Nerve conduction and vibrotactile perception thresholds

in female computer workers and hand-arm vibration-exposed male manual workers

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Abstract

Upper limb pain and disability are common problems, especially among working populations. The overall aim of this thesis was to investigate peripheral nerve function in the upper limb by nerve conduction test and vibration threshold test in working populations including female computer users (n = 82), hand-arm vibration-exposed male manual workers (n = 116), and female workers with chronic diffuse upper limb pain (n = 35). The studies have a cross-sectional design regarding peripheral nerve function measurements.

Exposure assessments regarding computer work were made using questionnaires, and the cumulative hand-arm vibration dose in manual workers was calculated as the product of self-reported occupational exposure, as collected by questionnaire and interviews, and the measured or estimated hand-arm vibration exposure in 1987, 1992, 1997, 2002, and 2008.

In contrast to nerve conduction measurements, the vibration threshold test is a psychophysical test. To investigate whether mood influences the measurements, perceived stress and energy were assessed using a two-dimensional mood adjective checklist, before the vibration threshold test.

Adequate control of tissue temperature is a crucial factor in nerve conduction studies, and a bicycle ergometer test proved to be a simple and effective method of raising hand temperature.

Nerve conduction measurements revealed no signs of early neural deficits of large myelinated nerve fibres measured in the upper limbs of either women who intensively use computer keyboard equipment or hand-arm vibration-exposed male manual workers, or female workers with chronic diffuse upper limb pain. In the present studies, the majority of the subjects did not have severe neurological symptoms and most subjects had not been referred to a clinic.

Vibration threshold test revealed no signs of early nerve affliction in the upper limbs in women who intensively used computer keyboard equipment. Women with chronic pain had a small elevation of vibrotactile perception thresholds in the territories of the ulnar and radial nerves. Perceived stress and energy before the vibration threshold testing did not influence the thresholds. Although a peripheral mechanism cannot be excluded, the findings support the idea that increased vibration perception thresholds in chronic diffuse upper limb pain may be secondary to pain.

Keywords: Computer use, Hand-arm vibration, Chronic upper limb pain, Nerve conduction, Vibrotactile perception threshold, Mood, Bicycle ergometer test, Temperature

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III. Sandén H, Wallin BG, Hagberg M: Chronic pain has a small influence and mood has no influence on vibrotactile perception thresholds among working women. *Muscle Nerve* 2010; 42(3):401–409.

IV. Sandén H, Jonsson A, Wallin BG, Burström L, Lundström R, Nilsson T, Hagberg M: Nerve conduction in relation to vibration exposure — a non-positive cohort study. *J Occup Med Toxicol* 2010; 5:21.

Abbreviations

COP	Critical opening pressure
CTS	Carpal tunnel syndrome
EMG	Electromyography
HAVS	Hand-arm vibration syndrome
IASP	International Association for the Study of Pain
ICC	Intraclass correlation coefficient
ISO	International Organization for Standardization
NCT	Nerve conduction test
RIV	Relative intertrial variation
ROC	Receiver operating characteristic
SCV	Sensory conduction velocity
TN	Tohr Nilsson
VAS	Visual analogue scale
VPT	Vibrotactile perception threshold
VTT	Vibration threshold test

Contents

1 Introduction

Upper limb pain and disability are common problems, especially among working populations. Dysfunction of peripheral nerves in the arm or hand can cause pain, loss of sensation, paresthesias, and impairment of manual dexterity. Hence, it is essential to identify risk factors for peripheral nerve affliction in the workplace. Many studies have already sought to highlight risk factors across large epidemiological surveys with questionnaires and job-exposure matrices. There are few studies with clinical measurements of nerve function together with thorough exposure assessment. This thesis focuses on the effects of occupational biomechanical loading on peripheral nerves in the upper limb.

1.1 The somatosensory system

The somatosensory system contains components of both the peripheral and the central nervous system. The peripheral nervous system is composed of the peripheral nerves and their associated endings.

The peripheral nerves that arbitrate perception of touch, pressure, and vibration are myelinated and 10–15μm in diameter (Aβ-fibres) [1]. Their sensory endings are associated with a variety of mechanoreceptors that transduce mechanical energies into action potentials, that is, neural impulses [2]. There are four different types of mechanoreceptors in non-hairy skin [3]. They are distinguished by their receptive-field properties and their adaptation to sustained indentation [1, 2]. Slow adaptation is mediated by intensity detectors: Merkel's cells and Ruffini endings. Moderately rapid adaptation is mediated by Meissner corpuscles, which are referred to as velocity detectors, and very rapid adaptation is mediated by Pacinian corpuscles, which are referred to as acceleration detectors and responsible for transduction of vibratory stimuli in the range of 100–200Hz [2]. The action potentials generated from the mechanoreceptors are conducted along the large myelinated Aβ-nerve fibres through the dorsal root into the spinal cord and run in the dorsal column up to medulla, where a first synapse occurs. Fibres from the second-order afferent neurons cross the midline and pass through the medial meniscus to the thalamus, where a second synapse occurs, and the third-order neurons pass to the sensory cortex [2, 4].

The peripheral nerves that convey pain from nociceptors and temperature from thermoreceptors are small myelinated Aδ-fibres or small unmyelinated C-fibres. The action potentials are conducted along the nerve fibres through the dorsal root into the dorsal horn where the axons branch into ascending and descending collaterals before the first synapse occurs. Fibres from the second-order neuron cross the spinal cord and run along the anterolateral column into the brainstem and the thalamus, where the second synapse occurs [4]. The third-order neurons pass to the sensory cortex, but there are also additional pathways in the central nervous system that mediate the affective and motivational responses to pain stimuli [4].

The speed of propagation of the action potential depends on the fibre diameter; the greater the cross-sectional area of the fibre, the more rapid the propagation. Myelin has a high electrical resistance in the myelinated fibres and action potentials occur only at the nodes of Ranvier and jump from one node to the next, which greatly increases the speed of transmission. The conduction velocity of a large myelinated fibre is about 35–70 m/s, and of a small unmyelinated fibre of 0.2–1.5 µm, it is about 0.4–2 m/s [1].

1.2 Peripheral neuropathy

Disturbance of sensory or motor function can be caused by dysfunction of any component of the nervous system. The peripheral neuropathy may be due to dysfunction in mechanoreceptors, local damage to a specific nerve, as in nerve compression syndromes, or more diffuse damage, as in polyneuropathies.

1.2.1 Nerve compression syndromes

Nerve compression syndromes involve peripheral nerve dysfunction as a result of localized interference of microvascular function and structural changes in the nerve or adjacent tissues [5]. Risk factors include a superficial position of the nerve, a long course through an area at high risk of trauma, and a narrow path through a bony canal [6]. Elevated extraneural pressure can, within minutes or hours, inhibit intraneural microvascular blood flow, axonal transport, and nerve function, and also cause endoneural edema with increased intrafascicular pressure and displacement of myelin [5]. The cascade of the biological response to prolonged compression includes endoneural edema, demyelination, inflammation, distal axonal degeneration, fibrosis, growth of new axons, remyelination, and thickening of the perineum and endothelium [5]. There are six nerves emerging from the brachial plexus, and three of them are mainly innervating the hand and forearm. The ulnar, radial, and median nerves are important for the hand function.

Ulnar nerve. A common site at which the ulnar nerve is damaged is at the elbow. There could be a chronic compression as it passes around the elbow or entrapment of the nerve as it enters the *cubital tunnel* [7]. A lesion at the elbow causes local tenderness of the nerve, weakness of all the intrinsic hand muscles innervated by the ulnar nerve, and sensory disturbances in the little finger and the lateral half of the ring finger, extending proximally to the wrist. An association between ‘holding of a tool in position’ at work and entrapment at the cubital tunnel has been described [8]. The *Guyon canal* at the wrist is another area of entrapment in the ulnar nerve. The deep palmar branch is often involved and the entrapment is then characterized by wasting of intrinsic hand muscles without sensory symptoms [1]. Injury of the ulnar nerve at the wrist may appear among cyclists because the nerve gets compressed against the handlebar during cycling, resulting in ‘*cyclist palsy*’ [6]. The injury also occurs with other activities involving extended pressure on the volar wrist [6]. It presents with paresthesias in the fourth and fifth digits, but motor weakness is uncommon because the motor portion of the nerve at the wrist is less superficial [6].

Radial nerve. *Radial nerve palsy* may be caused by fracture of the humerus, especially in the middle-third part. It could also be a compression injury, as it passes around the spiral groove that typically occurs in prolonged deep sleep when the upper arm is hung over the edge of a chair. The pattern of extensor weakness depends on the level of the injury [1]. The radial nerve divides into a superficial branch (sensory only) and a deep branch (posterior interosseous nerve) at the lateral elbow [1]. Compression neuropathies may occur if there is a lesion when the radial nerve passes the arcade of Frohse through the supinator muscle. Entrapment can result in two separate syndromes: *posterior interosseous nerve compression*, involving muscular paresis and no sensory changes (weakness of long finger extensors, with preservation of wrist extension), and *radial tunnel syndrome* of the forearm, consisting of forearm pain without weakness [9]. Symptoms of radial tunnel syndrome are almost identical to those of lateral epicondylitis, except for location of maximal tenderness [6]. Work-related associations between handling loads, static work of the hand, and full extension of the elbow have been described [8]. The radial nerve is vulnerable to compression by anything wound tightly around the wrist, '*handcuff neuropathy*', which leads to numbness of the dorsoradial aspect of the hand. The motor function is typically intact [6].

Median nerve. The most common condition is *carpal tunnel syndrome* (see below). More unusual is *anterior interosseous palsy*. The anterior interosseous nerve is a major branch of the median nerve at the elbow and innervates the flexors of the most distal phalanx of the index finger and the thumb: flexor pollicis longus and pronator quadratus. The ability to form an 'o' with these digits is impaired. The palsy is caused by a direct trauma, a penetrating injury, or a forearm fracture [1]. Another rather unusual condition is *pronator teres syndrome*, in which there is a compression of the median nerve in the forearm by the pronator teres muscle. The main characteristic is pain in the forearm, exacerbated by use of the hand or arm; local hypertrophy of the pronator might occur. It is typically unilateral and often occurs in the dominant hand. Only a few have sensory loss or muscle weakness [1]. In pronator syndrome there may be sensory loss of the thenar eminence, which is not a finding of carpal tunnel syndrome [6].

1.2.2 Carpal tunnel syndrome

Carpal tunnel syndrome (CTS) is the most frequently reported upper limb neuropathy [7] and accounts for approximately 90% of all entrapment neuropathies [10]. In an epidemiological study of the general population in Sweden, the overall prevalence of CTS was 2.7%-3.8%, and depended upon the criteria used for diagnosis [11]. CTS is more common among middle-aged women, and in the majority of cases, its exact cause and pathogenesis is unclear. Several theories have been put forward, such as mechanical compression [5, 12, 13], microvascular insufficiency [14], and vibration theories [5, 15]. The carpal tunnel is shaped by the flexor retinaculum attached at either side to the carpal bones, and the median nerve is a superficial structure in it. The classic symptoms of CTS consist of nocturnal pain with related tingling and numbness in the distribution of the median nerve in the hand, that is, the thumb,

index and middle finger, and the radial half of the ring finger, but pain proximally to the wrist in the forearm and upper arm has also been frequently reported in this condition [16]. Sometimes there is flattening of the thenar eminence and weakness with feelings of clumsiness. Many predisposing factors or associated conditions have been reported with CTS, including diabetes, rheumatoid arthritis, gout, hypothyroidism, amyloidosis, systemic lupus erythematosus, pregnancy, previous trauma to the wrist, obesity, and hormonal changes due to menopause [10, 17, 18].

