From INSTITUTE OF ENVIRONMENTAL MEDICINE
Karolinska Institutet, Stockholm, Sweden

MARKERS OF STRESS AS PREDICTORS OF WELLBEING AND WORKABILITY

Katarina Aili

Karolinska Institutet

Stockholm 2015

Published by Karolinska Institutet.
Printed by E-print AB

ISBN 978-91-7676-111-3

MARKERS OF STRESS AS PREDICTORS OF WELLBEING AND WORKABILITY
THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

Katarina Aili

Principal Supervisor:
Associate Professor Lena Hillert
Karolinska Institutet
Institute of Environmental Medicine
Unit of Occupational Medicine

Co-supervisor(s):
Professor Magnus Svartengren
Uppsala University
Department of Medical Sciences
Occupational Environmental Medicine

PhD Teresia Nyman
KTH Royal Institute of Technology
STH School of Technology and Health

PhD Ulrich Stoetzer
Karolinska Institutet
Institute of Environmental Medicine
Unit of Intervention and Implementation Research

Opponent:
Professor Andreas Holtermann
National Research Centre for the Working Environment
Copenhagen, Denmark

Examination Board:
Professor Emeritus Ulf Lundberg
Stockholm University
Department of Psychology

Professor Birgitta Öberg
Linköping University
Department of Medical and Health Sciences
Division of Physiotherapy

Associate Professor Frida Eek
Lund University
Faculty of Medicine
Department of Health Sciences

To My Family

ABSTRACT

In order to prevent sickness absence and to maintain a safe and sound work climate, interventions may be needed in the workplace. Occupational Health Services (OHS) are special advisers, with the opportunity to suggest/perform interventions at individual and group level. The use of methods for evaluating changes in health is a precondition when assessing that such interventions are meaningful and successful. The aim of this thesis is to study markers of general stress as indicators of changes in the risk of negative health effects, which are feasible when evaluating interventions at group as well as at individual level. Sleep disorders are common in conjunction with stress, and are also associated with negative health effects. Sleep has been investigated in this thesis using: (1) a questionnaire assessing global sleep (during the last six months) (studies I and II); (2) self-reported sleep during one or several specific nights of interest (in a sleep diary) (studies III and IV); (3) objectively measured sleep with an actigraph (study IV). Heart rate variability during sleep is another potential marker, and is examined in study III. Study I and study II are five-year prospective studies investigating sleep as a predictor of: (I) sickness absence in three groups with different pain conditions, and (II) change in number of pain sites between baseline and follow-up. Study III is a cross-sectional twin study investigating self-reported stress during the day and changes in heart rate variability, heart rate and self-reported sleep quality the subsequent night. Further, study III investigated whether individual factors related to genes and/or familial environment had an effect on the associations between stress and heart rate variability/heart rate and stress and self-reported sleep quality. In study IV, repeated objective and subjective sleep measurements during seven consecutive nights were performed. The measurements took place in a workplace, i.e., under conditions translatable to an OHS setting. The number of consecutive measurements that are needed for a reliable sleep measure, and the correlation between subjective and objective sleep measures, are investigated in this study.

Sleep disturbances were found to be an indicator of increased risk of sickness absence during five-year follow-up within all the three pain groups that presumably represent three different levels of wellbeing at baseline (study I). Further, sleep was an indicator of change in number of self-reported pain sites between baseline and the five-year follow-up. Associations between perceived daytime stress and changes in heart rate variability, heart rate, and self-reported sleep quality the subsequent night were seen in study III. The results of study III further indicate that these associations are influenced by individual factors related to genes and/or the familial environment. In study IV, it was shown that subjective (sleep quality) and objective (sleep efficiency) measures correlate poorly on a day-by-day basis, which indicates that objective and subjective sleep may capture different dimensions of sleep. If only week nights are included in repeated sleep measurements, fewer measurements are needed to obtain a reliable measure of sleep as compared with when weekend nights are included. In all, measurements of sleep are easier to use than measurements of heart rate variability, which makes sleep a more realistic marker, especially when considering larger groups.

SAMMANFATTNING

För att förebygga sjukskrivning och främja ett säkert och hälsosamt arbetsklimat kan interventioner behöva göras på arbetsplatser. Företagshälsovården (FHV) har med sin specialistkompetens möjlighet att föreslå/driva interventioner av sådant slag. Att använda utvärderingsmetoder som mäter förändring av hälsoläget är en förutsättning för att värdera om sådana interventioner är meningsfulla och framgångsrika. Syftet men denna avhandling var att studera markörer för generell stress som indikatorer för förändring i risk för negativa hälsoeffekter, som kan vara användbara vid utvärdering av interventioner. Sömnbesvär är vanligt förekommande i samband med stress och även kopplat till negativa hälsoeffekter. Sömn har undersökts (1) med ett frågeformulär som mäter sömn globalt (under de senaste sex månaderna) (studie I och II); (2) självrapporterad sömn under specifika nätter (sömndagbok) (studie III och IV); (3) objektivt uppmätt sömn med aktigraf (sömnklocka) (studie IV). Hjärtfrekvensvariabilitet under sömn är en annan möjlig användbar objektiv stressmarkör, vilken undersökts i studie III. I studie I och II har självrapporterade sömnbesvär undersökts i longitudinella studier med 5-års uppföljning som indikatorer för risk för sjukskrivning (studie I) och förändring av antal självrapporterade smärtlokalisationer (studie II) bland individer grupperade efter smärttillstånd vid basmätningen. Studie III är en tvärsnittstudie som undersökt självrapporterad stress under dagen och skillnader i hjärtfrekvensvariabilitet och hjärtfrekvens (under sömn) och självrapporterad sömnkvalitet under nästföljande natt bland tvillingar. Vidare undersöktes i studie III om sambandet mellan upplevd stress och hjärtfrekvensvariabilitet/hjärtfrekvens och sambandet upplevd stress och sömnkvalitet påverkades av faktorer som är relaterade till gener och/eller gemensam uppväxtmiljö. Studie IV är en metodstudie där upprepade objektiva och subjektiva sömnmätningar under sju sammanhängande nätter, utförts. Mätningarna utfördes på en arbetsplats, dvs. under förhållanden som liknar de som är verklighet för en FHV. I studien undersöks hur många nätters mätning som krävs för ett reliabelt mått på sömn, hur mätningar påverkas av att inkludera helgnätter samt korrelationer mellan objektivt och subjektivt uppmätt sömn. Resultaten visade att sömnbesvär indikerade ökad risk för sjukskrivning under en femårsperiod inom alla tre smärtgrupperna som antogs representera tre olika nivåer av välmående vid basen (studie I). Sömn indikerade även sannolikheten att fem år efter basmätningen rapportera förändrat antal smärtlokalisationer. I studie III sågs ett samband mellan upplevd stress under dagen och skillnader i hjärtfrekvensvariabilitet, hjärtfrekvens och självrapporterad sömnkvalitet (sömndagbok) nästföljande natt. Resultaten från studie III indikerar vidare att effekten påverkas av individuella faktorer relaterade till gener och/eller uppväxtmiljö. I studie IV där upprepade sömnmätningar studerades korrelerade subjektivt (sömndagbok) och objektivt (sömnklocka) uppmätt sömn dåligt vilket i enighet med tidigare studier indikerar att objektiv och subjektiv sömn mäter olika dimensioner av sömnbesvär. Om enbart vardagar inkluderades i de upprepade mätningarna krävdes färre dagars mätning för att få ett reliabelt mått på sömn. Sömnmätningar är en enklare metod att använda och tolka än hjärtfrekvensvariabilitet vilket gör sömn till en mer realistisk markör att använda, framförallt på större grupper.

LIST OF PUBLICATIONS

This thesis is based on the following publications, referred to in the thesis by their Roman numerals. All published papers are reprinted with permission from the publishers.

I. Aili K, Nyman T, Hillert L, Svartengren M. Sleep disturbances predict future sickness absence among individuals with lower back or neck-shoulder pain: A 5-year prospective study. Scand J Public Health, 2015, 43: 315-323.

II. Aili K, Nyman T, Svartengren M, Hillert L. Sleep as a predictive factor for the onset and resolution of multi-site pain: A 5-year prospective study. Eur J Pain, 2015, 19: 341-349.

III. Aili K, Hillert L, Balliu N, Anderson M, Bogo R, Skjönsberg Å, Svartengren M. Genetic and early environmental factors influence markers of stress. *Submitted*

IV. Aili K, Åström-Paulsson S, Stoetzer U, Svartengren M, Hillert L. Reliability of objective and subjective sleep measurements in adults: the design of sleep assessments. *Submitted*

CONTENTS

LIST OF ABBREVIATIONS

ANS	Autonomic Nervous System
CI	Confidence Interval
CWP	Chronic Widespread pain
DZ	Dizygotic
HF	High Frequency
HR	Heart Rate
HRV	Heart Rate Variability
IBI	Inter Beat Intervals
LBP	Low Back Pain
LF	Low Frequency
MZ	Monozygotic
NSP	Neck Shoulder Pain
OHS	Occupational Health Services
OR	Odds Ratio
PNS	Parasympathetic Nervous System
RMSSD	Root Mean Squares of Successive Differences between adjacent normal-normal intervals
RSA	Respiratory Sinus Arrhythmia
SDNN	Standard Deviation of Normal-Normal intervals
SNS	Sympathetic Nervous System
VLF	Very Low Frequency

1 INTRODUCTION

In Sweden in 2012, 5% of women and 3% of men aged 20-64 reported their health to be bad or very bad. The proportion with sickness absence was in 2012 just above 2% [1]. The two most common causes of receiving sickness cash benefits in Sweden today (sickness absence of more than 14 consecutive days) are musculoskeletal pain and psychological ill-health, and together they represent approximately 60% of all individuals receiving sickness cash benefits[2].

In a survey investigating work-related disorders in the working population in Sweden in 2014, self-reported data on sickness absence and work-related disorders were assessed (i.e., all sickness absence, not only sickness absence of >14 consecutive days). Of the individuals who were absent from work due to sickness at the time of interview, 26% of women and 21% of men reported work-related disorders as a cause of (self-reported) sickness absence [3].

Stress is one of the most common work-related causes of complaints [3]. Diminished psychological wellbeing and musculoskeletal pain commonly co-occur, and decreased psychological health is associated with the prognosis of musculoskeletal pain [4, 5]. Moreover, work stress has been shown, inter alia, to be associated with elevated risk of incident coronary heart disease and stroke [6]. Including a measurement of stress when evaluating health in a workplace would be highly relevant.

One of the important tasks of Occupational Health Services (OHS) as special advisers is to prevent ill-health in the workplace, e.g., by different types of interventions to maintain a safe and sound work environment. OHS have the opportunity to suggest interventions for a favorable workplace, for an individual employee with special needs, and also for the entire staff to prevent overall illness or accidents in the workplace. For OHS to be successful in evaluating the overall condition of employees in a workplace, it would be beneficial to have markers that indicate changes in wellbeing and potentially increased risk of reduced workability.

The term “stress” as it is used today was coined by Hans Selye in 1936 who defined it as: “the non-specific response of the body to any demand for change”. Stress, or strain, is often described as the overload of different body systems after continuous response to stressors [7, 8]. The term is problematic since it may refer to different aspects of stress, such as stress as an exposure (stressful living), as the outcome/effect (strain as a body response to stress), or as an intermediate factor (e.g., as a factor related to vulnerability to stress) affecting the relationship between exposure and outcome. Further, exposures inducing stress can be of both a psychological (e.g., worry, anxiety) and a physical (e.g., injury, disease, or musculoskeletal pain) nature.

There are individual differences in how people respond to or tolerate different types of stress [7]. When including measures of stress as indicators of changes in health in a population, it would therefore be relevant to include a marker of general stress that indicates increased risk

of diminished wellbeing as a complement to subjective ratings of stress and ratings of the magnitude of the stress exposure.

Sleep disturbances are one such potential marker, indicating a non-beneficial stress response. Supressed sleep is a common consequence of increased activity in stress systems [9], and self-rated sleep disturbances and self-rated stress are closely related [10]. Further, sleep problems have been shown to be associated with sickness absence [11, 12] and pain [13-15]. Sleep is also appealing as a marker from the perspective of clinical feasibility since it can be measured rather easily, both subjectively (by administering a questionnaire) and objectively (e.g., by actigraph).

Another potentially objective marker, to be used as a complement to subjective ratings of stress, is heart rate variability (HRV). HRV is a widely used non-invasive objective method for measurement of the activation of autonomic nervous system in stress research. Further, HRV is associated with a range of health effects. Depressed HRV has been shown to predict mortality and arrhythmic complications after acute myocardial infarction, and is also an early sign of diabetic neuropathy [16]. Reduced vagal activity during sleep has also been seen among persons with fibromyalgia [17]. It has also been shown to predict self-reported sleep problems among individuals with chronic fatigue syndrome [18].

In this thesis, sleep disturbance and HRV are investigated as feasible potential markers of general stress, indicating change in wellbeing and risk of sickness absence.

2 BACKGROUND

2.1 SICKNESS ABSENCE AND WORK ABILITY

The number of individuals receiving sickness benefit has fluctuated over the years [2]. The statistics in figure 1 describe sickness benefit cash disbursed by Sweden's Social Insurance Agency. In Sweden, employees with sickness absence of more than 14 consecutive days receive their cash sickness benefit from the Insurance Agency. During years 1997 and 2003 however, there were temporary changes in the legislation, and the employer was made responsible for disbursing sick pay for the first 28 and 21 days, respectively. In 2008 new stricter rules regarding disability pension were introduced.

Musculoskeletal disorders and psychological illnesses jointly represent approximately 60% of registered diagnoses for sickness benefit, and are by far the two most common groups of diagnoses. In recent years, the proportion of cases of sickness absence due to diagnoses related to psychological illness has increased. In 2005, musculoskeletal disorders represented 29.3%, and psychological illness 28.9% of all diagnoses. In 2014, musculoskeletal disorders represented 21.5%, and psychological illnesses 39.5% of registered diagnoses, as a cause of sickness benefit. Among women, psychological illnesses were the most prevalent cause of sickness absence as early as in 2005, and in 2011 they became the most common cause among men [2] (fig. 2).

There has also been an increase in the prevalence of sleeping problems. In Sweden, it doubled from 1980 to 2012. The prevalence in 2012 was 32% among women and 21% among men [1].

Many individuals with a musculoskeletal diagnosis also have a psychological diagnosis. It is therefore not clear whether it is an actual increase in psychological ill-health that is seen in the statistics, or whether it is the culture among physicians, who choose which diagnosis to put as the cause of sickness absence, that has changed.

The most commonly occurring self-reported reasons for complaints in the Swedish working population in 2014 were back pain, sleep disturbances and distress/anxiety/depression. Stress was the most common work-related cause of complaints in Sweden in 2014, followed by strenuous working postures [3].

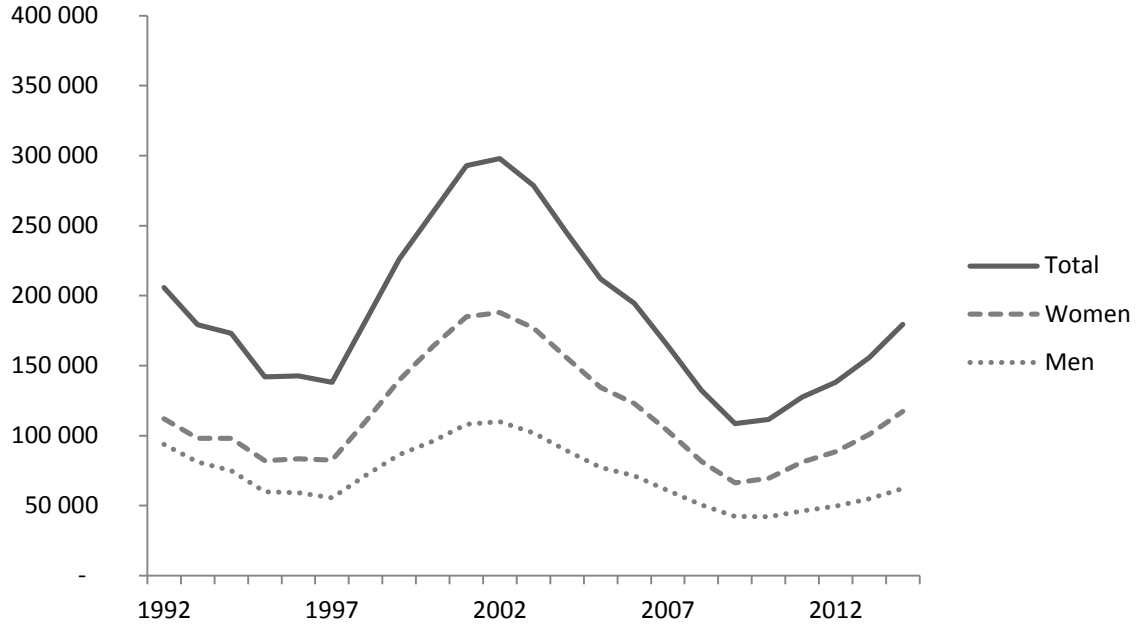


Figure 1. *Number of ongoing cases of receipt of sickness cash benefit in Sweden in December in years 1992 to 2014. Stratified by gender. Source: The Swedish Social Insurance Agency* [2].

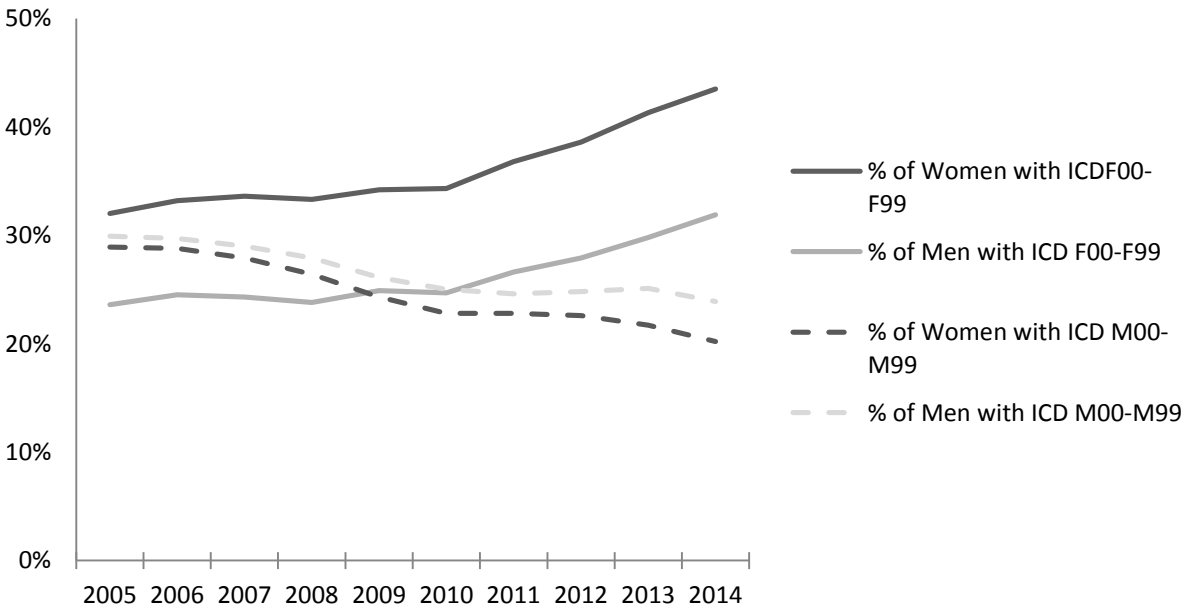


Figure 2. *Percentages of ongoing cases (percentages of men and women) of cash sickness benefit in Sweden in December (years 2005 to 2014), diagnosed with ICD codes F00-F99 (Mental and behavioural disorders) and M00-M99 (Diseases of musculoskeletal system and connective tissue). Stratified by gender and diagnose. Source: The Swedish Social Insurance Agency* [2].

2.2 STRESS

The phenomenon of stress can be described as an overload of bodily systems after repeated exposure to stressors that puts strain on the systems maintaining homeostasis. Prolonged exposure to stress has been shown to be associated with several mental and physical conditions, including cardiovascular events [19]. A recent review concluded that work stressors, such as job strain and long working hours, are associated with moderately elevated risks of incident coronary heart disease and stroke [6].

The acute activation of physiological systems during stress is a natural reaction, and prepares the body to respond adequately to the stressor. Allostasis is a term that describes the ability of physiological (stress) systems to increase or decrease vital organ functions to attain a new steady state. This is achieved mainly by activation of the autonomic nervous system (ANS) and the hypothalamic-pituitary-adrenal (HPA) axis. Allostatic load describes the strain on the body produced by repeated ups and downs in physiological responses [7, 20, 21].

