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NECK PAIN – FACTORS OF IMPORTANCE FOR THE RISK AND PROGNOSIS

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Stockholm 2014

Published by Karolinska Institutet. Printed by US-AB

ISBN 978-91-7549-633-7

ABSTRACT

Introduction: Considering the recurring nature of neck pain, and that it is a big societal as well as individual burden, it is of great importance to increase the knowledge about what factors that affect the risk and prognosis of neck pain.

Objectives: The objective of this thesis was to study factors of potential importance for the risk and prognosis of neck pain, including whiplash-associated disorders (WAD). The specific objectives for study I were to assess the sex specific role of disposable income for onset and prognosis of neck pain in the general population, and if economic stress influences such potential associations. In study II the objectives were to investigate if work related physical activity and physical activity during leisure time are of importance for the risk and prognosis of neck pain. The objective of study III was to investigate if pre-treatment expectations of recovery is a prognostic factor for recovery from neck pain at seven weeks follow-up in patients seeking manual therapy treatment. And in study IV the objective was to determine if prevalent self-reported cardiovascular disorders (CVD) are associated with poor self-rated recovery in persons with WAD.

Material and methods: Study I and II were based on the Stockholm Public Health Cohort (n=23 794) with information on exposures and potential confounders collected at baseline in 2002-2003. The outcome Long Duration troublesome Neck Pain (LDNP) was measured at follow-up in 2007. Those answering "yes" to the question: "During the last five-year period, have you had neck pain for at least three consecutive months that bothered you considerably?" were classified as cases. Study III was based on the Stockholm Manual INtervention Trial (n=1057), a randomized controlled trial where patients with neck pain were studied as one cohort for the objectives of this thesis. The outcome was "recovery" measured by a modified version of the Global Perceived Recovery Question at seven weeks follow-up. Study IV was based on the Saskatchewan Government Insurance cohort including individuals who made a traffic-injury claim or received health care after a traffic injury, between 1997 and 1999. Included in study IV were 6011 participants reporting WAD. The outcome "recovery" was measured at six weeks, three months, six months, nine months, and twelve months post injury by the Global Perceived Recovery Question.

Results and conclusions: Having a low income yielded a higher odds of getting LDNP in both a cohort without neck pain at baseline (assessing risk) and a cohort with occasional neck pain at baseline (assessing prognosis), and among both sexes. Combining low income with perceived economic stress in the analyses indicates that income and economic stress interact in their association with LDNP. Higher levels of leisure physical activity than sedentary are protective of developing LDNP in a population free from neck pain at baseline. The prognosis for neck pain was not affected by leisure physical activity according to the results and physical activity within the work tasks was neither associated with risk nor prognosis of neck pain. The results from study III show that expectations of recovery is a prognostic factor for recovery from neck pain in a population seeking and receiving treatment. In study IV the results showed no associations between CVD and recovery from WAD among men and likely there is no association among women either as only weak associations were detected, and they are possibly subject to bias from residual confounding.

LIST OF PUBLICATIONS

I. Palmlöf L., Skillgate E., Alfredsson L., Vingård E., Magnusson C., Lundberg M., Holm L.W. Does income matter for troublesome neck pain? A population-based study on risk and prognosis. *J Epidemiol Community Health. 2012 Nov;66(11):1063-70.*

II. Palmlöf L., Holm L.W., Alfredsson L., Magnusson C., Vingård E., Skillgate E. The impact of work related physical activity and leisure physical activity on the risk and prognosis of neck pain – A population-based cohort study on workers
Manuscript

III. Palmlöf L., Holm L.W., Alfredsson L., Skillgate E. Expectations of recovery - a prognostic factor in patients with neck pain undergoing manual therapy treatment
Manuscript

IV. Palmlöf L., Côté P., Holm L.W., Carroll L.J., Cassidy J.D., Skillgate E. Are prevalent self-reported cardiovascular disorders associated with delayed recovery from whiplash-associated disorders: a population-based cohort study
Clinical J of Pain. 2014 [Epub ahead of print]
DOI:10.1097/AJP.0000000000000107

CONTENTS

LIST OF ABBREVIATIONS

CI	Confidence interval
CPQ	Chronic pain questionnaire
CVD	Cardiovascular disorders
HRR	Hazard rate ratio
ICF	International classification of functioning
LDNP	Long duration troublesome neck pain
MINT	Manual intervention trial
NRS	Numerical rating scale
OR	Odds ratio
RERI	Relative excess risk due to interaction
RR	Relative risk
SEK	Swedish kroner
SGI	Saskatchewan government insurance
SPHC	Stockholm public health cohort
WAD	Whiplash-associated disorders

1 INTRODUCTION

Most people will experience neck pain sometime during their lifetime, some more severe than others. Neck pain is a condition that causes individual suffering and high societal costs throughout the world. It is ranked as the fourth most burdening condition in terms of disability in a study from 2010 ranking the global burden of disease.[1] So far neck pain is reported a larger burden in the high income countries, but this may be due to other diseases and problems overshadowing neck pain burden in the low and middle-income countries. Neck pain is increasing in the world [2] and is also estimated to become a more substantial problem in low and middle-income countries in the future as their population grows and become older.[1]

To meet patients with neck pain intrigued me as a physiotherapist as it struck me to be a very frequent condition, and also very individual in how it emerged. It seemed different to many other musculoskeletal conditions in the way that it demanded more from me as a therapist to see the full picture of the individual, in order to be successful in my treatment of neck pain. These patients were always the most interesting ones for me, and I wanted to dive deeper into the research about neck pain to better understand what made neck pain so frequent and multifactorial. After four years of studying how to conduct research and getting to know the field of neck pain research I conclude that the more I learn, the more I realize I need to learn.

This thesis is based on four studies investigating diverse factors that potentially affect the risk and prognosis of neck pain. Epidemiology is the method used in conducting the studies.

2 BACKGROUND

2.1 STUDYING RISK AND PROGNOSIS OF DISEASE

The risk of disease most commonly refers to the proportion of new cases of a given disease, during a certain time period, in a population. When we study risk the population under study needs to be free from disease at baseline in order for us to be certain that the detected cases are new.

Prognosis refers to an estimation of the future outcome of a disease when it has already been established. Therefore, when studying the prognosis of a disease, the population under study needs to have the disease at baseline. A prognostic factor is something that determines the course of the disease and may, but need not, also be a risk factor for the disease.

2.2 NECK PAIN

2.2.1 Definition (Non-specific/specific)

Spinal pain is often classified into specific and non-specific. Spinal pain is considered to be specific when the pain is due to a specific structural cause, for example disc hernia, spinal stenosis, ankylosing spondylitis etc. Consequently all neck pain due to unknown causes is classified as non-specific, and this is also the largest part of the total neck pain cases. The World Health Organization (WHO) reports that out of all spinal pain cases, the non-specific accounts for 80-85%.[3]

Whiplash-associated disorders (WAD) is a condition caused by an acceleration-deceleration mechanism of energy transfer to the neck. The whiplash violence to the neck is most commonly caused by a motor vehicle accident, but may also be related to accidents within for example sports or work. It may result in different clinical manifestations such as pain, sensory deficits, decreased range of motion or strength, and these manifestations, or a combination of them, constitute WAD. This definition of WAD was suggested by the Quebéc Task Force on Whiplash-Associated Disorders,[4] and is widely used in research today. Since the pathophysiology of WAD is not fully known it is categorized as non-specific neck pain.

The definition of neck pain varies to a large extent across different scientific studies. This restrains the possibility of drawing conclusions regarding risk factors and prognostic factors as several, comparable, studies pointing in the same direction are needed to make that type of conclusions. The Bone and Joint Decade 2000-2012 Task Force on Neck Pain and its Associated Disorders [5] have suggested a conceptual model for non-specific neck pain, where five axis should be included in the definition of neck

pain; 1) the source of subjects and data, 2) the setting or sampling frame, 3) the severity of neck pain and its consequences, 4) the duration of neck pain, and 5) its pattern over time. The more of these axis that are used in the definition of neck pain in research studies, the better the chance of being able to compare the results between different studies.

In this thesis neck pain was studied in four different populations; the general population, the working population, a care seeking population and a population with WAD. The working population is a general population where study participants have reported to be working. This is somewhat different from studies on populations from certain workgroups or companies. But both types of populations are regarded as working populations. The care seeking population in this thesis can be regarded as a type of general population as seeking care is voluntary, and the study participants are not found by advertising or other ways of recruiting. Even though risk factors and prognostic factors to a large extent are similar between the populations they are often studied separately. Therefore information about the epidemiology of neck pain in this thesis is separated into these three types of populations.

2.2.2 Incidence and prevalence

The annual cumulative incidence of neck pain in the general population is reported by a recent systematic review to be between 10.4% and 21.3% and was concluded from the results of four studies. [6]

According to a systematic review the one year prevalence of neck pain in the general population varied between 12.1% -71.5% with the majority of estimates between 30-50%. [2] For activity limiting neck pain the one year prevalence was estimated between 1.7-11.5%, depending on which activity was indicated; work, social activity or activity in total. For bothersome neck pain the one year prevalence is reported to be 16% among men and 25% among women. [7]

In working populations sampled from the general population the one year prevalence of neck pain ranges between 27.1-48.8%, [8] which is not surprisingly quite similar to the prevalence in the general population.

2.2.3 Course

The course of neck pain is often characterized by episodic pain over time. [9] Individuals presenting with acute pain seems to have the most substantial improvement regarding pain during the first two months according to a population based study from Norway. [10] After that the improvement levels off and the recovery rate was about 30% at two months, as well as at 12 months follow-up. Another study in a population seeking and

receiving care for their pain demonstrated that patients experience a substantial improvement within the first two weeks. [11] It seems that if individuals recover well, they do it within the first two months, and if they have remaining pain after 2-3 months the recovery is unsure.

In the working population about 60% of the individuals with neck pain at baseline reported having neck pain also after one year. [12] Similarly among individuals with WAD, about 50% experience neck pain one year post injury. [13] The evidence synthesis supports the fact that the course of neck pain among WAD patients is similar to that of individuals with neck pain in the general population.

2.2.4 New episode or recurrence?

It is important in risk factor research about neck pain to ascertain that it is truly risk for neck pain being studied, as it is a recurring condition. The definition of being neck pain free varies between studies, which complicates this matter. The time period between two episodes of neck pain is also of importance since the closer they are in time, the easier it is to assume that they are connected to the same etiological reason or cause, making the second episode rather a recurrence of the previous event. Evidently, these circumstances stress the need for clear definitions of these concepts. The mass of literature about neck pain use different definitions which makes it difficult to compare and contrast studies, and also to draw conclusions about factors affecting risk and/or prognosis of neck pain. In order to state that there is an effect of a specific factor on neck pain, there need to be several studies of good quality coming to the same conclusion.