A study of patients with CTS using current perception thresholds revealed that sensory dysfunction begins in larger fibres, extending stepwise to smaller fibres, as the clinical grade of CTS progresses [19].

In a consensus conference, a golden standard for diagnosis of CTS in epidemiological studies was established that included a combination of symptom characteristics and abnormal nerve function based upon nerve conduction studies [20].

A recent systematic review of associations between work-related factors and CTS provided consistent indications that CTS is associated with an average hand force requirement of >4kg, repetitiveness at work (cycle time <10s, or >50% of cycle time performing the same movements), and working with hand-held vibration tools with a daily 8-hour energy-equivalent frequency-weighted acceleration of 3.9 m/s [21]. Conversely, Nathan et al. [22] reported in a 17-year prospective study of industrial workers that workplace factors appeared to bear an uncertain relationship to carpal tunnel syndrome.

In recent years it has been a matter of concern whether computer use could be a risk factor for development of CTS. In 1996 Murata et al. [23] found reduced sensory conduction velocities in subjects using visual display computer terminals compared to a control group. In 1998, Greening and Lynn [24] reported significantly raised vibration thresholds within the territory of the median nerve in a group of office workers using computer keyboard equipment and concluded that the results indicated a change in the function of large sensory fibres. Also, in a patient group with repetitive strain injury, they found that the thresholds were further elevated following use of the keyboard. Decreased vibration sensitivity can be an early sign of a peripheral neuropathy such as carpal tunnel syndrome.

In light of the results from the aforementioned studies and an increased number of referred computer users to our clinic presenting with chronic diffuse upper limb pain, the question arose as to whether there is an occupational risk for peripheral neuropathy such as carpal tunnel syndrome in computer users.

Since then there have been several studies regarding the association of computer use and CTS. A systematic review by Thomsen et al. [25] concluded in 2008 that there was insufficient evidence that computer work causes CTS. A population-based study, using clinical examination and nerve conduction tests to establish the diagnosis of CTS, revealed that persons who reported intensive keyboard use were less likely to be diagnosed as having CTS than those who reported little keyboard use [26].

1.2.3 Vibration-induced neuropathy

Prolonged exposure to hand-arm transmitted vibration in several occupations causes a variety of disorders of the vascular, neural, and musculoskeletal systems, collectively known as hand-arm vibration syndrome (HAVS). Patients with HAVS have reported lower quality of life [27], and HAVS can result in impaired hand function, such as difficulties in opening lids, writing, lifting, carrying, and working outdoors in cold weather [28]. The implementation of the European directive for hand-arm vibration emphasized the health effects of vibrations emerging from vibrating machinery [29].

Peripheral neuropathy is one of the principal clinical disorders in workers with hand-arm vibration syndrome. Workers exposed to hand-arm transmitted vibration may experience tingling and numbness in their fingers and hands, and if the vibration exposure continues, they may exhibit a reduction in the normal sense of touch and temperature, and also an impairment of manual dexterity. In vibration-associated neuropathy, conceivable target structures could be peripheral sensory receptors, large or thin myelinated nerve fibres, and the small-calibre non-myelinated C-fibres. Electrophysiological studies aimed at defining the nature of the vibration injury have provided conflicting results [30]. Fractionated nerve conduction velocity of the median nerve across the carpal tunnel on vibration-exposed subjects with hand symptoms has revealed a bimodal velocity distribution suggesting affection both at the carpal tunnel and at a more distal level, such as the palm or finger [31]. Abnormalities that appear to be independent of clinical entrapment neuropathy have been recognized, and a distal pattern of delayed sensory nerve conduction localized at the digits has been described [32, 33]. Pathologic studies by cutaneous biopsy have demonstrated demyelinating neuropathy in the digital nerves of individuals with HAVS [34]. On the other hand, Lander et al. [35] found that median and ulnar neuropathies proximal to the hand are more common than digital neuropathies in hand-arm vibration-exposed workers with neurological symptoms. However, in the prospective study of Nathan et al. [22], the managing of vibratory tools appeared to bear an uncertain relationship to carpal tunnel syndrome and Cherniack et al. [36] found that the significant differences in digital sensory conduction velocities between vibration-exposed and unexposed workers were eliminated after systemic warming.

One reason for this lack of consistency might be the sparsity of published longitudinal studies that include both a good assessment of exposure and a well-defined measure of disease. In occupational studies that require specification of previous exposure, there is always a risk of recall bias. To get a better understanding of exposure-response relationships, it would be desirable to have a longitudinal study design to obtain a more accurate exposure assessment.

1.2.4 Polyneuropathy

Histological and electrophysiological characteristics indicate the presence of two relatively distinct categories of peripheral nerve disorders: (1) axonal degeneration with centripetal or dying-back degeneration from metabolic derangement of the

neuron due to vitamin B deficiency, alcoholism, drugs, heavy metals (e.g. lead, arsenic, thallium), and toxins (e.g. n-hexane, acrylamide, organophosphorous compounds) and (2) segmental demyelination with slowed nerve conduction due to Gullian-Barré syndrome, leprosy, or drugs, and due to hereditary polyneuropathy [1]. There are also mixed neuropathies with both demyelination and degeneration due to diabetes, uraemia, and hypothyroidism [1].

1.3 Pain

The International Association for the Study of Pain (IASP) has defined pain as 'an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage' [37]. Chronic pain (pain >3 months) is common, and a community-based population study in Sweden revealed a high prevalence of chronic pain (53.7%) [38]. The prevalence of regional chronic musculoskeletal pain in the west coast of Sweden has been reported to be 23.9% [39].

Pain is a complex sensory modality, and it is clinically characterized as nociceptive, neurogenic (peripheral or central), idopathic, or psychiatric.

In nociceptive pain a distinct set of pain afferents with membrane receptors called nociceptors transduce noxious stimulation and transmit this information in the small unmyelinated C-fibres or the small myelinated Aδ- fibres into the dorsal horn of the spinal cord [4]. Descending pain-modulating pathways and local interactions between sensory mechanoreceptive afferents interact with the synapses in the dorsal horns to adjust the transmission of pain information to higher centres [4]. Peripheral sensitization results from the interaction of nociceptors with the 'inflammatory soup' of substances released when the tissue is injured. Central sensitization refers to an increase in the excitability of neurons in the dorsal horn in the spinal cord due to high levels of activity in the nociceptive afferents [4]. As injured tissues heal, the peripheral and central sensitization mechanisms normally decline, but sometimes the pain persists and the local, spinal, and supraspinal responses are altered, and the pain may be of long duration or chronic.

However, when the afferent fibres or central pathways themselves are damaged, for example, due to nerve entrapment, the condition is referred to as neuropathic pain [4]. In addition to pain, there is a complex combination of negative symptoms, such as partial or complete loss of sensation, and positive symptoms, which include dysaesthesia and paraesthesia [40].

Work-related chronic upper limb pain is a significant public health problem. The symptoms include varying degrees of pain, weakness, and numbness/tingling. The majority shows no specific clinical findings and the pathophysiological mechanism is unclear. Some studies, using vibration threshold measurement, suggest a peripheral neural tissue disorder [24, 41, 42]. Whether the changes identified are a consequence of ongoing pain, rather than being due to specific peripheral neural changes, is unclear.

1.4 Nerve conduction test

In the late 1950s, Gilliatt's group at the National Hospital for Nervous Diseases, in London, developed clinical methods for measuring nerve conduction [43]. A nerve conduction test (NCT) is an objective test that demonstrates the physiological function of the nerve. The nerve is stimulated by a transcutaneous electrical pulse, inducing an action potential in the sensory or motor nerve fibres, and a recording electrode (either distally or proximally) detects the wave of depolarization as it passes the surface electrode. The evaluation of conduction characteristics depends on the analysis of compound evoked potentials recorded from the muscle in studies of motor fibres and from the nerve itself, in the case of the sensory fibres [7]. Stimulating electrodes are composed of a cathode (negative pole) and an anode (positive pole) and while the current flows between them, negative charges that accumulate under the cathode depolarize the nerve [7]. The amplitude recorded is expressed in volts (V). Accurate calculation of conduction velocity depends on proper measurements of the distance between stimulation and recording. In motor conduction measurements the distal latency summarizes the time taken to depolarize the nerve by the stimulating pulse, the time for the impulse to travel from the site of stimulation to the motor end-plate, and the time to depolarize the muscle [1]. However, by stimulating also at a more proximal site, subtraction between the two measurements leaves the difference in time taken for the impulse to travel between the two sites. This result divided by the distance gives the conduction velocity expressed as metres per second (m/s) [1].

The main component of the fast-rising negative phase and the amplitude of the sensory action potential are generated by depolarization in the largest myelinated fibres (7–14 μm) [1]. Thus, only a limited proportion (less than 10%) of the whole nerve fibre population is examined [1]. No information about conduction in the small myelinated and unmyelinated fibres is obtained [1]. Covariates of interest in nerve conduction include age, body height, and temperature.

The electrophysiological findings depend on the type and degree of damage in individual axons within the nerve. In segmental demyelination, or during partial demyelination, thin myelin increases the internodal capacitance and conductance, resulting in loss or reduction of local current [44]. Failure to activate the next node of Ranvier leads to conduction block [44]. Thus, demyelinated axons typically show blocking of impulses, increases in temporal dispersion, and substantial decreases in conduction velocity [44]. In contrast, axonal degeneration leads to loss of conductive elements, which results in reduced amplitude, although surviving axons conduct normally and give a normal nerve conduction velocity [44].

Adequate control of tissue temperature is a crucial factor in nerve conduction studies. Nerve temperature influences conduction velocity in peripheral nerve fibres [45-47], and to avoid false low values, measurements of conduction velocity should be performed under standardized temperature conditions. Normally, a skin temperature of 31–33°C over the peripheral nerve to be examined is preferred [47]. If lower, one

strives to increase the temperature in the tissue, for example, by increasing room temperature, covering the person with blankets, or warming him or her with a lamp, warm water, or a hot pack. However, to warm an extremity to a desired temperature that remains constant during the measurement is time consuming, especially during the winter in cool climates, when finger temperatures may be as low as 20°C in some subjects. Thus, using warm water or infrared radiation, it may take 30–60 min to achieve an adequate increase of nerve temperature [48].

For practical reasons, therefore, measurements of conduction velocity sometimes have to be made at suboptimal temperatures. This is unfortunate, and especially in epidemiological studies and comparative research, a fast and reliable method of obtaining high and stable finger temperatures would be valuable.

Several investigators have reported on the reliability of nerve conduction in normal subjects and in diabetic polyneuropathy [49-52]. Salerno et al. assessed interexaminer and intraexaminer reliability of median and ulnar sensory nerve measurements in 158 workers (keyboard operators). The intraexaminer reliability in median nerve measurements were higher (intraclass correlation coefficient [ICC] range, 0.76 – 0.92) than in ulnar measurements (ICC range, 0.22 – 0.85) [52]. Temperature corrections improved the reliability in the ulnar nerve. Pinheiro et al. [50] examined healthy subjects, and in median nerve sensory latency the ICC was 0.81 and the relative intertrial variation (RIV) was -20% to 12%. Overall the F-wave latency seems to be the most reliable, considering reproducibility [49-51]. However, short distances magnify focal conduction abnormalities, despite increased measurement errors, and long distances (e.g. F-latency), although insensitive to focal lesions, provide better yields and reliability for a diffuse multisegmental process [51].

