Title

Do the key prognostic factors for non-specific neck pain have moderation effects? – A study protocol

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ABSTRACT

Neck pain is one of the common musculoskeletal conditions prevalent in the general population in Norway. Patients with neck pain, seek treatment from different health professionals such as general practitioners, physiotherapists, chiropractors and alternative medicine practitioners. The interventions for neck pain are typically provided in a primary care or specialised healthcare setting depending on the general practitioners' referral patterns. Clinicians are interested to know the various prognostic factors that can explain the recovery from neck pain. In order to know this, studies have explored and reported on a range of prognostic factors that contribute to the outcomes in patients with neck pain. This information is currently available only for neck pain following whiplash injury that has a traumatic origin. There is limited information on the role of prognostic factors specifically for non-specific neck pain without a traumatic episode. Moreover, there is a lack of data on whether there are interactions (moderation effects) between the prognostic factors. Therefore, we propose a hypothesis to elucidate whether the same set of prognostic factors found in neck pain associated with whiplash injuries are also identified in patients with neck pain without trauma. Additionally, we hypothesize that the association between a prognostic factor and the outcome variable (s) would be dependent on the third variable, thereby confirming the moderation effects. Clinicians could make informed decisions in the clinical management of neck pain with the knowledge of prognostic factors that explain the outcomes. It could also be used for the development of new interventions or for modifying the existing ones.

INTRODUCTION

Neck pain (NP) is a musculoskeletal condition with the highest impact on disability-adjusted life-years (1). In Norway, the 12-month prevalence of NP is estimated to be approximately 25% in the general population (2). Patients with NP can present in different forms; however, in a majority of cases, there is no identifiable underlying disease or abnormal anatomical structure; thus, it is termed as non-specific neck pain (3). Most often, either postural or mechanical factors, and in some instances, multifactorial reasons have been attributed to the cause of non-specific neck pain. Nevertheless, the aetiology of non-specific neck pain could also include whiplash injuries due to trauma, without any underlying structural damage. A number of studies have investigated the prognostic factors (PFs) that predict the recovery and/or delayed recovery from NP, which are synthesised in the systematic reviews (4-10). It must be noted that the primary studies included in these systematic reviews have included patients with NP either due to whiplash-associated or work-related disorders.

An 'overview of systematic reviews' (11) concluded that there was strong evidence for increased risk of poor outcome in the presence of high pain intensity (PI), high neck-related disability (ND) or older age. The conclusions were less evident for factors such as catastrophizing, cold hypersensitivity/hyperalgesia, post-traumatic stress symptoms and history of other musculoskeletal disorders. A recent systematic review (12) showed that there was robust evidence for some of the same set of prognostic factors. However, this review included patients with arm and shoulder pain, in addition to neck pain. Furthermore, they found that the strength of evidence for some factors varied with the outcome(s) used.

There were also differences in the impact of outcomes depending on whether there was a short-term or long-term follow-up. Thus, differences in research design and outcome measures utilised could play a role for explaining the influence of PFs in the recovery of neck pain.

The primary studies included in the earlier systematic reviews (4-10) have largely been exploratory prognostic factor research. In general, most of the prognostic factor studies in the field of health sciences have an exploratory aim rather than confirmatory (13). Considering the wide range of factors identified as possible prognostic factor, it should be examined how their effects relate. This is necessary in order to obtain results with a minimal or devoid of any bias. Therefore, it is time to improve our research with a different approach, which includes incorporating appropriate study designs, and a thorough and more robust statistical analysis. The aims of the proposed study are 1) to conduct a confirmatory prognostic factor research for prognostic factors previously identified in trauma related-neck pain patients, and 2) to explore and identify a set of prognostic factors in a non-specific neck pain cohort.

RATIONALE

The current evidence from the 'overview of systematic reviews' (11) is compelling. Nevertheless, the evidence has been generated by including patients with NP due to whiplash-associated disorder (trauma). Hence, it is not clear whether the same set of key PFs could be identified in patients with NP of a non-traumatic origin. The methodological approaches different to that used in the earlier studies could be adopted in the future for

obvious reasons. For instance, the primary studies included in all the systematic reviews (4-10) measured the outcomes only at a single time point. More precisely, the PFs were documented at baseline (startpoint) and the clinical outcomes were measured at one endpoint (e.g. 3 months). Thus, information related to PFs at varying time points (short-term and long-term) is presently not known. There is a possibility to identify PFs unique to different time points (e.g. 3, 6 and 12 months) in which the outcomes are measured.

