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Is there a relationship between psychological stress or anxiety and chronic nonspecific neck-arm pain in adults?: A systematic review and meta-analysis

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Abstract

Purpose: To systematically review and analyze the research evidence linking stress or anxiety to chronic nonspecific neck-arm pain (NSNAP) in adults.

Subjects and Methods: Data were obtained from Pubmed, Scopus, PsycInfo, Web of Science, Physiotherapy Evidence Database (PEDro) and The Cochrane library database from their inception to July 2015. Two authors independently conducted the searches, extracted data, and completed methodological quality assessments. The methodological quality of the cohort and case-control studies was evaluated using the Newcastle-Ottawa scale, whilst the quality of the Randomized Controlled Trial (RCT) was evaluated using the PEDro scale.

Results: Twenty-eight studies involving 39,166 participants met the inclusion criteria. Four studies, including 5 pair-wise comparisons, were included in the meta-analysis: Three were cohort studies and 1 was a cross-sectional study. The meta-analysis outcome demonstrated a relationship between chronic NSNAP and psychological stress. The estimate odds ratio for all studies combined was 2.33 (95% CI, 1.04 - 5.18; p=0.039). A high heterogeneity of the findings appeared ($Q=28.94$, $I^2=86\%$ $p=0.00$).

Conclusion: This study shows that there is a strong relationship between stress and chronic NSNAP. Despite this finding, we cannot support that stress is a risk factor for

chronic NSNAP due to the low quality of the results according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE). It was not possible to make a quantitative analysis comparing the relationship between anxiety and chronic NSNAP. However, according to the qualitative analysis there is a strong relationship between anxiety and chronic NSNAP.

Key words: Psychological stress; Anxiety; Chronic pain; neck-arm; NSNAP

Introduction

Chronic pain is usually defined as pain that lasts more than three months (1). The prevalence of chronic pain is about 30% in Europe and entails a high economic and social burden for society (2). Evidence suggests that conditions of chronic pain may be the result of an increase in the activity and a hyperexcitability of sensory neurons in the central nervous system, a process called central sensitization (3). In conjunction with biological factors, the likelihood of appearance, development, and persistence of chronic pain has been extensively related to psychological and social risk factors (4, 5). Furthermore, in the absence of peripheral nociceptive afferents, psychosocial factors such as stress or anxiety (6) can increase the descending facilitation of pain via sensitization and over activation of a number of pain-related areas in the forebrain and brainstem regions, a process called Cognitive-Emotional Sensitization (7), finally facilitating the perception of pain. However, the strength and the nature of this association between psychosocial factors and pain is far from being completely understood (8, 9).

Regarding neck pain, several studies have pointed out the considerable heterogeneity across findings and difficulties in presenting a real prevalence of this pain (10, 11). It is considered that the 12-month prevalence of neck pain in the general population ranges between 30% and 50% (12, 13). In relation to arm pain, in Netherlands, for instance, the 12-month prevalence of shoulder pain was 30.3% (14). Further, complaints of the arms, neck, and shoulders affect most of the general population at least once in 15 years (15).

Due to its relatively highly variable clinical presentation (16), the term used in this study is *Nonspecific neck-arm pain (NSNAP)*, which is used to describe symptoms in the upper quadrant related to heightened nerve mechanosensitivity, but without neurological deficits (i.e. no clinical signs of the presence of a radiculopathy) (17, 18). In fact, a recent study based on 18 countries suggested that Generalised Musculoskeletal pain in neck / shoulder region tended to be more persistent over time than pain located in the neck or shoulder. Furthermore, this study suggested that widespread pain in the neck / shoulder was associated with somatizing tendency, older age, and poor mental health (19).

In chronic NSNAP, we have also considered subjects with pain induced by sudden acceleration-deceleration movement of the neck, which are called whiplash associated disorders (WAD). Despite the fact that they are classified as different groups, we have joined both and considered them as if they belonged to the same group, as long as selected studies included WAD patients comprehended between grade 0 and 2 (20),

meaning that patients had no dislocation, fracture, or neurological deficit (21). It is important to remark that up to 90% of WAD patients are diagnosed as grade I or II (22).

With regards to the management of chronic pain, at present, it remains unsatisfactory and has a poor prognosis for a significant proportion of patients (23). This lack of evidence of effective interventions may be partly due to the aforementioned multidimensional factors contributing to its appearance and development, but also due to the lack of knowledge on the precise associated psychosocial factors, its role on the pain system, how they are measured, and moreover, how strong their association to pain is (24). Nevertheless, there is research currently seeking beneficial strategies to improve chronic pain. For instance, a recent study suggests that taking into account gender, anxiety, and depression in patients with chronic pain might be relevant in developing strategies for disease management (25). According to this, a clear understanding of these relationships may allow clinicians to facilitate the approach to chronic NSNAP, providing information for the clinical decision-making, which includes prognosis, assessment, and management (26).

Based on the available scientific literature, this systematic review expands upon previous studies explicitly targeting a particular population of interest, and focusing on specific characteristics of outcome measures as a prognostic factor for chronic NSNAP.

The aim of this study is first to determine whether an association between anxiety or psychological stress factors and patients with chronic NSNAP exists, and second, to determine how strong this association is.

Methods

Our literature search aimed to identify all available studies that evaluated the association between stress or anxiety factors to chronic NSNAP in adults. We searched in Pubmed database from their inception to July 2015. The search terms used were: ("pain"[tiab] OR "musculoskeletal"[tiab]) AND ("neck"[tiab] OR "shoulder"[tiab] OR "arm"[tiab] OR "upper limb"[tiab] OR "NSNAP"[tiab] OR "upper quadrant"[tiab] OR "upper extremity"[tiab]) AND ("stress"[tiab] OR "anxiety"[tiab]), terms and text words of key articles that we identified a priori.

Similar search strategies were used in Scopus, PsycInfo, Web of Science, PEDro and The Cochrane library database.

These keywords were identified after preliminary literature searches. Two reviewers (GO, PH) independently applied the previously determined inclusion and exclusion criteria to select potentially relevant papers which had been initially identified based on title and abstract. Full text copies of relevant trials were then obtained and independently evaluated by the reviewers. When a disagreement between reviewers occurred, it was resolved by a meeting held in consultation with another author (JHV).

