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LOW BACK AND NECK-SHOULDER PAIN

WORK AND HERITABILITY

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To mom and dad

ABSTRACT

Low back pain (LBP) and neck-shoulder pain (NSP) represent a large public health problem being common disorders that often lead to negative consequences for the individual and large costs for Society. The main goal of the thesis is to explore how factors relating to aetiology, i.e. the influences of genetic factors and work-related physical load, as well as consequences in terms of sickness absence are associated with different combinations of LBP and NSP.

This thesis is based on three different data materials; the MUSIC-Norrtälje study, the STAGE study, and the Swedish orchestra study.

Paper I used the MUSIC-Norrtälje study material to explore sickness absence during a 5-year period (1995-2001) for subjects with consistent *Solely LBP, Solely NSP*, and *Concurrent LBP and NSP* (n= 817). The results showed that the odds ratio for sickness absence was OR 1.69 (95% confidence interval 1.14-2.51) and for long-term sickness absence OR 2.48 (95% CI 1.32-4.66), for subjects with *Concurrent LBP and NSP* compared to those with *Solely LBP or Solely NSP*.

In paper II, the STAGE study material was used to estimate the heritability of *Solely LBP, Solely NSP*, and *Concurrent LBP and NSP* using classical twin study methodology (n= 20,946). The results showed that 60% of the total variance for *Concurrent LBP and NSP* could be explained by additive genetic effects, which was twice as large as for *Solely LBP* (30%) and more than twice as large as for *Solely NSP* (24%).

Paper III, also used the STAGE study material for investigating if the associations between high physical workload and different combinations of LBP and NSP are confounded by genetic and shared environmental factors (n= 16,107). Only for *Concurrent LBP and NSP*, genetic and shared environmental factors seemed to have an influence on the association with high physical workload. The results also showed that high physical workload was associated with having any combination of *LBP and/or NSP* even after adjusting for genetic or shared environmental factors (OR 1.44, 95% CI 1.06-1.95).

In paper IV, the association between exposure to work with elevated arms and the prevalence of NSP was investigated using orchestra musicians, an occupational group that share many other physical and psychosocial work-related exposures (n= 235). This was done using the Swedish Orchestra study material. The results showed an association between a work posture with an elevated arm position and NSP for both those that had a longer duration (OR 5.35, 95% CI 1.96–14.62) and those that had a short duration (OR 4.15, 95% CI 1.30–13.22) of active playing time during a work day, compared to those with a neutral arm position.

In conclusion, this thesis has identified that subjects with *Concurrent LBP and NSP* constitutes a group with higher prevalence of sickness absence and for which genetic factors seem to have a great influence compared to *Solely LBP* or *Solely NSP*.

Further, having an occupation with an exposure to high physical workload was associated with the prevalence of LBP and/or NSP. Also, within an occupation there was an association between NSP and exposure to work with an elevated arm position.

Key words: Low back pain, Neck-shoulder pain, Co-morbidity, Heritability, Twin study, Sickness absence, Occupational exposure, Exposure assessment, Musicians, Performing arts medicine

SAMMANFATTNING

Besvär i ländryggen och i nacke/skuldror är mycket vanliga tillstånd som ofta leder till negativa konsekvenser för individen och stora kostnader för samhället. Det övergripande syftet med avhandlingen var att undersöka faktorer som kan relateras till uppkomst och konsekvenser av besvär i ländryggen och i nacke/skuldror; d.v.s. genetiska faktorer, arbetsrelaterade fysiska faktorer och sjukskrivning. Avhandlingen baseras på tre olika data material, MUSIC-Norrtälje studien, STAGE studien och den svenska orkesterstudien.

Syftet med delarbete I var att jämföra förekomsten av sjukskrivning under en 5-årsperiod mellan individer med kvarstående besvär *Enbart i ländryggen, Enbart i nacke/skuldror* och de med *Samtidiga besvär i både ländrygg och nacke/skuldror* (n= 817). Resultaten visade att oddskvoten (OR) för såväl förekomst av sjukskrivning (OR 1,69, 95% CI 1,14-2,51) som långtidssjukskrivning (OR 2,48, 95% CI 1,32-4,66) var högre för individer med *Samtidiga besvär i både ländrygg och nacke/skuldror* i jämförelse med de med *Enbart ländryggsbesvär* eller *Enbart nacke/skulderbesvär*.

Delarbete II använde data från STAGE studien för att undersöka ärftligheten av *Enbart ländryggsbesvär, Enbart nacke/skulderbesvär* och *Samtidiga besvär i både ländrygg och nacke/skuldror* med hjälp av klassisk tvillingstudiemetodologi (n= 20 946). Resultaten visade att 60% av den totala variansen för *Samtidiga besvär i både ländrygg och nacke/skuldror* kunde förklaras av genetiska faktorer, vilket var dubbelt så mycket som för *Enbart ländryggsbesvär* (30%) och *Enbart nacke/skulderbesvär* (24%).

Även delarbete III använde data från STAGE studien för att undersöka om sambandet mellan hög fysisk arbetsbelastning och förekomst av olika kombinationer av ländryggsbesvär och nacke/skulderbesvär påverkas av genetiska faktorer och delade miljöfaktorer (n= 16 107). Enbart när det gällde *Samtidiga besvär i både ländrygg och nacke/skuldror* verkade genetiska faktorer och delade miljöfaktorer påverka sambandet med hög fysisk arbetsbelastning. Resultaten visade även att när hänsyn togs till eventuell påverkan av genetiska faktorer och delade miljöfaktorer så fanns det ett samband mellan hög fysisk arbetsbelastning och *ländryggs- och/eller nacke/skulderbesvär* (OR 1,44, 95% CI 1,06-1,95).

Delarbete IV använde datamaterial från den svenska orkesterstudien för att undersöka sambandet mellan exponering för arbete med lyftade armar och förekomst av *Nacke/skulderbesvär* inom en yrkesgrupp. Orkestermusiker är en homogen grupp gällande många andra fysiska och psykosociala exponeringar i arbetet. Resultaten visade ett samband mellan såväl längre (OR 5,35, 95% CI 1,96–14,62) som kortare exponering (OR 4,15, 95% CI 1,30–13,22) för arbete med lyftade armar och *Nacke/skulderbesvär*.

Sammanfattningsvis visade resultaten i avhandlingen att individer med *Samtidiga besvär i både ländrygg och nacke/skuldror* är en grupp med ökad förekomst av sjukskrivning och för vilken genetiska faktorer verkar ha större betydelse än för individer med *Enbart ländryggsbesvär* eller *Enbart nacke/skulderbesvär*. Vidare visade resultaten ett samband mellan yrken med hög fysisk arbetsbelastning och förekomsten av *ländryggs- och/eller nacke/skulderbesvär*. Även inom en yrkesgrupp, orkestermusiker, identifierades ett samband mellan *nacke/skulderbesvär* och exponering för arbete med lyftade armar.

Nyckelord: ländryggsbesvär, nacke/skulderbesvär, komorbiditet, ärftlighet, tvillingstudie, sjukskrivning, arbetsrelaterade exponeringar, exponeringsmätning, musiker

LIST OF PUBLICATIONS

The thesis is based on the following papers, which are referred to in the text by their Roman numerals (I-IV).

I. Nyman T, Grooten WJA, Wiktorin C, Norrman L, and Liwing J. Sickness absence and concurrent low back- and neck-shoulder pain: Results from the MUSIC-Norrtälje study.
Eur Spine J 2007;16(5):631-638.

II. Nyman T, Mulder M, Iliadou A, Svartengren M, and Wiktorin C. High heritability for concurrent low back and neck-shoulder pain - a study of twins.
Submitted

III. Nyman T, Mulder M, Iliadou A, Svartengren M, and Wiktorin C. Physical workload, low back and neck-shoulder pain - a Swedish twin study.
Occup Environ Med (Accepted for publication)

IV. Nyman T, Wiktorin C, Mulder M, and Liljeholm-Johansson Y. Work postures and neck-shoulder pain among orchestra musicians.
Am J Ind Med 2007;50(5):370-376.

CONTENTS

LIST OF ABBREVIATIONS

95% CI	95% Confidence Interval
CDD	Cervical disc degeneration
DZ	Dizygotic
Genotype	The exact genetic makeup of an individual
LBP	Low Back Pain/Disorder
LDD	Lumbar disc degeneration
MUSIC	The MUsculoSkeletal Intervention Center
MZ	Monozygotic
NSP	Neck-shoulder pain/Disorder
NYK	Nordic occupational classification [Nordisk yrkesklassificering]
OR	Odds Ratio
Phenotype	An observable trait in an individual
SNQ	Standardised Nordic Questionnaire
STAGE	The Study of Twin Adults: Genes and Environment
STR	Swedish Twin Registry
TWA-MET	Time weighted average of metabolic rate

1 INTRODUCTION

Low back and neck-shoulder pain are amongst the most common disorders in the western world today. The average lifetime prevalence of low back pain (LBP) has been estimated to be 60-70%. For neck-shoulder pain (NSP), the corresponding percentage is approximately 50% (range 14-71%) [45, 104]. For many individuals the symptoms resolve within three months, but the recurrence rate is high [26, 27].

Both LBP and NSP are conditions that often are associated with high levels of disability and these disorders constitute one of the most common diagnostic groups causing sick leave and early retirement in Sweden today [133]. For the individual, long-term sick leave and disability pension often lead to negative consequences in the form of worsened economy and quality of life [137, 153].

Still, for the majority of individuals with LBP (85-90%) it is not possible to identify a pathoanatomical diagnosis, and their complaints are most commonly referred to as non-specific LBP [37]. Also for NSP there is a lack of specific diagnoses and it has been questioned whether neck pain and shoulder pain can be clearly distinguished from each other [110, 134].
Factors that have been found to influence the occurrence and course of LBP and NSP cover work-related and individual factors [58, 96, 105]. Among work-related factors, many exposures are related to high physical workload. However, there are large discrepancies between studies, and these inconsistent findings have often been attributed to methodological issues. The question has been raised, if it is possible to single out and investigate one specific potential risk factor [58, 90, 97, 105].

Both between and within different occupational groups there are large variations in intensity, frequency, and duration of different exposures. Further, individuals are often exposed to several work-related physical and psychosocial risk factors simultaneously [97]. In the present thesis, an attempt is made to look at the association between a work posture with elevated arm(s) and the presence of NSP within an occupational group, professional orchestra musicians. Musicians share many work-related physical and psychosocial exposures such as prolonged sitting, precision work, forceful exertion of the arms, social support, job demands, and control but the degree of arm elevation while playing and the duration of active playing time per work day vary depending on which instrument you play [6].

However, in populations with similar exposures there is still a variation in disorder prevalence, and focus has also been directed towards the potential influence of individual factors, e.g. genetic factors, in the aetiology of LBP and NSP. Earlier studies have reported, to a various degree, a genetic influence on LBP however for NSP the results were more disparate [14].

Among subjects reporting either LBP or NSP, many are also suffering from non-musculoskeletal related conditions such as migraine, respiratory disorders,

cardiovascular diseases as well as mental disorders, but also from musculoskeletal complaints from other parts of the body [123, 131, 136, 157].

One specific co-morbid condition of musculoskeletal complaints is the combination of having *Concurrent LBP and NSP*. This group has also been found to have a higher prevalence of other non-musculoskeletal conditions (including mental illnesses) compared to those with *Solely LBP* or *Solely NSP* [131]. The main focus of the present thesis is to further explore the characteristics of this group, including factors relating to aetiology, i.e. the influences of genetic factors and work-related physical load, as well as to consequences in the form of sickness absence.

2 BACKGROUND

Epidemiology is the study of factors relating to the health and disease in populations, and the etymological origin of the word is the Greek terms epi = upon, among; demos = people; and logos = study. Epidemiological studies are often aimed at disclosing unbiased relationships between exposures and outcome. Research using epidemiological methods is often used as a basis when interventions are made in the interest of public health and preventive medicine [83, 120].

This thesis is written within an epidemiological framework, with a broad perspective on two of the major public health concerns in the western world today, low back pain/disorder (LBP) and neck-shoulder pain/disorder (NSP) [45, 96, 104].

The title of the thesis, "Low back and neck-shoulder pain - Work and heritability", aims at describing fields which can be considered to be related to both the aetiology and the consequences of LBP and NSP; genetic factors, work-related exposures and sickness absence.

2.1 LOW BACK PAIN AND NECK-SHOULDER PAIN

2.1.1 Pain-intensity and pain-related disability

One of the more recognised definitions of pain has been formulated by the International Association for the Study of Pain (IASP) as "An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" [102]. IASP further states that "Many people report pain in the absence of tissue damage or any likely pathophysiological cause… …If they regard their experience as pain and if they report it in the same ways as pain caused by tissue damage, it should be accepted as pain" [102].

In epidemiological studies of LBP or NSP, the definitions of pain are often based on self-reported data, and it is seldom possible to identify the pathoanatomical origin. There are numerous scales, indexes and questionnaires for obtaining data about LBP and NSP. The different methods have their strengths and weaknesses, and the heterogeneity in assessment methods leads to a large diversity in study findings [38, 104].

Severity of pain does not only relate to pain-intensity but also to pain-related disability. The term disability can be used to describe limitations in different domains of activity and participation, such as personal care and other activities of daily living, working, and taking part in social activities. In 2001, the World Health Assembly (WHA) unanimously endorsed the *International classification of functioning, disability, and health* (ICF) (resolution WHA 54.21). In this system, the classification of disability is divided into *activity limitations* and *participation restrictions* [158]. Activity limitations cover areas concerning an individual's ability to execute specific activities, and participation restrictions aim at describing difficulties an individual may experience in

the involvement of life situations. For spinal disorders, a number of different instruments covering the dimensions of disability discussed above, have been developed for measuring the disability related to these disorders, e.g. the Neck Disability Index (NDI), the Neck pain disability scale, the Oswestry score, the Roland-Morris disability questionnaire, and the von Korff index [30, 119, 144, 145, 156].

Pain is often divided into acute (less than 6 weeks), sub-acute (6-12 weeks), or chronic conditions (>3 months). Studies have found that the majority of LBP episodes resolve within three months, but also that the recurrence of these complaints is high [32, 53, 64, 137]. For NSP, not as many studies have looked at the recovery rate, but a recent literature review conducted by Carroll et al. (2008), found that among workers with NSP, 60-80% still reported NSP one year later [26]. The natural course of LBP and NSP over a 5-year period has been investigated in the MUSIC-Norrtälje study [103, 112]. For both LBP and NSP there was a decrease in pain and disability; however, only a minority of the subjects were fully restored. Several studies have also shown that high pain-intensity as well as high levels of pain-related disability is associated with a lower recovery rate, higher health care utilisation and sickness absence [124].

There is a continuous need for a consensus concerning the definition of LBP and NSP. A recent study by Dionne et al. (2008), aiming at identifying standardised definitions of LBP for use in prevalence studies to provide comparable data, found that the minimum definition of LBP included two items; one question defining the site of low back pain, and time frame of the measure, and a second question on severity of low back pain in terms of activity limitations [38].

2.1.2 Epidemiology of low back and neck-shoulder pain

LBP can be defined as pain, muscle tension, or stiffness localised below the costal margin and above the inferior gluteal folds, with or without leg pain (sciatica) [96]. Experimental studies suggest that LBP may be caused by many spinal structures, including ligaments, facet joints, the vertebral periosteum, the paravertebral musculature and fascia, blood vessels, the anulus fibrosus, and spinal nerve roots [25]. A lesser proportion of LBP can be classified as specific LBP and these diagnoses include spinal fractures, cancers, infections, and cauda equina syndrome. However, the probability that an individual case of LBP has a specific cause identified on lumbar radiographs is very low [138]. For the majority of subjects with back pain (85-90%) it is not possible to identify a pathoanatomical diagnosis, and their complaints are most commonly referred to as non-specific LBP [37].

Neither for NSP has the medical community reached consensus regarding a general definition, and it has been questioned whether neck pain and shoulder pain can be clearly distinguished from each other [110, 134]. In a biomechanical context, the neck and shoulder regions constitute a functional entity. Many muscles originating from the neck and attaching at the shoulder are involved in the stabilisation and movement of the upper extremity. Further, nerves innervating the shoulders and upper extremities (with the exception of the trapezius muscle) emanate from the cervical spine, and pass through the brachial plexus.

NSP can be defined as pain, muscle tension, or stiffness originating from spinal structures (including ligaments, facet joints, the vertebral periosteum, the paravertebral musculature and fascia, blood vessels, the anulus fibrosus, and spinal nerve roots), muscles, and tendons in the cervical spine and shoulders [18, 128].

There are many theories about the aetiology of LBP and NSP, and previous research has found that the origin is multifactorial, involving both individual (e.g. genetic, lifestyle) and work-related factors (e.g. physical, psychosocial) [105]. This suggestion of a multifactorial aetiology of LBP as well as of NSP, together with difficulties in ascertaining pathoanatomical diagnoses (leading to variety of definitions of LBP and NSP in epidemiological studies), are some reasons for the large diversity between studies that have aimed at estimating the prevalence of these disorders [90, 104]. According to a systematic literature review on the scientific evidence of causes, diagnosis, and treatment by Nachemson et al. (2000), large international studies have reported point prevalence for LBP of 15-30%, 1-month prevalence between 19-43%, and lifetime prevalence of 60-70% [104].

For NSP, Fejer et al. (2006) performed a systematic literature review on the prevalence of neck pain, reporting point prevalence for NSP of 6-22%, 1-month prevalence between 15-41%, and lifetime prevalence of 14-71% [45]. The anatomical definition of NSP varied between studies, either including or excluding the shoulder region. However, there were no differences in the prevalence estimates between studies including or excluding the shoulder region in the definition of neck pain.

2.1.3 Co-morbidity

Among subjects reporting LBP or NSP, many are also suffering from non-musculoskeletal related conditions such as migraine, respiratory disorders, cardiovascular diseases as well as mental disorders [19, 36, 66, 123, 131, 157] (Table 1). According to a systematic literature review of co-morbidities with LBP, Hestbaek at al. (2003) concluded that "the nature of the relations between LBP and other diseases is still unclear: causal, coexisting, or common cause". In 2006 the same research group, in reporting results from a prospective study on the course of LBP from adolescences to adulthood, concluded that not only previous LBP, but also asthma and headache predicted LBP in adulthood [68]. Co-morbidity often plays a significant role for the disability associated with LBP and NSP and influences prevalence and length of sickness absence and quality of life [101].