2.2.5 Risk factors

Numerous studies have investigated potential risk factors for neck pain in the general population, but according to a systematic review evaluating literature up to year 2006 [2] only poor psychological health and prior health could be concluded to affect the risk for neck pain. Smoking potentially affects the risk for neck pain although the effect found in studies was not very strong. The results of the review regarding age and physical activity as potential risk factors were not consistent. Older age was associated with a higher prevalence of neck pain, up to the middle years, but this may be due to the fact that older age is a prognostic factor predicting worse recovery, rather than it being a risk factor. Also studies on gender as a risk factor showed varied results, a variation which is potentially linked to the case definition of neck pain, although some studies suggest that female gender is associated with a higher risk for neck pain [2]. In general, many studies have been conducted investigating different risk factors for neck pain, but with inconsistent results.

In the working population several factors have been identified to affect the risk of neck pain. The majority of the identified factors are work related and includes quantitative job demands, social support at work, job insecurity, poor computer workstation design and work posture, sedentary work position, repetitive work, and precision work. [8]Other risk factors in the working population, identified in the same systematic review, are age, previous musculoskeletal pain, and low physical capacity. A recent review including only office working populations concluded that there is strong evidence for female gender and previous history of neck complaints as risk factors for neck pain. [14]

The evidence on risk factors for WAD is still sparse. One potential reason for this is that it is hard to obtain appropriate data to use as denominator when calculating the risk. [15] Females seem to have a slightly higher risk, although results are not consistent across studies. Lower age also seems to be associated with a higher risk for WAD, as well as neck pain previous to the collision. The latter could potentially be the reason driving the association between female gender and increased risk for WAD, as the prevalence of neck pain in general may be higher among females.

2.2.6 Prognostic factors

There is a consensus among studies in a systematic review that lower age is a prognostic factor for better recovery in the general population. [9] Studies on gender as a prognostic factor in the same review have reached varied conclusions, although the studies that were methodologically more favorable showed no effect of gender on prognosis for neck pain. Factors related to pain, disability, [16] and general health at baseline and prior to baseline, as well as comorbid low back pain, are factors that give a worse recovery. [9] The evidence for physical activity as a prognostic factor differed between studies in one review, [9] and seemed not to be related to prognosis in another more recent overview of reviews. [16]

When looking at studies from working populations the populations differ in terms of work places and tasks. A review investigating the evidence available about prognostic factors in working populations of different types found eight studies being of adequate quality to be included. [12] The results for gender as prognostic factor vary between studies and therefore it cannot be confirmed to matter for the course of neck pain. Age however is not prognostic in a working population, according to consistent results from six out of seven studies in the review. Having had prior pain and prior sick leave gave a worse outcome regarding sick leave as well as persistence and recurrence of pain. Occupation type mattered for the prognosis of neck pain, however it did not appear as factors related to ergonomics, job demands or physical factors did. The majority of the studies investigating psychosocial factors did not find any association with the prognosis of neck pain. However, it seems like factors such as coping and others that are influential of prognosis in other populations were not studied to any large extent,

and not with good methodological quality. Exercising gave a more positive prognosis for neck pain, but this was a consensus from only two studies.[12]

In populations with WAD the findings for age as prognostic factors have not been consistent, neither have the findings for pre-injury neck pain. [13] Female gender yields a worse prognosis, although the effect does not seem to be very strong. [17] Higher level of pain and more symptoms at base line are factors that affect the prognosis in a negative direction, and different kinds of psychological factors, such as coping behavior, anxiety, depression and others, were evidently also affecting the prognosis of neck pain. Reporting of low back pain at baseline also gave a worse prognosis for neck pain.[17] Accident parameters have no impact on the prognosis of neck pain, which is consistently shown across studies.[16]

2.3 QUESTIONNAIRE AND REGISTER DATA

Questionnaires are a common form of collecting data in large population based studies. As they provide self-assessed information the quality of such data can vary, and this is a concern of many researchers. However, in some cases self-reported information is the only information that can measure what you want to capture. When it comes to assessment of pain, self-reported information is essential as the pain is a subjective experience. Intensity of pain cannot be measured objectively as pain is a multidimensional concept including emotional aspects. One important aspect of pain is whether the pain bothers the individual or not, regardless of the intensity of the pain, because this notion may be the factor restricting an individual in the daily activities in life.

Sweden has a long tradition of population registering, and in the modern times a lot of effort has been put on providing good quality health registers. There are census registers, which have nationwide coverage and also quality registers for example to register cases of a specific disease, and gather additional information on factors possibly related to the disease. The national registration number, which all Swedish citizens are provided with, enables linkage between registers leading to research with rich data and often very accurate information. Sweden is by many considered a goldmine of information for epidemiological research, because of its many registers. Although, one has to recognize that register information does not guarantee valid and reliable information, and may not be appropriate for in-depth research questions.

2.4 INTERNATIONAL CLASSIFICATION OF FUNCTIONING, DISABILITY AND HEALTH

The International Classification of Functioning, disability and health, also called ICF, is a framework for classifying a wide spectrum of health related information.[18] It is a

biopsychosocial model of disability[19] developed by the world health organization (WHO) and has been recognized as an international standard to measure disability and health by all its member states since 2001.[18] WHO also developed the International Classification of Diseases which is a framework for diagnosing health conditions and is used for different purposes, e.g. monitoring incidence and prevalence of diseases, and classifying diseases in health records.[18] ICF is complementing ICD in giving perspectives on functioning related to health problems, and when used together they provide information on diagnoses as well as functional capacity which gives a more clear and meaningful picture about the health condition of populations or individuals.[20]

ICF is for example used by physiotherapists to identify obstacles for function or areas with potential for improvement of an individuals' functioning.[20] ICF was developed for several purposes, and one of them was to give a scientific foundation for studying health, health related conditions and determinants of health. The conceptual framework which ICF supplies can be used in many areas of health related work and also in health prevention and the work for equal rights of participation in society.[20]

The base in the structure of ICF rests on the two parts: 1) Functioning and disability, and 2) Contextual factors. Each of these parts has two underlying components. For Function and disability the two components are: "Body functions, and structures", and "Activities and participation". For Contextual factors the two underlying components are: "Environmental factors", and "Personal factors", which can be expressed in negative as well as positive terms. Further, these four components are based on different domains, which in their turn contain categories (see Figure 1). By coding the categories with numerical codes, specifying the extent of that specific category of functioning or disability, an individuals´ health related condition is registered.[20-22]

	Part 1: Functioning and Disability		Part 2: Contextual Factors	
Components	Body Functions and Structures	Activites and Participation	Environmental Factors	Personal Factors
Domains	Boby functions Body structures	Life areas (tasks, actions)	External influences on functioning and disability	Internal influences on functioning and disability
Constructs	Change in body function (physiological) Change in body structures (anatomical)	*Capacity* Executing tasks in a standard environment *Performance* Executing tasks in the current environment	Facilitating or hindering impact of features of the physical, social, and attitudinal world	Impact of attributes of the person
Positive aspect	Functional and structural integrity	Activities Participation	Facilitators	not applicable
	Functioning			
Negative aspect	Impairment	Activity limitation Participation restriction	Barriers/hindrances	not applicable
	Disability			

Figure 1. Overview of the ICF framework, from the report International Classification of Functioning, Disability and Health: ICF, by the World Health Organization (WHO)

ICF is a model that covers many different aspects of neck pain as a health problem. It may therefore be useful for mapping the various consequences for individuals that can be caused by the potential risk and prognostic factors studied in this thesis. Hopefully this mapping can elucidate the different mechanisms through which the factors may play a role in the risk and prognosis of neck pain.

2.5 RATIONALE

As stated in the introduction of this thesis, neck pain is a large global public health burden. It affects individuals, communities and countries in several ways. It creates

human suffering, great costs for individuals as well as societies in terms of treatment costs, sick leave, disability pensions and productivity loss.
A great deal of research has been conducted within this field, but still the best evidence syntheses stress the need for more research. The major concerns are that the methodological quality often is too scarce and that results in many cases vary, often due to differences in the definitions of neck pain that are used. Our intention has been to conduct high quality studies to increase the knowledge about risk and prognosis of neck pain, and as far as possible use definitions suggested by these syntheses. The factors studied in this thesis were income, physical activity, expectations of recovery, and comorbid cardiovascular disorders (CVD). Income and CVD affect the general health and may therefor affect neck pain. Physical activity and expectations have been studied in the context of neck pain before, however this potential association needs to be investigated further.

3 AIM

3.1 OVERALL AIM

The overall aim of this thesis was to study factors of potential importance for the risk and prognosis of neck pain, including WAD.

3.2 SPECIFIC AIMS

To assess the sex specific role of disposable income for onset and prognosis of neck pain in the general population, and if economic stress influences such potential associations (study I).

To investigate if work related physical activity and physical activity during leisure time are of importance for the risk and prognosis of neck pain (study II).

To investigate if pre-treatment expectations of recovery is a prognostic factor for recovery from neck pain at seven weeks follow-up in patients seeking manual therapy treatment (study III).

To determine whether prevalent self-reported CVD are associated with poor self-rated recovery in persons with WAD (study IV).

4 MATERIALS AND METHODS

4.1 MATERIAL

4.1.1 Stockholm Public Health Cohort (study I and II)

The Stockholm Public Health Cohort (SPHC) is a population based longitudinal study.[23] The part of SPHC used had its baseline 2002-2003 and a follow-up 2007 (n=23 794). The source population constitutes of residents in the ages of 18-65, from 24 out of 26 municipalities in Stockholm County, Sweden. This geographical area is an urban environment with a total of 1.4 million inhabitants.

From this source population the study sample of 50 067 persons was randomly selected after stratification for gender and residential area. Between October 2002 and March 2003, these persons received a baseline questionnaire, which was followed by a maximum of three reminders in absence of reply. The baseline questionnaire was returned by 62% (31 182 persons), and the responders were sent a follow-up questionnaire between March and August 2007. The questionnaires were extensive and contained questions on, for example, demographic characteristics, lifestyle factors, physical and mental health. See Figure 2 for flowchart of inclusion process for SPHC.