CTS is one of the most common disorders for which NCT's are performed. A variety of median nerve motor and sensory tests have been introduced for the purpose of establishing the presence of median nerve neuropathy [53]. Measurements of wrist-palm sensory conduction or median-ulnar comparison have been considered superior to distal motor and digit-wrist sensory latency measurements, particularly in mild CTS [54, 55]. Chang et al. concluded that the most simple and reliable transcarpal conduction for diagnosis of CTS was median wrist-palm sensory conduction time with a sensitivity of 82% [56]. Lew et al. reported that the transcarpal short-segment latency yielded the highest sensitivity (75%) and the specificity was 83% [57]. There has only been one population-based study assessing the performance of various nerve conduction tests on CTS [58], and no difference was shown in the diagnostic accuracy of median nerve distal motor latency, digit-wrist sensory latency, wrist-palm sensory conduction velocity, and wrist-palm/forearm sensory conduction velocity ratio (area under ROC curve, 0.75–0.76). Median ulnar digit-wrist sensory latency difference had a higher diagnostic accuracy (area under curve 0.8). These figures entail a relatively high proportion of false-positive test results when the prevalence of CTS is low, as it is in a population-based study.

1.5 Vibration threshold test

The vibration threshold test (VTT) is a psychophysical test, since the outcome, which depends upon the integrity of the entire somatosensory pathway, has an objective physical stimulus but a subjective response from the tested subject. Thus, in contrast to nerve conduction measurements, the vibration threshold test requires cooperation from the subject and is affected by attention, concentration, and motivation.

Changes in vibrotactile perception thresholds (VPTs) may therefore be due to altered mood. To our knowledge, these factors have not been studied previously.

Increased vibrotactile perception thresholds can be caused by dysfunction of any component of the somatosensory system: peripheral mechanoreceptors, peripheral large myelinated sensory nerves (Aβ- fibres), and/or the central nervous system. The stimuli consist of sinusoidal signals at one or several frequencies presented on a probe perpendicular to the subject's skin. The vibration amplitude is adjustable and the subject reports when detecting the vibration.

Age is a well-known factor that influences the thresholds [2, 59]. Studies concerning the influence of skin temperature on VPTs have provided conflicting results. Gerr et al. [2] concluded in a 1991 review that VPTs are not affected by skin temperature over the range usually encountered in study subjects tested at normal ambient temperature. The International Organization for Standardization (ISO) [60] says that when frequency is less than 200 Hz, the receptors are not significantly influenced by skin temperature in the range of 27°C to 35°C. However, Harazin et al. [61] showed that at a frequency of 125Hz, the VPTs increased as the skin temperatures decreased, starting from the temperature of 28°C. However, the result from the latter study was a result of an experimental manipulation of skin temperature: short-time cooling and warming of hands using cold water and an infrared lamp.

There are different ways of measuring thresholds [62]; the stimulus can be presented as either the 'method of limits' or the 'method of levels'. In the method of limits the amplitude of the vibration is ramped up and down and the subjects respond to the appearance and disappearance of the vibration. The vibrotactile perception threshold is calculated from the arithmetic mean of ascending and descending thresholds. The results are dependent on the subjects' full cooperation and vigilance. The reaction time is included, and there may be a learning effect. The method of levels overcomes the disadvantages of the method of limits (reaction time) by using stimuli of predetermined levels of stimulus intensity and duration. The subject is then asked whether the stimulus was perceived. There are only a few studies comparing the two methods. The reproducibility is generally good with both the method of limits and the method of levels [62]. In this thesis we used the method of limits, which also is recommended by the ISO [60].

Peters et al. [63] reported on the reliability of the vibration threshold test in healthy subjects. The intraobserver reliability measured as ICC ranged from 0.55–0.99 and the corresponding figures for interobserver reliability were 0.32–0.88 [63].

Elleman et al. [64] investigated patients with neuropathies at the elbow, using multiple-frequency VTT and concluded that the sensitivity of VTT in relation to nerve conduction was 89%, and in relation to the patient's symptoms, 85%. Gerr et al. [65] reported that at specificities of 70% and 80%, the best sensitivity among single frequency VTT outcomes for CTS (symptoms and pathological NCT) were 35% and 28%.

Winn et al. compared the outcome of VTT and NCT in patients with CTS and controls and concluded that there was only little difference between VTT results and the nerve conduction velocity measurements in their ability to identify individuals with CTS [66].

1.6 Stress-Energy Questionnaire

Factor-analytic evidence has led many psychologists to describe affect as a set of dimensions. For several years it has been a matter of concern as to how to describe mood, that is, in how many and in what sort of dimensions. Fatigue, difficulty in concentration, and irritation are examples of expressions of mood and are often reported in connection with deficiencies in work environment. It is therefore interesting in occupational studies to be able to measure changes in mood. Kjellberg and Iwanowski have presented a model with two dimensions that describes mood during work; perceived stress and energy are assessed using a two-dimensional mood adjective checklist, the Stress-Energy (SE) Questionnaire [67, 68]. The instrument has been validated through studies concerning occupational burdens and pressures [68]. The questionnaire is not designed for deep depression or other severe psychiatric conditions.

This questionnaire has been used in several Swedish studies of occupational stress [69-74]. Larsman et al. [73] reported results indicating that perceived work demands influence neck-shoulder musculoskeletal symptoms in female computer users through their effect on felt stress. They revealed that 36% of the variation in felt stress was explained by the perceived work demands.

1.7 Exposure

1.7.1 Assessment of exposure

Physical exposure assessment in the workplace includes quantification of the level (amplitude), repetitiveness (frequency), and duration of the potential risk factor [75, 76]. Assessment techniques in musculoskeletal epidemiology can be broadly classified into three categories of data collection (1) subjective judgements, (2) systematic observations, and (3) direct measurements [77].

1.7.2 Computer work

A report on working conditions for the Swedish workforce concluded that, in 2009, 26% of the employed women and 21% of the employed men used the computer almost the entire working day (Statistics Sweden 2009) [78].

In this thesis we investigated secretaries at medical health care facilities whose work task was to write medical records using a computer keyboard. They did not use a computer mouse to any great extent. Several studies have measured wrist positions and forces exerted by computer users [25]. During keyboard work, electrogoniometer measurements showed a wrist extension of 14° at the 50th percentile and 20° at the 90th percentile [25, 79]. Gerr et al. [80] reported mean wrist extension of 24.3° (SD 9.6) during keyboard use and a mean ulnar deviation of 5.0° (SD 7.3). Fingertip forces exerted using a keyboard varied in different studies from less than 1 N to 7 N, but in most studies it was between 1 N and 4 N [25]. Hence, computer use involves very little force. Thomsen et al. concluded in a review in 2008 [25] that experiments on the effect of position of fingers, wrist, and forearm comparable to the positions common on computer work have shown that the carpal tunnel pressure increases, but not to levels generally believed to be harmful. However, in a recent study, Rempel et al. [81] investigated the effect of wrist posture on carpal tunnel pressure while typing and reported that the wrist/extension angle, the radial/ulnar angle, and the activity of typing independently were associated with an increase in carpal tunnel pressure, although pressures believed to be harmful were only exceeded with extreme wrist posture in keyboard work, such as wrist flexion of 30° and radial deviation of 15°.

1.7.3 Hand-transmitted vibration

A report on working conditions for the Swedish workforce concluded that, in 2009, 14% of all employed men and 3% of all employed women used vibrating tools at least 1/4 of the workday (Statistics Sweden, 2009) [78].

In this thesis we investigated manual workers, including, welders, grinders, turners, and steel platers at an engineering plant that manufactured pulp and paper machinery. Manual welding is common in the industry and removal of welding spatters generated during the welding process and surface finishing often includes the use of percussive tools such as chipping hammers and rotary tools such as grinders [82].

There is too little epidemiology data to allow reliable conclusions about exposure-response relationships for sensorineural disturbances caused by hand-transmitted vibration [83]. The vibration exposure required is not known precisely, either with respect to vibration magnitude and frequency spectrum, or with respect to daily and cumulative exposure duration [84].

There are international standards for describing measurements and evaluation of human exposure to hand-transmitted vibrations [84, 85]. Vibration is a vector quantity with properties of amplitude and frequency. The magnitude of a vibration is usually expressed in terms of acceleration (ms^{-2}) and measured by accelerometers. The vibration is measured in three orthogonal directions, often designated x, y, and z, and the vector root-sum-of-square for these directions is calculated. The frequency is expressed as the number of cycles per second (Hz). The measured vibration acceleration is frequency-weighted on the assumption that the harmful effects of acceleration depend on the vibration frequencies. The effects of vibration exposure are also dependent on the daily exposure time and the cumulative vibration exposure. The vibration exposure is often assessed by calculating daily energy–equivalent exposure normalized to an 8-hour reference period (A(8)) of the frequency-weighted value. In several epidemiological studies the estimations of exposure time are primary based on subjective assessments [86].

2 Aims

The overall aim of this thesis was to investigate peripheral nerve function in the upper limb by vibration threshold test and nerve conduction test in working populations including computer users, hand-arm vibration-exposed manual workers, and workers with chronic upper limb pain.

Specific study aims:

Study I: The aim of the study was to investigate whether a submaximal bicycle ergometer test before the nerve conduction examination would be a useful method of obtaining high finger temperatures that remained constant during the measurements.

Study II: The aim of the study was to compare the vibrotactile perception thresholds and nerve conduction measurements in the upper extremity between female secretaries who were frequent keyboard users and female nurses who did not use or seldom used a keyboard.

Study III: The aim of the study was to investigate the function of the somatosensory pathways, using vibration threshold testing and nerve conduction measurements in the upper extremity, in working women with and without chronic diffuse upper limb pain. Another aim was to examine whether mood influences the result of vibration threshold testing, and so, prior to the vibration threshold test, perceived stress and energy were assessed using a two-dimensional mood adjective checklist.

Study IV: The aim of the study was to assess the possible reductions in median and ulnar nerve conduction velocities in hand-arm vibration-exposed workers compared to unexposed workers. To this end, we measured the motor and sensory conduction velocities after having assessed vibration exposure over 21 years in a cohort of male manual workers.

3 Methods

3.1 Study populations and study designs

3.1.1 Studies I–III

Female subjects were invited to participate in the investigations, by means of advertisements posted on personnel notice boards. The invitation referred to working women with and without chronic upper limb pain. The subjects worked as secretaries or nurses in different health care facilities in the southwest of Sweden. There were 127 female participants who entered the studies, 88 secretaries and 39 nurses (controls), and of those, 51 reported having had chronic pain for more than three months and 76 were normally pain free (controls).

3.1.2 Study I

The study is a method study. Thirteen individuals were excluded because of missing data or inability to perform the test due to contraindications such as cardiovascular disease and/or musculoskeletal problems. There remained 114 women aged 25–65 (median 44) years in the study group.

3.1.3 Study II

The study has a cross-sectional design. Nine women were excluded because of missing data and one when she obtained the diagnosis polyneuropathy after the nerve conduction test. There remained 82 secretaries, aged 25–65 (median 44) years and 35 nurses, aged 24–57 (median 46) years.