The most common co-morbidities associated with LBP and NSP are other musculoskeletal complaints [123, 136, 157]. Urwin et al. (1998) found that among those with musculoskeletal complaints, about two thirds reported pain in more than one anatomical area. Von Korff et al. (2005), in a national co-morbidity survey in the USA, found that among those suffering from LBP, 69% reported other chronic pain conditions as well. The results were supported by Schneider et al. (2007), who in a population-based national health survey in Germany reported that among subjects with LBP, 50% also suffered from other musculoskeletal complaints compared to those without LBP, where the corresponding prevalence was 21%.

Table 1. Co-morbidities with LBP and/or NSP. As reported in some earlier studies [36, 66, 123, 131, 136, 157].

Cardiovascular disorders	*Respiratory disorders*	*Gastrointestinal disorders*	*Mental disorders*
Cardiovascular disease +	Asthma +++	Irritable bowl syndrome ++	Alcohol abuse +
Stroke ++	Other lung disease +	Ulcer +++	Drug abuse -
Coronary heart disease +	Chronic bronchitis ++	Gastritis +	Anxiety disorder ++
High blood pressure +++	Sinusitis +	Colitis/gall stones +	PTSD +
Heart failure +			Panic disorders ++
Myocardial infarction - -			Social phobia ++
Hypercholesterolemia +			Mood disorders +
Cardiovascular death -			Major depression ++
Angina pectoris +			Dysthymia ++
Perfusion disorder (leg) +			
Venous thrombosis -			

Musculoskeletal disorders	*Allergic disorders*	*Other disorders*
Inflammatory joint disease + (e.g. rheumatoid arthritis, ankylosing spondylitis)	Atopic disease -	General health +
Osteoporosis +	Allergic contact eczema +	Thyroid disease +
Degenerative joint disease +++ (e.g. osteoarthritis of the knee, hip, or spine)	Allergic urticaria +	Epilepsy/seizures ++
Pain in more than one anatomical area +	Food allergy ++	Cancer - - +
	Allergic rhinitis ++	Headache ++++++
		Migraine ++++
		Diabetes - - +
		Renal colic/kidney stones +
		Vision impairment -
		Hearing impairment +

(+) Marks the number of studies that reported evidence of a positive association between the disorder in question and LBP and/or NSP.
(-) Marks the number of studies that reported no evidence of an association between the disorder in question and LBP and/or NSP.

One specific co-morbid condition of musculoskeletal complaints is the combination of *Concurrent LBP and NSP*. IJzelenberg et al. (2004) found in a sample of industrial workers that among those with LBP, the prevalence of musculoskeletal co-morbidity of the neck and upper extremities was 68%. They also reported that workers with higher pain-intensity or disability related to LBP were more likely to also report co-morbidity of the neck and upper extremities. In addition, subjects with co-morbidity also showed worse general health and health related quality of life [73].

In 2007, Strine et al. in reporting data from the 2002 National Health Interview Survey in the USA, not only found that a broad spectra of different diseases, such as respiratory, cardiovascular, gastrointestinal, chronic pain and musculoskeletal conditions, and other chronic conditions were more prevalent among those with LBP and/or NSP, but also that this co-morbidity prevalence was significantly higher among those with *Concurrent LBP and NSP*, compared to those with *Solely LBP* or *Solely NSP* [131]. The same pattern was seen also for the co-morbidity of a number of psychological factors, where those with *Concurrent LBP and NSP* were 3.4 times more likely to have potential serious mental illness compared to those with *No LBP or NSP*. The corresponding numbers for *Solely LBP* and *Solely NSP* were 1.8 and 1.7, respectively.

2.1.4 Determinants of low back and neck-shoulder pain

When summarising the findings from earlier research concerning LBP and NSP a pattern with a multiplicity of definitions of the disorders, a lack of specific pathoanatomical diagnoses, and diversity in the consequences associated with these complaints is seen.

Acknowledging these difficulties, much research has aimed at finding determinants of LBP and NSP. Factors that have been identified as influencing the occurrence and course of these disorders cover individual and work-related factors [58, 96, 105]. More recently, focus has also been directed on the potential influence of genetic factors [14] (Table 2).

Table 2. Factors potentially associated with the occurrence and prognosis of LBP and NSP. As reported in some earlier studies [58, 96, 105].

Individual factors	***Work-related physical factors***	***Work-related psychosocial factors***
Age	Manual handling	Job satisfaction
Gender	Bending and twisting	Social support
Body mass index	High physical load	Night shifts
Physical fitness	Energy expenditure	High mental demands
Congenital abnormities	Prolonged sitting	Perceived work load
Low education		Low decision latitude
Obesity	*LBP*	
Smoking	Monotonous tasks	
Stress	Whole body vibration	
Pain behaviour		
Depressive mood	*NSP*	
Cognitive functioning	Repetitive work	
Somatisation	Static load	
Fear-avoidance behaviour	Forceful movements	
Unemployment	Hands above shoulder level	
Genetic influence	Neck position	
	Hand-arm vibration	
	Occupational driving	

In the present thesis, focus is set on exploring determinants which can be considered to be related to the aetiology (occurrence) of LBP and NSP; i.e. heritability and work-related physical load, and the consequences (prognosis) of LBP and NSP; i.e. sickness absence.

2.2 SICKNESS ABSENCE

Musculoskeletal disorders, in particular low back pain/disorders (LBP) and neck-shoulder pain/disorders (NSP), still constitute one of the most common diagnostic groups causing sick leave and early retirement in Sweden today [21, 104, 106, 107, 133].

During the second half of the 1990's Sweden, together with Norway and the Netherlands, experienced a dramatic increase in sickness absence compared to other countries in Europe [132]. In 2002, in Sweden, the total costs for disbursed sickness benefit and disability pension reached an all point high of 9.5 billion EUR [106] (Figure 1).

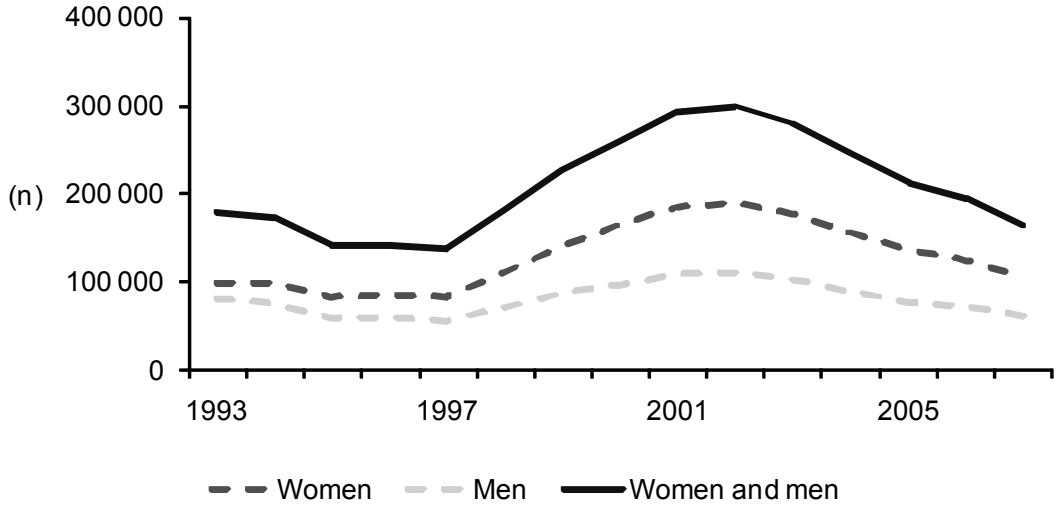


Figure 1. Total number of individuals receiving sickness benefit at December 31th in Sweden between the years 1993-2007. Stratified by sex. (Source: The Swedish Social Insurance Agency).

The sickness-benefit insurance system provides the possibility to prescribe sickness benefit and disability pension for individuals with impaired work ability. However, the underlying causes for sickness absence are considered to be multifactorial, with interaction of factors on both societal and individual levels. The design of the sickness-benefit insurance system, unemployment levels, workplace factors such as high physical workload, psychosocial factors, adjustment latitude and individual factors such as familial situation, age, pain behaviour and the co-morbidity of other illnesses are examples of such factors [2, 7, 8, 39, 71, 76]. Earlier studies have also found that for the individual, long-term sick leave and disability pension often lead to negative consequences in the form of worsened economy and quality of life [137, 153].

According to a systematic literature review on the scientific evidence for causes to and consequences of sickness absence, performed in Sweden in 2003, there is limited published research on causes for sick leave due to LBP and NSP. Factors that were found to influence the risk for sick leave due to these disorders were self-reported pain, physical impairment, and previous sick leave due to LBP [16, 39, 46, 59].

The influence of co-morbidity in terms of poor general health, psychological distress or non-musculoskeletal related physical disorders such as cardiovascular diseases has also been reported to affect disability and sickness absence due to LBP or NSP [47, 56, 92, 109, 140, 157].

Some earlier studies that have analysed sickness absence among subjects with LBP or NSP have not discriminated LBP from NSP or concentrated on one area of the spine without controlling for potential influence from other musculoskeletal complaints [16, 22, 39, 57, 142]. Other studies that have explored the influence of musculoskeletal co-morbidity for sickness absence show disparate results [73, 79, 109]. IJzelenberg and Burdorf (2004) assessed LBP and co-morbidity of the neck and upper extremities among industrial workers. Although they found that having co-morbid conditions was associated with worse general health and health related quality of life, they could not establish that this co-morbidity had an impact on care-seeking behaviour or sickness absence. Nordin et al. (2002) on the other hand, found that workers with musculoskeletal co-morbidity that were sick listed with LBP remained sickness absent for a longer period compared to those with solely LBP or solely NSP. These results were supported by Kamaleri et al. (2008), who showed a graded association between the prevalence of disability pensions and increasing number of pain sites.

2.2.1 The Swedish sickness-benefit insurance system

The official health insurance responsibility in Sweden is divided between the employer and the Insurance Office. This means that, if a person falls ill, he/she is entitled to sick pay from the employer for the first 14 days of the illness. After these two weeks, the employer notifies the Insurance Office who is then responsible for disbursing sickness benefit. A person may draw partial or full sickness benefit, depending on the extent to which he/she is unable to work. When a person is ill for a long period (usually more than one year) and unable to work, he/she may be entitled to disability pension. Disability pension, like sickness benefit, can be disbursed as either partial or full pension.

The Swedish Social Insurance Agency is responsible for the extensive social insurance data systems. From the social insurance offices at regional and local level, the Swedish Social Insurance Agency receives data containing the number of days a subject has drawn benefit from the Insurance Office, where the period is longer than 14 days (longer than 28 days for the period between 1 January 1997 until 1st April 1998 due to a temporary change in the legislation). Data for periods shorter than 14 days are reported only for unemployed individuals.

2.3 HERITABILITY

A first step in quantitative epidemiological research concerning genetic influence for a disorder is often to investigate familial aggregation of the disorder/trait (phenotype) in question. In an epidemiological sense, familial aggregation is found when there is a greater prevalence of the disorder among close relatives of individuals with the disorder, than among relatives of individuals without the disorder. Such studies are typically done using generation data on parents and siblings, or through looking at within-pair similarities among monozygotic (MZ) twins.

After establishing a familial clustering there is a need to distinguish between genetic and environmental (social/cultural) influence in the familial aggregation of a trait, and for this purpose more advanced epidemiological analyse methods with dizygotic (DZ) twins and monozygotic (MZ) twins are used. Using structural equation modelling it is possible to divide the total variance in a trait into Additive genetic effects (A), Dominant genetic effects (D), Shared (common) environmental effects (C), and Non-shared (unique) environmental effects (E).

Still, these methods do not provide information as to whether the presence of genetic influence can be attributed to a specific gene effect or if the genetic contribution is due to small effects of many genes. Indentifying specific genetic influences may lead to increased knowledge concerning the underlying mechanisms for a trait, and also bring light on possible gene-gene interactions and gene-environment interactions.

Two methods of investigating genetic variants (genotypes) are linkage analysis and association studies. Genetic linkage analysis can be used to identify regions of the genome that contain genes that predispose to the disorder in question [34]. However, using linkage analysis is more problematic for disorders where there are difficulties in ascertaining a pathological diagnosis. Association studies are aimed to analyse whether a certain allele (or genotype) is different between two groups (i.e. diseased cases and healthy controls). If the allele/genotype is associated with the phenotype, or is correlated with a causal allele, it will have a higher frequency among cases than controls [24].

Studies analysing the genetic influences for disorders in the low back and neck-shoulder regions, have mainly focused on unspecific LBP and lumbar disc degeneration (LDD). Only a few studies concerning NSP have been found, and no studies which have distinguished between the heritability of *Solely LBP, solely NSP*, and *Concurrent LBP and NSP* were identified.

2.3.1 Familial aggregation

Two studies concerning associations between LBP and a familial history of back pain were found. Two studies by Balague et al. (1994, 1995) concerning familial aggregation of low back pain analysed data from a Swiss Elementary School survey and investigated the association between parents or siblings with a history of LBP and self-reported LBP in schoolchildren [9, 10]. The two studies were performed in the same study population, but the mean age in the study groups differed slightly (12 compared to 14 years). The study analysing the younger study group found an association

between parent's history of treated LBP and self-reported lifetime prevalence of LBP in the child. These results were not confirmed in the study using the slightly older study group. However this second study found an association between sibling's history of LBP and self-reported lifetime LBP in the child.

As for familial aggregation of intervertebral disc degeneration, several earlier studies have consistently reported an association between LDD and a positive family history for the same condition [91, 98, 143]. The same findings were seen in two case-control studies of LDD [99, 127].

Three more studies have investigated LDD among MZ twin pairs [12, 13, 146]. One study found a higher within-pair correlation of prevalence of LDD compared to what was expected on a group level [12]. The second study showed a substantial influence of familial aggregation (genetic and/or shared environmental factors) for LDD [13]. Also for the 5-year progression of LDD genetic and/or shared environmental factors have been found to be of importance [146].

A summary of results from previous studies are reported in table 3.

2.3.2 Heritability estimates

Earlier epidemiological studies concerning estimations of heritability of LBP and NSP, have investigated the influence of genetic and environmental factors on self-reported pain in the low back or neck, or have focused on intervertebral disc degeneration [14, 15, 17, 40, 44, 61-63, 67, 94, 121].

The influence of genetic factors on self-reported LBP was investigated in seven studies. Of these, four studies reported a genetic contribution for the occurrence of LBP, with overall heritability estimates ranging between 21-68% [14, 63, 67, 94]. In addition, these findings were supported by results in a study by Bengtsson and Thorson (1991), that reported larger similarities concerning LBP status within MZ twin pairs, compared to within DZ twin pairs [15]. The findings in a study by Hartvigsen et al. (2004) were more ambiguous. They found a genetic influence on LBP for men (27%), but not for women [61]. However, the studied population was older (age 70-80+ years). One study, by El-Metwally et al. (2008), did not find any genetic influence on LBP [40]. However, the study specifically aimed at studying the genetic influence on LBP in 11-year old children. In this study, the results suggested a substantial influence of shared environmental factors on LBP. These findings were also seen in the youngest age strata (12-15 years) in a study by Hestbaek et al (2004) [67].

Three studies concerned the genetic influence on self-reported neck pain. Two studies found a substantial genetic contribution for the occurrence of neck pain, with overall heritability estimates between 44-58% [44, 94]. Hartvigsen et al. (2005) used an older study population (age 70 - >80 years) and reported only a weak genetic influence on neck pain [62]. Also, in the study by Fejer et al. (2006) sex differences in the heritability estimates of neck pain were reported. However, further investigation found no evidence that the sex differences in the heritability estimates were due to sex-specific genetic factors [43].

Three studies have made age-stratified analyses in estimating heritability of LBP and NSP. All studies found that the influence of non-shared environmental factors increased with age [44, 63, 67].

Two studies have estimated the genetic influence on lumbar and cervical intervertebral disc degeneration [17, 121]. Sambrook et al. (1999) found overall heritability estimates of 74% for LDD and 73% for CDD. These results were supported by Bijkerk et al. (1999), who found heritability estimates of 75% for multiple intervertebral disc herniations.

Given the above findings suggesting a genetic influence both for the occurrence of LBP and LDD, Battié et al. (2007) recently performed a study investigating whether genetic influences on LBP are mediated through genetic influences on disc degeneration. The results showed heritability estimates for LBP ranging between 30-46%. Less than one quarter of the genetic effects could be explained by a common pathway with genetic effects for disc degeneration [14].

A summary of results from previous studies are reported in tables 4-6.

Table 3. Familial aggregation of LBP and lumbar disc degeneration. Description of studies and author's conclusion about familial aggregation.