Population

Regarding population, inclusion criteria were: 1) Age of 18 years or older; 2) Pain located in the neck-shoulder-arm region; and 3) Pain lasting for more than 3 months. Trials were excluded if subjects had undergone surgery; or if any of the

participants had received a diagnosis such as myelopathy, fracture, infection, dystonia, tumor, inflammatory disease, fibromyalgia, or osteoporosis.

Types of studies

Published studies without any restrictions on publication date or language were included. Publications identified as “epidemiological” (those reporting on the prevalence of stress/anxiety factors in adults) were selected for further review. Using a standardized data extraction sheet, each reviewer then analyzed each epidemiological paper to determine whether the full text of the article permitted completion of all four cells pertaining to psychosocial risk factor (psychological stress or anxiety) and chronic NSNAP in the fourfold association table: Stress/anxiety (+) / chronic NSNAP; Stress/anxiety (+) / chronic NSNAP (-); Stress/anxiety (-) / chronic NSNAP (+); Stress/anxiety (-) / chronic NSNAP (-).

Quality assessment of included studies

The methodological quality of the cohort and case-control studies were evaluated using the Newcastle–Ottawa scale. This scale which has been shown to be reliable and valid for rating the quality of non-randomized studies(27), was moderated to fit our study design and served to assess the quality of the eligible studies. The Newcastle–Ottawa scale scores each study by assigning 0 to 9 stars and assesses the studies in three domains: 1) selection of patients and controls, 2) comparability between groups, and 3) outcome and follow-up. Zero to 3 stars indicate poor study quality, 4 to 6 stars indicate acceptable study quality, and 7 to 9 stars indicate good study quality.

The methodological quality of the RCT studies were assessed using the PEDro scale that has been shown to be reliable and valid (28, 29) for rating the quality of RCTs. Trials with a rating of at least 6/10 at PEDro scale were rated as high quality.

The methodological quality of studies was assessed by two authors (JHV, LB).

Two authors (GO, VD) independently conducted data extraction. Three other authors (JHV, LB, PH) were consulted in the case of persisting disagreement. Reviewers were not blinded to information regarding the authors, journal of origin, or outcomes for each paper reviewed. Using a standardized form, data extraction addressed authors, year of publication, country, number of participants, number of males and females, average age, and the outcome measurements that were reported.

Data Synthesis and Analysis

Standard methods recommended for meta-analyses of studies were used. The meta-analyses were performed by computing odds ratio (OR) using a random-effects model to give a more conservative estimate of effect. The random-effects model is appropriate to use for analyses of large studies with great heterogeneity as often are the non-randomized studies. OR and 95% confidence intervals for each side effect (and all side effects) were calculated. ProMeta V.2.0 software was used for the statistical analyses. Calculation of effect size was based on 2 x 2 contingency tables data. Q and I-square statistics were used to assess heterogeneity between studies. A significant Q value indicates a lack of homogeneity of findings of studies. Publication bias was

assessed formally using Egger's t test. The symmetry of such 'funnel plots' was also assessed visually.

A qualitative analyses using the GRADE approach was planned (30). GRADE is a systematic approach to making judgments about the quality of evidence and the strength of recommendations. Using GRADE, we don't rate evidence study by study, but across studies for specific clinical outcomes. Domains that may decrease the quality of evidence are: study design, risk of bias, inconsistency of results, indirectness (not generalizable), imprecision (insufficient data), and other factors (e.g. lack of follow-up). GRADE classifies the level of evidence (high, moderate, low, and none) based on 1) the methodological quality of the Systematic Review (SR), 2) the quality of the cohort studies included in the SR, and 3) the consistency of the results of the cohort studies (**Table 1**). The GRADE level of evidence indicates the extent to which one can be confident that a specific factor predicts musculoskeletal pain or their consequences.

Results

Study selection

We identified 3,408 studies through database searching (**Figure 1**). After screening by titles and abstracts of all remaining unique articles, 28 full-text articles needed to be assessed to verify their eligibility for the inclusion in the present study (**Table 2**). Four studies of these 28 selected articles, including 5 pair-wise comparisons, were included in the meta-analysis: 3 were cohort studies (31-33) and 1 was a cross-sectional study (34) (**Table 3**).

Study characteristics

The characteristics of studies are included in **Table 2**. Included studies were published between 1991 and July 2015. These studies involved 39,166 participants. Twenty-four studies were prospective cohort studies (31-54), 3 were case-control studies (55-57), and one was an RCT (58). Sixteen of the 24 prospective cohort studies investigated work related chronic NSNAP (31-36, 38-42, 45, 47, 49, 50, 54). One RCT, 3 case-control studies, and 2 cohort studies were related to subjects with chronic whiplash (48, 51, 53, 55, 57, 58). Seventeen of 28 articles studied the relationship between chronic NSNAP and stress factor (32-42, 45, 47-50, 58). Five of 28 articles studied the relationship between chronic NSNAP and anxiety (43, 44, 46, 51, 53), and 3 of 28 articles examined both factors (31, 54, 55). Many studies were followed for more than 6 months (33, 35, 37, 49, 55, 58) to 3 years (32, 48).

Analytic sample sizes ranged from 32 (39) to 20,799 (57) participants. Twelve studies (38, 39, 41, 43, 44, 46, 48, 51-53, 55, 56), had 200 or fewer participants. Mean sample ages ranged from 33 (42) to 46 (34) years.

Quality rating

The quality of studies conducted by the New Castles-Ottawa ranged between eight points (36) and 0 points (42) with an average score of 3.7/9. Most studies scored 3/9 points (33, 38, 41, 45, 47) and 4/9 points (16, 40, 43, 44, 46, 49, 51-54, 56). The RTC (58) was evaluated with the PEDro scale and the score was 1/10.

