (p = 0.04). I^2 was 89%. The "fixed effects model" did not change the result significantly. A dose-response effect was observed; an increase by 10 years of age was associated with a higher risk of disability than was a one-year increase. No statistical significant associations between disability and previous pain episodes (p = 0.08; figure 4a), longer baseline pain duration (p= 0.12; figure 4b), anxiety (p = 0.25; figure 4c), or depression (p = 0.14; figure 4d) were observed. The "fixed effects" model did not change the results notably for the four potential prognostic factors in figure 4.

Sensitivity analyses were conducted for the results of the meta-analysis presented in figure 3C and 3D. In figure 3C the study by Karjalainen et al. was omitted and in figure 3D the studies by Grotle et al, 2007 and Karjalainen et al. were omitted. The statistical signal did not change substantially after selective omitting studies with different effect value (Supplementary material S3

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Figure 3: Forest plots of the association between potential prognostic factors and long-term disability in patients with a sub-acute pain condition. 3A: Adjusted for: Age [41, 45], sex [41, 45], baseline disability [41], recruitment [41], factors adjusted for not described [44]. 3B: Adjusted for: Age [41, 45], sex [41, 45], baseline disability [41], recruitment [41], factors adjusted for not described [37, 40, 42].3C: Adjusted for: Age [41, 43], Sex [41, 43], BMI [43], duration (hours) between pain debut and inclusion [24], job status [24], previous spine surgery [24], compensation status [24], self rated health status [24], factors adjusted for not described [38, 40, 42, 44].3D: Adjusted for sex [4, 39], job [39], BMI [39], Baseline pain severity [39], recruitment [41], depression [39], anxiety [39], fear avoidance [39], activity level prior current pain episode [39], baseline disability [38, 41], factors adjusted for not described [37, 42, 44].

Figure 4: Forest plots of the association between potential prognostic factors and long-term disability in patients with a sub-acute pain condition. 4A: Adjusted for: age [4, 45], sex [4, 45], baseline disability [38], factors adjusted for not described [37]. 4B: Adjusted for: Age [43, 45], sex [43, 45], BMI [43], baseline disability [38]. 4C: Adjusted for: Age [41, 45], sex [41, 45], recruitment [41], baseline disability [41]. 4D: Adjusted for: Age [41, 43, 45], sex [41, 43, 45], BMI [43], recruitment [41], baseline disability [41].

Quality of evidence for the risk of developing disability

The quality of evidence for the potential prognostic factors for the risk of developing disability is presented in table 2. All the included studies in the meta-analysis were phase 1 studies, which are characterized as predictive modelling studies or explanatory studies conducted to generate a hypothesis.[20] Thus, the quality of evidence was low as a starting point. Reasons for up- or down-grading the quality of evidence for the given prognostic factor are described below in table 2. The quality of evidence was graded as either low or very low and thus the validity of the results is low.

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Table 2: GRADE evidence profile of the potential prognostic factors for long-term disability in patients with a sub-acute pain condition.

Prognostic factors (no. of studies)	Phase	Quality assessment						Summary of findings		
		Limitations	Inconsistency	Indirectness	Imprecision	Publication bias	Other considerations	No. of participants included in the analyzes	Estimated "Effect size"	Overall quality
Multiple-site pain [41, 45, 46] (3)	1	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected [A]		1,164	0.07 (0.02;0.13) p=0.01	Low ⊕⊕⊖⊖
High baseline pain severity [37, 38, 40-42, 45] (6)	1	Serious limitation (-1)	Serious inconsistency [B] (-1)	No serious indirectness	No serious imprecision	Detected [C] (-1)	Dose-respons effect detected (+1)	1,711	0.04 (0.02;0.06) p<0.0001	Very low ⊕⊖⊖⊖
Baseline disability [24, 38, 40-44] (7)	1	No serious limitations	No serious inconsistency [I]	No serious indirectness	No serious imprecision	Undetected [A]		1,263	0.01 (0.00;0.02) p=0.007	Low ⊕⊕⊖⊖
Older age [4, 37-39, 41, 42, 44] (7)	1	No serious limitations	No serious inconsistency [F]	No serious indirectness	No serious imprecision	Detected (-1)[G]	Dose-respons effect detected (+1)	1,296	0.01 (0.00;0.02) p=0.04	Low ⊕⊕⊖⊖
longer pain duration [38, 43, 45] (3)	1	Serious limitations (-1)	No serious inconsistency	No serious indirectness	No serious imprecision	Detected (-1)[H]		1,236	0.01 (0.00;0.03) p=0.12	Very low ⊕⊖⊖⊖
Previous episodes [4, 37, 38, 45] (4)	1	Serious limitation (-1)	No serious inconsistency [D]	No serious indirectness	Serious imprecision (-1)	Detected [E] (-1)		1,353	0.03 (0.00;0.06) p=0.08	Very low ⊕⊖⊖⊖
Anxiety [41, 45] (2)	1	Serious limitations (-1)	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected [A]		988	0.07 (-0.05;0.18) p=0.25	Very low ⊕⊖⊖⊖
Depression [41, 43, 45] (3)	1	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected [A]		1,157	0.02 (-0.01;0.05) p= 0.14	Low ⊕⊕⊖⊖

A: The association between the prognostic factor and disability is assessed only in the trials included in the meta-analyses.
B: Results of the meta-analyses were not robust when using the "fixed-effects" model.
C: Nine studies assessed the association between high baseline pain and disability at follow-up, but only six studies reported the results in the adjusted analyses.
D: Inconsistency in the results between the study by Boardman et al. and the study by Swinkels-Mewisse et al. can be explained by differences in the reporting of previous episodes. In the study by Swinkels et al., the participants could have experienced pain once 10 years ago, whereas Bordman looks at pain episodes one or more times per. week.
E: Nine studies reported previous pain episodes in the unadjusted analyses, but only seven studies included the results in the adjusted analyses.
F: Karjalainen et al. reported the association between an increase in age by 10 years and disability, whereas the other studies reported the association between age and disability by an increase of one year.
G: Nine studies reported the association between age and disability, but only seven studies included the results in the adjusted analyses.
H: The association between baseline pain duration and disability was reported in the unadjusted analyses in five studies, but only three studies included the results in the adjusted analyses.
I: In the study by Karjalainen et al., the association between baseline disability and disability at follow-up was reported by an increase by 20 % in max score at baseline, whereas the other studies reported an increase by 1 point. This difference could be a plausible reason for the inconsistency between the results.

Prognostic factors for long-term sick leave or return-to-work

Three of the included studies had long-term sick leave as an outcome[3, 33, 42]. Two of the studies, referring to patients with pain in the neck[33] and back,[42] respectively, had performed multivariable analysis. The follow-up period was three months in both studies. Long-term sick leave was defined

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as sick leave for more than 30 days in one study[42] and more than 7 days in the other.[33] Baseline disability was the only potential prognostic factor that was assessed in both studies. In the study by Karjalainen et al., however, the results were described only as being "non-significant."[42] Thus, it was not possible to present the results in a meta-analysis. In the study by Karjalainen and colleagues, factors like blue-collar work and long-term sick leave at baseline were associated with an increased risk of long-term sick leave at follow-up in patients with sub-acute back pain. Vos and colleagues found that factors like previous pain episodes, a follow-up appointment scheduled with a GP, and the GP's referring the patient to treatment and baseline disability all were associated with an increased risk of long-term sick leave among patients with acute neck pain[33]. Two studies described "return-to-work" as an outcome.[31, 32] Follow-up was 3 [31] and 12 months,[32] respectively. Both studies related to patients with back pain, so potential generic factors could not be extracted.

DISCUSSION

Four potential generic prognostic factors for developing disability following a sub-acute pain condition were identified. Risk factors across different pain sites included multiple-site pain, higher pain severity, higher age, and baseline disability. Previous pain episodes, pain duration at baseline, anxiety, and depression were not associated with the risk of disability at follow-up. Due to the limited number of studies, it was not possible to identify potential generic risk factors for long-term sick leave or return-to-work. Quality of evidence was low or very, low implying that confidence in the estimate is low.

Comparison with other studies or reviews

Despite sparse literature in this field, there is some evidence to support our findings. In concurrence with our findings, a previous review reported factors such as multiple-site pain, higher pain severity, higher age, and baseline disability as being potential prognostic factors for a poor outcome

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in patients with musculoskeletal pain.[8] A strong association between the number of pain sites and disability was also demonstrated in a previous cross-sectional study.[9] Similar, a prospective cohort study from 2008 found that the number of pain sites were a strong predictor of work disability14 years later regardless of diagnosis.[47] Furthermore, a recent systematic review found some evidence suggesting that the number of somatic symptoms and baseline severity of the condition influenced the future course in patients with medically unexplained symptoms.[48] Thus, despite the low quality of evidence of the results, we find it reasonable to believe that the factors indentified in our systematic review may act as central prognostic factors for the development of disability across pain sites. Therefore, future research should address confirming the role of these factors.

Interestingly, our review found that anxiety and depression at baseline were not associated with disability at follow-up. These findings are controversial because psychosocial factors also known as "yellow flags" are widely accepted as being key factors in the transition from acute to chronic pain conditions [49]. "Yellow flags" include depression, anxiety, catastrophic thoughts, and pain-related fear of movement/fear avoidance among others.[50, 51] Several national and international guidelines recommend that clinicians screen for the presence of these factors in the early phase[52-54]. In addition, several well-established screening tools for the risk of chronicity are based on the presence of these factors (e.g., the Orebro Musculoskeletal Pain Questionnaire,[55] the Fear-Avoidance Health Beliefs Questionnaire,[56] and the STarT Back Screening Tool[57]). Most studies, however, have not included pain duration at baseline when the importance of "yellow flags" was assessed.[16] A plausible explanation for the apparent discrepancy between our results and the widely accepted "yellow flags," therefore, could be the inclusion criteria in our review regarding short pain duration at baseline. It is likely that factors like anxiety and depression are of greater importance once pain has become chronic. Another explanation for the discrepancy could be that our review focuses on risk factors for future disability and sick leave and not on risk factors for developing a chronic pain

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condition. Nonetheless, future research should address and clarify the role "yellow-flag" factors play in the various phases of pain.

Strength and limitations

It is considered a strength in our systematic review that we followed a rigorous protocol (registered in PROSPERO) prespecifying all the outcomes and analyses; our adherence to the protocol likely strengthens the credibility of the evidence synthesis. We reported our findings as recommend by the PRISMA statement[18] and judged the quality of the evidence based on the recommendations from the GRADE Working group. We believe that the GRADE framework applied to prognostic factor research was valuable for assessing and transparently reporting the quality of the evidence of the possible prognostic factors. To our knowledge, this is the first time GRADE has been used in the evaluation of prognostic studies.

Limitations regarding the interpretation of the results from this study should be taken into consideration. A total of 14 of the 19 included studies in our review referred to patients with back pain. The high number of studies concerning patients with back pain may affect the external validity of the results to patients with pain at other sites. However, the vast majority of pain patients visiting general practice suffer from back pain, and the large number of studies on back pain included in the present review therefore reflects the distribution of patients seen in general practice.[58] Future studies assessing prognostic factors for non-spinal pain are needed. Publication bias is one of the most common biases in meta-analyses. Therefore, we conducted funnel plots to explore whether publication bias was present in our analysis. No obvious asymmetry was found. In accordance with current knowledge the use and appropriate interpretation of funnel plots are however, controversial because of questions about statistical validity, disputes over appropriate interpretation, and low power of the tests.[59] For instance, a funnel plot can be symmetrical even in the presence of

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publication bias.[59] Hence publication bias might be present in our analyses although undetected. Another common limitation in systematic reviews is the risk of selective reporting of primary study results. Our review was based primarily on observational cohort studies on prognostic factors (Phase 1 studies). Such studies harbour a high risk that non-significant findings are not reported or only included in the first (unadjusted) part of the analysis. Any non-reporting of non-significant results invites a risk that the findings in the meta-analysis were overestimated. We attempted to account for such bias due to selective outcome reporting by listing all the studies that examined a specific prognostic factor in the unadjusted analysis. If a factor was investigated in eight studies, for example, but included only in the adjusted analysis of five, the quality of the evidence was downgraded. A substantial limitation in this review was that results from original studies with different effect measures were combined in the meta-analysis. In order to interpret the clinical significance of the result of a meta-analysis it is essential that the characteristics of the effect measure are identical. However, prognostic factor studies have no standards for outcome reporting and thus the studies were by all means heterogeneous regarding statistical methods, as well as clinical and outcome heterogeneity. Hence, it was not possible to combine and compare the results from the original studies directly. In order to assess the statistical power for any given (i.e. reported) association between a prognostic factor and outcome Fishers z-transformation was used as previously suggested by Thompson S, et al.[60] This method can be considered controversial due to the difficulties interpreting the results. In order to account for this limitation, the robustness of the results was explored by sensitivity analysis. The statistical signal did not change substantially after selective omitting studies with different effect value. The robustness of the estimates in the sensitivity analysis increases the validity of the results. The meta-estimates (statistical signals) were however, low which might suggest that clinical relevance of the results is limited. These findings are not unique for this study.[41, 61] It is a general problem for prognostic factor studies. There are two plausible reasons for this: 1.important prognostic factors for disability may not have

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been identified yet or 2. tools for measurement of both risk factors and outcome might be associated with substantial measurement errors.[61] Consequently we cannot draw a strong conclusion on the clinical significance of the results.

Implications for clinical practice

No high-quality evidence was provided for any of the potential prognostic factors; therefore, no definite clinical conclusion can be made about how to identify patients at high risk of long-term disability or sick leave at an early stage in general practice. However, the empirical evidence illustrates what kind of prognostic factor research would be relevant to pursue in order to increase value and reduce waste in prognostic factor research on long-term disability among patients with sub-acute non-malignant pain.[62] It appears that multiple-site pain, high-baseline pain severity, older age, and baseline disability are associated with future disability across pain sites in sub-acute pain patients. Therefore, it may be helpful for GPs to have these factors in mind in clinical decision making.

Implications for future research on prognostic factors

Correctable weaknesses in biomedical and public health research studies can produce misleading results and waste valuable resources.[63] During the preparation of this review, it became clear that the current literature in this field falls short on a number of counts. As suggested by Ioannidis et al.,[63] this area of research also has weaknesses, such as selective reporting of results; lack of prespecified defined prognostic factors to be assessed; inadequate description of methods; inadequate or poor quality of statistical analysis; failure to distinguish between prognostic factors among patients with acute, sub-acute, and chronic pain; and lack of published studies on patients suffering from non-spinal pain. We suspect most of these limitations can be related to the absence of detailed written protocols and poor documentation of research in general.[63-66]

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Although good research ideas often yield unanticipated but valuable results, much research fails to effect worthwhile achievements. As long as the way in which research projects are prioritized for research is transparent and warranted, the disappointments should not be deemed wasteful; they are simply an inevitable feature of the way science works.[62] In order to gain further knowledge on which factors are central prognostic factors (sub-acute phase), future studies should take into account baseline pain duration at the time patients are enrolled. Future studies on prognostic factors in chronic pain should be conducted as large, prospective, registered, and protocol-based prognostic factor studies with sufficient study populations and transparent reporting of all factors studied. Once sufficient knowledge on risk factors has been obtained, documentation of effective treatment for high-risk pain patients is needed. Further, the effect of offering stratified care to pain patients based on their risk profiles should be tested in randomized controlled trials.[67]

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Conflicts of interest: None. Dr. Christensen declares, however, that he is involved in many health-care initiatives and research that could benefit from a wide uptake of this publication (including Cochrane, OMERACT, and the GRADE Working Group).

FIGURE LEGENDS

Figure 1: Flow diagram of the literature search

Table 1: Characteristics of the included studies

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Figure 2: Risk of bias of the six domains in QUIPS

Figure 3: Forest plots of the association between potential prognostic factors and long-term disability in patients with a sub-acute pain condition

Figure 4: Forest plots of the association between potential prognostic factors and long-term disability in patients with a sub-acute pain condition

Table 2: GRADE evidence profile of the potential prognostic factors for long-term disability in patients with a sub-acute pain condition

Supplementary Material

Supplementary Material S1: Potential prognostic factors for disability assessed in the included studies. A plus sign indicates a statistically significant association between the given factor and the outcome. A minus sign indicates a non-significant association.

Supplementary Material S2: Funnel plots of studies included in the meta-analyses.

Supplementary Material S3: Sensitivity analysis omitting studies with different effect value.