Reference	*Material*	*Variables*	*Results*	*Conclusion*
Balague (1994) (9)	♀ ♂ Age: 8-16 N=1 716	Self-reported LBP (Lifetime) Parents: History of LBP	Parents history of LBP was associated with lifetime LBP	+LBP
Balague (1995) (10)	♀ ♂ Age: 12-17 N=615	Self-reported LBP (Lifetime) Parents/siblings: History of LBP	Siblings' LBP was associated with lifetime LBP Parents history of LBP was NOT associated with lifetime LBP	+LBP -LBP
Battié (1995) (12)	♂ Age: 36-60 20 MZ pairs	MRI imaging of lumbar disc degeneration Age, Smoking	Age and smoking explained 0-15% of lumbar disc degeneration Addition of co-twin status explained 26-72%.	+LDD
Battié (1995) (13)	♀ ♂ Age: 35-69 115 MZ pairs	MRI imaging of upper and lower lumbar disc degeneration Age, mean job code, leisure time physical load	Age and leisure time physical load explained 9% of upper lumbar disc degeneration. Addition of co-twin status explained 43%. Age and mean job code explained 16% of lower lumbar disc degeneration. Addition of co-twin status explained 77%.	+LDD
Livshits (2001) (91)	♀ ♂ N=221, 18 families	MRI imaging of lumbar disc herniation Relatives: History of self-reported LBP or spine surgery	Relatives history of LBP or spine surgery was associated with lumbar disc herniation (OR 2.347)	+LDD
Matsui (1992) (98)	♀ ♂ Mean age: ♀16 ♂17 40 cases, 120 controls	Cases: Discectomy surgery Parents: Radiographic evidence of disc herniation	Parents history of disc herniation was associated with discectomy surgery (OR 5.61)	+LDD
Matsui (1998) (99)	♀ ♂ Age: 12-57 24 cases, 72 controls	Cases: Self-reported LBP. Family history of lumbar disc herniation Controls: Self-reported LBP. No family history of lumbar disc herniation	Higher incidence of disc herniation among cases than controls	+LDD
Simmons (1996) (127)	♀ ♂ Mean age: 33 65 cases, 67 controls	Cases: Surgery for degenerative disc disease Relatives: Self-reported LBP or spine surgery	Relatives history of LBP or spine surgery was associated with surgery for degenerative disc disease (OR 2.37-4.83)	+LDD
Varlotta (1991) (143)	♀ ♂ Age: <21 (mean 17) 63 cases, 63 controls	Cases: Radiographic evidence of disc herniation Parents: self-reported LBP, sciatica, or herniated disc	Parents history of LBP, sciatica, or herniated disc was associated with disc herniation (OR 2.91-7.85)	+LDD
Videman (2006) (146)	♂ Age: 35-69 75 MZ pairs	Progression of lumbar disc degeneration (MRI imaging) Resistance training, occupational physical loading	Co-twin status explained 47-66% of progression of lumbar disc degeneration Resistance training, occupational physical loading explained 2-10% of the progression of lumbar disc degeneration	+LDD

+LBP, +LDD. Author's conclusion of positive familial aggregation for LBP and LDD respectively.
-LBP, -LDD. Author's conclusion of positive familial aggregation for LBP and LDD respectively.

Table 4. Heritability of low back pain. Description of studies and author's conclusion about genetic effect.

Reference	*Material*	*Variables*	*Results*	*Conclusion*
Battié (2007) (14)	♂ Age: 35-70 147 MZ pairs 153 DZ pairs	Self-reported LBP (Previous year, Lifetime)	Genetic effects (30-46%) Shared/ Non-shared environmental effects (54-70%)	+LBP
Bengtsson (1991) (15)	♀ ♂ Age: 15-47 5,029 MZ pairs 7,876 DZ pairs	Self-reported BP (Last few years)	MZ>DZ within-twin pair concordance of LBP	+LBP
El-Metwally (2008) (40)	♀ ♂ Age: 11 610 MZ pairs	Self-reported LBP (Weekly/monthly)	No genetic effects Shared environmental effects (41%) Non-shared environmental effects (59%)	-LBP
Hartvigsen (2004) (61)	♀ ♂ Age: 70-80+ 433 MZ pairs 621 DZ pairs	Self-reported BP (Previous month)	Genetic effects (♀0%, ♂ 27%) No shared environmental effects (♀♂) Non-shared environmental effects (♀100%, ♂ 73%)	♀ -LBP ♂ +LBP
Heikkila (1989) (63)	♀ ♂ Age: 24-60+ 2,983 MZ pairs 6,133 DZ pairs	Self-reported LBP (Lifetime sciatica)	Genetic effects (11-21%) Shared/ Non-shared environmental effects (79-89%) (Environmental effects increased with age)	+LBP
Hestbaek (2004) (67)	♀ ♂ Age: 12-41 3,818 MZ pairs 4,469 DZ pairs	Self-reported LBP (Lifetime)	Genetic effects (40-44%) (Shared environmental effects decreased with age) (Non-shared environmental effects increased with age)	+LBP
MacGregor (2004) (94)	♀ Age: 45-79 181 MZ pairs 351 DZ pairs	Self-reported LBP (Lifetime)	Genetic effects (52-68%) No shared environmental effects (0%) Non-shared environmental effects (32-48%)	+LBP

+LBP. Author's conclusion of positive genetic effect.
-LBP. Author's conclusion of no genetic effect.

Table 5. Heritability of neck-shoulder pain. Description of studies and author's conclusion about genetic effect.

Reference	*Material*	*Variables*	*Results*	*Conclusion*
Fejer (2006) (44)	♀ ♂ Age: 20-71 33 794 twins	Self-reported NSP (Lifetime)	Genetic effects (44%) No shared environmental effects (0%) Non-shared environmental effects (66%) (Environmental effects increased with age)	+NSP
Hartvigsen (2005) (62)	♀ ♂ Age: 70-80+ 433 MZ pairs 621 DZ pairs	Self-reported NSP (Last month)	Genetic effects (♀3%, ♂5%) No shared environmental effects (0%) Non-shared environmental effects (♀97%, ♂95%)	+NSP
MacGregor (2004) (94)	♀ Age: 45-79 181 MZ pairs 351 DZ pairs	Self-reported NSP (Lifetime)	Genetic effects (35-58%) No shared environmental effects (0%) Non-shared environmental effects (42-65%)	+NSP

+NSP. Author's conclusion of positive genetic effect.
-NSP. Author's conclusion of no genetic effect.

Table 6. Heritability of cervical and lumbar disc degeneration. Description of studies and author's conclusion about genetic effect.

Reference	*Material*	*Variables*	*Results*	*Conclusion*
Battié (2007) (14)	♀ ♂ Age: 35-70 147 MZ pairs 153 DZ pairs	MRI imaging of lumbar disc degeneration	Genetic effects (51%) No shared environmental effects Non-shared environmental effects (49%)	+LDD
Bijkerk (1999) (17)	♀ ♂ Age: 55-65 257 siblings (118 families)	MRI imaging of thoracic and lumbar disc degeneration	Genetic effects (75%)	+LDD
Sambrook (1999) (121)	♀ ♂ Age: 24-60+ 86 MZ pairs 154 DZ pairs	MRI imaging of lumbar disc degeneration	Genetic effects (63-74%) No shared environmental effects Non-shared environmental effects (26-37%)	+LDD
Sambrook (1999) (121)	♀ ♂ Age: 24-60+ 86 MZ pairs 154 DZ pairs	MRI imaging of cervical disc degeneration	Genetic effects (63-79%) No shared environmental effects Non-shared environmental effects (21-37%)	+CDD

+LDD, +CDD. Author's conclusion of positive genetic effect.
-LBP. Author's conclusion of no genetic effect.

2.3.3 Gene association studies

Through recent years several different genes have been associated with intervertebral disc degeneration, but only a few have been verified over different ethnic populations [78]. Different categories of candidate genes have been identified in these association studies including; genes associated with the structural component of the disc, enzyme producing, bone structure related genes, and osteoporosis related genes [160]. There is an agreement among studies that the susceptibility of intervertebral disc degeneration is influenced by multiple genes and environmental factors, and that for some genes and some environmental factors, gene-gene, gene-environment and gene-age interactions may exist [78, 160].

Although research in this area has begun, there is a need for further research, focusing not only on intervertebral disc degeneration but also on finding genetic markers that may aid in the research on other pathophysiological causes for LBP and NSP.

2.4 PHYSICAL WORKLOAD

Factors that have been found to influence the occurrence and course of LBP and NSP cover individual, psychosocial, and work-related factors [58, 96, 105]. Among work-related factors, many exposures are related to high physical workload. Factors associated with high physical workload have often been studied in the relation to musculoskeletal disorders. As early as in 1713, Bernardino Ramazzini (often referred to as the father of occupational medicine) noted the importance of work-related exposures for the development of musculoskeletal disorders. In his publication about causes of diseases among workers, he stated "…the second cause I ascribe to certain violent and irregular motions and unnatural postures of the body, by reason of which the natural structure of the vital machine is so impaired that serious diseases gradually develop" [115].

During the last decades, the research society has turned more and more interest towards investigating the determinants of occupational musculoskeletal disorders. High physical workload is still very much in focus, and early studies during the 1980's and the 1990's identified associations between certain occupational groups known to be exposed to several physical load factors simultaneously (such as male farmers, construction workers, fire fighters, cleaners) and the occurrence of musculoskeletal disorders [54, 154].

However, the sizes of the associations found were moderate in strength and there were large discrepancies between studies. Among the critique that emanated were suggestions that using job titles as a proxy for occupational physical load were a too imprecise exposure assessment method, and more and more studies regarding single physical exposures (such as manual handling, awkward postures, force exertion, and vibration) were, and still are, performed [49, 114, 139]. Although many of these studies have found associations between a specific risk factor and LBP and NSP, the problems with weak associations and large discrepancies between studies remain [20].

The inconsistencies have often been attributed to methodological issues, such as heterogeneous study populations and imprecise exposure assessment methods, and the question has been raised, if it is possible to single out and investigate one specific

potential risk factor [58, 90, 97, 105]. Studies have found that individuals often are exposed to several potential risk factors simultaneously, and that this can affect the association with musculoskeletal disorders [4, 135]. A recent study which looked at the influence of work-related exposures and NSP, found that the prognosis of NSP was poorer for subjects with multiple biomechanical exposures at work [52].

To summarise the development of studies aiming at studying potential associations between work-related physical exposures and musculoskeletal disorders, using job titles to describe exposure may take into account the interaction of several specific exposures. However it does not discriminate exposure differences between individuals within a specific occupational group. Further, it does not give any information about the contribution of specific exposures in relation to the disorder studied. On the other hand, in studying specific exposures, it is often difficult to control for all other working conditions that can confound the associations.

One possibility could be to choose a study group where the working conditions are similar for all subjects in all other aspects than those studied. This can be exemplified using orchestra musicians and study the associations between the exposures to work in an elevated arm position and NSP. Musicians working in an orchestral setting share many psychosocial working conditions often mentioned as potential risk factors for neck-shoulder pain, such as social support, job demands, and control [6].

Playing any instrument demands precision work with hands and fingers, something which requires stabilising muscle activity in the neck-shoulder region. Orchestra musicians all work in a sitting position or are standing still and the weights of the hand-held instruments are similar, normally below 2.5 kg. Thus, the biomechanical load factors are similar except for the degree of arm elevation while playing and the duration of active playing time per work day (duration of static work), which vary depending on which instrument you play.

2.5 PHYSICAL WORKLOAD AND GENETIC CONFOUNDING

Several studies have, in different ways, investigated the potential influence of genetic factors for the association between physical work load and LBP or LDD [13, 14, 60, 146, 155]. No corresponding studies concerning NSP or CDD have been found.

Two studies that investigated effects of familial influences and suspected environmental risk factors on LDD, only found modest associations between occupational exposures and LDD, in comparison to the association between familial aggregation and disc degeneration signs [13, 146].
Virtanen et al. (2007) performed a gene-interaction study on full-time train drivers and investigated the potential interaction between whole body vibration and suspected genetic markers (selected on the basis of previous genetic association studies in low back disorders) for intervertebral disc degeneration and for self-reported LBP. The authors concluded that there was an interaction of genetic and environmental risk factors, as the exposure to whole-body vibration had additive effect with all included

genetic markers in an occupational cluster representing symptomatic intervertebral disc disease phenotypes [155].
Hartvigsen et al. (2003) in investigating genetic confounding in the association between physical workload and self-reported LBP, found that even when adjusting for genetic influences there was a graded association for increasing workload and LBP [60].

One study, by Battié et al. (2007) aimed at investigating how genetic influence on back pain disability was correlated with the genetic influence for occupational prolonged sitting at work and lumbar disc height narrowing, respectively. The results showed that a small portion of the genetic influences on occupational sitting was affecting both back pain disability and disc narrowing to some extent. In other words, less disc height narrowing, decreased back pain disability and more occupational sitting had a modest common genetic determinant. However, independent genetic effects for both back pain disability and disc narrowing accounted for most of the genetic variance in the two traits. Environmental effects on occupational sitting were partly shared with environmental effects on back pain disability, but not with disc narrowing [14].

2.6 SUMMARY

Low back pain and neck-shoulder pain represent a large public health problem being common disorders that often lead to negative consequences for the individual and large costs for Society. Research about the determinants of these disorders is continuing, but for the time being little is known about the pathoanatomical causes of LBP and NSP.

The role of heritability in the incidence of these disorders is a rather new research field and recent findings suggest that genetic factors may be of importance for the occurrence of both LBP and NSP.

More traditionally, the focus of the search for risk factors for LBP and NSP has concentrated on other individual factors and work-related exposures. Among the most commonly investigated work-related exposures are factors relating to physical workload. Although earlier research has found evidence for positive associations between different physical exposures and LBP and NSP, the problem of weak associations and heterogeneity between studies remain. Further, it still remains to be investigated to what extent genetic and shared environmental factors may influence these associations.

Co-morbidity of LBP and NSP with other disorders is fairly well documented, and is suggested to influence the prognosis and consequences of LBP and NSP. Having pain in more than one area of the spine represents a specific co-morbidity and little is known about subjects with *Concurrent LBP and NSP* and how they might differ from subjects with *Solely LBP* or *Solely NSP* with regard to factors relating to both the occurrence and consequences of the disorders such as the influence of genetic factors, exposure to physical workload and sickness absence.

3 AIMS

The main goal of the thesis is to explore how factors relating to aetiology, i.e. the influences of genetic factors and work-related physical load, as well as consequences in terms of sickness absence are associated with different combinations of LBP and NSP.

3.1 SPECIFIC RESEARCH QUESTIONS

Are there differences in sickness absence among individuals with *Solely LBP*, *Solely NSP*, and *Concurrent LBP and NSP*? *(Paper I)*

Are genetic factors of importance for the occurrence of *Solely LBP*, *Solely NSP*, and *Concurrent LBP and NSP*? *(Paper II)*

Are the associations between high physical workload and different combinations of LBP and NSP confounded by genetic and shared environmental factors? *(Paper III)*

Is there an association between a work posture with an elevated arm position and NSP among musicians? *(Paper IV)*

4 MATERIALS AND METHODS

4.1 DATA SOURCES

Paper I is based on the MUSIC-Norrtälje Study, papers II and III are based on the STAGE Study, and paper IV is based on the Swedish Orchestra Study.

4.1.1 The MUSIC-Norrtälje Study

The Musculoskeletal Intervention Center (MUSIC)-Norrtälje Study was initiated in order to identify and quantify risk factors and protective factors for low back and neck-shoulder disorders and to investigate the prognosis of these disorders. The study consisted of a baseline case-referent study with a 5-year follow-up study of all subjects. Moreover, census data from the National Social Insurance Board on sickness absence was linked to each of the 2,329 subjects that participated in both the baseline study and the follow-up study.

4.1.1.1 Baseline case-referent study

The study population comprised approximately 17,000 men and women, 20-59 years of age, who were living in and not working outside, the municipality and rural district of Norrtälje in central Sweden. The cases were defined as those in the study population who had sought care or treatment for nonspecific low back and/or neck-shoulder disorders from any of the approximately 70 caregivers in the region; physicians and physiotherapists as well as alternative caregivers such as chiropractors, osteopaths, and homeopaths. Referents were selected as a random sample stratified by sex and age (5-year categories) from the study population by means of the population register. At least one referent was chosen for each case, but when time permitted additional referents were invited. Cases and referents that had sought care or treatment during the previous six months were excluded so that "new" episodes of the disorder could be studied.
The study period lasted from January 1, 1994 to June 30, 1997. The participation rate of all potential cases is unknown. The caregivers asked their patients if they wanted to participate, but did not record refusals. According to interviews with the caregivers, only a few cases refused to participate. Approximately 69% of the referents took part in the whole investigation and another 11% filled out the questionnaires, but were unable to attend the clinical examination and interviews [135, 152].

For both cases and referents, individual and demographic data, data concerning low back pain, neck-shoulder pain, and other disorders (including non-musculoskeletal disorders and diminished psychological wellbeing) as well as psychosocial and physical exposures (e.g. manual handling, working with hands above shoulder level, working with vibrating tools, and energy expenditure) were collected through self-administered questionnaires and structured interviews [51, 52]. A standardised clinical examination was also performed.

4.1.1.2 Follow-up study

A self-administered postal questionnaire was sent four to six years after the baseline study to both cases and referents that were still living in Sweden. Subjects that participated in the baseline study in 1994-1995 received their follow-up questionnaires during the year 2000, whilst subjects that participated in the baseline study in 1996-1997 received their questionnaires during 2001. Thus, the follow-up period varied between four to six years (Figure 2). The response rate was 83% (n= 2,329). The proportion males and subjects less than 45 years of age were higher among the non-responders.

Data concerning low back pain, neck-shoulder pain, and other disorders (including non-musculoskeletal disorders and diminished psychological wellbeing) as well as psychosocial and physical exposures, was collected with similar questions as in the baseline study.

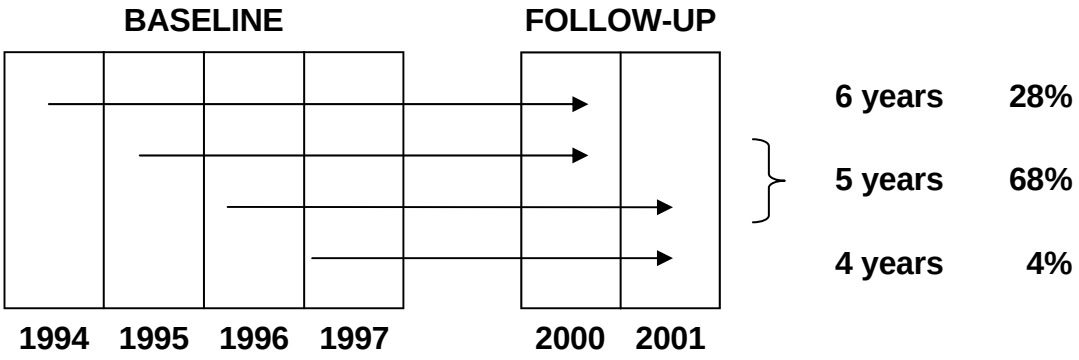


Figure 2. The MUSIC-Norrtälje baseline and follow-up study. Percentage of subjects with a follow-up time of 4, 5, or 6 years.