Similarly, an important question arises as to whether the identified PFs would have moderation (i.e. interaction) effects. The term 'moderation' and 'interaction' effects are used interchangeably in statistical literature. In order to explain the concept, the term 'moderation' is used below, however the term 'interaction' is used later while describing the planned approach on statistical analyses. By definition, a moderation effect is that, the association (magnitude and direction) between a prognostic factor and the outcome variable is dependent on the third variable (Figure 1). For instance, let us assume that one prognostic variable and dependent variable are continuous, and the other prognostic factor is a categorical variable, all included in the model. In the event of significant moderation effects, it simply means that the relationship between the continuous prognostic variable (e.g. age) and the dependent variable (e.g. pain intensity) is different at different levels of the categorical prognostic factor (e.g. gender). This example could be reflected by linking it to Figure 1, with X=age, M=gender and Y=pain intensity.

The exploration of moderation effects is important, because it could be speculated that key PFs may have these effects. The substantiation for this statement is the fact that the primary studies included in the systematic reviews (4-9), which investigated the PFs have not explored moderation effects in their statistical analyses. In statistical parlance, the interpretation of main effects of a prognostic variable becomes meaningless in the presence of significant moderation effects (14, 15). The problem is further compounded due to the lack of a clear description in the primary studies of the systematic reviews on whether the confounders were controlled during the analysis. This is a pertinent issue because it is most likely to introduce a significant bias in the analyses and subsequent findings (16). Thus, the moderating effects of a multitude of putative PFs warrant investigation.

THE HYPOTHESIS

We propose the following hypotheses in accordance with the rationale detailed above.

1) An association is likely to be demonstrated between each prognostic factor and the outcome measures of pain and neck disability individually – Unadjusted.
2) Associations may be expected between a number of prognostic indicators and each of the outcome measures of pain and neck disability – Adjusted.
3) Moderation effects are anticipated, possibly from one or more than one pair of prognostic factors in relation to the outcome measures of pain and neck disability.

Evaluation of the hypotheses

We propose to test all the above-cited hypotheses by employing a prospective observational study design. This design would involve collecting data over time (baseline, 3

months, 6 months and 1 year) from patients presenting with non-specific neck pain (<3 months), for treatment in primary health care settings. The various PFs considered for the future study are based on the work by Walton et al (11), and these include age, high PI and ND, catastrophizing and history of other musculoskeletal disorders (Table 1). These key prognostic indicators of interest are the variables documented at baseline from the inception cohort.

Each of the three hypotheses stated earlier is to be tested using a stepwise strategy. The first hypothesis will be tested by conducting a univariate linear regression analysis. This method would allow us to determine the association between each prognostic factor and the clinical outcomes of pain and neck disability individually. Following this, the next step would be to conduct multiple linear regression analyses with the inclusion of all the PFs simultaneously. While performing the multiple linear analysis, confounders will be controlled in the statistical modelling. These confounding factors include gender, marital status, education, work status and duration of sick leave. These confounders are chosen based on the previous studies carried out in patients with low back pain (17, 18). In doing so, the second hypothesis can be evaluated in which it is expected that more than one prognostic factor explains the outcomes.

Finally, the third hypothesis is tested by including all possible two-way interaction terms between the PFs by building separate multiple regression models for each of the outcomes of pain and neck disability. By doing this, we propose to demonstrate significant interactions for at least one pair of prognostic factors. For instance, we expect that the

association of a prognostic factor (e.g. catastrophizing) and the outcome measure (e.g. PI) to be moderated (interacted) by the third variable (e.g. older age). All the identified pairs of PFs found to have significant interactions will be further explored, by conducting a simple slope analysis (14) and regions of significance test (19). This will enable us to explore, understand and confirm the hypothesis on the moderation effects.