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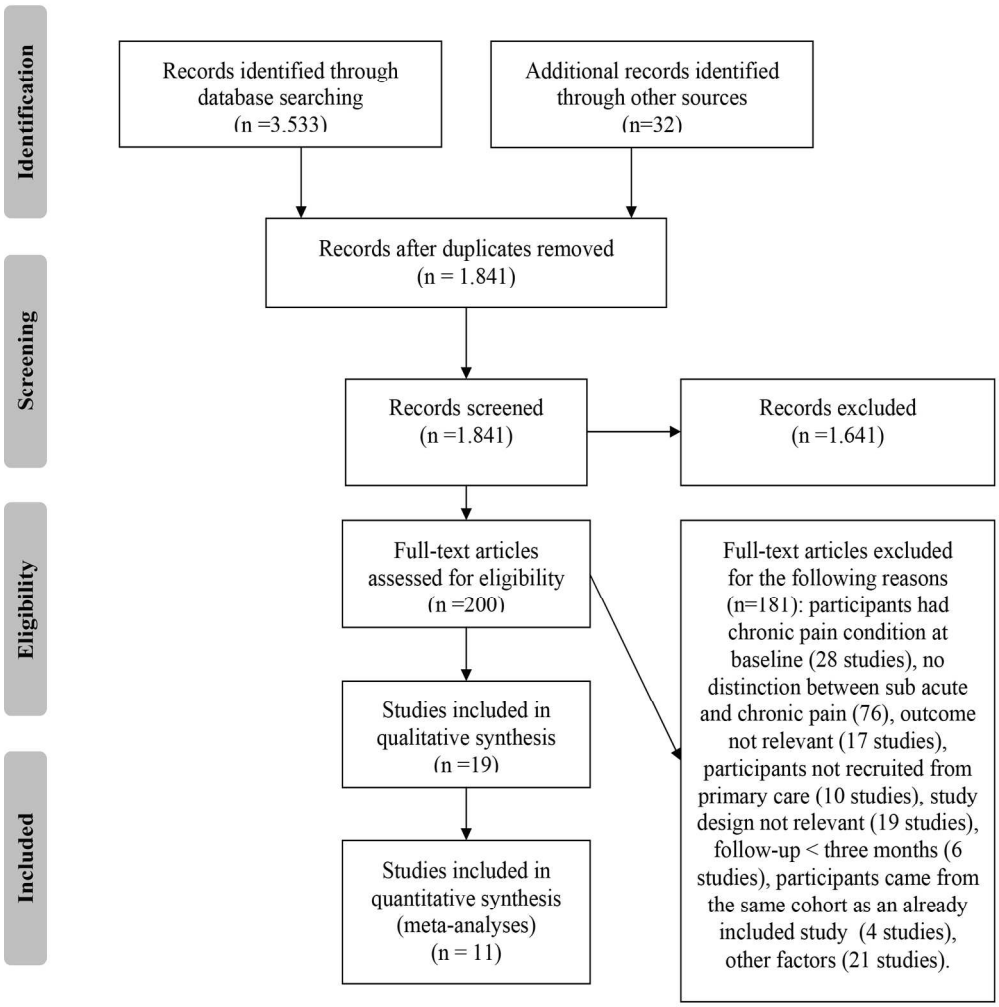

Figure 1: Flow-diagram of the literature search
173x196mm (300 x 300 DPI)

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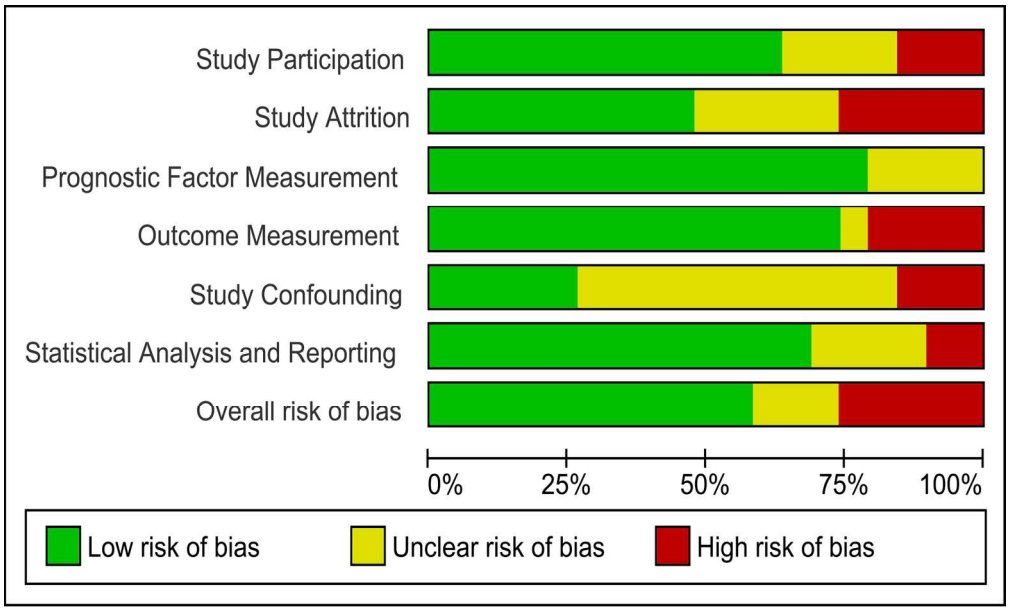

Figure 2: Risk of bias of the six domains in QUIPS
173x104mm (300 x 300 DPI)

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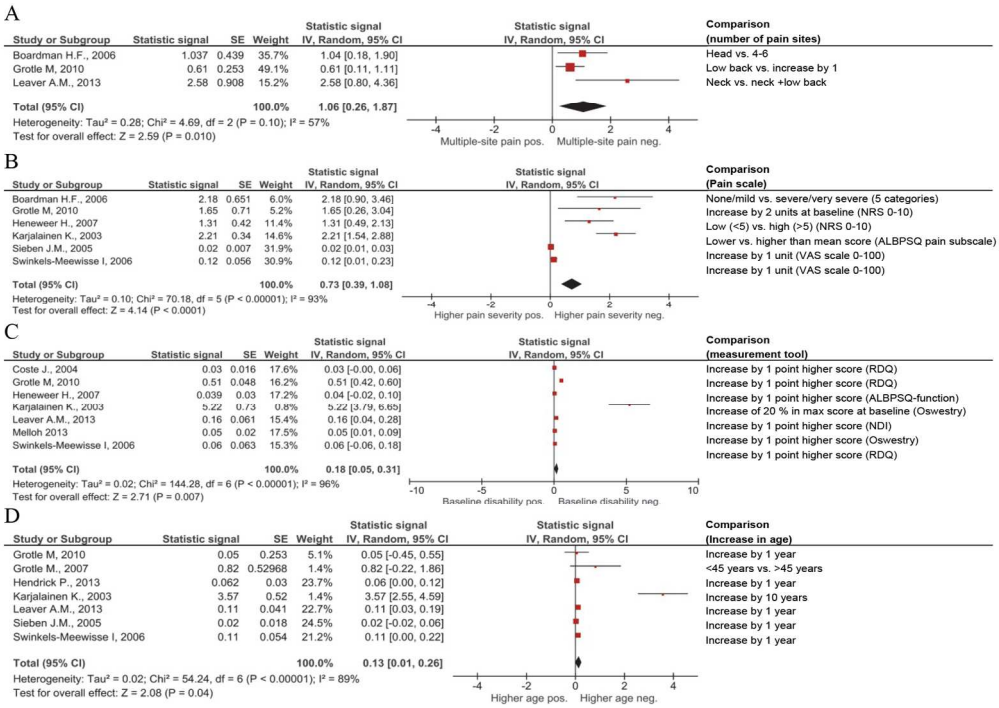

Figure 3: Forest plots of the association between potential prognostic factors and long-term disability in patients with a sub-acute pain condition. 3A: Adjusted for: Age 41, 45, sex 41, 45, baseline disability 41, recruitment 41, factors adjusted for not described 44. 3B: Adjusted for: Age 41, 45, sex 41, 45, baseline disability 41, recruitment 41, factors adjusted for not described 37, 40, 42.3C: Adjusted for: Age 41, 43, Sex 41, 43, BMI 43, duration (hours) between pain debut and inclusion 24, job status 24, previous spine surgery 24, compensation status 24, self rated health status 24, factors adjusted for not described 38, 40, 42, 44.3D: Adjusted for sex 4, 39, job 39, BMI 39, Baseline pain severity 39, recruitment 41, depression 39, anxiety 39, fear avoidance 39, activity level prior current pain episode 39, baseline disability 38, 41, factors adjusted for not described 37, 42, 44.
173x121mm (300 x 300 DPI)

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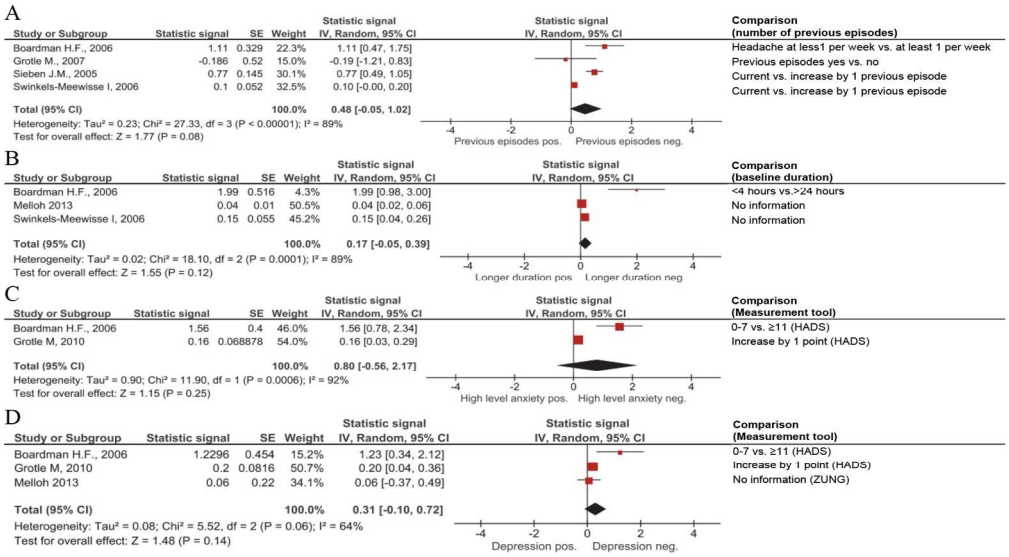

Figure 4: Forest plots of the association between potential prognostic factors and long-term disability in patients with a sub-acute pain condition. 4A: Adjusted for: age 4, 45, sex 4, 45, baseline disability 38, factors adjusted for not described 37. 4B: Adjusted for: Age 43, 45, sex 43, 45, BMI 43, baseline disability 38. 4C: Adjusted for: Age 41, 45, sex 41, 45, recruitment 41, baseline disability 41. 4D: Adjusted for: Age 41, 43, 45, sex 41, 43, 45, BMI 43, recruitment 41, baseline disability 41.

173x95mm (300 x 300 DPI)

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Supplementary material

Supplementary Material S1: Potential prognostic factors for disability assessed in the included studies. A plus sign indicates a statistically significant association between the given factor and the outcome. A minus sign indicates a non-significant association.

	Prognostic factor	**Boardman**	**Boersma**	**Childs**	**Coste**	**Grotle, 2007**	**Grotle, 2010**	**Hancock**	**Hendrick,**	**Heneweer**	**Karjalainen**	**Leaver**	**Lonnberg**	**Melloh**	**Sieben**	**Swinkels-Meewisse**	**Van der Windt**
	Pain site	**Head**	**Back or neck**	**LBP**	**LBP**	**LBP**	**LBP**	**LBP**	**LBP**	**LBP**	**LBP**	**Neck**	**LBP**	**LBP**	**LBP**	**LBP**	**LBP**
Socio demo-graphic	**Age**				÷	÷	÷		+ [a]		+	+	÷	÷	÷ [a]	+ [a]	
	Gender				÷	÷	÷				÷	+	÷	÷		÷ [a]	
	BMI										+	+		+			
	Smoking					÷								÷			
	Alcohol	÷ [a]												÷			
	Caffeine	÷ [a]															
	Civil status															÷ [a]	
	Origin				÷												
	Education					÷	+				÷	÷		÷	÷ [a]	÷ [a]	
	Social class						÷										
Pain	**Baseline intensity**	+ [a]			÷		+			+	+	÷		+	+ [a]	+ [a]	
	Baseline duration	+ [a]										+	÷	÷		+ [a]	
	Previous episodes	+ [a]			÷	÷						÷	÷		+ [a]	+ [a]	
	Associated symptoms	+ [a]															
	Duration of previous episodes													+			
	Permanent pain at nigth				÷												
	Pain increased by coughing				+												
	Pain increased by back movement				÷												
	Pain worse when standing				÷												
	Pain worse when lying down				+												
	Pain on passive movements				÷												
	Pain radiation					÷	+				÷		÷			+ [a]	
	Neurological signs					÷							÷				
	Onset (sudden)															÷ [a]	
	Sensory pain													+			
	Affective pain													+			
	Multiple-pain sites	+ [a]					+					+					
	Bothersomeness						+										

a: Only adjusted estimates presented

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Supplementary Material S1 (continued): Potential prognostic factors for disability assessed in the included studies. A plus sign indicates a statistically significant association between the given factor and the outcome. A minus sign indicates a non-significant association.

	Prognostic factor	Boardman	Boersma	Childs	Coste	Grotle, 2007	Grotle, 2010	Hancock	Hendrick	Heneweer	Karjalainen	Leaver	Lonmberg	Melloh	Sieben	Swinkels-Meewisse	Van der Windt
	Pain site	Head	Back or neck	LBP	LBP	LBP	LBP	LBP	LBP	LBP	LBP	Neck	LBP	LBP	LBP	LBP	LBP
Functional status at baseline	Forward lumbar bending (ROM[b])					÷							÷				
	Scoliosis												÷				
	Disability				+		+			÷ [a]	+	+		÷		÷ [a]	
	Physical activity								÷					÷		+ [a]	
	Participation																
	General health				+				÷ [a]		÷	+					
	Limitations physical				÷									+			
	Disability days last month					+											
Work related	Employed at baseline				÷		+					+					
	Changed work status											÷					
	Physically demanding work				÷						÷		÷	+			
	Job unsatisfaction				÷	÷	÷				÷			+			
	Resigned attitude towards the job													+			
	Uncertainty													÷			
	Organization													÷			
	Interruptions													÷			
	Concentration													÷			
	Time pressure													÷			
	Ergonomics													÷			
	Emotions (job related)													÷			
	Resources (job related)													÷			
	Social support at work													+			
	Compensation status				+							÷					
	Job difficulty				÷												
	Pain onset at work												+				
	Sick leave due to pain						+				÷		÷	÷			
	Past sick leave for pain											+					

a: Only adjusted estimates presented

b: Range of motion

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Supplementary Material S1 (continued): Potential prognostic factors for disability assessed in the included studies. A plus sign indicates a statistically significant association between the given factor and the outcome. A minus sign indicates a non-significant association.

	Prognostic factor	Boardman	Boersma	Childs	Coste	Grotle, 2007	Grotle, 2010	Hancock	Hendrick	Heneweer	Karjalainen	Leaver	Lonnberg	Melloh	Sieben	Swinkels-Meewisse	Van der Windt
	Pain site	**Head**	**Back or neck**	**LBP**	**LBP**	**LBP**	**LBP**	**LBP**	**LBP**	**LBP**	**LBP**	**Neck**	**LBP**	**LBP**	**LBP**	**LBP**	**LBP**
Psychological	Psychiatric disorder				÷												
	Anxiety	+ [a]					+										
	Depression	+ [a]					+							+			
	Emotional distress					+											÷ [a]
	Fear of pain						+										
	Fear of movement									÷						+ [a]	
	Fear avoidance		?			÷	+		÷ [a]	÷ [a]							÷ [a]
	Coping						÷			÷							
	Catastrophising						+							+			÷ [a]
	Somatisation													+			÷ [a]
	Perceived risk of not recovering										+						
	Expectation regarding the effectiveness of treatment										÷						
	Social functioning				÷												
	Vitality				÷												
	Physical problems				÷												
	Mental health				÷							+		+			
Other	Prescription of bed rest				÷												
	Prescription of sick leave				÷												
	Recruitment group					÷	÷										
	Sleeping/relaxation medication					÷											
	Pain medication					÷						+					
	Prior low back surgery				÷												
	Other co morbidity				÷												
	"Clinical prediction rule"			+				+									
	ALBPSQ* / CPG[d]				+		+			÷ [a]							

a: Only adjusted estimates presented

c: GP, chiropractor or physiotherapist.

d: Acute low back screening questionnaire.