4.1.1.3 Census data

Official register data concerning sickness absence was received from the National Social Insurance Board. For each year 1995-2001, and each subject, data about two types of benefit due to illness was received: (1) sickness benefit, and (2) disability pension. The data did not include any specified information about the reason for sickness absence, i.e. the diagnosis on the sickness certificate issued by the physician. Data concerning sickness benefit was received as reported number of sick spells per year, number of days per year, and as partial or full benefit. Received disability pension data complied (a) date for newly allowed disability pension, and (b) partial or full benefit.

4.1.2 The STAGE Study

The Swedish Twin Registry (STR) is a national resource maintained at Karolinska Institutet. It is one of the world's oldest and largest registries of its kind and contains information on more than 170,000 twins born 1886-2000.

The Study of Twin Adults: Genes and Environment (STAGE) was performed in 2005-2006. The study targeted 43,088 twins born 1959-1985 that had not participated in any previous STR administered data collection. The purpose was to screen for most common complex diseases, although a great deal of attention was put into evaluating exposure relevant during young adulthood and midlife. Data was collected through a web-based self administered questionnaire and concerned, among other things, present illnesses, medical history, self rated health, and sickness absence. The entire questionnaire contained approximately 1,300 questions in 34 sections. Many sections in the questionnaire were presented in a 'branching' format, meaning that the individuals were asked follow-up questions if they responded positively to key introductory items. Those twins that did not answer the web-based questionnaire were offered a telephone interview (performed by trained interviewers, using a computer-based data collection system) or a postal questionnaire. The overall response rate was 60%. Age did not differ between the responders and non-responders. However, there were more men than women among the non-responders.

4.1.2.1 Definition of zygosity

Zygosity was determined based on two questions in the questionnaire relating to similarity and mistaken identity during childhood. The first question was phrased "During childhood, were you and your twin partner as like as two peas in a pod or not more alike than siblings in general?". If both twins answered "alike as two peas in a pod" they were classified as MZ; if both twins answered "not alike" they were classified as DZ. If the twins did not agree the zygosity was considered undetermined. This is an often used and acknowledged method for determining zygosity in large twin studies, and comparison of the suggested method with laboratory studies has shown less than 5% misclassification [29, 33, 87, 122]. However, if the zygosity was undetermined after the "peas in a pod" question, another question "How often did strangers have difficulty in distinguishing between you and your twin partner when you were children?" was used. If both twins answered "almost always, or always" or "often" to this question they were classified as MZ, and if both twins answered "seldom" or "almost never or never", they were classified as DZ. However, if the twins answered differently also on this question the zygosity remained undetermined [87].

For determining zygosity on twins where only one of the twins had participated in the study (singleton twins), both the above questions were used. If the singleton twin answered "alike" on the "two peas in a pod" question and "almost always, or always" or "often" on the "difficulty distinguishing" question, he/she was classified as MZ. If he/she answered "not alike" on the "two peas in a pod" question and "seldom" or "almost never or never" on the "difficulty distinguishing" question, he/she was classified as DZ [87].

4.1.3 The Swedish Orchestra Study

The study was performed as a cross-sectional survey of psychosocial working conditions in professional Swedish orchestras in 1999-2000 [88, 89]. The study population comprised all 640 musicians employed in 12 professional Swedish orchestras, including symphony orchestras, symphoniettas/chamber orchestras, and theatre orchestras. From these orchestras, 50% of the members, in all 320 individuals, were

asked to fill out a questionnaire. This selection was made by dividing all 640 employed musicians into four different strata depending on duration of employment (0-5 years, 6-11 years, 12-19 years, and >19 years). These four strata were then subdivided by sex. For each of the eight strata, a proportional number of subjects were selected randomly, resulting in the distribution of questionnaires to the 320 subjects. With 250 questionnaires completed, the response rate was 78%. The drop-out analysis showed that individuals with longer duration of employment were less likely to respond [89].
The questionnaire contained questions concerning psychosocial working environment, musculoskeletal disorders and psychological distress.

4.2 DEFINITIONS OF LOW BACK AND NECK-SHOULDER PAIN

In all papers I-IV definitions of low back pain and neck-shoulder pain incorporating both pain and pain-related disability were used.

4.2.1 Paper I

Low back pain and/or neck-shoulder pain was defined based on self-reported pain and pain-related disability at both baseline and follow-up. All subjects answered three questions concerning low back pain intensity covering (1) current pain, (2) worst pain experienced during the previous 6 months, and (3) average pain during the previous 6 months. The subjects also answered three questions concerning low back pain-related disability that concerned how much the pain had affected (1) everyday activities, (2) social and family activities, and (3) ability to work (including domestic work)during the previous 6 months. All subjects also answered six corresponding questions concerning the neck-shoulder region. The rating scale for each of these in all 12 questions ranged from 0 to 10 where 0 meant no pain/ disability at all and 10 meant pain/disability as bad as it could be. The questions were formulated according to von Korff and have been tested for validity and reliability [156].

A pain intensity score for each subject and each body region was constructed using the three questions that concerned pain intensity [156]. The score was calculated as the sum of the three derived figures on the rating scales and divided by 3. A pain-related disability score was constructed in the same manner as the pain intensity score. The chosen limit for a subject to be considered to have low back pain or neck-shoulder pain was a pain intensity score ≥ 3 and/or a disability score ≥ 1.

4.2.2 Papers II and III

Low back pain and/or neck-shoulder pain was defined based on self-reported pain and pain-related disability in the same manner as in paper I, however with one difference. Before being given the chance to answer to the in all twelve above mentioned questions, subjects had to have answered positively to screening questions concerning pain in the low back or neck-shoulder region the preceding six months. These questions were formulated according to the Standardised Nordic Questionnaire (SNQ) and were accompanied by a drawing marking the areas of the low back and neck-shoulder regions [48, 82].

4.2.3 Paper IV

Neck-shoulder pain was defined based on self-reported pain and pain-related disability. The questionnaire contained three questions concerning present pain from the neck region, pain from the shoulder region, and pain from between the shoulder blades. A five graded response scale was used for each question; 0= completely healthy, 1= a little pain, but no problem, 2= quite a bit of pain, but it is possible to play, 3= very much pain, have to avoid certain movements, and 4= so much pain that I sometimes can't work. A subject was considered as having neck-shoulder complaints if he/she had scored at least "2" on at least one of the three items. The questions were formulated according to a pain screening questionnaire originally developed for ballet dancers, and the cut-off score in paper IV was chosen in accordance with the original study of ballet dancers [116].

4.3 DEFINITIONS OF SICKNESS ABSENCE

4.3.1 Paper I

A subject was considered as having sickness absence if he/she had received partial or full sickness benefit or disability pension during at least one period of >14 consecutive days (longer than 28 days for the period 1st January 1997 until 1st April 1998, see section 2.2.1), during the period between baseline and follow-up.

Long-term sickness absence was only analysed among those subjects that had been sickness absent at least 14 consecutive days between baseline and follow up. It was defined as >180 days with disbursed sickness benefit and disability pension during at least one one-year period between baseline and follow-up. Consideration was taken to whether the disbursed benefits were partial or full, in the manner that days with partial benefit were recalculated into whole days.

4.3.2 Paper II

In paper II, sickness absence was self-reported (not specifying the reason for the sickness absence) and based on the question "Have you during the previous 12 months been on sick leave with a doctor's certificate?". In Sweden, a doctor's certificate is needed for sickness absence periods of more than seven days. A subject was defined as having had sickness absence at least seven consecutive days during the previous 12 months if he/she had answered "yes" on this question.

4.4 DEFINITIONS OF PHYSICAL WORKLOAD

4.4.1 Paper III

Physical workload was based on self-reported occupation. The occupations were coded according to the Nordic Occupation Classification (NYK), which is comparable to the three-digit International Classifications (ISCO-88) [5, 75]. This was done manually by three experts within occupational medicine, highly experienced in the coding of

occupations. The coding was first done separately by each expert, and when questions aroused, consensus within the group was reached through discussions.

The occupations coded according to NYK were then classified into four groups on a graded scale from low, low-medium, high-medium to high physical workload.
This classification was done using a previously developed gender specific exposure classification system [161]. This system was developed using the Swedish Annual Level-of-Living Surveys (1977 and 1979-1981), which are based on a nation-wide representative sample of the Swedish population and contain questions concerning, among other things, occupation and working environment. These surveys were conducted by Statistics Sweden and quality issues and technical details are described elsewhere [129, 130]. In the development of the classification system, the occupations were coded according to NYK in the Swedish Annual Level-of-Living Surveys and the proportions of subjects reporting different physical strains at work were calculated. By using factor analysis the following eight factors were then extracted: heavy lifts daily, repetitive and one-sided working movements, unsuitable working postures, heavy shaking or vibration, daily perspiring from physical exertion, contact with dirt, deafening noise, and risk of exposure to accidents. For each occupation, factor scores for the eight factors were calculated and summarized into an index. Based on these index scores, the occupations were then ranked from lowest to highest, and grouped by quartiles into four groups from low (level 1), low-medium (level 2), high-medium (level 3) to high physical workload (level 4).

In paper III, due to problems with statistical power, this variable was dichotomised in the statistical analyses and subjects were classified into two groups; (1) Low physical workload (level 1-2), and (2) High physical workload (level 3-4).

4.4.2 Paper IV

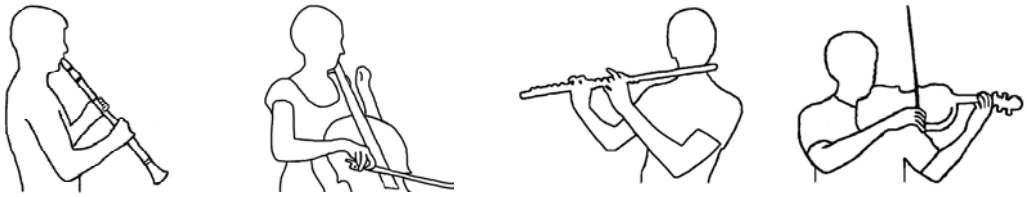
Physical workload was in paper IV defined as exposure to work (playing a musical instrument) in an elevated arm position. Arm elevation while playing was assessed by the authors using photographs of experienced instrumentalists playing each of twelve different instruments and were classified into (a) Elevated arm position (≥40° elevated arm position while playing), or (b) Neutral arm position (<40° elevated arm position while playing).

To assess the average duration of static work during a work day (the average active playing time during a work day) for each of the twelve instruments the following assumptions was made; (1) musicians working in an orchestral setting have about 25 hours of orchestral duty per week (divided in five work days), (2) about 80% of that time is time when the orchestra is playing a music piece, and (3) the percentage of actual active playing time during a music piece for each instrumentalist can be estimated using the percentage of bars played in the pieces of music.

For determining the percentage of bars played by each instrument in the pieces of music, three Swedish concert season programs, one for each type of orchestra (symphonic orchestra, symphonietta/chamber orchestra, theatre orchestra) were used. All orchestras played music from different time epochs. All the pieces of music

(approximately 100 pieces) in the season programs were grouped into three different categories; (1) 18th-century compositions, (2) 19th-century compositions, and (3) 20th-century compositions. This was made due to the differences in the use of wind and brass instruments in compositions from different time epochs. From each type of orchestra, one piece from each time epoch was randomly chosen (in all, nine pieces), and the percentage of bars played in each piece of music was calculated and summarized for each instrument.
Based on the above described assumptions and calculations, and the finding that no instrument had a playing time between two and three hours, two exposure duration groups were identified; (a) <2 h per work day, or (b) >3 h per work day.

By combining the definition for arm elevation and the definition for duration of active playing time per work day, the twelve different instruments were classified into four exposure groups; (1) *Neutral arm position, <2 h per work day*, (2) *Neutral arm position, >3 h per work day*, (3) *Elevated arm position, <2 h per work day*, and (4) *Elevated arm position, >3 h per work day* (Figure 3).



Neutral arm position <2 h per work day			***Neutral arm position >3 h per work day***			***Elevated arm position <2 h per work day***			***Elevated arm position >3 h per work day***		
	n	***h***		***n***	***h***		***n***	***h***		***n***	***h***
Bassoon	12	1.9	Cello	24	3.3	Flute	10	1.7	Violin	77	3.3
Clarinet	13	1.6	Double bass	18	3.2	Trumpet	12	1.0	Viola	25	3.2
French horn	18	1.6				Trombone	15	0.4			
Oboe	10	1.8									
Tuba	1	0.4									

Figure 3. The four exposure groups in paper IV. Types of instrument, number of subjects (n), and active playing time in hours (h) during a work day classified into the four exposure groups based on two criteria; (1) work posture while playing (elevated arm position or neutral arm position), and (2) <2 h per work day, or >3 h per work day.

4.5 SUBJECTS

Table 7. Descriptive data of subjects in papers I-IV. Number of subjects, proportion of women and men, and mean age and range.

	Paper I	*Paper II*	*Paper III*	*Paper IV*
Data source	MUSIC	STAGE	STAGE	Swedish orchestra
Subjects (n)	817	20,946	16,107	235
Women/Men (%)	64/36	57/43	57/43	39/61
Mean age (Range)	42 (20-59)[a)]	35 (21-47)	35 (21-47)	39 (23-68)

a) At the baseline study

4.5.1 Paper I

Included in this study were those 817 subjects who participated in both the MUSIC-Norrtälje baseline study and the 4-6-year follow-up study, who were working at least 17 hours per week at baseline and who at both baseline and follow-up reported LBP and/or NSP. Subjects that were completely pain free at one or both of the occasions were excluded (Table 7).

Subjects that consistently reported pain in the same region(s) at the two occasions were classified into the groups (1) *Solely LBP,* (2) *Solely NSP*, or (3) *Concurrent LBP and NSP*. Subjects who reported LBP and/or NSP at both baseline and follow-up, but did not give consistent answers with regard to region of pain at the two occasions were assigned a fourth group, (4) *Migrating LBP/NSP* (Figure 4).

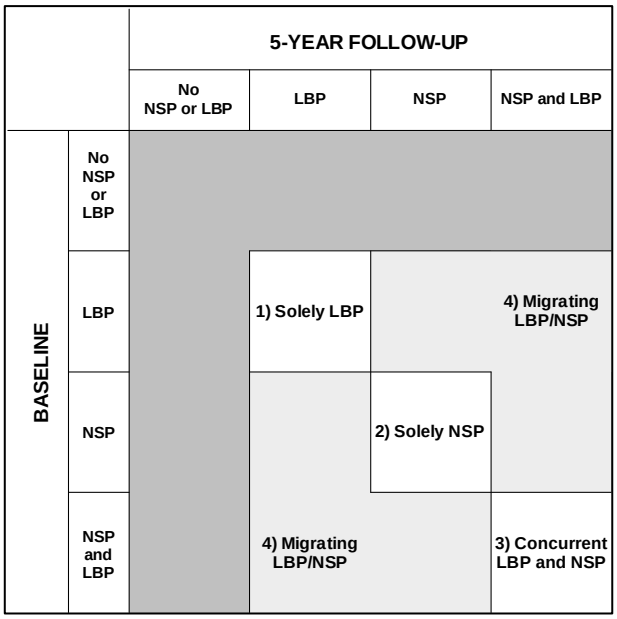


Figure 4. Description of the study group in paper I. Subjects classified into one of four groups according to self-reported pain and pain-related disability measured at two points in time, both at baseline and at follow-up; 1) Solely LBP (n=120), 2) Solely NSP (n=94), 3) Concurrent LBP and NSP (n=271), and 4) Migrating NSP/LBP (n=332). All other subjects were excluded.

4.5.2 Paper II

Included in this study were those complete 2,934 monozygotic (MZ) twin pairs, 2,009 same-sex dizygotic (DZ) twin pairs, 1,960 opposite-sex DZ twin pairs, as well as 2,249 MZ singleton twins and 4,891 DZ singleton twins from the STAGE-study that had given complete answers on the questions concerning pain and pain-related disability in the low back- and neck-shoulder regions, in all 20,946 subjects.

Subjects were then classified in four different groups; *No LBP or NSP, Solely LBP, Solely NSP,* or *Concurrent LBP and NSP*. Those twin pairs where one of the twins was classified as having *Solely LBP* and the other twin was classified as having *Solely NSP*, as well as twin pairs where one of the twins was classified as having *Solely LBP* or *Solely NSP* and the other twin was classified as having *Concurrent LBP and NSP* were used only in the descriptive analyses (Figure 5).

Twin pairs where at least one twin had answered that they had any of the rheumatic disorders Rheumatoid Arthritis, Systemic Lupus Erythematosus, or Pelvic Spondylitis were excluded from the study, arguing that these are disorders affecting several parts of the musculoskeletal system where there is a known heritability, and the purpose of the study was to investigate the genetic influence for non-specific LBP and NSP [93, 111, 117] (Table 7).

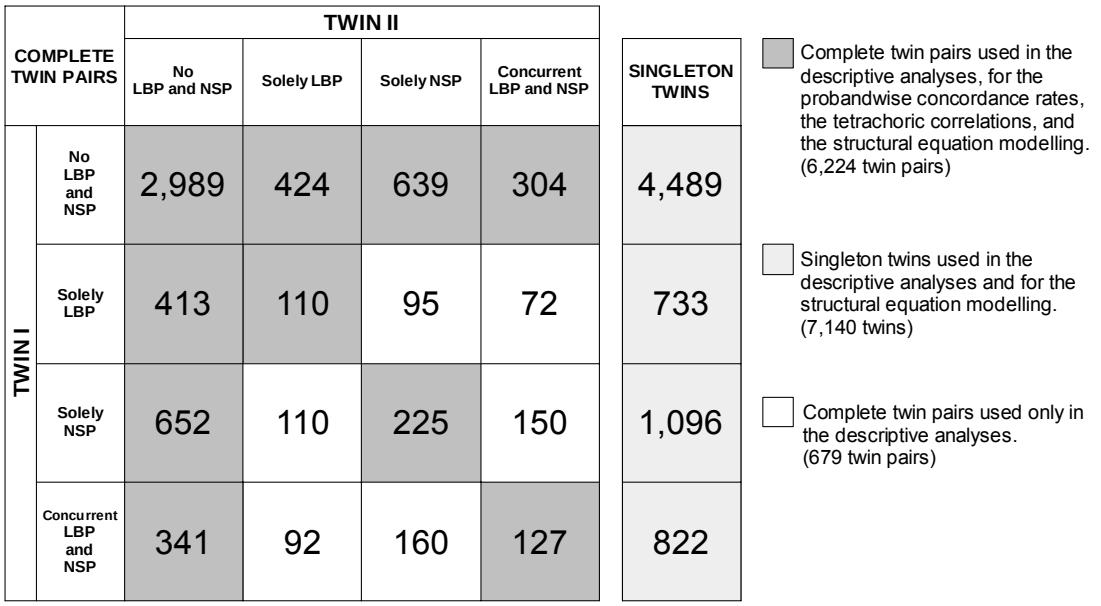


Figure 5. The study group in paper II. Number of complete twin pairs (twin I and twin II), and (to the right) singleton twins, classified into one of four groups; *No LBP or NSP*, *Solely LBP*, *Solely NSP*, or *Concurrent LBP and NSP*.