3.1.4 Study III

The study has a cross-sectional design. Six participants did not have pain in the upper limb. They had pain elsewhere in the body, such as lower back, leg, knee, or the non-dominant arm/hand, and these six were excluded. Ten were excluded from the analysis because of missing data. Five were excluded because of disorders predisposing to upper limb conditions and nerve affliction (multiple sclerosis, diabetes, rheumatoid arthritis, non-Hodgkin’s lymphoma, and vitamin B12 deficiency). One subject was excluded, as she was diagnosed with polyneuropathy after the nerve conduction test. Five subjects were excluded, as they were diagnosed with carpal tunnel syndrome (symptoms combined with sensory latency from palm to wrist greater than 1.73 ms at a distance of 60 mm). We excluded those with CTS because we only wanted to have subjects with chronic diffuse upper limb pain of unknown aetiology. The final study population thus included 35 individuals with chronic diffuse upper limb pain, aged 30–65 (median 46) years, and 65 individuals without chronic pain, aged 24–57 (median 42) years.

3.1.5 Study IV

The study has a cross-sectional design regarding the outcome of nerve conduction, but longitudinal regarding exposure assessment. The cohort consisted of male office workers and male manual workers, all full-time employees at an engineering plant that manufactured pulp and paper machinery. The subjects were recruited from the plant's payroll rosters in two stages: 151 subjects from the roster of January 1, 1987, and 90 subjects from that of January 31, 1992. An upper age limit of 55 years was set for inclusion. From the 1987 roster, 61 of 500 male office workers, including salesmen, managers, engineers, secretaries, and economic clerks, were randomly invited into the study. At the baseline examination in February 1987, 93 of 112 manual workers, including welders, grinders, turners, and steel platers, were available for invitation. Three manual workers declined to enter the study. A total of 151 subjects, 61 office workers and 90 manual workers, were examined and entered the cohort in 1987. In 1992, an additional 33 randomly invited office workers and 57 more manual workers who had been hired after 1987 were examined and added to the cohort (none of the invited subjects declined). Thus, in 1992 the cohort (baseline) consisted of 241 subjects.

Follow-ups were conducted in 1997, 2002, and 2008, that is, 10, 15, and 21 years after recruitment of the original cohort. At the 10-year follow-up the study group consisted of 220 subjects (9% loss from baseline); at 15 years there were 195 subjects (19% loss from baseline), and at the 21-year follow-up 197 subjects (18% loss from baseline) remained in the cohort (Table 1). The subjects who were lost to follow-up, as well as the returners, were analysed for age and exposure. None of these two groups differed from the subjects that remained in the study throughout all follow-ups. The exposure assessment at baseline revealed that some of the office workers had formerly been exposed to hand-arm vibration and some manual workers were not currently exposed to hand-arm vibration. To simplify, we used the terms exposed, currently exposed and unexposed subjects in the presentation of the study population (Table 1).

In 2008, all 197 subjects were invited to participate in nerve conduction measurements and 163 subjects were finally examined (83%). The most common reasons for not attending the nerve conduction measurements were that the subjects had retired or moved away from the area. Six subjects were excluded due to diabetes and two subjects due to polyneuropathy. Thus, the nerve conduction study group consisted of 155 subjects.

Five subjects reported a history of carpal tunnel release in the right hand, and one subject in the left hand. These hands were also excluded. In some subjects reliable measurements were not obtained due to electromagnetic interference, and some measurements were discontinued because of discomfort. Therefore, the final material of motor conduction measurements consisted of 150 right hands and 148 left hands for the median nerve and 152 right hands and 148 left hands for the ulnar nerve. Median sensory conduction measurements were made in 105 right, and 99 left, hands.

Table 1. Study population at baseline and follow-ups, 1987–2008

		1987	1987–1992[a]	1997	2002	2008
Study population	Total	151	241	220	195	197
	Exposed[d]	112 (83)	181(108)	165 (90)	141(57)	146 (52)
	Unexposed	39	60	55	54	51
Returners from baseline (1987–1992)[c]	Exposed[d]				8 (1)	26 (13)
	Unexposed				3	2
Lost to follow-up	Exposed[e]		9[b] (7)	16 (12)	32 (22)	21 (4)
	Unexposed		3[b]	5	4	5

[a]Baseline 1987–1992. Baseline consists of subjects entering the study in 1987 and 1992.
[b]Lost to follow-up between 1987 and 1992. The subjects are included in baseline (n = 241).
[c]Subjects who were included at baseline, lost to follow-up, but returned later to the study group in 2002 and/or 2008.
[d]Subjects who currently are or previously have been exposed, the currently exposed in brackets.
[e]Subjects who currently are or previously have been exposed, the currently exposed (based on the latest study) in brackets.

3.2 Permission from the Ethics Committee (I–IV)

Ethical approval was obtained from the Ethics Committee of the Medical Faculty at the University of Gothenburg (studies I–III) and the Regional Ethics Committee in Umeå (study IV).

3.3 Procedures

3.3.1 Procedures in study I

The bicycle ergometer test was performed after a medical examination and was conducted on a bicycle ergometer. Skin temperature was measured before and immediately after cycling, after one minute of rest, and after each nerve latency measurement.

3.3.2 Procedures in studies II–III

Each participant completed a questionnaire on exposure, symptoms in the upper extremity, and supplementary basic data. The questions covered age, work and years at work, exposure, chronic disease, symptoms, and use of nicotine/alcohol. Average pain intensity during the previous month was measured using a 10 cm visual analogue scale (VAS), and the subjects with chronic upper limb pain were then divided into two subgroups, with a cut point between mild and moderate/severe pain. [87]. The subjects underwent a brief clinical examination by a physician after, and in most cases on the same day as, the vibration threshold testing. Perceived stress and

energy were assessed using a two-dimensional mood adjective checklist before the vibration threshold test. In connection with the medical examination, ongoing pain intensity was measured using the VAS. The physician asked about the presence of chronic pain (pain >3 months). Nerve conduction was measured, and before the measurements, the subjects were systemically warmed by a bicycle ergometer test to ensure an adequate hand temperature and minimize temperature as a source of error. An overall flowchart for the procedures in studies II–III is presented in Figure 1.

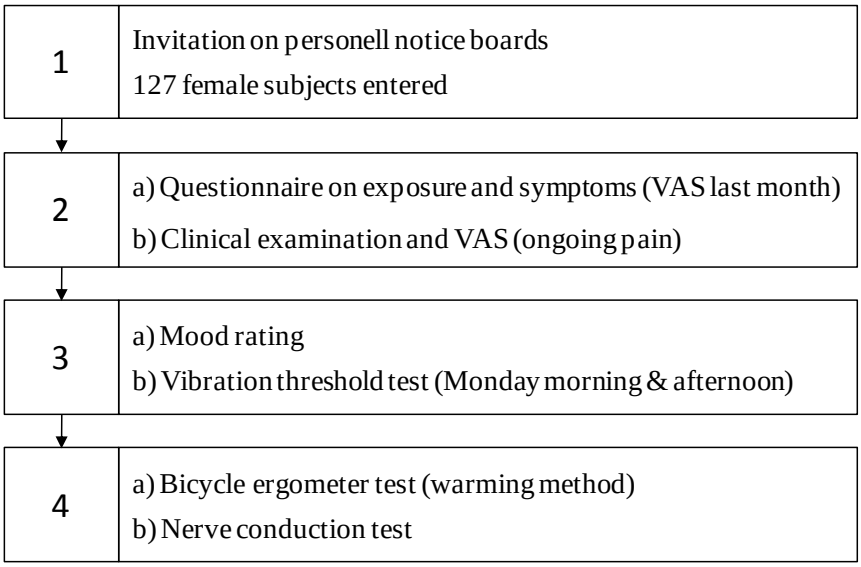

Figure 1. Flowchart for studies II–III.

3.3.3 Procedures in study IV

Hand-arm vibration dose was calculated as the product of self-reported occupational exposure collected by questionnaire and interviews and of the measured or estimated hand-arm vibration exposure at baseline and at all the follow-ups. At the 21-year follow-up, nerve conduction was measured, and before the measurements, the subjects were systemically warmed by a bicycle ergometer test. Each subject was interviewed regarding symptoms and examined by a physician (TN). A standard procedure was followed for physical examination of the upper extremities regarding the neuromuscular and skeletal systems, to check for and identify other diseases, primarily polyneuropathy. The subjects provided supplementary basic data through a questionnaire. The questions covered age, work and years at work, exposure, chronic disease, symptoms, and use of nicotine/alcohol.

3.4 Exposure assessment

3.4.1 Studies II–III

The subjective assessments of daily exposure time with computer work, including keyboard and mouse, were collected by questionnaire. There were questions about hours of duty, hours using computer keyboard (at work and at home), and experienced intensity at work (Table 2). All the subjects were also grouped into 3 classes, according to current daily computer keyboard use in hours. There was one unexposed group, and among those exposed, a division into 2 classes was made: one group with ≤4 hours of keyboarding per day and one group with >4 hours per day. The cumulative dose of keyboard use at work was calculated as the product of self-reported daily use of keyboard in hours/day, recruitment rate, 220 days/year, and years of employment. For example, a secretary using a computer 4 hours per day in 7 years with a recruitment rate of 90% had a cumulative dose of 4 hours/day × 220 days/year × 0.9 × 7 years = 5544 h. The interviews, which included questions about other risk factors for peripheral nerve affliction, did not reveal any previous employment with hand-arm vibration exposure.

Table 2. Exposure assessment, study II

Variable	Median (range) or number	
	Secretaries (n = 82)	Nurses (n = 35)
Years of employment	12 (0–41)	5 (0–26)
Recruitment rate (%)	100 (50–100)	100 (60–100)
Daily keyboarding at work (h)	6 (0–8.0)	1 (0–4.0)
Daily use of computer mouse (h)	0.8 (0–8.0)	0.5 (0–2.4)
Cumulative keyboard use at work (h)	13 860 (0–54 560)	880 (0–8800)
Hours using keyboarding at home during previous month (h)	1 (0–34)	2 (0–25)
Perceived high workload	13	8

3.4.2 Study IV

The cumulative hand-arm vibration dose was calculated as the product of self-reported occupational exposure, as collected by questionnaire and interviews, and the measured or estimated hand-arm vibration exposure in 1987, 1992, 1997, 2002, and 2008. In the calculations, the exposure during the periods between the investigations has been estimated based on values from the latest study. The assessment of vibration exposure was made under normal working conditions with standardized equipment and methods [88], by measuring the intensity of vibration on a random selection of the tools used by the manual workers in accordance with international standards [84, 85]. The total number of tools included in the study was 306 and during each investigation period the number of tools that measurements were conducted on

varied between 45 and 128, corresponding to between 50% and 90% of the total number of tools used at the workshop. For hand-held tools with two handles, measurements were made on both handles and the highest measured vibration intensity was used in the analysis. The most commonly used tools were grinders and hammers, and their mean frequency-weighted acceleration values have decreased over the investigation period from 5.8 to 4.5 m/s^2 and 11.0 to 7.6 m/s^2, respectively [82].