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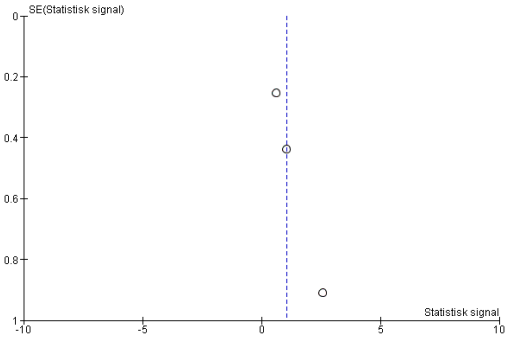
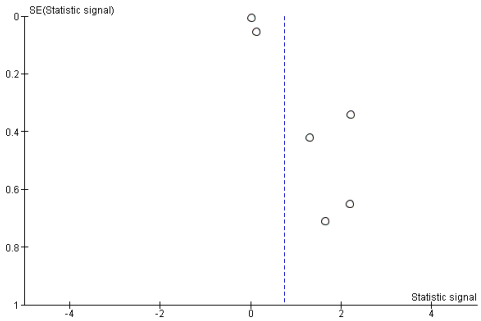
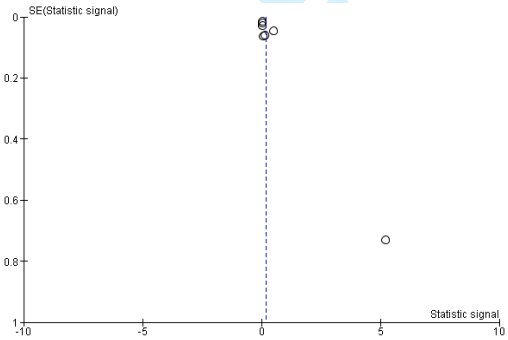
Supplementary Material S2: Funnel plots of studies included in the meta-analyses.



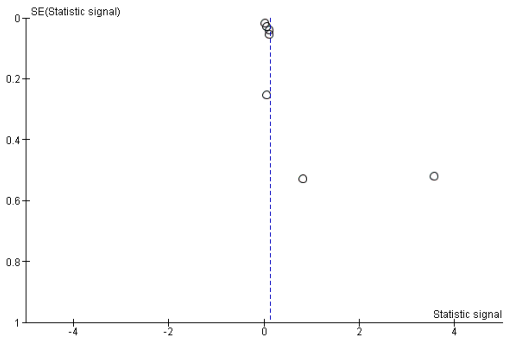
S2A: Multiple-site pain



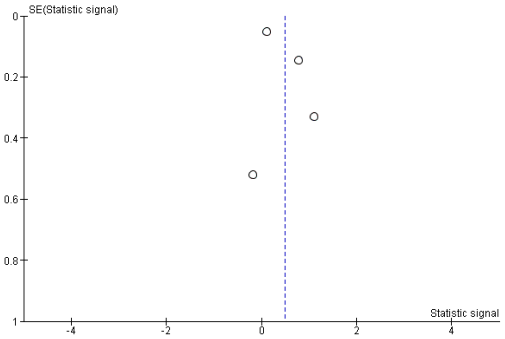
S2B: Higher pain severity



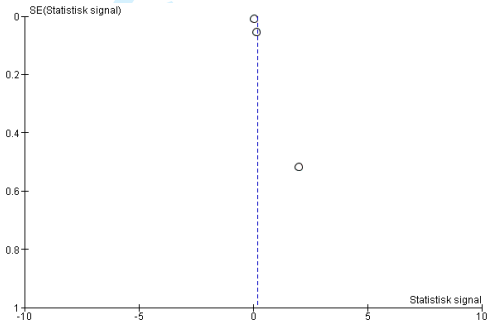
S2C: Disability



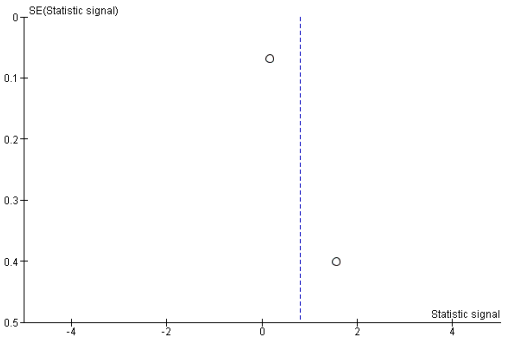
S2D: Higher age



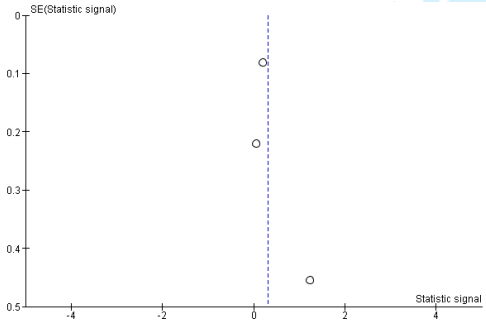
S2E: Previous episodes



S2F: Longer duration



S2G: High level anxiety



S2H: Depression

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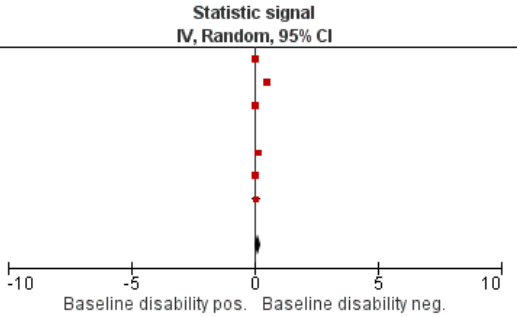
Supplementary Material S3: Sensitivity analysis omitting studies with different effect value.

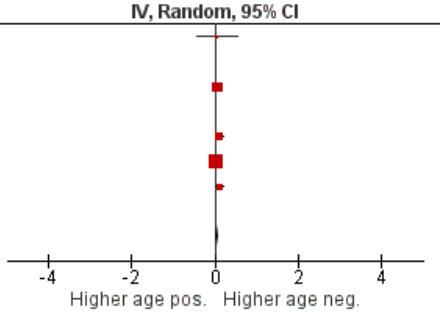
Study or Subgroup	Statistic signal	SE	Weight	Statistic signal IV, Random, 95% CI
Coste J., 2004	0.03	0.016	18.3%	0.03 [-0.00, 0.06]
Grotle M, 2010	0.51	0.048	16.2%	0.51 [0.42, 0.60]
Heneweer H., 2007	0.039	0.03	17.6%	0.04 [-0.02, 0.10]
Karjalainen K., 2003	5.22	0.73	0.0%	5.22 [3.79, 6.65]
Leaver A.M., 2013	0.16	0.061	15.0%	0.16 [0.04, 0.28]
Melloh 2013	0.05	0.02	18.1%	0.05 [0.01, 0.09]
Swinkels-Meewisse I, 2006	0.06	0.063	14.8%	0.06 [-0.06, 0.18]
Total (95% CI)			**100.0%**	**0.14 [0.03, 0.24]**

Heterogeneity: Tau² = 0.02; Chi² = 94.45, df = 5 (P < 0.00001); I² = 95%
Test for overall effect: Z = 2.55 (P = 0.01)



Study or Subgroup	Statistic signal	SE	Weight	Statistic signal IV, Random, 95% CI
Grotle M, 2010	0.05	0.253	0.7%	0.05 [-0.45, 0.55]
Grotle M., 2007	0.82	0.52968	0.0%	0.82 [-0.22, 1.86]
Hendrick P., 2013	0.062	0.03	27.1%	0.06 [0.00, 0.12]
Karjalainen K., 2003	3.57	0.52	0.0%	3.57 [2.55, 4.59]
Leaver A.M., 2013	0.11	0.041	18.4%	0.11 [0.03, 0.19]
Sieben J.M., 2005	0.02	0.018	41.7%	0.02 [-0.02, 0.06]
Swinkels-Meewisse I, 2006	0.11	0.054	12.2%	0.11 [0.00, 0.22]
Total (95% CI)			**100.0%**	**0.06 [0.02, 0.10]**

Heterogeneity: Tau² = 0.00; Chi² = 6.21, df = 4 (P = 0.18); I² = 36%
Test for overall effect: Z = 2.80 (P = 0.005)



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Prognostic Factors for Disability and Sick Leave in Patients with Sub-acute Non-malignant Pain: A systematic review and meta-analysis of cohort studies

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Prognostic factors for disability and sick leave in patients with sub-acute non-malignant pain: A systematic review and meta-analysis of cohort studies

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Abstract

Objective: This systematic review aims to identify generic prognostic factors for disability and sick leave in sub-acute pain patients.

Setting: General practice and other primary care facilities.

Participants: Adults (> 18 yrs) with a sub-acute (≤ 3 month) non-malignant pain condition. Eligibility criteria were cohort studies investigating the prediction of disability or long-term sick leave in adults with a sub-acute pain condition in a primary care setting. Nineteen studies were included, referring to a total of 6,266 patients suffering from pain in the head, neck, back, and shoulders.

Primary and secondary outcome measure: The primary outcome was long-term disability (> 3 months) due to a pain condition. The secondary outcome was sick leave, defined as "absence from work" or "return-to-work"

Results: Pubmed, Embase, CINAHL, and PEDro databases were searched from 16 January 2003 to 16 January 2014. Data were combined using random effects models, and quality of evidence was presented according to the GRADE WG recommendations. Four factors were found to be associated with disability at follow-up for at least two different pain complaints. Due to insufficient studies, no generic risk factors for sick leave were identified.

Conclusion: Multiple-site pain, high pain severity, older age, and baseline disability were identified as potential prognostic factors for disability across pain sites. Anxiety and depression were not associated with disability in patients with sub-acute pain, indicating that these factors may not play as large a role as expected in developing disability due to a pain condition. Quality of evidence was low, implying that confidence in the estimates is low. Large prospective prognostic factor studies are needed with sufficient study populations and transparent reporting of all factors examined.

Trial registration: PROSPERO: CRD42014008914

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Strength and limitations of this study

- This systematic review provides new knowledge on risk factors across pain sites, which may help physicians and researchers when initial referral decisions are made.
- The review also provides a solid foundation for planning future high-quality studies on risk factors for poor outcomes in pain patients.
- The protocol for the systematic review was registered beforehand in PROSPERO and reported according to the PRISMA statement, with the quality of the evidence judged as recommended by the GRADE Working Group.
- The review is based primarily on observational cohort studies on prognostic factors and thus the quality of evidence is low.

Key words: Prognostic factors, early detection, pain, disability, sick leave, primary care

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INTRODUCTION

Pain is the most common reason patients consult general practice,[1] and long-term disability and sick leave due to a pain condition are associated with huge negative consequences for the individual and for society.[2] It would be both costly and unnecessary, however, to offer specialized treatment to all patients presenting in primary care with a pain condition; despite its frequency, pain is in most cases a temporary phenomenon.[3] Still, a small group of patients will develop chronic or recurrent pain causing long-term disability and sick leave. It is estimated that approximately 3-10% of patients with acute pain develop a chronic pain condition.[3, 4] Chronic pain conditions are associated with social and family problems, loss of work, and loss of self-esteem and integrity.[5-7] Moreover, chronic pain is often associated with other symptoms or comorbidities like fatigue, concentration and memory problems, sleep disorders, depression, and anxiety.[5] Once pain has become chronic, treatment is complex and difficult.[2] Thus, early identification of pain patients at high risk of developing long-term problems would offer a great opportunity for reducing cost and suffering associated with long-term disability and sick leave because optimal care could be initiated at an early stage.

Most pain research focuses on one specific pain site (e.g., low back or shoulder pain[8, 9]). As a result, prognostic factor research is normally conducted on each site separately.[8] For example, substantial prognostic factor studies on back pain have been carried out, with several systematic reviews reporting prognostic factors for back pain.[10-14] However, this single-site approach limits clinical applicability for the general practitioner because most pain patients have pain at more than one anatomical location.[9, 15] Factors that have predictive value across different pain sites (i.e., generic factors) may exist,[8] but few attempts have been made to explore prognostic factors across pain sites.[8, 16]

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To our knowledge, no systematic review has performed a meta-analysis of prognostic factors across pain sites in patients with sub-acute pain. However, such an analysis would likely assist clinicians in identifying patients at high risk of developing disability, thereby allowing resources to be concentrated on those who are most in need of further attention.

This systematic review was conducted as part of a national Danish '*Health Technology Assessment*'(HTA) aimed to identify possibilities for early identification and timely treatment for pain patients across pain-sites with relevance to a broad range of stakeholders in Denmark.[17] The specific aim of the evidence synthesis was to identify potential factors for the development of long-term disability or sick leave in patients with sub-acute, non-malignant pain in primary care.

METHODS

The review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[18] on the basis of a predefined protocol available from the International Prospective Register of Systematic Reviews (PROSPERO: CRD42014008914).

Data sources and searches

Studies were identified via a systematic literature search in the following databases: PubMed, Embase, CINAHL, and PEDro. Additional studies were identified through experts and through review of the included studies´ reference lists. The following search terms were used: "Pain," "Prognosis," "Predictor," "Prognostic factor," "Primary Health Care," "General Practice," and "Family Practice." The search string tailored for PubMed database is presented below:

Search((("Pain"[Mesh]) OR "Chronic Pain "[Mesh] OR "persistent pain")) AND (("Prognosis" [Mesh]) OR "Outcome Assessment (Health Care)" [Mesh] OR predict* OR prognost* AND

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((English[lang] OR Danish[lang] OR Norwegian[lang] OR Swedish[lang] AND adult[Mesh]))) AND (((“Primary Health Care” [Mesh]) OR “General Practice” [Mesh]) OR “Family Practice” [Mesh] OR GP OR “primary care”). Filters: Published in the last 10 years; English; Danish; Norwegian; Swedish; Adult: 19+years. (full search is available on request). As part of the search and selection strategy, according to the HTA protocol, the major outcome was long-term disability (> 3 months) due to a pain condition. A secondary outcome was sick leave, defined as “absence from work” or “return-to-work”. The search was restricted to identify studies published in English, Danish, Norwegian, or Swedish between 16 January 2003 and 16 January 2014.

Study selection

Studies were eligible for inclusion if they met the following criteria: prospective cohort study (incl. randomized controlled trials), with at least 3 months' follow-up investigating the prediction of long-term disability and/or sick leave in adults (> 18 yrs) with a sub-acute (≤ 3 month) non-malignant pain condition, visiting general practitioners or other primary care facilities.Non-malignant pain condition" was defined as pain conditions of non-cancer origin. If two or more published studies originated from the same patient population, the study with the longest follow-up period was included. Two reviewers (GHV and MSP) independently assessed abstracts and full-text articles for eligibility, and disagreement was solved by a third reviewer (LØ).

Data extraction and quality assessment

Two review authors (GHV and MSP) independently performed data extraction using a customized data extraction form. To summarize the evidence following the systematic review in the HTA, we applied the "Grading of Recommendations Assessment, Development, and Evaluation" (GRADE) approach for rating quality of evidence (i.e., our confidence in the estimates). [19] Because we anticipated that the evidence base would come from cohort studies the GRADE approach for

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prognostic factor research[20] was applied. The risk of bias in the individual studies was assessed by two reviewers (GHV and MSP) using the Quality in Prognosis Studies tool (QUIPS).[21] The overall risk of bias for each of the studies was judged as: 1) low if there were a low risk of bias in all key domains, 2) unclear risk of bias if there were an unclear risk of bias for one or more key domains, and 3) high risk of bias if there were a high risk of bias for one or more key domains.[22] Disagreement was resolved by consensus. Publication bias was explored by funnel plots.