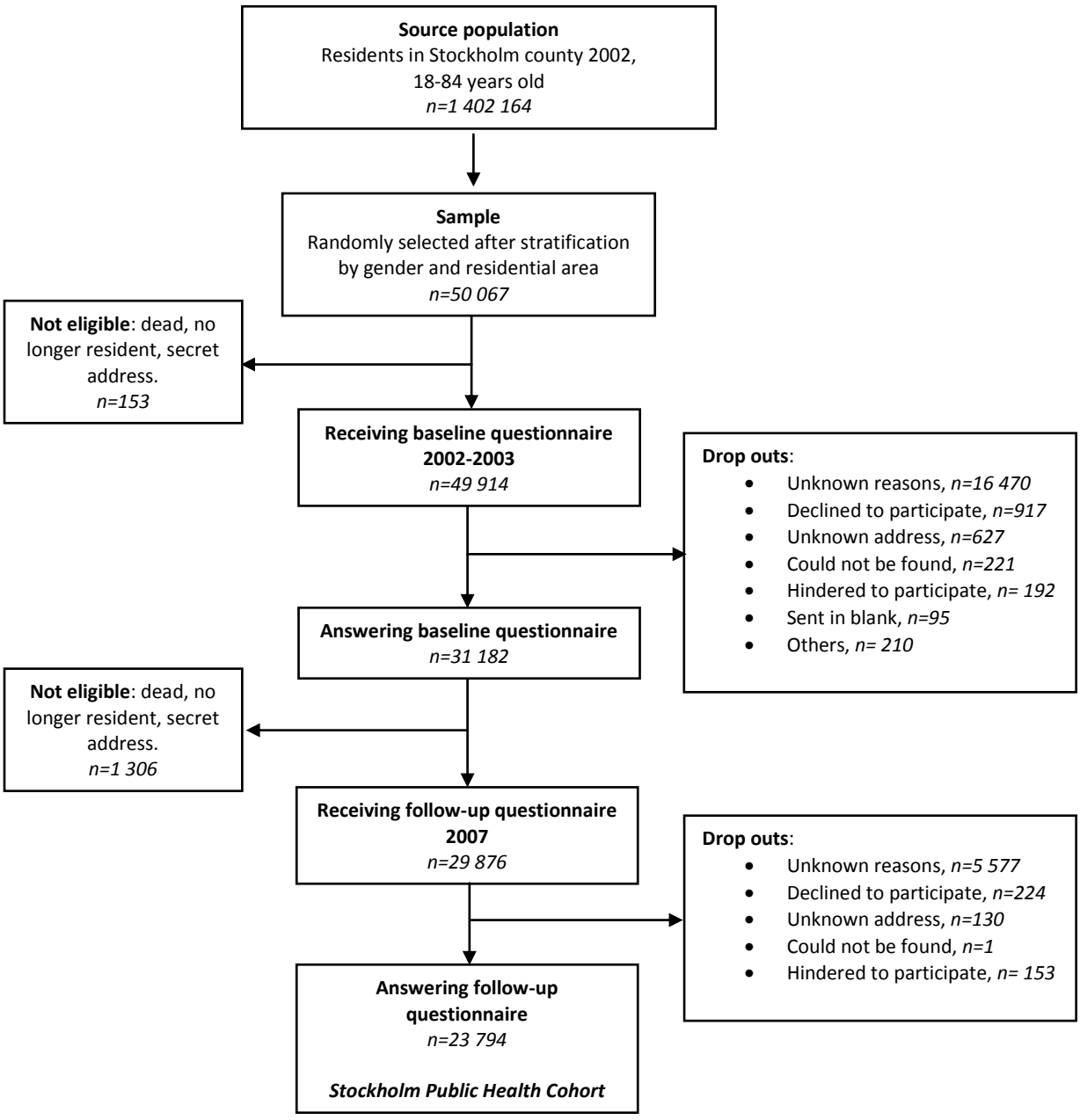

Figure 2. Inclusion process for the Stockholm Public Health Cohort

4.1.2 Stockholm Manual Intervention Trial (study III)

The Stockholm Manual INtervention Trial (MINT) study had the main aim to compare three different treatment regimens within manual therapy and also to assess whether the occurrence of adverse events differ between the regimens. Patients with back and/or neck pain seeking care at the educational clinic of the Scandinavian College of Naprapathic Manual Medicine in Stockholm, Sweden, were asked to participate in the

study. Inclusion criteria were ages 18-65, and no visits to the clinic during the previous month. Exclusion criteria were; 1) not mastering Swedish language well enough to independently complete the questionnaire, 2) low pain score (<2 on an 11-point numerical rating scale between 0-10) reporting present pain and worst pain the past four weeks, 3) pregnancy, 4) current or past cancer, 5) receiving treatment by a chiropractor, osteopath, physiotherapist or naprapath during the past month for the current complaint, 6) duration of current complaint less than one week , 7) demanding or refusing spinal manipulation or stretching, 8) contraindication for spinal manipulation according to the Swedish Board of Social Welfare,[24] 9) no indication for spinal manipulation in the area seeking care for, 10) red flags, 11) specific diagnoses (for example ankylosing spondylitis, spinal stenosis, rheumatoid arthritis), 12) sick leave due to planned/completed surgery for neck and/or back. Further information about the study is given in a previous publication. [25]

The treatment combinations given in the three intervention arms were; 1) a combination of manual therapy techniques, including spinal manipulation, spinal mobilization, muscle stretching and massage, 2) a combination of manual therapy techniques excluding spinal manipulation, and 3) a combination of manual therapy techniques excluding stretching. Each participant was offered a maximum of six treatments over a six weeks period.

At the first visit, before being assigned to a certain treatment, the participants filled out a baseline questionnaire asking about demographic information, lifestyle factors, previous problems, pain intensity, pain related disability, expectations of recovery etc. Participants were followed-up by questionnaires sent to their home or their email, at seven weeks, three, six and twelve months after baseline.

4.1.3 Saskatchewan Government Insurance cohort (study IV)

Saskatchewan Government Insurance (SGI) cohort was based on persons involved in traffic collisions in the province of Saskatchewan, Canada between December 1, 1997 and November 30, 1999. At the time, Saskatchewan had a population of one million inhabitants, a universal health care system and a single government insurance company that provides all traffic injury insurance. The cohort included all Saskatchewan residents 18 years of age or older, who required treatment for a traffic injury from a registered health professional (i.e., medical doctor, chiropractor, physical therapist or massage therapist), or filed an injury claim, within 42 days of a collision. Further information about the study is given in a previous publication. [26]

Baseline data were collected through a self-administered questionnaire included in the insurance claim application. The questionnaire included questions on demographic and socioeconomic characteristics, collision circumstances, injury related pain location and intensity, and pre-injury and post-injury physical and mental health.

Participants were followed up by structured telephone interviews at six weeks and three, six, nine and twelve months post injury. The information collected included self-rated information on global perceived recovery, pain assessment, mental health, physical exercise, pain coping, health care treatment, and self-rated health-related quality of life. The telephone interviewers were blinded to baseline information.

4.2 METHODS

4.2.1 Study I

4.2.1.1 Participants/inclusion criteria

From the SPHC 2002 two sub-cohorts were identified based on the presence of neck pain at baseline. One cohort included adults who reported no neck pain during the past six months, and this cohort was assessed for the risk of onset of neck pain (Cohort I, n=8 348). Another cohort included adults reporting that they have had neck pain up to a couple of days per month during the past six months (occasional neck pain), and those were assessed for the prognosis of neck pain (Cohort II, n=10 523). See flowchart Figure 3.

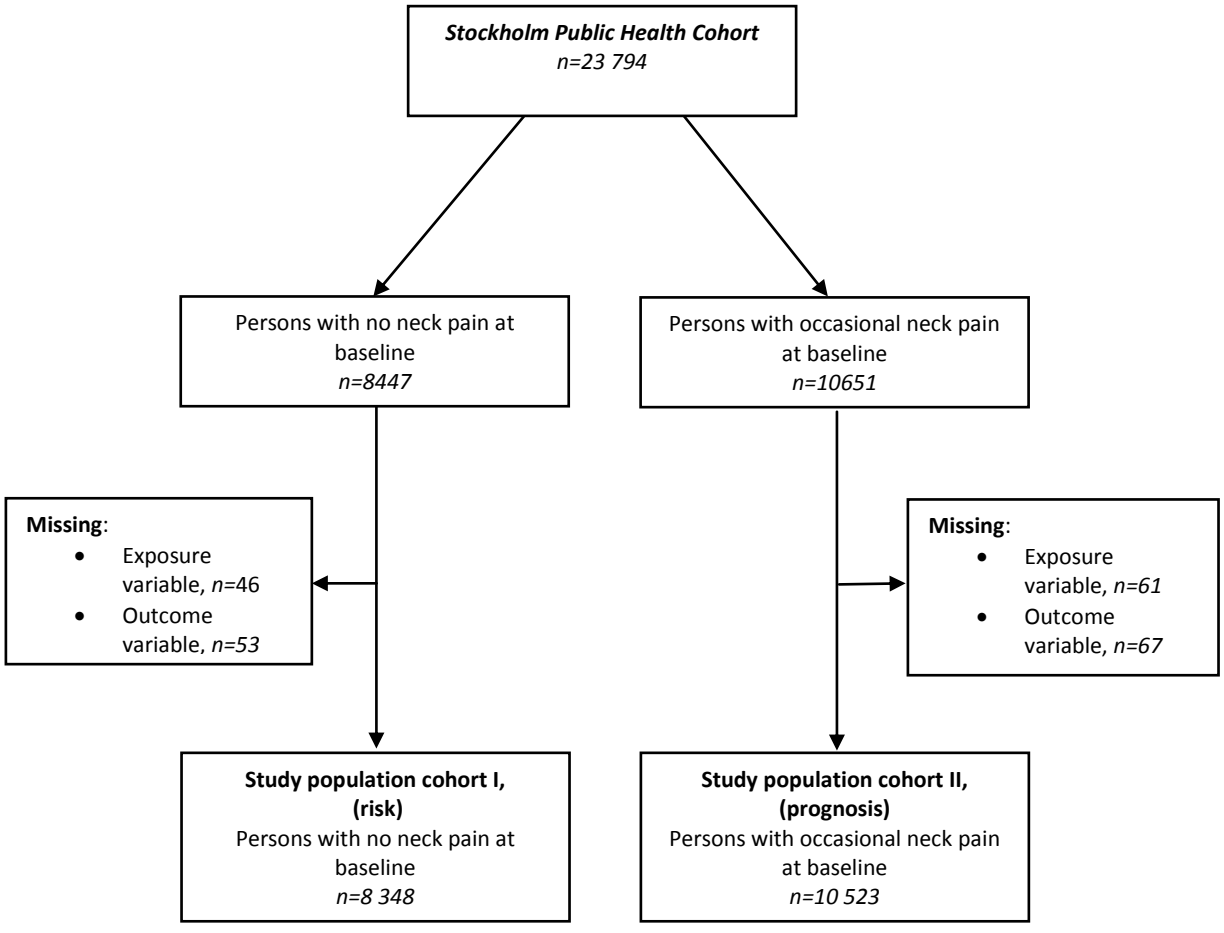

Figure 3. Flowchart of inclusion in study I

4.2.1.2 Exposure

Information on the exposure,"individual disposable income", was collected at baseline. It was based on the aggregated annual household income including all taxable income (wage earnings, complementary social allowances, pension), and also taking the final tax deductions into account. Further, the household income was individualized by multiplying it by the individual´s assigned consumption weight and dividing it by the total consumption weight of the family members.

The individual disposable income was grouped in quartiles; 0-115 299 SEK (EUR 0-12 302), 115 300-154 199 SEK (EUR 12 303-16 453), 154 200–207 499 SEK (EUR 164 54-22 140) and ≥207 500 SEK (≥ EUR 22 141).