Reasons for a different statistical approach

The testing of the associations between the PFs and each of the outcome variables of pain intensity (PI) and neck disability (ND) are to be conducted in relation to the time points in the following way:

a) Baseline to 3 months
b) Baseline to 6 months
c) Baseline to 1 year

A rationale for the requirement to adopt a different statistical approach is outlined hereafter. Separate regression models will be conducted for each follow-up time point with reference to the baseline data. A question could be raised as to why the data are not considered for analyses using linear mixed-effects modelling (LMM) for clustered data that would be obtained when using a longitudinal design. Additionally, an argument could be made that it is possible to demonstrate prognostic indicators unique to time points when the time variable is coded differently (20). In doing so, it is possible to obtain parameter estimates and standard errors of the PFs that are unique to the time points in which the data is obtained (20).

In fact, the LMM statistical technique is superior in that, it will also account for random effects along with the fixed effects (21, 22), unlike the regression modelling which includes only the fixed effects. However, these type of approaches could be applied when the aim of study is to investigate only the main effects of the PFs at different time points. It would become increasingly complex and a bit challenging with the interpretation of results, when the purpose is also to examine the interactions (moderation) between the prognostic factors.

Moreover, researchers conducting prognostic studies are interested in identifying potential factors at each time point of the progression of the disorder/condition. This enables clinicians to know whether the same set of or different factors contribute to the outcome(s) at each stage of the disorder/condition. For example, it is possible to obtain one set of prognostic indicators for a disorder/condition at 3 months from its onset, which is clinically defined as an acute stage. Meanwhile, a different set of prognostic indicators or a certain degree of overlap with those found in acute stage could be identified for a condition lasting over 3 months. This timeframe represents the chronic stage of the condition.

Hence, clearly demarcating the identification of PFs depending on the stage of the condition would assist clinicians in making informed decisions when implementing interventions. In summary, the adoption of this strategy of building separate regression models will allow us to identify the PFs unique to each time point. A similar approach has been followed elsewhere to identify PFs in patients with low back pain (17, 18), and to explore risk factors for pelvic girdle pain (23, 24).

IMPLICATIONS

The implications derived by conducting this type of research work are two-fold. Firstly, this research project would contribute to the area of PFs for NP. Specifically, the findings generated from this study could provide plausible explanations related to recovery from neck pain. Furthermore, this would add new knowledge with a thorough understanding on whether moderation effects exist between the prognostic factors. More precisely, it would inform whether a particular prognostic factor predicts poor outcomes either solely or in combination with another variable. Therefore, this information would be useful for the clinicians in the management of NP, and for the development of new interventions to alter the clinical course of neck pain.

Secondly, our proposed research would also advance the body of work from a methodological perspective. For example, it would further advance our knowledge of understanding the recovery from NP, when a cohort is followed over an extended period. In doing so, more information could be added in addition to the already existing body of literature, which is predominantly based on the cross-sectional studies. This work would also provide new insights into the identification of PFs for NP, when a different statistical approach is incorporated as part of the methodology.

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TABLES

Table 1: List of prognostic factors and the scales used for its measurement

Prognostic factor	Scale/Tool
Age	
High pain intensity	11-point numerical pain rating scale
High neck disability	Neck disability index
Catastrophizing	Pain catastrophizing scale
History of other musculoskeletal disorders	Self-reported (yes/no)

FIGURES

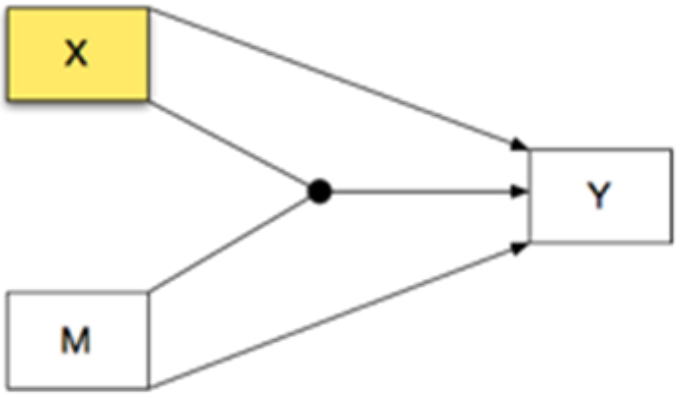

Figure 1: Diagram of a single moderator model.

(X=prognostic factor, M=moderator, and Y=outcome)