Data synthesis and analysis

If a baseline factor was associated with outcomes at follow-up in two or more studies of different pain sites, it was considered a "possible prognostic" factor and the results were combined and subsequently presented as part of the evidence profile. When data were available in different formats, data from the "fully adjusted" analyses were given preference and included in the meta-analysis. The studies in the meta-analyses were heterogenic regarding statistical methods. Hence, it was not possible directly to compare the results from the original studies. In order to assed the statistical power between a prognostic factor and outcome Fishers z-transformation was used. From each cohort study, the "statistical signal" (The "Wald-test"—the ratio between signal and noise) was derived from the effect size and the standard error of the estimate (SE). These were subsequently handled using Fisher's z-transformation.[23] This z-transformation was used to communicate the statistical power for any given association (i.e., correlation) between a given prognostic factor and an outcome. In one study the outcome was "absence of disability" as opposed to "disability". Thus the effect estimate (HR: 0.97) was reversed (HR: 1.03) before transformed into logscale and entered in RevMan.[24]

Summary estimates of associations across studies were derived from random effects meta-analysis, anticipating clinical heterogeneity, with modelling allowing for differences in the association from study to study.[25]

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Heterogeneity across studies was statistically assessed using the Q-test and quantified by the inconsistency (I^2) index.[26] I^2 represents the percentage of total variation across studies attributable to heterogeneity rather than (statistical) chance.[27] In cases with substantial heterogeneity across studies ($I^2 > 50\%$), the robustness of the results was checked using the "fixed effects" model. A result was considered robust if the point estimate for "fixed effects" was within the confidence interval of "random effects"; as a consequence, the risk of "small-study" bias was considered to be high if the point estimate was outside the confidence estimate. If this was the case, the evidence for the given prognostic factor was downgraded due to inconsistency. In order to explore the robustness of the pooled estimates sensitivity analyses were conducted in cases were three or more studies in the meta-analysis had similar effect value. Meta-analyses were performed using Review Manager (RevMan) provided by the Cochrane Collaboration.[28] A two-sided P-value of ≤ 0.05 (and 95% confidence interval excluding the null) was considered to be statistically significant in all analyses. For each outcome, we prepared an evidence profile based on the GRADE profiler software.[29]

RESULTS

Results of the literature search

The search in the selected databases returned a total of 3,533 references. A total of 32 references were identified through the additional search. After removing duplicates, 1,841 references remained. The 1,841 references were screened for eligibility, and 1,641 records were excluded. The remaining 200 articles were read in full-text; of these, 181 articles were excluded because they did not satisfy the inclusion criteria. A full list of excluded studies and the reason for exclusion is available from the authors upon request. A total of 19 studies satisfied the inclusion criteria and were included in the systematic review. However, only 11 were eligible for inclusion in the meta-analysis; the other 8 studies were excluded from the quantitative synthesis due to: 1) inadequate statistical analyses,[3, 30] 2) the factors studied were assessed in only one study,[31-33] or 3) the factors

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studied were assessed for only one pain site (e.g., only studies on back pain).[34-36] See **Figure 1** for a flow diagram of the included studies.

Figure 1: Flow-diagram of the literature search

Included studies

The 19 included studies consisted of 17 cohort studies and two randomized controlled trials. Fourteen of the studies referred to patients with back pain[4, 24, 30-32, 34, 35, 37-43] and one referred to patients with pain in the neck or back.[3] Two studies referred to patients with neck pain,[33, 44], one referred to patients with headache,[45] and one referred to patients with shoulder or back pain.[36] From this last-mentioned study, only the cohort with back pain was included in the synthesis because the cohort with shoulder pain comprised both patients with sub-acute pain and patients with chronic pain.[36] Outcome measures were disability in 16 studies,[3, 4, 24, 30, 34-45] sick leave in three studies,[3, 33, 42] and return-to-work in two studies.[31, 32]

Characteristics of the 19 included studies are presented in Table 1. The total number of patients included in the 19 studies was 6,266. The median number of patients per study was 184 (range: 56–2,662). In eleven of the studies, more women than men participated. Age was reported in 18 studies, with a median average of 42 years (range: 34–52 years). Pain duration at baseline was reported in eight studies with a median average of 12.6 days (range: 1–27 days). Follow-up period ranged from 3 months to 22 years (with a median of 9 months). Most of the studies recruited patients from general practice.[3, 4, 24, 30, 32-34, 36-39, 41-43, 45] The remaining studies recruited patients from physiotherapy or chiropractor clinics[35, 40, 44] and workers compensation board.[31]

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Table 1: Characteristics of the included studies

[A]: 2,662 patients were included in the study but only 730 respondents are included in the relevant analyses.

Author (publication year)	Country of origin	Participant eligibility criteria	No. of participants at baseline	Age at baseline Mean (SD)	Pain site	Recruitment	Outcome measure	Follow up (months)
Boardman HF. (2006)	UK	Adults > 18 years.	730[A]	52 (18-90)[B]	Head	GP[D]	Disability (Migraine Disability Assessment)	12
Boersma K. (2005)	Sweden	No information	363	47 (10.2)	Back or neck	GP[D]	Disability (Örebro Musculoskeletal Pain Screening Questionnaire) and sick leave (> 15 days)	12
Childs J. (2004)	US	Patients 18 to 60 years; with a primary symptom of LBP, with or without referral into the lower extremity; and an Oswestry Disability Questionnaire (ODQ) score of at least 30%.	131	33.9 (10.9)	LPB[C]	Physiotherapy	Disability (Modified Oswestry Disability Index)	6
Coste J. (2004)	France	Patients > 18 years, self-referring to GP (n: 40) or rheumatologists (n: 7) for a primary complaint of LBP with pain duration < 72 hours and without radiation below the gluteal fold	113	44.3 (13.7)	LBP[C]	GP[D]	Disability (VAS and Roland Morris Disability Questionnaire)	3
Grotle M. (2007)	Norway	Patients 18–60 years; acute LBP of less than 3 weeks duration, with or without radiating pain to the limb; and had not been treated for LBP earlier	123	37.9 (10.1)	LBP[C]	GP[D]	Disability (Roland Morris Disability Questionnaire)	12
Grotle M. (2010)	Norway	Patients consulting GP with non-specific LBP of varying duration and localization	258	46 (9)	LBP[C]	GP[D]	Disability (Roland Morris Disability Questionnaire)	12
Hancock M. (2008)	Australia	Primary complaint of pain in the area between the 12th rib and buttock crease causing moderate pain and moderate disability (measured by adaptations of items 7 and 8 of the SF-36).	240	40.7 (15.6)	LPB[C]	GP[D]	Disability (Roland Morris Disability Questionnaire)	3
Hendrick P. (2013)	New Zealand	Patients aged 18–65 years with an episode of LBP of ≤ 6 weeks, preceded by a minimum period of 3 months during which participants had not sought treatment for LBP, and no other pre-existing conditions that limited their mobility.	101	38.8 (14.6)	LBP[C]	GP[D], Physiotherapy clinics and newspaper advertisement	Disability (Roland Morris Disability Questionnaire)	3
Heneweer H. (2007)	Holland	Patients aged 21–60 years with sufficient knowledge of the Dutch language to complete the questionnaires.	56	42 (9.2)	LBP[C]	Physiotherapy clinics	Disability (recovery yes/no and sick leave yes/no)	3

[B]: Median (range).
[C]: Low back pain
[D]: General practitione

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Table 1(continued): Characteristics of the included studies

Author (publication year)	Country of origin	Participant eligibility criteria	No. of participants at baseline	Age at baseline Mean (SD)	Pain site	Recruitment	Outcome measure	Follow up (months)
Karjalainen K. (2003)	Finland	25 to 60-year-old patients having disabling LBP for the preceding 4 to 12 weeks.	164	44 (8.8)	LBP[C]	GP[D]	Disability (Oswestry Disability Index) and sick leave (1: 0 days, 2: 1–30 days, 3: > 30 days)	12
Leaver AM. (2013)	Australia	Patients aged 18–70 years with a new episode of non-specific neck pain.	181	38.8 (10.7)	Neck	Physiotherapy and chiropractor clinics	Disability (Neck Disability Index)	3
Lonnberg F. (2010)	Denmark	Patients seeking care for the first time regarding an episode of LBP.	78	57[E]	LBP[C]	GP[D]	Disability (Limitations- no further information)	264
Melloh M. (2013)	New Zealand	Patients 18–65 years.	315	34.9 (12.6)	LBP[C]	GP[D]	Disability (Oswestry Disability Index)	6
Schultz IZ. (2004)	Canada	Participants 18–60-year old remaining off work 4–6 weeks post-injury (sub-acute group) or remaining off work 6–12 months after injury (chronic).	253	40.3 (11.4)	LBP[C]	Workers´Compensation Board	Return-to-work status	3
Sieben JM. (2005)	Holland	Patients aged 18–60 years with a new episode of non-specific LBP.	222	No information	LBP[C]	GP[D]	Disability (Graded Chronic Pain Scale)	12
Storheim K. (2005)	Norway	Patients sick listed from a permanent job and receiving between 50% and 100% compensation for non-specific LBP for 8–12 weeks, but with no sick leave due to LBP during a period of 12 weeks before the current sick-listing period; aged between 20 and 60 years.	93	RTW:40.5 (9.8) NRTW: 42.3 (11.7)	LBP[C]	GP[D] and National Insurance Offices	Return-to-work status	12
Swinkels-Meewisse, (2006)	Holland	Patients aged 18–65 years having an episode of nonspecific LBP independent of radiation.	374[F]	42.4 (11.3)	LBP[C]	GP[D] and Physiotherapy clinics	Disability (Roland Morris Disability Questionnaire)	6
Van der Windt DA. (2007)	Holland	Patients 18–65 years with a duration of LBP < 12 weeks at presentation, or exacerbation of mild symptoms of back pain.	171 (Back group)	42.0 (12.0) (back group)	LBP[C]	GP[D]	Disability (Roland Morris Disability Questionnaire)	3
Vos CJ. (2008)	Holland	Patients > 18 years with neck pain < 6 weeks.	187	40.7 (14.1)	Neck	GP[D]	Sick leave (> 7 days)	12

[E]: Median (range)
[F]: 555 Participants are included in the trial, but data regarding disability were available from only 374 of the participants

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Risk of bias within studies

Risk of bias in the included studies was assessed using QUIPS (figure 2). Overall, the agreement between the two assessors (GHV and MSP) on the different aspects of Risk of Bias assessment was 85.5% (weighted Kappa 0.49), which corresponds to a moderate degree of agreement. In all cases, any disagreement between the assessors was settled by consensus discussion. The domain "Study Confounding" carried the highest risk of bias. In this domain, three studies were judged as having high risk of bias, and eleven studies were assessed as having a moderate risk of bias. The high number of studies judged as having a high or moderate risk of bias in this domain was due mainly to insufficient description of the factors that were included in the multivariable analysis. Based on the judgement of the six domains, eleven studies were judged to have low risk of bias,[4, 24, 32, 34-36, 39, 41-44] three studies had moderate risk of bias,[33, 37, 38] and five studies had high risk of bias.[3, 30, 31, 40, 45] Publication bias was assessed by funnel plots for all eight prognostic factors. No obvious asymmetry was found (Supplementary Material S2).

Figure 2: Risk of bias of the six domains in QUIPS

Prognostic factors for disability

Prognostic factors for disability were assessed in 16 studies.[3, 4, 24, 30, 34-45] A total of 81 factors were assessed in the unadjusted analysis (Supplementary Material S1). Of the 81 factors assessed, 53 were included in the multivariable analysis of the primary studies. Of these factors, the following eight were assessed in two or more studies and for at least two different pain sites: multiple-site pain, higher baseline pain severity, previous pain episodes, older age, longer baseline pain duration, baseline disability, anxiety, and depression. A total of eleven studies were included in the meta-analysis (figure 3 and 4).[4, 24, 37-45] The association between multiple-pain sites and disability at follow-up was assessed in three studies, including patients with headache,[45] low back pain,[41] and

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neck pain[44] (figure 3a). The combined estimate showed a statistically significant association between multiple-pain sites at baseline and risk of disability at follow-up (p = 0.010). The test for heterogeneity was I^2 =57%. However, "fixed effects" did not change the result significantly.

The association between higher pain severity at baseline and disability was assessed in six studies including patients with headache[45] and low back pain[37, 38, 40-42] (figure 3b). The combined estimate showed a statistically significant association between higher baseline pain severity and disability (p < 0.001). I^2 was 93% and the result was not robust when using the "fixed effects" model, so small-study bias is therefore likely. Consequently, the quality of evidence was downgraded due to inconsistency. The association between baseline disability and disability at follow-up was examined in seven studies relating to patients with neck pain[44] and low back pain[24, 38, 40-43] (figure 3c). Baseline disability was associated with a higher risk of disability at follow-up (p = 0.007). I^2 was 96%. The "fixed effects" model did not change the result significantly.The association between higher age and the risk of disability was assessed in seven studies concerning patients with neck pain[44] and low back pain[4, 37-39, 41, 42] (figure 3d). A significant association was seen between higher age and risk of disability (p = 0.04). I^2 was 89%. The "fixed effects model" did not change the result significantly. A dose-response effect was observed; an increase by 10 years of age was associated with a higher risk of disability than was a one-year increase. No statistical significant associations between disability and previous pain episodes (p = 0.08; figure 4a), longer baseline pain duration (p= 0.12; figure 4b), anxiety (p = 0.25; figure 4c), or depression (p = 0.14; figure 4d) were observed. The "fixed effects" model did not change the results notably for the four potential prognostic factors in figure 4.

Sensitivity analyses were conducted for the results of the meta-analysis presented in figure 3C and 3D. In figure 3C the study by Karjalainen et al. was omitted and in figure 3D the studies by Grotle et al, 2007 and Karjalainen et al. were omitted. The statistical signal did not change substantially after selective omitting studies with different effect value (Supplementary material S3

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Figure 3: Forest plots of the association between potential prognostic factors and long-term disability in patients with a sub-acute pain condition. 3A: Adjusted for: Age [41, 45], sex [41, 45], baseline disability [41], recruitment [41], factors adjusted for not described [44]. 3B: Adjusted for: Age [41, 45], sex [41, 45], baseline disability [41], recruitment [41], factors adjusted for not described [37, 40, 42].3C: Adjusted for: Age [41, 43], Sex [41, 43], BMI [43], duration (hours) between pain debut and inclusion [24], job status [24], previous spine surgery [24], compensation status [24], self rated health status [24], factors adjusted for not described [38, 40, 42, 44].3D: Adjusted for sex [4, 39], job [39], BMI [39], Baseline pain severity [39], recruitment [41], depression [39], anxiety [39], fear avoidance [39], activity level prior current pain episode [39], baseline disability [38, 41], factors adjusted for not described [37, 42, 44].

Figure 4: Forest plots of the association between potential prognostic factors and long-term disability in patients with a sub-acute pain condition. 4A: Adjusted for: age [4, 45], sex [4, 45], baseline disability [38], factors adjusted for not described [37]. 4B: Adjusted for: Age [43, 45], sex [43, 45], BMI [43], baseline disability [38]. 4C: Adjusted for: Age [41, 45], sex [41, 45], recruitment [41], baseline disability [41]. 4D: Adjusted for: Age [41, 43, 45], sex [41, 43, 45], BMI [43], recruitment [41], baseline disability [41].

Quality of evidence for the risk of developing disability

The quality of evidence for the potential prognostic factors for the risk of developing disability is presented in table 2. All the included studies in the meta-analysis were phase 1 studies, which are characterized as predictive modelling studies or explanatory studies conducted to generate a hypothesis.[20] Thus, the quality of evidence was low as a starting point. Reasons for up- or down-grading the quality of evidence for the given prognostic factor are described below in table 2. The quality of evidence was graded as either low or very low and thus the validity of the results is low.

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Table 2: GRADE evidence profile of the potential prognostic factors for long-term disability in patients with a sub-acute pain condition.

Prognostic factors (no. of studies)	Phase	Quality assessment						Summary of findings		
		Limitations	Inconsistency	Indirectness	Imprecision	Publication bias	Other considerations	No. of participants included in the analyzes	Estimated "Effect size"	Overall quality
Multiple-site pain [41, 45, 46] (3)	1	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected [A]		1,164	0.07 (0.02;0.13) p=0.01	Low ⊕⊕⊖⊖
High baseline pain severity [37, 38, 40-42, 45] (6)	1	Serious limitation (-1)	Serious inconsistency [B] (-1)	No serious indirectness	No serious imprecision	Detected [C] (-1)	Dose-respons effect detected (+1)	1,711	0.04 (0.02;0.06) p<0.0001	Very low ⊕⊖⊖⊖
Baseline disability [24, 38, 40-44] (7)	1	No serious limitations	No serious inconsistency [I]	No serious indirectness	No serious imprecision	Undetected [A]		1,263	0.01 (0.00;0.02) p=0.007	Low ⊕⊕⊖⊖
Older age [4, 37-39, 41, 42, 44] (7)	1	No serious limitations	No serious inconsistency [F]	No serious indirectness	No serious imprecision	Detected (-1)[G]	Dose-respons effect detected (+1)	1,296	0.01 (0.00;0.02) p=0.04	Low ⊕⊕⊖⊖
longer pain duration [38, 43, 45] (3)	1	Serious limitations (-1)	No serious inconsistency	No serious indirectness	No serious imprecision	Detected (-1)[H]		1,236	0.01 (0.00;0.03) p=0.12	Very low ⊕⊖⊖⊖
Previous episodes [4, 37, 38, 45] (4)	1	Serious limitation (-1)	No serious inconsistency [D]	No serious indirectness	Serious imprecision (-1)	Detected [E] (-1)		1,353	0.03 (0.00;0.06) p=0.08	Very low ⊕⊖⊖⊖
Anxiety [41, 45] (2)	1	Serious limitations (-1)	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected [A]		988	0.07 (-0.05;0.18) p=0.25	Very low ⊕⊖⊖⊖
Depression [41, 43, 45] (3)	1	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected [A]		1,157	0.02 (-0.01;0.05) p= 0.14	Low ⊕⊕⊖⊖

A: The association between the prognostic factor and disability is assessed only in the trials included in the meta-analyses.
B: Results of the meta-analyses were not robust when using the "fixed-effects" model.
C: Nine studies assessed the association between high baseline pain and disability at follow-up, but only six studies reported the results in the adjusted analyses.
D: Inconsistency in the results between the study by Boardman et al. and the study by Swinkels-Mewisse et al. can be explained by differences in the reporting of previous episodes. In the study by Swinkels et al., the participants could have experienced pain once 10 years ago, whereas Bordman looks at pain episodes one or more times per. week.
E: Nine studies reported previous pain episodes in the unadjusted analyses, but only seven studies included the results in the adjusted analyses.
F: Karjalainen et al. reported the association between an increase in age by 10 years and disability, whereas the other studies reported the association between age and disability by an increase of one year.
G: Nine studies reported the association between age and disability, but only seven studies included the results in the adjusted analyses.
H: The association between baseline pain duration and disability was reported in the unadjusted analyses in five studies, but only three studies included the results in the adjusted analyses.
I: In the study by Karjalainen et al., the association between baseline disability and disability at follow-up was reported by an increase by 20 % in max score at baseline, whereas the other studies reported an increase by 1 point. This difference could be a plausible reason for the inconsistency between the results.