4.2.1.3 Other covariates of interest

Information on potential confounders was retrieved from the baseline questionnaire. The following factors were considered as potential confounders: Immigrant status (born in or outside of Sweden), alcohol consumption (expressed in gram of 100% alcohol per day and categorized into no, low, moderate and high level of consumption), smoking (never, ever or current smoker), concurrent low back pain (during the past six months measured on a five level Likert scale ranging from "never" to "daily"), physical activity during leisure time (four categories from mainly sedentary activity with less than two hours of light physical activity up to regular activity at least three times per week for at least 30 minutes sessions). Week hours of household work, and physical occupational work load (measured on a four level Likert scale anchoring sedentary to heavy work) were also tested. The baseline questionnaire contained some of the questions from the Job Content Questionnaire (JCQ), concerning psychosocial occupational work load[27] of which the two following were tested; freedom to decide how the work shall be performed, and freedom to decide what should be performed. Lastly, levels of psychological distress (measured by the 12-item General Health Questionnaire (GHQ12) were considered as potential confounder.[28] A sum score of ≥ 3 (using the recommended standard 0-0-1-1 scoring on the four answering alternatives) was used to denote psychological stress.

Economic stress was considered a potential effect measure modifier. The response to the following question was used to address this; *"Did it during the previous 12 months happen that you ran out of salary/money and that you had to borrow from relatives and friends to be able to pay for food or rent?".* Answering "yes" was defined as having been exposed to economic stress.

4.2.1.4 Outcome

The outcome in the analyses of both *cohort I* and *cohort II* was long duration troublesome neck pain (LDNP) measured in the 2007 questionnaire. The following operationalization for LDNP was used: having answered "yes" to the question *"During the past five year period, have you had neck pain that lasted at least three consecutive*

months that bothered you considerably?". This definition is in line with the conceptual framework for the definition of neck pain outlined by the Bone and Joint Decade 2000-2012 Task Force on Neck Pain and its Associated Disorders.[5]

4.2.1.5 Statistical analysis

Multivariable logistic regression was used to assess the association between individual disposable income and LDNP. Four different models were built based on gender and the outcome. Potential confounders were tested in each model by including them one by one in the crude model. If the crude odds ratio (OR) was changed with more than 10%, the variable was considered to be a confounder and was included in the final model.[29] All analyses were adjusted for age. The exposure was dichotomized based on the median when conducting confounding control.

To test potential effect measure modification by economic stress, income level and economic stress was combined in a dummy variable. In the analyses the reference group contained individuals without economic stress and having an income higher than the lowest quartile of individual disposable income (≥115 300SEK). Also included as covariates were those factors considered to be confounders in the main analyses, as well as sex, as stratified analyses would likely have given too low power.

Results are presented as crude and adjusted OR with 95 % confidence intervals (95% CI). Statistical analyses were run with SAS®statistical software system version 9.1 and STATA®statistical software system version 11.

The relative excess risk due to interaction (RERI) is a measure of deviation of additivity of effects that gives an estimation of the interaction between two factors in their association with an outcome. The RERI and 95% confidence intervals (CI) were calculated for individual disposable income and economic stress in study I by using an Excel sheet. [30] The basic formula used for calculating RERI is the following:

$$RERI = RR_{11} - RR_{10} - RR_{01} + 1$$

These calculations were additional and are not included in the original article.

4.2.2 Study II

4.2.2.1 Participants/inclusion criteria

A working population was identified through excluding those who were neither employed nor self-employed, and those over 60 years of age at baseline. Two sub cohorts were formed, one for analyses on risk and one for analyses on prognosis of neck pain. Individuals who reported no neck pain during the past 6 months in the baseline questionnaire (n=4 681) were assessed for the risk of onset of neck pain (Cohort I). The cohort for assessment of the prognosis of neck pain (Cohort II) included

individuals with occasional neck pain at baseline, defined as having had neck pain up to a couple of days per month during the previous six months reported in the baseline questionnaire (n=6 820).

4.2.2.2 Exposure

Work related physical activity was assessed in the baseline questionnaire with the question; "How much have you been physically active or exerted yourself physically at your work during the past twelve months?" The answering categories were; 1) Sedentary work: you have a predominantly sedentary work, 2) Light but somewhat active work: you have a work situation where you walk quite a lot but do not carry or lift heavy things, 3) Moderately heavy work: you walk a lot as well as lifting quite a lot and also climb stairs or walk uphill, and 4) Heavy work: you have a heavy manual labor, lifting heavy things and physically exert yourself to a high degree. The question is considered to have good validity and reproducibility. [31]

Leisure physical activity was measured through the following question in the baseline questionnaire; "How much have you been physically active in your leisure time during the past twelve months?" The participants were asked to state an average if their leisure time physical activity varied over the seasons. The four answering categories were; 1) Sedentary leisure time: you spent most of your time reading, watching TV, going to the movies or other sedentary activity during leisure time. You walk, ride a bike or engage in physical activity in some other way less than 2 hours/week, 2) Moderate physical activity during leisure time: You walk, ride a bike or engage in physical activity in some other way for a minimum of 2 hours/week, often without perspiring. This also includes walking or riding a bike to or from work, Sunday walks, ordinary gardening, fishing, table tennis and bowling, 3) Moderate, regular physical activity during leisure time: you exercise regularly 1-2 times/week, each time for a minimum of 30 minutes, with jogging, swimming, tennis, badminton or other activity that makes you perspire, and 4) Regular physical activity and exercise: you are active with running, swimming, tennis, badminton, aerobics or something similar at least 3 times/week. Each occasion lasts for at least 30 minutes. The leisure physical activity question has acceptable validity when compared to results from an accelerometer. [32]

4.2.2.3 Other covariates of interest

Information from the baseline questionnaire was used to identify potential confounders in the analyses of associations between the both exposures respectively, and the outcome. The following variables were evaluated as potential confounders; immigrant status (born in or outside of Sweden), alcohol consumption (expressed in gram of 100% alcohol per day and categorized into no, low, moderate and high level of consumption), smoking (categorized into never, ever and current smoker), concurrent low back pain (during the past six months measured on a five level scale ranging from "never" to "daily"), and individual disposable income (individualized share of family income based on income, social benefits and tax deductions, categorized into quartiles). The baseline questionnaire contained some of the questions from the JCQ, concerning

psychosocial occupational work load.[27] Of the available questions we chose to test two as potential confounders; "freedom to decide how the work shall be performed", and "freedom to decide what should be performed". Also considered as potential confounders were "Working with arms above shoulder level at least 30 minutes per day" and "working with arms under knee level at least 30 minutes per day" (both with four answering categories ranging from "Almost never or never" to "Every day"). How big part of the work day spent in front of a computer (with six answering categories ranging from "Never" to "Almost all the time") was tested as potential confounder only in the analyses of associations between leisure physical activity and LDNP. Furthermore we evaluated amount of time that work is considered to be stressful (categorized into five, ranging from "about 1/10 of the working hours" to "almost all working hours") and also levels of psychological distress (measured by the GHQ12) with regard to potential confounding.[28] A sum score of ≥ 3 (using the recommended standard 0-0-1-1 scoring on the four answering alternatives) was used to denote psychological distress. Sex was tested as a confounder in the analysis of both sexes. Lastly we evaluated work related physical activity as a potential confounder for the associations between leisure physical activity and the outcome, and vice versa. Age was divided into five categories (18-25, 26-35, 36-45, 46-55 and >55) because of its non-linear relationship with LDNP and was included as a covariate in all final models.

4.2.2.4 Outcome

The outcome in the analyses of both *cohort I* and *cohort II* was LDNP. Those who answered "yes" to the following question in the follow-up questionnaire were identified as cases; "During the last five-year period, have you had neck pain for at least three consecutive months that bothered you considerably?". This definition is in line with the conceptual framework for the definition of neck pain outlined by the Bone and Joint Decade 2000-2012 Task Force on Neck Pain and its Associated Disorders.[5]

4.2.2.5 Statistical analysis

Multivariable logistic regression was used to assess the association between the exposures and the outcome, and the results were presented as OR with 95% CI. Multivariable logistic regression models were built for each exposure and sex, in *cohort I* and *cohort II* respectively, and also one including both sexes for each exposure and cohort. The potential confounders were evaluated by adding them one by one to the crude models. If the crude OR was changed with more than 10%, the variable was considered to be a confounder for that specific association and was included as a covariate in the final model.[29] Individuals with missing data on the outcome or exposure were excluded from the analyses. Statistical analyses were run with STATA® statistical software system V.11.

4.2.3 Study III

4.2.3.1 Participants/inclusion criteria

Among the participants in the Stockholm MINT study all study participants seeking care mainly for neck pain, and those seeking care for neck pain with concurrent back pain that was equally disturbing as the neck pain, were selected and formed as a cohort (n=697). The inclusion to the study is described further in Figure 4.

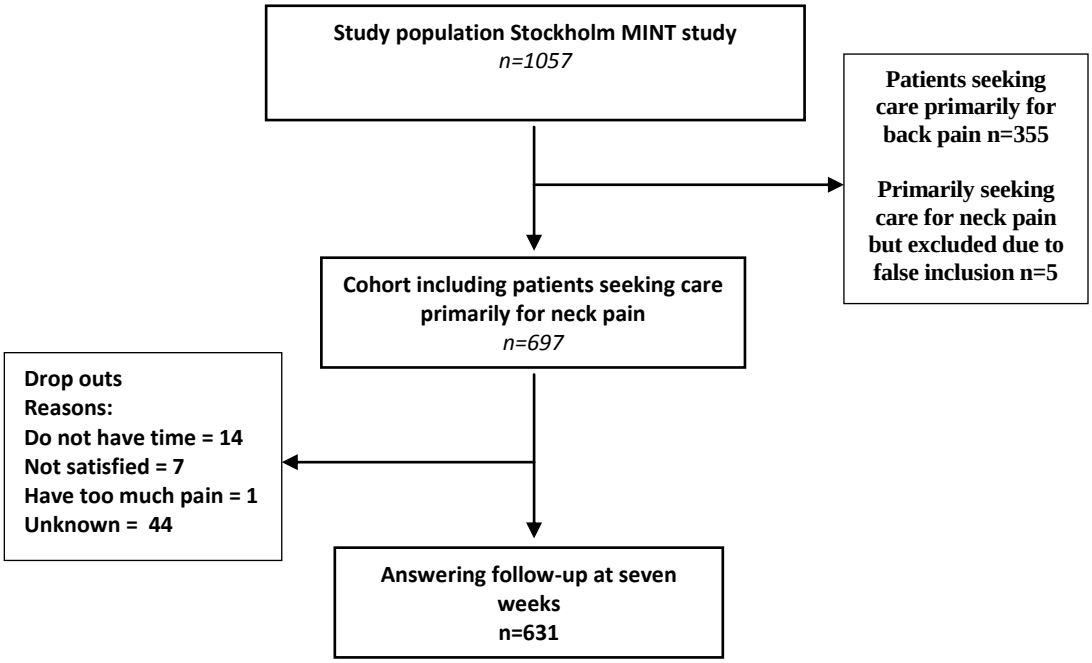

Figure 4. Inclusion process for participants in study IV

4.2.3.2 Exposure

Expectations of recovery was measured with a question in the baseline questionnaire; "How likely is it, according to your judgment, that you are completely recovered from your neck/neck and back condition in seven weeks". Participants answered on an 11 point scale anchoring at 0 "Not at all likely that I will be completely recovered" and 10 "Very likely that I will be completely recovered". There are many existing definitions of expectations in the literature, and the one used in this study is in line with the definition "predicted expectations", suggested by Thompson and Sunol.[33]

4.2.3.3 Other covariates of interest

Baseline factors considered as potential effect measure modifiers were sex, pain duration and pain related disability. Pain duration was dichotomized into acute/subacute (three months duration or less) and chronic (more than three months duration). A modified version of CPQ [34], with the recall time of four weeks instead of the original six months, measured pain related disability. The disability measure was based on three questions regarding the effect of pain on the daily activities, leisure activities, and work, respectively. Answers were given on an 11 point numerical rating scale (NRS) ranging from 0 (Not at all) to 10 (Impossible to conduct these activities). The mean of the three questions was calculated and further categorized into low disability (0-3), moderate disability (4-6), and high disability (7-10).