The subjective assessments of daily exposure time were collected by questionnaire and interview. In the questionnaire, the workers were asked to estimate the amount of time (minutes per day) they were exposed to vibration while using the different types of hand-held vibrating tools during their most recent working day. In the interview, workers who had been exposed before 1987 or ended exposure before 1987 were questioned about their use of hand-held vibrating tools (type, exposure time). The total daily exposure time for vibrating tools has decreased from 108 min per day in 1987 to 52 min per day in 2008 [82]. Leisure-time exposure (hobbies, snowmobiling, motorcycling, etc.) was not included in this measure. In 1987 the leisure exposure was only 5% of the cumulative lifetime vibration dose.

In the part of Sweden where the plant is located job change is infrequent. When students finish vocational school at approximately 18 years old, they often find well-paid employment as manual workers and usually stay in the job as long as possible. Our interviews revealed that occupational exposure to hand-arm vibration usually started at age 16 when most workers were in vocational school. Thus, we used the age 16 as onset of exposure time. In vocational school, the two last years consist mainly of work as a trainee. No worker who had any extended time away from hand-arm vibration exposure returned to exposure again. However, some workers left exposed jobs and some of them did so due to vibration-induced vascular symptoms (‘vibration white finger’).

The cumulative lifetime hand-arm vibration dose was calculated as the product of self-reported occupational exposure in hours and the squared acceleration of the measured or estimated hand-arm vibration exposure (i.e. dose = $a^2 \cdot t$; unit $m^2s^{-4}h$). As an example, a worker using a grinder 3 hours per day and a hammer 30 minutes per day for 7 years at exposure values of 5 m/s^2 and 10 m/s^2, respectively, would have had a dose of 7 years × 220 days/year × 3 hours/day × 5^2 $(m/s^2)^2$ + 7 years × 220 days/year × 0.5 hours/day × 10^2 $(m/s^2)^2$ = 192 500 $m^2s^{-4}h$. Those exposed were grouped into exposure quartiles with divisions at Q1 (25th centile), Q2 (median), and Q3 (75th centile). Class 1 includes subjects with hand-arm vibration exposure values from 0 to ≤Q1; class 2 includes subjects with values >Q1 to ≤Q2; class 3 includes >Q2 to ≤Q3; and class 4 includes the subjects with the highest exposure values of >Q3. Class 0 contains unexposed subjects (hand-arm vibration exposure equal to zero) and is set as the reference category. Thus 5 classes of cumulative lifetime hand-arm vibration dose were obtained (Table 3a).

Table 3a. Cumulative lifetime hand-arm vibration exposure dose

Class	n	Cumulative vibration dose ($m^2s^{-4}h$)		
		Min	Median	Max
0	39	0	0	0
1	29	2 475	56 320	84 865
2	29	85 800	128 700	192 500
3	29	197 120	252 648	359 680
4	29	365 420	566 764	857 813

Moreover, at the time for nerve conduction measurements, we calculated the current daily energy-equivalent exposure value normalized to an 8-hour reference period (i.e. A(8); unit ms^{-2}), in accordance with the European directive for vibration [29]. The subjects were grouped into 4 classes, according to current daily exposure. Class 0 contains not ever exposed subjects and class 1 contains subjects with cumulative vibration hand-arm exposure, but no current vibration exposure. Among those with current vibration exposure, a division into 2 classes was made: class 2 includes subjects with hand-arm exposure values from 0 to ≤Q2 and class 3 includes subjects with values >Q2 (Table 3b).

Table 3b. Current daily vibration exposure value

Class	n	Current daily vibration value, A(8),ms^{-2}		
		Min	Median	Max
0	39	0	0	0
1	70	0	0	0
2	23	0.41	0.84	1.19
3	23	1.27	1.59	4.12

Unless otherwise indicated, when referring in the text and tables to ‘exposed subjects’, we mean those subjects who currently are or earlier were exposed to hand-arm vibration, and consequently, the ‘unexposed subjects’ are those who have never been exposed to hand-arm vibration.

3.5 Outcome assessment

3.5.1 Bicycle ergometer test

The bicycle ergometer test was performed after a medical examination to exclude contraindications, that is, serious cardiovascular diseases or active infection with fever. The test, which was supervised by a physiotherapist, was conducted on an electrically braked bicycle ergometer (Siemens-Elema) (Figure 2). The subjects were asked to sit in an upright position on the bicycle, not leaning with any weight on the handlebars, and have a neutral position in the wrists.

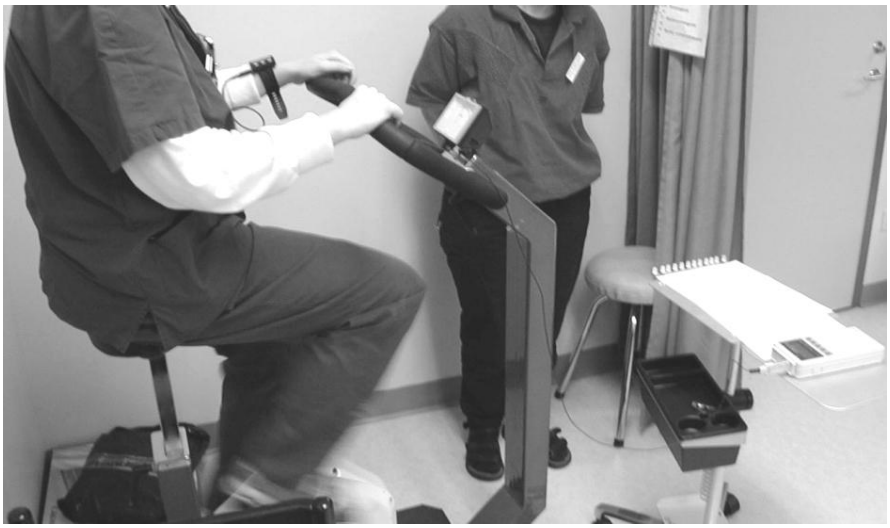

Figure 2. Bicycle ergometer test.

Two consecutive runs of 6 minutes each were conducted. In studies I–II, women under 35 years of age began at a load of 75 W, and after 6 minutes this was increased to 100 W. The equivalent loads for women over 35 were 50 W and 75 W, respectively. In study IV, men under 45 years of age began at a load of 100 W, and after 6 min this was increased to 150 W. The equivalent loads for men over 45 were 50 W and 100 W, respectively. After cycling, the subject was allowed to lie down on a bunk bed and covered with electrically heated blankets to maintain the temperature throughout the measurement period.

Skin temperature was measured using a thermistor taped to the tip of digit IV. In studies I–III, measurements were made before and immediately after cycling, after one minute of rest, and after each nerve latency measurement. The measurements were performed in the following order in studies II–III: median sensory nerve digit II, median sensory nerve digit III, ulnar sensory nerve digit V, median motor nerve conduction. The time between the first and the last measurement was about 25 (±5) minutes. In study IV, measurements were only made after each nerve latency measurement.

3.5.2 Nerve conduction test

Nerve conduction measurements were made on the dominant hand in studies II–III and in both hands in study IV, using an electromyography (EMG) apparatus (Keypoint® Portable, Keypoint software ver. 3.0, Medtronic NeuroMuscular, Denmark). The test was performed by an experienced EMG technician, who was blinded to the results of all other tests. In order to ensure an adequate hand temperature and minimize temperature as a source of error, [45, 47] the determination of conduction velocity was preceded by the bicycle ergometer test.

In studies II–IV the median nerve motor conduction velocity was determined using surface electrodes for stimulation at the elbow and proximal to the wrist, and for recording over the abductor pollicis brevis muscle. The distance between the recording and stimulation electrodes at the wrist was 7 cm. The F-wave latency was measured as the shortest latency obtained with 20 stimuli at the wrist. In study IV the ulnar nerve motor conduction velocity was determined using surface electrodes for stimulation 2 cm proximal to the elbow and proximal to the wrist, and for recording over the abductor digiti minimi muscle. The distance between the recording and stimulation electrodes at the wrist was 7 cm. The F-wave latency was measured as the shortest latency obtained with 20 stimuli at the wrist.

In studies II–III sensory conduction velocity (SCV) of the median nerve was determined orthodromically from the second and third finger to the palm and the wrist, respectively, using surface electrodes mounted at fixed sites in a plastic splint held against the skin over the nerve (Figure 3). In study IV the sensory conduction velocity was conducted in the same way, but only from the third finger. In studies II–III, the distances between recording and stimulation electrodes in the plastic splint for the third finger was 85 mm and 145 mm, respectively, and the corresponding figures in study IV were 66 mm and 126 mm. In the second finger in studies II–III, the corresponding figures were 83 mm and 143 mm. The distance between palm and wrist was 60 mm in all the plastic splints. In studies II–III the ulnar SCV was measured from the fifth finger to the wrist using electrodes fixed in a similar splint as for the median nerve. The distance between the recording and the stimulation at the finger-wrist was 123 mm. In studies II–IV the sural nerve SCV was also measured, to control for non-symptomatic polyneuropathy. In study IV the measurements were made on the second floor in the factory, and we experienced some technical problems with electromagnetic interference. Consequently, the sural nerve measurements in study IV were unreliable and not analysed in the study.

With 80% power we would have been able to detect a difference of 0.17 ms in the sensory latency at the carpal segment (digit III) in the dominant hand between secretaries and nurses in study II. The corresponding difference between the chronic diffuse upper limb pain group and controls in study III was 0.10 ms, and between hand-arm vibration-exposed and unexposed in study IV, it was 0.26 ms in the right hand and 0.14 ms in the left hand.

Figure 3. Sensory nerve conduction measurements at digit III, using a plastic splint with fixed distances. (EMG technician: Ann-Britt Andrén)

3.5.3 Vibration threshold test

A handheld vibrometer (type IV, Somedic AB, Stockholm, Sweden), operating at a frequency of 120 Hz and a tissue displacement range of 0.1– 400 μm, was used to deliver mechanical stimulation to the hand. The vibrating probe was 1 cm in diameter, and the amplitude of the vibration was displayed digitally. Readings were taken at five sites on the dominant hand: (1) the distal pad of the index finger (median nerve), (2) the distal pad of the 5th finger (ulnar nerve), (3) the dorsum of the 5th metacarpal bone (ulnar nerve), (4) the dorsum of the 2nd metacarpal bone (radial nerve), and (5) the palmar aspect between the 1st and 2nd metacarpal bones (median nerve). During the measurements at the metacarpal bones and at the palmar aspect between the 1st and 2nd metacarpal bones, the probe was placed perpendicular to the skin surface, and a pressure display enabled the applied pressure to be standardized to approximately 8 N/cm^2 (Figure 4a). During the measurements at the fingertips, the subject was asked to place the distal pad of the test finger over the probe and push down with a force of 0.4 N, visually controlled by the pressure display, which had been calibrated with a weight of 41 g (Figure 4b).

All vibration threshold examinations were performed by one assistant, who was blinded both to the group of the subjects and to the results of the preceding examination. The subjects were asked not to wear ordinary work wear and to remove their nameplates. The subjects were seated comfortably and examined in a quiet room without distractions. They could not see the vibrometer display. The stimulus was increased at a constant rate, until the subject could just detect vibration. From this threshold, the stimulus was then decreased until the subject could no longer feel the vibration. This ramping up and down was repeated four times. The means of four readings for both detection and loss of vibration stimulation at each site were calculated, and the average of the two figures was taken as a measure of vibrotactile perception threshold [60].

The subjects were tested both on a Monday morning after a weekend off work and on a Monday afternoon after at least 4 hours of working with either a computer keyboard or in their usual duties of nursing.

