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Systematic Review

Prognostic factors for persistent pain after a first episode of nonspecific idiopathic, non-traumatic neck pain: A systematic review

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ABSTRACT

Background: Prognosis of acute idiopathic neck pain is poor. An overview of modifiable and non-modifiable prognostic factors for the development of chronic musculoskeletal neck pain after an episode of idiopathic, non-traumatic neck pain is needed.
Objective: Identify prognostic factors for pain intensity and perceived non-recovery at three, six and 12 months after a first episode of idiopathic, non-traumatic neck pain.
Study design: Systematic review
Methods: Systematic literature search up to October 21, 2017 for prospective prognostic studies with main outcomes perceived non-recovery and pain intensity. The QUIPS was used for quality assessment.
Results: Out of 2737 screened articles six prospective studies with high-risk-of-bias were identified, analyzing 47 and 43 factors for the outcome variables 'pain intensity' and 'perceived non-recovery', respectively. Based on univariate- and multivariate analyses we found moderate evidence for 'age > 40 years' and 'concomitant back pain' to be prognostic for 'pain intensity'. For the outcome 'perceived non-recovery' at 12 months, we found moderate evidence for both 'a previous period of neck pain' and 'accompanying headache' as prognostic variables for persistent pain, based on univariate analysis. No prognostic factor was found which was retained in more than one multivariate analysis for the outcome variable 'perceived non-recovery'. However, the quality of the evidence for these prognostic factors was low to very low.
Conclusion: This review identifies prognostic factors for neck pain, of which only a few are modifiable. Further research is needed before drawing definite conclusions about the prognostic value of these factors.

1. Introduction

Musculoskeletal (MSK) conditions pose an enormous burden on individuals, health systems, and social care systems, and are dramatically increasing in developing countries, particularly due to rapidly ageing populations and increasing obesity (Hoy et al., 2014). Trends of non-fatal diseases show that neck pain is third in the rating of 'years lived with disability' in Europe (GBD, 2016). The incidence of neck pain in the general population is estimated between 15 and 18% per year (Côté et al., 2004; Croft et al., 2001). In 2016, the prevalence was 20.8 per 1000 patient years in general practitioner practices in the Netherlands. (Koppes, 2016).

Most episodes of acute neck pain are thought to resolve with or without treatment. However, Hush et al. found Level 1 evidence that the prognosis of acute idiopathic neck pain is worse than currently recognized (Hush et al., 2011). Childs et al. (2008) suggest that rates of persistent neck pain are substantial: 30% of patients with neck pain will develop chronic symptoms (Bovim et al., 1994), and 37% of individuals who experience neck pain will report persistent problems for at least 12 months (Côté et al., 2004).

Chronic pain negatively affects patient perception of general health, interferes considerably with everyday activities as a function of pain severity, is associated with depressive symptoms, and dramatically and negatively affects relationships and interactions with others (Reid et al., 2011). Studies report that the effect of physiotherapy treatment after the occurrence of chronic musculoskeletal pain is at best only moderate (Geneen et al., 2017; Bertozzi et al., 2013; Gross et al., 2015). It is therefore essential to prevent chronic pain and ensuing disability in the first place. Knowledge of the clinical course of neck pain and prognostic potentially modifiable and non-modifiable prognostic variables help health care providers to improve clinical decision-making and to manage expectations of people with neck pain. Prognostic factors are

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defined as characteristics that are associated with clinical outcomes in patients with a given health condition (Riley et al., 2013), whereas predictive factors are defined as characteristics that identify subgroups of treated patients having different outcomes (Adolfsson and Steineck, 2000). Before clinical characteristics can be used to justify specific treatments, it is imperative that the prognostic effects of these characteristics are distinguished from their ability to predict a differential clinical benefit from a specific treatment (Clark, 2008). Previous research has often used these terms imprecisely (Wingbermühle et al., 2018; Kelly et al., 2017). Prior systematic reviews on prognostic factors in nonspecific neck pain have included a majority of studies on patients with whiplash-associated disorder (WAD) (Wingbermühle et al., 2018; Walton, 2013; Kelly et al., 2017). The findings of these reviews cannot be generalized to patients with idiopathic nonspecific, non-traumatic, acute- or subacute neck pain because patients with WAD are different in muscle function, cervical pressure pain thresholds, self-reported and patient-specific function, depression, active range of motion, pain intensity and disability in the chronic phase and have different beliefs with regard to recovery (Stenneberg et al., 2017; Anstey et al., 2016; Ris et al., 2017). Only one study was found that reported comparable improvement in and prognostic factors for pain, function and recovery between patients with WAD and patients with nonspecific neck pain (Verhagen et al., 2011).

Consequently, we think it is essential to analyze the group of nonspecific, acute- and subacute neck pain patients separately. Even though Hush et al. did analyze the prognosis of acute idiopathic neck pain, they did not analyze the prognostic factors (Hush et al., 2011). To the best of our knowledge, prognostic factors in this subgroup have not yet been reviewed systematically.

Chronicity has been variously described in three core domains 'persisting symptoms', 'disability' and 'work status' (Pincus et al., 2002). As our primary interest is the prevention of chronic pain, we chose 'pain intensity' and 'perceived non-recovery' as our outcome variables. This is also in line with the IMPACT recommendations and different observational studies and systematic reviews on chronification of musculoskeletal pain (Gewandter et al., 2015; Pierik et al., 2015; Bérubé et al., 2017; Traeger et al., 2016; Struyf et al., 2016). Besides, in clinical practice patients most often report pain as the most important problem and their treatment aim is to reduce (Sanderson et al., 2010; Casarett et al., 2001; Bromley Milton et al., 2013).

The purpose of this study is to identify and synthesize the evidence regarding modifiable and non-modifiable prognostic factors for the development of chronic musculoskeletal neck pain after a first episode of idiopathic, non-traumatic neck pain, operationalized by the outcome variables 'pain intensity' and 'perceived non-recovery'.

2. Methods

2.1. Protocol and registration

We registered the review protocol in the international prospective register of systematic reviews (Prospero) database with registration number CRD42016050346 in October 2016. At that time, there was no other similar review protocol registered on this topic.

This review is written in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009).

2.2. Search

Potentially relevant studies were identified through systematic searches in the following electronic databases: Medline (PubMed), PsycINFO, EMBASE, SPORTdiscus and CINAHL. The databases were searched from inception up to October 21, 2017.

A comprehensive search strategy was developed in consultation with a medical information specialist. The search strategy consisted of three major elements: (1) chronification; (2) neck pain; and (3) prognostic factors.

For each element, we collected all known synonyms and related terms to extract the maximum number of articles from the databases. To ensure sufficient precision, the key terms were mapped to medical subject headings (MeSH), and title and abstract search words and phrases were added.

We build the search string for PubMed and then translated it into a syntax for the other databases. All databases were individually searched. We imported all references into RefWorks and excluded duplicate articles. Furthermore, to ensure a maximum number of eligible studies, we scanned the reference lists of all included articles.

The complete search strategy can be found in Appendix 1. The translations of the search string to all databases are available on request from the first author.

As a supplement to the systematic search, we also searched the grey literature.

For grey literature we used the following electronic sources up to October 21, 2017: DART-Europe E-theses Portal, Open Access Theses and Dissertations, Networked Digital Library of Theses and Dissertations (NDLTD), ClinicalTrials.gov and WHO International Clinical Trials Registry Platform (ICTRP).

2.3. Eligibility criteria

Table 1 provides an overview of the in- and exclusion criteria. As we specifically focused on musculoskeletal idiopathic, non-traumatic neck pain, we defined musculoskeletal pain as pain that arises as part of a disease process directly affecting bone(s), joint(s), muscle(s), or related soft tissue(s) (Treede et al., 2015). Idiopathic, non-traumatic neck pain was defined as neck pain of unknown origin (Hush et al., 2011). We included only studies with a follow-up period of at least 3 months in univariate or multivariate analysis, because chronic pain is defined as pain that persists longer than 3 months or is recurring (Treede et al., 2015). We specifically excluded studies that reported predictive factors for a specific treatment.

Table 1
Study selection criteria.

Inclusion	Exclusion
Prospective cohort studies	Neck surgery, Radiculopathy and Myelopathy, Headache, wide spread pain, no neck pain at baseline
Univariate to identify prognostic factors	Pain not due to musculoskeletal pain (affecting bone(s), joint(s), muscle(s), or related soft tissue(s))
Human adults (18 years or older) formed at least 60% of the sample[a], had to have idiopathic, non-traumatic acute- (0–3 weeks) and/or sub-acute (3–12 weeks) neck pain	> 40% of the sample has whiplash related neck pain[a]
Follow-up period at least 3 months	
Published in English, Dutch, French or German	
Outcomes pain or perceived non-recovery	

[a] A threshold of 60% was randomly chosen for pragmatic reasons to not overlook potentially useful prognostic factors.

2.4. Study selection

Screening was done by two reviewers (MV and HW) in a two-step procedure. During the first step, the two reviewers independently screened all articles for eligibility based on their title and abstract. During the second step, the same reviewers independently performed a review of the full text articles that were included after the first step. If consensus could not be reached, a third reviewer (FM) made the final decision.

Our final set of studies consisted of all papers for which both reviewers independently decided that they met the inclusion criteria. All disagreements were resolved by discussion.