Psychological stress factor

Twenty studies reported the association between psychological stress factor and chronic NSNAP ((31-42, 45, 47-50, 54, 55, 58). Psychological stress was measured using Job content questionnaire (36, 49) 10-division Borgscale (38), Karasek' s demand/control questionnaire (40, 54), Short version of the Copenhagen Psychosocial Questionnaire (41), Korean Occupational Stress Scale Short Form (45), Occupational stress validated by Elo (33), Wellbeing Scale (WBS) (55), CUPID Questionnaire (35), VIBRISKS questionnaire (32), Impact of event scale (IES) (48, 58), and Short version of the Copenhagen Psychosocial Questionnaire (COPSOQ) (41). However, other authors were measured using Not standardized questionnaires (31, 34, 37, 39, 42, 47, 50).

Seventeen of the studies suggested that there was a relationship between psychological stress and chronic NSNAP (31-33, 36-42, 45, 47-50, 54, 58). Two articles suggested that there was no relationship (34, 55), and 1 article concluded that this relationship was not clear (35).

Anxiety factor

Eleven studies reported the association between anxiety factor and chronic NSNAP (31, 43, 44, 46, 51-57). Anxiety was measured using Beck Anxiety Inventory (BAI) (16, 43), Hospital Anxiety and Depression scale (HADS) (44, 46, 53, 56, 57), Anxiety Sensitivity Index (ASI) (46), Pain Anxiety Symptoms Scale-20 (PASS-20) (46), HSCL-25-item questionnaire (51), State-Trait Anxiety Inventory (STAI-Y) (52) and Goldberg's 9-items scales (54). Some authors used a not-standardized scale (31) or non-specific scale (55). Nine of eleven articles concluded that there was a relationship

between chronic NSNAP and anxiety (31, 44, 46, 51-54, 56, 57); nevertheless, 2 articles suggested that there was no relationship (43, 55).

Meta-analysis

Four studies from these 28 selected articles in the systematic review, including 5 pair-wise comparisons, were included in the meta-analysis: 3 were cohort studies (31-33) and 1 was a cross-sectional study(34) (table 3). In total, there were 8,944 participants. The meta-analysis outcome was the relationship between chronic NSNAP and psychological stress. Forest plots for random-effects meta-analysis for all studies combined are presented in **Figure 2**. The estimate odds ratios for all studies combined are presented in **Figure 2**. The estimate for all studies combined was 2.33 (95% CI, 1.04 - 5.18; $p=0.039$). A high heterogeneity of findings appeared ($Q = 28.94$, $I^2 = 86\%$ $p=0.00$). Egger t test was negative and was not significant. Successively, we excluded the cross-sectional study from the analyses (Alperovich et al. (34)) and combined cohort studies, yielding results with better homogeneity. In fact, the OR for the cohort studies was 3.27 (95% CI, 1.79-5.97; $p=0.00$; $Q = 6.85$, $I^2 = 56\%$ $p=0.07$).

With regards to anxiety, we did not find enough studies with homogeneous quantitative data; therefore it was not possible to make a meta-analysis with anxiety and chronic NSNAP.

The strength of the evidence was assessed using the GRADE system by which the outcomes of all 28 articles were assessed. Study quality was assessed by reviewing whether the studies had limitations or flaws. The following limitations were noted: All

articles selected, except RCT articles, resulted in an initial quality of evidence rated as low, based simply upon the observational nature of the investigations to date and that they were largely uncontrolled. In addition, different methods for assessing outcome were used and the following differences between studies have been observed: sample size, inclusion/exclusion criteria, follow-up schedule and duration of follow-up.

These differences made it difficult to compare the four studies in meta-analysis. Important inconsistencies were noted in the results of these four studies leading to some uncertainty in the directness of the evidence.

Discussion

This updated meta-analysis and systematic review aimed to determine precisely the relationship of stress or anxiety factors in chronic NSNAP in adults. Four studies, including 5 pair-wise comparisons, with large sample sizes, mostly involving adults with chronic NSNAP, were selected and subjected to meta-analysis. The meta-analysis outcome showed that there was a relationship between chronic NSNAP and psychological stress (OR 95% 2.33 CI, 1.04- 5.18) but the heterogeneity analysis (I^2) was significant ($I^2 > 50$); indicating substantial variability in the findings.

From a qualitative point of view, although the quality of evidence of articles on stress or anxiety in chronic NSNAP is low, 85% of the articles (17 of 20 articles) on psychological stress and chronic NSAP suggest a strong relationship (31-33, 36-42, 45, 47-50, 54, 58). Regarding anxiety factor, 81% of the articles (9 of 11 articles) suggest that there is also a strong association (31, 44, 46, 51-54, 56, 57).

Our results are in line with those presented by most of the literature in recent years (59, 60) that has supported how stress can influence chronic pain and how an educational strategy can have a positive effect on pain. Many of the articles reviewed agree that stress or anxiety are significant predictors of chronic NSNAP (31-33, 36-42, 44-54, 56-58), although there are other authors showing that there is no relationship (34, 43, 55) between these psychosocial factors and pain. This difference may be due to the difficulty of assessing quantitative factors such as anxiety, pain, or stress.

When analyzing results by areas, most of the studies considered pain due to work and whiplash. Regarding work studies, we identified sixteen studies that focused on certain professional groups (31-36, 38-42, 45, 47, 49, 50, 54); fourteen of them concluded that subjects with psychological stress at work had a significantly higher occurrence of NSNAP (31-33, 36, 38-42, 45, 47, 49, 50, 54). Only one study with negative findings was identified (34) and another was not clear (35). Regarding chronic WAD, we identified six studies (48, 51, 53, 55, 57, 58) and all of them concluded that subjects with psychological stress (48, 58) or anxiety (51, 53, 55, 57) had a significantly higher occurrence of NSNAP. These findings suggest that psychological factors such as anxiety and stress may have an association with chronic WAD.

The most important finding we obtained by pooling 4 studies (31, 33-35) was a significant relationship between stress and chronic NSNAP (OR 95% 2.33 CI, 1.04-2.33). This relationship became more important when we analyzed more homogeneous studies (OR 95% 3.27 CI, 1.79-5.97).