Prognostic factors for long-term sick leave or return-to-work

Three of the included studies had long-term sick leave as an outcome[3, 33, 42]. Two of the studies, referring to patients with pain in the neck[33] and back,[42] respectively, had performed multivariable analysis. The follow-up period was three months in both studies. Long-term sick leave was defined

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as sick leave for more than 30 days in one study[42] and more than 7 days in the other.[33] Baseline disability was the only potential prognostic factor that was assessed in both studies. In the study by Karjalainen et al., however, the results were described only as being "non-significant."[42] Thus, it was not possible to present the results in a meta-analysis. In the study by Karjalainen and colleagues, factors like blue-collar work and long-term sick leave at baseline were associated with an increased risk of long-term sick leave at follow-up in patients with sub-acute back pain. Vos and colleagues found that factors like previous pain episodes, a follow-up appointment scheduled with a GP, and the GP's referring the patient to treatment and baseline disability all were associated with an increased risk of long-term sick leave among patients with acute neck pain[33]. Two studies described "return-to-work" as an outcome.[31, 32] Follow-up was 3 [31] and 12 months,[32] respectively. Both studies related to patients with back pain, so potential generic factors could not be extracted.

DISCUSSION

Four potential generic prognostic factors for developing disability following a sub-acute pain condition were identified. Risk factors across different pain sites included multiple-site pain, higher pain severity, higher age, and baseline disability. Previous pain episodes, pain duration at baseline, anxiety, and depression were not associated with the risk of disability at follow-up. Due to the limited number of studies, it was not possible to identify potential generic risk factors for long-term sick leave or return-to-work. Quality of evidence was low or very, low implying that confidence in the estimate is low.

Comparison with other studies or reviews

Despite sparse literature in this field, there is some evidence to support our findings. In concurrence with our findings, a previous review reported factors such as multiple-site pain, higher pain severity, higher age, and baseline disability as being potential prognostic factors for a poor outcome

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in patients with musculoskeletal pain.[8] A strong association between the number of pain sites and disability was also demonstrated in a previous cross-sectional study.[9] Similar, a prospective cohort study from 2008 found that the number of pain sites were a strong predictor of work disability14 years later regardless of diagnosis.[47] Furthermore, a recent systematic review found some evidence suggesting that the number of somatic symptoms and baseline severity of the condition influenced the future course in patients with medically unexplained symptoms.[48] Thus, despite the low quality of evidence of the results, we find it reasonable to believe that the factors indentified in our systematic review may act as central prognostic factors for the development of disability across pain sites. Therefore, future research should address confirming the role of these factors.

Interestingly, our review found that anxiety and depression at baseline were not associated with disability at follow-up. These findings are controversial because psychosocial factors also known as "yellow flags" are widely accepted as being key factors in the transition from acute to chronic pain conditions [49]. "Yellow flags" include depression, anxiety, catastrophic thoughts, and pain-related fear of movement/fear avoidance among others.[50, 51] Several national and international guidelines recommend that clinicians screen for the presence of these factors in the early phase[52-54]. In addition, several well-established screening tools for the risk of chronicity are based on the presence of these factors (e.g., the Orebro Musculoskeletal Pain Questionnaire,[55] the Fear-Avoidance Health Beliefs Questionnaire,[56] and the STarT Back Screening Tool[57]). Most studies, however, have not included pain duration at baseline when the importance of "yellow flags" was assessed.[16] A plausible explanation for the apparent discrepancy between our results and the widely accepted "yellow flags," therefore, could be the inclusion criteria in our review regarding short pain duration at baseline. It is likely that factors like anxiety and depression are of greater importance once pain has become chronic. Another explanation for the discrepancy could be that our review focuses on risk factors for future disability and sick leave and not on risk factors for developing a chronic pain

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condition. Nonetheless, future research should address and clarify the role "yellow-flag" factors play in the various phases of pain.

Strength and limitations

It is considered a strength in our systematic review that we followed a rigorous protocol (registered in PROSPERO) prespecifying all the outcomes and analyses; our adherence to the protocol likely strengthens the credibility of the evidence synthesis. We reported our findings as recommend by the PRISMA statement[18] and judged the quality of the evidence based on the recommendations from the GRADE Working group. We believe that the GRADE framework applied to prognostic factor research was valuable for assessing and transparently reporting the quality of the evidence of the possible prognostic factors. To our knowledge, this is the first time GRADE has been used in the evaluation of prognostic studies.

Limitations regarding the interpretation of the results from this study should be taken into consideration. A total of 14 of the 19 included studies in our review referred to patients with back pain. The high number of studies concerning patients with back pain may affect the external validity of the results to patients with pain at other sites. However, the vast majority of pain patients visiting general practice suffer from back pain, and the large number of studies on back pain included in the present review therefore reflects the distribution of patients seen in general practice.[58] Future studies assessing prognostic factors for non-spinal pain are needed. Publication bias is one of the most common biases in meta-analyses. Therefore, we conducted funnel plots to explore whether publication bias was present in our analysis. No obvious asymmetry was found. In accordance with current knowledge the use and appropriate interpretation of funnel plots are however, controversial because of questions about statistical validity, disputes over appropriate interpretation, and low power of the tests.[59] For instance, a funnel plot can be symmetrical even in the presence of

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publication bias.[59] Hence publication bias might be present in our analyses although undetected. Another common limitation in systematic reviews is the risk of selective reporting of primary study results. Our review was based primarily on observational cohort studies on prognostic factors (Phase 1 studies). Such studies harbour a high risk that non-significant findings are not reported or only included in the first (unadjusted) part of the analysis. Any non-reporting of non-significant results invites a risk that the findings in the meta-analysis were overestimated. We attempted to account for such bias due to selective outcome reporting by listing all the studies that examined a specific prognostic factor in the unadjusted analysis. If a factor was investigated in eight studies, for example, but included only in the adjusted analysis of five, the quality of the evidence was downgraded. A substantial limitation in this review was that results from original studies with different effect measures were combined in the meta-analysis. In order to interpret the clinical significance of the result of a meta-analysis it is essential that the characteristics of the effect measure are identical. However, prognostic factor studies have no standards for outcome reporting and thus the studies were by all means heterogeneous regarding statistical methods, as well as clinical and outcome heterogeneity. Hence, it was not possible to combine and compare the results from the original studies directly. In order to assess the statistical power for any given (i.e. reported) association between a prognostic factor and outcome Fishers z-transformation was used as previously suggested by Thompson S, et al.[60] This method can be considered controversial due to the difficulties interpreting the results. In order to account for this limitation, the robustness of the results was explored by sensitivity analysis. The statistical signal did not change substantially after selective omitting studies with different effect value. The robustness of the estimates in the sensitivity analysis increases the validity of the results. The meta-estimates (statistical signals) were however, low which might suggest that clinical relevance of the results is limited. These findings are not unique for this study.[41, 61] It is a general problem for prognostic factor studies. There are two plausible reasons for this: 1.important prognostic factors for disability may not have

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been identified yet or 2. tools for measurement of both risk factors and outcome might be associated with substantial measurement errors.[61] Consequently we cannot draw a strong conclusion on the clinical significance of the results.

Implications for clinical practice

No high-quality evidence was provided for any of the potential prognostic factors; therefore, no definite clinical conclusion can be made about how to identify patients at high risk of long-term disability or sick leave at an early stage in general practice. However, the empirical evidence illustrates what kind of prognostic factor research would be relevant to pursue in order to increase value and reduce waste in prognostic factor research on long-term disability among patients with sub-acute non-malignant pain.[62] It appears that multiple-site pain, high-baseline pain severity, older age, and baseline disability are associated with future disability across pain sites in sub-acute pain patients. Therefore, it may be helpful for GPs to have these factors in mind in clinical decision making.

Implications for future research on prognostic factors

Correctable weaknesses in biomedical and public health research studies can produce misleading results and waste valuable resources.[63] During the preparation of this review, it became clear that the current literature in this field falls short on a number of counts. As suggested by Ioannidis et al.,[63] this area of research also has weaknesses, such as selective reporting of results; lack of prespecified defined prognostic factors to be assessed; inadequate description of methods; inadequate or poor quality of statistical analysis; failure to distinguish between prognostic factors among patients with acute, sub-acute, and chronic pain; and lack of published studies on patients suffering from non-spinal pain. We suspect most of these limitations can be related to the absence of detailed written protocols and poor documentation of research in general.[63-66]

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Although good research ideas often yield unanticipated but valuable results, much research fails to effect worthwhile achievements. As long as the way in which research projects are prioritized for research is transparent and warranted, the disappointments should not be deemed wasteful; they are simply an inevitable feature of the way science works.[62] In order to gain further knowledge on which factors are central prognostic factors (sub-acute phase), future studies should take into account baseline pain duration at the time patients are enrolled. Future studies on prognostic factors in chronic pain should be conducted as large, prospective, registered, and protocol-based prognostic factor studies with sufficient study populations and transparent reporting of all factors studied. Once sufficient knowledge on risk factors has been obtained, documentation of effective treatment for high-risk pain patients is needed. Further, the effect of offering stratified care to pain patients based on their risk profiles should be tested in randomized controlled trials.[67]

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Contributorship statement

All authors were responsible for the design and search strategy. GHV and MSP were responsible for conducting the search. GHV, MSP and RC conducted the data analysis and produced the tables and graphs. RC provided input into the data analysis and interpretation. The initial draft of the manuscript was prepared by GHV then circulated among all authors for critical revision. All authors helped to evolve analysis plans, interpret data and critically revise successive drafts of the manuscript.

Competing interests

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None. Dr. Christensen declares, however, that he is involved in many health-care initiatives and research that could benefit from a wide uptake of this publication (including Cochrane, OMERACT, and the GRADE Working Group).

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Data sharing statement

There are no additional data available.

FIGURE LEGENDS

Figure 1: Flow diagram of the literature search
Table 1: Characteristics of the included studies
Figure 2: Risk of bias of the six domains in QUIPS
Figure 3: Forest plots of the association between potential prognostic factors and long-term disability in patients with a sub-acute pain condition
Figure 4: Forest plots of the association between potential prognostic factors and long-term disability in patients with a sub-acute pain condition
Table 2: GRADE evidence profile of the potential prognostic factors for long-term disability in patients with a sub-acute pain condition

Supplementary Material

Supplementary Material S1: Potential prognostic factors for disability assessed in the included studies. A plus sign indicates a statistically significant association between the given factor and the outcome. A minus sign indicates a non-significant association.
Supplementary Material S2: Funnel plots of studies included in the meta-analyses.
Supplementary Material S3: Sensitivity analysis omitting studies with different effect value.

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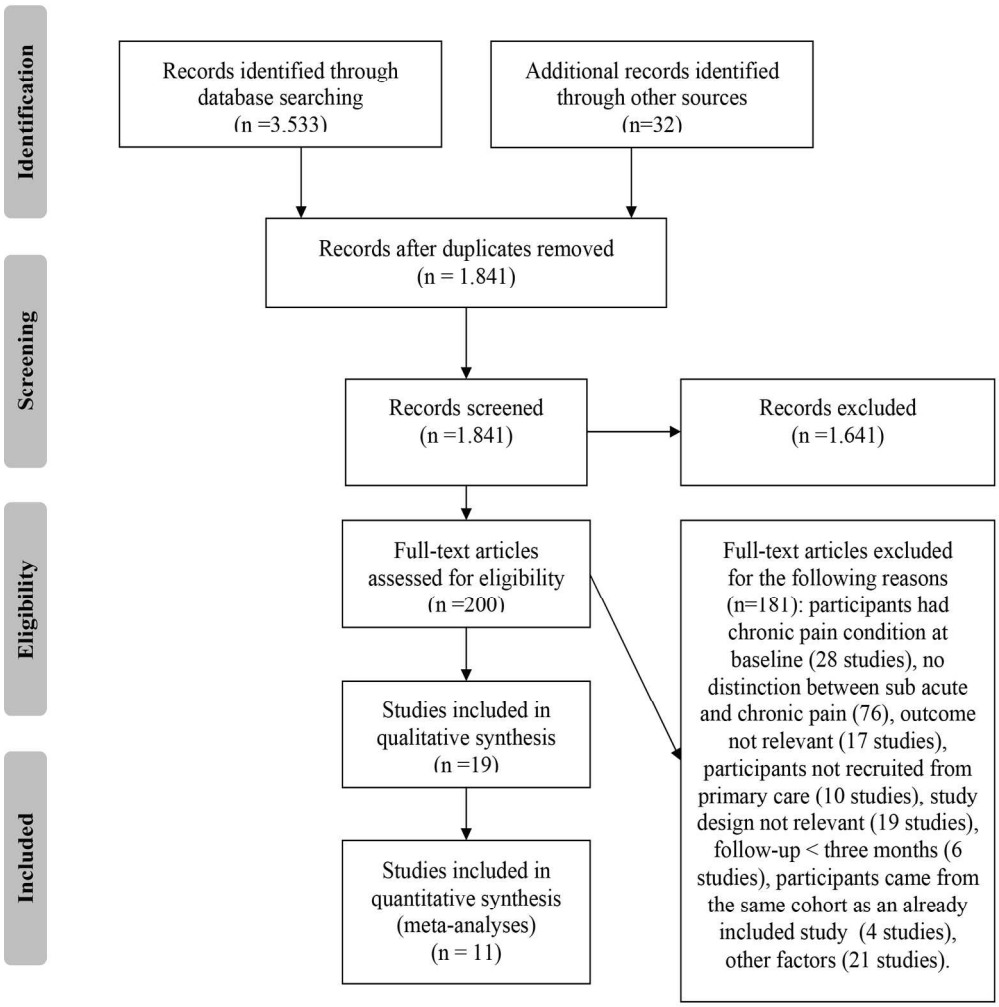

Figure 1: Flow-diagram of the literature search
173x196mm (300 x 300 DPI)

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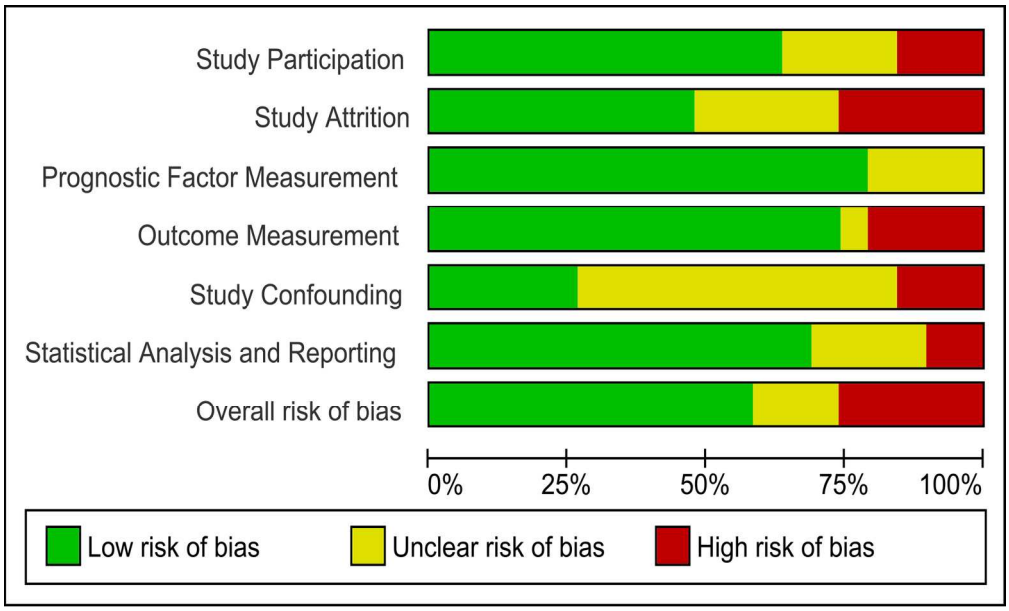