2.5. Data extraction

Two reviewers (MV and HW) independently extracted data from each included study. An extraction manual was designed to facilitate the data collection process. In addition, the reviewers performed a test session to calibrate the extraction process. The following information was collected:

a) study article (authors, publication date, country), b) study design and statistical methods, c) characteristics of the study population, d) baseline prognostic factors, e) primary outcome measurements; i.e. pain intensity, patient perceived non-recovery, f) time to follow-up, number of patients at follow-up, g) statistical analyses, h) % patients recovered and i) quality of the study.

2.6. Risk of bias in individual studies

Risk of bias (RoB) was assessed by two independent reviewers (MV and HW) using the Quality In Prognostic Studies (QUIPS) tool. The QUIPS is a six-item, useful and reliable tool to guide comprehensive assessment of six bias domains in studies of prognostic factors (Hayden et al., 2013). The six domains are study participation, attrition, prognostic factor measurement, outcome measurement, study confounding, and statistical analysis and reporting. The six domains are rated as high, moderate or low RoB. Prior to assessing bias of the included studies, the QUIPS was tested on several non-included studies for calibration purposes. For overall RoB of individual studies, recommendations by Hayden et al. (2013) were followed, in which a study was considered to be at low RoB when each of the six bias domains was rated as having low RoB. Studies that scored moderate or high RoB on at least one domain were rated as high RoB (Hayden et al., 2013).

2.7. Synthesis or results

A prognostic factor was defined as a variable that was significantly associated with the main outcomes 'pain intensity' or 'perceived non-recovery'. A significant association was defined as a univariate or multivariate association, or an association adjusted for confounding or other prognostic variables, with a p value < 0.05, or an Odds Ratio (OR) or Relative Risk with a $\geq$90% CI not including one (Artus et al., 2017). To be consistent in the direction of the association we calculated the inverse of the Odds Ratios (OR) to determine the OR for non-recovery as four studies used good recovery as their main outcome (Pool et al., 2010; Hoving et al., 2004; Wirth et al., 2016; Vos et al., 2008) and two studies used poor recovery as their main outcome (Schellingerhout et al., 2010; Hill et al., 2004).

Meta-analysis was not performed as the included studies were dissimilar with respect to patient population and outcome(s). Therefore, a qualitative data synthesis was performed according to Hayden et al., 2013, 2014 taking into account the strength and consistency of results (Table 2). Following Hayden et al., 2013, 2014, a prognostic factor is considered to be of 'limited evidence' if it was researched in only one study. A prognostic factor is considered to be of 'moderate evidence' if more than one high risk of bias study and/or one low risk of bias study provide consistent evidence ($>$ 75% of the studies showing the same direction of effect). 'Strong evidence' is given if more than one low risk of bias study provide consistent evidence.

Two independent reviewers (MV and HW) used a modified GRADE approach (Huguet et al., 2013) to judge the overall quality of evidence of all included studies. The approach classifies evidence into high, moderate, low, or very low quality (see Table 3), whereby six study characteristics downgrade the quality of evidence (phase of investigation, study limitation, inconsistency, indirectness, imprecision, publication bias), and two study characteristics upgrade the quality of evidence (moderate or large effect size, exposure-response gradient).

3. Results

3.1. Study selection

The review selection process is outlined in Fig. 1. The search strategy resulted in 2737 articles after removing 1692 duplicates. After screening titles and abstracts we included 25 articles for detailed full-text screening (see Appendix 3). The inspection of all reference lists of these 25 articles and the systematic reviews in our orientation phase resulted in one additional study for detailed screening. The search in the grey literature resulted in 283 full text articles, none of which met our eligibility criteria.

After the detailed full-text screening procedure, our final sample consisted of six articles. Most articles were excluded as they (1) not only analyzed acute- and/or sub-acute idiopathic neck pain patients, but also $>$ 40% traumatic- or chronic neck pain patients, or (2) the study did not differentiate between neck pain and other musculoskeletal pain, or (3) the study included healthy participants at baseline. All disagreements were resolved by consensus.

3.2. Study characteristics

The characteristics of the six included studies are presented in Appendix 2. The six studies (Pool et al., 2010; Hoving et al., 2004; Wirth et al., 2016; Vos et al., 2008; Schellingerhout et al., 2010; Hill et al., 2004) were conducted in the Netherlands (four studies) (Pool et al., 2010; Hoving et al., 2004; Vos et al., 2008; Schellingerhout et al., 2010), in the UK (one study) (Hill et al., 2004) and in Switzerland (one study) (Wirth et al., 2016), and analyzed prognostic factors in 2446 patients with acute- and sub-acute neck pain of which 1497 (61%) were female and 949 (39%) male.

Of the six studies, four were prospective cohort studies (Hoving et al., 2004; Wirth et al., 2016; Vos et al., 2008; Hill et al., 2004) and two studies (Pool et al., 2010; Schellingerhout et al., 2010) reanalyzed data from randomized controlled (RCTs) trials. One study (Schellingerhout et al., 2010) included six months follow-up data from two RCTs (Pool et al., 2010; Hoving et al., 2004) that were also separately included in this review. As the original RCTs did not report on these data, this study was retained.

Four studies recruited patients from general primary care practices (Pool et al., 2010; Hoving et al., 2004; Vos et al., 2008; Schellingerhout et al., 2010), one study from chiropractic practices (Wirth et al., 2016) and one from the general population (Hill et al., 2004).

Three (Pool et al., 2010; Hoving et al., 2004; Hill et al., 2004) out of the six studies focused on pain intensity, and five (Pool et al., 2010; Hoving et al., 2004; Wirth et al., 2016; Vos et al., 2008; Schellingerhout et al., 2010) studies on self-perceived non-recovery as the dependent variable. The follow-up periods varied across the included studies. In the three studies that used pain as their main outcome, the follow-up period was three months (Pool et al., 2010) and one year (Hoving et al., 2004; Hill et al., 2004), respectively. Of these three studies, two studies (Pool et al., 2010; Hoving et al., 2004) used a NRS pain score (0–10), and in one study (Hill et al., 2004) the patients were asked whether they had had any ache or pain, which lasted for one day or more (yes/

Table 2
Data synthesis (Hayden et al., 2013, 2014).

Strong evidence	Consistent findings (defined as > 75% of studies showing the same direction of effect) in multiple low risk of bias studies
Moderate evidence	Consistent findings in multiple high risk of bias and/or one study with low risk of bias
Limited evidence	One study available
Conflicting evidence	Inconsistent findings across studies
No evidence	No association between variables

Table 3
Adapted definitions of the four quality categories according to the original Grading of Recommendations Assessment, Development and Evaluation (GRADE) (Balshem et al., 2011), applicable to the modified GRADE (Huguet et al., 2013).

High Quality	High confidence that the true effect lies close to that of the estimate of the effect
Moderate Quality	Moderate confidence in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low Quality	Limited confidence in the effect estimate: the true effect may be substantially different from the estimate of the effect
Very Low Quality	Very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

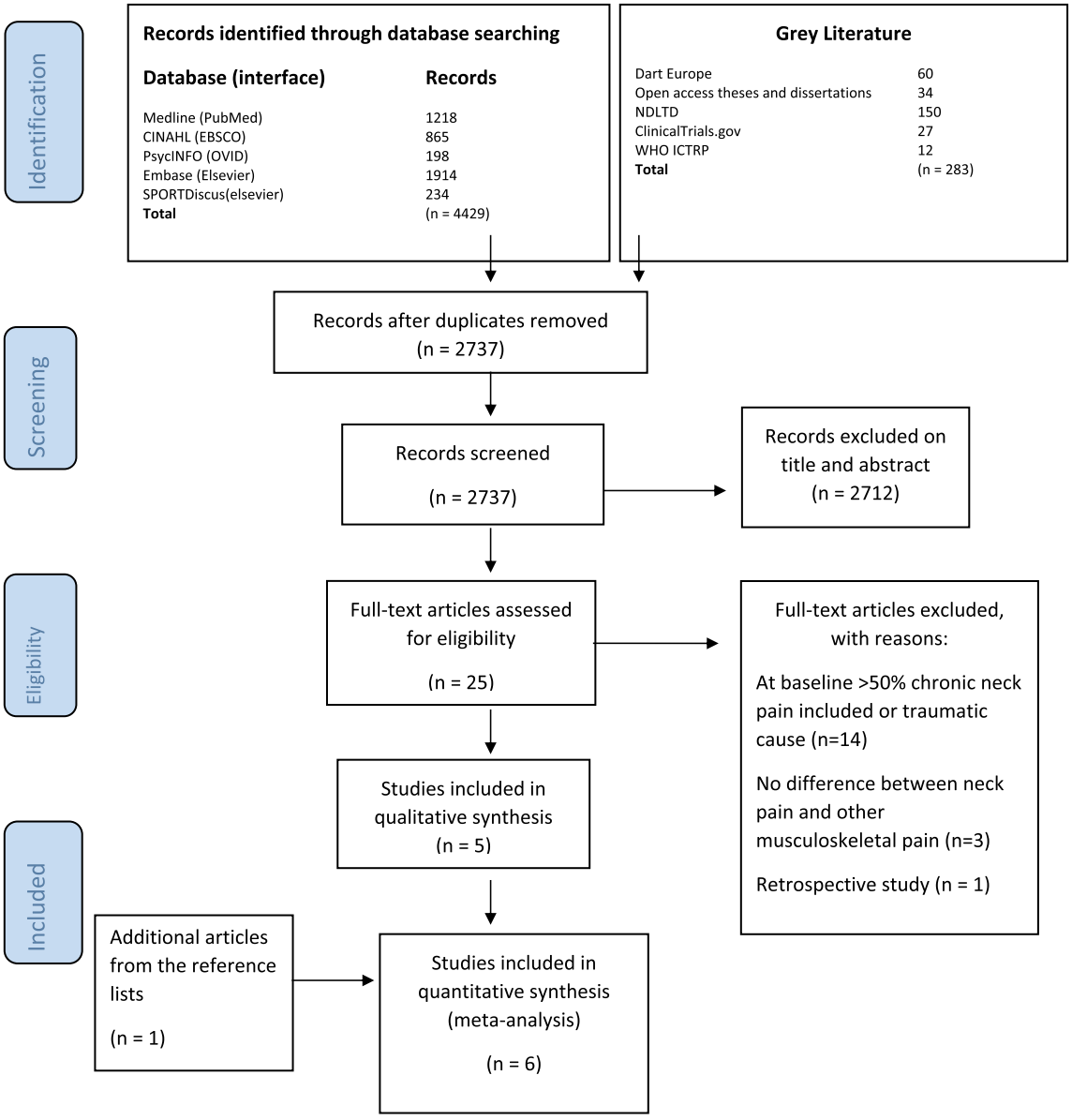

Fig. 1. PRISMA 2009 flow diagram.

no).