4.5.3 Paper III

Included in this study were those complete 1,802 MZ twin pairs, 1,334 same-sex DZ twin pairs, 1,282 opposite-sex DZ twin pairs, and 7,271 singleton twins between the ages of 21-47 years. These, in all 16,107 subjects, had given complete answers on the questions concerning pain and pain-related disability in the low back- and neck-shoulder regions and could be categorised into two different groups regarding exposure to physical workload.

As in paper II, pairs where at least one twin had answered that they had Rheumatoid Arthritis, Systemic Lupus Erythematosus, or Pelvic Spondylitis were excluded from the study. This, since the aim in paper III was to investigate the association between high physical workload and non-specific LBP and NSP (Table 7).

4.5.4 Paper IV

Subjects included in the study were those 235 musicians from the Swedish orchestra study who could be identified as to what instrument they played, and who were playing an instrument where it was possible to classify the work posture (twelve different instruments). Subjects that had missing data on the questions concerning ongoing pain from the neck-shoulder region were excluded from the study (Table 7) (Figure 3).

4.6 METHODS

4.6.1 Paper I

In paper I, the aim was to investigate potential differences in sickness absence between four different disorder groups; *Solely LBP*, *Solely NSP*, *Concurrent LBP and NSP*, and *Migrating LBP/NSP* (Figure 4). This was done using logistic regression analysis. Since there was no difference in sickness absence between the groups *Solely LBP* and *Solely NSP*, these two groups were merged into one group; *Solely LBP or Solely NSP*. This merged group was then used as a reference group in the analyses.

Two different measures of sickness absence were analysed; (1) prevalence of sickness absence, defined as at least one period of governmental compensated sickness absence >14 consecutive days between baseline and follow-up and (2) long-term sickness absence, defined as >180 days during at least one of the five 1-year periods between baseline and follow-up among those subjects with sickness absence.

Three potential confounders were considered; sex, age, and other non-musculoskeletal related disorders (which included physical illnesses and diminished psychological wellbeing). All three potential confounders were found to be of importance for the prevalence of sickness absence. However, for the prevalence of long-term sickness absence, sex did not influence the associations and was dropped as a confounder in the succeeding analysis.

4.6.2 Paper II

In paper II, the aim was to investigate the influence of genetic factors for the occurrence of *Solely LBP*, *Solely NSP*, and *Concurrent LBP and NSP*. This was done using classical quantitative twin study methodology which makes use of the fact that MZ twins share their segregating genes to a much greater extent than DZ twins.

To analyse similarities within twin pairs with regard to the occurrence of *Solely LBP*, *Solely NSP*, and *Concurrent LBP and NSP* two different measures of similarity were used; probandwise concordance rate and tetrachoric correlation.
The probandwise concordance rate estimates the risk that a twin in a pair is affected, given that the co-twin in the pair is affected [100]. A genetic component is indicated when the probandwise concordance rate for MZ twins is higher than for DZ twins.
A tetrachoric correlation is correspondent to an intraclass correlation and measures the similarity of disease within a twin pair. A genetic component is indicated when the tetrachoric correlation for MZ twins is more than twice that of DZ twins [113].

These similarity measures are not suitable for estimating heritability. In paper II, heritability was estimated with structural equation modelling which was used to partition the total variance of *Solely LBP*, *Solely NSP*, and *Concurrent LBP and NSP* respectively into parts due to genetic and environmental influences. In these models, the total variance can be divided into the following components; Additive genetic variance (A), Dominant genetic variance (D), Shared (common) environmental variance (C), and Non-shared (unique) environmental variance (E).

A structural equation model estimates the A, D, C and E components by comparing MZ twin pairs to DZ twin pairs. The model takes into consideration that MZ twins share 100% of their additive genetic effects and dominant genetic effects, whereas DZ twins share only 50% of their additive genetic effects and 25% of their dominant genetic effects. The influence of shared environment (family environment early in life) is assumed to be equal for MZ twins and DZ twins. The non-shared environmental component explains all other causes of disease, including measurement error [41] (Figure 6).

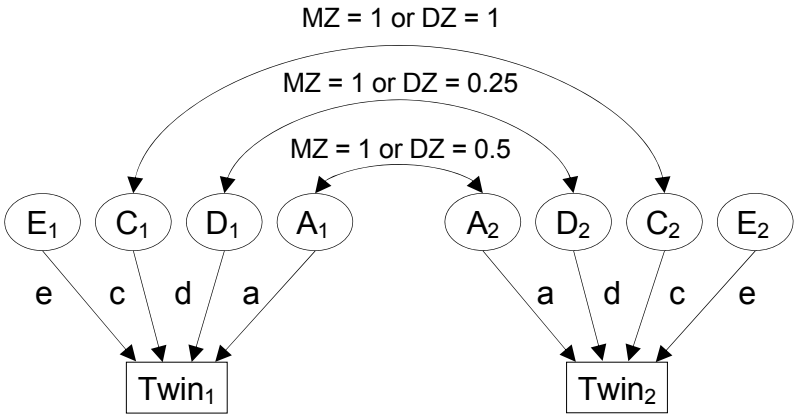


Figure 6: Path diagram for a univariate twin model. The additive (A) and dominance (D) components are correlated 1 between MZ twins and 0.5 and 0.25 between DZ twins, respectively. Shared environment (C) is correlated 1 for both MZ and DZ twins. Non-shared environment (E) component explains all other causes of disease including measurement error, thus, is uncorrelated between members of MZ and DZ pairs. a, d, c and e are the path coefficients for the A, D, C and E effects. (Modified from Rijsdijk et al. (2002) [118])

Dominant genetic effects and shared environmental effects are confounded and can only be estimated in separate models [41]. Hence, structural equation modelling was used to calculate an ACE model and an ADE model respectively for each disorder group (*Solely LBP, Solely NSP,* and *Concurrent LBP and NSP*). For each model, parameter estimates for the included components were calculated, with the corresponding 95% confidence intervals and model fit statistics, -2 log likelihood and Akaike's information criterion (AIC). The ACE model and the ADE model were then compared by examining the AIC values (a lower value indicating a better fit).

In paper II, there were negligible differences in AIC between the two models, and since the ACE model was considered to be more plausible it was the only model analysed in the subsequent analyses. This decision was based on earlier studies, where it has been hypothesised that variables such as parental behavioural influence, physical activity, and nutrition during childhood (which in the twin study setting would be assigned to the shared environmental variance component) could influence the occurrence of LBP and NSP [11].

The significance of the variance components were then tested through comparisons between the ACE model and the subsequent nested models (AE, CE and E) for each disorder group (*Solely LBP, Solely NSP,* and *Concurrent LBP and NSP*). This was done

using log-likelihood tests. If $p \geq 0.05$ in these tests, the simpler nested model was preferred to the ACE model since it did not provide a significant worse fit to the data, even though it contained fever parameters. To enhance the precision of the estimated variance components, singleton twins were included in all structural equation analyses. In paper II, the log-likelihood tests found the ACE and the AE model to be the most suitable models. However, the difference in fit between these two models was so small that the log-likelihood test (-2LL) statistic was incalculable.

Potential differences between women and men regarding the influence of additive genetic effects, shared environmental effects and non-shared environmental effects can be analyzed in a sex-limitation model. A sex-limitation model is a structural equation model where opposite-sex dizygotic twins are also included in the analysis. In paper II, all sex-limitation models assumed that the same genes were present in both males and females (that is, it was assumed that the genetic correlation between the sexes, was equal to 0.5).

In the sex-limitation analyses, the full model for each disorder group (*Solely LBP*, *Solely NSP* and *Concurrent LBP and NSP*) was an ACE model where the A, C, and E estimates were allowed to differ across the sexes. The consequent nested models were ACE, AE, CE and E where the components were constrained to be equal across the sexes.

By using log-likelihood test (-2LL), the full model could be tested against each nested model. If $p \geq 0.05$ in these tests, it was concluded that the models where the components were constrained to be equal across the sexes did not provide a significantly worse fit to the data than the full model. Hence, men and women could be analysed together and opposite-sex dizygotic twins could be included with same-sex dizygotic twins in the analyses [74, 108].

4.6.3 Paper III

In paper III, the aim was to investigate if high physical workload is associated with *LBP and/or NSP* when taking into account the influence of genetic and shared environmental factors. Further, the study aims to explore the potential influence of genetic and shared environmental factors in the associations between high physical workload and the three disorder subgroups *Solely LBP, Solely NSP,* and *Concurrent LBP and NSP.*

To analyse the association between high physical workload and the group *LBP and/or NSP,* as well as the three disorder subgroups *Solely LBP, Solely NSP,* and *Concurrent LBP and NSP*, an initial cohort analysis was performed. This was done using generalised estimation equations (GEE) which take into account the correlation within twin pairs. The analyses were adjusted for sex and age. Also, physical activity and duration of exposure to physical workload were considered as potential confounders. However, adjusting for physical activity did not change the odds ratios. Duration of exposure (years) in the occupation was strongly correlated with age (r=0.75) and was therefore not included in the analysis. Further, including duration of exposure in the analyses did not change the odds ratios.

To be able to investigate potential confounding from genetic and shared environmental factors co-twin control analyses were performed choosing twin pairs discordant for LBP and/or NSP. The design resembles a matched case-control design, where one twin (case) has the disorder of interest and the co-twin (control) has not. The analyses are made separately for DZ and MZ twins. Due to potential sex differences with regard to both exposure to physical workload and prevalence of LBP and/or NSP, only MZ twins and same-sex DZ twins were used in the co-twin control analyses.

By studying the changes in odds ratios from the cohort and co-twin control analyses, it can be concluded about the importance of common genes and environment shared by the twins early in life for the association studied. For example, a decrease in the association between the cohort and co-twin control analyses, but where the OR's for DZ and MZ twins remain similar, indicates the importance of shared environmental effects. Also, since DZ twins share approximately 50 % and MZ twins share 100 % of their segregating genes, a graduate decline between the associations for DZ and for MZ twins compared to the cohort analyses indicates a genetic influence for the association between exposure and outcome (i.e. $OR_{cohort} > OR_{DZ} > OR_{MZ}$).

Further, in paper III, probandwise concordance rates and tetrachoric correlations (see section 4.6.2) were used to explore the similarities within twin pairs with regard to exposure to *High physical workload.*

4.6.4 Paper IV

In paper IV, the aim was to examine potential associations between work posture and NSP, within an occupational group where the exposure to work in an elevated arm position varies. The subjects were classified into four exposure groups; *Neutral arm position, <2 h per work day*, *Neutral arm position, >3 h per work day*, *Elevated arm position, <2 h per work day*, and *Elevated arm position, >3 h per work day*.

The associations were examined using logistic regression analysis, where the group *Neutral arm position, <2 h per work day* was used as a reference group.

The outcome measure was defined as having NSP to a degree where the subject had answered "quite a bit of pain, but it is possible to play".

Seven potential confounders were considered; sex, age, type of orchestra, weekly playing activities outside work , work content , influence, and social support at work. None of the potential confounders were found to be significant in the univariate analyses and were not included in the initial crude model in the logistic regression analysis. Nonetheless, since the sex distribution differed between the exposure groups and since age is often considered as a confounder for NSP, another model, adjusted for age and sex, was also analysed. However, these adjustments only rendered minor changes in the odds ratios.

4.7 SUMMARY OF STATISTICAL METHODS

The statistical methods and statistical software used in papers I-IV in this thesis are presented in table 8.

Table 8. Statistical methods and software used in the thesis. For further details, see paper I-IV.

Method	*Software*	*Paper I*	*Paper II*	*Paper III*	*Paper IV*
Logistic regression	SPSS[a)]	X			X
Probandwise concordance rate	SAS[b)]		X	X	
Tetrachoric correlation	SAS[b)]		X	X	
Structural equation modelling	MX[c)]		X		
Generalised estimation equations	SAS[b)]			X	
Co-twin control analysis	SAS[b)]			X	

a) SPSS Inc (2006). SPSS version 13.0 and 15.0 for Windows. Chicago, IL.
b) SAS Institute Inc (2003). SAS Version 9.1 for Windows. Cary, NC.
c) Neale, M. C., S. M. Boker, et al. (2004). MX: statistical modeling. 6th ed., Virginia Commonwealth University Department of Psychiatry.

4.8 ETHICAL APPROVAL

The studies in paper I was approved by the ethics committee of Karolinska Institutet (DNr 93-255, DNr 03-139). The study in paper II and III were approved by the regional ethical vetting board in Stockholm (DNr 2006/870-31/1). The study in paper IV was approved by the ethics committee of Karolinska Institutet (DNr 99-351).

5 RESULTS

5.1 SICKNESS ABSENCE

In paper I, the total prevalence of sickness absence (sickness absence including disability pension at least 14 consecutive days between baseline and follow-up) was 49% (95% CI 46-52). Among those with sickness absence, 33% (95% CI 29-38) had been long-term sickness absent (>180 days during at least one 1-year period between baseline and follow-up).

Both for the prevalence of sickness absence, and the prevalence of long-term sickness absence, the group that consistently reported *Concurrent LBP and NSP* had a higher prevalence compared to the subjects that consistently reported pain in just one area of the spine (*Solely LBP* or *Solely NSP*) (Table 9).

Table 9. Prevalence of sickness absence. Prevalence of sickness absence in paper I (5-year prevalence) and in paper II (1-year prevalence) with 95% confidence intervals (95% CI), stratified by disorder group.

	Solely LBP *% (95% CI)*	***Solely NSP*** *% (95% CI)*	***Concurrent LBP and NSP*** *% (95% CI)*	***Migrating LBP and/or NSP*** *% (95% CI)*
Paper I[a] *(The MUSIC-Norrtälje study)*	42 (33-50)	41 (32-51)	59 (53-65)	46 (40-51)
Paper II[b] *(The STAGE study)*	22 (21-24)	21 (20-23)	31 (29-33)	-

a) Sickness absence including disability pension at least 14 consecutive days between baseline and follow-up (5 years). Census data.
b) Sickness absence at least seven consecutive days during the previous twelve months. Self-reported data.

In the adjusted logistic regression analyses, the OR for sickness absence in the group with *Concurrent LBP and NSP* was 1.69 (95% CI 1.14-2.51) compared to the reference group *Solely LBP or Solely NSP*. For long-term sickness the corresponding OR for the group with *Concurrent LBP and NSP* was 2.48 (95% CI 1.32-4.66) (Table 10).

Table 10. Odds ratios for sickness absence. Adjusted Odds Ratios (OR) with 95% confidence intervals (95% CI) for sickness absence and long-term sickness absence in three disorder groups. The total number of subjects in each group (Subjects), and the number of subjects with sickness absence and long-term sickness absence are also presented. The merged group *Solely LBP or Solely NSP* was used as reference category.

	Solely LBP or NSP	***Concurrent LBP and NSP***	***Migrating LBP and/or NSP***
Subjects (n)	214	271	332
Sickness absence (n)	89	159	152
OR[a] ***(95% CI)***	-	1.69 (1.14-2.51)	1.00 (0.69-1.46)
Long-term sickness absence (n)	19	68	46
OR[b] ***(95% CI)***	-	2.48 (1.32-4.66)	1.62 (0.84-3.13)

a) Adjusted for female sex, age, and other non-musculoskeletal related disorders.
b) Adjusted for age, and other non-musculoskeletal related disorders.

The result that the group with *Concurrent LBP and NSP* had a higher prevalence of sickness absence (including disability pension) is supported by results in paper II where the prevalence of sickness absence (at least seven consecutive days during the previous twelve months) was higher in the group with *Concurrent LBP and NSP* (31%) compared to the group with *Solely LBP* (22%) or the group with *Solely NSP* (21%) (Table 9).

5.2 HERITABILITY

In paper II, the influence of genetic factors for the occurrence of *Solely LBP*, *Solely NSP*, and *Concurrent LBP and NSP* were investigated, and the first step towards estimating heritability of LBP and NSP was to investigate the similarities within twin pairs with regard to *Solely LBP*, *Solely NSP*, and *Concurrent LBP and NSP*. This was done using probandwise concordance rates and tetrachoric correlations which indicated the presence of a genetic component predominantly for the occurrence of *Concurrent LBP and NSP*, where the tetrachoric correlation was 0.57 (95% CI 0.48-0.66) for MZ twins compared to 0.24 (95% CI 0.14-0.34) for DZ twins. Also for *Solely LBP* the tetrachoric correlation was more than twice as large for MZ twins, 0.33 (95% CI 0.22-0.43) compared to DZ twins 0.08 (95% CI -0.02-0.18). Similarly, for *Solely NSP* the tetrachoric correlation for MZ twins was 0.24 (95% CI 0.15-0.33) compared to DZ twins 0.10 (95% CI 0.02-0.17) (Table 11).

Table 11. Probandwise concordance rate and tetrachoric correlation with 95% confidence intervals (95% CI) for *Solely LBP*, *Solely NSP*, and *Concurrent LBP and NSP*. Stratified by zygosity (MZ, DZ).