Figure 2: Risk of bias of the six domains in QUIPS
173x104mm (300 x 300 DPI)

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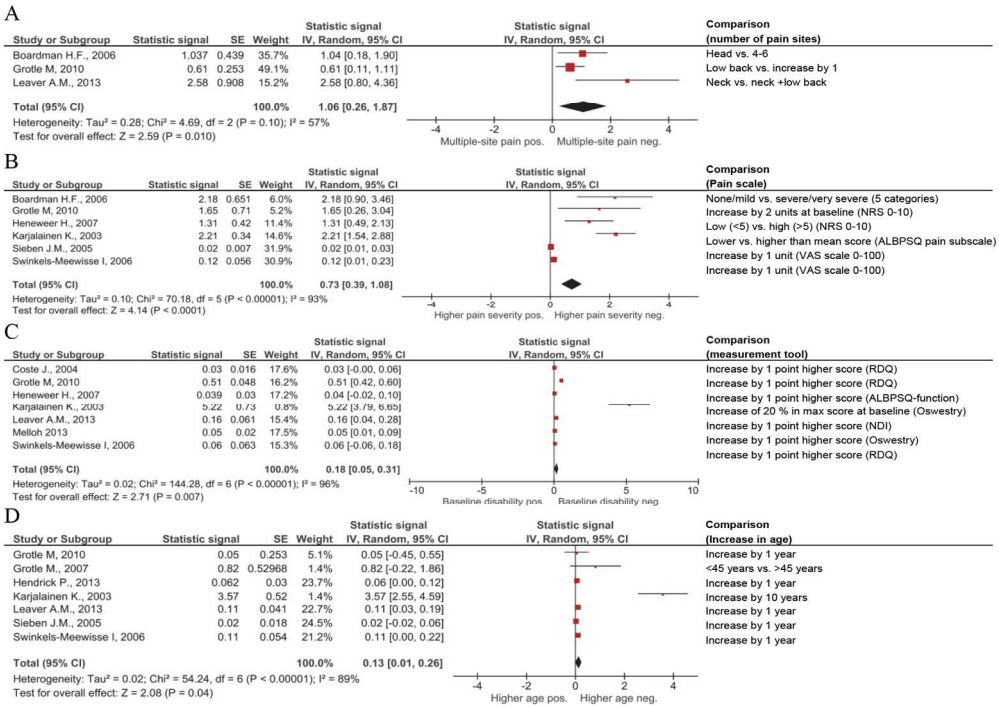

Figure 3: Forest plots of the association between potential prognostic factors and long-term disability in patients with a sub-acute pain condition. 3A: Adjusted for: Age 41, 45, sex 41, 45, baseline disability 41, recruitment 41, factors adjusted for not described 44. 3B: Adjusted for: Age 41, 45, sex 41, 45, baseline disability 41, recruitment 41, factors adjusted for not described 37, 40, 42.3C: Adjusted for: Age 41, 43, Sex 41, 43, BMI 43, duration (hours) between pain debut and inclusion 24, job status 24, previous spine surgery 24, compensation status 24, self rated health status 24, factors adjusted for not described 38, 40, 42, 44.3D: Adjusted for sex 4, 39, job 39, BMI 39, Baseline pain severity 39, recruitment 41, depression 39, anxiety 39, fear avoidance 39, activity level prior current pain episode 39, baseline disability 38, 41, factors adjusted for not described 37, 42, 44.
173x121mm (300 x 300 DPI)

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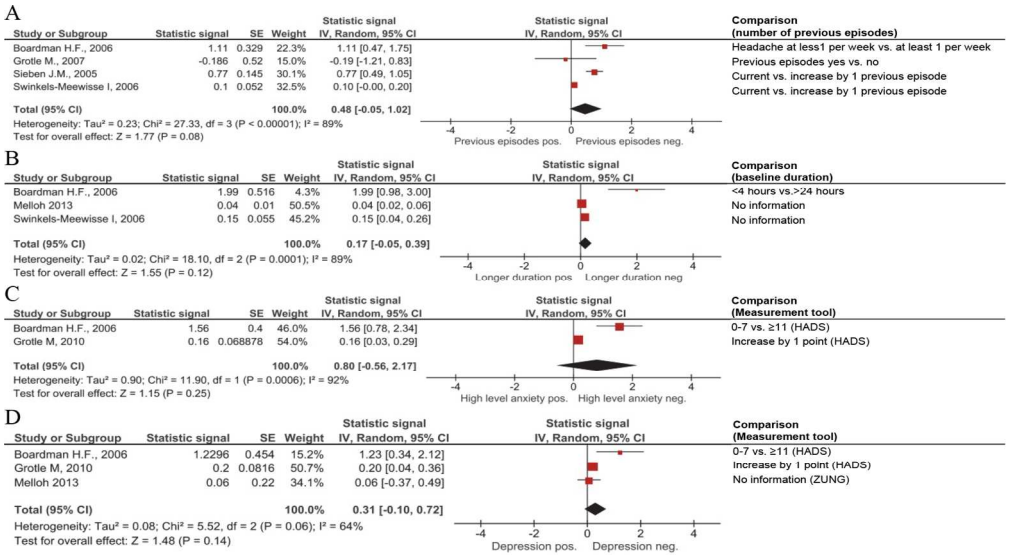

Figure 4: Forest plots of the association between potential prognostic factors and long-term disability in patients with a sub-acute pain condition. 4A: Adjusted for: age 4, 45, sex 4, 45, baseline disability 38, factors adjusted for not described 37. 4B: Adjusted for: Age 43, 45, sex 43, 45, BMI 43, baseline disability 38. 4C: Adjusted for: Age 41, 45, sex 41, 45, recruitment 41, baseline disability 41. 4D: Adjusted for: Age 41, 43, 45, sex 41, 43, 45, BMI 43, recruitment 41, baseline disability 41.

173x95mm (300 x 300 DPI)

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Supplementary material

Supplementary Material S1: Potential prognostic factors for disability assessed in the included studies. A plus sign indicates a statistically significant association between the given factor and the outcome. A minus sign indicates a non-significant association.

Prognostic factor		Boardman	Boersma	Childs	Coste	Grotle, 2007	Grotle, 2010	Hancock	Hendrick,	Heneweer	Karjalainen	Leaver	Lonnberg	Melloh	Sieben	Swinkels-Meewisse	Van der Windt
	Pain site	Head	Back or neck	LBP	LBP	LBP	LBP	LBP	LBP	LBP	LBP	Neck	LBP	LBP	LBP	LBP	LBP
Socio demo-graphic	**Age**				÷	÷	÷		+ [a]		+	+	÷	÷	÷ [a]	+ [a]	
	Gender				÷	÷	÷				÷	+	÷	÷		÷ [a]	
	BMI										+	+		+			
	Smoking					÷								÷			
	Alcohol	÷ [a]												÷			
	Caffeine	÷ [a]															
	Civil status															÷ [a]	
	Origin				÷												
	Education					÷	+				÷	÷		÷	÷ [a]	÷ [a]	
	Social class						÷										
Pain	**Baseline intensity**	+ [a]			÷		+			+	+	÷		+	+ [a]	+ [a]	
	Baseline duration	+ [a]										+	÷	÷		+ [a]	
	Previous episodes	+ [a]			÷	÷						÷	÷		+ [a]	+ [a]	
	Associated symptoms	+ [a]															
	Duration of previous episodes													+			
	Permanent pain at nigth				÷												
	Pain increased by coughing				+												
	Pain increased by back movement				÷												
	Pain worse when standing				÷												
	Pain worse when lying down				+												
	Pain on passive movements				÷												
	Pain radiation					÷	+				÷		÷			+ [a]	
	Neurological signs					÷							÷				
	Onset (sudden)															÷ [a]	
	Sensory pain													+			
	Affective pain													+			
	Multiple-pain sites	+ [a]					+					+					
	Bothersomeness						+										

a: Only adjusted estimates presented

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Supplementary Material S1 (continued): Potential prognostic factors for disability assessed in the included studies. A plus sign indicates a statistically significant association between the given factor and the outcome. A minus sign indicates a non-significant association.

	Prognostic factor	**Boardman**	**Boersma**	**Childs**	**Coste**	**Grotle, 2007**	**Grotle, 2010**	**Hancock**	**Hendrick**	**Heneweer**	**Karjalainen**	**Leaver**	**Lomberg**	**Melloh**	**Sieben**	**Swinkels-Meewisse**	**Van der Windt**
	Pain site	**Head**	**Back or neck**	**LBP**	**LBP**	**LBP**	**LBP**	**LBP**	**LBP**	**LBP**	**LBP**	**Neck**	**LBP**	**LBP**	**LBP**	**LBP**	**LBP**
Functional status at baseline	Forward lumbar bending (ROM[b])					÷							÷				
	Scoliosis												÷				
	Disability				+		+			÷ [a]	+	+		÷		÷ [a]	
	Physical activity								÷					÷		+ [a]	
	Participation																
	General health				+				÷ [a]		÷	+					
	Limitations physical				÷									+			
	Disability days last month					+											
Work related	Employed at baseline				÷		+					+					
	Changed work status											÷					
	Physically demanding work				÷						÷		÷	+			
	Job unsatisfaction				÷	÷	÷				÷			+			
	Resigned attitude towards the job													+			
	Uncertainty													÷			
	Organization													÷			
	Interruptions													÷			
	Concentration													÷			
	Time pressure													÷			
	Ergonomics													÷			
	Emotions (job related)													÷			
	Resources (job related)													÷			
	Social support at work													+			
	Compensation status				+							÷					
	Job difficulty				÷												
	Pain onset at work												+				
	Sick leave due to pain						+				÷		÷	÷			
	Past sick leave for pain											+					

a: Only adjusted estimates presented

b: Range of motion

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Supplementary Material S1 (continued): Potential prognostic factors for disability assessed in the included studies. A plus sign indicates a statistically significant association between the given factor and the outcome. A minus sign indicates a non-significant association.

	Prognostic factor	Boardman	Boersma	Childs	Coste	Grotle, 2007	Grotle, 2010	Hancock	Hendrick	Heneweer	Karjalainen	Leaver	Lonnberg	Melloh	Sieben	Swinkels-Meewisse	Van der Windt
	Pain site	**Head**	**Back or neck**	**LBP**	**LBP**	**LBP**	**LBP**	**LBP**	**LBP**	**LBP**	**LBP**	**Neck**	**LBP**	**LBP**	**LBP**	**LBP**	**LBP**
Psychological	Psychiatric disorder				÷												
	Anxiety	+ [a]					+										
	Depression	+ [a]					+							+			
	Emotional distress					+											÷ [a]
	Fear of pain						+										
	Fear of movement									÷						+ [a]	
	Fear avoidance		?			÷	+		÷ [a]	÷ [a]							÷ [a]
	Coping						÷			÷							
	Catastrophising						+							+			÷ [a]
	Somatisation													+			÷ [a]
	Perceived risk of not recovering										+						
	Expectation regarding the effectiveness of treatment										÷						
	Social functioning				÷												
	Vitality				÷												
	Physical problems				÷												
	Mental health				÷							+		+			
Other	Prescription of bed rest				÷												
	Prescription of sick leave				÷												
	Recruitment group					÷	÷										
	Sleeping/relaxation medication					÷											
	Pain medication					÷						+					
	Prior low back surgery				÷												
	Other co morbidity				÷												
	"Clinical prediction rule"			+				+									
	ALBPSQ* / CPG[d]				+		+			÷ [a]							

a: Only adjusted estimates presented

c: GP, chiropractor or physiotherapist.

d: Acute low back screening questionnaire.

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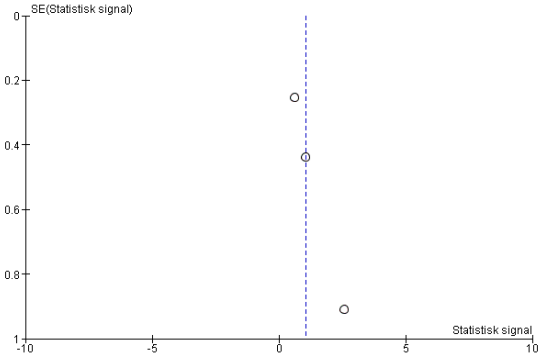
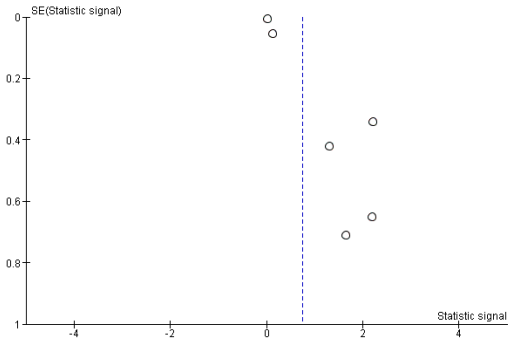
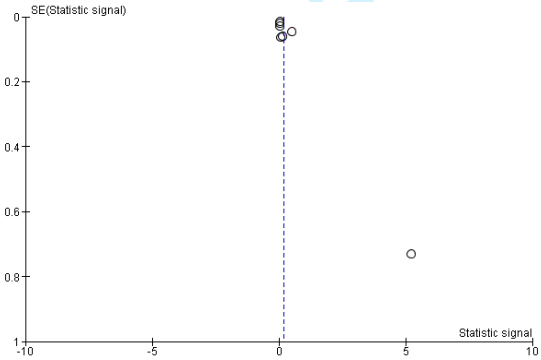
Supplementary Material S2: Funnel plots of studies included in the meta-analyses.



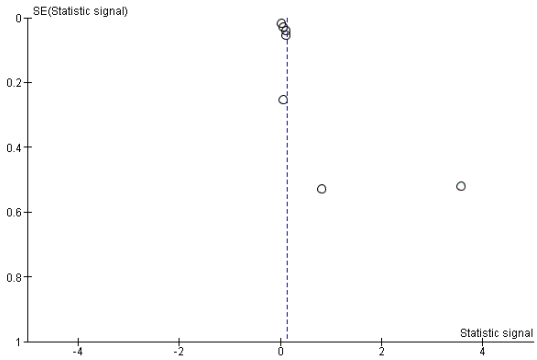
S2A: Multiple-site pain



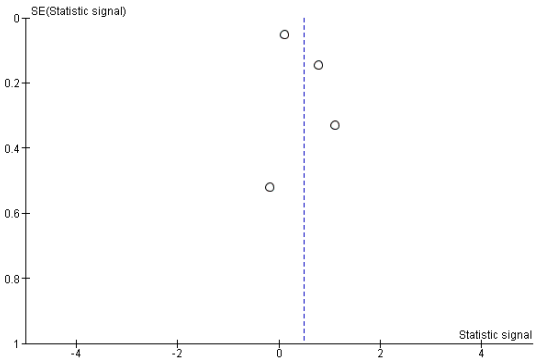
S2B: Higher pain severity



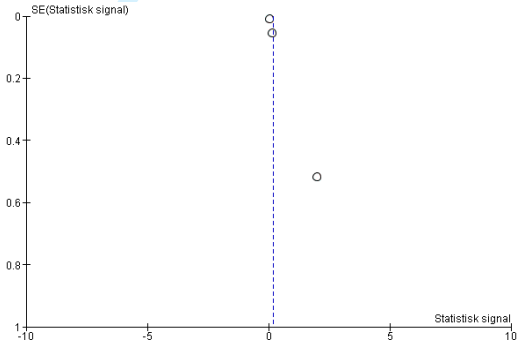
S2C: Disability



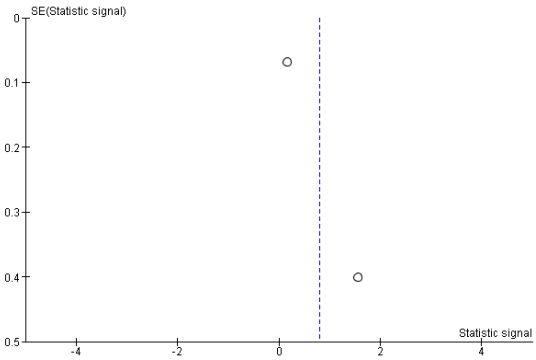
S2D: Higher age



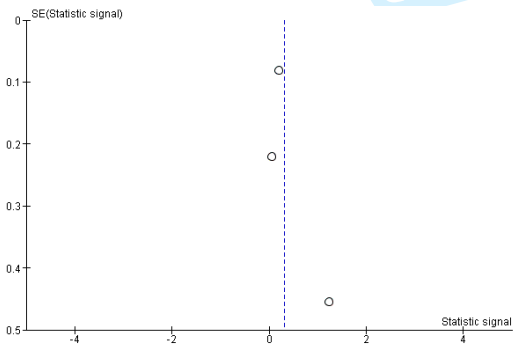
S2E: Previous episodes



S2F: Longer duration



S2G: High level anxiety



S2H: Depression

Supplementary Material S3: Sensitivity analysis omitting studies with different effect value.