In the studies that used perceived non-recovery as their main outcome, two studies had a follow-up period of three months (Pool et al., 2010; Wirth et al., 2016), one study of six months (Schellingerhout et al., 2010), and two studies of one year (Hoving et al., 2004; Vos et al., 2008). Out of the five studies that measured self-perceived non-recovery, three studies used a 7-point Likert scale (Pool et al., 2010; Wirth et al., 2016; Vos et al., 2008), one study a 6-point Likert scale (Hoving et al., 2004), and one study combined the 6- and 7-point scales (Schellingerhout et al., 2010). All scales ranged from 'completely recovered' or 'much improved' to 'worse than ever'. Hoving et al. (2004) and Pool et al. (2010) defined recovery as 'completely recovered' or 'much improved', as reported by the patient. Wirth et al. (2016) defined recovery as "much better" or "better" on their 7-point Likert scale (Wirth et al., 2016). Vos et al. (2008) analyzed only the group that reported 'completely recovered' in their univariate regression analysis. Five studies presented univariate- and multivariate analyses. Wirth et al. (2016) only presented the outcomes of the multivariate analyses.

3.3. Risk of bias within studies

The two reviewers agreed 100% on the overall score regarding RoB using the QUIPS tool for all studies. On average there was low RoB in study participation, prognostic factor measurement and outcome measurement. The highest RoB was found in 'study confounding' and 'study attrition' across the six assessed studies. The following Table 4 outlines the results of the RoB assessment.

3.4. Synthesis of results

We conducted a qualitative data synthesis for both univariate and multivariate results and for each different follow-up period, taking into account the number of studies and their methodological quality.

The included studies analyzed a total of 47 and 43 variables for the outcome variables 'pain intensity' and 'perceived non-recovery', respectively.

At three months follow-up, 18 prognostic factors were investigated for 'pain' as outcome variable. There were no studies at six months for pain, and 34 prognostic factors were investigated in univariate analyses at 12 months follow-up. Multivariate analyses were found in three studies (Pool et al., 2010; Hoving et al., 2004; Hill et al., 2004) with follow up at three or 12 months.

Two studies (Schellingerhout et al., 2010; Hill et al., 2004) used poor recovery as their main outcome variable and four studies (Pool et al., 2010; Hoving et al., 2004; Wirth et al., 2016; Vos et al., 2008) used good recovery as their main outcome variable. For perceived non-recovery, 18 prognostic factors were investigated in univariate analyses at three months and six months follow-up, and 23 prognostic factors at 12 months follow-up. Multivariate analyses were reported in five studies (Pool et al., 2010; Hoving et al., 2004; Wirth et al., 2016; Vos et al., 2008; Schellingerhout et al., 2010) with follow up at three, six or 12 months. However, these studies only reported on the significantly associated variables and not on which factors were included in the primary multivariate analysis.

We present the syntheses of the results for the univariate analysis for the outcome variable 'pain' in Table 5 and the outcome variable 'perceived non-recovery' in Table 6. The description of the multivariate analyses, for both outcome variables, are presented in Table 7. The extensive description and the syntheses of the results can be found in Appendix 3 and 4.

3.5. Pain intensity

In total 47 variables were tested for their prognostic significance (Table 5) in three studies; one high RoB study with a follow-up at three months (Pool et al., 2010) and two high RoB studies (Hoving et al., 2004; Hill et al., 2004) with a follow-up of 12 months. Only 16 of these 47 variables had a statistically significant association with higher pain, while two of the 47 variables had a statistically significant association with decreased pain.

Based on the univariate- and multivariate analysis (Pool et al., 2010; Hoving et al., 2004; Wirth et al., 2016; Vos et al., 2008; Schellingerhout et al., 2010; Hill et al., 2004) we found *moderate evidence* for 'age > 40 years' and 'concomitant back pain' to be prognostic for 'pain intensity' at 12 months follow-up. Two high RoB studies found these variables to be significant in these analyses.

Based on the univariate analyses we found *conflicting evidence* for the variables 'female gender' and 'neck injury/traumatic cause' at 12 months follow-up (Hoving et al., 2004; Hill et al., 2004).

As each of in total 16 variables was only measured in one study (Pool et al., 2010; Hoving et al., 2004; Hill et al., 2004), we considered these variables as having *limited evidence* for an association with higher pain. Five of these 18 variables were measured at three months, and 11 variables at 12 months.

In multivariate analyses (Table 7) only older age and concomitant LBP were retained in the model in more than one study, confirming *moderate evidence* for these variables. Distress was retained as a significant prognostic variable in the multivariate analyses at 12 months in one study with high RoB, which was considered as *limited evidence* (Pool et al., 2010).

3.6. Perceived non-recovery

Perceived non-recovery was measured in five studies at three (Pool et al., 2010; Wirth et al., 2016), six (Schellingerhout et al., 2010), and twelve (Hoving et al., 2004; Vos et al., 2008; Hill et al., 2004) months follow-up. In total, 43 variables were tested on their prognostic value (Table 6).

We found *moderate evidence* for a 'previous period of neck pain' and 'accompanying headache' at 12 months. The results of Vos et al. (2008) showed a significant association with non-recovery, Hoving et al. (2004) showed the similar results, however the association was non-significant. We therefore considered this as moderate evidence.

We found *limited evidence* for 'accompanying headache' and an 'increased fear of movement (TSK)' for perceived non-recovery and 'female gender' for perceived non-recovery at three months. At six months

Table 4
Risk of bias QUIPS-tool.

Studies	Study Participation	Study Attrition	Prognostic Factor Measurement	Outcome measurement	Study Confounding	Statistical Analysis and reporting	Overall score
Hoving et al. (Hoving et al., 2004)	Low	Low	Low	Low	High	Low	**High**
Hill et al. (Hill et al., 2004)	Low	Moderate	Low	Low	Low	Low	**High**
Vos et al. (Vos et al., 2008)	Low	Moderate	Low	Low	Moderate	Moderate	**High**
Pool et al. (Pool et al., 2010)	Moderate	Moderate	Low	Low	High	Moderate	**High**
Schellingerhout et al. (Schellingerhout et al., 2010)	Moderate	Low	Low	Low	Moderate	High	**High**
Wirth et al. (Wirth et al., 2016)	Low	High	High	Low	High	Low	**High**

Table 5
Univariate level of evidence of positive association with a higher pain intensity.

Prognostic factors	3 months	12 months
Social demographic		
Age ≥ 40 years		+
Age 18-29 years (ref)		
30-44 years		+
45-59 years		+*
60-75 years		+*
Age (in years)	+	
Gender (female)	+*	+/-
Social class		
- Nonmanual (ref)		
- Manual		+
Marital status		
- Married/partner		
- Other		+
Children		
- None (ref)		
- 1		-
- 2		+
- ≥ 3		+
Nonworking		+*
Symptoms		
Low Back Pain		+*
Pain intensity at baseline	+	+*
Severity of complaints	+*	
Duration of the neck pain		
- 2-6 weeks (ref)		
- 7-12 weeks		+
- ≥13 weeks		+*
Radiating pain below elbow		+
Headache (of cervical origin)		+
No change in neck pain previous 2 weeks		+
Disturbed sleep due to neck pain		+
High severity of physical dysfunctioning		+
GCPS (grade)		
- 1 = low intensity (ref)		

(*continued on next page*)

Table 5 (*continued*)

- 2 = high intensity	-	
- 3 = moderately limiting	+	
- 4 = severely limiting	+	
Prior conditions/ cause problem		
Previous episodes of neck pain	+	+*
Neck injury/ Traumatic cause		+/-
Physical activities		
Standing/walking in last job ≥ 2 hours		+
Driving in last job ≥ 4 hours		-
Digging/shoveling in last job		-
Sitting in last job ≥ 2 hours		-
Lifting in last job ≥ 25 lb weights		+*
Gardening at last once or twice a week		+*
Do-it-yourself work often		+
Walking each day > 30 min		+
Cycling each day		+*
TV hours > 3 hours per day		-
Physical activity last than average		+*
Psychological factors		
Catastrophizing (PCCL)	+	
Coping (PCCL)	+	
Internal pain control (PCCL)	-	
External pain control (PCCL)	+	
TSK (higher score)	+*	
Somatization (4DSQ)	+*	
Fear (4DSQ)	+*	