		Discordant pairs	*Concordant pairs*	*Probandwise concordance rate (95% CI)*	*Tetrachoric correlation (95% CI)*
Solely LBP	***MZ***	326	58	0.26 (0.22-0.31)	0.33 (0.22-0.43)
	DZ	511	52	0.17 (0.14-0.20)	0.08 (-0.02-0.18)
Solely NSP	***MZ***	513	102	0.28 (0.25-0.32)	0.24 (0.15-0.33)
	DZ	778	123	0.24 (0.21-0.27)	0.10 (0.02-0.17)
Concurrent	***MZ***	212	64	0.38 (0.32-0.43)	0.57 (0.48-0.66)
LBP and NSP	***DZ***	433	63	0.23 (0.19-0.26)	0.24 (0.14-0.34)

In the next step, when estimating the heritability of LBP and NSP with structural equation modelling the AE model was found to be most suitable indicating no influence of shared environmental factors (C). In this model 60% (95% CI 51-68) of the total variance for *Concurrent LBP and NSP* was explained by additive genetic effects (A) and 40% (95% CI 32-49) by non-shared environmental effects (E). The additive genetic variance component was twice as large for *Concurrent LBP and NSP* compared to *Solely LBP* (30%, 95% CI 20-39) and more than twice as large as for *Solely NSP* (24%, 95% CI 16-31) (Figure 7).

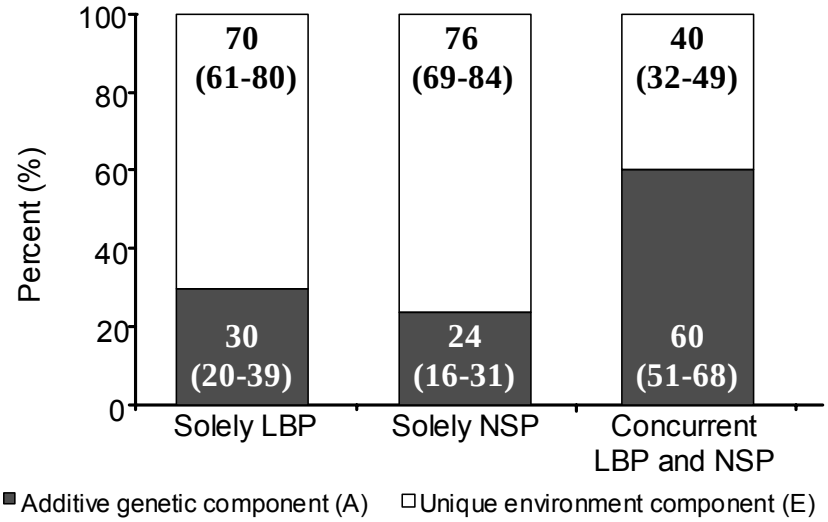


Figure 7. Heritability of LBP and NSP. The partition of the total variance (%) into an additive genetic component (A), and a non-shared environmental component (E) with 95% confidence intervals (95% CI) for *Solely LBP, Solely NSP,* and *Concurrent LBP and NSP*.

Further in paper III, familial aggregation of exposure to *High physical workload* was assessed using probandwise concordance rates and tetrachoric correlations. The results showed that for exposure to *High physical workload,* the probandwise concordance rates and tetrachoric correlations were consistently higher for MZ twins compared to DZ twins. The same pattern was seen for both men and women (Table 12).

Table 12. Probandwise concordance rate and tetrachoric correlation with 95% confidence intervals (95% CI) for exposure to *High physical workload*. Stratified by sex, and zygosity (MZ, same-sex DZ, opposite-sex DZ).

		Discordant pairs	*Concordant pairs*	*Probandwise concordance rate (95% CI)*	*Tetrachoric correlation (95% CI)*
Men	***MZ***	172	226	0.72 (0.69-0.76)	0.72 (0.65-0.80)
	Same-sex DZ	165	151	0.65 (0.60-0.69)	0.53 (0.42-0.64)
Women	***MZ***	283	269	0.66 (0.62-0.69)	0.65 (0.59-0.82)
	Same-sex DZ	291	182	0.56 (0.52-0.59)	0.40 (0.30-0.50)
	Opposite-sex DZ	505	294	0.54 (0.51-0.57)	0.31 (0.23-0.39)

5.3 PHYSICAL WORKLOAD

The results in paper III showed that the distribution of exposure to physical workload did not differ across zygosity, however a higher proportion of men (48%, 95% CI 47-49) than of women (43%, 95% CI 42-44) was exposed to *High physical workload*.
For both women and men, the over-all prevalence of *LBP and/or NSP* was lower in the group with exposure to *Low physical workload*, and higher within the group with exposure to *High physical workload* (Table 13).

Table 13. Physical workload and LBP and NSP. Over-all prevalence of *LBP and/or NSP* as well as prevalence of *Solely LBP*, *Solely NSP*, and *Concurrent LBP and NSP* with 95% confidence intervals (95% CI). Stratified by sex and exposure to physical workload (Low physical workload and High physical workload).

		LBP and/or NSP *% (95% CI)*	***Solely LBP*** *% (95% CI)*	***Solely NSP*** *% (95% CI)*	***Concurrent LBP and NSP*** *% (95% CI)*
Women	***Low physical workload***	41 (40-43)	9 (9-10)	20 (19-21)	12 (11-13)
	High physical workload	47 (46-49)	11 (10-12)	20 (19-22)	16 (15-17)
Men	***Low physical workload***	27 (25-28)	11 (10-12)	11 (10-12)	5 (5-6)
	High physical workload	37 (35-39)	13 (12-14)	14 (13-15)	10 (9-11)

The initial cohort analysis was performed using the group with any one symptom (*LBP and/or NSP*). The results showed an association between *High physical workload* and *LBP and/or NSP*, OR 1.47 (95% CI 1.37-1.57). In the following co-twin control analyses on this group the corresponding associations were OR 1.34 (95% CI 1.02-1.75) for DZ twins and 1.44 (95% CI 1.06-1.95) for MZ twins. The findings that the odds ratio did not decrease in co-twin control analyses compared to the cohort analysis indicated that the association was not confounded by genetic and/or shared environmental factors (Figure 8).
In the cohort analyses, the association between *High physical workload* and the subgroup with *Concurrent LBP and NSP* was stronger (OR 1.80; 95% confidence interval 1.62-1.99) than for those with *Solely LBP* (OR 1.41; 95% CI 1.27-1.57) or *Solely NSP* (OR 1.31; 95% CI 1.20-1.43) (Figure 8).

Concurrent LBP and NSP was the only disorder group that showed a stepwise decrease of the point estimates from the initial cohort analysis, and then further between DZ and MZ twins, where the corresponding associations were OR 1.71 (95% CI 1.00-2.94) for DZ twins, and OR 1.29 (95% CI 0.64-2.59) for MZ twins. This might suggest that there is genetic confounding in the association between *High physical workload* and the occurrence of *Concurrent LBP and NSP*. However, the 95% confidence intervals were wide and overlapping between the zygosity groups (Figure 8).

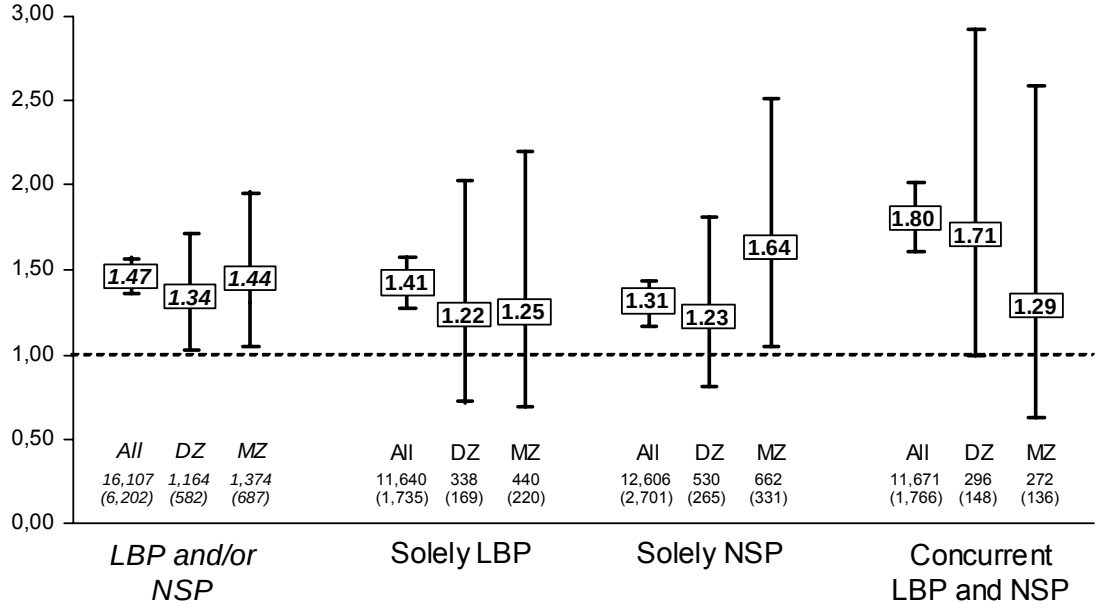


Figure 8. Cohort and co-twin control analyses. Odds ratios (OR) with 95% confidence intervals (95% CI) for the association between *High physical workload* and the group with any one symptom (LBP and/or NSP) as well as OR with 95% CI for the three disorder subgroups *Solely LBP, Solely NSP,* and *Concurrent LBP*. Results from the cohort (All) and co-twin control analyses respectively (DZ, MZ). Total number of subjects and (cases) included in each analysis are also presented.

Thus, in paper III, the results showed associations between high physical workload and *LBP and/or NSP*. However, the exposure assessment did not take into consideration exposure differences within an occupation. The associations found were also moderate in strength. However, paper IV explored differences in the association between high physical workload and NSP within an occupation.

In paper IV, the over-all prevalence of NSP in the study group of musicians was 26%. In the group *Neutral arm position, <2 h per work day* the prevalence of neck/shoulder pain was 9%. This can be compared to 19% in the group *Neutral arm position, >3 h per work day*, 30% in the group *Elevated arm position, <2 h per work day*, and 35% in the group *Elevated arm position, >3 h per work day* (Figure 9).

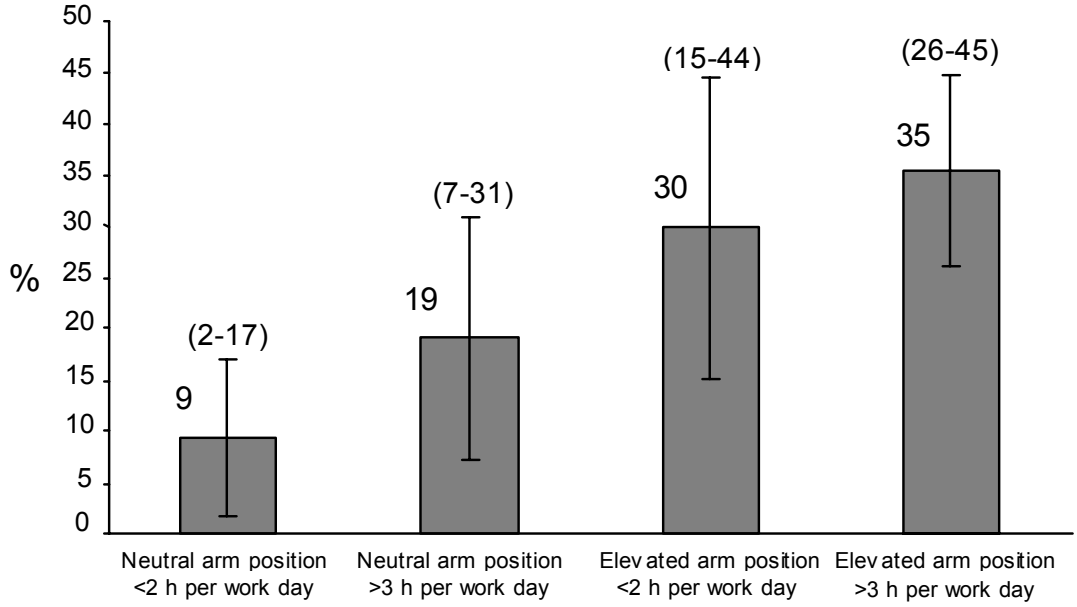


Figure 9. Prevalence of NSP among Swedish orchestra musicians with 95% confidence intervals (95% CI) stratified by exposure group.

When analysing the association between exposure to physical workload and NSP, the groups *Elevated arm position, <2 h per work day* [OR 4.15 (1.30–13.22)], and *Elevated arm position, >3 h per work day* [OR 5.35 (1.96–14.62)] had a higher odds ratio compared to the group *Neutral arm position, <2 h per work day*. The analysis was also done adjusting for age and sex. However, these adjustments only rendered minor changes in the odds ratios (Table 14).

Table 14. Odds ratios for NSP. Odds Ratios (OR) with 95% confidence intervals (95% CI) for NSP in the different exposure groups. The total number of subjects (Total), and number of subjects with NSP in each group is also presented.

	Subjects		***Crude Model***	***Adjusted model*** [b]
	Total (n)	***NSP (n)***	***OR (95% CI)***	***OR (95% CI)***
Neutral arm position <2 h per work day [a]	54	5	-	-
Neutral arm position >3 h per work day	42	8	2.31 (0.70-7.66)	2.20 (0.66-7.34)
Elevated arm position <2 h per work day	37	11	4.15 (1.30-13.22)	4.35 (1.35-14.03)
Elevated arm position >3 h per work day	102	36	5.35 (1.96-14.62)	5.02 (1.79-14.09)

a) The group *Neutral arm position <2 h per work day* was used as reference category.
b) Adjusted for age and sex.

5.4 CONCURRENT LOW BACK AND NECK-SHOULDER PAIN

The results in paper I and paper II showed that subjects with *Concurrent LBP and NSP* had a higher prevalence of sickness absence compared to those with *Solely LBP* or *Solely NSP*. Further, paper II showed that genetic factors seemed to be of greater importance for the occurrence of *Concurrent LBP and NSP* compared to for *Solely LBP* or *Solely NSP*. Genetic and shared environmental factors also influenced the association between high physical workload and *Concurrent LBP and NSP*, which was not seen for the associations between *High physical workload* and *Solely LBP* or for *Solely NSP* (paper III).

In addition, both in papers I and II, there was a tendency that the prevalence of other illnesses (i.e. other illnesses not directly related to musculoskeletal pain) was higher for the group with *Concurrent LBP and NSP* compared to for the groups with *Solely LBP* or *Solely NSP* (Table 15).

Table 15. Prevalence of other illnesses with 95% confidence intervals (95% CI) in papers I and II. Stratified by disorder group.

	Solely LBP % (95% CI)	*Solely NSP % (95% CI)*	*Concurrent LBP and NSP % (95% CI)*	*Migrating LBP/NSP % (95% CI)*
Paper I [a] ***(The MUSIC-Norrtälje study)***	13 (6-19)	30 (20-39)	36 (30-42)	28 (23-33)
Paper II [b] ***(The STAGE study)***	16 (14-17)	19 (18-20)	26 (24-28)	-

a) Including physical illnesses and diminished psychological wellbeing.
b) Including physical illnesses.

Further, in paper II, subjects were asked to rate their health on a rating scale ranging from 0 to 100 where 0 meant worst imaginable health state and 100 meant best imaginable health state. Also for this variable the results showed that subjects with *Concurrent LBP and NSP* reported their self-rated health to be worse (73, 95% CI 72-75) compared to those with *Solely LBP* (82, 95% CI 80-83) or *Solely NSP* (80, 95% CI 79-81).

5.5 ADDITIONAL ANALYSES

5.5.1 The definition of low back and neck-shoulder pain

In the MUSIC-Norrtälje data material, the proportion of subjects with *Solely LBP*, S*olely NSP*, and *Concurrent LBP and NSP* differed very little between the baseline study and the follow-up study (Table 16).

Table 16. The six-month's prevalence of *Solely LBP*, S*olely NSP*, and *Concurrent LBP and NSP* with 95% confidence intervals (95% CI) in the MUSIC-Norrtälje baseline study and the MUSIC-Norrtälje follow-up study, shown separately for women and men.

		Solely LBP *% (95% CI)*	***Solely NSP*** *% (95% CI)*	***Concurrent LBP and NSP*** *% (95% CI)*
Women	***The MUSIC-Norrtälje baseline study***	19 (17-19)	17 (15-19)	29 (27-31)
	The MUSIC-Norrtälje follow-up study	14 (12-16)	18 (16-20)	30 (27-32)
Men	***The MUSIC-Norrtälje baseline study***	23 (21-26)	11 (9-13)	23 (21-26)
	The MUSIC-Norrtälje follow-up study	18 (16-21)	10 (8-12)	22 (20-25)

However, although the proportions remained approximately the same for the study group as a whole, the analyses showed that only 32% of the subjects with *Solely LBP* at baseline, and 34% of the subjects with *Solely NSP* at baseline answered consistently at follow-up. For the group *Concurrent LBP and NSP*, the corresponding number was 56%. About two thirds (68%) of the subjects that were pain free at baseline, remained pain free also at follow-up (Figure 10).

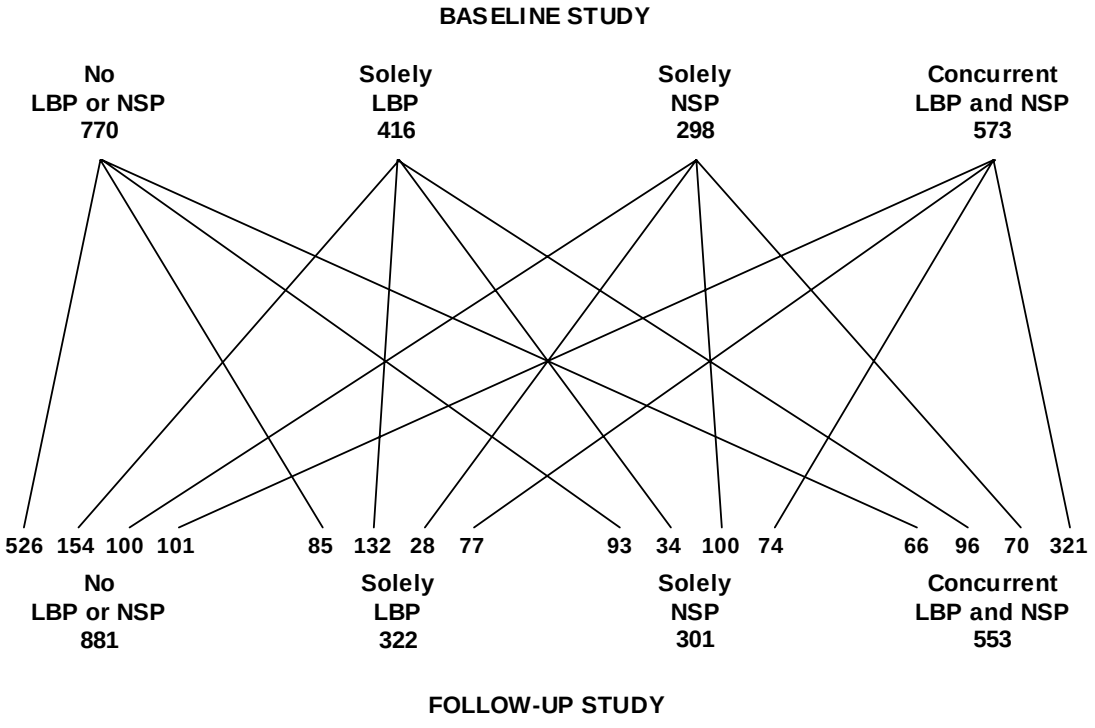


Figure 10. Number of subjects with *No LBP or NSP, Solely LBP*, S*olely NSP*, and *Concurrent LBP and NSP* in the MUSIC-Norrtälje baseline and follow-up studies. Further, the migration of subjects between disorder groups is presented as lines and number of subjects.