The ANS is a key stress regulatory system that has effects on peripheral organs via centres in the central nervous system. The periphery systems of the ANS constitute the sympathetic nervous system (SNS) and the parasympathetic nervous system (PNS). The SNS and PNS constantly interact, which enables dynamic modification of bodily states as responses to changes in the environment. Increased activity in the SNS increases cardiac output and facilitates motor activity, whereas activity in the PNS promotes recovery processes, lowers blood pressure and heart rate, and increases gut movements [22].

Stress refers to an exposure (external or internal stress stimuli), an outcome (the strain on bodily stress systems), and the intermediates influencing the relationship between the stressful exposure and the strain on the body (e.g., individual vulnerability).

There are individual differences in how we respond to or handle stress. These differences have been generally explained by: 1) individual differences in perceptions or interpretations of the situation potentially causing stress, and 2) the condition of the body itself [7]. Resilience is a term that is used to describe reduced vulnerability to risk exposure when experiencing a relatively good outcome, despite stressful or adverse experiences [23, 24].

One aspect of importance when discussing stress responses associated with negative health effects may be how individuals respond differentially to the prolonged activity of stress systems, e.g., with disturbed sleep. Bonnet and Arand [25] identified individuals responding with sleep disturbances by comparing baseline sleep with sleep across different stressful situations, including caffeine intake, first-night sleep in a laboratory, and having their sleep time advanced by three or six hours. The group of individuals responding to the stressful situation with poor sleep also showed increased sympathetic activity [25].

Sleep reactivity to stress has been shown to be 43% heritable among men and 29% among women [26], which entails that heritability factors may be one explanatory mechanism behind individual differences in vulnerability to insomnia. Further, FIRST scores (sleep reactivity)

and insomnia have been shown to share genetic influences, which implies that sleep reactivity may mark a genetic vulnerability to developing insomnia [26].

2.2.1 Markers of general stress with potential negative health effects

Most research measuring physiological stress response objectively has focused on acute effects during stress [27]. Even though the evidence for health effects as a consequence of prolonged activation of physiological stress systems is still modest [27], it is likely that markers indicating sustained activation of stress systems are of importance when estimating the long-term effects of stress.

When looking for markers of general stress with potential negative health effects, it is important that the investigatory method employed captures changes in the effects of everyday life stressors. It is of further importance that the markers are feasible in the field.

Sustained physiological effect after stress is discussed in a review by Brosschot, which investigated markers of chronic stress [27]. In the review, perseverative cognition, describing rumination on the past and worry about the future, is presented as a potential mediator of the prolonged effect of stressors on physiology and development of disease [27]. Further perceived stress or worry when going to bed has been shown to be associated with subsequent polysomnography-measured sleep disturbances [28].

Another review, by Pieper and Brosschot [29], contains a discussion of the reactivity model. The model suggests that individuals responding to stress with increased cardiovascular reactivity have an increased risk of developing cardiovascular disease. In this review, it is suggested that the duration, rather than the magnitude, of the stress response may be important when estimating the risk of cardiovascular disease [29]. Markers of stress showing a prolonged physiological stress response during sleep may be important indicators of stress with potential negative health effects.

Sleep and recovery have been shown to be important for many body functions, including immunological defence and health maintenance [30]. Further, sleep disturbances have been shown, inter alia, to predict mortality [31], acute myocardial infarction [32], and sickness absence [11, 12, 33-45]. The onset of impaired sleep has also been shown to predict adverse changes in health-related behaviours, such as weight control, smoking, use of alcohol, and physical inactivity [46]. Moreover, sleeping problems have been shown to mediate the association seen between organizational justice and employee ill-health [47], which implies that sleep disturbances may be an important factor in the relationship between work-related stress and ill-health.

A recent study by Åkerstedt and colleagues [48] found that higher work demands predicted disturbed sleep two years later. Further, sleep disturbances at baseline predicted subsequent higher work demands, perceived stress, less social support, and lower degree of control two years later [48]. Also, de Lange and colleagues [49] investigated the effect of the (rather well-established) work stress indicator, from the demand/control/support model [50], and found that

a change from a low strain job to a high strain job over a period of three years was associated with increased sleep problems at follow-up [49]. All this suggests that sleep may be a feasible marker of stress, indicating an increased risk of negative health effects. Sleep has the further advantage of being relatively easy to measure in the field, both subjectively and objectively (e.g., with an actigraph).

Primary insomnia has been shown to be associated with physiological arousal, including higher activation of the SNS and an elevated heart rate during sleep [51], and it has been argued that reactivity is a key individual factor in vulnerability to insomnia [52]. When studying sleep in individuals *free* from insomnia but with high scores on sleep reactivity tests (FIRST[1]) after stress, those with high ratings on stress reactivity had significantly lower sleep quality and physiological hyperarousal [53]. In line with other studies, this indicates that there are individual differences in vulnerability to transient insomnia, and that vulnerability is associated with physiological hyperarousal [25, 51, 53, 54]. Further, vulnerability to insomnia (high sleep reactivity) has been shown to be associated with an elevated risk of developing persistent insomnia among good sleepers [54].

Including an objective marker of stress with potential negative health effects would be valuable as a complement to subjective ratings when evaluating interventions. In addition to sleep, one potential marker may be heart rate variability (HRV), which is a non-invasive measure of activity in the autonomic nervous system (ANS). Several types of stress have been shown to be associated with sustained cardiovascular effects (by altered HR, HRV or blood pressure) during sleep [29].

It has been suggested that imbalance in the ANS is a link in the pathway between psychological ill-health and somatic disease [55], and that altered HRV is one possible explanatory mechanism behind the increased risks of mortality and medical morbidity associated with depression among patients with coronary heart disease [56].

In experimental settings, acute effects on night time HRV have been seen among individuals manipulated into stressful tasks during the day (compared with controls) [57], and also among children playing violent video games [58].

In studies where stress exposure is not induced experimentally, altered night time HRV has been shown to be associated with, for example, daily worry [59], fibromyalgia [17] chronic fatigue syndrome [18], and prolonged daytime sleepiness (lasting >3 months) among irregular shift workers [60].

Both sleep and HRV during sleep have the potential of being a feasible marker of physiological stress response of a longer duration. Moreover, both markers are associated with ill-health, which made them interesting to investigate further in this thesis.

[1] FIRST: the Ford Insomnia Response to Stress Test, which measures perceived vulnerability to symptoms of situational insomnia after stressful situations.

2.2.2 Sleep measurements

Sleep can be measured objectively or subjectively. The most commonly used methods for objective measurements are polysomnography and actigraphy. Polysomnography is a comprehensive method, with which brain activity (EEG), muscle activity (EMG), eye movement (OEG), heart rhythm (ECG) and respiratory air flow may be assessed. Actigraphy is a simpler form of sleep measurement, which registers the gross motor activity from which estimates of sleep-wake patterns can be made. The advantage of actigraphy is that it is easy to use (an actigraph is designed as a wrist watch, and attached as such), and reasonably easy to access data from. Commonly used parameters measured by actigraphy are sleep duration, sleep latency (time from going to bed to falling asleep), wake after sleep onset (awakenings during the night), and sleep efficiency (percentage of sleep period with actual sleep). Actigraphy has shown good validity when validated against polysomnography. In laboratory studies, epoch-by-epoch sleep estimates have been shown to have correlations of at least 0.85 in normal individuals [61]. The main source of criticism in validity studies has been its ability to detect wake if the subject is lying very still, resulting in underestimations of sleep latency and wake after sleep onset [62].

There are several questionnaires available for assessing sleep subjectively. In sleep questionnaires, items related to different dimensions of sleep, including sleep latency, awakenings during nights and self-rated sleep quality, are assessed with reference to how sleep usually has been during a certain period of time. Another commonly used form of questionnaire is a sleep diary, assessing sleep on a daily basis, where the items refer to the preceding night.

Studies investigating the correlation between subjective and objectively measured sleep have had inconsistent results [63-71], and a substantial portion of non-laboratory studies show rather low agreement overall [64, 67-69, 71, 72]. In a review of studies of breast cancer survivors, it was found that sleep onset latency was typically overestimated, and that sleep quality was typically underestimated, by subjective sleep measures as compared with objective measures [73]. The overall low agreement implies that the subjective and objective measures capture different dimensions of sleep [72, 74]. It has been found that going to bed late, use of medications, being in employment, higher body mass index (BMI), increased daylight hours, and longer menstrual cycles are associated with poorer objective (actigraphic) sleep, and that unemployment and perceived stress are associated with poorer subjective sleep quality [75]. Another study, using Actiheart to assess objective sleep, found that subjective sleep efficiency was associated with over-commitment, low level of social support and poorer self-rated health, whereas objective sleep measures were not [74]. This study, however, used objectively recorded sleep data from one week night and one leisure night only, and a subjective measure referring to sleep problems over the last month [74]. The intra-individual day-by-day variance in objective sleep parameters has been found to be large [76]. The limited body of research investigating how many nights of measurement are needed for a reliable sleep measure to be obtained suggest that at least five nights are required when performing measurements on children and adolescents [77], at least three nights for a reliable measure of

sleep efficiency among women [75], and at least five nights for sleep duration in an adult population including males and females [76].

2.2.3 Heart rate variability

Heart rate variability (HRV) can be used as a "probe" to reflect responses to stress in central regulatory systems. The rhythm of the heart is modulated by innervation from both the SNS, associated with energy mobilization, and PNS, associated with vegetative and restorative functions. The activities of the two systems are in dynamic balance, but they can be rapidly modulated in response to changing environmental demands [78]. HRV is based on the two systems (sympathetic and parasympathetic) having antagonistic effects on the rhythm of the heart (inter-beat intervals, IBI, or R-R intervals), and that there is a constant fluctuation of rhythm. It has been found that discrepancies in time between activation and inhibition correspond to the different autonomic systems, and that cardiac response to SNS activity is slower than response to PNS (vagal) activity. The most prominent parasympathetic modulated fluctuation of the beat-to-beat interval in young healthy individuals is respiratory sinus arrhythmia (RSA) [79].

Two principal domains are used for analyzing HRV, the time domain, and the frequency domain. In time-domain analysis, heart rate (HR) is treated as a mean for a certain recording epoch, and the standard deviation of the mean as a measure of HRV. Four time-domain parameters have been recommended in the Task Force report (1996). Two of these estimate overall HRV: a) the standard deviation of all normal (NN) intervals (SDNN), and b) the triangular index. A third estimate is: c) the standard deviation of the average NN interval (SDANN), which estimates the long-term components of HRV. And, fourth, there is: d) the root mean square of successive (beat) differences (RMSSD), which estimates the short-term components of HRV [16]. Both the SDNN and the RMSSD have been shown to be useful indices of vagal activity [78]. The frequency domain involves transforming IBI data into different frequency patterns by spectral analyses using the fast Fourier transform technique (FFT), or auto-regression techniques (AR). The three main parameters from frequency-domain analyses estimate power from very low frequencies (VLF, $\leq$0.04 Hz), low frequencies (LF, 0.04-0.15 Hz,), and high frequencies (HF, 0.15-0.4 Hz) [16, 79]. It is rather well established that HF power primarily reflects parasympathetic influences. It has been suggested that LF power reflects both parasympathetic and sympathetic activity, but the physiological meaning and interpretation of LF and the LF/HF ratio (interpreted as an estimate of sympathovagal balance) are currently under debate [80, 81]. It has also been suggested that thermoregulation and vasomotor activity are two activities that are reflected by VLF power [82], but little is known about the specific physiological process attributable to VLF power, and the existence of such a process has been questioned [16].

Overall, despite these uncertainties, lower values on these indices of vagal function have been shown to be associated prospectively with mortality and disability in several studies [78]. Further, alterations in HRV have been shown to be associated with diabetes [83], arrhythmic events and sudden cardiac death after acute myocardial infarction [84]. Thus, regardless of the

difficulties in interpreting specific physiological processes attributable to the different HRV parameters, alterations in HRV in conjunction with intervention may capture changes relevant to health effects.

2.3 MUSCULOSKELETAL PAIN AND STRESS

Pain has been defined 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". This definition is the most widely used [85].

Musculoskeletal pain is often described as either acute (duration of less than 6 weeks), sub-acute (6-12 weeks), or chronic (>3 months).

Even if studies differ in their estimates of the prevalence of low back pain, LBP (a review of studies published between 1966 and 1998 reported a LBP life-time prevalence of 11-80%, a point estimate of 12-33%, and a one-year prevalence of 22-65% [86]), it is considered to be common and recurrent [87, 88].

In approximately 85% of cases with LBP complaints it is not possible to diagnose a pathoanatomical cause of the pain, which is commonly referred to as non-specific LBP [89], and symptoms of LBP are poorly associated with radiographic findings [90].

Diminished psychological wellbeing, such as depressive symptoms [91, 92] and stress [93], have been shown to increase the risk of decreased work ability and sickness absence in individuals with musculoskeletal pain. Also, concurrency of pain from multiple sites [91, 94-96] has been shown to increase the risk of sickness absence.

Localised pain and pain from multiple sites may reflect different types of conditions. Having pain from several sites is more common than having localised pain. As compared with having pain from a single site, pain from several sites has been shown to be a stronger predictor of sickness absence [94, 95, 97], disability pension [98], and decreased work ability [99]. A linear relationship has been seen between number of pain sites and functional ability [100]. Moreover, number of pain sites has shown an almost linear relationship to reduction in overall subjective health, sleep disturbances and psychological health in a general Norwegian population [101]. Number of painful locations has further been shown to be more strongly associated with health-related functioning than chronicity or location of the pain [102].

The term multisite or multiple-site musculoskeletal pain refers to pain from several body sites, concurrently or within a specified period of time. The concept is relatively new and lacks a clear definition. Multisite pain differs from the more widely studied phenomenon of chronic widespread pain (CWP) in several aspects. According to the definition of CWP developed by the American College of Rheumatology, it represents pain in two contralateral quartiles of the body, above and below the waist and in the axial skeleton, and the pain should have been present for at least three months [103]. The term multisite pain, however, usually describes pain from multiple sites, irrespective of location or chronicity.

How to identify individuals at risk of developing chronic conditions is a challenging task for caregivers. The complexity behind the pain phenomenon challenges researchers to find the key factors associated with prognosis, so as to provide an answer to the "holy grail type of questions" (as phrased in the Cochrane Back Review Group): "Which interventions are most efficient for which type of patients?", and "Which are the most important prognostic factors?"[104].

To suggest that psychological factors interplay with pain perception is neither new nor controversial. In 1965, Melzack and Wall presented the gate control theory of pain. The theory suggests that there is a gate regulating the transmission and intensity of nerve signals in the dorsal horn of the spinal cord. The authors propose that sensation from a pain stimulus is inhibited by conflicting activity in larger fibres (Aβ fibres) transmitting signals for non-painful stimuli [105]. Even though the theory has been questioned in more recent research, suggesting that the modulation of pain perception by non-painful stimuli also occurs in the brain [106], gate control theory is regarded as important for understanding the complex phenomenon of pain, taking both psychological and sensory phenomena into consideration. It suggests, for example, that psychological factors (e.g., past experience, attention and emotion) influence perception by acting on the control system [105, 107].

The biopsychosocial model of pain integrates the individual`s physiological, biological, cognitive, affective, behavioural, and social attributes. The model suggests that chronic pain should signal to the clinician that there is something wrong in the patient`s life, and that the origin of the problem is either biological, psychological or social, and that psychosocial factors play an increasing role in pain behaviour as the duration of the pain lengthens [107].

In a review of studies of LBP and NSP by Linton and colleagues [5] it was found that psychological factors clearly had an impact on the transition from acute to chronic pain disability. Passive coping, pain cognitions (e.g., catastrophizing), fear-avoidance beliefs, depression, anxiety, distress and self-perceived poor health were the most evident psychosocial predictors of pain (LBP/NSP) and disability found in the review [5]. More recent longitudinal studies have suggested that belief that LBP will last for a long time, pain intensity [108], not being in employment [109, 110], work absence, long duration of pain, high function disability, high pain intensity, anxiety, poor self-rated health [109], high risk according to a psychological screening questionnaire, high emotional distress [111], catastrophizing, widespread pain, and high level of chronic pain grade [110] are all predictors of poor LBP prognosis.

Increased knowledge about the impact of psychosocial factors on the prognosis of musculoskeletal pain has generated multiple questionnaires for practitioners and researchers to use for risk estimation (yellow flags), and for the evaluation of individuals with musculoskeletal pain, and LBP and NSP in particular. The Subgroup for Targeted Treatment (STarT) [112], the Örebro Musculoskeletal Pain Screening Questionnaire (ÖMPSQ) [113, 114], the LBP Patient Perception Scale (PPS) [115], and the Multidimensional Pain Inventory (MPI) [116] are some examples.

2.4 SLEEP AND PAIN

Sleep disturbances are common in individuals with musculoskeletal pain [13, 117], and it has been well demonstrated that pain and sleep are related [13, 15]. A recent study of LBP patients assessed pain (LBP) and sleep once a week over a six-month period. It was seen in the study that a week with more days of bothersome pain was typically followed by a week with more days of (pain-related) sleep disturbances [117].

The direction of causality between sleep and pain is, however, not entirely clear, albeit it is most likely reciprocal [14, 15, 118, 119]. One of the studies that supports the theory of a bidirectional relationship is a recent large investigation that found that self-reported insomnia, sleep onset latency and sleep efficiency were associated with increased pain sensitivity [120], which is in line with previous findings from smaller studies [121, 122]. Another relatively large study found that sleep duration (<6 or >9 hours) was associated with greater next-day pain [123]. In long-term prospective studies, sleep disturbances have been shown to predict fibromyalgia (10 year follow-up) [124], and chronic pain (17-year follow-up) [125], and good sleep quality has been shown to predict the resolution of widespread pain (15-month follow-up) [126]. Further, a recent review presents a trend showing sleep disturbances to be a stronger predictive factor for pain than vice-versa [118].

The mechanisms explaining the relationship between pain and sleep are not yet entirely understood. Several potential mechanisms are discussed in a recent review by Finan and colleagues[118]. According to the authors, an influence of sleep deprivation on dopamine with a potential effect on concurrent changes in pain sensitivity may be one of the explanatory mechanisms. Another pathway discussed is diminished opioid analgesia following sleep disruption. Further, the impact of negative affect is discussed, and it is suggested that sleep, pain and negative mood have shared variance. However, the authors report a lack of research explaining the dynamics of the associations. Also, the moderating effects of sociodemographic factors, such as (female) gender and (older) age, on the relationship between sleep disturbances and pain are discussed as potential mechanisms [118].

2.5 HYPOTHETICAL MODEL

The purpose of this thesis, to investigate markers of stress as predictors of wellbeing and workability, is based on the assumptions presented in the hypothetical model below (fig. 3). External exposure is here meant to refer to exposure to stressors in a broad sense, including, for example, a change in workplace environment, having musculoskeletal pain, or being exposed to other physical or psychosocial stressors. Being exposed to various stressors is presumed to induce an individual risk of change in wellbeing. It is hypothesised that a marker of (general) stress indicates change in risk of decreased wellbeing (e.g., worse pain or sickness absence), at both group and individual level.