Before the study started, we did power calculations based on figures from the study of Greening and Lynn [24]. With 80% power, we wanted to be able to find approximately half of the mean difference that was found between office workers and controls in the median nerve, that is, we used the figure 0.15 µm. When analysing power after the study, the figures were changed because we lost some subjects due to missing data, and also because of different standard deviations of the outcome measurement. With 80% power we would have been able to detect a difference in the median nerve of 0.18 µm between secretaries and nurses in study II. The corresponding difference between the chronic diffuse upper limb pain group and controls in study III was 0.19 µm. In the ulnar nerve the figures were 0.13 µm and 0.12 µm, respectively, and in the radial nerve the corresponding figures were 0.10 µm and 0.11 µm. However, the differences that we would have been able to detect were still lower than those found by Greening and Lynn [24].

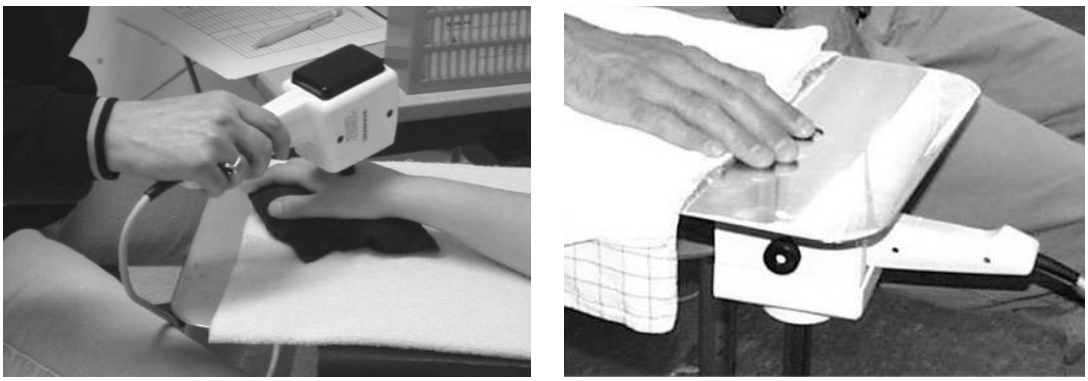

Figure 4a-b. Vibration threshold test at (a) the dorsum of the 2nd metacarpal bone (radial nerve) and (b) the distal pad of the index finger (median nerve).

3.5.4 Stress-Energy Questionnaire

The stress-energy checklist was used just before the vibration threshold testing on a Monday morning. Twelve adjectives represent two fundamental dimensions: stress and energy. The overall question to be answered by the checklist was: ‘How did you feel over the past ten minutes?’ The participants indicated on a six-point scale (0–5) how well each adjective described their state. The stress dimension uses the following adjectives: *tense*, *stressed*, *pressured*, *relaxed*, *rested*, and *calm*, while the energy dimension uses *focused*, *energetic*, *active*, *inefficient*, *dull*, and *passive*. Before analysis, the scores for the negative items (inefficient, dull, passive, relaxed, rested, and calm) were reversed, with a score of 5 being mapped to a score 0, a score of 4 to a score of 1, and so on. Stress and energy scores were calculated as mean

ratings of the six items in each dimension, after reversal of the negative items. Cronbach's alpha for stress was 0.85 and for energy 0.69. The neutral points of the scales have previously been calculated; the neutral point for the stress scale (neither stressed nor calm) is 2.4, and the neutral point for the energy scale is 2.7 [68].

3.5.5 Physical examination

In studies II–III the physical examination of neck and upper limbs (shoulders, elbows, wrists, hands, fingers) included the following steps: (1) inspection, (2) testing for range of active and passive motion, (3) testing for muscle contraction, pain, and muscle strength, (4) palpation of muscle tendons, insertions, and joints, (5) bedside neurologic examination, including muscle stretch reflexes (biceps, triceps, brachioradialis, achilles), sensory exam in hands/fingers evaluating different kinds of sensation, including light touch (cotton wool), two-point-discrimination, and temperature (a tuning fork at room temperature should be perceived as cold on the digital pulp of index and fifth fingers), and (6) specific tests: Spurling's test (neck compression test), cervical spine Lasègue test (extending the plexus by axial compression of the acromion with simultaneous lateral flexion of the subject's cervical spine towards the contralateral side), Roos test (abduction external rotation test), bursa test for shoulder bursitis, pronator compression test, palpation at the arcade of Frohse, Maudsley's test (middle finger extension test), Finkelstein's test, Phalen's test (wrist compression test) and Tinel's test. A detailed list of the physical examination specifications for studies II–III and details concerning tests are available at our homepage (www.amm.se/vptstudy). In study IV the physical examination was approximately the same. Further details concerning some of these tests can also be found in Nilsson [89].

3.5.6 Questionnaire

In studies II–IV supplementary basic data was collected by means of a questionnaire. The questionnaire served as a supplement to the interview in connection with the physical examination. The questions covered age, weight, height, work and years at work, physical exposure, chronic diseases, symptoms, presence of chronic pain (studies II–III), medications being taken, and use of nicotine/alcohol.

3.6 Statistical methods

P-values <0.05 were considered to be statistically significant. JMP® and SAS® were used to perform the analyses.

3.6.1 Studies II–III

Student's two-sample t-test for comparison between independent groups was used in the analysis of the variables in the nerve conduction test, VAS, mood ratings, and age. Wilcoxon's rank sum test was used to compare the groups in the analysis of the VPTs, as the values were not normally distributed. Paired t-test was used to compare

each individual's first and second measurements. In multivariate analysis, linear regression of the VPTs and nerve conduction measurements were used to model the impact of individual exposure variables. Backward elimination and forward selection procedures were used to verify the multivariate linear regression model. In study II, the predictor variables in the model that were considered to be of biological importance were age, body height, weight, smoking, alcohol consumption, occupation, ongoing pain, chronic pain, hours of duty, experienced intensity at work, daily use of computer keyboard at work and at home, and cumulative keyboard exposure. In study III, the predictor variables in the model that were considered to be of biological importance were age, body height, weight, smoking, alcohol consumption, daily use of computer keyboard, chronic pain, and mood.

3.6.2 Study IV

To compare nerve conduction, temperature, and age between groups, the Student's two-sample t-test for independent groups was used. Paired t-test was used to compare an individual's nerve conduction velocities between the right and left hands. A multivariate linear regression model was used to assess the association between nerve conduction outcome and exposure variables. Backward elimination and forward selection procedures were used to verify the multivariate linear regression model. The predictor variables in the model that were considered to be of biological importance were age, body height, weight, skin temperature, smoking, alcohol consumption, class of vibration exposure, and years since last vibration exposure to date of test. Since cumulative vibration exposure and current vibration exposure partly include the same information, two separate models were considered, one for each vibration exposure. For comparing prevalence of median nerve neuropathy, chi-square test and a variant of Fisher's exact test [90] were used.

4 Results

4.1 Study I

Before cycling, the mean finger temperature was 28.1ºC (range 20.5–35.4), with a large variation among individuals (Table 4). Immediately after cycling, the average skin temperature had risen 5ºC; however, the interindividual variation of skin temperatures was still large. After a one-minute rest, the average skin temperature had increased by almost an additional 2ºC to 35.1ºC (range 30.3–36.9), but more importantly, the interindividual variation was reduced. Moreover, the variation in skin temperature between occupational groups with and without chronic pain was reduced (Figure 5). During the rest of the examination, both the mean values and the standard deviations remained approximately constant, with only a slow, gradual reduction occurring (Table 4). For example, the lowest skin temperature was 31.4ºC after the median nerve sensory measurement in digit III, and only 7 individuals had a temperature value below 33ºC. After the last measurement, the mean skin temperature was still above 34.3ºC.

Table 4. Temperature data for 114 subjects before and after a bicycle ergometer test and during subsequent measurements of distal median and ulnar latencies. Mean difference in temperature between measurements.

	Temperature in connection with cycling (°C)			Temperature when measuring nerve conduction (°C)[a]			
	Before cycling	After cycling	Rest, after cycling	Digit II	Digit III	Digit V	Median motor
Mean	28.1	33.3	35.1	34.9	34.8	34.6	34.4
SD	4.4	3.8	1.1	1.0	1.0	1.1	1.3
95% CI	(27.3; 28.9)	(32.6; 34.0)	(34.9; 35.3)	(34.7; 35.1)	(34.6; 35.0)	(34.4; 34.8)	(34.1; 34.6)
Min	20.5	21.6	30.3	29.7	31.4	29.3	29.5
Max	35.4	36.7	36.9	36.4	36.4	36.2	36.4
Mean difference	5.2	1.8	-0.2	-0.1	-0.2	-0.2	
95% CI	(4.4; 6.0)	(1.2; 2.4)	(-0.3; -0.0)	(-0.2; -0.0)	(-0.3; -0.1)	(-0.3; -0.1)	

[a] The nerve conduction and temperature measurements were made in the following order: median sensory nerve digit II, median sensory nerve digit III, ulnar sensory nerve digit V, median motor nerve conduction.

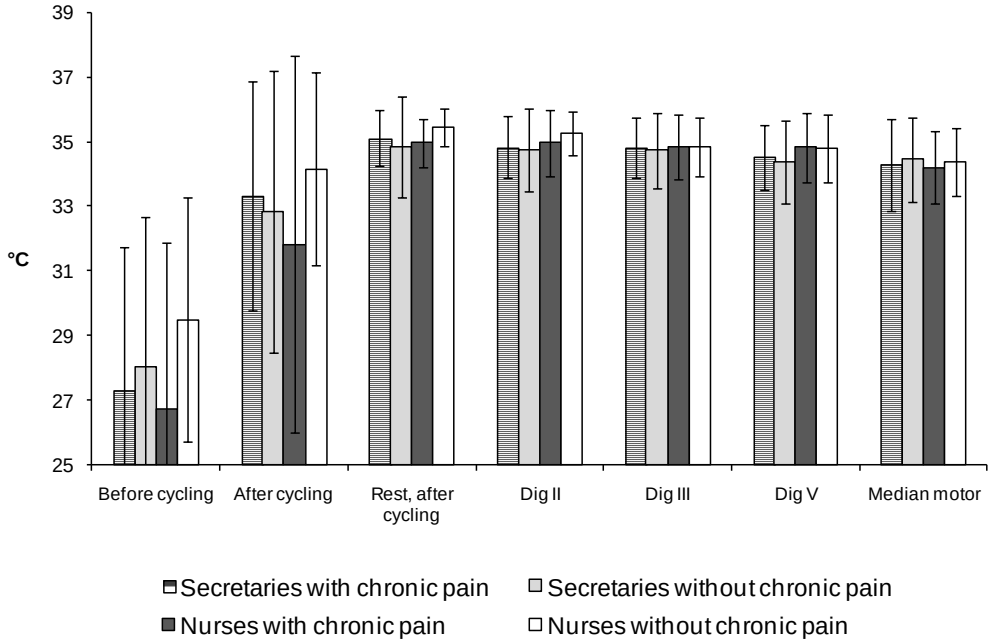

Figure 5. Temperature data for secretaries and nurses with and without chronic pain before and after a bicycle ergometer test and during subsequent measurements of distal median and ulnar latencies.

4.2 Study II

The groups did not differ, regarding age, height, or weight. Group characteristics of the secretaries and nurses are presented in Table 5.