Information on potential confounders was retrieved from the baseline questionnaire, and the factors tested as potential confounders were: sex, age (tested as continuous and categorized into ages 18-25, 26-35, 36-45, 46-55 and >55), pain duration (acute/subacute or chronic), pain related disability derived from CPQ (tested as continuous and categorized into low, moderate or high), highest level of education (categorized into elementary school 1-9 years, high school 10-12 years, university 13-15 years or higher academic education ≥16 years) previous periods of similar neck problems (yes or no) and treatment arm (1, 2 or 3). Further we tested pain intensity as a potential confounder, derived from the CPQ. The mean of three questions about pain right now, worst pain the past four weeks and average pain the past four weeks was calculated from the patients' answers on a 11 point NRS ranging from 0 (no pain) to 10 (the worst imaginable pain). The mean values were tested as continuous and also as further categorized into low (NRS 0-3), medium (NRS 4-6), and high (NRS 7-10) Also tested as potential confounder was downheartedness measured by the following question; "How much of the time during the past four weeks have you felt downhearted and blue?". Answering alternatives were "All of the time", "Most of the time", "A good bit of the time", "Some of the time", "A little of the time", and "None".

4.2.3.4 Outcome

The dichotomized outcome was measured by the Global Perceived Recovery Question, with a slight change in the wording. The questions states: "Which of the following statements is most consistent with your perception of the change in your neck/neck and back complaint since you joined this study?" Answering alternatives were; 1)"Is completely free from pain and have no other complaints originating from neck/neck and back", 2)"Is considerably improved", 3)"Is slightly improved", 4)"No change", 5)"Is slightly worse" and 6)"Is much worse". Participants answering alternatives 1 and 2 were considered as cases.

4.2.3.5 Statistical analysis

Mantel-Heanzel test was used to assess potential effect measure modification, and log-binomial regression was used to assess the association between baseline expectations of recovery and self-perceived recovery at seven weeks follow-up. Each potential

confounder was tested by adding it to the crude model one at a time, and if it changed the point estimate with 10% or more it was added in the final model.[29] Patients with missing data on the outcome were excluded from the analyses. There were no patients with missing data on the exposure. In order to adjust for potential differences in treatment effect, treatment arm was included as a covariate in all models. Statistical analyses were run with STATA® statistical software system V.11.

4.2.4 Study IV

4.2.4.1 Participants/inclusion criteria

Included in study IV were persons from the SGI cohort who reported WAD by answering "yes" to the question "Did the accident cause neck or shoulder pain?". Persons were considered not eligible for the study if they were not able to answer the questionnaire due to lack of English language or serious illness (e.g. Alzheimer's disease), or if they made a Worker's compensation claim. Persons were excluded if they sustained a serious injury (hospitalized for more than two days) or if they were not injured in an automobile collision. The number of potentially eligible persons was 8,634, and after exclusion according to exclusion criteria the study population included 6,021 persons.

4.2.4.2 Exposure

The following two questions from the Comorbidity Questionnaire were used to measure the presence of CVD: 1)"Do you currently have heart and circulation problems (such as angina, heart attack, heart failure, heart valve problem, hardening of arteries, varicose veins, claudication, foot or leg ulcers, others)?" Answering categories were "yes" or "no", 2) "If you do, to what extent have these problems affected your health in the last six months?" Answering categories were "Not at all", "Mild", "Moderate" and "Severe". The responses were combined to create a three-level exposure variable: 1) No CVD, 2) CVD with no or mild effect on health, and 3) CVD with a moderate or severe effect on health. The Comorbidity Questionnaire is considered valid and reliable to measure comorbid conditions.[35 36]

4.2.4.3 Other covariates of interest

Age was considered a potential effect measure modifier as previous studies have suggested CVD to affect persons´ health differently depending on age.
[37 38] Age was categorized it into three categories (18-30, 31-40, >40 years) for the analyses, based on statistical efficiency. Other studies have found disparities between men and women in symptoms, management, and outcomes of CVD, [39] thus sex was also considered a potential effect measure modifier in study IV.

Potential confounders were selected a priori. When exposure and potential confounders are measured at the same point in time, like in this study, it can sometimes be hard to determine the temporal relationship between the two. This may create a concern as a

potential confounder lying in the causal pathway between exposure and outcome may introduce bias to the results if it is added to the statistical model. [29]. Due to this concern, two sets of potential confounding variables were created; those that were clearly not in the casual pathway between the exposure and outcome (age and level of education) and those that may be in the causal pathway (other comorbidities).

Presence of pre-injury musculoskeletal problems and mental or emotional problems prior to accident, measured with the Comorbidity Questionnaire, [35 36] were two factors selected as confounders. Similar to the categorization of the exposure the health impact of the comorbidities was summarized into three categories: 1) absent, 2) present with no or mild effect on health, and 3) present with moderate or severe effect on health. The two questions measuring self-reported mental health problems were: 1)"Did you have mental or emotional problems before the accident (such as depression, anxiety, substance abuse: alcohol or drugs, others)?" Answering categories were "yes" or "no", 2) "If you did, to what extent have these problems affected your health in the last six months?" Answering categories were "Not at all", "Mild", "Moderate" and "Severe". Pre-injury musculoskeletal problems was measured using the following two questions: 1)"Did you have muscle, bone or joint problems before the accident (such as rheumatoid arthritis, osteoarthritis, back or neck pain, fibromyalgia, thin bones or osteoporosis, fracture , infection, others)?" Answering categories were "yes" or "no", 2) "If you did, to what extent have these problems affected your health in the last six months?" Answering categories were "Not at all", "Mild", "Moderate" and "Severe". Education was also considered a confounder and was divided into six categories; "Grade 8 or less", "Higher than grade 8 but did not graduate from high school", "High school graduate", "Post secondary or some university", "Technical school graduate", and "University graduate". Also age was considered a confounder and was used as a continuous variable.

4.2.4.4 Outcome

The outcome in study IV was Global Perceived Recovery, measured by the question: "How well do you feel you are recovering from your injuries?". Answering categories were: 1)"All better", 2)"There has been quite a bit of improvement", 3)"There has been some improvement", 4)"There has been no improvement", 5)"I am getting a little worse" and 6)"I am getting much worse". Considered as cases were those who reported "All better" or "There has been quite a bit of improvement" and did not report a relapse (reporting a lower grade of recovery) at a subsequent follow-up. Previous studies have found the Global Perceived Recovery question to have adequate reliability [40] and to correlate with other validated measurements of WAD recovery. [41]

4.2.4.5 Statistical analysis

Cox proportional hazards models were built to assess the association between CVD and time to recovery from WAD. Firstly the crude association between CVD and recovery was measured. Potential effect measure modification was tested by stratifying analyses by age and sex respectively, as well as by testing the statistical significance of an

interaction term between CVD and the two potential effect modifiers respectively. The median time to recovery together with 95% confidence intervals (95% CI) were computed for the three exposure categories. Further, the combined effect of the factors age and level of education (those not in the causal pathway) was tested by adding them to the crude model. Then, as a sensitivity analysis, the combined effect of all potential confounders together was tested. The proportionality assumption of our model was tested by plotting the Schoenfeld's residuals and by testing the statistical significance of a time-exposure interaction term in the model. Effect measures presented are hazard rate ratios (HRR) with 95% CIs. Statistical analyses were run with STATA®statistical software system version 11.

5 RESULTS

5.1 STUDY I

5.1.1 Cohort I (assessed for risk)

In the analysis of men only, after adjusting for age, a clear association between income and LDNP was found in the lowest income category (OR 1.8, 95% CI 1.1-2.8). Among women adjustment was made for age and alcohol consumption, and the adjusted OR in the lowest and second lowest category of income was 1.6 (95% CI 1.0-2.6) and 1.7 (95% CI 1.0-2.7) respectively. No difference in risk for LDNP was found for the second highest income categories compared to the highest.

Analysis of effect measure modification
A weak association was found among those with only one exposure present. Low income without economic stress yielded an OR of 1.3 (95% CI 1.0-1.7). Individuals with economic stress but not belonging to the lowest income quartile had an OR of 1.2 (95% CI 0.7-2.1). Having both exposures yielded a twofold increase in odds (OR 2.0, 95% CI 1.3-3.2).

5.1.2 Cohort II (assessed for prognosis)

Men in the lowest category of income had an OR of 1.6 (95% CI 1.2-2.1) of getting LDNP compared to men with a high income, and no additional confounders were found in the association. Analysis among women were adjusted for age and immigrant status and showed an OR of 1.3 (95% CI 1.1-1.6) for women in the lowest income category, and an OR of 1.2 (95% CI 1.0–1.5) in the second highest category compared to the highest. In the second lowest category of income no associations were found, neither among men nor women.

Analysis of effect measure modification
Individuals with economic stress but not belonging to the lowest quartile of income had an OR of 1.3 (95% CI 1.0-1.6), and having low income without economic stress yielded an OR of 1.1 (95% CI 0.9-1.3). Individuals with both exposures present had an odds of 1.8 (95% CI 1.4-2.2) of getting LDNP compared to the reference group.

5.1.3 Additional analyses

The RERI calculated in cohort I and II showed interaction effects that were not statistically significant. The RERI calculated for cohort I was 0.470 (95% CI -0.586 - 1.526) and for cohort II the corresponding were 0.415 (95% CI -0.036 - 0.866).

5.2 STUDY II

5.2.1 Cohort I (assessed for risk)

Work related physical activity
In the analysis of both sexes combined the ORs for the three categories of work related physical activity were adjusted for age, alcohol consumption, individual disposable income, work above shoulder level, and were all close to one. In the sex stratified analyses the adjusted point estimates varied from being protective to pointing to an increased risk. However, the CIs indicated uncertainty of effects.

Leisure physical activity
In the analysis of both sexes combined the results were adjusted for age, alcohol consumption, immigration status, work above shoulder level, work under knee level and computer work. The odds of getting LDNP were lower in all active categories compared to the sedentary. Being physically active was associated with 30-50% reduction of the odds of getting LDNP. There was no indication that the estimates differed between men and women.