Although it has been suggested that the relation between psychological factors and pain might be bi-directional (61), in regard to stress or anxiety, the corroboration or refusal of this statement is beyond the scope of this study. Nevertheless, stress and anxiety are different entities over which literature suggests that both may have underlying mechanisms through which they can sensitize the pain system and thus facilitate the pain experience (61, 62); Pain acts as a stressor that in the long term can produce a dysfunction in the hypothalamic-pituitary-adrenal (HPA) axis, which in turn has been associated to chronic pain, chronic distress and depression, amongst others factors (63). Additionally, “Cognitive-Emotional Sensitization” (7), the increased influence that forebrain centers exert on some descending pain-facilitatory brainstem nuclei (6), is a proposed mechanism to explain the potential association between the chronification of pain and psychosocial factors, via facilitation and up regulation of the nociceptive transmission and the impairment of the central pain inhibitory mechanisms (64).

Limits

We found the following limitations. Firstly, we did not find many studies with homogeneous quantitative data, which prevented us from making additional analyses and resolving other methodological issues. As a consequence, we were not able to calculate the effect size for anxiety. In addition, the quantitative factors such as anxiety were difficult to assess and for this reason it was not possible to make a quantitative analysis comparing the relationship between anxiety and chronic NSNAP.

On the basis of the GRADE results, we found low quality of the included studies (limitations in design, imprecision, and inconsistency) regarding the relationship between stress or anxiety, and chronic NSNAP. Few authors used standardized questionnaires (outcome measures in table 2) and this fact causes serious problems when we tried to make statistical comparisons of articles. Many authors have used custom assessments including any item on stress or anxiety. However, for correct investigation it would be necessary to use standardized questionnaires. Other authors (65) have pointed out the necessity of assessing and measuring psychosocial factors considering not only the individual as the unit of analysis, and proposed for example a more suitable method to measure job-related stress, which consists of obtaining the difference between individual and group levels of stress at the workplace, a procedure that would be sensitive to the interdependent characteristics of this psychosocial factor (9). Moreover, the lack of standardized methods to evaluate stress (and other psychosocial factors) is of significant concern and therefore a consensus to be implemented in future research is warranted.

In regard to chronic WAD, two of the articles on whiplash include subjects with grade III (48, 58) and other articles did not specify the degree of injury (53, 55, 57) but we decided to include them knowing that 90% of cases of whiplash are grade I and II (22).

Additionally, there was a lack of follow-up research. We found only eight studies with follow-up data (32, 33, 35, 37, 48, 49, 55, 58).

Due to the lack of literature that indicates which one is the best measure for stress, this systematic review highlights the need for developing RCTs which include standardized and homogeneous questionnaires to effectively evaluate psychosocial factors and also the need of a follow-up measurement.

Conclusions

This study shows that there is a strong relationship between stress and chronic NSNAP, but in spite of this, we have not found enough evidence to say that stress is a risk factor for chronic NSNAP due to the low quality of the results according to the GRADE. It was not possible to make a quantitative analysis comparing the relationship between anxiety and chronic NSNAP. However, according to the qualitative analysis there is a strong relationship between anxiety and chronic NSNAP. Our findings also suggest that psychological stress and anxiety may have a strong association with chronic Whiplash pain.

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This study was not supported by any grant and the authors declare that there are no conflicts of interest.

Competing Interest Statement

No Conflict of Interest has been declared by the author(s).

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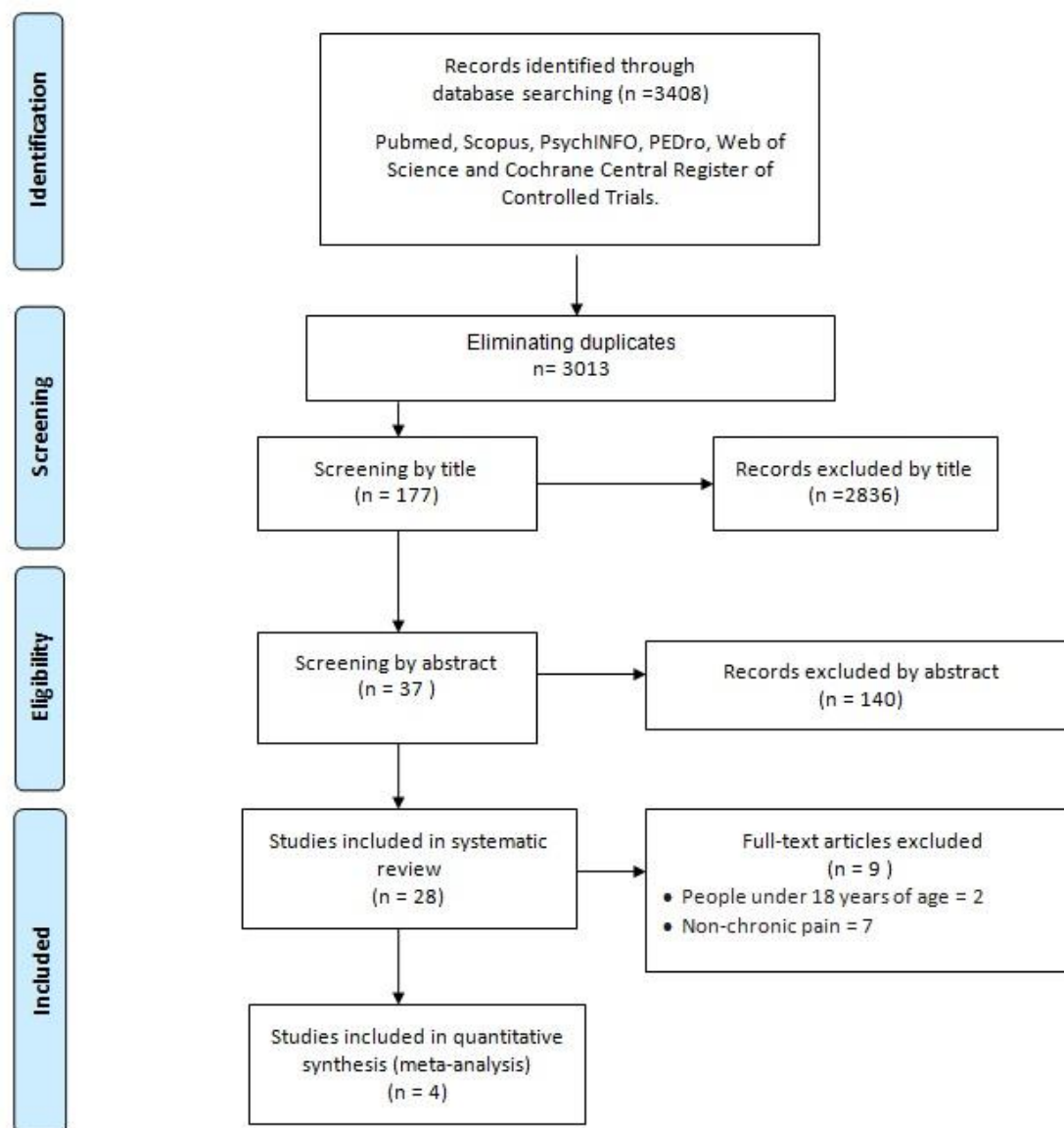


Figure 1. Flow diagram of studies through the different phases of the review.