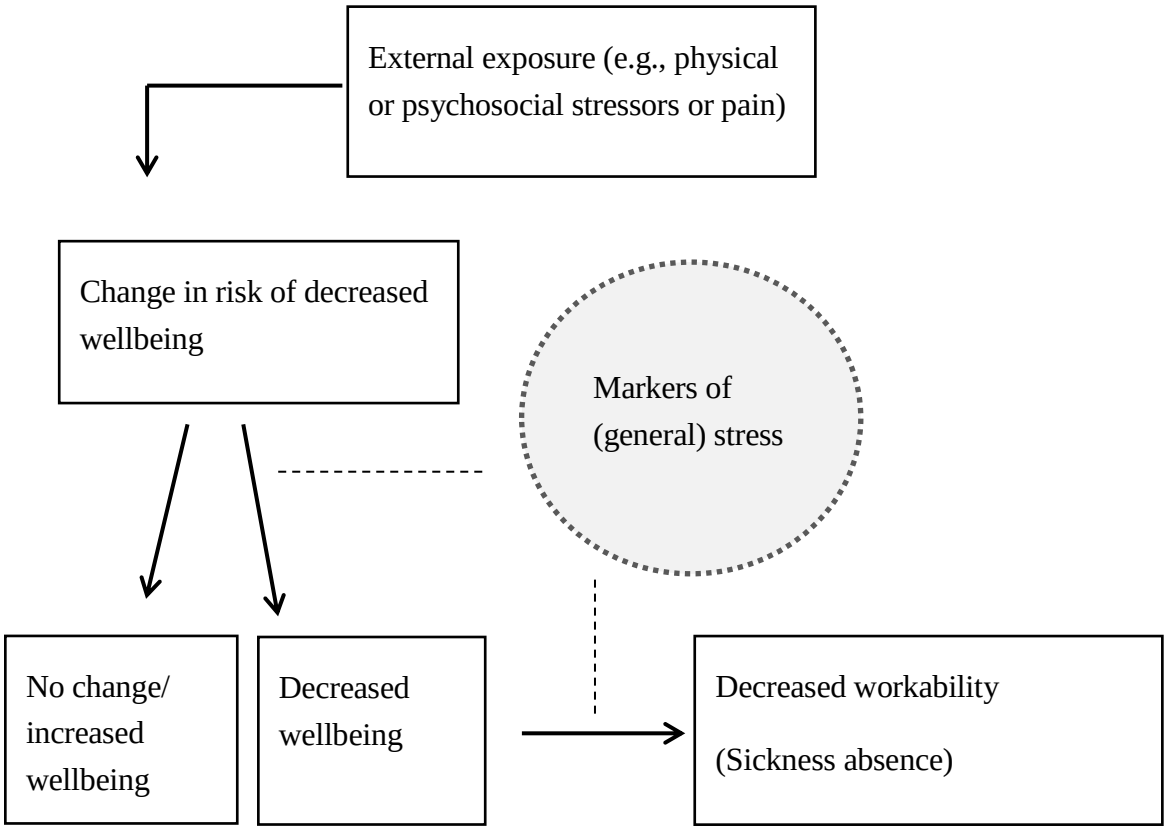


Figure 3. *A hypothetical model of how markers of stress may indicate risk of change in wellbeing and risk of sickness absence.*

3 AIMS OF THE THESIS

3.1 OVERALL AIM

The overall purpose of this thesis was to study markers of general stress as early indicators of change in strain. Such markers would be feasible measures to include when evaluating health outcomes at group as well as at individual level in conjunction with interventions in clinical settings and in workplaces. The markers of stress are investigated as potential predictive markers of change in wellbeing and workability.

3.2 SPECIFIC AIMS

The aim of *study I* was to investigate whether self-reported sleep disturbances predicted sickness absence among individuals with, and without, LBP and/or NSP. The study is a five-year prospective study.

The aim of *study II* was to investigate whether sleep predicts the onset and resolution of multisite pain in a five-year prospective perspective.

In *study III*, the aim was to study whether everyday life stress was captured by changes in HRV during sleep and self-reported sleep quality the subsequent night. Further, the impact of factors related to genetic or familial similarities on such associations were investigated. The study is a cross-sectional twin study.

The aim of *study IV* was to describe objective and subjective sleep assessments and to investigate how many nights of consecutive sleep measurements are required to obtain a reliable sleep measure.

4 MATERIAL AND METHODS

4.1 DATA SOURCES

Studies I and II are based on the MUSIC-Norrtälje study. Data for study III were assessed in collaboration with a longitudinal hearing study of twins (TWINHEAR), and data for study IV were assessed as a part of the SHIP study.

4.1.1 The MUSIC Norrtälje Study

The MUSIC (Musculoskeletal Intervention Center)-Norrtälje study was initiated to identify and quantify risk and protective factors, and to investigate the prognosis, for low back and neck-shoulder disorders. The study was designed as a case referent study at baseline with five-year follow-up. Register data on sickness absence was obtained from the National Social Insurance Agency and linked to the 2329 individuals who participated at both baseline and follow-up.

The baseline case-referent study was based on a sample from a study population that embraced 17,000 men and women, 20-59 years-old, living and working in the rural municipality of Norrtälje. People in the study population who had sought care or treatment for nonspecific low back and/or neck-shoulder pain during the study period January 1st 1994 to June 30th 1997 from any of the approximately 70 caregivers in the region, including not only physicians and physiotherapists but also other caregivers such as chiropractors, osteopaths and homeopaths, were defined as cases. The caregivers asked their patients if they wanted to participate in the study, but they did not record refusals. Thus, the rate of potential participants who refused to join the study is unknown. According to interviews with the caregivers, only a few refused to take part. A random sample of referents, stratified by sex and age in five-year categories, were selected through the population register. At least one referent per case was selected. Only cases and referents who had not sought care or treatment for low back or neck-shoulder pain during the six months preceding their enrolment were included in the study. The rate of referents who participated was approximately 69% [127, 128].

Demographic and individual data concerning low back pain (LBP), neck-shoulder pain (NSP), other non-musculoskeletal disorders, psychological wellbeing, and physical and psychosocial work-related exposures were assessed through self-administered questionnaires and structured interviews at baseline. Clinical examinations were also performed [129, 130].

At follow-up, four to six years after the baseline study, a self-administered postal questionnaire was sent out to all participants (cases and referents) who were still living in Sweden. Data concerning LBP, NSP, non-musculoskeletal disorders, diminished psychological wellbeing, and physical and psychosocial work-related exposures were assessed using items similar to those in the baseline study. Those who entered the baseline study in 1994-1995 received their follow-up questionnaires in year 2000, and those who entered in 1996-1997 in 2001. 28% received their follow-up questionnaire six years after entering the baseline study, 68% five years from baseline, and 4% four years from baseline.

The response rate was 83% (n=2329). Among the non-responders, there were higher proportions of males and participants younger than 45 [129]. Further, register data concerning sickness absence (sickness benefit and disability pension) were received yearly from the National Social Insurance Agency from 1995 to 2001 and linked to each participant. The sickness benefit data included number of sick spells per year, number of days per year, and partial or full benefit. Data concerning disability pension consisted of the date for newly allowed disability pension, and partial or full benefit. Data did not include the diagnosis issued by the physician on the sickness certificate, so no information on the reason for registered sickness absence was available [94].

4.1.2 Study III

Participants in study III, investigating stress, heart rate variability (HRV) and sleep quality, were recruited through collaboration with a hearing study of twins (TWINHEAR). The hearing study was designed as a follow-up to a previous hearing study [132] carried out between 1991 and 1995. The participants for the original twin hearing study were recruited through the Swedish Twin Registry [131]. For inclusion in the original study, both members of a twin pair should be male and living in Stockholm or Uppsala County, and there should be a twin registry classification of their zygosity. In all, 1629 twins born between 1914 and 1958 were identified for invitation to the study, and after drop-out due, for example, to refusal to participate, major disease, death or emigration, 1114 individuals took part in the original hearing study [132].

The follow-up study was performed from 2010 to 2013. The 1114 individuals who had participated in the original study were approached for the follow-up study. By the time of follow-up, 219 individuals had died. Out of the 895 remaining twins, 583 participated in the follow-up TWINHEAR study [133].

All individuals who participated in the follow-up hearing study were considered for inclusion in cross-sectional study III, for which additional data concerning stress, heart rate variability and sleep quality were assessed. For a participant to be included in the additional study, he should: 1) not have a pacemaker, 2) have his hearing examined by audiologists on the project, and 3) be physically and mentally able to remove and restore the equipment used for HRV measurements. Since the study primarily was a sub-study of the hearing study, as well as participants being willing to participate in the additional study, time available also influenced whether researchers and the participants found it possible to conduct the necessary HRV measurements.

Data for study III were collected between September 2010 and March 2013. In all, 206 HRV measurements were performed of which 7 had too much noise in the data, so 199 HRV measurements were eligible for further analysis. The 199 individuals included in the study were all male monozygotic or dizygotic twins between 52 and 77 years-old. Zygosity was based on DNA typing [134].

4.1.3 The SHIP study

The participants in the SHIP study (Study of a Health Intervention Programme) were working within correctional treatment at an institution in Sweden. In all, 259 individuals who were working at the correctional institution in November 2012 were invited to participate in the SHIP study. The study was launched in connection with the start-up of an intervention focusing on promoting health among the staff, and was carried out by Occupational Health Services (OHS). It was a longitudinal study with yearly follow-up. In all, data were assessed at three (yearly) time points, the most recent in early spring 2015. The aim of SHIP was to evaluate health effects in connection with the start-up of the intervention, and on a yearly basis during/after implementing the intervention, and also to elaborate methods for the evaluation of health effects feasible for OHS in general. The questionnaires distributed within the frame of SHIP included items on several indicators of (ill) health, such as symptoms of depression and anxiety, sleep, organizational justice, workability, and self-rated health.

Of the individuals who joined SHIP, 60 (men and women) were approached for participation in a sub-study including additional yearly sleep measurements with an actigraph and a sleep diary for seven consecutive nights. The invited individuals were chosen to represent three different areas of the workplace. The underlying assumption was that these three groups would represent different degrees of stress in the everyday work situation. In addition, the participants included for additional sleep measurements were not to work night shifts during the study period in conjunction with the days/nights of measurement. Data from the SHIP study and the sub-study were assessed in winter/early spring in years 2013, 2014 and 2015. Study IV is based on data from assessments at baseline. Of the 60 individuals invited to participate in the sub-study at baseline, 58 agreed to take part.

4.2 MAIN VARIABLES IN STUDY I

4.2.1 Definitions of LBP and NSP

The definitions of LBP and NSP were based on items in the baseline questionnaire, which covered both pain intensity and pain-related disability. Items concerning pain intensity and pain severity from The Severity of Chronic Pain Questionnaire by Korff and colleagues was used [135]. The three items concerning LBP intensity and NSP intensity, respectively, covered: (1) current pain, (2) worst pain experienced during the previous 6 months, and (3) average pain during the previous 6 months. The three items concerning LBP-related and NSP-related disability covered how much the pain had affected: (1) everyday activities, (2) social and family activities, and (3) ability to work (including domestic work).

The ordinal rating scale for the items ranged from 0 to 10, where 0 meant no pain/disability at all and 10 meant pain/disability as bad as it can be. A *pain intensity score* for each participant and each of the two body regions was constructed by calculating the mean values of the three items that concerned pain intensity [136]. A *pain-related disability score* was constructed in the same manner as the *pain intensity score*. Hence, the *pain intensity score* and the *pain-related disability score* both ranged between 0 and10. A participant was defined as having LBP or

NSP if he/she had a pain intensity score ≥3 and/or a pain-related disability score ≥1 in the body region in question [94, 130]. These cut-off points were based on the distribution in the cohort of all 2329 subjects who participated at both baseline study and five-year follow-up (n= 2329) in the MUSIC-Norrtälje study. About one-third of the subjects had a pain score ≥3 and/or a pain-related disability score ≥1. Using these cut-off points in the present study, the prevalence of LBP only was 16%, and of NSP only 12%, proportions that are in line with earlier population studies [87, 137]. The prevalence of concurrent LBP and NSP was 21%. These levels of pain and pain-related disability were considered appropriate levels of pain, i.e., levels where it was still possible for the participants to be able to work (since the outcome considered in study I was sickness absence).

4.2.2 Definitions of sleep disturbances

Data regarding sleep disturbances were obtained using the self-administered Karolinska Sleep Questionnaire, which uses a five-item Likert scale [138]. Five questions, with a single stem, were used to form an index for sleep disturbances [138]: During the last six months have you had/experienced … 1) Difficulties falling asleep? 2) Repeated awakenings with difficulties going back to sleep? 3) Not being well rested on awakening? 4) Premature awakening? 5) Disturbed/restless sleep? There were five response options: 1. Never; 2. Seldom/a few times per year; 3. Sometimes/several times per month; 4. Mostly/several days per week; 5. Always/every day. Cronbach`s alpha for the index was 0.77.

The distribution of the sleep scores enabled division of the cohort into tertiles, with total scores ranging between 5 and 25. The first tertile (Sleep A, indicating best sleep) scored ≤10, the second (Sleep B) 11-13, and the third (Sleep C, indicating worst sleep) ≥14.

4.2.3 Definitions of sickness absence

Data on sickness absence were obtained from a register held by the Swedish Social Insurance Agency, which received data on the number of days an individual had drawn sickness benefit. To be entitled to benefit from the Insurance Agency, the sickness absence had to be >14 consecutive days. During the period 1st January 1997 to 1st April 1998, the number of consecutive days required for sickness benefit from official health insurance was 28 (due to a temporary change in legislation). A participant was considered to have been absent due to sickness if he/she had received partial or full sickness benefit or disability pension from the Agency for at least one period during the years between baseline and follow-up.

Long-term sickness absence was defined as >180 days of absence entitled to sickness benefit or disability pension during at least one one-year period between baseline and follow-up. Days with partial benefit were recalculated into full days [94].

4.3 MAIN VARIABLES IN STUDY II

4.3.1 Definition of sleep disturbances

Sleep disturbance was assessed and defined in the same manner as in Study I (see section 4.2.2). Again, the three sleep tertiles, Sleep A, indicating best sleep, Sleep B, and Sleep C, indicating worst sleep were used to define different levels of sleep disturbances.

4.3.2 Definition of multisite pain

Multisite pain was defined using items from a modified version of the Standard Nordic Questionnaire [139]: Have you had discomfort (pain, ache, discomfort) at any time during the last six months from: 1) neck; 2) shoulder/shoulders; 3) elbow/elbows; 4) hand/hands/wrist/wrists; 5) upper back (thoracic); 6) lower back; 7) hip/hips; 8) knee/knees; 9) foot/feet? We made no distinction between unilateral and bilateral pain, entailing, for example, that if pain was reported from both elbows, the two elbows were treated as just one pain location. Thus, the total number of pain locations was nine.

The same items for assessment of pain sites were used at both baseline and follow-up. In both questionnaires, the questions were supplemented with an illustration of the body parts in question. The expression "multisite pain" has been used in other studies [98, 140], but with different specifications of how many sites should, in general, form a cut-off. The cut-off used in study II (≥3 sites) is based on the results of a study by Kamaleri and colleagues, using the same questionnaire. In that study, individuals with three or more pain sites were found to show an increased risk of work disability [98]. To establish whether the same cut-off was reasonable for study II, a binary logistic regression analysis of sickness absence (of >14 consecutive days at any time during the five-year study period) was made with numbers of pain sites as independent factors, adjusted for age and gender. The analysis showed an OR of 1.9 (p=0.001) at the level of three pain sites (for two pain sites: OR=1.4, p=0.04; and for four pain sites: OR=3.0, p=0.000).

4.4 MAIN VARIABLES IN STUDY III

The assessment of HRV data was performed over approximately 24 hours, starting when the participants came to the Division of Audiology at Karolinska Institutet, Stockholm, for hearing examination by the audiologists. The twins arrived at their pre-booked appointment either in pairs or alone, depending on what suited them best. In addition to the audiometry, assessments of blood pressure, weight and length for BMI, and attachment of the Actiheart device (for HRV measurement) were performed. The participants also received a questionnaire including items on perceived stress during the day, to be completed before they went to bed at night, and a sleep diary for them to fill in after awakening the subsequent morning. The appointment times varied between 8.00 a.m. and 6.00 p.m., and the visit lasted between one and two hours. The participants were not given any restrictions regarding performing any activities, and they slept at home. They were told to keep the device for HRV measurement on until the subsequent morning.

4.4.1 Stress

Perceived stress during the day was assessed by the question: "Have you felt stressed today?" (responses on a visual analogue scale, ranging from "not at all" [score 0] to "maximum stress" [score 100]). Due to its skewed distribution, the stress variable was transformed into logarithmic units.

Health-related stress is a potential daily stressor that may not necessarily be acknowledged as stress by the people affected. Hearing disability and tinnitus have been shown to be associated with long-term stress [141]. Data on hearing disabilities and tinnitus were available due to collaboration with the twin hearing study which gave us an opportunity also to investigate influences from the two health-related stressors. Hearing loss was measured by audiologists, and pure tone average thresholds (PTA4s) were obtained by calculating the mean values of decibel hearing loss measured for frequencies 500, 1000, 2000 and 4000 Hz. PTA4s for the better and worse ear were used in the analysis. The assessment of hearing disability is described in greater detail by Bogo and colleagues [133]. Tinnitus was assessed by the single question: "Have you suffered from tinnitus today?" (responses on a visual analogue scale, ranging from "not at all" [score 0] to "maximum discomfort" [score 100]).

The variables derived from VAS scoring (perceived stress and perceived tinnitus) were log-transformed in order to obtain approximately normal distributions

4.4.2 Sleep quality

Sleep quality was assessed using the Karolinska Sleep Diary [70, 142] , which was filled in upon awakening. A sleep quality sum index [142] was constructed on the basis of responses to questions in four categories: (1) Sleep quality "How did you sleep?" [very well (5) – very poorly (1)]; (2) Restless sleep [not at all (5) – very restless (1)]; (3) Difficulties falling asleep [not at all (5) – very difficult (1)], and (4) premature (final) awakening [not at all (5) – woke up far too early (1)]. The same index has previously shown to be correlated (0.49- 0.66) with objectively sleep efficiency (measured by polysomnograph) [69, 70]. Sleep quality index scores ranged from 4 to 20, where score 4 indicated the worst sleep quality, and score 20 the best quality.

4.4.3 Heart rate and heart rate variability

Heart rate (HR) and HRV were measured using an Actiheart (Actiheart, Cambridge Neurotechnology, Ltd., Papworth, UK) with a sample frequency of 128 Hz. The device, tested for reliability and validity [143], samples data through two electrodes, one at the sternum (by costae 4), and one attached approximately 10 cm laterally (on the left-hand side of the chest) from the first electrode. Before recordings started, a signal test was performed, where the individual was asked to stand up and move his arms for approximately one minute. If the recording was noisy, the electrodes were re-positioned and the signal was tested again. This procedure was repeated until a satisfactory signal was obtained. The participant was instructed to keep the device on until the subsequent morning. A three-hour data window for

nocturnal HRV was selected, starting 30 minutes after self-reported sleep start (assessed in the sleep diary). For subjects who did not report any time for sleep start (n=13), a window between 01 a.m. and 04 a.m. was selected.

The method is based on recording regular QRS complexes, defining the R-peak, and measuring the RR intervals between (i.e., the inter-beat intervals, IBIs). Fluctuation in the lengths of the RR intervals, mirroring activation and inhibition of the regulatory systems, was analyzed in spectral analyses (autoregressive) that integrated the power spectrum from three frequency bands: very low frequency (VLF) <0.04 Hz; low frequency (LF) 0.04 to <0.15 Hz, and high frequency (HF) 0.15 to <0.40 Hz. From the time-domain analysis, the parameters RMSSD (the square root of the mean squared differences between successive NN intervals) and SDNN (the standard deviation of the NN interval) were used in study III. All cyclical components responsible for variance in heart rate are reflected by SDNN, whereas the RMSSD estimates show high frequency variations in heart rate [144]. The spectral analysis and time-domain analysis were performed in a software program [145] that uses linear interpolation to filter ectopic beats and noise. Data were analyzed in five-minute epochs in accordance with Task Force recommendations [144].

The HRV variables were log-transformed in order to obtain approximately normal distributions.

4.5 MAIN VARIABLES IN STUDY IV

Measurements with actigraph and sleep diaries were performed for seven consecutive nights at some point between 4th of February and 6th of March 2013.

4.5.1 Self-rated sleep

Self-rated sleep was measured by the Karolinska Sleep Diary [70, 142] for the seven consecutive nights. In the same manner as in study III (see section 4.4.2), a sleep quality sum index [142] was constructed. Sleep quality sum index scores range from 4 to 20, where score 4 indicates worst sleep quality and score 20 best sleep quality.

4.5.2 Objectively measured sleep

A wrist-worn actigraph, Motionwatch 8 (Camntech® Ltd), was used for objective sleep measurements in study IV. The Motionwatch actigraph has a tri-axial accelerometer capable of sensing motions in a resultant force range between 0.01g and 8g. It registers total motor gross activity, to be analysed in a software program for sleep-wake analysis. Participants were instructed to wear the watch on their non-dominant wrist, day and night for seven consecutive days. Recording was made at one-minute epochs.

Several studies have investigated the validity of the actigraph for sleep measurements. In a review from 1995, approved by the American Sleep Disorder Association, it was concluded that epoch-by-epoch sleep estimated by actigraphic measurements in laboratory studies had a correlation with polysomnographic measurements of at least 0.85 in normal individuals [61].