(*continued on next page*)

Table 5 (*continued*)

Distress (4DSQ)	+	
Depression (4DSQ)	+	
Job satisfaction		+
Satisfaction at not working		+
General health		
BMI		
- < 22.5 (ref)		
- 22.5-25.0		+
- 25.1-27.4		+
- ≥ 27.5		+
-		
Smoking status		
- Never (ref)		
- Past		+
- Current		+
Alcohol intake < 3 days per week (ref)		-*
>3 days per week		
Perceived General Health		
- Excellent (ref)		
- Good		+
- Fair		+
- Poor		+*
GHQ		
- <8 (ref)		
- 8-11		+*
- 12-17		+

(*continued on next page*)

Table 5 (*continued*)

- ≥ 18 poor psychological health		+*
Remaining factors		
Patients preference		
- None (ref)		
- Pt	-	
- Mt	-	
GP attitude		
- Purely biomedical (ref)		
- More biomedical	-	
- Neutral	-	

\+ = positive association of prognostic factor with a higher pain intensity

\- = negative association of prognostic factor with a higher pain intensity

* = Significant prognostic value

GCPS = Graded Chronic Pain Scale. GHQ = general health questionnaire. GP = General Practioner.
PCCL = Pain Coping and Cognition list. TSK = Tampa Scale of Kinesiophobia.
4DSQ =Four Dimension Psychological Symptomatology Questionnaire.

Strong Moderate Limited Conflicting No evidence

follow-up limited evidence was found for 10 variables (Schellingerhout et al., 2010). With regard to one-year follow-up, nine variables in one study had a statistically significant association with perceived non-recovery and were considered as limited evidence (Hoving et al., 2004; Vos et al., 2008; Hill et al., 2004). One factor (GP advice to wait and see) had a positive impact on recovery (Vos et al., 2008).

In one multivariate analysis, depression was not retained as a significant prognostic factor at three months (Pool et al., 2010), but was retained in another study (Table 7). (Wirth et al., 2016) At six months seven variables were found to be significantly associated with non-recovery (Schellingerhout et al., 2010). Three studies tested prognostic factors at 12 months in a multivariate analysis (Pool et al., 2010; Hoving et al., 2004; Vos et al., 2008). No common factor across the three studies was identified that was significantly associated with persistent complaints defined as non-recovery.

Based on the analysis of the multivariable models we found no prognostic factor that was retained as significant in more than one model (Table 7). This does not lend support for the evidence of some prognostic factors found in the univariate analyses.

3.7. Quality of evidence

We present the assessment of the modified GRADE in Appendix 5 and 6. We included 5 primary studies (phase 1) and one phase 3 study. The quality of evidence was downgraded for all prognostic factors researched in the primary studies. We also downgraded all prognostic factors on 'study limitation' due to the high risk of bias assessed with the QUIPS tool (Table 4). 'Publication bias', 'imprecision' and 'inconsistency' were for most of the prognostic factors not applicable due to the limited number of included studies, resulting in a limitation (down) grading. When a prognostic factor showed consistent evidence over different follow-up periods, 'inconsistency' was graded as no serious limitation. No serious limitations for 'imprecision' were graded when there were 2 included studies on one prognostic factor, large enough sample sizes and no intervals reported in both no effect and appreciable risk and protective values. There were no serious limitations on 'indirectness'. We could only increase the quality of evidence for moderate effect size for a few prognostic factors with an OR of > 2.5. For the outcome variable pain intensity we found only low quality evidence for the prognostic factor 'older age'. For the outcome variable perceived-recovery we found only low quality evidence for 'older age' and 'accompanying headache', and low back pain, a previous episode of neck pain and a higher score on the TSK at 6 months. For the other prognostic factors we had to downgrade the quality of evidence to very low.

4. Discussion

We systematically synthesized the evidence of prognostic factors for the development of chronic musculoskeletal neck pain or perceived non-recovery after a first episode of idiopathic, non-traumatic neck pain. We found moderate evidence for 'age > 40 years' and 'concomitant back pain' to be prognostic for 'pain intensity'. For the outcome 'perceived non-recovery', we found moderate evidence for both 'a previous period of neck pain' and 'accompanying headache'. However, we found only low or very low quality evidence for these prognostic factors.

Other studies found similar prognostic factors in musculoskeletal problems (Artus et al., 2017; Bier et al., 2017; Mallen et al., 2007;

Table 6
Univariate level of evidence of positive association with perceived non-recovery.

Prognostic factors	3 months	6 months	12 months
Social demographic			
Age ≥ 40 years	+		+*
Age (in years)	+	-*	
Age-square		+*	
Gender (female)	+	-	+* / -
Level of education			
- High (ref)			
- Middle		+	
- Low		+	
Employment status (yes = 1)		-	
Symptoms			
Low Back Pain		+*	+*
Severe initial pain	+	-	+
Severe initial pain square		+*	
Severity of complaints	-		
Duration of complaints >2 weeks			+*
> Duration current episode			
- 1-3 months		-	+
- >3 months		+	+
Pain in the upper part of the neck			+*
Accompanying headache	+*	+*	+*
Radiating pain below elbow			+

(*continued on next page*)

Table 6 (*continued*)

Radiating to the back			+*
Radiating pain (yes = 1)		-*	
No change in neck pain previous 2 weeks			+*
Disturbed sleep due to neck pain			-
Accompanying dizziness (yes = 1)		+	
High severity of physical dysfunction			+
GCPS (grade)			
- 1 = low intensity (ref)			
- 2 = high intensity	-		
- 3 = moderately limiting	+*		
- 4 = severely limiting	-		
Total score on the NDI (higher score)		+*	+*
Total score on the ALBPSQ			+*
Prior conditions/ cause problem			
Previous episodes of neck pain	+	+*	+*
Traumatic cause		+*	+
Psychological factors			
Catastrophizing (PCCL)	+		

(*continued on next page*)

Table 6 (*continued*)

Coping (PCCL)	-		
Internal pain control (PCCL)	-		
External pain control (PCCL)	-		
TSK (higher score)	+*	+*	
Somatization	+		
Fear (4DSQ)	+		
Distress (4DSQ)	+		
Depression (4DSQ)	+*		
General health			
EuroQOL VAS		+*	
Remaining factors			
Patients preference			
- None (ref)			
- Pt	-	-	
- Mt	-	+	
GP attitude			
- Purely biomedical (ref)			
- More biomedical	+		
- Neutral	-		
Treated for neck pain in the past (yes=1)		+*	
Treated by physiotherapist before			+*
Treated by manual therapist before			+*
GP advised to wait and see			-*
GP advised to improve posture			-
GP prescribed medication			+
GP instructed in physical exercises			-

\+ = positive association of prognostic factor with perceived non-recovery

\- = negative association of prognostic factor with perceived non-recovery

* = Significant prognostic value

ALBPSQ =Acute Low Back Pain Screening Questionnaire EuroQOL = Quality of Life Scale. GCPS = Graded Chronic Pain Scale. GP = General Practioner. NDI = Neck Disability Index. PCCL = Pain Coping and Cognition list. TSK = Tampa Scale of Kinesiophobia. 4DSQ = Four Dimension Psychological Symptomatology Questionnaire

Strong Moderate Limited Conflicting No evidence

Table 7
Summary of the multivariable models.

Auteur	3 months	12 months		Explained variance/discriminative ability model
Prognostic factors for a positive association with pain				
Pool et al. (Pool et al., 2010)	Gender (male) OR 3.13 (1.5–6.67) Less severity of complaints OR 0.74 (0.57–0.95) Fear of movement (TSK) OR 1.09 (1.02–1.15)	Distress (4DSQ) (not given)		R^2 explained variance 16% for non-recovery of pain at 3 months. R^2 explained variance at 12 months not given.
Hoving et al. (Hoving et al., 2004)		**> 40 year β 1.11 (0.38–1.84)** **Low back pain β 0.80 (-0.02–1.61)** Duration of the neck pain ≥13 weeks β 1.35 (0.34–1.93) Previous episodes of neck pain β *1.35 (0.13-1.58)* Pain intensity at baseline β 0.26 (0.07–0.45)		R^2 explained variance 30% for non-recovery of pain at 12 months.
Hill et al. (Hill et al., 2004)		**45–59 years OR 3.9 (2.2–6.7)** **Low back pain OR 1.6 (1.1–2.2)** Nonworking OR 1.6 (1.1–2.3) Cycling each day OR 2.4 (1.5–4.0)		R^2 explained variance not given
Prognostic factors for perceived non-recovery				
Pool et al. (Pool et al., 2010)	Accompanying headache OR 3.70 (1.47–9.09) *Patient preference physiotherapy* OR 0.22 (0.05–1,03)		Fear of movements (TSK) (Pool et al., 2010) (not given)	R^2 explained variance 17% for perceived non-recovery at 3 months. R^2 explained variance at 12 months not given.
Hoving et al. (Hoving et al., 2004)			> 40 year OR 3.85 (1.64–9.09) Concomitant LBP OR 2.7 (1.25–5.88) No change in neck pain previous 2 weeks OR 3.03 (1.52–5.88) Traumatic cause OR 2.5 (0.95–6.67) High severity of physical dysfunction OR 1.85 (0.90–3.7)	R^2 explained variance not given.
Vos et al. (Vos et al., 2008)			Female gender OR 4.55 (1.39–14.29) Pain in the upper part of the neck OR 1.85 (1.32–2.56) Duration of complaints > 2 weeks OR 3.03 (1.10–8.33) Pain radiating to the back OR 1.89 (1.23–2.86) *GP advised to wait and see* OR 0.15 (0.03–0.63)	R^2 explained variance 38% for perceived non-recovery at 12 months.
Schellingerhout et al. (Schellingerhout et al., 2010)		Age OR 1.03 (1.01–1.05) Previous episode of neck pain OR 1.67 (1.25–2.24) Trauma as cause of the complaints OR 1.26 (1.02–1.56) Concomitant LBP OR 2.29 (1.27–4.12) Paid employment OR 1.45 (1.03–2.05) Accompanying headache * pain intensity OR 1.12 (1.01–1.24) Accompanying headache * radiation pain OR 1.48 (1.03–2.12) *Radiation of pain to elbow/shoulder OR 0.57 (0.42-0.77)* *Accompanying headache * previous neck complaints OR 0.69 (0.48-0.98)* *Accompanying headache * employment status OR 0.44 (0.30-0.65)*		Discriminative ability 0.66 (95% CI, 0.61–0.71)). A confidence interval of 84.3% corresponds with their criterion ($P < 0.157$). Multivariable model tested in independent cohort: Discriminative ability (AUC) of 0.66 (95% confidence intervanl, 0.59–0.72)