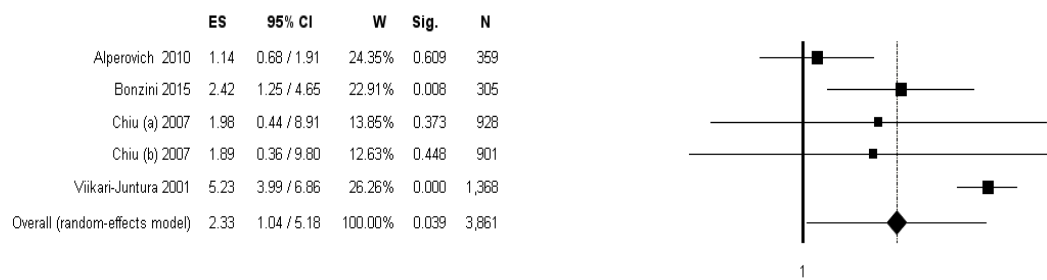


Figure 2. Forest plots for random-effects meta-analysis

Table 1. GRADE level of evidence (66)

Level of Evidence Quality	Based on:
High-quality evidence	One or more updated, high-quality systematic reviews based on at least 2 high-quality cohort studies ^a with consistent ^{by} results
Moderate-quality evidence	One or more updated systematic reviews of high or moderate quality based on at least 1 high-quality cohort study based on at least 2 cohort studies of moderate quality with consistent results
Low-quality evidence	One or more systematic reviews of variable quality based on cohort studies of moderate quality based on inconsistent results in the reviews based on inconsistent results in cohort studies
No evidence	No systematic review identified

^a The assessment of the methodological quality of cohort studies was extracted from the included systematic review

^b Consistent means more than 75% of the included cohorts pointed towards the same direction

Table 2. Studies included in systematic review

Ref.	Author	Study	Participants	Outcome measures	Reported results	Quality score	Association
			359 subjects: Drivers with neck pain ($N = 76$) Drivers without neck pain ($N = 283$) Mean age: 46 years	1.The modified Nordic Questionnaire	OR1.01 (95% CI 0.58-1.74)		
	Alperovich et al. (2010)	Cohort	Inclusion criteria		Author's conclusion	6	Stress:Yes Anxiety:No
(34)			Bus drivers with 12-month prevalence of upper quadrant pain.	2.Not standardized questionnaire	Work-related organizational stress factors were not associated with neck pain prevalence.		
			Exclusion criteria				
			Drivers with a history of traumatic				

		road or work accidents, with major traumatic injuries to their musculoskeletal systems				
		78 subjects.	1.Freiburg personality inventory (FPI)	No significant differences between groups in the WBS		
		Inclusion criteria		The CFQ score was significantly higher in the group with persistent symptoms (p = 0.01).		Stress: Yes
Radanov et al. (1991) (55)	Case control	Injury mechanism that accorded with the above definition (patients who had lately incurred common whiplash as soon as possible after trauma)	2.Wellbeing scale (WBS)		0	Anxiety: Yes
		German native language	3.Cognitive failures questionnaire (CFQ)	Author's conclusion		
		Age 55 or younger		Psychosocial factors have little power to explain the course of recovery from common whiplash		
			Follow-up: 6 months			

Bonzini et al. (2015) (35)	Cohort	305 subjects. Mean age: 39 years	1.Siegrist’s ERI questionnaire	ERI >1 at follow-up pain in neck-shoulder (RR 2.6, 95 % CI 1.3–5.1).	6	Stress:Yes Anxiety:No		
			2.CUPID Questionnaire	No corresponding association with persistence of ERI in nurses ERI >1				
		Inclusion criteria						
		Italian nurses						
				Author’s conclusion				
				Association between job stress and musculoskeletal pain is not explained entirely by an effect of stress on reporting of pain.				
				Follow-up: 12				

			months			
Bovenzi et al. (2015) (32)	Cohort	<p>537 subjects. Mean age: 41 years</p> <p>Group 1: earth-moving machines in marble quarries and laboratories</p> <p>Group 2: forklift trucks in marble laboratories, dockyards and paper mills</p> <p>Group 3: Buses in public transport and garbage machines in public services</p> <p>Inclusion criteria</p>	<p>1.VIBRISKS questionnaire</p> <p>2.Modified version of the Nordic questionnaire</p> <p>3.pain scale</p> <p>4.Not standardized questionnaire</p>	<p>Limited job decision, low social support and job dissatisfaction were significant predictors of neck outcomes</p> <p>Author's conclusion</p> <p>Psychological distress was associated with all NSP outcomes</p>	6	<p>Stress:Yes</p> <p>Anxiety:No</p>

		Male professional drivers (n ¼ 628) employed in several industries and public utilities located in various Provinces of Italy	Follow-up: 3 years		
		A minimum of one year of professional driving in the current job			
Chiu et al. (2007) (31)	Cohort	3100 subjects Inclusion criteria Full-time secondary school teachers in Hong Kong	1. Not standardized questionnaire	High level of anxiety (neck pain: OR = 1.49, 95% CI 1.07–2.07; upper limb pain: OR = 1.75, 95% CI 1.28–2.39) 5	Stress: Yes Anxiety: Yes
				Author's conclusion	