The software program, Actiwatch Activity & Sleep Analysis, CamNtech® Ltd version 7.38, was used for sleep-wake analysis. A medium sensitivity level was used for estimation of sleep-wake patterns. Time for bed was estimated by data from the sleep diary, and entered into the sleep analysis software. The software program then calculated when sleep started for the night and when sleep ended in the morning. If there was a poor fit between what was reported in the sleep diary and what was registered by the actigraph, or if data on time for bed and/or time for awakening were missing in the diary, *sleep start* was estimated by the researcher by finding the time when the activity count was lower than 40 for at least five minutes, and *sleep end* when the activity count was higher than 40 for at least ten minutes.

The objective sleep parameters investigated in Study IV were as follows:

Actual sleep (%) is a percentage of actual sleep time (assumed sleep minus wake time) and was used as an additional parameter for sleep efficiency. Actual sleep derives from calculations on the total period between sleep start and sleep end, minus wake periods during the night.

Sleep efficiency (%) describes actual sleep time (assumed sleep time minus wake time) divided by time in bed. Thus, by contrast with the actual sleep parameter, calculation of sleep efficiency also includes sleep latency.

Sleep duration represents the total period of time between sleep start and sleep end.

The fragmentation index derives from addition of percentage minutes moving (number of minutes moving/sleep duration) and percentage minutes immobile (number of immobile phases of 1 minute as a proportion of the number of immobile phases).

4.6 SUBJECTS

The data sources used in the studies included in the thesis are described in table 1.

Table 1. Number of subjects, proportion women and men and mean age of the participants in studies I-IV.

	Study I (MUSIC)	**Study II (MUSIC)**	**Study III**	**Study IV (SHIP)**
Subjects (n)	2286	1599	199	54
Women/Men (%)	61/59	60/40	0/100	46/54
Mean age (range)	42 (20-60)	41 (20-60)	65 (52-77)	45 (26-63)

4.6.1 Study I

From the 2329 who participated in the MUSIC-Norrtälje study, individuals who had missing data on LBP, NSP or sleep disturbances (n=43) were excluded. 2286 individuals were included in Study I. The participants were stratified into three groups: (1) No LBP or NSP; (2) Solely LBP or NSP; (3) Concurrent LBP and NSP.

In all, 90% of the cohort included in Study I were: (a) Working now and the last 12 months, (b) Working now, but not throughout the last 12 months, (c) Working at some point during the year, but not the last 8 weeks. The working groups contrasted with the remaining 10%, who were: (d) Unemployed for the last year, or (e) Not working.

All participants in Study I were treated as one cohort, regardless of whether they had been included as a case or a referent in the MUSIC-Norrtälje baseline study. Of the 2286 individuals who participated in study I, 41% had been included as cases in the MUSIC-Norrtälje study.

4.6.2 Study II

Study II is also based on data from the MUSIC-Norrtälje study, from baseline and follow-up. In the baseline questionnaire, the participants were asked to state whether they had: (1) vascular pain from legs; (2) disease of the nerves (brain, spinal cord, peripheral nerves); (3) joint reconstruction (arthroplasty) in hip, knee or other joint; (4) any congenital defect in joints, muscles or back; (5) been diagnosed with rheumatoid arthritis; and (6) been diagnosed with ankylosing spondylitis (Bechterew's disease). If the response was 'yes' to any one of these items, the individual was excluded from the study (resulting in exclusion of 10% of the cohort). The cohort included all subjects (n=1599) with valid data at baseline and follow-up not reporting any of the medical conditions above.

The cohort was stratified into three groups from baseline data: (1) No pain; (2) Pain from 1-2 sites; (3) Multisite pain (pain from ≥3sites).

Out of the 1599 individuals included, 38% had been included as a case in the original MUSIC-Norrtälje study.

4.6.3 Study III

Of the 199 men included in the study, there were 70 full twin pairs, and 59 participants were included as singletons. Of the full pairs, 47 were monozygotic (MZ) twins, and 23 dizygotic (DZ). The mean age was 65 (range 52-77), which was somewhat lower than that of the 583 included in the TWINHEAR study (mean age: 67; range: 52-95).

Three different sets of analysis were performed in the study, of either the full group or only the full twin pairs. In all analyses where HR and HRV were outcomes, only individuals not using medications potentially affecting heart rate were included (for SEM, however, the analysis was performed both including and excluding participants using the medications). In all, 169 individuals did not take medications.

For analytic set 1, linear associations between all the dependent and independent variables were tested, for both the full group and for the full twin-pair group separately. For the within-pair analyses in set 2, only full twin pairs were included. Only the independent variables that showed significant associations (stress) with the outcomes in set 1 were tested. For SEM, performed on set 3, the full group (including singletons) was included. In the cases of HR and HRV, SEM analyses were performed both including and excluding individuals using medications potentially altering heart rate.

4.6.4 Study IV

The 54 individuals in study IV came from the 58 on whom objective sleep measurements had been performed. They were the ones who remained after excluding: (a) those who did not have at least three days of valid objectively measured sleep data (n=2), and (b) those who had reported that they had been out of bed most of/all the night (n=2). All participants in study IV were working at the same correctional institution in Sweden. The invited individuals were chosen to represent three different groups in the workplace: (1) those working with tasks that involved daily/constant contact with prison inmates (27 participants, 13 women and 14 men); (2) those with working tasks with no direct or no constant contact with prison inmates (13 participants, 6 women and 7 men); (3) those working with tasks with no contact with prison inmates at all (14 participants, 6 women and 8 men). The underlying assumption was that these three groups would have different degree of stress in their everyday work situation. In addition, the participants included for additional sleep measurements were not to work night shifts during the study period in conjunction with the days/nights of measurement. Eleven of the participants were working during the weekend.

4.7 METHODS

4.7.1 Study I

In study I, the aim was to explore the influence of self-reported sleep disturbances on future sickness absence among individuals with LBP and/or NSP. This was achieved by logistic regression analysis. Previous research has found that having both LBP and NSP is associated with higher risk of sickness absence than having pain from either the lower back or neck/shoulder, or having no LBP or NSP [94]. Under these assumptions, analyses were performed for the three different strata: (1) No LBP or NSP; (2) Solely LBP or NSP; (3) Concurrent LBP and NSP. The effect of level of sleep disturbances on sickness absence was tested within each group, with the best sleepers acting as referents within each stratum.

Two different outcomes for sickness absence were used in the study: (1) sickness absence (>14 consecutive days) at any period between baseline and follow-up; (2) long-term sickness absence (>180 days) during at least one of the five one-year periods between baseline and follow-up.

The confounders considered were age, gender, other physical illnesses (including cardiovascular, respiratory, gastrointestinal, urogenital, and metabolic diseases), regular

physical activity, and smoking. Physical activity and smoking did not affect the associations and were dropped as confounders in the subsequent analysis.

4.7.2 Study II

In study II, the aim was to investigate whether sleep disturbances predict the onset of multisite pain 5 years later among individuals free from pain at baseline, and whether good sleep predicts the resolution of multisite pain five years later.

Three groups were formed based on number of pain sites: (1) no pain; (2) pain from 1-2 pain sites; (3) pain from ≥3 pain sites (defined as multisite pain). Through multinomial logistic regression analysis, the effect of the level of sleep disturbance (best, medium, worst sleep) on having migrated to another pain group at follow-up five years later was investigated. Best sleep was the reference category in the stratum `no pain', and worst sleep was the reference category in the stratum `multisite pain' (fig. 4).

<table>
<tr><td></td><td colspan="4">5-year follow-up</td></tr>
<tr><td rowspan="4">Baseline</td><td></td><td>No Pain</td><td>Pain from 1-2 sites</td><td>Multisite pain (≥3 pain sites)</td></tr>
<tr><td>No pain</td><td></td><td colspan="2">Does sleep disturbance predict the direction of migration?</td></tr>
<tr><td>Pain from 1-2 pain sites</td><td colspan="2" rowspan="2"></td><td></td></tr>
<tr><td>Multisite pain (≥3 pain sites)</td><td colspan="2">Does sleep disturbance predict the direction of migration?</td></tr>
</table>

Figure 4 *Flow-chart describing the study design. Study II is designed to examine how individuals migrate from one stratum at baseline to a different one at follow-up. Does sleep disturbance predict the direction of the change in pain sites?*

The confounders considered in the study were: age, gender, BMI (dichotomised into <25 and >25 kg/m^2), inclusion as case or referent in the MUSIC-Norrtälje study, smoking, physical activity, psychosocial exposure at work, and biomechanical exposures at work. The potential confounders were tested one by one in a stratified multinomial logistic regression analysis, and included in the modeling if, after adjustment for age and gender, they were significantly associated with outcome at a 0.05 level and altered the beta coefficient by more than 10%. The influence of the confounders differed across the strata. Age, gender, BMI, inclusion as

case or referent in the MUSIC-Norrtälje study, manual handling and prolonged sitting were included in at least one of the analyses.

4.7.3 Study III

The overall aim of study III was to investigate stress during everyday life in a natural setting and its association with changes in HRV measured during night time or decreased sleep quality the subsequent night and also to identify the possible influences of genetic and/or familial factors on such reactions. The following research questions needed to be answered:

1) Does perceived daytime stress influence measures of night time HR and HRV?

2) Does perceived daytime stress influence measures of sleep quality?

3) Do genetic and/or familial factors influence any identified effects of daytime stress on night time HR, HRV or sleep quality?

The study is cross-sectional, investigating the associations between stressors during the day and alterations in HR, HRV and sleep quality the subsequent night. It is designed to examine the effects of stressors occurring/being reported in an everyday life setting. Measurements were taken in the home environment, using simple one-item questions to quantify exposure.

A set of three types of analyses was performed to investigate the above.

First, the linear associations between the stress/potential health-related stressors and HR, HRV and Sleep quality were investigated to identify which stressors affected outcomes significantly under the conditions offered in study III. A marginal linear regression model was estimated from generalised estimating equations (GEEs) that take into account correlation within a twin pair.

In a second set of analyses, the impacts of genetic and/or familial factors on the associations found at step 1 were investigated using within-pair analysis [146]. The analysis was performed using the MIXED procedure, allowing for a random intercept for each twin pair.

Within-pair analysis is a way of taking into account within-twin-pair similarities. This was achieved by including two independent variables, one for explaining differences in stress ratings within each twin pair (or more precisely, each twin`s difference from the twin-pair mean), and one for explaining the twin pair`s mean. Including a variable describing the difference in (stress) scoring within a twin-pair entails that even if a (male) twin rated his stress as very high, his value on the independent axis would be zero if his twin brother had exactly the same stress score. This would also be the case for a twin pair where both twins made exactly the same ratings, but very low ones. The two zeros would then contribute very little to describing the relationship between the x and y axis. By contrast, a pair where two twins rate their stress differently (a discordant pair) contributes more to the estimation of the relationship between the two axes. Two beta values are then interpreted for the regression.

One is estimated by within-pair differences in stress ratings (beta within) and one is estimated by the twin pair`s mean.

Finally, in the third set of analyses, intra-class correlation and structural equational modeling (SEM) were used to investigate how much of the variance in the outcomes (HR, HRV and self-reported sleep quality) could be explained by heritability (A), shared environment (C) and unique environment (E), respectively.

Intra-class correlation (ICC) coefficients were calculated by zygosity to determine whether, and if so to what extent, the monozygotic (MZ) twin pairs were more similar than the dizygotic (DZ) twin pairs. A SEM analysis was performed to partition the total variance of each HRV parameter, HR, and sleep quality respectively into components due to influences from genetic factors, environment shared within a twin pair, and an individual`s unique environment. In the models, the total variance is divided into additive genetic variance (A); dominant genetic variance (D); shared environmental variance (C), and unique environmental variance (E). The components are estimated in the models by comparing MZ twin pairs (assumed to share 100% of their additive and dominant genetic effects) and DZ twin pairs (assumed to share 50% of their additive genetic effects and 25% of their dominant genetic effects). The shared environmental effect is assumed to be equal for MZ and DZ twin pairs. The unique environmental effect is assumed to be explained by all other causes of the trait, including measurement error [147].

Two separate models, ACE and ADE, were fitted for each variable using SEM, as too were the sub-models AE, CE, DE, and E. Parameter estimates as well as model fit statistics, -2 log likelihood, and Aikaike`s information criterion (AIC) values were calculated for each model. The fits of the model ACE and ADE were then compared by examining their AIC values (a lower value indicating better fit). The ACE model was estimated to have the best fit for all parameters. By log likelihood tests the fit of the nested sub-models AE, CE and E were tested against the full ACE model. A simpler sub-model (AE, CE or E) was preferred if it did not provide a significantly worse fit to data. Singleton twins were included in the analyses to enhance the precision of the estimated data.

4.7.4 Study IV

The aim of study IV was to investigate how many nights of measurement are needed for a reliable measure of sleep in a working population, including adult women and men, to be obtained. The measurements were performed in conjunction with the start-up of an intervention carried out by OHS, and thus in a “real life” setting.

Sleep measurements were performed objectively with an actigraph, and subjectively with a sleep diary. Data were assessed for seven consecutive nights, including both weekday nights and weekend nights.

The analyses were stratified by gender to investigate potential gender differences in reliability. Also, two different conditions in the time-period setting were investigated, where one condition included weekdays only, and the other both weekend and weekdays.

Also, the correlation between the actigraphic parameter sleep efficiency and self-rated sleep quality (indexed from the sleep diary) was calculated by Spearman correlation. The correlation was calculated for each day, ordered by study day and weekday, respectively.

The intra-class correlation coefficient was calculated using a two-way random model, providing a ratio of the between-subject variance to the sum of all variance components [148]. The intra-class correlation estimates the reliability of a measure of each parameter on a single night of measurement. A low single measure intra-class correlation indicates higher intra-individual day-by-day variance in this study setting.

The Spearman-Brown formula was then applied to estimate the effect of change in the number of aggregated days of measurement on the reliability of each test:

$RR_{SB}=N*(ICC)/ (1+ (N-1) *ICC)$

A Spearman-Brown reliability coefficient of ≥ 0.7 was used to indicate acceptable reliability, in accordance with the previous literature [77].

4.8 SUMMARY OF STATISTICAL METHODS

Table 2. Statistical methods and software used in studies I-IV.

Method	Software	Paper I	Paper II	Paper III	Paper IV
Logistic regression	SPSS v. 19	x			
Multinomial logistic regression	SPSS v. 19		x		
Generalized estimating equations	SAS v. 9.3			x	
Within-pair analysis	SAS v.9.3			x	
Intra-class correlation	SPSS v 22[a]			x	x
Structural equation modeling	R, Open Mx			x	
Spearman correlation	SPSS v.22				x

[a] In paper III, SAS v. 9.3 was used.

4.9 ETHICAL APPROVAL

The MUSIC-Norrtälje study, providing data for studies I and II, was approved by the Ethics Commitee of Karolisnka Institutet (dnr 03-139; dnr 93-255). Study III and study IV were approved by the Regional Ethical Review Board in Stockholm (study III: dnr 2009/378-31, and study IV: dnr 2013/677-31).

5 RESULTS

5.1 Sleep and musculoskeletal pain

Sleep disturbances were more common among participants who reported pain. In the group with concurrent LBP and NSP in study I, 46% belonged to the tertile in the full MUSIC cohort reporting worst sleep (Sleep C). In the group with multisite pain in study II, 38% reported Sleep C (table 3).

Table 3. Proportions within each pain group from study I and study II reporting Sleep A (best sleep), Sleep B, and Sleep C (worst sleep).

		Sleep A n (%)	**Sleep B** n (%)	**Sleep C** n (%)
Study I	No LBP or NSP (n=878)	419 (48)	251 (29)	208 (24)
	Solely LBP or NSP (n=799)	295 (37)	253 (32)	251 (31)
	Concurrent LBP and NSP (n=609)	148 (24)	183 (30)	278 (46)
Study II	No pain (n=188)	106 (56)	53 (28)	29 (15)
	Pain from 1-2 sites (n=530)	254 (48)	147 (28)	129 (24)
	Multisite pain (n=881)	262 (30)	281 (32)	338 (38)

5.2 SLEEP, LBP/NSP AND SICKNESS ABSENCE

Among the 2286 participants in Study I, the prevalence of sickness absence of >14 consecutive days at some point between baseline and follow-up was 36%. Within the group No LBP or NSP, the prevalence of sickness absence was 25% for >14 consecutive days, and 10% for sickness absence of >90 days (defined as long-term sickness absence). In the group with solely LBP or NSP, the prevalence of sickness absence for >14 consecutive days was 38%, out of which 18% had long-term sickness absence. Among participants with concurrent LBP and NSP, the prevalence of sickness absence was 50%, out of which 25% had long-term sickness absence.

Sleep had an effect on the odds ratio for sickness absence, and the odds ratio for sickness absence (>14 consecutive days) was significantly higher when Sleep C was compared with Sleep A within each pain group respectively. See table 4.

Table 4. The effect of sleep disturbances (Sleep A=best sleep; reference category, Sleep C=worst sleep) on sickness absence (>14 consecutive days), stratified by No LBP or NSP, Solely LBP or NSP and Concurrent LBP, presented by odds ratios (OR) and 95% confidence Intervals (95% CI). The results presented are after adjusting for age, gender, and physical illnesses.

	No LBP/NSP OR (95% CI)	**Solely LBP/NSP** OR (95% CI)	**Concurrent LBP/NSP** OR (95% CI)
Sleep A	1.00	1.00	1.00
Sleep B	1.26 (0.87-1.83)	1.19 (0.82-1.71)	1.23 (0.79-1.93)
Sleep C	1.59 (1.08-2.32)*	2.22 (1.55-3.18)**	1.62 (1.07-2.46)*

*p<0.05; **p<0.01

5.3 SLEEP AND MULTISITE PAIN

In study II, the participants were grouped by number of self-reported pain sites at baseline into: 1) no pain, 2) pain from 1-2 sites, and 3) multisite pain (pain from ≥3 sites). The effect sleep had on whether individuals had migrated to a group with less or more pain sites at five-year follow-up was investigated. Of the 1599 included in the study, 943 (59%) reported the same number of pain sites at baseline and follow-up, 16% had migrated to a group with fewer pain sites, and 22% reported more pain sites at follow-up than at baseline (fig. 5).

		5-year follow-up		
Baseline		No Pain	Pain from 1-2 sites	Multisite pain (≥3 pain sites)
	No pain	N=83	N=84	N=21
	Pain from 1-2 pain sites	N=124	N=249	N=157
	Multisite pain (≥3 pain sites)	N=53	N=217	N=611

N=262 individuals migrated to a group with more pain sites
N=394 individuals migrated to a group with fewer pain sites
N=943 individuals did not migrate to a group with a different number of pain sites

Figure 5. *Number of participants in the different pain groups at baseline and whether or not they had migrated to different pain groups by the time of follow-up.*

The results of the multinomial logistic regression analysis showed that sleep had an effect on the direction in which the participants migrated to a different pain group. Within the group with no pain at baseline reporting worst sleep (Sleep C), there was an OR of 4.55 (95% CI 1.28-16.12) for reporting multisite pain at five-year follow-up compared with reporting best sleep (Sleep A), adjusted for age, gender and BMI. Within the group with multisite pain and best sleep (Sleep A) at baseline there was an OR of 3.96 (1.69-9.31 95% CI) for reporting no pain at follow-up, compared with worst sleep (Sleep C), adjusted for age, gender, inclusion as case or referent in the MUSIC-Norrtälje study, manual handling, and prolonged sitting. See figure 6.