4.2.1 Nerve conduction test

There was no significant difference in any parameter of the nerve conduction test between secretaries and nurses (Table 6). Specifically, there was no difference between the two occupational groups in motor or sensory conduction in the median nerve or in the sensory conduction of the ulnar nerve. Neuropathy of the median nerve was considered to be present when the sensory latency from palm to wrist (digit III) was greater than 1.73 ms at a distance of 60 mm (the cut-off point represents 3 standard deviations of the mean value of a normal sample collected with similar plastic splint equipment in our laboratory). With this cut-off point, there were 4 secretaries (5%) and 3 nurses (9%) with median nerve neuropathy. Among these, there were 3 secretaries (4%) and 2 nurses (6%) with symptoms of numbness in hands and fingers. The temperature (ºC) during the examination was similar between the secretaries (34.7 ± 1.1) and nurses (34.9 ± 0.9) (Table 6) and remained stable during the whole measurement period.

Table 5. Study population characteristics, study II

Variable	Median, (range) or number	
	Secretaries (n = 82)	Nurses (n = 35)
Age (years)	44 (25–65)	46 (25–57)
Height (cm)	165 (154–177)	167 (159–176)
Weight (kg)	63 (50–105)	66 (53–85)
Cigarette smokers	20	6
Alcohol ≥once/week	7	7
Chronic diffuse upper limb pain (>3 months)	30	5
Ongoing pain (VAS)	2.3 (0–8.0)	0 (0–5.4)
Rheumatic disease	1	0
Thyroid disease	2	1
Nocturnal symptoms (numbness/tingling)		
Right hand	18	5
Left hand	10	2
Pain (hand)		
Right hand	20	1
Left hand	11	1
Clumsiness (difficulties in buttoning clothing)		
Right hand	2	1
Left hand	3	1

Table 6. Nerve conduction test, dominant hand, study II

		Secretaries		Nurses		95% CI	t-test
		Mean	SD	Mean	SD	group difference	P-value
Motor examination							
Median nerve	Velocity (m/sec)	57.3	3.2	56.6	2.7	-1.7; 0.6	0.30
	Amplitude (elbow) (mV)	9.7	2.7	9.5	2.8	-1.3; 0.9	0.74
	Amplitude (wrist) (mV)	10.1	2.8	10.0	2.9	-1.3; 1.1	0.88
	Distal latency (ms)	3.4	0.5	3.5	0.7	-0.1; 0.4	0.36
	F-latency (ms)	21.7	1.3	22.0	1.0	-0.2; 0.7	0.21
Sensory examination							
Distal Latency	Palm-wrist, digit II (median nerve) (ms)	1.3	0.5	1.4	0.3	-0.1; 0.2	0.28
	Palm-wrist, digit III (median nerve) (ms)	1.3	0.3	1.4	0.3	-0.1; 0.1	0.39
	Finger-wrist, digit V (ulnar nerve) (ms)	2.2	0.1	2.2	0.2	-0.02; 0.1	0.16
Velocity	Finger-wrist, digit II (median nerve) (m/s)	51.1	4.6	50.1	5.5	-2.7; 1.4	0.33
	Finger-wrist, digit III (median nerve) (m/s)	51.9	4.7	50.8	5.6	-3.3; 1.1	0.33
	Finger-Wrist, digit V (ulnar nerve) (m/s)	56.3	3.3	55.3	3.5	-2.3; 0.5	0.48
	Sural nerve (m/s)	51.5	4.8	51.1	4.7	-1.9; 1.8	0.67
Temperature	Finger pad digit IV (^{o}C) (during sensory examination digit III)	34.7	1.1	34.9	0.9	-0.2; 0.5	0.48

No difference between the two occupational groups was seen after adjustment for age, body height, weight, smoking, alcohol consumption, ongoing pain, chronic pain, hours of duty, experienced intensity at work, daily use of computer keyboard at work and at home, and cumulative keyboard exposure. There were no differences between groups of current daily keyboard use (data not shown), except for median motor velocity. The most exposed group, with >4 hours of keyboarding per day, had slightly faster nerve conduction velocity (mean 57.9 SD 3.3) m/s, than the group with ≤4 hours of keyboarding per day (mean 56.5, SD 2.8) m/s.

Table 7. Vibrotactile perception thresholds before work on Monday morning**,** dominant hand**,** study II

	Vibrotactile perception thresholds before work on Monday morning				Pre/post work difference[a]	
	25%	Median	75%	Wilcoxon P-value	Median	Wilcoxon P-value
Distal pad dig. II (μm)						
Secretary	0.444	0.601	0.882	0.37	-0.031	0.87
Nurse	0.401	0.556	0.754		-0.016	
Palmar aspect of metacarpal I–II (μm)						
Secretary	0.698	0.874	1.306	0.55	0.004	0.85
Nurse	0.602	0.795	1.249		-0.029	
Distal pad dig. V (μm)						
Secretary	0.596	0.844	1.202	0.61	-0.031	0.21
Nurse	0.552	0.831	1.127		-0.071	
Metacarpal V (μm)						
Secretary	0.395	0.491	0.660	0.34	0.011	0.62
Nurse	0.375	0.494	0.564		0.009	
Metacarpal II (μm)						
Secretary	0.380	0.474	0.609	0.13	-0.006	0.26
Nurse	0.359	0.427	0.546		0.004	

[a]Differences in vibrotactile perception thresholds after 4 hours' work as a secretary using computer keyboard equipment or 4 hours of nursing (individual VPT after work minus individual VPT before work). The reduction after workshift is extremely small and not significant between groups.

4.2.2 Vibration threshold test

There was no significant difference in any parameter of the vibration threshold test between secretaries and nurses and there was no change in the vibrotactile perception thresholds after four hours of using computer keyboard equipment (Table 7).

Again, there was no difference between the two occupational groups after adjustment for age, body height, smoking, alcohol consumption, ongoing pain, chronic pain, hours of duty, experienced intensity at work, daily use of computer keyboard at work and at home, and cumulative keyboard exposure. The VPT values were not normally

distributed, and so we also performed a multivariate regression model analysis with logarithmically transformed vibration thresholds; the results were similar. Furthermore, there were no differences between groups of current daily keyboard use (data not shown).

4.3 Study III

4.3.1 Group characteristics and mood

The chronic diffuse upper limb pain group, which was significantly older than the control group (Table 8), passed the medical examination without signs of nervous disease. All subjects had non-specific arm and/or neck pain without specific signs of disease (e.g. tenosynovitis, nerve entrapment, arthrosis). After analysis of the questionnaire regarding estimated average pain intensity during the previous month (VAS), the chronic diffuse upper limb pain group —'chronic pain (all)'— was divided into two subgroups [87], 'chronic pain (VAS ≥ 5)' (n = 12) and 'chronic pain (VAS < 5)' (n = 23).

The control group also passed the medical examination without signs of nervous disease and had no history of pain with long duration in recent years. Only a few members of this group reported acute temporary pain in connection with medical examination and/or vibration threshold testing. A few reported pain during the preceding month when filling out the questionnaire, but in these cases the physician could not confirm any long periods of pain when talking to the participant.

The VAS results regarding pain during the medical examination (on the same day as the vibration threshold testing) and average pain intensity during the previous month are presented in Table 8. The chronic pain (VAS ≥ 5) group had significantly higher stress scores than the control group, but the groups did not differ significantly in mean energy scores (Table 8).

Table 8. Group characteristics: Age, VAS, (estimated average pain during the previous month and ongoing pain in connection with medical examination), and mood.

Subject group	n	Age (years)	VAS previous month (cm)	VAS ongoing (cm)	Energy	Stress
		Median (range)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Controls	65	42 (24–57)	1.2 (1.5)	0.2 (0.7)	3.1 (0.7)	1.4 (0.7)
Chronic pain (VAS < 5)	23	48 (30–65)	2.4 (1.6)	2.5 (2.0)	3.2 (0.5)	1.4 (0.6)
Chronic pain (VAS ≥ 5)	12	42 (32–61)	6.1 (0.9)	2.8 (2.8)	3.2 (0.5)	2.1 (0.7)
Chronic pain (all)	35	46 (30–65)	3.7 (2.3)	2.6 (2.3)	3.2 (0.5)	1.6 (0.7)

4.3.2 Vibration threshold test

Compared to the control group, VPT was significantly higher among the chronic pain (all) group, the chronic pain (VAS < 5) group, and the chronic pain (VAS ≥ 5) group within the territory of the radial nerve (p-values: 0.001, 0.012, 0.009, respectively) and within the territory of the ulnar nerve at the metacarpal site (p-values: 0.004, 0.015, 0.045, respectively), but not at the fingertip (Figure 6). In the multivariate regression model analysis with age, stress, and energy as covariates, the VPT was still significantly higher in the chronic pain (all) group (Table 9) and the chronic pain (VAS ≥ 5) group for the radial nerve and at the metacarpal site for the ulnar nerve, whereas the chronic pain (VAS < 5) group showed significantly higher thresholds only in the radial nerve. Moreover, there were still differences between groups in a multivariate regression model with all the predictor variables in the model that were considered to be of biological importance: age, body height, smoking, alcohol consumption, current daily use of computer in hours, and mood (data not shown). The differences in VPT were small. There were no significant differences in VPT for the median nerve.

We also made a VPT index by calculating the mean of the VPTs from the territory of all three nerves and the VPT index was significantly higher in the chronic pain (all) group (Figure 7).

The VPT values were not normally distributed, and so we also performed a multivariate regression model analysis with logarithmically transformed vibration thresholds; the results were similar and the R^2 figures increased. For simplicity, we present only non-logarithmic values.

The changes in vibrotactile perception thresholds after 4 h of work were small, went in both directions, and did not differ significantly between the chronic pain (all) group and the controls. A paired t-test for individual VPT (all subjects) between the first and second tests gave mean differences of -0.08 µm (SE 0.03, p = 0.02) for the median nerve/distal pad, 0.01 µm (SE 0.03; p = 0.71) for the median nerve/metacarpal, 0.04 µm (SE 0.05; p = 0.40) for the ulnar nerve/distal pad, 0.01 µm (SE 0.01; p = 0.40) for the ulnar nerve/metacarpal, and -0.00 µm (SE 0.01; p = 0.99) for the radial nerve.

In the multivariate regression model, neither stress nor energy influenced the VPT, and the group difference in VPT did not change when adjusted for stress and energy (Table 9). We also dichotomized the variables for stress and energy at the scale values, which represent the neutral point of the respective scale, and there was still no influence on VPT or change in VPT difference between groups.