			High anxiety is significant on affecting the neck pain and upper limb			
Gerr et al. (2014) (36)	Cohort	386 subjects. Mean age: 43 years	1.Subscales of the Job Content Questionnaire	Association between the low-demand/low-control job strain category and neck-shoulder disorders.	8	
		Group 1: Psychological job demands	2.Full Positive and Negative Affectivity Scale	(HR=6.46, 95% CI = [1.46, 28.6])		Stress:Yes
		Group 2: Decision latitude				Anxiety:No
		Inclusion criteria		Author's conclusion		
		All full-time employees of a household appliance manufacturing facility in Iowa	3.Multimedia Video Task Analysis™	Associations between psychosocial risk factors and work organizational factors and musculoskeletal		

		computer use pattern				
Follow-up: 2 years						
Holte et al. (2002) (38)	Cohort	93 subjects				
		Group 1: Pain-afflicted workers	1.EMG	The mean perceived tension score for pain-afflicted and pain-free workers: 4.2 vs. 2.4 during work (P<0.005) and 2.9 vs. 1.8 during leisure time (P<0.01)	3	Stress:Yes Anxiety:No
		Group 2: Pain free workers				
		Inclusion criteria	2.Visual analogscales (VAS)			
		Shoulder and neck pain without injury or systemic disease	3.10-division Borgscale	Author's conclusion		
		Non-pregnant women		The study does not provide conclusive answers.		
		Workers without fibromyalgia				

Joslin et al. (2014) (39)	Cohort	32 subjects. Mean age: 43.3 years Inclusion criteria Avon Orthopaedic Centre, Bristol, United Kingdom nurses staff	1.SF-36 2.Not standardized questionnaire	Five (41.7%) subjects with current neck pain and 5 (38.5%) subjects with neck pain in the previous year attributed it to psychological stress Author's conclusion Over 1/3 of nurses have symptomatic neck pain and significantly lower mental and physical health scores	5	Stress:Yes Anxiety:No
Hagen et al. (1998) (40)	Cohort	835 subjects: (1) 645 manual workers; (2) 66 machine operators; and (3) 124 administrative workers.	1.Karasek's demand/control questionnaire	Psychological demands: Low [prevalence(21.5%), adjusted OR (1.00)] Medium [prevalence (27.7%) adjusted OR (1.53)],High [prevalence	4	Stress:Yes Anxiety:No

		2.StandardizedNordic questionnaire	(34.2%) adjusted OR (2.40)(p<0.001)]		
		Inclusion criteria		Author's conclusion	
		Forestry industry workers		Increasing level of psychological demands + decreasing level of intellectual discretion = an increased prevalence of neck-shoulder disorders	
<hr/>					
Kongsted et al.(2008)	Trial	737 subjects	1.Impact of event scale (IES)	Stress response: Men (OR 4.4; 95% CI 1.2–15.9) females' threefold risk (OR 2.7, 95% CI 1.4–5.2).	1
(58)		Inclusion criteria			
		Age 18–70 years	2.SF-36		
		Debut of symptoms within 3 days		Author's conclusion	
<hr/>					

		after the motor vehicle accident (MVA) and a maximum of 10 days should pass from the MVA.	3.11-point box scales	The association between the acute stress reaction and persistent WAD suggests that post-traumatic stress reaction may be important to consider		
Follow-up: 1 year						
Larsman et al. (2006) (41)	Cohort	148 subjects Case: People with symptoms in the region of interest for more than 30 days during the previous 12-month period. Control: People without symptoms at all, or symptoms in	1.Short version of the Copenhagen Psychosocial Questionnaire (COPSOQ) 2.Two-dimensional mood adjective checklist	Perceived work demands influence neck-shoulder musculoskeletal symptoms through their effect on felt stress	3	Stress:Yes Anxiety:No

		the region of interest for up to 7 days during the same period.			
		Inclusion criteria	3.Nordic Musculoskeletal Questionnaire (NMQ)		
		Danish, Dutch, Swedish and Swiss female computer users aged 45 or older			
Iizuka et al. (2012) (42)	Cohort	484 subjects. Mean age: 33 years	1.Not standardized questionnaire	Subjects with psychological stress at work had a significantly higher occurrence of NSP (OR= 2.83 95% IC= 1.37-5.83) (P = 0.001).	Stress:Yes Anxiety:No
		Inclusion criteria			
		Nursing staff at Gunma University Hospital in Japan			

		83 subjects				
			1.Subjective pain rating (NRS-101)	According to pain intensity, no statistically significant difference was observed between the resulting sub-groups (p = 0,064)		
Myburgh et al.(2010)	Cohort	Inclusion criteria Female subjects between the ages of 20-45 years old who performed at least 4 hours of office work per day and reported neck pain in the region of the upper Trapezius muscle	2.Beck Anxiety Inventory (BAI)		4	Stress:No Anxiety:Yes
(43)			3.Standardized Nordic Pain Questionnaire	Author's conclusion Chronic, intense pain and anxiety do not always appear to be related		

Dimitriadis et al.(2015) (44)	Cohort	Inclusion criteria Patients with idiopathic chronic neck pain of more than six months and with pain complaints of at least once a week.	1.Hospital Anxiety and Depression scale			
			2.Pain Catastrophizing scale	Neck pain intensity significantly correlated with anxiety ($r = 0.32, p < 0.05$).	4	Stress:No
			3.Tampa Scale for Kinesiophobia.	Neck pain intensity significantly correlated with NDI ($r = 0.35, p < 0.05$)		Anxiety:Yes
			4.Self-reported disability: Neck Disability Index.			
			5. Pain intensity: Visual analog scale			

(VAS).