			5-year follow-up		
Baseline			No Pain OR (95% CI)	Pain from 1-2 sites OR (95% CI)	Multisite pain OR (95% CI)
	No pain[a]	Sleep A Sleep B Sleep C	-	ref 1.43(0.70-2.90) 0.90(0.34-2.40)	ref 2.31 (0.66-8.09) 4.55 (1.28-16.12)*
	Pain from 1-2 pain sites[b]	Sleep A Sleep B Sleep C	-		Ref 1.55 (0.86-2.79) 1.94 (1.08-3.49)*
	Multisite pain[c]	Sleep C Sleep B Sleep A	ref 2.40 (1.00-5.76) 3.96 (1.69-9.31)*	ref 1.19 (0.79-1.78) 1.72 (1.15-2.57)*	-

Figure 6. *Odds ratios (OR) and 95% confidence intervals (95% CI) for reporting an increased or decreased number of pain sites at follow-up. The effects of Sleep A (best sleep), Sleep B and Sleep C (worst sleep). Ref=Reference category for respective analysis.* *p<0.05; [a] *Adjusted for age, gender and BMI;* [b] *Adjusted for age, gender, and inclusion as a case or referent in the MUSIC-Norrtälje study;* [c] *Adjusted for age, gender, inclusion as a case or referent in the MUSIC-Norrtälje study, manual handling, and prolonged sitting.*

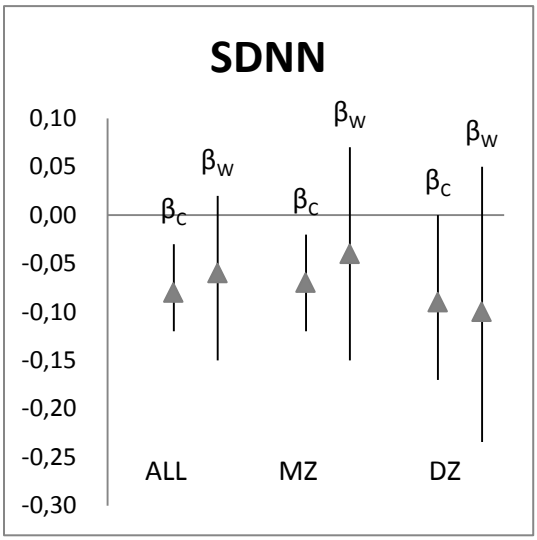
5.4 STRESS, HRV AND SLEEP QUALITY

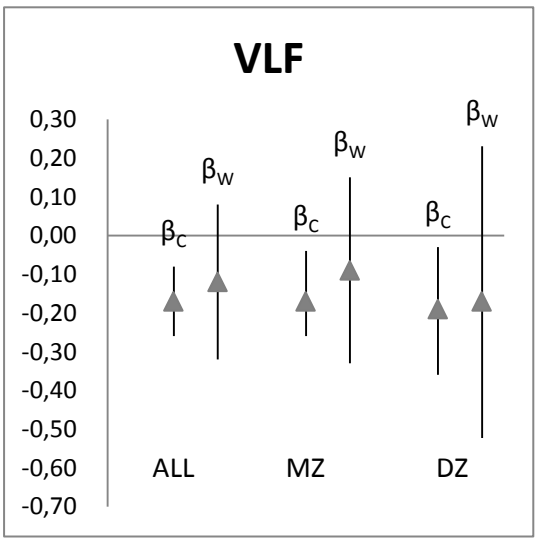
The results from paper III show that higher ratings on perceived stress during the day was significantly associated with altered night time HRV (SDNN, VLF and LF), higher HR ,and lower sleep quality the subsequent night (fig.7).

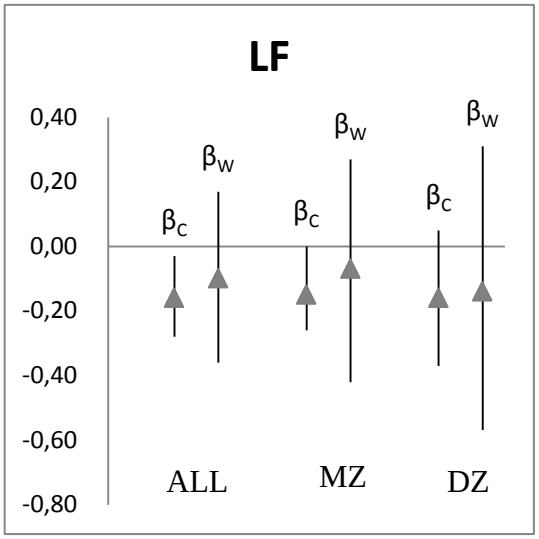
Also, associations between the potential (health-related) daily stressors, hearing disabilities and tinnitus and HRV, HR and sleep quality were investigated in paper III. No associations between the health-related stressors and the outcomes were detected.

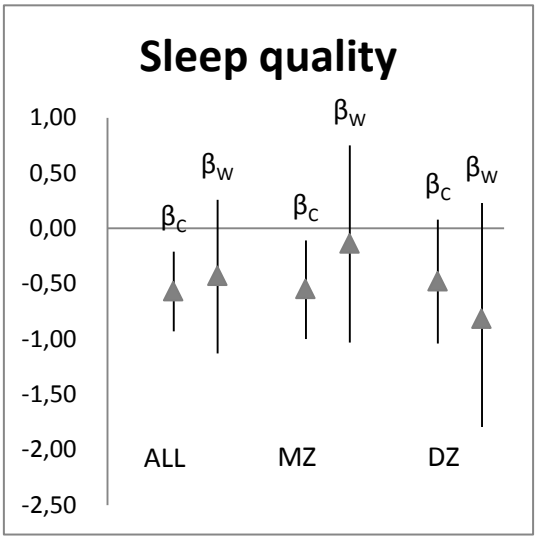
In the within-pair analysis, taking within-twin-pair similarities into account among both MZ and DZ twins, the associations were attenuated, and no longer significant. The results indicate that changes in HR, HRV and sleep quality subsequent perceived stress during the day, are influenced by within-twin-pair similarities, i.e., genetic and shared familial environmental factors (fig. 7).

Further, estimates of the proportions of heritability, shared environment and unique environment explaining individual variance on the HRV indices, HR and sleep quality were made using SEM. The results show that heritability explained 33-49% of the variance of the HRV indices HF, LF, VLF, RMSSD, and SDNN. Variance in HR was influenced mainly by shared and unique environment, and variance in sleep quality was estimated to be influenced to 82% by factors related to unique environment, and to 18% by heritability factors.









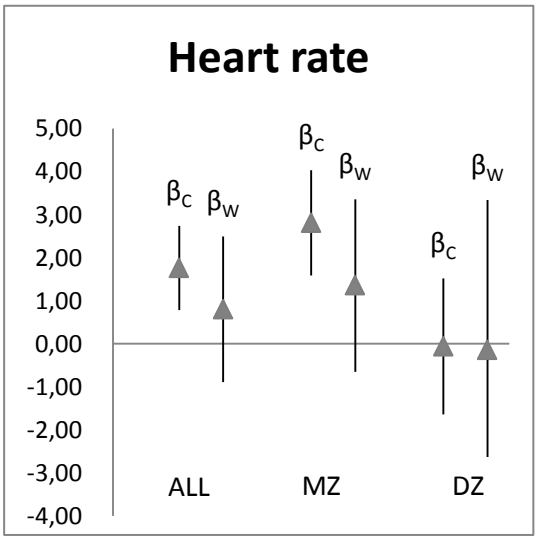


Figure 7. *Crude beta estimates and 95% confidence intervals describing associations between perceived stress and SDNN, VLF, LF, heart rate, and sleep quality.* β_C *= Expected change in outcome for one unit increase in perceived stress;* β_W*= Expected change in outcome for one unit increase in twin`s deviation from the twin-pair mean score on perceived stress. ALL=All twins eligible for the analysis in question; MZ= Monozygotic twins; DZ= Dizygotic twins*

5.5 RELIABILITY AND GENDER DIFFERENCES IN SLEEP ASSESSMENTS

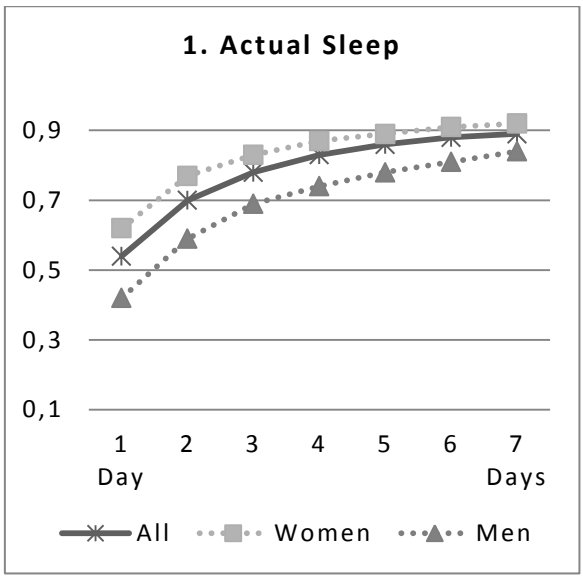
In paper IV, some methodological concerns when performing sleep measurements, subjective and objective, were investigated. The correlation between objectively measured sleep efficiency and subjectively measured sleep quality was low overall and altered over the different days of the study. Over the different study days, the correlation was at its highest on day 2 (0.37), and lowest on day 7 (-0.02). Over the different days of the week, the correlation was highest on Thursday night (0.32) and lowest on Saturday (0.05).

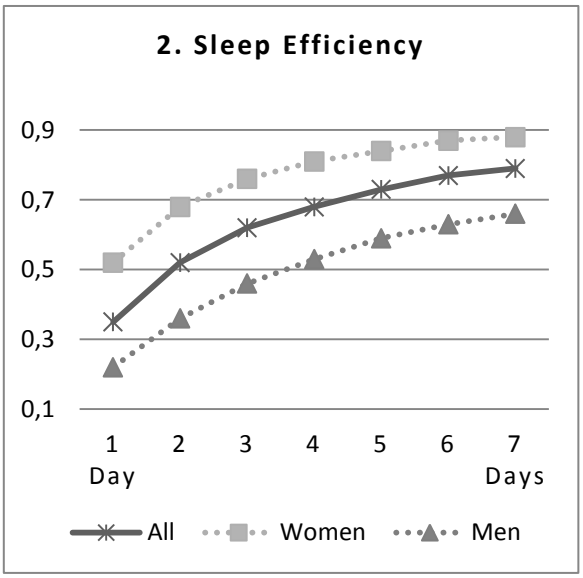
Through intra-class correlation using the Spearman-Brown formula, correlation coefficients were calculated for sleep measurements of one up to seven subsequent nights. The results show that the objective (actigraphic) sleep parameters, actual sleep (2 days), sleep efficiency (5 days) and fragmentation index (4 days), required fewer days of measurements for a reliable sleep measure than objective sleep duration (>7 days) and self-reported sleep quality (6 days). There were, however, gender differences in the reliability of the measurements. Sleep duration and sleep efficiency had the largest gender differences, and self-reported sleep quality and fragmentation the smallest gender differences (fig. 8). Including weekends in sleep measurements attenuated the reliability of all the sleep parameters as compared with only including week nights in the period of measurement (table 5).

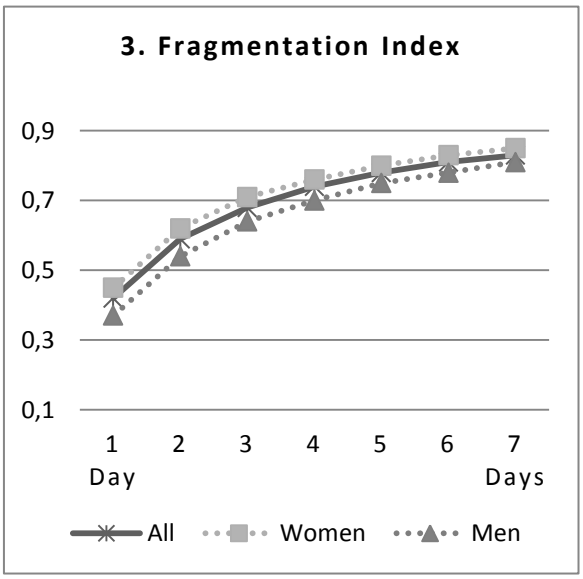
Table 5. Estimates for a single measure (ICC for a single measure, equivalent to the Spearman-Brown coefficient for a single measure) and the number of days of measurement (1 to 4) required for the reliable measuring of objective sleep parameters and subjective sleep quality. Results from when only week days are included in the period of measurement (Monday through Thursday) and from when weekend days are also included (Thursday through Sunday). When 4 days were not sufficient to reach reliability (a Spearman-Brown coefficient of >0.7), number of days required are presented in parentheses.

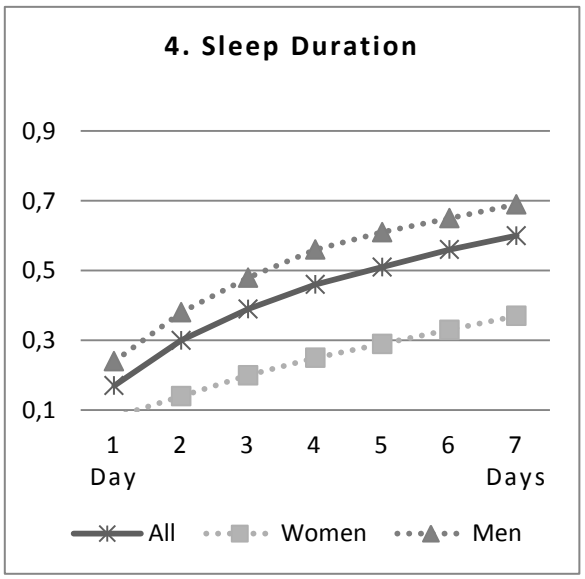
	Mon through Thurs		**Thurs through Sun**	
	ICC single measure	Days required	ICC single measure	Days required
Actual Sleep %	0.635	≥2	0.480	≥3
Sleep efficiency %	0.449	≥3	0.336	(>4)
Fragmentation index	0.452	≥3	0.404	≥4
Sleep duration[a]	0.386	≥4	0.017	(>4)
Sleep quality index[b]	0.370	≥4	0.206	(>4)

[a] Sleep end – sleep start; [b] Self-reported sleep quality from sleep diary.









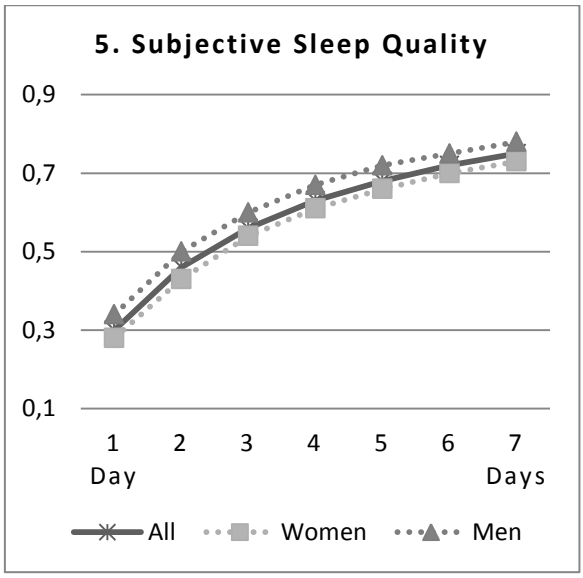


Figure 8. *Presentation of Spearman-Brown coefficients (y-axis) by number of days of measurement (x-axis) for All (the full group, n=54); Women-only (n=25), and Men-only (n=29). Graphs 1-4 present sleep parameters from the objective actigraphic measures, and graph 5 subjectively reported sleep quality (indexed from the sleep diary). A coefficient >0.7 indicates satisfactory reliability. The Spearman-Brown coefficient for day 1 is equivalent to the ICC coefficient for a single measure.*

5.6 ADDITIONAL ANALYSIS

5.6.1 Sleep, pain and sickness absence

Previous research has shown that pain intensity predicts poor prognosis of LBP [108] and increased risk of sickness absence in LBP and NSP [149]. Thus, additional adjustments were made for pain intensity. Grouping was performed according to: 1) Solely LBP; 2) Solely NSP; 3) Concurrent LBP and NSP. The trend for pain intensity with different sleep disturbances showed small differences in pain intensity between Sleep A and Sleep C within all three pain conditions, with the largest difference in the group with concurrent LBP and NSP (table 6). After adjusting for pain intensity in the analysis investigating the odds ratio for sickness absence, the effect of sleep remained for the groups with solely LBP and solely NSP, not (just) for the group with concurrent LBP and NSP. The results show that sleep disturbances had a larger effect on sickness absence within the group with solely NSP as compared with the group with solely LBP, but the confidence intervals were rather wide (table 7).

Table 6. The three levels of sleep disturbance among participants with solely LBP, solely NSP and concurrent LBP and NSP. Number of individuals (n), proportion (%) of sickness absence (sick. abs.), and mean pain intensity (pain int. 0-10).

	Solely LBP			**Solely NSP**			**Concurrent LBP and NSP**		
	n	% Sick abs.	Pain int. Mean (sd)	n	% Sick. abs.	Pain int. Mean (sd)	n	% Sick. abs.	Pain int. Mean (sd) Neck/ low back
Sleep A	190	31	4.2(1.6)	105	30	4.2(1.5)	148	41	3.8(2.0)/ 4.3(1.6)
Sleep B	147	37	4.1(1.5)	106	30	4.1(1.7)	183	47	4.3(1.9)/ 4.4(1.6)
Sleep C	133	47	4.5(1.8)	118	55	4.4(1.8)	278	56	4.7(2.0)/ 4.8(1.8)
Total n	**470**			**329**			**609**		

Table 7. The effect of sleep on odds ratios (OR) and 95% confidence intervals (95% CI) for sickness absence ≥14 consecutive days, stratified into Solely LBP, Solely NSP, and Concurrent LBP and NSP.

	Solely LBP	**Solely NSP**	**Concurrent LBP and NSP**
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Model 1			
Sleep A	1	1	1
Sleep B	1.31 (0.83-2.07)	1.00 (0.55-1.82)	1.25 (0.80-1.95)
Sleep C	**1.89 (1.19-3.00)****	**2.83 (1.61-4.96)****	**1.71 (1.14-2.58)***
Age	1.01 (1.00-1.02)	1.02 (1.00-1.04)	1.01 (1.00-1.03)
Gender	1.42 (0.97-2.10)	1.48 (0.88-2.48)	1.70 (1.20-2.40)**
Model 2			
Sleep A	1	1	1
Sleep B	1.31 (0.83-2.06)	1.01 (0.55-1.82)	1.21 (0.77-1.90)
Sleep C	**1.84 (1.15-2.92)***	**2.80 (1.60-4.91)****	1.50 (0.99-2.30)
Age	1.01 (0.99-1.03)	1.02 (1.00-1.04)	1.01 (1.00-1.03)
Gender	1.42 (0.96-2.09)	1.46 (0.87-2.46)	1.56 (1.10-2.22)*
LBP intensity	1.01 (0.99-1.02)	-	1.01 (1.00-1.02)**
NSP intensity	-	1.01 (0.99-1.02)	1.02 (1.00-1.03)

*p<0.05; **p<0.01

6 DISCUSSION

The overall purpose of this thesis was to study markers of general stress as early indicators of changes in strain. Markers of this kind are assumed to be feasible measures to include when evaluating health outcomes in conjunction with interventions in clinical settings and workplaces.

Work ability and sickness absence are relevant factors to consider in relation to health in a working population. When evaluating interventions it would be of value to use markers that indicate early general changes in wellbeing and risk of sickness absence. As a step towards identifying feasible markers of stress, this thesis has considered sleep disturbances and HRV during sleep. More specifically, sleep has been studied as a potential indicator of change in the risk of increased/decreased wellbeing (based on reported pain) and sickness absence. Further, the influence of genetic and/or familial environmental factors on indicators of prolonged stress responses after daytime stress (measured by HRV and sleep quality) has been investigated. The hypothesis is that changes in markers that indicate early signs of general stress predict general change in wellbeing and risk of sickness absence.

6.1 MAIN FINDINGS

In paper I and paper II participants were grouped by their pain status. By doing so, three contrasting groups with regard to pain (and baseline exposure) were investigated. In paper I sleep disturbances assessed by a global sleep questionnaire was found to indicate an increased risk of sickness absence among individuals free from spinal pain, among individuals with solely LBP or NSP, and among individuals with concurrent LBP and NSP. Further, sleep seems to tell us something about the prognosis of pain development. It was shown in paper II that worse sleep predicted the onset of multisite pain five years from baseline, and that sleeping well if having multisite pain predicted resolution from multisite pain five years later. Taken together, all this implies that having sleep problems is a factor indicating individual vulnerability to lower wellbeing. In both study I and study II, the study participants were grouped according to musculoskeletal pain. Having musculoskeletal pain may be considered a stressor and a vulnerability factor in itself. The overall results from study I and study II, based on the hypothetical model presented in fig. 3, are presented in fig. 9.