5.2.2 Cohort II (assessed for prognosis)

Work related physical activity
In the analysis of men and women combined the results were adjusted for age, individual disposable income and work above shoulder level, and the odds of getting LDNP were close to one in all active categories compared to the sedentary. A similar result was seen also for each sex respectively.

Leisure physical activity
In the analyses of men and women combined the results were adjusted for age and immigration status and showed that active individuals did not differ clearly in odds of getting LDNP compared to the sedentary. Similarly, in the sex stratified analyses, no clear differences in odds were detected between the categories of different levels of activity compared to the reference category.

5.2.3 Additional analyses

To compare the effect for the risk of LDNP to the effect on the prognosis of neck pain, the estimates of cohort I and cohort II were tested for heterogeneity of effects. The test was performed on leisure physical activity only, and on all levels of the exposure. These results were not part of the original article.

The results showed that the estimates were statistically significantly different for the levels “moderate physical activity” and “moderate regular physical activity”, but not for the “regular physical activity and exercise”, when analyzing all individuals in each cohort (p-values 0.03, 0.05, and 0.08 respectively). The same comparison between estimates among women only showed no statistically significant differences (p-values 0.06, 0.07, and 0.20 respectively). Neither did the comparisons between the estimates among men only (p-values 0.46, 0.28, and 0.33 respectively).

5.3 STUDY III

Sex was an effect measure modifier in the association between expectations of recovery and recovery from neck pain, thus the analyses were stratified for sex. However, due to power considerations analyses were also performed with the sexes combined.

All
After adjusting for treatment arm and pain duration, individuals reporting high expectations had about 50% increased chance of being recovered at seven weeks follow-up (relative risk (RR) 1.47, 95% CI 1.16-1.84) compared to those reporting low expectations. Having moderate expectations also indicated a better chance of recovery with a RR of 1.22 (95% CI 0.94-1.57).

Men
Men with moderate expectations had an almost twofold chance of recovery compared to the reference category after adjusting for treatment arm and pain duration (RR 1.92, 95% CI 1.03-3.58), and among men with high expectations the chance was more than twofold (RR 2.26, 95% CI 1.26-4.07).

Women
Analyses of women were adjusted for treatment arm only, as none of the tested confounders affected the association. Women with moderate expectations did not differ in chance of recovery compared to the reference category with low expectations. However, women with high expectations had 43% higher chance of recovery compared to the reference category (RR 1.43, 95% CI 1.12-1.83).

5.4 STUDY IV

Sex modified the investigated associations and therefore all analyses were stratified by sex.

Men
For those reporting no CVD the median time to recovery was 124 days (95% CI, 109-183 days), the corresponding for those reporting CVD with no or mild impact on health

was 121 days (95% CI, 97-201 days), and for those reporting CVD with moderate or severe impact on health it was 133 days (95% CI, 95-316 days).

Controlling for age and level of education yielded a HRR of 1.10 (95% CI 0.84-1.45) for those reporting CVD with no or mild effect on health, and 1.16 (95% CI 0.79, 1.70) for those reporting CVD with moderate or severe effect on health. Adjusting also for musculoskeletal problems prior to accident and mental health prior to accident yielded HRRs of 1.09 (95% CI 0.83, 1.44) and 1.24 (95% CI 0.84, 1.83), respectively.

Women

Among women reporting no CVD the median time to recovery was 110 days (95% CI, 106-120 days), and the corresponding for those reporting CVD with no or mild impact on health was 186 days (95% CI, 115-199 days), and 277 days (95% CI, 99- . days) for those reporting CVD with moderate or severe impact on health.

The HRRs adjusted for age and level of education were 0.98 (95% CI 0.83, 1.16) for those reporting CVD with no or mild impact on health, and 0.69; (95% CI 0.47 -1.03) for those reporting CVD with moderate or severe impact on health. The HRRs adjusted for the additional factors that may lie in the causal pathway were 0.99 (95% CI 0.84, 1.17), and 0.74 (95% CI 0.50, 1.10), respectively.

6 DISCUSSION

6.1 MAIN FINDINGS

6.1.1 Study I

The results from study I suggests that income is a factor to consider when evaluating the risk for and the prognosis of neck pain. Having an individual disposable income below the 25th percentile (0-115 299SEK) consistently yielded a higher odds for LDNP in both cohort I (analyzed for risk) and cohort II (analyzed for prognosis), as well as in both men and women. Combining low income with perceived economic stress yielded even higher odds than the expected added effect, indicating that income and economic stress interact in their association with LDNP. Additional analyses not presented in the original article were made to give the RERI of the interaction between the two exposures. These analyses showed an indication of an interaction, as presented in the article, however it was only close to statistically significant.

To our knowledge there are no previous studies investigating income as a risk factor or prognostic factor for neck pain, but some studies have been conducted in related subjects. Social factors have been seen to play a role in the risk of developing neck pain,[2] and the results of study I may potentially be effects of the same phenomenon, namely possibility of social participation. A study by Kosidou et al.[42] shows that psychological distress, which is often associated with neck pain,[43] is affected by individual disposable income. And lastly, studies have shown that income is associated with self-rated health[44] and health in general.[45]

It can be argued that economic stress is a result of low income, in which case it would introduce bias to our results if we adjusted for it as it would be an intermediate factor in the association between income and LDNP. Additionally, the income and economic stress are linked as concepts and separating them by adjusting away part of the concept would not make sense. The associations found between income and LDNP may partially be related to the possibilities of consuming goods and services, to help counteract neck pain. But it may also be related to the possibilities of social participation, which may be limited when having a lower income. The economic stress was present also among those with a high income indicating that the ability to manage your economy is not entirely depending on level of income. It is also possible that social participation cost more as one moves up in social class, and therefore the economic stress is present also in higher income categories.

6.1.2 Study II

The results from study II show that higher levels of leisure physical activity than sedentary is protective of developing LDNP in a population free from neck pain at baseline. No differences in effect between men and women were demonstrated in the results, although the stratification for sex yielded wider confidence intervals, bringing larger uncertainty to the estimates. The prognosis for neck pain was not affected by leisure physical activity according to the results.

Physical activity within the work tasks was neither associated with risk nor prognosis of neck pain.

A systematic review from 2010 concluded that results regarding physical activity as a risk factor for neck pain are inconclusive. [2] More recent studies have followed this pattern with one study indicating that physical activity is a protective factor for neck pain[46], and another study not finding any association between the two. [47]

Studies on physical activity as prognostic factor for neck pain are sparse, and the two studies suggesting that there is an association [48 49] use improvement of neck pain as outcome as opposed to study II in this thesis where worsening of neck pain is the outcome.

Firstly, these results suggest that physical activity affects the risk for neck pain differently depending on within which arena it is conducted. This may be due to that different psychological factors mediate the effect of physical activity, for example freedom to choose when and what physical activity to engage in. Physical activity at work is a "demand" connected to your job description and may therefore be perceived as a burden rather than a strengthening activity.

Secondly, the results suggest that higher levels of leisure physical activity is protective of developing neck pain from being neck pain free, but not from developing more severe neck pain if one already has some neck pain complaints. Additional analyses of heterogeneity of effects (not part of paper III) were made to investigate if the difference in effect of leisure physical activity on LDNP was statistically significant, when comparing the effect in the risk cohort and the prognostic cohort. The results showed that the estimates were statistically significantly different for the levels "moderate physical activity" and "moderate regular physical activity", but not for the "regular physical activity and exercise", when analyzing all individuals in each cohort. The same comparisons were made among men and women separately, which showed no statistically significant differences. However, since these analyses suffer from power problems they are precarious to interpret.

The hypothesis was that physical activity would affect the neck pain through increased blood flow [50] and analgesic effect [51]. However, the results from analysis of both sexes

indicate that leisure physical activity is of benefit in primary prevention, but if neck pain is already present other strategies are needed to prevent worsening. It is important to remember though that this study investigates physical activity in general. It may still be beneficial to do neck specific training given as treatment by a health professional to counteract worsening of an already established neck pain.

Thirdly, the results indicate that being active is not worsening for the neck pain, as the prognosis was not affected in any direction from the physical activity measured in this study. This finding is in line with the recommendations about staying active which is an evidence based advice that healthcare professionals give spinal pain patients today.

6.1.3 Study III

The results from study III show that expectations of recovery is a prognostic factor for recovery from neck pain in a population seeking and receiving treatment. This result was consistent with other studies investigating the same type of association in similar populations. [52 53] The associations were not confounded by any other factors than pain duration and this was a confounder among men only.

Several factors were tested as confounders including disease related factors, such as history of neck pain, and it is interesting that not more of them turned out to confound the associations between expectations of recovery and recovery from neck pain. Expectations could be assumed to be a construct from experiences from previous similar pain episodes and qualities regarding the current pain episode. However that seemed not to be the case in this population. This indicates that expectations may be a separate process, maybe dependent on other more intrinsic and perhaps psychological factors. We cannot however exclude the possibility that the factors tested as confounders may suffer from measurement error, thus not fully capturing the true confounding effect.

6.1.4 Study IV

In study IV the results showed no associations between CVD and recovery from WAD among men. Among women the analyses showed a weak association, but possibly this association was due to residual confounding from pre-injury mental health and pre-injury musculoskeletal problems, as the sensitivity analysis yielded estimates that were driven towards the null. Due to the weak effect, possible residual confounding and the fact that there is no clear biological reason to why CVD would affect recovery from WAD differently among men and women, the conclusion was that the hypothesis that CVD affects recovery from WAD could not be supported by the results of this study.

No previous studies have investigated a similar association. The association was hypothesized based on that several cross-sectional studies[54 55 56], and one longitudinal study[57] detected an association between CVD and neck pain. Additionally, poor pre-injury physical health was in a recent study reported to be associated with reporting of WAD and neck pain lasting more than three months,[58] and self-assessed poor health in general seems to be associated with both the risk of neck pain[2] and the prognosis of low back pain.[59]

6.2 METHODOLOGICAL ASPECTS

When measuring the same thing several times there is always a random variation in the measurement. If you measure an infinite number of times this would not create a biased mean value, however in studies with restricted sample size these random diversities may affect the results.[60] This random error can be dealt with through statistical methods, commonly by using confidence intervals when presenting the results. Systematic errors, however, needs a different approach. Systematic errors can occur due to different reasons and affect the results of a study in a somewhat predictable way. Considering and analyzing the potential systematic errors can give an indication of how such bias affects the results (the parameter under study e.g. RR or OR). In epidemiological studies this is often one of the biggest challenges.