(*continued on next page*)

Table 7 (*continued*)

Auteur	3 months	12 months	Explained variance/discriminative ability model
Wirth et al. (Wirth et al., 2016)	Depression BQ 1.30 (1.02–1.64) Age 1.03 (0.98–1.09) Pain at baseline 1.14 (0.76–1.67)		Nagelkerke R^2 = 0.21; AUC = 0.80 (95% CI 0.69–0.91; p = 0.002

OR = Odds Ratio > 1 positive association, < 1 negative association with non-recovery (Pool et al., 2010; Hoving et al., 2004; Wirth et al., 2016; Vos et al., 2008; Schellingerhout et al., 2010; Hill et al., 2004). β = Regression coefficient, 95% CI > 0 bad/ < 0 good for pain intensity (Hoving et al., 2004). Variables with a statistically prognostic value of a lower probability of persistent complaints shown in red. TSK = Tampa Scale of Kinesiophobia. 4DSQ = Four Dimension Psychological Symptomatology Questionnaire, BQ = Bournemouth Questionnaire. Prognostic factors with a negative association with pain or perceived non-recovery shown in italics. Prognostic factors who retained in 2 multivariable models shown in bold.

Walton et al., 2013). Concomitant headache and low back pain (LBP) were found to be prognostic for 'chronicity' after an acute whiplash injury (Walton et al., 2013) and for 'time to recover' from a new episode of idiopathic neck pain (Leaver et al., 2013). A previous episode of pain has been reported as a generic prognostic factor for musculoskeletal pain (Artus et al., 2017; Mallen et al., 2007) and chronic WAD (Walton et al., 2013). Were Mallen et al. (2007) and Leaver et al. (2013) found 'older age' of prognostic value.

Posttraumatic stress symptoms, passive coping and high catastrophizing are prognostic factors for chronification of WAD (Walton et al., 2013; Campbell et al., 2018). Avoidance beliefs, catastrophizing, depressive symptoms and distress were found to be prognostic factors for chronification of LBP (Wertli et al., 2014a, 2014b; George and Beneciuk, 2015; Nicholas et al., 2011). The literature found similar psychological problems (e.g. psychological stress, anxiety, fear-avoidance beliefs and catastrophizing) associated with chronic idiopathic, non-traumatic neck pain (Ortego et al., 2016; Thompson et al., 2010; Landers et al., 2008). It is therefore surprising that in prognostic studies on the persistence of acute idiopathic neck pain so very few of these modifiable psychological variables were researched. Only one study (Pool et al., 2010) included a number of relevant psychological variables on both outcome variables at 3 months. Hill et al. (2004) measured two psychological variables for the outcome variable pain at 12 months, whereas Schellingerhout et al. (2010) and Wirth et al. (2016) measured 'kinesiophobia' and 'depression', respectively, as a modifiable variable at 6 and 3 months, respectively, on perceived non-recovery.

We assessed study quality with the QUIPS-tool. The QUIPS-tool considers an overall high RoB when only one of the six-domains is of moderate or high RoB. We are well aware that the QUIPS-tool does not make any difference in degree of bias and is thereby strict in its conclusions. However, the overall high RoB is comparable with other systematic reviews that have included the same studies (Wingbermühle et al., 2018; Kelly et al., 2017).

4.1. Strengths and limitations

Our study contributes to the literature by identifying prognostic factors for chronicity in patients with idiopathic, non-traumatic acute- and/or sub-acute neck pain. We do so by only reviewing studies of which at least 60% of the population consisted of these patients. Ideally, all studies that included patients with chronic neck pain and/or with a traumatic cause would be excluded from the review. However, this would have resulted in an even much lower number of studies making it impossible to synthesize any evidence. We only found six studies, five of which were phase 1 explanatory studies. For example, the study of Schellingerhout et al. (2010) included data from one RCT on chronic neck pain (34% of subjects), which explains why variables such as 'duration of complaints ≥ 13 weeks' and 'traumatic cause' were included in this review. Consequently, one cannot consider these variables as prognostic factors for the group of patients with idiopathic, acute- and sub-acute neck pain although they could have influenced the outcomes of these specific studies (Hoving et al., 2004; Schellingerhout et al., 2010; Hill et al., 2004).

A strength of our study is that we did not only judge the level of evidence, but that we also critically assessed the quality of our findings. This allowed to distinguish between level and quality of evidence, and hence, for a more reliable assessment of the results of existing studies.

The results found in our systematic review have to be interpreted with caution. A first point of attention is that Vos et al. (2008) used a CI of 90% in their univariate analysis whereas the other five studies (Pool et al., 2010; Hoving et al., 2004; Wirth et al., 2016; Schellingerhout et al., 2010; Hill et al., 2004) used a CI of 95%. In the multivariate analysis five studies (Pool et al., 2010; Hoving et al., 2004; Wirth et al., 2016; Vos et al., 2008; Hill et al., 2004) used a 95% CI; Schellingerhout et al. (2010), however, used a CI of 84.3%. By using a smaller confidence interval the chance that type 1 errors occurs increases

(Akobeng, 2016).

Second, we included studies that used data from randomized clinical trials (Pool et al., 2010; Hoving et al., 2004; Schellingerhout et al., 2010). It is questionable whether data from randomized clinical trials are appropriate to identify modifiable variables for persistent pain or non-recovery. The applied therapy could have affected the found associations: if the therapy is effective, these patients will experience less or no pain, and the effect of the prognostic factors is mitigated. The effect of treatment can be seen as an effect modifier (Hancock et al., 2009). Prognostic factors could be at best researched in the non-treatment or placebo arm of RCT's (Adolfsson and Steineck, 2000), instead of adjusting for intervention in regression analysis.

Third, there is still some uncertainty about the exact sample composition and the analyzed factors in the study from Schellingerhout et al. (2010) as this study pooled data from three other studies (Pool et al., 2010; Hoving et al., 2004; Vonk et al., 2009). These three studies, however, analyzed different factors and also used different selection criteria for their cohorts. Combining these studies therefore resulted in large amounts of missing data for some of the variables. It is not clear how the authors dealt with missing data. We therefore have to interpret these findings with caution.

Fourth, despite the fact that the included studies used a similar tool for measuring perceived recovery, they interpreted it differently in their data analyses. While Vos et al. (2008) analyzed only the group who was 'completely recovered' as recovered, Hoving et al. (2004) and Pool et al. (2010) also included the group who were 'much improved'. Wirth et al. (2016) considered 'much better' and 'better' as recovered. Based on these different interpretations, it can be questioned whether the results for this outcome variable can be compared. In addition, the prognostic variables have to be well described and measured with valid tools. The included studies used different tools for measuring the same construct, for instance depression (Pool et al., 2010; Wirth et al., 2016). Additionally, the interpretation of some variables is unclear. Pool et al. (2010) measured 'pain at inception' and 'severity of complaints' at baseline. It is unclear whether practitioners and patients can differentiate between the two. We therefore recommend to develop a Core Outcome Set for neck pain and the use of consistent measurements and definitions for the dependent and independent variables in further research. Only then is it possible to obtain valuable evidence and useful data for practice.

Another limitation of our study could be that we did not include secondary measures, such as pain related disability. However, it is known that pain and disability are distinct constructs as not every person with persistent pain also experiences disability (Lee et al., 2015). Nevertheless from a clinical and health perspective neck-related disability and work status are important outcomes, and further research should measure pain intensity, disability and work status as distinct dimensions of persistent pain. However, identifying prognostic factors for disability and work status was beyond the scope of this review.

4.2. Further research

The focus in health care must be on the prevention of chronic pain. As mentioned above, chronic neck pain influences not only quality of life, but also impacts health care costs worldwide. Prevention is therefore key in combatting this, and opportunities for the prevention of chronicity only exist in acute- and subacute patients.

Given that we found no low RoB study, and because of the specific limitations as outlined above, there is much need for a conclusive and comprehensive cohort study on prognostic factors for chronification of acute- or subacute idiopathic, non-traumatic, neck pain. Special attention must be given to modifiable prognostic factors.