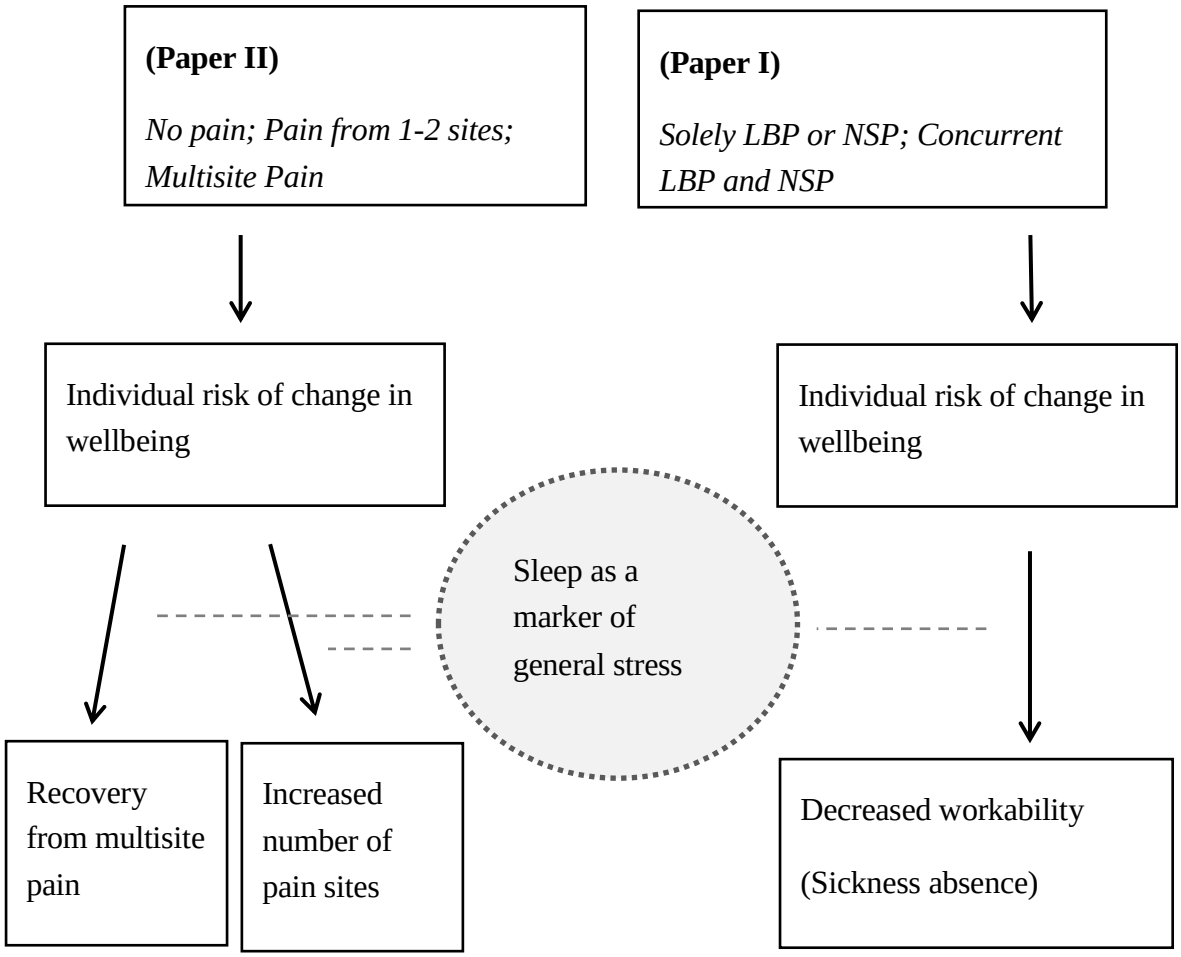


Figure 9. *Model integrating results from paper I and paper II in the hypothetical model (fig.3, presented in the Background). Different pain status at baseline represents different baseline exposure, with individual risk of change (increased/decreased) in wellbeing. The present or absence of sleep disturbances is a marker of the individual risk of increased/decreased wellbeing (paper II) and decreased workability (paper I).*

As shown in paper III, individual differences in responses to everyday life stress, by suppressed sleep quality, increased HR, or differences in HRV, may be explained by factors related to familial similarities. This indicates that familial factors (genetic and/or shared environment) at least partly explain the individual differences in stress responses captured by sleep, HR, and night time HRV. In the search for a feasible prognostic marker to use in interventions, sleep has the advantage of being easy to measure and interpret. However, as shown in paper IV, when measured repeatedly over several subsequent nights, some methodological considerations arise. Objectively measured sleep (using an actigraph) requires fewer nights of measurement, especially if only measurements during weeknights are used, than subjectively measured sleep. However, objectively and subjectively measured sleep correlates poorly on a day-by-day basis, and it is likely that objective and subjective sleep measures capture different dimensions of sleep.

6.2 SLEEP AS A PREDICTOR OF WELLBEING AND SICKNESS ABSENCE

In paper I, the effect of sleep disturbances on risk of sickness absence was investigated. The result implies that sleep disturbances increase the risk (OR) of sickness absence (of >14 consecutive days) up to five years from baseline. The OR of sickness absence was investigated in three different groups: 1) people with no LBP or NSP; 2) people with solely LBP or NSP; and 3) people with concurrent LBP and NSP. The stratification was made under the presumption that it represents three separate groups with regard to wellbeing at baseline, assuming that the third group represents individuals with poorer wellbeing, and already at heightened risk of sickness absence.

In all three groups, sleep had an impact on the risk of sickness absence. The effect of sleep was highest in the second group, with solely LBP or NSP. That sleep disturbances predict sickness absence is in line with the findings of previous prospective studies. In fact, out of 16 identified studies [11, 12, 33-45, 150] only one presented a conflicting result [150].

There seems to be only one previous study investigating the joint effect of sleep disturbances and musculoskeletal pain on risk of sickness absence. The results of this recent Finnish study, with one Norwegian and one Finnish cohort, were that comorbid insomnia and pain was more strongly associated with higher risk of sickness absence than solely insomnia or solely pain, which is in line with the finding in paper I [36].

In a large prospective study, of 56,700 employees in Finland by Salo and colleagues [12], sleep disturbances were found to predict all-cause sickness absence, sickness absence due to mental disorders, diseases of the circulatory systems, and musculoskeletal diseases. Further, they found that poor sleep at baseline was associated with delayed return to work after a period of work disability due to musculoskeletal disorders (men and women), and due to mental disorders (men only) [12]. In another study by Salo and colleagues [39], sleep disturbances were measured at two time points (with approximately two years in-between) and sickness absence of >9 days during the year subsequent to time point 2. The fully adjusted results from the study showed that fluctuating sleep disturbances (decreasing, or increasing) and stable moderate and stable severe sleep disturbances predicted all-cause sickness absence and sickness absence due to musculoskeletal disorders. Increasing sleep disturbances predicted sickness absence due to mental disorders, and stable severe sleep disturbances between the two time points predicted sickness absence due to injuries and poisonings [39]. Another large Finnish study, by Vahtera and colleagues [44], showed that individuals with sleep disturbances were more likely to have sickness absence spells after a stressful life event (death or severe illness in the family) for up to 30 months after the occurrence of the event, as compared with individuals experiencing death or illness in the family who slept well [44]. The results of the studies imply that sleep disturbances mark a vulnerability with a general increased risk of poorer wellbeing and workability, which is in line with what is suggested in this thesis.

In paper II, number of pain sites was investigated as an indicator of wellbeing, both at baseline and at five-year follow-up. A majority (69%) of people reporting multisite pain at

baseline also reported multisite pain at five-year follow-up (fig. 5). Only 6% of those individuals reporting multisite pain at baseline reported being pain free at follow-up. Sleep was shown to predict the prognosis of pain. Disturbed sleep predicted the onset of multisite pain assessed five years later among people who were pain free at baseline, and good sleep predicted the transition from multisite pain to no pain five years from baseline.

In a recent study of Finnish firefighters with 13-year follow-up, sleep disturbances predicted the onset of radiating LBP and membership of a group experiencing chronic radiating LBP throughout the study period [151]. Sleep disturbances have further been shown to predict hospitalization due to back pain [152], the onset of chronic widespread pain [153], and increased number of pain sites [154]. That good sleep predicts the resolution of (at least chronic widespread) pain has also been shown previously [126], which supports the hypothesis that sleep predicts prognosis of musculoskeletal pain, as suggested in this thesis. Further, sleep problems among patients with persistent pain have been shown to predict depression in a recent British study by Campbell and colleagues. Pain interference (in people with normal work during the past 4 weeks) proved to have a significant, albeit minor, mediating effect on the relationship [155].

6.2.1 Clinical significance

Musculoskeletal pain disorders are often complex and recurrent by nature. It would be of great value to identify individuals at risk of poorer prognosis at an early state. Including sleep in the anamnesis when meeting a patient with musculoskeletal pain may be one strategy for identifying individuals at risk at an early stage. Further, sleep is reasonably easy to measure by questionnaire.

Musculoskeletal pain and psychological illness are the two most common causes of sickness absence. Many patients affected become involved in rehabilitation programs, sometimes including workplace interventions under the regime of OHS. In handling these patients, it would be of great value to evaluate not only the progress of the specific disorder but also to include markers of wellbeing in a more general sense. Studies I and II suggest that sleep is a feasible general marker, indicating changes in wellbeing and risk of decreased workability.

Moreover, the results presented above imply that it may be beneficial to have interventions that target sleep among patients with musculoskeletal pain and concurrent sleep disturbances. However, only a few studies have investigated such potential effects. Two studies that support beneficial effects of sleep interventions on pain have been found. One found that treating sleep problems with cognitive behavioural therapy among patients with musculoskeletal pain reduced pain intensity [156], the other saw effects on pain interference with daily life [157]. Hopefully, more studies of this kind will be presented in the near future.

6.2.2 Methodological considerations

The MUSIC-Norrtälje study (from which data for papers I and II were used) was a case-referent study, where cases were included when people sought care for LBP or NSP. Thus, there was probably a higher prevalence of musculoskeletal pain in the cohort investigated in the two studies than there would have been in the general population. The studied cohort also probably included a larger proportion of individuals who had sought care for their pain than in the general population. Pain was self-rated, so some individuals recruited as referents also reported pain. Among those with "No LBP or NSP" in study I, 9% were recruited as cases, whereas within the groups "Solely LBP or NSP" and "Concurrent LBP and NSP", the proportions were 57% and 66% respectively. In study II, 1% within the group "No Pain" were recruited as cases, 31% in the group with "1-2 pain sites" and 51% in the "Multisite pain group". It has been suggested that individuals seeking care for their pain have worse pain, more disabling pain, and a poorer health status overall [158]. Thus, the grouping may have led to the creation of groups that contrasted with each other with regard to more aspects of wellbeing than that induced by pain, which is considered a strength of the study. Sleep proved to predict sickness absence in all three group despite these differences.

Further, both pain and sleep disturbances were self-reported, which may give rise to some problems in interpreting the results. Apart from capturing grade of pain and sleep disturbances, the scoring may also reflect individual tendencies to extreme or neutral scores. Even from this perspective, the stratification may have had a useful purpose.

The benefit of grouping, i.e., obtaining three contrasting groups with regard to baseline wellbeing, however, was realised at the cost of reduced statistical power. This was seen above all in paper II, whose results are presented with very wide confidence intervals. Larger studies are needed to obtain more certain risk estimates.

In paper I age, gender, physical illness (including cardiovascular, respiratory, gastrointestinal, urogenital and metabolic diseases), regular physical activity and smoking were included as potential confounders. Other studies that have investigated the association between sleep disturbances and sickness absence have also adjusted for emotional symptoms or mental illness (e.g., depression/anxiety) [12, 33, 35, 38-45, 150] as well as sociodemographic variables [11, 12, 34, 36-38, 40, 41, 43, 44, 150, 159]. Even though the effect of pain on the association between sleep and sickness absence was accounted for in most previous studies [12, 33, 35-37, 40-42, 45], only one investigated the separate and joint effects of pain and sleep disturbances (insomnia) on risk of sickness absence [36]. Unfortunately, for paper I, no variable measuring mental illness (that did not include sleep disturbances) was available. Nor did the Finnish study investigating the joint effect of pain and insomnia on risk of sickness absence include mental illness as a covariate [36]. In paper I and in this thesis, however, our main interest in sleep lay in its feasibility as a prognostic marker among individuals with increased risk of decreased wellbeing. Eliminating all other explanatory factors in a model, thereby leaving a model that explains causality was not the main focus of the thesis. Although sleep disturbances among individuals with musculoskeletal pain may be closely related to factors like ability to cope,

distress, anxiety, depression and worry about the future, responding with sleep disturbances may still be the marker of interest.

Including pain intensity as a covariate in the additional analysis somewhat attenuated the effect of sleep disturbances on sickness absence in the stratum with concurrent LBP and NSP (OR 1.50; 95% CI 0.99-2.30), which resulted in a (just) non-significant OR. Pain intensity had, however, very little effect on the stratums including individuals with solely LBP or solely NSP (table 7). Pain intensity was a significant predictor of sickness absence for the stratum with concurrent LBP and NSP, but the effect was low (OR 1.01; 95% CI 1.0-1.02). The results imply that sleep disturbances are more closely related to perceived pain intensity among individuals with concurrent LBP and NSP than among individuals with solely LBP or solely NSP. The results also imply that sleep disturbances are a stronger independent predictor (i.e., independent of pain intensity) of poorer wellbeing and sickness absence in individuals with spinal pain from a single site.

6.3 MARKERS OF STRESS AND INDIVIDUAL DIFFERENCES

The markers of stress investigated in this thesis included sleep and HRV during sleep, so as to capture markers of prolonged daytime stress with potential health effects. There are most likely large individual differences in how we respond to stressful situations. McEwen [7] regards these differences as dependent upon two principal factors: 1) Behaviour, how the individual perceives and interprets the situation, and 2) Biological mechanisms, that individual differences in reactivity are based upon genetic make-up, gender and developmental history [7]. In paper III, individual differences in responses to everyday life daytime stress were investigated by considering the influence of genetic and/or environmental factors (shared within the family). The results show that when including the effect of genetic and/or familial environmental factors in models describing the relationship between 1) daytime stress and HRV during sleep and 2) daytime stress and sleep quality the subsequent night, the strength of the relationship is attenuated (fig. 7). The findings suggest that individual differences in vulnerability to daytime stress, captured by differences in sleep quality, HR or HRV during sleep (with the potential increased risk of negative health effects), are at least partly explained by genetic and/or familial environmental differences.

Further, the estimated proportion of the variance in HRV, heart rate and self-reported sleep quality, attributed to heritability was investigated in paper III. Between 33-49% of the variance of HRV (except for the LF/HF parameter) and 18% of the sleep-quality variance were estimated to be explained by heritability. The influence of a heritability factor in the HRV and sleep quality parameters is supported also by the results of the intra-class correlation, where MZ twin pairs were found to be more similar on the HRV and sleep quality parameters than the DZ twin pairs. Between 67% and 51% of the variance in the HRV parameters and 82% of the variance of sleep quality were attributed to unique environmental factors (not shared within the family). The variability in heart rate was best estimated by a model including only environmental factors shared within the family and unique environmental factors, at a rate of approximately 50/50. However, after excluding individuals

using medications altering heart rate, the results came out differently; 58% of the variance in heart rate was explained by heritability, 42% by unique environmental factors. One explanation for the observed change in heritability after exclusion lies in loss of statistical power. Another possible explanation is that exclusion of individuals using the medications rules out an important group to investigate. If you select a sample of 50+ men not using beta blockers, antidepressants or anti-epileptics because you believe that use of those medications might alter HRV, you may have excluded an important group from the sample if depressed HRV actually has health effects.

Altogether, the results in paper III indicate that some of the sustained reactions to daytime stress may be explained by heritability, which is supported by previous research. Heritability has been found to explain 29% (among women) and 43% (among men) of the variance in sleep reactivity to stress [26]. Heritability of cardiovascular reactivity to stress has been investigated in the laboratory, investigating reactivity to acute stress, where 18-49% of the reactivity was seen to be explained by heritability [160].

According to the results of study III, HRV (at least SDNN, VLF and LF), HR and sleep quality capture differences in daytime levels of stress. The perceived stress during the day in paper III was measured by a single item ("Have you felt stressed today?") using a VAS (0-100) scale. This item was chosen in order to capture stress or symptoms of stress in a global sense, without separating out work-related stressors, family-related stressors, worry, and other stressors. The question (or similar) is likely to be one of the most commonly used in clinical anamnesis, e.g., when meeting patients. The findings of paper III, that individual differences related to familial factors influence sustained stress response, fit well with the hypothesis that sleep disturbances and HRV during sleep are feasible markers of individuals' vulnerability to stress.

6.3.1 Clinical significance

The results suggest that perceiving general (non-specified) stress during the day can be captured by changes in sleep quality and HRV the subsequent night. This suggests that both measures may be sensitive enough also to capture changes in everyday life stress. Both measures were influenced by genetics and/or familial factors related to the environment when growing up. It also suggests that sleep disturbances (and HRV during sleep) subsequent to daytime general stress not only is relative to the magnitude of the exposure, but also says something about the individual's vulnerability to stress. Using sleep disturbances and/or HRV during sleep as markers of general stress with potential health effects may then be more informative than asking about stress (at least in one general question).

The results, however, also point to difficulties in using HRV as a marker in clinical settings. Even though the method is interesting because of its ability to measure ANS activity relatively easily, there are still some difficulties in interpreting the physiological meaning of the HRV outcome. In study III, perceived stress was found to be associated with altered SDNN, VLF and LF, but not with RMSSD or HF. SDNN is a global measure of HRV, and

the physiological meaning of LF and VLF (with regard to sympathetic and parasympathetic tone) is still not entirely understood [80, 81]. Further, the method is sensitive to other physiological responses, such as physical activity, and, even if the measurements are taken during sleep, it may be difficult to interpret the outcomes of the HRV variables at an individual level (at least as markers of stress). Sleep has the advantage of being easier to measure and interpret, and is therefore probably a more feasible marker in clinical settings. Moreover, sleep disturbances serve as a better indicator of how to intervene than HRV.

6.3.2 Methodological considerations

The study participants described in paper III differed from the other studied groups, in papers I, II and IV. In study III, all participants were men, and they were older, and most of them had retired from work. This probably affected the study results, and should be considered when interpreting their meaning for a general working population. A higher age is associated with decreased HRV [161], and being retired may have influenced the rates of perceived stress. Further, it has been suggested that prevalence of insomnia increases with age and is less common among men [162]. In the twin study (with an older population), mean sleep quality was 16.0, while in the SHIP study (including a working population, men and women), it was 16.7, indicating that the individuals in the SHIP study rated their sleep to be somewhat better.

The purpose of using a single item, with VAS (0-100) scoring, to assess daytime stress was to capture general everyday life stress with a relatively continuous variable. If a scale with fewer rating steps had been used, there would have been less variance, which would have decreased statistical power. However, the clinical significance of the differences in stress ratings from this scale, with millimetre-wide scale steps, is difficult to interpret.

Overall, the participants in study III scored rather low on the stress scale. The results may have come out differently if the study had included individuals with higher stress levels.

6.4 SLEEP ASSESSMENTS

There are different approaches to assessing sleep, and assessments differ according to the context in which sleep is of interest. A commonly used method to capture general sleep disturbances is to use questionnaires about how sleep typically has been during a particular past period of time. This approach was adopted for studies I and II in this thesis. If the interest lies in investigating how sleep was for one or a few specific nights, a sleep diary and/or objective measures (such as polysomnography or actigraphy) can be used. A sleep diary was used to assess sleep in paper III, capturing sleep for one night only. For paper IV, a sleep diary and actigraphy were used simultaneously to assess sleep repeatedly over seven consecutive nights.

As well as choosing between a more general questionnaire regarding how sleep typically is and sleep assessments of one or several nights during a specific period of time, there are some methodological issues to consider.

First of all, do subjectively and objectively assessed sleep capture the same thing? In paper IV, the correlation between self-rated sleep quality and actigraphy-measured sleep efficiency was low overall, indicating that they do not completely translate into one another. Other studies have also found discrepancies between subjective and objective measurements of sleep, suggesting that they capture different dimensions of sleep [72-74]. It has been found that going to bed late, use of medications, employment, higher body mass index (BMI), increased daylight hours and longer menstrual cycles are associated with poorer objective (actigraphic) sleep, and that unemployment and perceived stress are associated with poorer subjective sleep quality [75]. Further, another study found that subjective sleep efficiency was associated with over-commitment, low level of social support, and poorer self-rated health, whereas objective sleep measures were not [74].

Second, if repeated measures over a specific time period are of interest to assess, how many days of measurement would be required for a reliable measure of sleep? And does it matter which days of the week that are included in the measurements? Overall, the results from paper IV show that fewer nights of measurements are needed for actigraphy-measured sleep than for self-reported sleep. If measurements are performed during week nights only, fewer nights of measurement are needed for a reliable sleep measure than when including weekends; four nights would then be sufficient for both subjective (if using a sleep quality index) and objective (actigraphy) measurement. Previous studies have not found as large differences in sleep measurements between week nights and weekend nights as seen in paper IV [75, 77]. This may be explained by different study populations (previous studies have included children and adolescents only [77] and women only [75]). However, sleep during weekends may provide valuable information about recovery during leisure time.