Ryu et al.(2014) (45)	Cohort	620 subjects	1. ANSI Z-365 checklist 2. Korean Occupational Stress Scale Short Form	The group with a high ANSI checklist grade had odds ratio of 3.59 (95% CI 1.48 ~ 8.76), and the group with high job stress had 3.19 (95% CI 2.01 ~ 5.07). Author's conclusion Job stress had high relation with musculoskeletal symptoms	3	Stress:Yes Anxiety:No
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Sjörs et al.(2011) (46)	Cohort	49 subjects. Mean age: 40 years	1. Electronic algometer		
		Group 1: 19 females with neck pain	2. Injection of 0.5 ml sterile hypertonic saline (5.8%) into the tibialis anterior muscle	NSP group lower pressure pain thresholds	Stress:No
		Group 2: 30 females without neck pain			Anxiety:Yes
		Inclusion criteria Women with pain in region of the trapezius muscle during the last seven days and reported neck and shoulder pain more than 90 days over the last 12 months. Exclusion criteria Chronic widespread pain	3. Pain intensity: paper visual analogue scale (VAS) 4. Karolinska Sleep Questionnaire (KSQ) 5. Hospital Anxiety and Depression Scale (HADS)	Author's conclusion Psychological status interact with the perception, intensity, duration and distribution of induced pain	4

according to the Manchester definition	6. Anxiety Sensitivity Index (ASI)
Signs of tendinitis or joint affections in the shoulders	7. Pain Anxiety Symptoms Scale-20 (PASS-20)
Prior neck trauma	8. Pain Catastrophizing Scale (PCS),
Rheumatoid arthritis or other systemic diseases,	9. Fear-Avoidance Beliefs Questionnaire (FABQ)
Neurological diseases	10. Pain Disability Index (PDI)
Metabolic diseases	
Fibromyalgia	

Smith et al. (2009) (47)	Cohort	664 subjects	1) Standardized Nordic Questionnaire	Significant correlations between musculoskeletal disorders and psychosocial risk factors among veterinarians.	3	Stress: Yes Anxiety: No
		Inclusion criteria Veterinarians registered with the Veterinary Surgeons Board of Queensland during 2006.	2) Not standardized questionnaire			
Sterling et al (2006). (48)	Cohort	65 subjects	1) Range of active cervical movement (ROM) and joint position error (JPE)	Post-traumatic stress symptoms (OR 1.03–1.2) remained significant predictors of poor outcome at long-term follow-up ($r^2 = 0.56$).	2	Stress: Yes Anxiety: No
		Group 1: Recovered group (26) Group 2: Mild pain and disability (25) Group 3: Moderate/severe pain	2) EMG			

and disability (14)		Author's conclusion
Inclusion criteria	3) General Health Questionnaire 28 GHQ-28	Psychological factors will be important in the acute stage following whiplash injury
Quebec Task Force Classification of WAD II or III		
Exclusion criteria	4) TAMPA Scale of Kinesphobia (TSK)	
WAD IV		
Experienced concussion	5) Impact of Events Scale (IES)	
Loss of consciousness or head injury as a result of the accident		
Reported a previous history of whiplash, neck pain or headaches that required treatment	6) Neck Disability Index (NDI)	

Follow-up: 2-3
years

5180 subjects: 3899 men and 1281 women. Mean age: 41.8 years

1) Modified version of the Nordic Questionnaire

Inclusion criteria

Viikari-Juntura et al. (2001)
(33)

Cohort

Blue and white collar workers of a large forest industry enterprise in Finland (all workers in mechanical and chemical forest industry processes and their maintenance tasks, foremen, technical designers, laboratory staff, and office clerks)

2) Occupational stress validated by Elo

Items showing associations with mental stress

3

Stress:yes

Anxiety:No

		Exclusion criteria	Follow-up: 3 years		
		Subjects with rheumatoid arthritis and part time workers.			
<hr/>					
Van den Heuvel et al. (2005) (49)	Cohort		1) Adapted version of the Nordic Questionnaire		
		787 subjects	2) Job Content Questionnaire	High job demands risk factor for neck-shoulder symptoms (RR: 2.1; CI: 1.2–3.6) and elbow/wrist/hand symptoms (RR:1.9; CI: 1.0–3.7),	4
		Inclusion criteria			
		Job for at least 1 year and working 24 h per week or more.	3) Standardized Dutch Musculoskeletal Questionnaire		
			4) 7 item sub-scale		
					Stress:Yes Anxiety:No

of the Dutch version
of the Maslach
Burnout Inventory

5): Utrecht Coping
List

6) PANAS Scales

Follow-up:3 years

Magnavita et al. (2009) (54)	Cohort	342 subjects	1) Karasek's demand/control model (short version) 2) Goldberg's 9-items scales	Symptoms from the neck were related to psychological demands, authority over decisions, gender and anxiety.	3	Stress: Yes Anxiety: Yes
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Holmström et al. (1992) (50)	Cohort	1773 subjects Mean age: 39.5 years	1) Not standardized questionnaires	The 1-year prevalence rate: neck and shoulder trouble (56%) and neck and shoulder pain (12%)	2	Stress: Yes Anxiety: No
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Author's conclusion

The psychosocial indices; psychosomatic and psychic

				symptoms, stress and job satisfaction showed the highest age-standardized prevalence rate ratios for both neck and shoulder trouble and neck and shoulder pain.	
Myrtveit et al. (2013) (57)	Case - control	<p>20,799 subjects: Chronic Whiplash (N=199) No chronic Whiplash (N= 20,600) Mean age: 44.4 years</p> <p>Inclusion criteria</p> <p>Participants with a whiplash injury more than 1 year ago</p> <p>Subjects with neck pain</p> <p>Exclusion criteria</p> <p>Participants who didn't answered questions on mental and somatic</p>	<p>1. Hospital Anxiety and Depression Scale (HADS)</p> <p>2. Standardized Nordic Questionnaire</p>	<p>OR 1.93 (95% CI 1.39–2.68)</p> <p>Author's conclusion</p> <p>Mental health problems have been found to be strong risk factors for the development of chronic whiplash</p>	<p>4</p> <p>Stress: No</p> <p>Anxiety: Yes</p>

		health , chronic whiplash, questions on health- related behavior and questions on socio-demographics.			
Ihlebaek et al. (2006) (51)	Cohort	171 subjects. Low Comorbidity (N=64), Medium comorbidity (N=59), High comorbidity (N=48). Inclusion criteria Patients of both genders (18-60 years) that had experienced a traffic accident 6-12 months earlier and with symptoms according to WAD grade I-II Exclusion criteria Patients that were pregnant, had	1.Subjective Health Complaints Inventory (SHC) 2.Modified version of the Roland & Morris disability questionnaire 3.HSCL-25-item questionnaire 4.Cervical	Stress Chi-square tests: HSCL-case % Low Comorbidity (21.9) Medium comorbidity (42.4) High comorbidity (79.2). Anxiety Chi-square tests: HSCL, mean (95% CI) Low Comorbidity: 1.3 (1.2-	4 Stress: Yes Anxiety: Yes

known abuse
of alcohol and drugs, serious
illness, or pronounced language
difficulties

Measurement System
(CMS)

1.4)
Medium comorbidity: 1.5
(1.4-1.6)

5 Aastrand's
test

High comorbidity: 1.9 (1.8-
2.1)

Author's conclusion

The high comorbidity of other
complaints, the strong
relationships between degree
of comorbidity and

psychological factors, and the
lack of relationships between
degree of comorbidity and
collision factors

and physical tests, suggest that
chronic WAD is best
understood as a syndrome and
not as a neck injury.