5. Conclusion

We have identified moderate and limited evidence to support the presence of a number of prognostic factors in patients with acute or subacute musculoskeletal, non-traumatic neck pain that are associated with pain or perceived non-recovery up until one year after onset of pain. Such factors include higher age (> 40 years), concomitant LBP or headache and a previous period of neck pain. Nevertheless, the quality of this evidence is graded as low to very low. Further research is needed before drawing definite conclusions about the prognostic value of these factors.

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Appendix 1. Search strategy

Review question

Which factors predict the development of chronic musculoskeletal neck pain after a first episode of idiopathic, non-traumatic neck pain?

MEDLINE (PubMed)

(chronic OR "non specific" OR nonspecific OR "long standing" OR longstanding OR persistent) AND ("Neck Pain" [Mesh] OR neck pain [tiab] OR neckache*[tiab] OR neck ache*[tiab] OR cervicodynia*[tiab] OR cervicalgia*[tiab] OR cervical pain [tiab] OR cervical ache [tiab] OR cervical aches [tiab]) AND (factor*[tiab] OR affordance*[tiab] OR constraint*[tiab] OR obstacle*[tiab] OR impediment*[tiab] OR enabler*[tiab] OR motivat*[tiab] OR inhibit*[tiab] OR stimulat*[tiab] OR correlat*[tiab] OR determin*[tiab] OR facilitat*[tiab] OR barrie*[tiab])

PsycINFO(OVID)

((chronic OR non specific OR nonspecific OR long standing OR longstanding OR persistent) AND (neck pain OR neckache* OR neck ache* OR cervicodynia* OR cervicalgia* OR cervical pain OR cervical ache*) AND (factor* OR affordance* OR constraint* OR obstacle* OR impediment* OR enabler* OR motivat* OR inhibit* OR stimulat* OR correlat* OR determin* OR facilitat* OR barrie*)). mp.

Embase(Elsevier)

chronic OR 'non specific' OR nonspecific OR 'long standing' OR longstanding OR persistent AND ('neck pain'/exp OR neckache* OR 'neck ache*' OR cervicodynia* OR cervicalgia* OR 'cervical pain' OR 'cervical ache*') AND (factor* OR affordance* OR constraint* OR obstacle* OR impediment* OR enabler* OR motivat* OR inhibit* OR stimulat* OR correlat* OR determin* OR facilitat* OR barrie*) AND [embase]/lim.

SPORTDiscus(EBSCO)

(chronic OR "non specific" OR nonspecific OR "long standing" OR longstanding OR persistent) AND (DE "NECK pain" OR "neck pain" OR neckache* OR "neck ache*" OR cervicodynia* OR cervicalgia* OR "cervical pain" OR "cervical ache*") AND (factor* OR affordance* OR constraint* OR obstacle* OR impediment* OR enabler* OR motivat* OR inhibit* OR stimulat* OR correlat* OR determin* OR facilitat* OR barrie*)

CINAHL(EBSCO)

(chronic OR "non specific" OR nonspecific OR "long standing" OR longstanding OR persistent) AND (MH "Neck Pain" OR "neck pain" OR neckache* OR "neck ache*" OR cervicodynia* OR cervicalgia* OR "cervical pain" OR "cervical ache*") AND (factor* OR affordance* OR constraint* OR obstacle* OR impediment* OR enabler* OR motivat* OR inhibit* OR stimulat* OR correlat* OR determin* OR facilitat* OR barrie*)

Grey literature databases

Dart Europe: "neck pain" AND factor*
Open access Theses and Dissertations: "neck pain" AND factor*
NDLTD: "neck pain" AND factor*
Clinical trials. gov: "neck pain" AND factor*
WHO ICTRP: "neck pain" AND factor*

Appendix 2. Data extraction table

Authors	Population	N (at baseline)	Patients characteristics	Mean age (SD)	Outcome variables	Follow-up period	N (at follow-up)	Statistical analyses	Recovery	Quality of the study (QUIPS)
Hoving et al. (Hoving et al., 2004)	GP NL	183 60.7% F	Pain and/or stiffness of the neck for at least two weeks Previous 6 months no pain	66.7% > -40 yrs	Pain intensity NRS PGIC	7 and 52 weeks	7 weeks 183 (100%) 52 weeks 178 (97%)	Logistic regression analysis Multiple regression	7 weeks 51.4% 52 weeks 63.4% recovered	High Risk of bias
Hill et al. (Hill et al., 2004)	Adults general population UK	1359 61% F (follow-up responders)	1 month period prevalent neck pain	51 yrs (follow-up responders)	Persistent neck pain	12 months	786 (58%)	Logistic regression analysis Multiple regression	381 (48%) neck pain after 1 year	High Risk of bias
Vos et al. (Vos et al., 2008)	GP NL	187 64% F	Non-specific neck pain < 6 weeks first episode or after a pain free period > 3 months	Females 38.2, SD 13.3 yr Males 43.2, SD 14.9 yr	PGIC	6, 12, 26, and 52 weeks	138 (74%)	Logistic regression analysis Multiple regression	76% recovered or much improved, 47% ongoing pain	High Risk of bias
Wirth et al. (Wirth et-al., 2016)	Chiropractic practices CH	103 60.7% F	First episode acute non-specific neck pain < 4 weeks	38.3 SD 13.8 yrs	PGIC	One week, 1 and 3 months	82 (80%)	Logistic regression analysis Multiple regression	86.6% improved after 3 months	High Risk of bias
Schellingerhout et al. (Schellingerhout et al., 2010)	GP NL	468 61% F	Non-specific neck pain. Acute – and sub-acute (61%)	45.4 SD 11.8 yrs	PGIC	6 months	Missing value differ per variable (1–43%)	Logistic regression analysis Multiple regression	43% persistent complaints	High Risk of bias
Pool et al. (Pool et al., 2010)	GP NL	146	Sub-acute neck pain	45.1 SD 11.2	GPE NRS pain	12 weeks 52 weeks	12 weeks 146 (100%) 52 weeks 128 (87.7%)	Logistic regression analysis Multiple regression	GPE 12 weeks: 70.5% 52 weeks: 77.2% NRS 12 weeks: 48.6% 52 weeks 68.2%	High Risk of bias

(N = number, F = female, N = number of patients, NRS= Numerical rating scale, BQ= Bournemouth questionnaire, PGIC = patient global impression of change, GPE = Global perceived recovery SD = standard deviation, GP = general practice, NL = Netherlands, UK = United Kingdom, CH = Switzerland).

Appendix 3. Univariate level of evidence of positive association with a higher pain intensity

Prognostic factors	3 months	12 months	Level of Evidence	Overall Quality of Evidence
Social demographic characteristics				
>Age 40 Hoving et al. Age Hill et al. 18-30 years (ref) 30-44 years 45-59 years 60-75 years		**1.04(0.27-1.80)** [37] 1.5(0.9-2.6)[41] **3.4(2.0-5.7)*** [41] 2.1(1.3-3.4)* [41]	*Moderate evidence for a positive association with a higher pain intensity at 12 months*	Low
Age (measured in years) Pool et al.	1.00[36]			
Gender (female) Pool et al. Hoving et al. Hill et al.	**0.38 (0.19-0.76)***[36]	1.0(0.8-1.3)[41] -0.15(-91-0.60)[37]	*Limited evidence for a positive association with a higher pain intensity at 3 months*	Very low
Social class Hill et al. Nonmanual (ref) Manual		 1.1(0.8-1.4)[41]		
Marital status Hill et al. Married/partner (ref) Other		 1.3(0.9-1.7)[41]		
Children Hill et al. None (ref) 1 2 >-3		 0.7(0.4-1.1)[41] 1.2(0.8-1.9)[41] 1.1(0.7-1.6)[41]		
Nonworking Hill et al.		**1.8(1.3-2.5)***[41]	*Limited evidence for a positive association with a higher pain intensity at 12 months*	Very low
Symptoms				
Low Back Pain Hoving et al. Hill et al.		**1.7(1.3-2.3)***[41] 1.13(0.29-1.97)*[37]	*Moderate evidence for a positive association with a higher pain intensity at 12 months*	Very low
Pain intensity at baseline Pool et al. Hoving et al.	1.10(0.17-1.19)[36]	0.26(0.07-0.45)*[37]	*Limited evidence for a positive association with a higher pain intensity at 12 months*	Very low
Severity of complaints Pool et al.	**0.78(0.61-0.91)***[36]		*Limited evidence for a positive association with a higher pain intensity at 3 months*	Very low
Duration of the neck pain Hoving et al. 2-6 weeks (ref) 7-12 weeks >-13 weeks		 0.07(-0.76-0.91)[37] **1.03(0.19-1.86)***[37]	*Limited evidence for a positive association with a higher pain intensity at 12 months*	Very low
Radiating pain below elbow Hoving et al.		0.77(-0.23-1.71)[37]		
Headache (of cervical origin)	1.67(0.81-3.33)[36]	0.52(-0.29-1.32)[37]		