Sleep duration seem to be the parameter that differs the most on a day-by-day basis, especially when including weekend measures. It is reasonable to believe that if sleeping poorly or too few hours one night, people try to compensate for sleep loss by going to bed earlier the next night. Previous studies have shown that a larger day-by-day variability in (actigraphy) sleep duration is associated with poorer subjective sleep quality, and poor subjective wellbeing [163] and stress [164].

6.4.1 Clinical significance

When sleep is to be measured as part of evaluating an intervention or in a clinical setting, there are some specific issues to take into account (as indicated in study IV). Actigraphy has the advantage of providing an objective measure of sleep, and is potentially more sensitive to capturing small changes in sleep after intervention. However, it seems that objectively and subjectively measured sleep capture different dimensions of sleep. Thus, there is the possibility that self-rated sleep is more strongly associated with some of the self-rated health effects of interest when evaluating an intervention.

6.4.2 Methodological considerations

All participants in study IV were working in the same workplace, and may therefore be more homogenous than a random sample from a general population would be. Being in a study together with colleagues can also have increased compliance, which may explain the overall low proportion of missing data (90% had full actigraphy data). Previous studies have found up to 28% missing data on weekly recordings with actigraphy [77].

Repeatedly responding to the same questionnaire for seven subsequent days may have influenced the results, which is worth considering when performing measurements of sleep repeatedly in the field. The respondent`s attitude to and interpretation of the questions may not be the same on the first day as when responding to the same questionnaire the fifth or sixth time. From this perspective, having an objective complement to subjective sleep measures when they are performed repeatedly can be of value.

Future prospective studies should investigate whether objective and subjective sleep differ with regard to how they predict health outcomes.

6.5 DISCUSSION OF THE INCLUDED STRESS MARKERS AND FEASIBILITY IN THE FIELD

In order to maintain a healthy workforce, it is reasonable to believe that interventions targeting a workplace at group level, as well as at individual level, are of importance. The markers investigated in this thesis were chosen based on the hypothesis that they were feasible in field when performing repeated measurements to capture changes at a group level.

In all, four different ways of assessing markers of stress have been used in this thesis:

- A sleep questionnaire measuring global sleep disturbances (sleep disturbances over the past six months) (papers I and II) *(subjective)*
- Sleep quality for one specific night (by sleep diary) (papers III and IV) *(subjective)*
- Objective measure of sleep by actigraphy (paper IV) *(objective)*
- HRV and HR during sleep (paper III) *(objective)*

Subjective measurements: A questionnaire for the assessment of global sleep disturbances by referring to the recent period of time have the advantages of being easy to distribute to a large group and easy to extract data from. One possible advantage of a global measure of sleep is that it can distinguish short-term periodic sleep disturbances from long-term or recurrent disturbances. It is possible that the tendency repeatedly to suffer from sleep disturbances is a more informative indicator of general stress than a short period of sleep loss (captured when assessing sleep over a shorter specific period of time) followed by recovery.

However, if changes over shorter periods of time are of interest, measurements during some specific days may be preferable. Then, a subjectively measured sleep diary, an objective actigraph, or objective HRV over a set of specific nights may be feasible options.

The subjective sleep diary is easy to distribute and easy to extract data from.

Objective measurements: An actigraph may be a feasible objective complement to subjectively measured sleep. The actigraph is also easy to distribute and relatively easy to extract data from. One advantage of the actigraph is that it can be administered at a distance. This was tested in study IV, where actigraphs were uploaded at the researcher`s office, then distributed to the study participant, together with simple instructions for use via the workplace.

The HRV measure is relatively easy to administer, and the device can be attached in the field, although it requires a computer to start measurement. The disadvantage of HRV is that it is rather time-consuming to extract data from. There are some technological issues to consider, e.g., which software program to use and how to handle noise in the data. From the experiences of assessing data in study III (HRV) and study IV (actigraph), the risk of (at least partly) missing data due to technical issues (or, for example, episodes with bad electrode contacts) is higher with HRV. Further, even though changes in HRV may be seen at group level, interpretation of the physiological meaning of the data is difficult. Another advantage of sleep measurement as compared with HRV measurement is that sleep is easier to influence at individual level, e.g., with cognitive behavioural therapy [156, 157].

Both the associations between everyday life stress and HRV, and everyday life stress and sleep quality, were influenced by factors related to genetics and/or familial environment (at least in the group with overall relatively low stress scores, as seen in paper III). This knowledge is of importance when interpreting the data assessed, i.e., in order to understand why, at group level, changes are seen among some, but not others.

7 SUMMARY AND CONCLUSIONS

- Disturbed sleep predicted sickness absence for up to five years from baseline. This was seen within all three groups with different baseline exposures (wellbeing/stress) 1) No LBP or NSP, 2) Solely LBP or NSP, and 3) Concurrent LBP and NSP.

- Disturbed sleep predicted the onset of multisite pain five years later in a group reporting no pain at baseline.

- Good sleep predicted migration from a group with multisite pain at baseline to reporting no pain at five year follow-up.

- Daytime stress influenced changes in HRV measures and sleep quality the subsequent night.

- Responding with changes in HRV during sleep or decreased sleep quality to perceived daytime stress was seen to be influenced by factors related to genetic and/or early familial environmental factors.

- Some issues need to be taken into account when performing a sleep measurement, depending on the context. If performed repeatedly over several consecutive nights, at least four nights of measurement are recommended to obtain a reliable measure, for both actigraphy and subjective sleep quality.

- There seems to be a difference between sleep measurements taken over weeknights and weekend nights. If a set of measurements includes weekend nights, more (consecutive) nights of measurement are needed for a reliable measure.

- Objective sleep measurement (using a wrist-worn actigraph) is easier to administer, easier to interpret, and less time-consuming than HRV measurement, and may therefore be more feasible in the field.

7.1 FUTURE RESEARCH

More research is needed to understand the feasibility of sleep as an early marker of wellbeing and stress. One way would be to test the ability of sleep measurements (objective and subjective) to capture repeated small changes at several time points before, during and after an intervention. Moreover, the impacts of these changes in sleep patterns on different health outcomes need to be investigated further.

Further, it would be interesting to pursue research aiming to increase our knowledge on level of prolonged stress and reactivity to stress (i.e., to investigate whether stress exposure is transformed into a response that is associated with harmful health effects).

Further research is needed better to understand the difference between subjective and objective sleep. Prospective studies investigating differences in what (health outcomes) the two methods predict are welcome. Also, more knowledge is needed to understand the effect of responding more than once to the same questionnaire (e.g., over several subsequent days/nights). What does it really measure?

Potentially, interventions targeting sleep (e.g., cognitive behavioural therapy) may be relevant as complements to traditional therapy targeting pain disorders. More research is needed to understand the effect of such interventions on recovery from pain disorders.

8 ACKNOWLEDGEMENTS

I would like to express my deepest gratitude to all of you who have been around, supporting and cheering me on during my work. It has been a challenging journey and I can`t express in words how grateful I am for being given the opportunity to undertake it. There are many people who have crossed my path during the work, who have made it worthwhile and fun. I would like to take this opportunity to deliver special thanks to:

My four great supervisors for all their support. You have all been great teachers of research, life and wine. I am looking forward to continuing to work with you.

My main supervisor, Lena Hillert. From day one you have encouraged me, taught me and provided your unfailing support. Thank you for sharing your knowledge about epidemiology, and for showing me the importance of precision and scientific critical thinking. How you manage to always stay in a good mood is beyond my understanding.

My co-supervisor, Magnus Svartengren, for sharing your extensive knowledge of research and keeping me on my toes by asking difficult questions, for believing in me, and not least for employing me at the outset.

Teresia Nyman, co-supervisor, for being a great teacher and friend throughout the process with your sharp mind and generous personality. Thank you for fruitful discussions, for all help with the MUSIC-Norrtälje data, for cheering me on and for all the good laughs.

Ulrich Stoetzer, co-supervisor, for all your support and guidance throughout my work. Thanks for all the work with MiiNA and SHIP, for putting up with my stupid questions, and for uploading me with pretzels in New York.

Sofia Åström-Paulsson, fellow doctoral student and partner in crime, for sharing outbursts, mistakes and laughter, and for all your support when analysing the pros and cons of using "remove" before attaching electrodes.

The Huddinge crew working with the TWINHEAR study, and especially Renata Bogo and Åsa Skjönsberg, co-authors, for all help and good times during measurement of the twins, and for providing a never ending supply of cardamom cookies.

Martin Anderson, co-author, for so patiently explaining HRV to me, over and over and over again.

Natalja Balliu, co-author and statistics adviser, for so patiently explaining statistics to me, over and over and over again.

Pirjo Savlin and Marianne Parmsund for all help, good times, and fine dining during the work with MiiNA.

The Stockholm Stress Centre for financing my work, for interesting workshops and research schools.

To all the study participants who have made this research possible, Occupational Health Services, and the staff of the correctional institution for their invaluable help with SHIP. Thank you!

Alma Sörberg - Wallin, co-doctoral student, for being a great room-mate always up for discussing thoughts on research and life.

My fellow ergonomists and co-workers, Ida-Märta Rehn, Mikael Forsman and Katarina Kjellberg. I am looking forward to joining your gang!

Anna and Lotten, for much needed mini-breaks and lunches in town. Gun, Jenny, Marian, Gunnar, Mattias, Lotta, Theo, Andreas, Filip, Cecilia, Pernilla, Helena, Elin … and all my other former and present colleagues at PHS, IMM and CAMM who made going to work fun, who provided support when needed, who asked the crucial questions when needed, and laughed over mistakes when needed. Thanks!

To all my fabulous friends who I have forced to listen to my worries, and who have endured my ups and downs – thank you for good pep talks and for helping me take my mind off work when needed.

The best family one could ever wish for. My parents, Karin and Mats, for believing in me, for being the best supporters ever, for treating me as a princess when I have visited Halmstad, and for just being the best parents imaginable. My siblings, Lisa, Anki and Arvid, and my brother-in-law, Magnus, and sister-in-law, Cecilia. Although your collective choice to leave Stockholm about two seconds after I moved here may have been a hint (…), I am just so amazed you have put up with me. Don`t know what I would have done without you. And finally the younger crew, Valle, Selma, Hanna, Elsa, Hilda and Signe. I might just be the luckiest aunt in the world.

9 REFERENCES

1. Social Insurance Report 2014:17. Analys av sjukfrånvarons variation [Swedish] Accessed at January 7 2015. Available at: https://www.forsakringskassan.se/

2. The Swedisch Social insurance agency. Accessed at October 2 2015. Available at: http://www.forsakringskassan.se/statistik/sjuk/sjuk_rehabiliteringspenning/sjukochrehabpagaendesjukfall/pagaende_sjukfall

3. Arbetsmiljöverket Report 2014:4. Work-related disorders 2014. Stockholm 2014. Accessed at september 15 2015. Available at: http://www.av.se/dokument/statistik/officiell_stat/ARBORS2014.pdf.

4. Pincus T, Burton AK, Vogel S, Field AP A systematic review of psychological factors as predictors of chronicity/disability in prospective cohorts of low back pain. *Spine (Phila Pa 1976)* 2002;27:E109-20.

5. Linton SJ A review of psychological risk factors in back and neck pain. *Spine* 2000;25:1148-56.

6. Kivimaki M, Kawachi I Work Stress as a Risk Factor for Cardiovascular Disease. *Curr Cardiol Rep* 2015;17:630.

7. McEwen BS Stress, adaptation, and disease. Allostasis and allostatic load. *Ann. N. Y. Acad. Sci.* 1998;840:33-44.

8. McEwen BS Protective and damaging effects of stress mediators. *N. Engl. J. Med.* 1998;338:171-9.

9. Chrousos GP Stress and disorders of the stress system. *Nat Rev Endocrinol* 2009;5:374-81.

10. Akerstedt T, Kecklund G, Gillberg M Sleep and sleepiness in relation to stress and displaced work hours. *Physiol. Behav.* 2007;92:250-5.

11. Akerstedt T, Kecklund G, Alfredsson L, Selen J Predicting long-term sickness absence from sleep and fatigue. *J. Sleep Res.* 2007;16:341-45.

12. Salo P, Oksanen T, Sivertsen B et al. Sleep Disturbances as a Predictor of Cause-Specific Work Disability and Delayed Return to Work. *Sleep* 2010;33:1323-31.

13. Alsaadi SM, McAuley JH, Hush JM, Maher CG Prevalence of sleep disturbance in patients with low back pain. *Eur. Spine J.* 2011;20:737-43.

14. Fishbain DA, Cole B, Lewis JE, Gao JR What Is the Evidence for Chronic Pain Being Etiologically Associated with the DSM-IV Category of Sleep Disorder Due to a General Medical Condition? A Structured Evidence-Based Review. *Pain Medicine* 2010;11:158-79.

15. Smith MT, Haythornthwaite JA How do sleep disturbance and chronic pain inter-relate? Insights from the longitudinal and cognitive-behavioral clinical trials literature. *Sleep Med. Rev.* 2004;8:119-32.

16. Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. *Eur. Heart J.* 1996;17:354-81.

17. Mork P, Nilsson J, Loras H, Riva R, Lundberg U, Westgaard R Heart rate variability in fibromyalgia patients and healthy controls during non-REM and REM sleep: a case-control study. *Scand. J. Rheumatol.* 2013.

18. Burton AR, Rahman K, Kadota Y, Lloyd A, Vollmer-Conna U Reduced heart rate variability predicts poor sleep quality in a case-control study of chronic fatigue syndrome. *Exp. Brain Res.* 2010;204:71-8.

19. Melamed S, Shirom A, Toker S, Berliner S, Shapira I Burnout and risk of cardiovascular disease: evidence, possible causal paths, and promising research directions. *Psychol. Bull.* 2006;132:327-53.

20. McEwen BS, Stellar E Stress and the individual. Mechanisms leading to disease. *Arch. Intern. Med.* 1993;153:2093-101.

21. Ulrich-Lai YM, Herman JP Neural regulation of endocrine and autonomic stress responses. *Nat Rev Neurosci* 2009;10:397-409.

22. Critchley HD Neural mechanisms of autonomic, affective, and cognitive integration. *J. Comp. Neurol.* 2005;493:154-66.

23. Rutter M Implications of resilience concepts for scientific understanding. *Ann. N. Y. Acad. Sci.* 2006;1094:1-12.

24. Rutter M Resilience as a dynamic concept. *Dev. Psychopathol.* 2012;24:335-44.

25. Bonnet MH, Arand DL Situational insomnia: consistency, predictors, and outcomes. *Sleep* 2003;26:1029-36.

26. Drake CL, Friedman NP, Wright KP, Jr., Roth T Sleep reactivity and insomnia: genetic and environmental influences. *Sleep* 2011;34:1179-88.

27. Brosschot JF Markers of chronic stress: prolonged physiological activation and (un)conscious perseverative cognition. *Neurosci. Biobehav. Rev.* 2010;35:46-50.

28. Akerstedt T, Kecklund G, Axelsson J Impaired sleep after bedtime stress and worries. *Biol. Psychol.* 2007;76:170-3.

29. Pieper S, Brosschot JF Prolonged stress-related cardiovascular activation: Is there any? *nn. Behav. Med.* 2005;30:91-103.

30. Irwin MR Why Sleep Is Important for Health: A Psychoneuroimmunology Perspective. *Annu. Rev. Psychol.* 2014.

31. Kripke DF, Garfinkel L, Wingard DL, Klauber MR, Marler MR Mortality associated with sleep duration and insomnia. *Arch. Gen. Psychiatry* 2002;59:131-6.

32. Laugsand LE, Vatten LJ, Platou C, Janszky I Insomnia and the risk of acute myocardial infarction: a population study. *Circulation* 2011;124:2073-81.

33. Eriksen W, Natvig B, Bruusgaard D Sleep problems: a predictor of long-term work disability? A four-year prospective study. *Scand. J. Public Health* 2001;29:23-31.

34. Jansson C, Alexanderson K, Kecklund G, Akerstedt T Clinically diagnosed insomnia and risk of all-cause and diagnosis-specific sickness absence: a nationwide Swedish prospective cohort study. *Scand J Public Health* 2013;41:712-21.

35. Lallukka T, Kaikkonen R, Harkanen T et al. Sleep and sickness absence: a nationally representative register-based follow-up study. *Sleep* 2014;37:1413-25.

36. Lallukka T, Overland S, Haaramo P, Saastamoinen P, Bjorvatn B, Sivertsen B The joint contribution of pain and insomnia to sickness absence and disability retirement: a register-linkage study among Norwegian and Finnish employees. *Eur J Pain* 2014;18:883-92.

37. Overland S, Glozier N, Sivertsen B et al. A comparison of insomnia and depression as predictors of disability pension: The HUNT Study. *Sleep* 2008;31:875-80.

38. Rahkonen O, Lallukka T, Kronholm E, Vahtera J, Lahelma E, Laaksonen M Sleep problems and sickness absence among middle-aged employees. *Scandinavian Journal of Work Environment & Health* 2012;38:47-55.

39. Salo P, Vahtera J, Hall M et al. Using repeated measures of sleep disturbances to predict future diagnosis-specific work disability: a cohort study. *Sleep* 2012;35:559-69.

40. Sivertsen B, Overland S, Neckelmann D et al. The long-term effect of insomnia on work disability - The HUNT-2 historical cohort study. *Am. J. Epidemiol.* 2006;163:1018-24.

41. Sivertsen B, Overland S, Bjorvatn B, Maeland JG, Mykletun A Does insomnia predict sick leave? The Hordaland Health Study. *J. Psychosom. Res.* 2009;66:67-74.

42. Sivertsen B, Overland S, Pallesen S et al. Insomnia and long sleep duration are risk factors for later work disability. The Hordaland Health Study. *J. Sleep Res.* 2009;18:122-8.

43. Sivertsen B, Bjornsdottir E, Overland S, Bjorvatn B, Salo P The joint contribution of insomnia and obstructive sleep apnoea on sickness absence. *J. Sleep Res.* 2013;22:223-30.

44. Vahtera J, Pentti J, Helenius H, Kivimaki M Sleep disturbances as a predictor of long-term increase in sickness absence among employees after family death or illness. *Sleep* 2006;29:673-82.

45. Westerlund H, Alexanderson K, Alkerstedt T, Hanson LM, Theorell T, Kivimaki M Work-related sleep disturbances and sickness absence in the Swedish working population, 1993-1999. *Sleep* 2008;31:1169-77.

46. Clark AJ, Salo P, Lange T et al. Onset of impaired sleep as a predictor of change in health-related behaviours; analysing observational data as a series of non-randomized pseudo-trials. *Int. J. Epidemiol.* 2015;44:1027-37.

47. Elovainio M, Kivimaki M, Vahtera J, Keltikangas-Jarvinen L, Virtanen M Sleeping problems and health behaviors as mediators between organizational justice and health. *Health Psychol.* 2003;22:287-93.

48. Akerstedt T, Garefelt J, Richter A et al. Work and Sleep-A Prospective Study of Psychosocial Work Factors, Physical Work Factors, and Work Scheduling. *Sleep* 2015;38:1129-36.

49. de Lange AH, Kompier MA, Taris TW et al. A hard day's night: a longitudinal study on the relationships among job demands and job control, sleep quality and fatigue. *J. Sleep Res.* 2009;18:374-83.

50. Theorell T, Perski A, Akerstedt T et al. Changes in job strain in relation to changes in physiological state. A longitudinal study. *Scand. J. Work. Environ. Health* 1988;14:189-96.

51. Bonnet MH, Arand DL Hyperarousal and insomnia: State of the science. *Sleep Med. Rev.* 2010;14:9-15.

52. Hall MH Reciprocal Associations between Job Strain and Disturbed Sleep-Opportunities for Sleep Health. *Sleep* 2015;38:1007-8.

53. Drake C, Richardson G, Roehrs T, Scofield H, Roth T Vulnerability to stress-related sleep disturbance and hyperarousal. *Sleep* 2004;27:285-91.

54. Jarrin DC, Chen IY, Ivers H, Morin CM The role of vulnerability in stress-related insomnia, social support and coping styles on incidence and persistence of insomnia. *J. Sleep Res.* 2014;23:681-8.

55. Thayer JF, Brosschot JF Psychosomatics and psychopathology: looking up and down from the brain. *Psychoneuroendocrinology* 2005;30:1050-8.

56. Carney RM, Freedland KE, Veith RC Depression, the autonomic nervous system, and coronary heart disease. *Psychosom. Med.* 2005;67 Suppl 1:S29-33.

57. Hall M, Vasko R, Buysse D et al. Acute stress affects heart rate variability during sleep. *Psychosom. Med.* 2004;66:56-62.