5.5.2 Sickness absence – alternate definition of the disorder groups

Paper I used the MUSIC-Norrtälje data material to explore the prevalence of sickness absence (and long-term sickness absence) between baseline and follow-up for subjects that consistently reported *Solely LBP, Solely NSP,* and *Concurrent LBP and NSP* at the two occasions. Another approach could be to investigate the prevalence of sickness absence during the same period, but defining the disorder groups based solely on disorder status at the baseline study.

The results from these analyses showed that the odds ratio for sickness absence was higher for *Concurrent LBP and NSP* (OR 1.36, 95% CI 1.07-1.75) compared to for *Solely LBP or Solely NSP*. For long-term sickness absence the corresponding odds ratio was not statistically significant (OR 1.28, 95% CI 0.86-1.90). Thus, the associations for both sickness absence and long-term sickness absence were weaker compared to the original definition (Section 5.1).

5.5.3 The definition of physical workload

In the present thesis, several different data materials were used. This made it possible to validate the exposure classification system applied on the STAGE-study data material for the analyses in paper III by using the MUSIC-Norrtälje data material.

The exposure classification system used in paper III was developed using occupational codes (NYK) and questionnaire questions from the Swedish Annual Level-of-Living Surveys concerning different work-related physical exposures [129, 130].
The MUSIC-Norrtälje data material also contained occupational codes (NYK) which made it possible to apply the exposure classification system used in paper III on this data material. The MUSIC-Norrtälje data material also comprised data concerning work-related physical exposures, in terms of both biomechanical exposures and energy expenditure [51, 52]. A comparison could then be made as to what extent the prevalence of different physical exposures in the MUSIC-Norrtälje questionnaires and interviews corresponded to the four exposure groups created according to the exposure classification system; *Low, Low-medium, High-medium* and *High physical workload*.

Data concerning the biomechanical exposures and energy expenditure were collected through interviews and questionnaires, and has previously been found to be sufficiently reliable [84, 149-151]. Three different biomechanical exposures were considered; (1) *Manual handling (≥50 Newton, ≥60 min/workday)*, (2) *Working with hands above shoulder level (≥30 min/workday)*, and (3) *Working with vibrating tools (≥60 min/workday)*.
Exposure to high energy expenditure was based on a structured, task-oriented interview concerning biomechanical load factors. Each subject was asked to specify the various work tasks performed during a typical working day and the time spent on each task [151]. After the interview, the energy expenditure for each task was quantified in terms of multiples of the resting metabolic rate (MET). Furthermore, a time-weighted average of the energy expenditure (TWA-MET) was calculated for this typical working day. The cut-off for exposure to *High energy expenditure* was set at ≥3.0 TWA-MET for women, ≥3.5 TWA-MET for men. This cut-off was chosen to represent 30-35% of the maximal aerobic capacity of 45-year-old Swedish women and men in average physical condition [51, 77].

The results from these analyses showed that the prevalence of being exposed to ≥1 of the following biomechanical exposures; *Manual handling*, *Working with hands above shoulder level*, and *Working with vibrating tools* as well as the prevalence of exposure to *High energy expenditure,* showed an increase from *Low physical workload* to *High physical workload*. This pattern was clearer for men compared to for women (Figure 11).

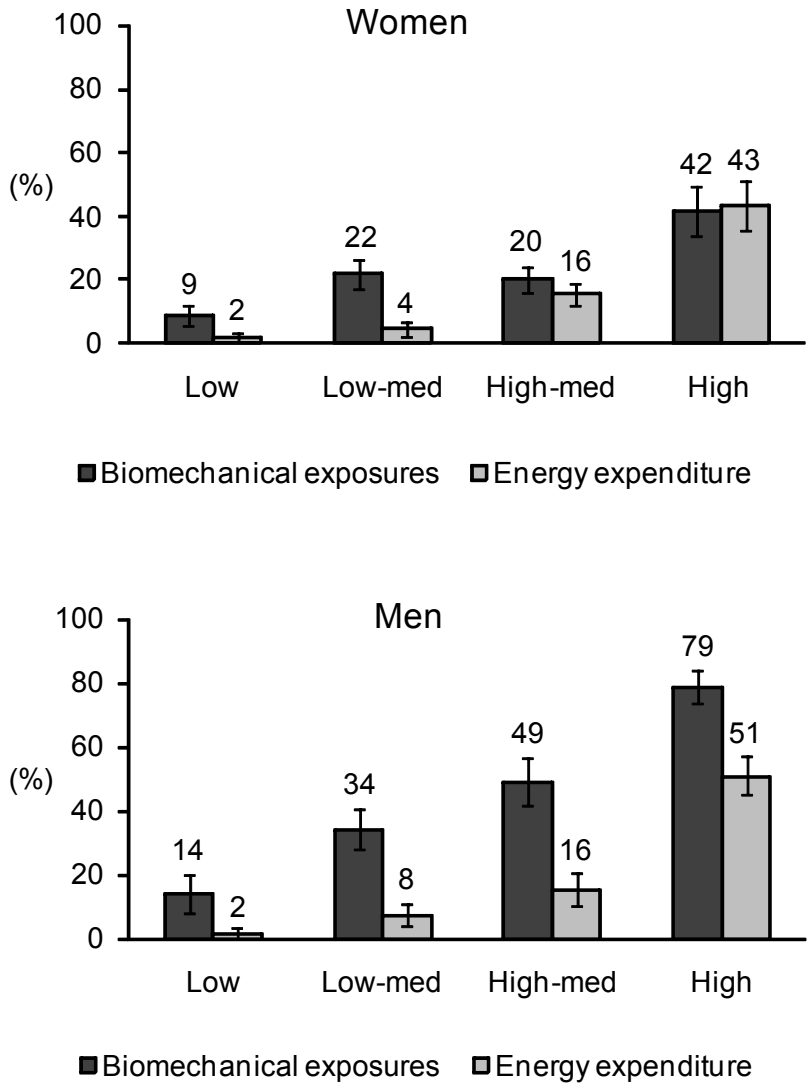


Figure 11. Prevalence of biomechanical exposures and high energy expenditure. Prevalence of exposure to one or more than one of the biomechanical exposures; *Manual handling*, *Working with hands above shoulder level*, and *Working with vibrating tools*. Also, prevalence of exposure to *High energy expenditure* with 95% CI in the MUSIC-Norrtälje study. Stratified according to the classification of physical workload based on occupational codes.

6 DISCUSSION

6.1 SICKNESS ABSENCE

The results in both paper I and paper II showed that a substantial proportion of subjects with LBP and/or NSP were sickness absent, and that there were differences in the prevalence of sickness absence depending on whether an individual was suffering from *Solely LBP, Solely NSP*¸ or *Concurrent LBP and NSP*.

In paper II, sickness absence was used to describe the characteristics of the disorder groups. The results showed that the prevalence of self-reported sickness absence (at least seven consecutive days during the previous twelve months) was higher in the group with *Concurrent LBP and NSP* (31%) compared to the group with *Solely LBP* (22%) or the group with *Solely NSP* (21%).

In paper I, sickness absence was the main outcome and also in this study subjects with *Concurrent LBP and NSP* had the highest prevalence of both sickness absence (>14 consecutive days at least once between baseline and follow up) and also of long-term sickness absence (>180 days during at least one of the five one-year periods between baseline and follow up). No differences in any of the two sickness absence measures were found between subjects with *Solely LBP* and subjects with *Solely NSP*. This may suggest that the number of body regions affected, rather than the localisation of the complaint, (low back region or neck-shoulder region) has the greater influence on sickness absence. However, the mixed group *Migrating LBP/NSP* partly consisted of subjects that at least at one of the two occasions suffered from *Concurrent LBP and NSP*. Still, this group did not show significantly higher sickness absence compared to the group with *Solely LBP* or *Solely NSP*, neither in prevalence of sickness absence nor in long-term sickness absence. This might indicate that using at least two measuring points in time gives a higher precision when identifying subjects with these types of musculoskeletal disorders.

Within this thesis, an additional analysis on the MUSIC-Norrtälje material was performed to investigate if the findings in paper I were seen also when using only one measuring point for identifying the disorder groups. The results from this analysis showed that when defining the disorder groups based solely on disorder status at the baseline study, the prevalence of sickness absence was still higher for subjects with *Concurrent LBP and NSP*, compared to for subjects with *Solely LBP* or *Solely NSP*. However, the differences between the disorder groups decreased. This strengthens the suggestion that the use of repeated measures is essential when looking at long-term consequences of musculoskeletal disorders.

The higher prevalence of sickness absence among subjects with *Concurrent LBP and NSP* is supported by a previous study by Nordin et al. (2002) who found that workers with LBP and concurrent musculoskeletal complaints from another anatomical region (including pain in more than one area of the spine) were more likely to remain sick listed than subjects with *Solely LBP* [109]. On the other hand, IJzelenberg et al. (2004) did not find that *Concurrent LBP and NSP* increased the risk of sickness absence [73]. This

discrepancy in results in comparison with paper I could be explained by the fact that IJzelenberg et al. (2004) used self-reported sickness absence data and in paper I official register data was used [125, 141]. Another explanation could be the use of two measuring points, as was used in paper I. Further, the study was performed in the Netherlands and it might be that the differences could be due to national differences in the insurance systems.

In several studies it has been found that having poor general health or a medical or psychological complaints in addition to having LBP or NSP, increased the risk of sickness absence [46, 47, 109, 124, 140]. Hence, in paper I having other non-musculoskeletal related disorders (including diminished psychological wellbeing) was adjusted for. Still, after adjustments, having *Concurrent LBP and NSP* was associated with a higher prevalence of sickness absence.

Further, it is plausible that work-related exposures might influence the prevalence of sickness absence. This was not adjusted for in paper I or in the additional analyses, due to problems with sample size. However, in future studies on prevalence of sickness absence, physical workload should be taken into consideration.

6.1.1 Sickness absence as an outcome variable

Sickness absence research can be considered a very diverse field. The theoretical framework and explanatory models vary, since research is conducted within a large number of scientific disciplines [3]. There are several difficulties when trying to compare studies on sickness absence, since not only the study designs but also outcome measures, terminology, and insurance systems (among nations as well as over time) differ widely [65].

An example of differences in outcome measures was seen within this thesis when comparing the estimates for sickness absence in paper I and paper II. Paper I used census data for sickness absence and included sickness benefit and disability pension in the definition, and paper II used self-reported sickness absence. Another difference between the two papers was that paper I covered sickness absence during a period of five years, while paper II estimated sickness absence the previous 12 months.
However, the comparison of these two estimates did not aim at comparing the absolute prevalence of sickness absence, but looking at the differences in sickness absence between disorder groups within each study.

In paper I, official register data was used as outcome measurement which makes it possible not only to get accurate figures concerning length and frequency of sickness absence, and hereby eliminating any recall bias, but also to summarise all sickness related governmentally compensated sickness absence including rehabilitation and disability pension. This is a strength in paper I. However, the official register data from the National Social Insurance Board in Sweden did not allow analyses of short term sickness absence (less than 14 consecutive days).
Moreover, the official register data used in paper I did not contain the official reason for the sickness absence, i.e. the diagnosis on the sickness certificate (issued by a physician) which the Insurance Office needs for making their decision about disbursing

sickness benefit. However, this certificate usually contains only one diagnosis/reason for sickness absence, and the objective in paper I was to compare general sickness absence behaviour between subjects with pain in more than one area of the spine, *Concurrent LBP and NSP*, and subjects with *Solely LBP* or *Solely NSP*. It would not have been possible to use a single diagnosis/reason for sickness absence in the analyses in paper I.

6.1.2 Clinical and research significance

The findings concerning sickness absence in the present thesis confirmed the results from previous studies that sickness absence is a common consequence of LBP and NSP.

The results further suggested that subjects with *Concurrent LBP and NSP* constitute a group where both sickness absence and long-term sickness absence is more frequent.

Both in a clinical view as well as when research is performed, the findings concerning the group *Concurrent LBP and NSP* stresses the importance of taking into account any pain from other areas of the spine in the prevention of sickness absence.

6.2 HERITABILITY

The results in paper II showed that the genetic influence was twice as large for *Concurrent LBP and NSP* (60%) than for *Solely LBP* (30%) and *Solely NSP* (24%).

Comparing the heritability estimates in paper II with estimates found in other twin studies on LBP is not unproblematic, since earlier studies have not taken into consideration the possible co-morbidity of LBP and NSP. That is, the heritability estimates for LBP are based on study samples where part of the subjects with LBP could have concurrent NSP.
However, it can be argued that a study sample containing both subjects with *Solely LBP* and subjects with *Concurrent LBP and NSP* would render heritability estimates with the size of the genetic component somewhere in between the estimates for *Solely LBP* (30%) and for *Concurrent LBP and NSP* (60%) found in paper II. Following this line of reasoning, the findings in paper II are in line with a study by Hestbaek et al. (2004) which found the size of the genetic component for lifetime LBP to be 44% for men and 40% for women (age 16-41), a study by Battié et al. (2007) which found the size of the genetic component for LBP to be 30-46% (age 35-70), and MacGregor et al. (2004) which found the size of the genetic component for lifetime LBP to be 52-68% (age 45-79) [14, 67, 94].

The reasoning above could also apply for NSP. When comparing the estimates in paper II (with a genetic component for *Solely NSP* of 24%) to results in earlier studies, MacGregor et al. (2004) found the size of the genetic component for lifetime NSP to be 35-48% (age 45-79), and Fejer et al. (2006) found the size of the genetic component for lifetime NSP to be 44% (age 20-71) [44, 94].

In paper II, it was possible to exclude subjects with Rheumatoid Arthritis, Systemic Lupus Erythematosus, or Pelvic Spondylitis. However, there could still be subjects included suffering from undiagnosed rheumatic disorders, or other systemic disorders of high heritability which affects the musculoskeletal system.

Consequently, for *Concurrent LBP and NSP* it might be feasible to do a comparison of the size of the genetic component with other disorders affecting several parts of the musculoskeletal system. Earlier studies have estimated the size of the genetic component to be 53-65% for rheumatoid arthritis, and 48-54% for chronic widespread pain [80, 93]. These estimates are similar to the estimates for *Concurrent LBP and NSP* in paper II.

In paper II the heritability estimates for *Solely LBP, Solely NSP,* and *Concurrent LBP and NSP* were based on self-reported data concerning pain-intensity and pain-related disability and the size of the genetic components were in line with previous studies.
The only more specific spinal diagnosis where heritability estimations have been made is concerning intervertebral disc degeneration. Two studies have estimated the genetic influence on low back disc degeneration (LDD) and cervical disc degeneration (CDD) [91, 121]. Sambrook et al. (1999) found overall heritability estimates of 63-74% for LDD and 63-73% for CDD. Given the above findings suggesting a genetic influence both for the occurrence of LBP and LDD, Battié et al. (2007) recently investigating whether genetic influences on LBP are mediated through genetic influences on disc degeneration. The findings in that study suggested that less than one quarter of the genetic effects for LBP could be explained by a common pathway with genetic effects for disc degeneration [14]. This indicates that other tissues besides the disc may be the origin of pain in the low back region. However, as many as 85% of patients with LBP and NSP lack a specific pathoanatomical diagnosis and self-perceived symptoms are often the only basis for a diagnosis [37, 95]. For future research concerning the heritability of spinal disorders there is a continuous need for improved diagnostics and more precise definitions for use in epidemiological studies.

Some earlier studies have found that the heritability estimates for LBP and NSP varied with age. However, the age span in paper II was relatively narrow (21-47 years), and did not include those age spans that in earlier studies have been found to display notably different patterns of the heritability estimates [44, 61, 62, 67]. However, the findings in paper II should be seen in this light, and further studies are needed to explore the variability of heritability estimates over the life course.

In paper II, the prevalence of *Solely NSP* and *Concurrent LBP and NSP* was significantly larger for women than for men. However, the sex-limitation analyses concluded that the same genes were present in women and men and that there were no differences regarding the size of the additive genetic effects. This finding is supported by one earlier study that found no evidence of sex-specific genetic effects for unspecific neck pain [43]. However, no corresponding study concerning LBP has been found.

The effects of shared environmental factors (C) were negligible in paper II. This is in line with Hestbaek et al. (2004) who found that the importance of shared environmental factors for the occurrence of LBP decreased with age [67]. The only study that has found

substantial influence of shared environmental factors for LBP is El-Metwally et al. (2008), who among 11-year old twins found shared environmental effects of 41% [40]. This might suggest that the influence of factors such as influence of parental pain-related behaviour, physical activity, and nutrition, which are often shared by twins during childhood, is of less importance for the occurrence of LBP and NSP later in life. However, findings of no or very little influence of shared environmental effects are common in twin studies and could be due to problems with statistical power [72].

Another possible explanation could be departures from the equal environment assumption which assumes that the effects of the shared environment are independent of zygosity [118]. If, for example, MZ twins are treated more similar by their parents during childhood compared to DZ twins, this would lead to an increase of the additive genetic component and a decrease of the shared environmental component. However, the possible trait-specific shared environmentally mediated factors associated with LBP and NSP, such as parental behavioural influence, physical activity, and nutrition during childhood, are not likely to be dependent of zygosity. Hence, the equal environment assumption seems to be applicable in paper II.