Pool et al. Hoving et al.				
No change in neck pain previous 2 weeks Hoving et al.		0.66(-0.08-1.39)[37]		
Disturbed sleep due to neck pain Hoving et al.		0.33(-0.41-1.06)[37]		
High severity of physical dysfunctioning Hoving et al.		0.66(-0,10-1.42)[37]		
GCPS (grade) Pool et al. 1= low intensity 2= high intensity 3= Moderately limiting 4= severely limiting	 0.75(0.25-2.22)[36] 1.04(0.28-3.85)[36] 1.19(0.33-4.35)[36]			
Prior conditions/ cause problem				
Previous episodes of neck pain Pool et al. Hoving et al.	1.03(0.52-2.08)[36]	**0.83(0.06-1.59)***[37]	*Limited evidence for a positive association with a higher pain intensity at 12 months*	Very low
Neck injury/ Traumatic cause Hoving et al. Hill et al.		1.5(1.1-2.2)*[41] 0.72(-0.71-1.25)[37]	*Conflicting evidence for a positive association with a higher pain intensity at 12 months*	Very low
Physical activities				
Standing/walking in last job ≥2 hours Hill et al.		1.2(0.9-1.7)[41]		
Driving in last job ≥ 4 hrs Hill et al.		0.8(0.5-1.2)[41]		
Digging/shoveling in last job Hill et al.		0.8(0.4-1.7)[41]		
Sitting in last job ≥ 2 hours Hill et al.		0.9(0.6-1.2)[41]		
Lifting in last job ≥ 25 lb weights Hill et al.		1.3(1.0-1.8)*[41]	*Limited evidence for a positive association with a higher pain intensity at 12 months*	Very low
Gardening at last once or twice a week Hill et al.		0.8(0.6-1.0)*[41]	*Limited evidence for a negative association with a higher pain intensity at 12 months*	Very low
Do-it-yourself work often Hill et al.		1.0(0.7-1.4)[41]		
Walking each day >30 min Hill et al.		1.1(0.8-1.4)[41]		
Cycling each day Hill et al.		**2.0(1.3-3.2)***[41]	*Limited evidence for a positive association with a higher pain intensity at 12 months*	Very low
TV hours >3 hrs per day Hill et al.		0.9(0.7-1.3)[41]		
Physical activity Less than average Hill et al.		1.4(1.0-1.9)*[41]	*Limited evidence for a positive association with a higher pain intensity at 12 months*	Very low
Psychological factors				
Catastrophizing (PCCL) Pool et al.	2.38(0.98-5.88)[36]			
Coping (PCCL) Pool et al.	1.12(0.77-1.67)[36]			

Internal pain control (PCCL) Pool et al.	0.82(0.68-1.41)[36]			
External pain control(PCCL) Pool et al.	1.03(0.72-1.47)[36]			
TSK (higher score) Pool et al.	**1.06(1.00-1.12)***[36]		*Limited evidence for a positive association with a higher pain intensity at 3 months*	Very low
Somatization (4DSQ) Pool et al.	1.09(1.01-1.18)*[36]		*Limited evidence for a positive association with a higher pain intensity at 3 months*	Very low
Fear (4DSQ) Pool et al.	1.75(1.11-2.78)*[36]		*Limited evidence for a positive association with a higher pain intensity at 3 months*	Very low
Distress (4DSQ) Pool et al.	1.39(0.95-2.00)[36]			
Depression (4DSQ) Pool et al.	1.52(0.81-2.86)[36]			
Job satisfaction Hill et al.		1.1(0.7-1.7)[41]		
Satisfaction at not working Hill et al.		1.4(0.9-2.2)[41]		
General health				
BMI Hill et al. <22.5 (ref) 22.5-25.0 25.1-27.4 >- 27.5		 1.1(0.8-1.7)[41] 1.0(0.7-1.6)[41] 1.4(0.9-2.1)[41]		
Smoking status Hill et al. Never (ref) Past Current		 1.1(0.7-1.5)[41] 1.0(0.7-1.6)[41]		
Alcohol intake Hill et al. <3 days per week >3 days per week		 0.7(0.5-0.9)*[41]	*Limited evidence for a negative association with a higher pain intensity at 12 months*	Very low
Perceived General health Hill et al. Excellent (ref) Good Fair Poor		 1.3(0.8-2.3)[41] 1.5(0.8-2.6)[41] 1.9(1.0-3.7)*[41]	*Limited evidence for a positive association with a higher pain intensity at 12 months*	Very low
GHQ Hill et al. <8 (ref) 8-11 12-17 ≥18 poor psychological health		 1.6(1.0-2.7)*[41] 1.5(0.9-2.5)[41] 2.2(1.3-3.6)*[41]	*Limited evidence for a positive association with a higher pain intensity at 12 months*	Very low
Remaining factors				
Patients preference Pool et al. None Pt Mt	 0.43(0.15-1.23)[36] 0.86(0.39-1.25)[36]			
GP attitude Pool et al. Purely biomedical (ref) More biomedical	 0.67(0.24-1.85)[36] 0.46(0.17-1.12)[36]			
Neutral				

*OR[4136]. Regression coefficient, 95% CI >0 bad / <0 good for pain intensity[37] * = Significant prognostic value. Variables that remained after the multivariate analysis shown in bold. GCPS = Graded Chronic Pain Scale. GHQ = general health questionnaire. GP = General Practioner. PCCL = Pain Coping and Cognition list. TSK = Tampa Scale of Kinesiophobia. 4DSQ =Four Dimension Psychological Symptomatology Questionnaire.*

Appendix 4. Univariate level of evidence of positive association with perceived non-recovery

Prognostic factors	3 months	6 months	12 months	Level of Evidence	Overall Quality of Evidence
Social demographic characteristics					
Age ≥ 40 years Pool et al. Hoving et al.	1.03(0.98 -1.09)[36]		**2.94(1.45-5.88)***[37]	*Limited evidence for perceived non-recovery at 12 months*	Low
Age (in years) Pool et al. Schellingerhout et al.	1.01(0.98-1.04)[36]	0.88(0.79-0.99)*[40]		*Limited evidence for a better outcome at 6 months*	Very low
Age-square Schellingerhout et al.		1.00(1.00-1.06)*[40]		*Limited evidence for perceived non-recovery at 6 months*	Very low
Gender (female) Pool et al. Hoving et al. Vos et al. Schellingerhout et al.	2.00(1.10-4.35)*[36]	0.98(0.65-1.46)[40]	**2.5(0.99-6.25)***[39] 0.69(0.37-1.28)[37]	*Limited evidence for a better outcome at 3 months*	Very low
Level of education Schellingerhout et al. High (ref) Middle Low		 1.26(0.79-2.02)[40] 1.23(0.75-2.02)[40]			
Employment status (yes = 1) Schellingerhout et al.		0.60(0.39-0.92)*[40]		*Limited evidence for a better outcome at 6 months*	Very low
Symptoms					
Low Back Pain Hoving et al. Schellingerhout et al.		2.07(1.31-3.27)*[40]	**2.17(1.06-4.35)***[37]	*Limited evidence for perceived non-recovery at 6 and 12 months*	Low for 6 months Very low for 12 months
Severe initial pain Pool et al. Vos et al. Schellingerhout et al.	1.14(0.76-1.67)[36]	0.70(0.46-1.07)[40]	1.04(0.52-2.09)[39]		
Severe initial pain square Schellingerhout et al.		**1.05(1.01-1.09)***[40]		*Limited evidence for perceived non-recovery at 6 months*	Very low
Severity of complaints Pool et al.	0.95(0.75-1.22)[36]				
Duration of complaints >2 weeks Vos et al.			**2.44(1.03-5.56)***[39]	*Limited evidence for perceived non-recovery at 12 months*	Very low
> Duration current episode Hoving et al. Schellingerhout et al. 1-3 months >3 months		 0.68(0.38-1.22)[40] 1.25(0.68-2.31)[40]	 1.14(0.53-2.44)[37] 2.04(0.97-4.35)[37]		
Pain in the upper part of the neck Vos et al.			**1.64(1.22-2.17)***[39]	*Limited evidence for perceived non-recovery at 12 months*	Very low
Accompanying headache Pool et al. Hoving et al. Vos et al. Schellingerhout et al.	**3.45(1.41-8.33)***[36]	1.92(1.23-3.00)*[40]	3.33(1.35-8.33)*[39] 1.37(0.69-2.70)[37]	*Limited evidence for perceived non-recovery at 3 and 6 months.* *Moderate evidence for perceived non-recovery at 12 months.*	Low for 3,6 and 12 months
Radiating pain below elbow			1.49(0.66-3.33)[37]		