58. Ivarsson M, Anderson M, Akerstedt T, Lindblad F Playing a violent television game affects heart rate variability. *Acta Paediatr.* 2009;98:166-72.

59. Brosschot JF, Van Dijk E, Thayer JF Daily worry is related to low heart rate variability during waking and the subsequent nocturnal sleep period. *Int. J. Psychophysiol.* 2007;63:39-47.

60. Lindholm H, Sinisalo J, Ahlberg J et al. Attenuation of vagal recovery during sleep and reduction of cortisol/melatonin ratio in late afternoon associate with prolonged daytime sleepiness among media workers with irregular shift work. *Am. J. Ind. Med.* 2012;55:643-9.

61. Sadeh A, Hauri PJ, Kripke DF, Lavie P The role of actigraphy in the evaluation of sleep disorders. *Sleep* 1995;18:288-302.

62. Sadeh A, Acebo C The role of actigraphy in sleep medicine. *Sleep Med Rev* 2002;6:113-24.

63. Argyropoulos SV, Hicks JA, Nash JR et al. Correlation of subjective and objective sleep measurements at different stages of the treatment of depression. *Psychiatry Res.* 2003;120:179-90.

64. Bakken LN, Kim HS, Finset A, Lerdal A Subjective sleep quality in relation to objective sleep estimates: comparison, gender differences and changes between the acute phase and the six-month follow-up after stroke. *J. Adv. Nurs.* 2014;70:639-50.

65. Bianchi MT, Williams KL, McKinney S, Ellenbogen JM The subjective-objective mismatch in sleep perception among those with insomnia and sleep apnea. *J. Sleep Res.* 2013;22:557-68.

66. Boudebesse C, Geoffroy PA, Bellivier F et al. Correlations between objective and subjective sleep and circadian markers in remitted patients with bipolar disorder. *Chronobiol. Int.* 2014;31:698-704.

67. Dhruva A, Paul SM, Cooper BA et al. A longitudinal study of measures of objective and subjective sleep disturbance in patients with breast cancer before, during, and after radiation therapy. *J. Pain Symptom Manage.* 2012;44:215-28.

68. Girschik J, Fritschi L, Heyworth J, Waters F Validation of self-reported sleep against actigraphy. *J. Epidemiol.* 2012;22:462-8.

69. Keklund G, Akerstedt T Objective components of individual differences in subjective sleep quality. *J. Sleep Res.* 1997;6:217-20.

70. Akerstedt T, Hume K, Minors D, Waterhouse J The meaning of good sleep: a longitudinal study of polysomnography and subjective sleep quality. *J. Sleep Res.* 1994;3:152-58.

71. Lauderdale DS, Knutson KL, Yan LL, Liu K, Rathouz PJ Self-reported and measured sleep duration: how similar are they? *Epidemiology* 2008;19:838-45.

72. Buysse DJ, Hall ML, Strollo PJ et al. Relationships between the Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale (ESS), and clinical/polysomnographic measures in a community sample. *J Clin Sleep Med* 2008;4:563-71.

73. Budhrani PH, Lengacher CA, Kip K, Tofthagen C, Jim H An integrative review of subjective and objective measures of sleep disturbances in breast cancer survivors. *Clin. J. Oncol. Nurs.* 2015;19:185-91.

74. Jackowska M, Dockray S, Hendrickx H, Steptoe A Psychosocial factors and sleep efficiency: discrepancies between subjective and objective evaluations of sleep. *Psychosom. Med.* 2011;73:810-6.

75. Tworoger SS, Davis S, Vitiello MV, Lentz MJ, McTiernan A Factors associated with objective (actigraphic) and subjective sleep quality in young adult women. *J. Psychosom. Res.* 2005;59:11-9.

76. Knutson KL, Rathouz PJ, Yan LL, Liu K, Lauderdale DS Intra-individual daily and yearly variability in actigraphically recorded sleep measures: the CARDIA study. *Sleep* 2007;30:793-6.

77. Acebo C, Sadeh A, Seifer R et al. Estimating sleep patterns with activity monitoring in children and adolescents: how many nights are necessary for reliable measures? *Sleep* 1999;22:95-103.

78. Thayer JF, Yamamoto SS, Brosschot JF The relationship of autonomic imbalance, heart rate variability and cardiovascular disease risk factors. *Int. J. Cardiol.* 2010;141:122-31.

79. Berntson GG, Bigger JT, Jr., Eckberg DL et al. Heart rate variability: origins, methods, and interpretive caveats. *Psychophysiology* 1997;34:623-48.

80. Heathers JA Everything Hertz: methodological issues in short-term frequency-domain HRV. *Front Physiol* 2014;5:177.

81. Pagani M, Lucini D, Porta A Sympathovagal balance from heart rate variability: time for a second round? *Exp. Physiol.* 2012;97:1141-2.

82. Kleiger RE, Stein PK, Bigger JT, Jr. Heart rate variability: measurement and clinical utility. *Ann Noninvasive Electrocardiol* 2005;10:88-101.

83. Pagani M, Malfatto G, Pierini S et al. Spectral analysis of heart rate variability in the assessment of autonomic diabetic neuropathy. *J. Auton. Nerv. Syst.* 1988;23:143-53.

84. Reinhardt L, Makijarvi M, Fetsch T et al. Reduced beat-to-beat changes of heart rate: an important risk factor after acute myocardial infarction. *Cardiology* 1996;87:104-11.

85. Merskey H Logic, truth and language in concepts of pain. *Qual. Life Res.* 1994;3 Suppl 1:S69-76.

86. Walker BF The prevalence of low back pain: a systematic review of the literature from 1966 to 1998. *J. Spinal Disord.* 2000;13:205-17.

87. Cassidy JD, Cote P, Carroll LJ, Kristman V Incidence and course of low back pain episodes in the general population. *Spine* 2005;30:2817-23.

88. Hestbaek L, Leboeuf-Yde C, Manniche C Low back pain: what is the long-term course? A review of studies of general patient populations. *Eur. Spine J.* 2003;12:149-65.

89. Deyo RA, Weinstein JN Low back pain. *N. Engl. J. Med.* 2001;344:363-70.

90. Atlas SJ, Deyo RA Evaluating and managing acute low back pain in the primary care setting. *J. Gen. Intern. Med.* 2001;16:120-31.

91. Haukka E, Kaila-Kangas L, Luukkonen R, Takala EP, Viikari-Juntura E, Leino-Arjas P Predictors of sickness absence related to musculoskeletal pain: a two-year follow-up study of workers in municipal kitchens. *Scand. J. Work. Environ. Health* 2014;40:278-86.

92. Shiri R, Kaila-Kangas L, Ahola K et al. The relation of co-occurring musculoskeletal pain and depressive symptoms with work ability. *J. Occup. Environ. Med.* 2013;55:1281-5.

93. Lindegard A, Larsman P, Hadzibajramovic E, Ahlborg G, Jr. The influence of perceived stress and musculoskeletal pain on work performance and work ability in Swedish health care workers. *Int. Arch. Occup. Environ. Health* 2013.

94. Nyman T, Grooten WJA, Wiktorin C, Liwing J, Norrman L Sickness absence and concurrent low back and neck-shoulder pain: results from the MUSIC-Norrtalje study. *Eur. Spine J.* 2007;16:631-38.

95. Haukka E, Kaila-Kangas L, Ojajarvi A et al. Pain in multiple sites and sickness absence trajectories: A prospective study among Finns. *Pain* 2013;154:306-12.

96. Kaaria S, Laaksonen M, Leino-Arjas P, Saastamoinen P, Lahelma E Low back pain and neck pain as predictors of sickness absence among municipal employees. *Scand. J. Public Health* 2012;40:150-56.

97. Neupane S, Leino-Arjas P, Nygard CH, Miranda H, Siukola A, Virtanen P Does the association between musculoskeletal pain and sickness absence due to musculoskeletal diagnoses depend on biomechanical working conditions? *Int. Arch. Occup. Environ. Health* 2015;88:273-9.

98. Kamaleri Y, Natvig B, Ihlebaek CM, Bruusgaard D Does the number of musculoskeletal pain sites predict work disability? A 14-year prospective study. *Eur J Pain* 2009;13:426-30.

99. Miranda H, Kaila-Kangas L, Heliovaara M et al. Musculoskeletal pain at multiple sites and its effects on work ability in a general working population. *Occup. Environ. Med.* 2010;67:449-55.

100. Kamaleri Y, Natvig B, Ihlebaek CM, Bruusgaard D Localized or widespread musculoskeletal pain: Does it matter? *Pain* 2008;138:41-46.

101. Kamaleri Y, Natvig B, Ihlebaek CM, Benth JS, Bruusgaard D Number of pain sites is associated with demographic, lifestyle, and health-related factors in the general population. *Eur. J. Pain* 2008;12:742-48.

102. Saastamoinen P, Leino-Arjas P, Laaksonen M, Martikainen P, Lahelma E Pain and health related functioning among employees. *J. Epidemiol. Community Health* 2006;60:793-8.

103. Wolfe F, Smythe HA, Yunus MB et al. The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. *Arthritis Rheum.* 1990;33:160-72.

104. Bouter LM, Pennick V, Bombardier C Cochrane back review group. *Spine (Phila Pa 1976)* 2003;28:1215-8.

105. Melzack R, Wall PD Pain mechanisms: a new theory. *Science* 1965;150:971-9.

106. Inui K, Tsuji T, Kakigi R Temporal analysis of cortical mechanisms for pain relief by tactile stimuli in humans. *Cereb. Cortex* 2006;16:355-65.

107. Gatchel RJ, Gardea MA Psychosocial issues: their importance in predicting disability, response to treatment, and search for compensation. *Neurol. Clin.* 1999;17:149-66.

108. Campbell P, Foster NE, Thomas E, Dunn KM Prognostic indicators of low back pain in primary care: five-year prospective study. *J Pain* 2013;14:873-83.

109. Dunn KM, Jordan KP, Croft PR Contributions of prognostic factors for poor outcome in primary care low back pain patients. *Eur J Pain* 2011;15:313-9.

110. Grotle M, Foster NE, Dunn KM, Croft P Are prognostic indicators for poor outcome different for acute and chronic low back pain consulters in primary care? *Pain* 2010;151:790-7.

111. Grotle M, Brox JI, Glomsrod B, Lonn JH, Vollestad NK Prognostic factors in first-time care seekers due to acute low back pain. *Eur J Pain* 2007;11:290-8.

112. Hill JC, Dunn KM, Lewis M et al. A primary care back pain screening tool: identifying patient subgroups for initial treatment. *Arthritis Rheum.* 2008;59:632-41.

113. Linton SJ, Boersma K Early identification of patients at risk of developing a persistent back problem: the predictive validity of the Orebro Musculoskeletal Pain Questionnaire. *Clin. J. Pain* 2003;19:80-6.

114. Linton SJ, Hallden K Can we screen for problematic back pain? A screening questionnaire for predicting outcome in acute and subacute back pain. *Clin. J. Pain* 1998;14:209-15.

115. Reis S, Borkan J, Vanraalte R, Tamir A, Dahan R, Hermoni D The LBP patient perception scale: a new predictor of LBP episode outcomes among primary care patients. *Patient Educ. Couns.* 2007;67:191-5.

116. Kerns RD, Turk DC, Rudy TE The West Haven-Yale Multidimensional Pain Inventory (WHYMPI). *Pain* 1985;23:345-56.

117. Axen I Pain-related Sleep Disturbance - A Prospective Study with Repeated Measures. *Clin. J. Pain* 2015.

118. Finan PH, Goodin BR, Smith MT The association of sleep and pain: an update and a path forward. *J Pain* 2013;14:1539-52.

119. Alsaadi SM, McAuley JH, Hush JM et al. The bidirectional relationship between pain intensity and sleep disturbance/quality in patients with low back pain. *Clin. J. Pain* 2014;30:755-65.

120. Sivertsen B, Lallukka T, Petrie KJ, Steingrimsdottir OA, Stubhaug A, Nielsen CS Sleep and pain sensitivity in adults. *Pain* 2015;156:1433-9.

121. Haack M, Scott-Sutherland J, Santangelo G, Simpson NS, Sethna N, Mullington JM Pain sensitivity and modulation in primary insomnia. *Eur. J. Pain* 2012;16:522-33.

122. Onen SH, Alloui A, Gross A, Eschallier A, Dubray C The effects of total sleep deprivation, selective sleep interruption and sleep recovery on pain tolerance thresholds in healthy subjects. *J. Sleep Res.* 2001;10:35-42.

123. Edwards RR, Almeida DM, Klick B, Haythornthwaite JA, Smith MT Duration of sleep contributes to next-day pain report in the general population. *Pain* 2008;137:202-07.

124. Mork PJ, Nilsen TI Sleep problems and risk of fibromyalgia: longitudinal data on an adult female population in Norway. *Arthritis Rheum.* 2012;64:281-4.

125. Nitter AK, Pripp AH, Forseth KØ Are sleep problems and non-specific health complaints risk factors for chronic pain? A prospective population-based study with 17 year follow-up. *Scandinavian Journal of Pain* 2012;3:210-17.

126. Davies KA, Macfarlane GJ, Nicholl BI et al. Restorative sleep predicts the resolution of chronic widespread pain: results from the EPIFUND study. *Rheumatology (Oxford).* 2008;47:1809-13.

127. Tornqvist EW, Kilbom A, Vingard E et al. The influence on seeking care because of neck and shoulder disorders from work-related exposures. *Epidemiology* 2001;12:537-45.

128. Vingard E, Mortimer M, Wiktorin C et al. Seeking care for low back pain in the general population: a two-year follow-up study: results from the MUSIC-Norrtalje Study. *Spine (Phila Pa 1976)* 2002;27:2159-65.

129. Grooten WJ, Wiktorin C, Norrman L, Josephson M, Tornqvist EW, Alfredsson L Seeking care for neck/shoulder pain: a prospective study of work-related risk factors in a healthy population. *J. Occup. Environ. Med.* 2004;46:138-46.

130. Grooten WJA, Mulder M, Josephson M, Alfredsson L, Wiktorin C The influence of work-related exposures on the prognosis of neck/shoulder pain. *Eur. Spine J.* 2007;16:2083-91.

131. Lichtenstein P, Sullivan PF, Cnattingius S et al. The Swedish Twin Registry in the third millennium: an update. *Twin Res Hum Genet* 2006;9:875-82.

132. Karlsson KK, Harris JR, Svartengren M Description and primary results from an audiometric study of male twins. *Ear Hear.* 1997;18:114-20.

133. Bogo R, Farah A, Johnson AC et al. The role of genetic factors for hearing deterioration across 20 years: a twin study. *J. Gerontol. A. Biol. Sci. Med. Sci.* 2015;70:647-53.

134. Hannelius U, Gherman L, Makela VV et al. Large-scale zygosity testing using single nucleotide polymorphisms. *Twin Res Hum Genet* 2007;10:604-25.

135. Smith BH, Penny KI, Purves AM et al. The Chronic Pain Grade questionnaire: validation and reliability in postal research. *Pain* 1997;71:141-7.

136. Korff MV, Ormel J, F. J. Keefe, Dworkin SF Grading the severity of chronic pain. *Pain* 1992;50:133-49.

137. Fejer R, Kyvik KO, Hartvigsen J The prevalence of neck pain in the world population: a systematic critical review of the literature. *Eur. Spine J.* 2006;15:834-48.

138. Akerstedt T, Ingre M, Broman JE, Kecklund G Disturbed sleep in shift workers, day workers, and insomniacs. *Chronobiol. Int.* 2008;25:333-48.

139. Kuorinka I, Jonsson B, Kilbom A et al. Standardized nordic questionnaires for the analysis of musculoskeletal symptoms. *Appl. Ergon.* 1987;18:233-37.

140. Solidaki E, Chatzi L, Bitsios P et al. Work-related and psychological determinants of multisite musculoskeletal pain. *Scandinavian Journal of Work Environment & Health* 2010;36:54-61.

141. Canlon B, Theorell T, Hasson D Associations between stress and hearing problems in humans. *Hear. Res.* 2013;295:9-15.

142. Akerstedt T, Hume K, Minors D, Waterhouse J The subjective meaning of good sleep, an intraindividual approach using the Karolinska Sleep Diary. *Percept. Mot. Skills* 1994;79:287-96.

143. Brage S, Brage N, Franks PW, Ekelund U, Wareham NJ Reliability and validity of the combined heart rate and movement sensor Actiheart. *Eur. J. Clin. Nutr.* 2005;59:561-70.

144. Camm AJ, Malik M, Bigger JT et al. Heart rate variability - Standards of measurement, physiological interpretation, and clinical use. *Circulation* 1996;93:1043-65.

145. Storck N, Ericson M, Lindblad L, Jensen-Urstad M Automatic computerized analysis of heart rate variability with digital filtering of ectopic beats. *Clin. Physiol.* 2001;21:15-24.

146. Begg MD, Parides MK Separation of individual-level and cluster-level covariate effects in regression analysis of correlated data. *Stat. Med.* 2003;22:2591-602.

147. Evans DM, Gillespie NA, Martin NG Biometrical genetics. *Biol. Psychol.* 2002;61:33-51.

148. Shrout PE, Fleiss JL Intraclass correlations: uses in assessing rater reliability. *Psychol. Bull.* 1979;86:420-8.

149. Holtermann A, Hansen JV, Burr H, Sogaard K Prognostic factors for long-term sickness absence among employees with neck-shoulder and low-back pain. *Scand. J. Work. Environ. Health* 2010;36:34-41.

150. Bultmann U, Nielsen MB, Madsen IE, Burr H, Rugulies R Sleep disturbances and fatigue: independent predictors of sickness absence? A prospective study among 6538 employees. *Eur J Public Health* 2013;23:123-8.

151. Lusa S, Miranda H, Luukkonen R, Punakallio A Sleep disturbances predict long-term changes in low back pain among Finnish firefighters: 13-year follow-up study. *Int. Arch. Occup. Environ. Health* 2015;88:369-79.

152. Kaila-Kangas L, Kivimaki M, Harma M et al. Sleep disturbances as predictors of hospitalization for back disorders - A 28-year follow-up of industrial employees. *Spine* 2006;31:51-56.

153. Gupta A, Silman AJ, Ray D et al. The role of psychosocial factors in predicting the onset of chronic widespread pain: results from a prospective population-based study. *Rheumatology (Oxford).* 2007;46:666-71.

154. Kamaleri Y, Natvig B, Ihlebaek CM, Benth JS, Bruusgaard D Change in the number of musculoskeletal pain sites: A 14-year prospective study. *Pain* 2009;141:25-30.

155. Campbell P, Tang N, McBeth J et al. The role of sleep problems in the development of depression in those with persistent pain: a prospective cohort study. *Sleep* 2013;36:1693-8.

156. Vitiello MV, Rybarczyk B, Von Korff M, Stepanski EJ Cognitive Behavioral Therapy for Insomnia Improves Sleep and Decreases Pain in Older Adults with Co-Morbid Insomnia and Osteoarthritis. *Journal of Clinical Sleep Medicine* 2009;5:355-62.

157. Jungquist CR, O'Brien C, Matteson-Rusby S et al. The efficacy of cognitive-behavioral therapy for insomnia in patients with chronic pain. *Sleep Med* 2010;11:302-9.

158. Cote P, Cassidy JD, Carroll L The treatment of neck and low back pain: who seeks care? who goes where? *Med. Care* 2001;39:956-67.

159. Sivertsen B, Krokstad S, Overland S, Mykletun A The epidemiology of insomnia: Associations with physical and mental health. The HUNT-2 study. *J. Psychosom. Res.* 2009;67:109-16.

160. Wang X, Ding X, Su S et al. Genetic influences on heart rate variability at rest and during stress. *Psychophysiology* 2009;46:458-65.

161. Zhao R, Li D, Zuo P et al. Influences of age, gender, and circadian rhythm on deceleration capacity in subjects without evident heart diseases. *Ann Noninvasive Electrocardiol* 2015;20:158-66.

162. Leger D, Guilleminault C, Dreyfus JP, Delahaye C, Paillard M Prevalence of insomnia in a survey of 12,778 adults in France. *J. Sleep Res.* 2000;9:35-42.

163. Lemola S, Ledermann T, Friedman EM Variability of sleep duration is related to subjective sleep quality and subjective well-being: an actigraphy study. *PLoS One* 2013;8:e71292.

164. Mezick EJ, Matthews KA, Hall M et al. Intra-individual variability in sleep duration and fragmentation: associations with stress. *Psychoneuroendocrinology* 2009;34:1346-54.