		Swedish. No abuse of alcohol or drugs Not involved in litigation.	5.Beck Depression Inventory (BDI) 6.Multidimensional Pain Inventory (MPI)		
Cho et al. (2013) (56)	Case - contr ol	190 subjects: shoulder pain group (N=130), control group (N= 60). Mean age: Shoulder pain group: 54.8 years. Control group: 53.9 years. Inclusion criteria Patients with shoulder pain for 3 months or longer despite any prior	1.Visual analog scale (VAS) 2.American Shoulder and Elbow Surgeons (ASES) 3.Korean Shoulder Scale (KSS)	Shoulder pain group had higher mean scores than group II for the HADS-D (4.9 vs 3.8; P¼.01), HADS-A (4.6 vs 3.6, P¼.04). Shoulder pain group had higher preprevalences than control group for anxiety (P=.04)	4 Stress: No Anxiety: Yes

conservative treatment		Author's conclusion
Exclusion criteria	4.Hospital Anxiety and Depression Scale (HADS)	High prevalence and close relationships of depression, anxiety, and sleep disturbance in patients
Shoulder pain for no more than 3 months		
Shoulder pain combined other musculoskeletal pain	5.Pittsburgh Sleep Quality Index (PSQI)	with shoulder pain for 3 months or longer may indicate the importance of a psychologic approach as well as adequate pain control.
Systemic diseases such as diabetes, cardiac disease, and thyroid disease, among others		
History of shoulder surgery		
Psychiatric disorders, such as depression, anxiety, or insomnia.		
Exclusion criteria control group		
History of musculoskeletal		

		problems				
		Any systemic diseases				
		Any psychiatric disorders.				
		45 subjects	1.Shirom Melamed Burnout Questionnaire (SMBQ)	25 patients (56%) had a likely anxiety disorder.		
		Mean age: 39 years				
		Inclusion criteria		HAD-Anxiety:11 (9;15)		
Clementz et al. (2012)	Cohort	18 years of age or older	2.Visual analogue scale (VAS)	The median score on NDI in our patient group was for severe	4	Stress: No
		Subjects with persistent symptoms for at least 3 months after a whiplash injury	3.Hospital Anxiety and Depression Scale (HAD)	disability and 56% scored for anxiety		Anxiety: Yes
		Subjects referred to a specialized rehabilitation centre for a multidisciplinary investigation and/or rehabilitation during a 2-	4. Neck Disability			

year period

Index (NDI)

5. EQ-5D

Table 3. Studies included in Meta-analysis.

Ref.	Author	Study	Participants	Outcome measures	Reported results	Quality score	Association
	Alperovich et al. (2010) (34)	Cohort	<p>359 subjects: Drivers with neck pain ($N = 76$) Drivers without neck pain ($N = 283$) Mean age: 46 years</p> <p>Inclusion criteria</p> <p>Bus drivers with 12-month prevalence of upper quadrant pain.</p> <p>Exclusion criteria</p> <p>Drivers with a history of traumatic</p>	<p>1.The modified Nordic Questionnaire</p> <p>2.Not standardized questionnaire</p>	<p>OR1.01 (95% CI 0.58-1.74)</p> <p>Author's conclusion</p> <p>Work-related organizational stress factors were not associated with neck pain prevalence.</p>	6	<p>Stress:Yes</p> <p>Anxiety:No</p>

		road or work accidents, with major traumatic injuries to their musculoskeletal systems			
Bonzini et al. (2015) (35)	Cohort	305 subjects. Mean age: 39 years Inclusion criteria Italian nurses	1.Siegrist's ERI questionnaire 2.CUPID Questionnaire	ERI >1 at follow-up pain in neck-shoulder (RR 2.6, 95 % CI 1.3–5.1). No corresponding association with persistence of ERI in nurses ERI >1 Author's conclusion Association between job stress and musculoskeletal pain is not explained entirely by an effect of stress on reporting of pain.	6 Stress:Yes Anxiety:No

				Follow-up: 12 months		
Chiu et al. (2007) (31)	Cohort	3100 subjects Inclusion criteria Full-time secondary school teachers in Hong Kong	1. Not standardized questionnaire	High level of anxiety (neck pain: OR = 1.49, 95% CI 1.07–2.07; upper limb pain: OR = 1.75, 95% CI 1.28–2.39) Author's conclusion High anxiety is significant on affecting the neck pain and upper limb	5	Stress: Yes Anxiety: Yes

Viikari-Juntura et al. (2001) (33)	Cohort	5180 subjects: 3899 men and 1281 women. Mean age: 41.8 years	1) Modified version of the Nordic Questionnaire			
		Inclusion criteria				
		Blue and white collar workers of a large forest industry enterprise in Finland (all workers in mechanical and chemical forest industry processes and their maintenance tasks, foremen, technical designers, laboratory staff, and office clerks)	2) Occupational stress validated by Elo	Items showing associations with mental stress	3	Stress:yes Anxiety:No
		Exclusion criteria				
		Subjects with rheumatoid arthritis and part time workers.	Follow-up: 3 years			

Highlights

- This updated meta-analysis and systematic review aimed to determine whether an association between anxiety or psychological stress factors and patients with chronic nonspecific neck-arm pain (NSNAP) exists, and second, to determine how strong this association is.
- The meta-analysis outcome showed that there was a relationship between chronic NSNAP and psychological stress.
- From a qualitative point of view, our results supports the influence of psychological stress in chronic NSNAP.
- According to the qualitative analysis there is a strong relationship between anxiety and chronic NSNAP