6.2.1 Systematic errors

6.2.1.1 Misclassification of exposure

Misclassification of exposure is one type of systematic error that may occur in a study. When the misclassification of a dichotomous exposure occurs to the same extent among cases and non-cases a non-differential misclassification is present often resulting in a diluted effect of the association between the exposure and the outcome.[61] This is the situation most likely to happen in prospective cohort studies as the exposure is measured prior to the outcome. This thesis is based on four prospective studies and thus non-differential misclassification may be a concern, as a high degree of non-differential misclassification of exposure could lead to false negative findings. In study I the exposure income is divided into quartiles, without considering any real-life threshold values, which could lead to misclassification of the exposure. Physical activity is the exposure in study II, and a factor that individuals sometimes tend to over report. [62] The exposures of both study I and study II could be altered during the follow-up time. For individual disposable income this is not very likely as it is a derived variable calculated from the family income and not only depends on the income of one individual. It is more likely regarding physical activity. Contradicting this theory, a study has concluded that physical activity behavior is relatively persistent over time.[63] Regarding physical activity at work, this is not often easy to change, as it may be hard to move between work positions. It may happen that individuals who report neck pain

at baseline would try to alter their physical activity at work to counteract the neck pain. The direction of this potential change in physical activity would be hard to predict, as it would depend on the individuals' belief of the effect of physical activity on neck pain. The exposure in study III, expectations of recovery, is measured with a question that is not validated. A systematic review of measurements of recovery expectations and their predictive value among low back pain patients suggested that the best predictive measurement was time-based and specific regarding the outcome to be predicted.[64] The measurement used in study III was time-based, but asked for recovery overall, instead of being specific. The exposure in study III may be subject to misclassification, but would in that case likely be non-differential. In study IV CVD is the self-rated exposure, measured by the Comorbidity Questionnaire. Despite that this is an instrument that is considered a reliable and valid instrument to measure comorbidities, there could be some diversities in individuals' knowledge about CVD that introduce some misclassification of the exposure. This would however be a difference that was equally distributed among cases and non-cases.

6.2.1.2 Misclassification of outcome

Misclassification of outcome is another potential systematic error able to bring bias to the study. Similar to the misclassification of exposure it can be differential or non-differential, depending on whether it is related to the exposure or not. In study I and II the outcome is LDNP which includes several axis of information according to the recommendations from the Bone and Joint Decade 2000-2012 Task Force on Neck Pain and its Associated Disorders [5] in order to be a proper measure of outcome within neck pain research; 1) the severity of neck pain and its consequences, 2) the duration of neck pain, and 3) its pattern over time. The recall time for the outcome is five years, which is a fairly long time to be able to recall pain. On the other hand the outcome requires persistent pain that have bothered the individual substantially over a minimum period of three months. This type of pain episode is rather severe and may therefore still be relatively easy to remember.

The outcome in study III and IV was recovery from neck pain and WAD respectively. In study IV the Global Perceived Recovery Question was used, which is tested and considered to have adequate reliability and correlate with other validated measurements of recovery from WAD.[41] In study III the outcome question was based on the Global Perceived Recovery Question, but slightly modified and translated into Swedish language. Recovery in study IV was further defined as reporting being recovered with no relapse at a subsequent follow-up. This is a matter of definition and could be somewhat tricky since the symptoms may be fluctuating. If the definition would have been only time to first recovery, there would have been a risk of overestimation of recovery since individuals having a particularly "good" day, in terms of symptoms, could have been falsely classified as recovered. A sustainable recovery is the meaningful thing to capture given the research question of study IV.

To get a better picture of the fluctuations of recovery in study IV Table 1 shows the probabilities for different combinations of recovery answers throughout the three and six months follow-up in study IV. This indicates that it is quite rare to change recovery status from being recovered at three and relapsing at six months. And it is also rare to report recovery at six months if having remaining problems at three months follow-up. The largest improvement after WAD occurs within the first three months, and after that it levels off.[65]

Table 1. Probabilities of different combinations of recovery from whiplash-associated disorders at three and six month's follow-up in study IV.

		Interview at 6 months	
		Recovered	Not recovered
Interview at 3 months	Recovered	0.51	0.09
	Not recovered	0.16	0.24

6.2.1.3 Confounding

Confounding appears if there is a certain factor that covariates with the exposure investigated and at the same time affects the outcome in question. In that case the confounding factor may be the drive of the association between the exposure and the outcome. This can be handled in the statistical analysis by adjusting for the confounding factor. It requires theorization of potential confounding factors, through knowledge about their relationship with the exposure and outcome (previously detected or suspected), and also that there is useful information about the confounder. To be considered a potential confounder the factor may not however lie in the causal pathway between the exposure and outcome, as it then is part of the exposure's effect on the outcome. In this case it would be called an intermediate factor. If adjustment is made for an intermediate, then part of the effect of the exposure is removed.

In all four studies included in this thesis we have controlled for confounding. It has been a large variety in how many confounders needed to be included in the different analysis, which is natural as different associations are investigated. There are different ways of deciding if a factor should be included in the statistical model. In study I, II and III the potential confounders were decided upon by methodological and empirical considerations. Further, each single factor was added to the crude model, and if it changed the OR/RR with 10% or more, it was included in the final model. This strategy has been suggested by Rothman et al. [29] One advantage with testing the potential confounders is that it sometimes give fewer factors to include in the statistical model.

This could be preferable as some models become instable when many covariates are included.

In study IV the confounders were selected a priori through methodological and empirical considerations, and were included in the model without testing. Some of the factors considered could not be guaranteed to be true confounders, and may instead be intermediates. These factors, pre-injury musculoskeletal problems and mental or emotional problems prior to accident, could be important confounders in the investigated association, but the temporality between them and the exposure could not be determined. Therefore they were added separately to the model and considered a sensitivity analysis to detect possible residual confounding. The results of the sensitivity analysis showed that there may be confounding from these factors in our results, indicating that these factors need to be considered in future similar studies.

6.2.1.4 Selection bias

If the probability of being selected to or participate in a study is related to the exposure and the outcome this could affect the results of the study by introducing a systematic error. [29] This concept is called selection bias and constitutes a potential threat of bias in all studies with selected samples.

In the SPHC, which was used in study I and II, one potential threat is the selective non-response in the cohort. There is an analysis made on the non-responders of this cohort which shows that they are more likely to be younger, male, less educated, have a lower income and being born outside the Nordic countries.[23] This means that in study I we may have missed some individuals with a lower income, and our results may have been diluted if these individuals had a higher incidence of LDNP than those with the same exposure who participated. But it is also possible that those with a lower age are less likely to get LDNP, in which case it would be hard to know in which direction the total effect of loss to follow up has. However, since the loss to follow-up was at maximum 21% in these two studies it is not likely that it has affected the results substantially.

The participants that were lost to follow-up in study III did not differ much in terms of age, sex and exposure status. Also the attrition rate was low (12%), thus it is not likely that it would have affected the results of the study.

In study IV the population studied was the total population of WAD patients, making their injury claim to the only insurance company available within the province of Saskatchewan. The attrition rate was about 16%, which can be considered as low, and that makes it unlikely that selection bias would have affected the results extensively.

6.2.1.5 Summary

In all four studies in this thesis rich data was available to test and adjust for confounders in the different associations investigated. Another common strength across the studies was that the different data materials included a fairly large amount of

observations, and the attrition rates were relatively low. Additionally, the outcome in study III and IV, as well as the exposure in study IV, had good psychometric properties shown by previous studies.

The studies also had some limitations. One main limitation in study I and II was that a possible alteration of the exposures during the follow-up time was not measured. However, this potential misclassification was most likely non-differential as the studies are prospective. Also, self-reported physical activity, which is the exposure in study II is a factor that is difficult to measure accurately. In study III the exposure measurement is not validated, creating a potential source of bias, and in study IV the main weakness is the lack of information about temporality between the exposure CVD and the potentially important confounders: musculoskeletal problems prior to accident and mental health prior to accident. Residual confounding is a potential threat of bias that cannot be ruled out in any of the studies.

6.2.2 Generalizability

Good generalizability infers that the result in the population under study is applicable to other populations. In the context of epidemiological studies this does not always mean that the sample under study needs to be a statistically representative sample of a target population. In studies investigating the association between two factors the sample representative for other populations is rare, and is of less importance as long as there is appropriate testing for confounders. [66]

6.2.3 Measures of association

In study I and II the effect measure used to estimate the association between the exposure and outcome was OR. It is a measure of the odds of developing the outcome in one or several categories of exposure in relation to the odds of developing the outcome in another category of exposure (reference category).[67] Therefor it is a relative measure making comparisons between different categories of exposure. The odds per se is not a very intuitive measurement. It is calculated by dividing the number of exposed cases (of the outcome) by the number of unexposed cases.

In study III RR is used as the measurement of association. The RR is a relative measure based on risk of developing the outcome, and the RR is the risk in one or several exposure categories in relation to a reference category.[68] The risk is more intuitive than the odds and is calculated by dividing the number of cases of the outcome by the total number of individuals.

The HRR is used in study IV. This is a measurement calculating the risk of developing the outcome in one or several exposure categories compared to a reference category,

over person time. Thus this estimate has a time component, as indicated by the word hazard, compared to the other effect measurements used in the thesis.

Under the premise that the outcome studied is rare it can be accurate to assume that the OR is similar to the RR, which is often tempting to do as RR is somewhat easier to relate to. But the relationship between OR and RR is also dependent on the prevalence of the exposure. The more common the exposure, the larger the difference between RR and OR.[69] When they differ, the OR systematically overestimates the RR if the RR > 1, and the OR systematically underestimates the RR when the RR<1. In cohort studies with multiple follow-ups and time to event data it is common to use Cox regression and estimate the HRR. In study I and II the data was from SPHC. The data offered baseline information in 2002 and follow-up information in 2007. The individuals' person time was not varying as they were all measured for the outcome at the same single point in time, and therefore the logistic regression yielding OR was used for these studies instead of the Cox regression. A log binomial model is an alternative way to analyze data in this context (giving RR as an output), but to our experience this model is often less stable compared to the logistic model and was therefore not considered the best option in study I and II.

In study III there were only one confounding factor and that allowed using the log binomial model which yields RR. In Study IV the follow-ups were multiple, and person time was calculated which provided data fit for using the Cox model and presenting HRR.

6.3 GENERAL DISCUSSION

6.3.1 The studies within the ICF framework

The studies of this thesis investigated factors that were hypothesized to be of importance for the risk and prognosis of neck pain. The factors studied are of different types, some modifiable some not, some intrinsic and some more extrinsic. The etiology of neck pain is regarded as multifaceted,[70] and the different exposures investigated in this thesis mirror that fact.

All four studies in this thesis together touch upon all components of the ICF structure. Doing research on neck pain requires this holistic view as not only one or two areas of the life and environment of individuals may affect the risk and prognosis of neck pain. This has been established before, by the Bone and Joint Decade 2000-2012 Task Force on Neck Pain and its Associated Disorders [71] among others.