Study or Subgroup	Statistic signal	SE	Weight	Statistic signal IV, Random, 95% CI
Coste J., 2004	0.03	0.016	18.3%	0.03 [-0.00, 0.06]
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Total (95% CI)			**100.0%**	**0.14 [0.03, 0.24]**

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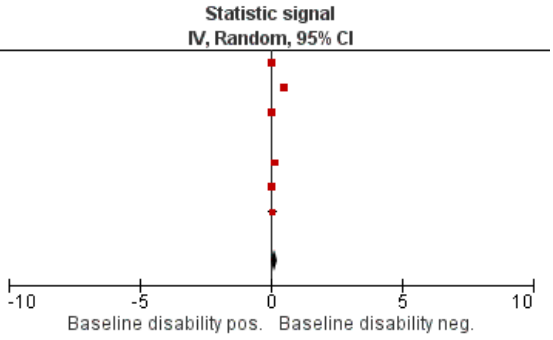

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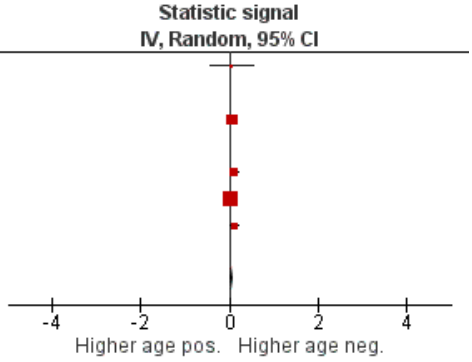

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5-6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6-7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Not relevant
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9-10
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	12-13
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	14
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	16-17
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	16-17
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	18
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Not relevant
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	19-20
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	21
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	22-23
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	23

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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Prognostic Factors for Disability and Sick Leave in Patients with Sub-acute Non-malignant Pain: A systematic review of cohort studies

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Manuscript ID	bmjopen-2015-007616.R3
Article Type:	Research
Date Submitted by the Author:	20-Nov-2015
Complete List of Authors:	Valentin, Gitte; CFK- Public Health and Quality Improvement, Central Denmark Region Pilegaard, Marc; University of Southern Denmark, Denmark, Research Initiative for Activity Studies and Occupational Therapy, General Practice, Department of Public Health, Vaegter, Henrik; University Hospital Odense, Denmark, Pain Research Group, Pain Centre South, Department of Anaesthesiology and Intensive Care Medicine, Rosendal, Marianne; Research Unit for General Practice, Aarhus University Ørtenblad, Lisbeth; Health Technology Assessment and Health Services Research, CFK-Public Health and Quality Improvement, Central Denmark Region Væggemose, Ulla; Health Technology Assessment and Health Services Research, CFK-Public Health and Quality Improvement, Central Denmark Region Christensen, Robin; Copenhagen University Hospital, The Parker Institute, Department of Rheumatology
Primary Subject Heading:	General practice / Family practice
Secondary Subject Heading:	Health services research
Keywords:	Prognostic factors, Early detection, Pain
Note: The following files were submitted by the author for peer review, but cannot be converted to PDF. You must view these files (e.g. movies) online.	
Prognostic factors for disability and sick leave_24 11 15.docm	

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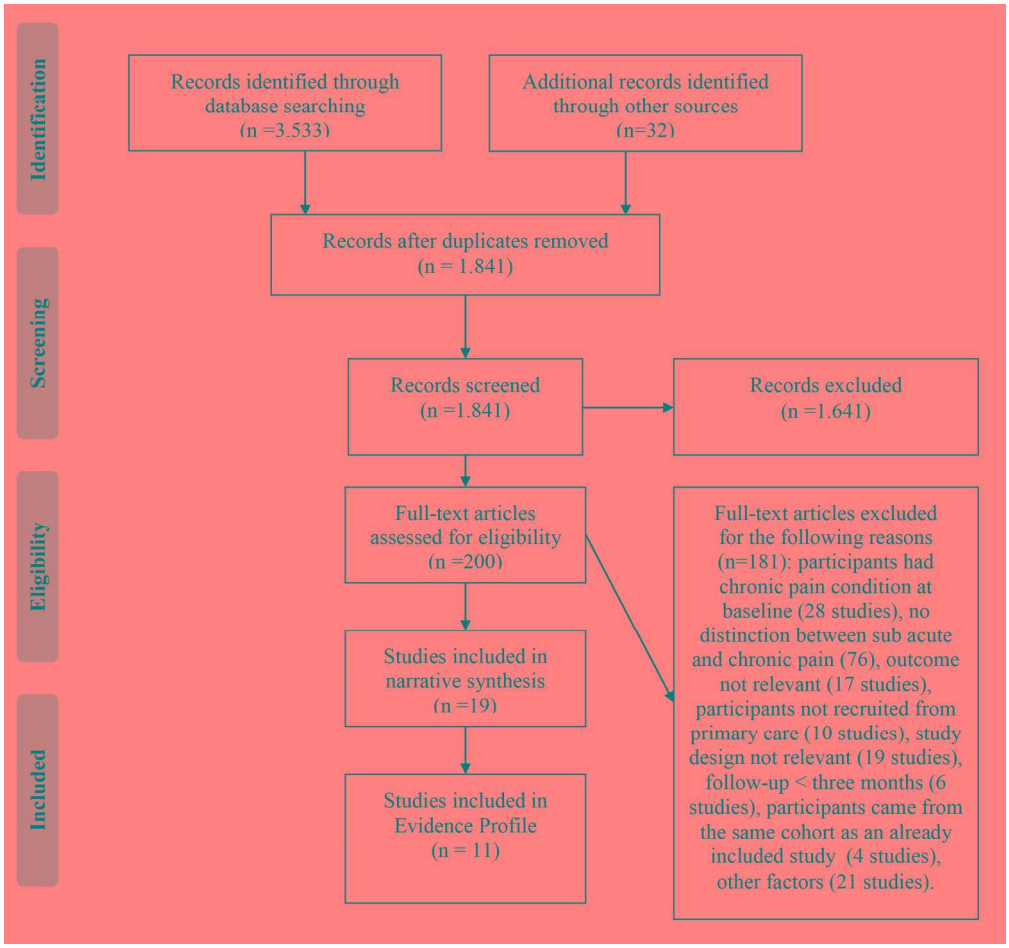

Figure 1: Flow-diagram of the literature search
198x186mm (300 x 300 DPI)

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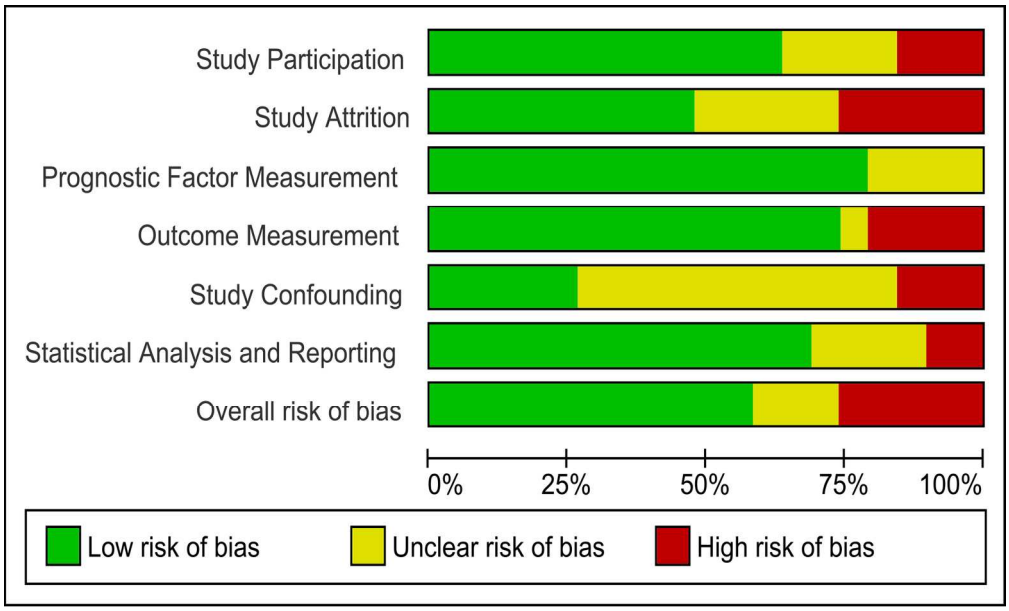

Figure 2: Risk of bias of the six domains in QUIPS
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Supplementary material

Supplementary Material S1: Description of meta-analysis including forest plots of the association between potential prognostic factors and long-term disability in patients with a sub-acute pain condition.

Data synthesis and analysis

If a baseline factor was associated with outcomes at follow-up in two or more studies of different pain sites, it was considered a "possible prognostic" factor and the results were combined and subsequently presented as part of the evidence profile. When data were available in different formats, data from the "fully adjusted" analyses were given preference and included in the meta-analysis. The studies in the meta-analyses were heterogenic regarding statistical methods. Hence, it was not possible directly to compare the results from the original studies. In order to assed the statistical power between a prognostic factor and outcome Fishers z-transformation was used. From each cohort study, the "statistical signal" (The "Wald-test"—the ratio between signal and noise) was derived from the effect size and the standard error of the estimate (SE). These were subsequently handled using Fisher's z-transformation.[23] This z-transformation was used to communicate the statistical power for any given association (i.e., correlation) between a given prognostic factor and an outcome. In one study the outcome was "absence of disability" as opposed to "disability". Thus the effect estimate (HR: 0.97) was reversed (HR: 1.03) before transformed into logscale and entered in RevMan.[24]

Summary estimates of associations across studies were derived from random effects meta-analysis, anticipating clinical heterogeneity, with modelling allowing for differences in the association from study to study.[25]

Heterogeneity across studies was statistically assessed using the Q-test and quantified by the inconsistency (I^2) index.[26] I^2 represents the percentage of total variation across studies attributable to heterogeneity rather than (statistical) chance.[27] In cases with substantial heterogeneity across studies ($I^2 > 50\%$), the robustness of the results was checked using the "fixed effects" model. A result was

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considered robust if the point estimate for "fixed effects" was within the confidence interval of "random effects"; as a consequence, the risk of "small-study" bias was considered to be high if the point estimate was outside the confidence estimate. If this was the case, the evidence for the given prognostic factor was downgraded due to inconsistency. In order to explore the robustness of the pooled estimates sensitivity analyses were conducted in cases were three or more studies in the meta-analysis had similar effect value. Meta-analyses were performed using Review Manager (RevMan) provided by the Cochrane Collaboration.[28] A two-sided P-value of ≤ 0.05 (and 95% confidence interval excluding the null) was considered to be statistically significant in all analyses. For each outcome, we prepared an evidence profile based on the GRADE profiler software.[29]

Prognostic factors for disability

Prognostic factors for disability were assessed in 16 studies.[3, 4, 24, 30, 34-45] A total of 81 factors were assessed in the unadjusted analysis (Supplementary Material S1). Of the 81 factors assessed, 53 were included in the multivariable analysis of the primary studies. Of these factors, the following eight were assessed in two or more studies and for at least two different pain sites: multiple-site pain, higher baseline pain severity, previous pain episodes, older age, longer baseline pain duration, baseline disability, anxiety, and depression. A total of eleven studies were included in the evidence profile (figure ?).[4, 24, 37-45] The association between multiple-pain sites and disability at follow-up was assessed in three studies, including patients with headache,[45] low back pain,[41] and neck pain[44] (figure ?). All three studies found a statistically significant association between multiple-pain sites at baseline and risk of disability at follow-up. The combined estimate showed a statistically significant association between multiple-pain sites at baseline and risk of disability at follow-up (p = 0.010). The test for heterogeneity was I^2 =57%. However, "fixed effects" did not change the result significantly.

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The association between higher pain severity at baseline and disability was assessed in six studies including patients with headache[45] and low back pain[37, 38, 40-42] (figure 3b). The combined estimate showed a statistically significant association between higher baseline pain severity and disability ($p < 0.001$). I^2 was 93% and the result was not robust when using the "fixed effects" model, so small-study bias is therefore likely. Consequently, the quality of evidence was downgraded due to inconsistency. The association between baseline disability and disability at follow-up was examined in seven studies relating to patients with neck pain[44] and low back pain[24, 38, 40-43] (figure 3c). Baseline disability was associated with a higher risk of disability at follow-up ($p = 0.007$). I^2 was 96%. The "fixed effects" model did not change the result significantly.The association between higher age and the risk of disability was assessed in seven studies concerning patients with neck pain[44] and low back pain[4, 37-39, 41, 42] (figure 3d). A significant association was seen between higher age and risk of disability ($p = 0.04$). I^2 was 89%. The "fixed effects model" did not change the result significantly. A dose-response effect was observed; an increase by 10 years of age was associated with a higher risk of disability than was a one-year increase. No statistical significant associations between disability and previous pain episodes ($p = 0.08$; figure 4a), longer baseline pain duration ($p= 0.12$; figure 4b), anxiety ($p = 0.25$; figure 4c), or depression ($p = 0.14$; figure 4d) were observed. The "fixed effects" model did not change the results notably for the four potential prognostic factors in figure 4.

Sensitivity analyses were conducted for the results of the meta-analysis presented in figure 3C and 3D. In figure 3C the study by Karjalainen et al. was omitted and in figure 3D the studies by Grotle et al, 2007 and Karjalainen et al. were omitted. The statistical signal did not change substantially after selective omitting studies with different effect value (Supplementary material S3

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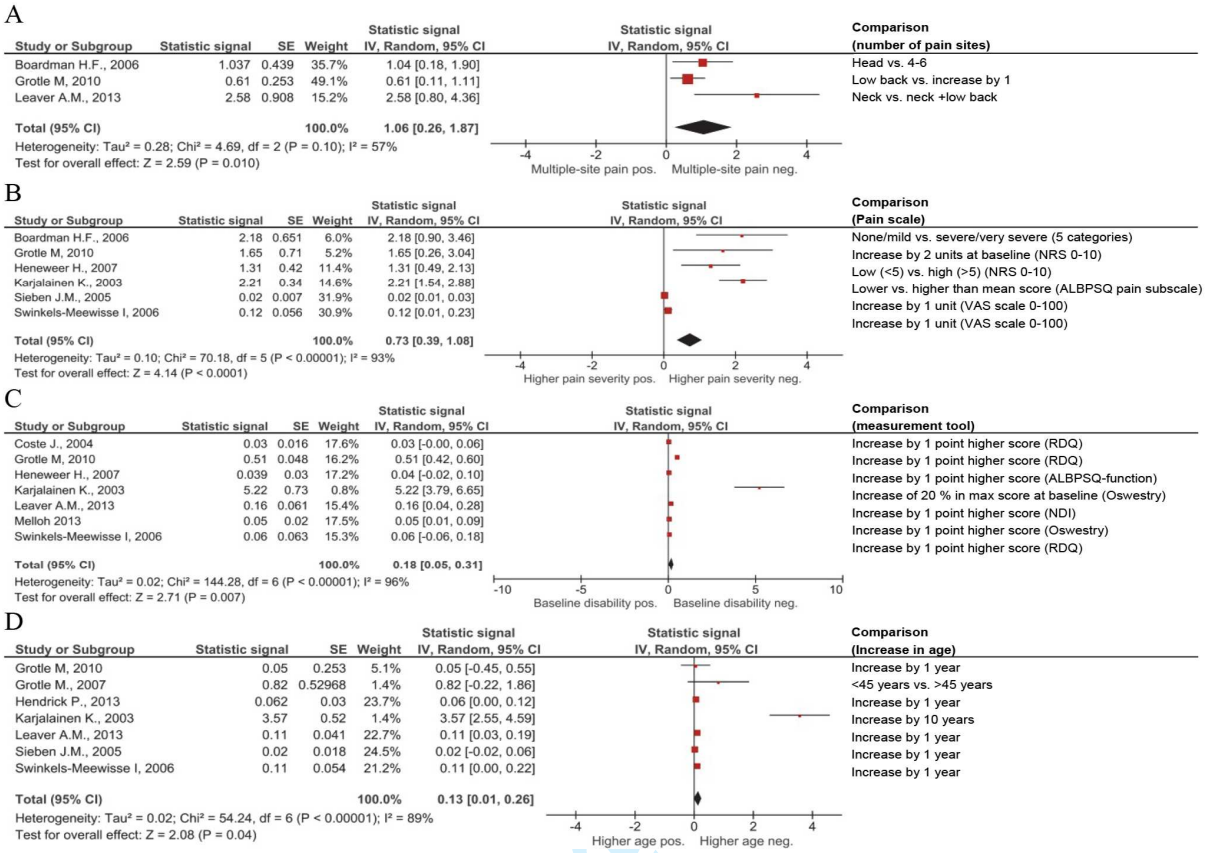

Figure 3: Forest plots of the association between potential prognostic factors and long-term disability in patients with a sub-acute pain condition. 3A: Adjusted for: Age [41, 45], sex [41, 45], baseline disability [41], recruitment [41], factors adjusted for not described [44]. 3B: Adjusted for: Age [41, 45], sex [41, 45], baseline disability [41], recruitment [41], factors adjusted for not described [37, 40, 42].3C: Adjusted for: Age [41, 43], Sex [41, 43], BMI [43], duration (hours) between pain debut and inclusion [24], job status [24], previous spine surgery [24], compensation status [24], self rated health status [24], factors adjusted for not described [38, 40, 42, 44].3D: Adjusted for sex [4, 39], job [39], BMI [39], Baseline pain severity [39], recruitment [41], depression [39], anxiety [39], fear avoidance [39], activity level prior current pain episode [39], baseline disability [38, 41], factors adjusted for not described [37, 42, 44].