Hoving et al.					
Radiating to the back Vos et al.			**1.45(1.09-1.92)*[39]**	*Limited evidence for perceived non-recovery at 12 months*	Very low
Radiating pain (yes =1) Schellingerhout et al.		**0.66(0.45-0.97)*[40]**		*Limited evidence for a better outcome at 6 months*	Very low
No change in neck pain previous 2 weeks Hoving et al.			**2.63(1.39-4.76)*[37]**	*Limited evidence for perceived non-recovery at 12 months*	Very low
Disturbed sleep due to neck pain Hoving et al.			0.88(0.48-1.61)[37]		
Accompanying dizziness (yes = 1) Schellingerhout et al.		1.47(0.99-2.17)[40]			
High severity of physical dysfunctioning Hoving et al.			1.59(0.84-3.03)[37]		
GCPS (grade) Pool et al. 1= low intensity 2= high intensity 3= Moderately limiting 4= severely limiting	 0.56(0.18-1.75)[36] 1.64(0.44-6.25)[36] 0.77(0.20-3.03)[36]				
Total score on the NDI (higher score) Vos et al. Schellingerhout et al.		1.05(1.02-1.08)*[40]	1.08(1.01-1.14)*[39]	*Limited evidence for perceived non-recovery at 6 and 12 months*	Very low
Total score on the ALBPSQ Vos et al.			1.02(1.00-1.03)*[39]	*Limited evidence for perceived non-recovery at 12 months*	Very low
Prior conditions/ cause problem					
Previous episodes of neck pain Pool et al. Hoving et al. Vos et al. Schellingerhout et al.	1.56(0.75-3.23)[36]	**1.79(1.18-2.72)*[40]**	1.20(1.03-1.41)*[39] 1.75(0.90-3.45)[37]	*Limited evidence for perceived non-recovery at 6 months.* *Moderate evidence for perceived non-recovery at 12 months.*	Low for 6 months Very low for 12 months
Traumatic cause Hoving et al. Schellingerhout et al.		1.94(1.12-3.34)*[40]	**1.47(0.65-3.33)**[37]	*Limited evidence for perceived non-recovery at 6 months*	Very low
Psychological factors					
Catastrophizing (PCCL) Pool et al.	1.75(0.68-4.55)[36]				
Coping (PCCL) Pool et al.	0.82(0.54-1.23)[36]				
Internal pain control (PCCL) Pool et al.	0.83(0.56-1.25)[36]				
External pain control(PCCL) Pool et al.	0.93(0.62-1.37)[36]				
TSK (higher score) Pool et al. Schellingerhout et al.	1.05(1.00-1.11)*[36]	1.03(1.01-1.06)*[40]		*Limited evidence for perceived non-recovery at 3 and 6 months*	Very low for 3 months Low for 6 months
Somatization (4DSQ) Pool et al.	1.04(0.95-1.11)[36]				
Fear (4DSQ) Pool et al.	1.27(0.81-1.96)[36]				
Distress (4DSQ) Pool et al.	1.08(0.72-1.61)[36]				
4DSQ Depression Pool et al.	1.33(0.71-2.5)[36]			*Limited evidence for perceived non-recovery at 3 months*	Very low

General health					
EuroQOL VAS Schellingerhout et al.		0.99(0.98-1.00)*[40]		*Limited evidence for a better outcome at 6 months*	Very low
Remaining factors					
Patients preference Pool et al. Schellingerhout et al. None Pt Mt	 **0.25(0.05-1.15)**[36] 0.58(0.69-1.45)[36]	 0.77(0.45-1.32)[40] 1.19(0.73-1.93)[40]			
GP attitude Pool et al. Purely biomedical (ref) More biomedical Neutral	 2.13(0.76-5.88)[36] 0.46(0.16-1.35)[36]	 			
Treated for neck pain in the past (yes = 1) Schellingerhout et al.		1.77(1.20-2.61)*[40]		*Limited evidence for perceived non-recovery at 6 months*	Very low
Treated by physiotherapist before Vos et al.			1.25(1.10-1.89)*[39]	*Limited evidence for perceived non-recovery at 12 months*	Very low
Treated by manual therapist before Vos et al.			1.28(1.00-1.67)*[39]	*Limited evidence for perceived non-recovery at 12 months*	Very low
GP advised to wait and see Vos et al.			**0.26(0.07-0.93)*[39]**	*Limited evidence for a better outcome at 12 months*	Very low
GP advised to improve posture Vos et al.			0.96(0.72-1.28)[39]		
GP prescribed medication Vos et al.			1.64(0.81-3.33)[39]		
GP instructed in physical exercises Vos et al.			0.93(0.66-1.32)[39]		

*Results shown in OR = Odds Ratio > 1 positive association, < 1 negative association with non-recovery. * = Significant prognostic value. Variables that remained after the multivariate analysis shown in bold. ALBPSQ =Acute Low Back Pain Screening Questionnaire EuroQOL = Quality of Life Scale. GCPS = Graded Chronic Pain Scale. GP = General Practioner.*

NDI = Neck Disability Index. PCCL = Pain Coping and Cognition list. TSK = Tampa Scale of Kinesiophobia. 4DSQ = Four Dimension Psychological Symptomatology Questionnaire.

Appendix 5. Grading assessment quality of evidence for a higher pain intensity

Prognostic factor for pain intensity	# Participants	# Studies	Phase	Study limitations	Inconsistency	Indirectness	Imprecision	Publication bias	Moderate/large effect size	Dose effect	Overall quality
Age	1542	2	1	X	✓	✓	✓	X	✓	X	+ +
Gender (female)	146	1	1	X	X	✓	X	X	X	X	+
Non-working	1359	1	1	X	X	✓	X	X	X	X	+
Low Back Pain	1542	2	1	X	✓	✓	✓	X	X	X	+
Pain intensity	183	1	1	X	X	✓	X	X	✓	X	+
Severity of complaints	146	1	1	X	X	✓	X	X	X	X	+
Duration neck pain	183	1	1	X	X	✓	X	X	X	X	+
Previous episodes neck pain	183	1	1	X	X	✓		X	X	X	+
Neck injury	1542	2	1	X	✓	✓	✓	X	X	X	+
Lifting in last job	1359	1	1	X	X	✓	X	X	X	X	+
Gardening	1359	1	1	X	X	✓	X	X	X	X	+
Cycling	1359	1	1	X	X	✓	X	X	X	X	+
Physical activity	1359	1	1	X	X	✓	X	X	X	X	+
TSK (higher score)	146	1	1	X	X	✓	X	X	X	X	+
Somatisation	146	1	1	X	X	✓	X	X	X	X	+
Fear	146	1	1	X	X	✓	X	X	X	X	+
Alcohol intake	1359	1	1	X	X	✓	X	X	X	X	+
Perceived General Health	1359	1	1	X	X	✓	X	X	X	X	+
GHQ (higher score, poor psychological health	1359	1	1	X	X	✓	X	X	X	X	+

Phase, phase of investigation. For GRADE factors: √, no serious limitations; X, serious limitations (or not applicable; for publication bias, imprecision and inconsistency only one study available). For overall quality of evidence: +, very low; + +, low. TSK = Tampa Scale of Kinesiophobia, GHQ = General Health Questionnaire.

Appendix 6. Grading assessment quality of evidence for the outcome variable perceived non-recovery

Prognostic factor for perceived non-recovery	# Participants	# Studies	Phase	Study limitations	Inconsistency	Indirectness	Imprecision	Publication bias	Moderate/large effect size	Dose effect	Overall quality
Age ≥40	183	1	1	X	X	✓	X	X	✓	X	+
Age (years)	468	1	3	X	X	✓	X	X	X	X	+
Age-square	468	1	3	X	X	✓	X	X	X	X	+
Gender	146	1	1	X	X	✓	X	X	X	X	+
Employment status (yes = 1)	468	1	3	X	X	✓	X	X	X	X	+
Low Back Pain											
6 months	468	1	3	X	✓	✓	✓	X	X	X	+ +
12 months	183	1	1	X	✓	✓	✓	X	X	X	+
Severe initial pain square	468	1	3	X	X	✓	X	X	X	X	+
Duration neck pain ≥2 weeks	187	1	1	X	X	✓	X	X	X	X	+
Pain in upper part neck	187	1	1	X	X	✓	X	X	X	X	+
Accompanying headache											
3 months	146	1	1	X	✓	✓	✓	X	✓	X	+ +
6 months	468	1	3	X	✓	✓	✓	X	X	X	+ +
12 months	370	2	1	X	✓	✓	✓	X	✓	X	+ +
Radiating to the back	187	1	1	X	X	✓	X	X	X	X	+
Radiating pain (yes = 1)	468	1	3	X	X	✓	X	X	X	X	+
No change in neckpain previous 2 weeks	183	1	1	X	X	✓	X	X	✓	X	+
Total score on the NDI (higher score)											
6 months	468	10	3	X	X	✓	X	X	X	X	+
12 months	187	1	1	X	X	✓	X	X	X	X	+
Total score on the ALBPSQ	187	1	1	X	X	✓	X	X	X	X	+
Previous episodes of neck pain											
6 months	468	1	3	X	✓	✓	✓	X	X	X	+ +
12 months	370	2	1	X	✓	✓	✓	X	X	X	+
Traumatic cause	468	1	3	X	X	✓	X	X	X	X	+
TSK (higher score)											
3 months	146	1	1	X	✓	✓	X	X	X	X	+
6 months	468	1	3	X	✓	✓	X	X	X	X	+ +
Depression (4DSQ)	146	1	1	X	X	✓	X	X	X	X	+
EuroQOL VAS	468	1	3	X	X	✓	X	X	X	X	+
Treated for neck pain in past	468	1	3	X	X	✓	X	X	X	X	+
Treated by physio before	187	1	1	X	X	✓	X	X	X	X	+
Treated by MT before	187	1	1	X	X	✓	X	X	X	X	+
GP wait and see advise	187	1	1	X	X	✓	X	X	✓	X	+

Phase, phase of investigation. For GRADE factors: √, no serious limitations; X, serious limitations (or not applicable; for publication bias, imprecision and inconsistency only one study available). For overall quality of evidence: +, very low; + +, low. NDI = Neck Disability Index, ALBPSQ = Acute Low Back Pain

Questionnaire, TSK = Tampa Scale of Kinesiophobia, 4DSQ = Four Dimension Psychological Symptomatology Questionnaire, EuroQOL = Quality of Life Scale, GP = General Practioner.

Appendix 7. Reviewer agreement for full text screening after screening title and abstract

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.msksp.2019.03.009.

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