In the ICF framework individual disposable income can be regarded as a contextual factor and would be under the code "financial assets". It was hypothesized that low income was a factor that negatively affected the risk and prognosis for LDNP. It may

be a hindrance for different reasons, for example it may lead to inability to consume goods or services that can help to avoid getting neck pain. A low income can inhibit a healthy lifestyle which has been seen to affect the prognosis for back pain. [72] If the individual lives in a context where paid social activities are important a low income could also have a big impact on participation in social activities, which is one form of "poverty" that may affect individuals.[45] In the study on income also economic stress was investigated as a potential effect measure modifier in the associations between income and neck pain. Economic stress is likely a product of the ability of being able to manage one's own economy, as it exists among both those with high and low income. This factor is also a contextual factor, but related more to the personal level.

Naturally, physical activity which is the exposure in study II belongs to the category of functioning and disability and the component activity in the ICF framework. The hypothesis was that a higher level of physical activity would be protective against neck pain, thus constituting a positive aspect of activity.

Expectations of recovery is the exposure investigated in study III. This factor is a contextual factor, and as such within the personal domain. It is an internal factor that seems to facilitate improvement of neck pain during treatment with manual therapy, according to the results of study III.

CVD comorbidity can be classified under the domain body function and structures. It may entail both change in body function (a physiological change), as well as a change in body structures (an anatomical change) depending on the type of CVD, and would likely most often be both. In study IV CVD was hypothesized to be an impairment that would lead to prolonged recovery in individuals with WAD. One hypothesized pathway to prolonged recovery was through activity limitation and participation restriction, also linking the activities and participation component of ICF to this study.

6.3.2 Neck pain specific research challenges

Much research has been conducted to investigate the risk of neck pain, and more studies investigating the prognosis are emerging. Many factors have been investigated repeatedly, but the studies have yielded different results. This may be due to that the studies are not equivalent enough to be compared in different aspects. But it may also indicate that it is highly individual what factors that cause, and affects the prognosis for, neck pain. It is highly individual how a person copes with different matters of life and how resilient the person is towards stress. These psychological factors may play an important role in the etiology of neck pain and may be linked to many different environmental factors under study, such as the ones investigated in this thesis. The fluctuations in effect of the different factors on the risk and prognosis of neck pain may be due to individual differences in perspective and individual variations in handling the different stressors. Stress is associated with muscle pain trough several potential

mechanisms,[73] and it is likely that those reporting neck pain suffer from muscle pain. At the same time as stress may be important for the development of neck pain it is also often created by other factors such as income, social participation, and different health complaints. Further, stress level is also a factor that can be altered with physical activity. Thus stress may possibly be linked with most of the exposures in this thesis. In future studies on risk and prognosis for neck pain, it is therefore important to consider a potential linkage between the exposure and psychological factors.

All studies in this thesis were stratified by sex. Study I and II were stratified a priori according to the research questions, and in study III and IV sex turned out to be an effect modifier (potentially in study III), thus the analysis were stratified by sex. Previous studies have shown that there are sex differences in reporting and perceiving pain. [74 75] In study II the sex differences were substantial, whereas in study III they were not very distinct. It may of course vary between the factors studied, but it seems important to consider sex when investigating risk or prognosis for neck pain.

7 CONCLUSIONS

- Low individual disposable income is a risk as well as prognostic factor for developing LDNP. Economic stress is a factor that may modify these associations and should therefore be considered in analysis of such associations.

- Physical activity during leisure time is associated with the risk of developing LDNP in a population without neck pain, but does not affect the prognosis negatively in a population with occasional neck pain. Work related physical activity is not a risk factor nor a prognostic factor for developing LDNP

- Expectations of recovery is a prognostic factor for recovery in patients with neck pain seeking manual therapy treatment. Both sexes benefitted from having high expectations, but the detected effect was stronger among men than women.

- CVD comorbidity is not associated with recovery from WAD. There is a strong need of replication of these results with studies including depression and prior musculoskeletal problems as potential confounding factors.

7.1 GENERAL CONCLUSIONS REGARDING NECK PAIN RESEARCH

Neck pain is a condition that is challenging to study considering its recurring nature and the complex interplay between different factors affecting the prognosis and the risk. Sex is important to consider in most studies on factors and their association with neck pain.

8 POPULÄRVETENSKAPLIG SAMMANFATTNING

Nacksmärta är en vanligt förekommande åkomma som kan ha stora konsekvenser både för den enskilda individen och för samhället. Med tanke på detta, samt att nacksmärta ofta är ett återkommande besvär så är det viktigt att öka kunskapen om vilka faktorer som kan påverka risken och prognosen för nacksmärta.

Syftet med den här avhandlingen var därför att undersöka faktorer som kan påverka risk och prognos för nacksmärta, inklusive whiplash relaterade besvär. Mer specifikt syftade studie I till att undersöka om inkomst påverkar risken och prognosen för nacksmärta, samt att se om ekonomisk stress påverkar ett potentiellt samband mellan inkomst och nacksmärta. Studie II syftade till att undersöka om fysisk aktivitet på fritid och i arbete påverkar risken och prognosen för nacksmärta. I studie III var syftet att undersöka om förväntningar på tillfrisknande påverkar tillfrisknandet hos patienter som söker behandling med manuell terapi för sin nacksmärta. Slutligen syftade studie IV till att undersöka om samsjuklighet i hjärt- och kärlsjukdom ger sämre tillfrisknande från whiplash relaterade besvär.

Studie I och II baserades på data från Stockholm Folkhälsokohort där information om studiedeltagarna samlats in vid baslinjen 2002-2003 samt vid uppföljningen 2007. Inkomst, ekonomisk stress, fysisk aktivitet samt andra faktorer som potentiellt kunde påverka sambandet mellan dessa faktorer och nacksmärta mättes vid baslinjen. Individerna mättes sedan vid uppföljningen för att undersöka om de utvecklat ihållande nacksmärta som påverkat dem avsevärt.

Studie III baserades på data från Stockholm Manual INtervention Trial som är en randomiserad kontrollerad studie där deltagare med nacksmärta valdes ut för at undersöka syftet med studie III. Förväntningar på tillfrisknande mättes vid baslinjen innan behandlingsstart, och utfallet ”tillfrisknande” mättes efter sju veckor.

Data till studie IV kom från Saskatchewan Government Insurance cohort, ett material som samlats in i Canada innehållande individer som anmält till försäkringsbolag att de fått whiplash relaterade besvär i samband med en bilolycka. Information om samsjuklighet i hjärt- kärlsjukdom mättes vid baslinjen och utfallet ”tillfrisknande” mättes vid uppföljningar sex veckor, tre månader, sex månader, nio månader, och tolv månader efter olyckan.

Resultaten visade att låg inkomst påverkade risken för att få mer allvarlig nacksmärta och även gav en sämre prognos för de som hade enstaka episoder med nacksmärta, och ekonomisk stress verkade kunna ha en inverkan på dessa samband. Att vara fysiskt aktiv på fritiden var skyddande mot att utveckla nacksmärta i jämförelse om man var i huvudsak stillasittande på fritiden. Det gav däremot ingen bättre prognos om man redan

hade enstaka episoder med nacksmärta. Fysisk aktivitet på arbetet påverkade varken risk eller prognos för nacksmärta.

Att ha höga förväntningar på tillfrisknande från nacksmärta ledde till högre grad av tillfrisknande hos individer som sökte behandling med manuell terapi i studie III. I studie IV visade resultaten att samsjuklighet med hjärt- kärlsjukdom inte påverkade tillfrisknande från whiplash relaterade besvär hos männen. Sannolikt påverkar det inte heller tillfrisknande hos kvinnor med tanke på att det samband som kunde ses var svagt, samt att sambandet som sågs kan ha berott på andra påverkande faktorer.

9 ACKNOWLEDGEMENTS

I have appreciated the four years of PhD education in many more ways than I could imagine before I started. I wish to express my sincere gratitude to all those who in different ways contributed to this thesis and my overall PhD experience, and especially to the following persons:

Eva Skillgate, my main supervisor, for always being available for my endless questions and discussions about research and epidemiologic concepts, and for always giving me very thoughtful and valuable comments on my work. Your sense of details amazes me!

Lars Alfredsson, my co-supervisor (and previous main supervisor), for providing epidemiological expertise at times when I needed it most.

Thank you both *Eva* and *Lars* for giving me this opportunity!

Lena Holm, my co-supervisor, for many enjoyable epidemiological discussions, valuable advice, and gentle pushes in the right direction.

Therese Ljungquist, my mentor, for discussions about life with research.

Eva Vingård, for valuable comments on articles and advice regarding my study plan.

Pierre Côté, for giving me the opportunity to work together with you and to take part of your experience within research and epidemiology. And also for your great hospitality during my stay in Toronto.

Linda J. Carroll and *J. David Cassidy* for allowing me to use your data and giving me valuable advice on my work.

Cecilia Magnusson and *Michael Lundberg,* for valuable comments on articles and for giving me the opportunity to work with the Stockholm Public Health Cohort.

Anna Peterson, Kari Paanalahti and *Tony Bohman*, my colleagues, roommates and dear friends. I have enjoyed our discussions about work and life tremendously! Thanks for all the energizing laughs we have shared.

My second set of roommates, *Karin Kai-Larsen* for you immensely valuable friendship, and *Germán Carrasquilla* for all the wonderful, honest talks.

Ilais Moreno Velasquez, for sharing your knowledge and life experience and for being a very good friend.

My journal club friends *Abquariyah Yahya, David Pettersson, Dong Yang*, and *Jessica Magnusson* for all our interesting discussions.

AnnMarie Wesley, for all the pep-talks and for sharing your positive energy.

Henrik Källberg, for always taking the time to answer all my big and small questions about epidemiology and statistics.

Sara Wedrén, for valuable advice and perspective.

Marie Holmquist, for inspiration and wise words at the beginning.

And to *all other colleagues*, former and present, for making my time at IMM very enjoyable!

Maja Stupar, for all our interesting talks about research and life in general, and for being my private guide in Toronto.

Charlotta Åsell, for being a dear friend giving me advice and perspective.

Familjen Palmlöf, foremost *Fredrik* for being an amazing father to Aston and a key figure in my life. *Johan*, you have taught me so much about life. You will always be in my heart.

My dearest friends, *Tilla* and *Katta*, for always being there for me. I cannot express in words how much you mean to me. You are my "sisters in life".

My brother *Johan and his family*, for sharing your lives and holidays with me and Aston.

My aunt *Anneli*, for encouraging me from a young age to be curious and explorative, and for all the support during these four years, as well as throughout my life.

Mina far- och morföräldrar, *Björg* och *Gösta*, *Ing-Marie* och *Gert*, för allt stöd och alla fina stunder ni gett mig under hela mitt liv.

My mother *Annette* and her husband *Sven Åke*. Thank you for all your help and support during these four years, it has been tremendously valuable. Thank you for providing me and Aston with a paradise where we can "recharge", helping me to get back on track when I lost my strength and my way.

My father *Yngve*, my rock and an endless source of support and inspiration. By providing me with a solid base and unconditional love you have given me the opportunity and the drive to push my own limits. For that I am eternally grateful.

My son *Aston*, the most important person in my life and the one I hold dearest. Thank you for giving me perspective and teaching me new things about myself and the world surrounding us on a daily basis. Jag älskar dig mest i hela världen!

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