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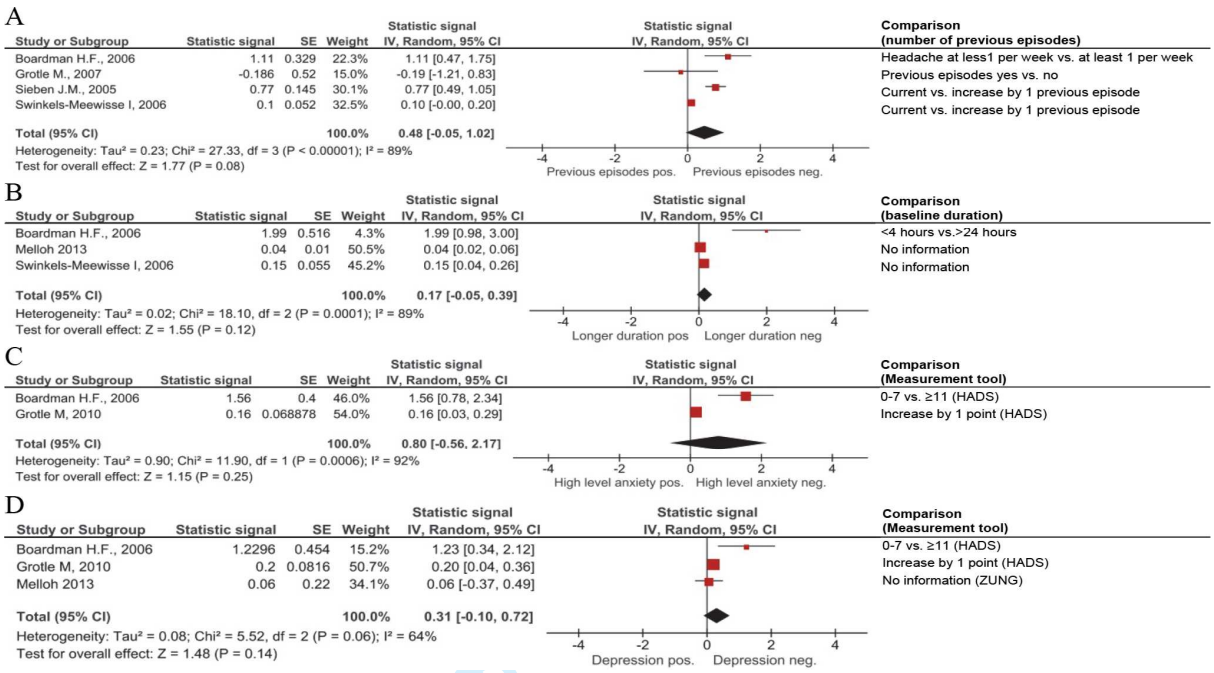

Figure 4: Forest plots of the association between potential prognostic factors and long-term disability in patients with a sub-acute pain condition. 4A: Adjusted for: age [4, 45], sex [4, 45], baseline disability [38], factors adjusted for not described [37]. 4B: Adjusted for: Age [43, 45], sex [43, 45], BMI [43], baseline disability [38]. 4C: Adjusted for: Age [41, 45], sex [41, 45], recruitment [41], baseline disability [41]. 4D: Adjusted for: Age [41, 43, 45], sex [41, 43, 45], BMI [43], recruitment [41], baseline disability [41].

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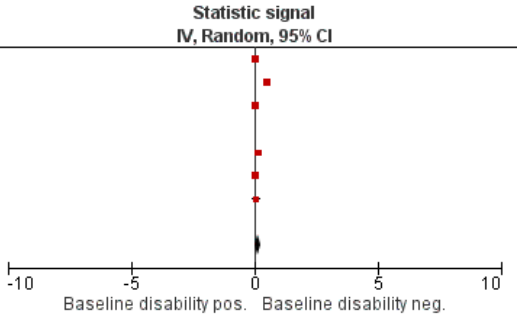

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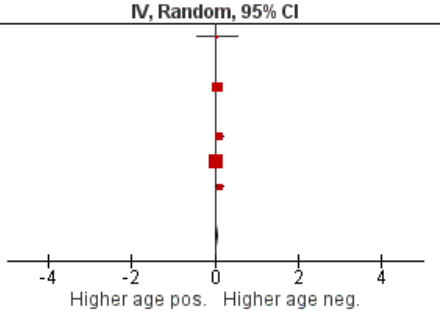

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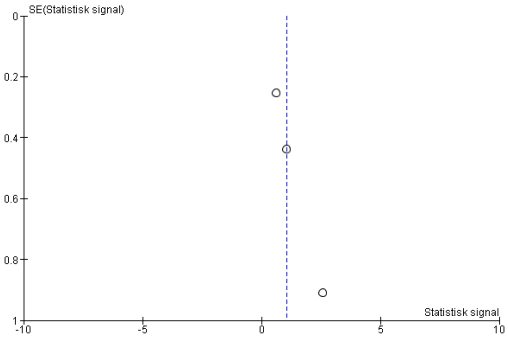
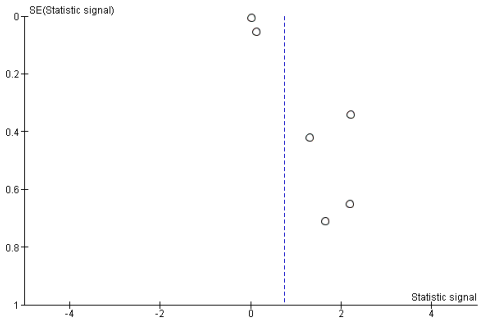
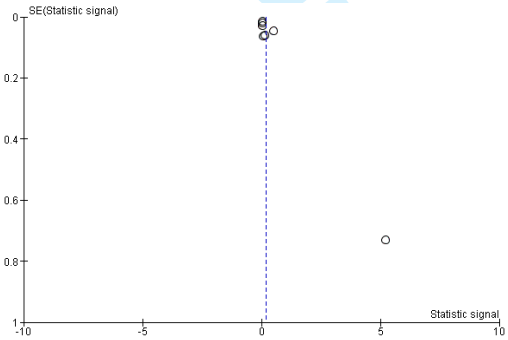
Supplementary Material S2: Funnel plots of studies included in the meta-analyses.



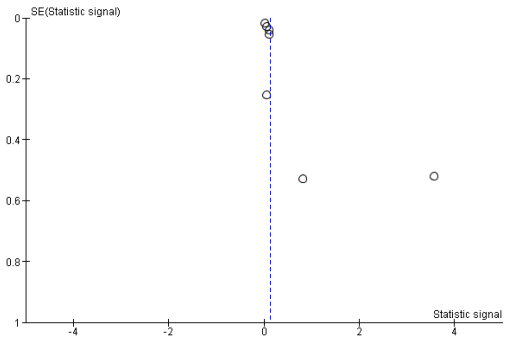
S2A: Multiple-site pain



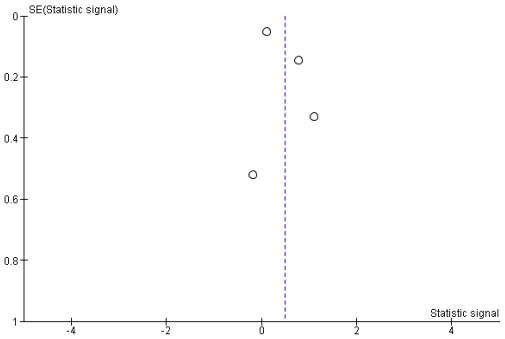
S2B: Higher pain severity



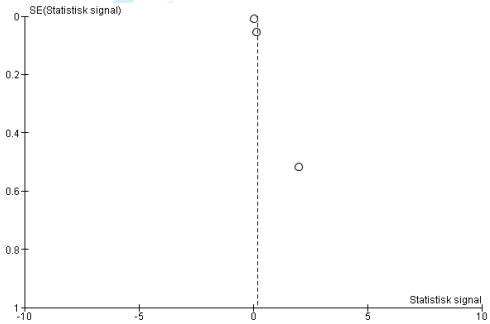
S2C: Disability



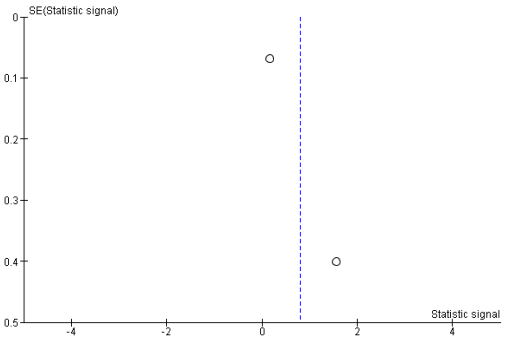
S2D: Higher age



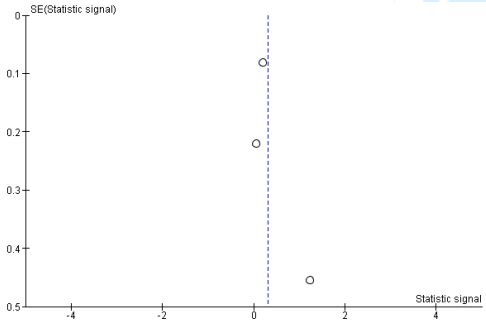
S2E: Previous episodes



S2F: Longer duration



S2G: High level anxiety



S2H: Depression

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Supplementary Material S3: Potential prognostic factors for disability assessed in the **unadjusted analysis** of the included studies. A plus sign indicates a statistically significant association between the given factor and the outcome. A minus sign indicates a non-significant association.

	Prognostic factor	**Boardman**	**Boersma**	**Childs**	**Coste**	**Grotle, 2007**	**Grotle, 2010**	**Hancock**	**Hendrick,**	**Heneweer**	**Karjalainen**	**Leaver**	**Lonnberg**	**Melloh**	**Sieben**	**Swinkels-Meewisse**	**Van der Windt**
	Pain site	**Head**	**Back or neck**	**LBP**	**LBP**	**LBP**	**LBP**	**LBP**	**LBP**	**LBP**	**LBP**	**Neck**	**LBP**	**LBP**	**LBP**	**LBP**	**LBP**
Socio demo-graphic	**Age**				÷	÷	÷		+ [a]		+	+	÷	÷	÷ [a]	+ [a]	
	Gender				÷	÷	÷				÷	+	÷	÷		÷ [a]	
	BMI										+	+		+			
	Smoking					÷								÷			
	Alcohol	÷ [a]												÷			
	Caffeine	÷ [a]															
	Civil status															÷ [a]	
	Origin				÷												
	Education					÷	+				÷	÷		÷	÷ [a]	÷ [a]	
	Social class						÷										
Pain	**Baseline intensity**	+ [a]			÷		+			+	+	÷		+	+ [a]	+ [a]	
	Baseline duration	+ [a]										+	÷	÷		+ [a]	
	Previous episodes	+ [a]			÷	÷						÷	÷		+ [a]	+ [a]	
	Associated symptoms	+ [a]															
	Duration of previous episodes													+			
	Permanent pain at nigth				÷												
	Pain increased by coughing				+												
	Pain increased by back movement				÷												
	Pain worse when standing				÷												
	Pain worse when lying down				+												
	Pain on passive movements				÷												
	Pain radiation					÷	+				÷		÷			+ [a]	
	Neurological signs					÷							÷				
	Onset (sudden)															÷ [a]	
	Sensory pain													+			
	Affective pain													+			
	Multiple-pain sites	+ [a]					+					+					
	Bothersomeness						+										

a: Only adjusted estimates presented

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Supplementary Material S3 (continued): Potential prognostic factors for disability assessed in the **unadjusted analysis** of the included studies. A plus sign indicates a statistically significant association between the given factor and the outcome. A minus sign indicates a non-significant association.

	Prognostic factor	**Boardman**	**Boersma**	**Childs**	**Coste**	**Grotle, 2007**	**Grotle, 2010**	**Hancock**	**Hendrick**	**Heneweer**	**Karjalainen**	**Leaver**	**Lonnberg**	**Melloh**	**Sieben**	**Swinkels-Meewisse**	**Van der Windt**
	Pain site	**Head**	**Back or neck**	**LBP**	**LBP**	**LBP**	**LBP**	**LBP**	**LBP**	**LBP**	**LBP**	**Neck**	**LBP**	**LBP**	**LBP**	**LBP**	**LBP**
Functional status at baseline	Forward lumbar bending (ROM[b])					÷							÷				
	Scoliosis												÷				
	Disability				+		+			÷ [a]	+	+		÷		÷ [a]	
	Physical activity								÷					÷		+ [a]	
	Participation																
	General health				+				÷ [a]		÷	+					
	Limitations physical				÷									+			
	Disability days last month					+											
Work related	Employed at baseline				÷		+					+					
	Changed work status											÷					
	Physically demanding work				÷						÷		÷	+			
	Job unsatisfaction				÷	÷	÷				÷			+			
	Resigned attitude towards the job													+			
	Uncertainty													÷			
	Organization													÷			
	Interruptions													÷			
	Concentration													÷			
	Time pressure													÷			
	Ergonomics													÷			
	Emotions (job related)													÷			
	Resources (job related)													÷			
	Social support at work													+			
	Compensation status				+							÷					
	Job difficulty				÷												
	Pain onset at work												+				
	Sick leave due to pain						+				÷		÷	÷			
	Past sick leave for pain											+					

a: Only adjusted estimates presented

b: Range of motion

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Supplementary Material S3 (continued): Potential prognostic factors for disability assessed in the **unadjusted analysis** of the included studies. A plus sign indicates a statistically significant association between the given factor and the outcome. A minus sign indicates a non-significant association.

	Prognostic factor	**Boardman**	**Boersma**	**Childs**	**Coste**	**Grotle, 2007**	**Grotle, 2010**	**Hancock**	**Hendrick**	**Heneweer**	**Karjalainen**	**Leaver**	**Lonnberg**	**Melloh**	**Sieben**	**Swinkels-Meewisse**	**Van der Windt**
	Pain site	**Head**	**Back or neck**	**LBP**	**LBP**	**LBP**	**LBP**	**LBP**	**LBP**	**LBP**	**LBP**	**Neck**	**LBP**	**LBP**	**LBP**	**LBP**	**LBP**
Psychological	Psychiatric disorder				÷												
	Anxiety	+ [a]					+										
	Depression	+ [a]					+							+			
	Emotional distress					+											÷ [a]
	Fear of pain						+										
	Fear of movement									÷						+ [a]	
	Fear avoidance		?			÷	+		÷ [a]	÷ [a]							÷ [a]
	Coping						÷			÷							
	Catastrophising						+							+			÷ [a]
	Somatisation													+			÷ [a]
	Perceived risk of not recovering										+						
	Expectation regarding the effectiveness of treatment										÷						
	Social functioning				÷												
	Vitality				÷												
	Physical problems				÷												
	Mental health				÷							+		+			
Other	Prescription of bed rest				÷												
	Prescription of sick leave				÷												
	Recruitment group					÷	÷										
	Sleeping/relaxation medication					÷											
	Pain medication					÷						+					
	Prior low back surgery				÷												
	Other co morbidity				÷												
	"Clinical prediction rule"			+				+									
	ALBPSQ* / CPG[d]				+		+			÷ [a]							

a: Only adjusted estimates presented

c: GP, chiropractor or physiotherapist.

d: Acute low back screening questionnaire

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5-6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6-7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Not relevant
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9-10
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	12-13
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	14
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	16-17
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	16-17
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	18
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Not relevant
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	19-20
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	21
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	22-23
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	23

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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