To be able to extrapolate the findings in twin studies to the general population, it has to be assumed that the prevalence of LBP and NSP among twins do not differ from non-twins. For the Swedish twin cohort this generalisation has been found to be valid for a variety of common disorders in several previous studies where the cohort has been shown to be representative for a Swedish population.[87] Further, in paper II, the six-month's prevalence of LBP (21%) and NSP (26%) (without taking concurrent complaints into consideration) were similar to what has been found in earlier studies on the general population [27, 42, 50].
Another assumption in twin studies is that mating occurs randomly. If mating instead occurs based on similarities in a trait (assortative mating), it may lead to an overestimation of the shared environmental effect [41]. No research has been performed concerning random mating and LBP and NSP, but since no shared environmental influence was found in paper II, there is no reason to suspect that a possible presence of assortative mating have influenced the results.

In the analyses in paper II, no consideration was taken to potential interaction of genetic and environmental effects (i.e. gene-environment interaction) [118]. This kind of interaction may occur if the effects of the environment are conditional on an individual's genotype, such as when some genotypes are more sensitive to the environment than others. However, in general, gene-environment interaction accounts for less than 20% of the variance of a trait in the population [113]. Still, it might be possible that this type of interaction could explain some of the differences between the heritability estimates for *Concurrent LBP and NSP* and the heritability estimates for *Solely LBP* or *Solely NSP*. For example, a presence of a gene - non-shared environment interaction would result in an overestimation of the effects of the non-shared environment, while a presence of a gene-shared environment interaction would lead to an overestimation of the genetic and shared environment effects [41]. This is something which needs to be further investigated. However, one condition for exploring potential gene-environment interaction is that the specific environmental factors are explicitly measured.

In paper III, the probandwise concordance rates and the tetrachoric correlations showed that genetic and shared environmental factors may be of importance for the exposure to *High physical workload*. Further, in the co-twin control analyses in paper III, genetic and shared environmental factors were also found to work as a confounder in the association between *High physical workload* and *Concurrent LBP and NSP*. Given these findings, one specific environmental factor which might be of interest for gene-environment interaction analyses in heritability estimations of *Concurrent LBP and NSP* is the exposure to *High physical workload*.

It also remains to be investigated if there are different genes which influence the liability to *Concurrent LBP and NSP*, *Solely LBP*, and *Solely NSP*, or if it is the same gene(s) that in association with factors not investigated in paper II, (e.g. physiological or structural differences in the spine, pain-reporting behaviour, or general pain related factors) explain the differences in the heritability estimates between these disorder groups.

6.2.1 Clinical and research significance

In a clinical view, possible etiological differences for *Concurrent LBP and NSP* compared to for *Solely LBP* and *Solely NSP* may influence the choice of treatment and the prognosis of these disorders.

Further, when research on heritability of LBP and NSP is performed, the findings indicated that it is important to take into consideration any concurrent pain from other areas of the spine.

6.3 PHYSICAL WORKLOAD

Different aspects of physical workload and their associations with pain in the low back and/or neck-shoulder regions were investigated in papers III and IV. Although using different exposure assessment methods and different definitions of LBP and/or NSP, both paper III and paper IV found positive associations between work-related physical workload and LBP and/or NSP (paper III) and NSP (paper IV).

6.3.1 High physical workload, low back and/or neck-shoulder pain

In paper III, the results indicated a significant association between *High physical workload* and the occurrence of pain in the low back *and/or* neck shoulder region. This association was still present even after adjusting for genetic and shared environmental factors. The findings are in line with Hartvigsen et al. (2003), who after adjusting for genetic factors found a graded association for increasing workload and LBP [60]. Further, two earlier studies focusing on the genetic influence for intervertebral disc degeneration also found some evidence for an independent association between physical workload and intervertebral disc degeneration [12, 146].

Concurrent LBP and NSP was the only disorder subgroup that exhibited a stepwise decrease in odds ratio from the initial cohort analysis and the co-twin control analyses

between DZ and MZ twins, indicating that the association between high physical workload and *Concurrent LBP and NSP* was confounded by both shared environmental and genetic factors. However, in the co-twin control analyses of *Concurrent LBP and NSP*, the 95% confidence intervals were wide and overlapping and no statistically significant differences between the analysis of DZ twins and the analysis of MZ twins were found. This can be explained by problems with statistical power, since the numbers of discordant twin pairs (concerning LBP and/or NSP) in the study were few.

Earlier research has found sex-differences in the associations between work-related risk factors and musculoskeletal complaint [35, 69]. In paper III, the size of the study sample did not allow for analysing women and men separately, and hence nothing can be concluded about possible sex-differences in the association between high physical workload and *Solely LBP, Solely NSP,* and *Concurrent LBP and NSP*. However, the descriptive analyses displayed sex-differences in the prevalence of *Solely LBP, Solely NSP,* and *Concurrent LBP and NSP*. Further, even though the exposure classification was done separately for women and men, there were sex-differences in the distribution of exposure to physical workload, with a smaller proportion of women in the group with *High physical workload*. These findings are in line with previous studies [70]. Further studies are needed to explore possible sex-differences in the association between high physical workload and NSP and LBP.

6.3.2 Work posture and neck-shoulder pain

The results in paper IV showed an association between exposure to a work posture with an elevated arm position and NSP. This association was seen both for the group with longer duration and the group with short duration of active playing time during a work day. This is in line with findings in a previous study concerning musicians by Hagberg et al. (2005), who found that violinists and violists (instrumentalists that work with elevated arms) had twice the incidence of neck pain and pain in the right shoulder compared to pianists (that work in a more neutral position) [55]. However, the association between working with elevated arms and NSP is also supported by some earlier research on other populations [31, 126]. Further, for the subjects working in a neutral arm position the results showed a tendency that subjects with >3 h per work day had a higher prevalence of neck-shoulder pain (19%), than those with <2 h per work day (9%). Although these point estimates differed noticeably, the odds ratios did not differ (p= 0,172). This could be an effect of the relatively small number of subjects in the exposure groups, and calls for further research with larger study groups. However, since playing an instrument is associated with high precision demands and often a repetitiveness of arm and/or finger movements, the tendency that a longer duration of active playing time was associated with NSP is in line with previous research that has found an association between repetitiveness and precision work and NSP [31].

The study design in paper IV makes it difficult to compare the results to those in earlier studies on musculoskeletal problems among musicians. Firstly, in earlier studies it is more common to group instrumentalist according to the "instrument families" (strings, brass, and wood wind) and the authors have not found any previous studies where the subjects were grouped according to work posture as in paper IV. Secondly, according to the only published review article concerning musculoskeletal pain among musicians

that the authors have found, very few studies have singled out neck-shoulder complaints [159].

The findings in paper IV indicated that age did not have an influence on the associations between the exposure and NSP, although such differences were found in an earlier study by Cassou et al. (2002) [28]. This discrepancy might be explained by the "healthy worker effect", that subjects with more severe NSP have already left the occupation (early retirement, long term sick leave, change of occupation) or were on sick leave at the time of the data collection [85]. Another explanation can also be that, according to the drop-out analysis, the non-responders were mostly subjects with longer time of employment (>19 years), hence being older [89]. These two factors might have led to an underestimation of the estimates for NSP in paper IV.

Sex did not have an influence on the associations in paper IV. This is inconsistent with earlier findings that have found gender differences in the work-relatedness of NSP, also in occupations where women and men perform the same work tasks [69, 70]. This is something which needs to be further investigated.

6.3.3 Exposure assessments – methodological issues

In epidemiological studies on the work-relatedness of different disorders, one of the methodological problems is the diversity and lack of precision in the exposure assessment methods, something which can explain the contradictory findings in different studies [90]. Often, the exposures are self-reported, and several studies have found the precision in self-reported exposures to be low [23, 86, 139, 147, 148].

A strength in paper III is that the exposure to *High physical workload* was assessed based on a classification system which had been developed using another data material where consideration had been taken to eight different physical strain dimensions, among others heavy lifting, repetitive work, and awkward work postures [161]. This classification system was developed based on self-reported data on work-related exposures which could lead to differential misclassification, as subjects with LBP and NSP tend to overestimate the exposure to physical strains, which in turn may result in overestimations of the association between exposure and outcome [20]. However, the influence of any potential differential misclassification should be minor since the exposure classification system was developed using a different data material, and subjects in paper III only reported their occupation (and not the exposure to physical workload).

Moreover, in the additional analyses within this thesis, it was possible to validate the exposure classification system by comparing it to self-reported data on work-related exposures using the MUSIC-Norrtälje data material. The results from these analyses showed that both the prevalence of biomechanical exposures, as well as the prevalence of exposure to high energy expenditure showed a graded increase over the four different exposure categories, from; low, low-medium, high-medium to high physical workload. Still, using an exposure classification system based on occupation codes also has limitations. Firstly, it has to be assumed that the level of exposures to physical workload in an occupation is stable over time. Secondly, exposure differences between

individuals within an occupation are not taken into account. However, there is no reason to assume that this exposure misclassification would differ between the exposure groups; low, low-medium, high-medium, and high physical workload.

The issue of exposure differences within an occupational group was addressed in paper IV, where the exposure assessment was based on differences in exposure to work with elevated arm(s) among orchestra musicians.

A strength in the exposure assessment in paper IV was that it was based on external assessment and not on self-reported data, minimising the risk of differential misclassification due to present pain in the neck-shoulder region (see above). The exposure assessment was made using two dimensions; degree of arm elevation and duration of static work during a workday. Arm elevation was assessed through photographs of the playing position for the different instruments, and was aggregated to group level. This assessment did not externally quantify and take into consideration the personal work style of each subject, and the results should be interpreted on a group level only. However, the variations in the shape and size between different samples of a certain instrument are small, leaving few opportunities to hold the instrument in different ways. Hence, this approach in assessing the work posture could be considered to give a higher precision in the assessment, compared to self-reported data.

The assumptions made for the assessment of duration of static work (average active playing time for an orchestra during a work day and percentage of bars played by each instrument) was chosen after consulting several orchestra musicians freelancing in the different orchestras in Sweden. However, these measures did only take into account exposure during performance and rehearsals. The duration of static work during the subjects' individual preparation time (practice time) was not taken into consideration, but it is reasonable to assume that subjects that have more music to play during rehearsals and performances need more preparation time, than those with less music to play. Besides practice time, subjects might also have other regular playing activities such as teaching or chamber music, but in paper IV "weekly playing activities outside work" was not found to be a confounder.

Neither in paper III nor in paper IV, was the long-term duration of exposure (in years) included in the analyses. In paper III, the mean exposure duration was slightly longer for men with exposure to *High physical workload* (12 years), compared to those with exposure to *low physical workload* (10 years) which hypothetically could lead to an overestimation of the association between *High physical workload* and LBP and/or NSP. However, duration of exposure (years) in the occupation was strongly correlated with age (r=0.75) and when including duration of exposure in the analyses the odds ratios did not change. In paper IV, it is plausible to assume a strong correlation between age and exposure duration, since the major part of professional musicians start practising their instruments early in childhood.
Still, the lack of precision in the exposure assessment and/or in the outcome measurements can lead to non-differential misclassification, diluting the association [1, 20]. To quantify and assess the between-worker variation in personal work style as well as the within-worker variation of exposure over time calls for studies with direct

technical field measurements during whole work days. Further studies with a prospective design and more precise exposure assessment methods are needed.

6.3.4 Clinical and research significance

The results concerning the association between *High physical workload* and LBP and/or NSP emphasises the continuous need for preventive workplace interventions in occupations with high physical workload.

For the association with *High physical workload*, subjects with *Concurrent LBP and NSP* seemed to differ in some respects from those with *Solely LBP* or *Solely NSP*. An early onset of counselling about choice of occupation or ergonomic interventions might be of great importance for these individuals.

Further *Concurrent LBP and NSP* is an important factor to consider for occupational health providers when instigating workplace interventions, since an ergonomic intervention aimed at reducing complaints from one body region could have a deficient impact on another body region.

In prevention of NSP for musicians in an orchestral setting it is difficult, to a larger extent, to alter the work posture for different instrumentalists. Instead, interventions should be pointed towards organizational changes in work schedules such as length of rehearsals, breaks during the work day, and time for recovery.

Using an exposure classification system based on occupational codes in research aiming at exploring associations between *High physical workload* and LBP and/or NSP may be as valid as using self-reported data on exposure to high energy expenditure or a combination of exposure to different biomechanical exposures.

6.4 THE DEFINITION OF LOW BACK AND NECK-SHOULDER PAIN

In all the papers included in this thesis, the definitions of LBP and NSP were based on self-reported data, concerning both pain-intensity and pain-related disability. The use of both pain-intensity and pain-related disability for the definition of these non-specific disorders has been emphasised in several other studies [38, 104].

In paper I, II, and III the same definition and the same cut-off limits were used. The cut-off limits were based on the distribution in the cohort of all 2,329 subjects (cases and referents) who participated in both the baseline study and the 5-year follow-up study in the MUSIC-Norrtälje study. The MUSIC-Norrtälje study was designed as a case-referent study, but in the analyses in this thesis the data material has been treated as a cohort. It can be argued that the cohort in the MUSIC-Norrtälje study comprised a concentration of subjects with LBP and/or NSP, since one of the original aims of the study was to investigate care-seeking due to LBP and NSP. However, in both the baseline study and the follow-up study, about one third of the subjects (cases and referents) had a pain score of ≥3 and/or a pain-related disability score of ≥1. These distributions correspond to the 1-year prevalence of LBP and NSP in several earlier studies [45, 96]. The authors also considered that these levels of pain and pain-related

disability had a clinical relevance, and since paper I and paper III were aimed at studying sickness absence and work-related exposures, the chosen cut-off score was at a level where it was still possible for the subjects to be able to work.

In paper I, the definition of LBP and/or NSP was based on assessments at two occasions (both baseline and follow-up), and to be considered to have *Solely LBP, Solely NSP,* or *Concurrent LBP and NSP* a subject had to have given the same response at the two occasions. In the additional analyses in this thesis, the results showed that although the prevalence of LBP and NSP was similar in the MUSIC-Norrtälje baseline and follow-up studies, only 32% of the subjects with *Solely LBP*, 34% of the subjects with *Solely NSP*, and 56% of the subjects with *Concurrent LBP and NSP* at baseline answered consistently at follow-up.

6.4.1 Clinical and research significance

Since LBP and NSP often are considered to be recurrent disorders, the use of two measuring points may increase the precision of the definition and could lead to more homogenous groups when planning treatment and studying the determinants of these non-specific disorders.

6.5 CONCURRENT LOW BACK AND NECK-SHOULDER PAIN

Results from papers I-III all indicated that subjects with *Concurrent LBP and NSP* constitutes a group which differ from those with *Solely LBP* or *Solely NSP* with regard to several factors. Paper II showed that genetic factors seemed to be of greater importance for the occurrence of *Concurrent LBP and NSP* compared to for *Solely LBP* or *Solely NSP*, with heritability estimates as large as 60%. Further, paper III found that genetic and shared environmental factors also influenced the association between high physical workload and *Concurrent LBP and NSP*, something which was not seen for the associations between *High physical workload* and *Solely LBP* or for *Solely NSP*. No earlier studies have been found that have addressed influences of genetic factors on the association between *High physical workload* and *Concurrent LBP and NSP*.

In addition, results from papers I and II, showed that subjects with *Concurrent LBP and NSP* reported their self-rated health to be worse, were more often sickness absent and reported more often other non-musculoskeletal disorders compared to those with *Solely LBP* or *Solely NSP*. Similar results have been reported in an earlier study by Strine et al. (2007) [131].

These findings in this thesis might suggest that having *Concurrent LBP and NSP* reflects a musculoskeletal pain syndrome with somewhat different underlying causes than for *Solely LBP* and *Solely NSP*. It remains to be investigated if there are different genes which influence the liability to *Concurrent LBP and NSP, Solely LBP,* and *Solely NSP,* or if it is the same gene(s) that in association with other factors (e.g. physiological or structural differences in the spine, pain-reporting behaviour, or general pain related factors) explain the differences in the heritability estimates between these disorder groups.

It might be that there are genetic factors which are specific for the group with pain in more than one area of the spine, with a possible underlying increased general vulnerability that also make them more susceptible to other illnesses. However, it cannot be ruled out that subjects with *Concurrent LBP and NSP* may represent a group with a low threshold for perceiving or reporting pain, something which have been raised as a potential source of bias in earlier studies [81].

6.5.1 Clinical and research significance

Regardless of the aetiological question marks, subjects with pain in more than one area of the spine seem to constitute a group where it is especially important to take early signs of pain/discomfort seriously. Counselling about choice of occupation or ergonomic interventions might be of great importance for these individuals. It may also be that the rehabilitation process needs to be different for this group, since consequences such as prevalence of sickness absence and long-term sickness absence were much more common for these individuals.

7 CONCLUSIONS

- Genetic factors were associated with the occurrence of *Solely LBP, Solely NSP* and *Concurrent LBP and NSP*. The genetic influence was twice as large for *Concurrent LBP and NSP* than for *Solely LBP* and *Solely NSP*.

- Subjects with *Concurrent LBP and NSP* had a higher prevalence of sickness absence as well as long-term sickness absence. They also reported lower self-rated health and had a higher prevalence of other non-musculoskeletal disorders (including diminished psychological wellbeing compared to those with *Solely LBP* or *Solely NSP*.

- Only for *Concurrent LBP and NSP* did genetic and shared environmental factors have an influence on the association with *High physical workload*.

- *High physical workload* was associated with LBP and/or NSP even after adjusting for genetic and shared environmental factors.

- An association between working in an elevated arm position and NSP was found when investigating an occupational group where the exposure to other physical workload factors was similar within the group.

7.1 FUTURE RESEARCH

In future studies concerning determinants for LBP and/or NSP the use of at least two measuring points for defining LBP and NSP should be applied. Further, it is important to take into consideration any concurrent complaints for other areas of the spine.

Future research concerning the heritability of LBP and NSP should include studies concerning the interaction between genes and the environment in relation to the occurrence of LBP and NSP, and continue the search for identification of specific gene(s) associated with LBP and NSP.

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