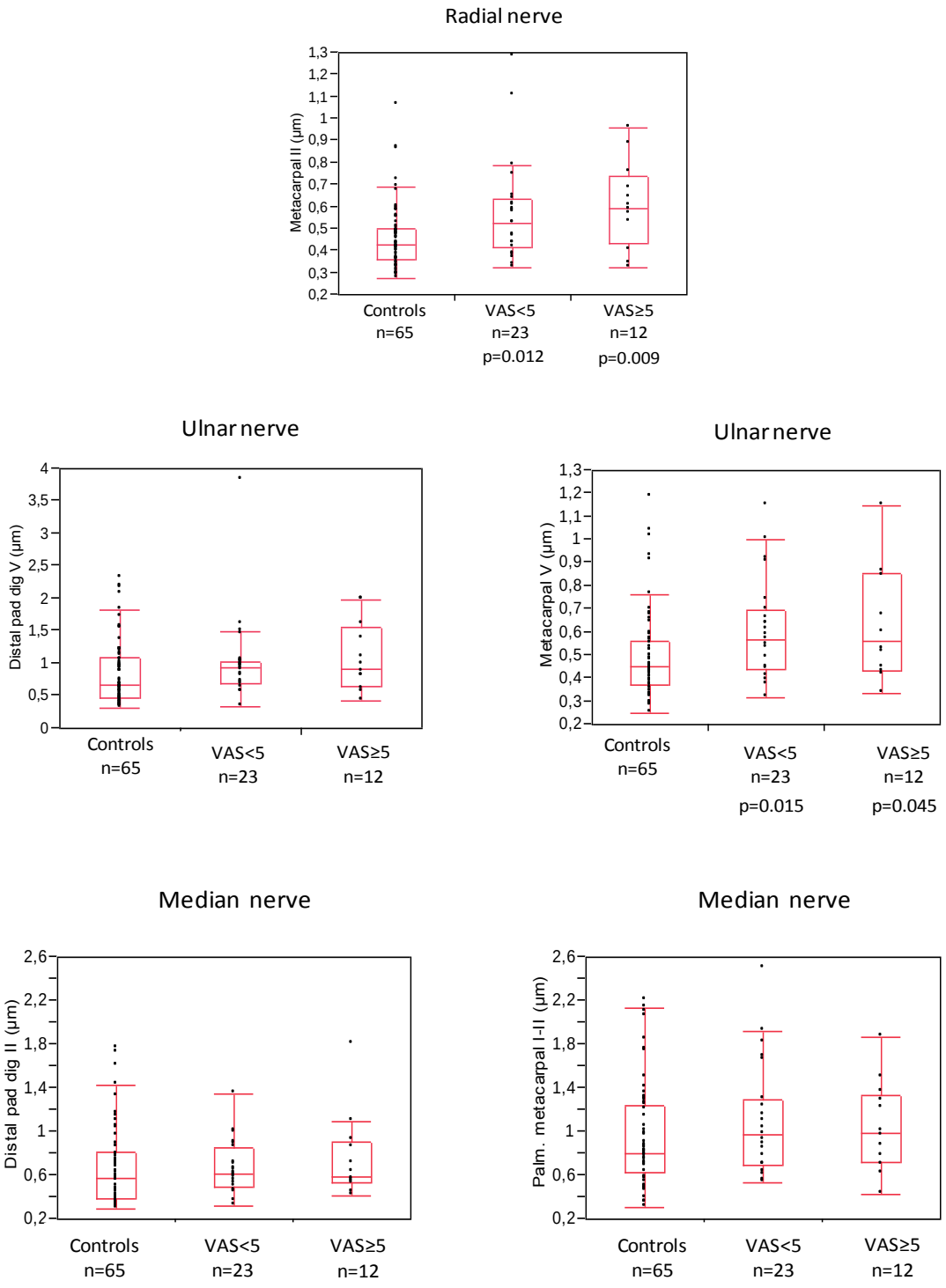

Figure 6. Vibrotactile perception thresholds in the area of radial, ulnar, and median nerve (dominant hand). The ends of the box are the 25th and 75th quantiles, and the median values (-) are presented in the box. The difference between the quartiles is the interquartile range (Q3–Q1). The whiskers extend from the farthest point that is still within 1.5 interquartile ranges from the box.

Table 9. Multivariate regression analysis of vibrotactile perception thresholds (dominant hand), study III.

	Median nerve				Ulnar nerve				Radial nerve	
	Distal pad digit II		Palmar aspect of metacarpal I-II		Distal pad digit V		Metacarpal V		Metacarpal II	
	β	95% CI	β	95% CI	β	95% CI	β	95% CI	β	95% CI
Model A[a]										
Intercept	0.204	(-0.109;0.517)	0.279	(-0.158;0.716)	0.213	(-0.305;0.731)	0.227	(0.036;0.419)	0.274	(0.107;0.441)
Chronic pain (all)	-0.025	(-0.163;0.113)	0.055	(-0.137;0.248)	0.124	(-0.105;0.352)	0.091	(0.007;0.175)	0.106	(0.032;0.179)
Age	0.011	(0.004;0.018)	0.016	(0.006;0.026)	0.016	(0.003;0.028)	0.006	(0.002;0.011)	0.004	(0.001;0.008)
R^2	0.089		0.107		0.090		0.148		0.152	
Prob > F	0.012		0.004		0.010		<0.001		<0.001	
Model B[b]										
Intercept	0.202	(-0.247;0.651)	0.363	(-0.265;0.992)	0.042	(-0.702;0.785)	0.220	(-0.055;0.495)	0.262	(0.023;0.501)
Chronic pain (all)	-0.015	(-0.156;0.125)	0.059	(-0.139;0.256)	0.110	(-0.123;0.343)	0.091	(0.004;0.177)	0.112	(0.037;0.187)
Age	0.011	(0.004;0.018)	0.016	(0.006;0.026)	0.016	(0.003;0.028)	0.006	(0.002;0.011)	0.004	(0.0005;0.008)
Stress	-0.040	(-0.132;0.052)	-0.009	(-0.138;0.120)	0.050	(-0.103;0.203)	0.002	(-0.055;0.059)	-0.027	(-0.076;0.022)
Energy	0.020	(-0.079;0.119)	-0.023	(-0.162;0.116)	0.031	(-0.133;0.196)	0.002	(-0.059;0.062)	0.016	(-0.036;0.069)
R^2	0.096		0.108		0.096		0.148		0.165	
Prob > F	0.046		0.027		0.045		0.004		0.002	

[a] In model A: Chronic pain and age were explanatory factors ($VPT = \beta_0 + \beta_1 \times \text{chronic pain} + \beta_2 \times \text{age}$).
[b] In model B: Chronic pain, age, stress, and energy were explanatory factors ($VPT = \beta_0 + \beta_1 \times \text{chronic pain} + \beta_2 \times \text{age} + \beta_3 \times \text{stress} + \beta_4 \times \text{energy}$).

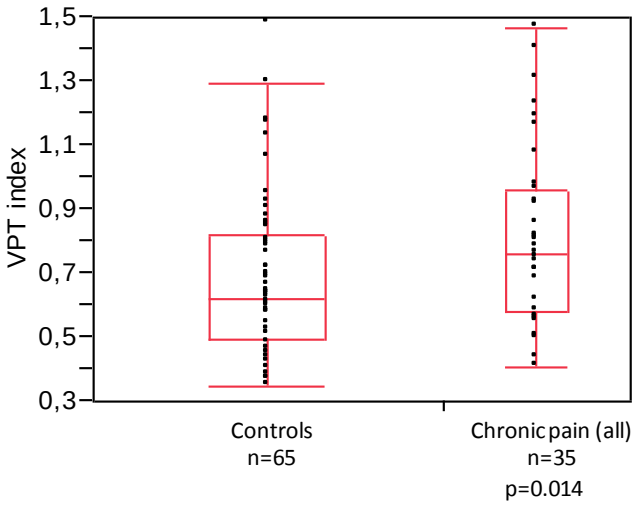

Figure 7. VPT index**.** The mean of all VPTs measured in the dominant hand. The ends of the box are the 25th and 75th quantiles and the median values (-) are presented in the box. The whiskers extend from the farthest point that is still within 1.5 interquartile ranges from the box.

4.3.3 Nerve conduction test

There was no significant difference in any parameter of the nerve conduction test between the chronic pain (all) group and the controls (Table 10). Specifically, there was no difference between the two groups in motor or sensory conduction velocity in the median nerve and no difference in sensory conduction velocity in the ulnar nerve. Furthermore, there was no significant difference in any parameter of the nerve conduction test between the controls and any pain group, and for simplicity, we do not present the figures for the subgroups. No difference between the groups was seen after adjustment for age, body height, weight, smoking, alcohol consumption, or current daily use of computer in hours. Temperature during the examination was similar in both the chronic pain (all) group (34.9 ± 1.0°C) and the control group (34.7 ± 1, 1°C) (Table 10), and it remained stable during the whole measurement period.

Table 10. Nerve conduction test, dominant hand, study III.

	Chronic pain (all)		Controls		95% CI group	t-test
	Mean	SD	Mean	SD	difference	P-value
Motor examination						
Median nerve						
Velocity (m/s)	57.4	2.9	57.3	2.9	-1.3; 1.2	0.94
Amplitude (elbow) (mV)	10.1	2.4	9.6	2.9	-1.6; 0.6	0.39
Amplitude (wrist) (mV)	10.5	2.4	10.1	3.0	-1.5; 0.8	0.52
Distal latency (ms)	3.3	0.3	3.4	0.3	-0.1; 0.2	0.53
F-latency (ms)	21.7	1.2	21.7	1.2	-0.5; 0.5	0.98
Sensory examination						
Distal latency						
Palm-wrist, digit II (median nerve) (ms)	1.2	0.6	1.3	0.2	-0.1; 0.3	0.50
Palm-wrist, digit III (median nerve) (ms)	1.3	0.2	1.3	0.1	-0.1; 0.1	0.73
Finger-wrist, digit V (ulnar nerve) (ms)	2.2	0.1	2.2	0.2	-0.1; 0.1	0.75
Velocity						
Finger-wrist, digit II (median nerve) (m/s)	51.3	4.4	51.8	3.3	-1.2; 2.3	0.51
Finger-wrist, digit III (median nerve) (m/s)	49.2	4.0	49.2	3.0	-1.6; 1.6	0.96
Finger-wrist, digit V (ulnar nerve) (m/s)	56.1	3.1	55.9	3.7	-1.6; 1.2	0.82
Sural nerve (m/s)	52.3	4.6	51.1	4.8	-3.3; 0.9	0.25
Temperature						
Finger pad, digit IV (°C) (during sensory examination of digit III)	34.9	1.0	34.7	1.1	-0.6; 0.3	0.51

4.4 Study IV

Subjects in the unexposed group and formerly exposed group were older than those in the currently exposed group. The groups did not differ regarding height or weight (Table 11).

The subjects who did not attend the nerve conduction measurements were analysed for age and lifetime cumulative hand-arm vibration exposure and did not differ from the studied subjects.

4.4.1 Motor conduction latencies

Median and ulnar nerves, distal latency. There were no significant differences in median or ulnar nerve distal latencies in either arm between exposed and unexposed subjects (Table 12), nor between classes, with cumulative lifetime exposure or current daily exposure (data not shown).

Table 11. Study population characteristics, study IV

Variable	Median (range) or number			
	Exposed			Unexposed
	All (n = 116)	Formerly (n = 70)	Currently (n = 46)	(n = 39)
Age (years)	55 (37–75)	58 (37–75)	46 (38–64)	60 (41–74)
Height (cm)	179 (166–193)	180 (167–193)	178 (166–190)	178 (170–192)
Weight (kg)	86 (62–161)	86 (64–116)	86 (62–161)	80 (63–135)
Cigarette smokers	24	14	10	3
Alcohol ≥14 units/week	8	4	4	2
Rheumatic disease	0	0	0	1
Thyroid disease	3	2	1	1
Nocturnal symptoms (numbness/tingling)				
Right hand	28	17	11	6
Left hand	29	19	10	7
Pain (wrist)				
Right hand	27	18	9	2
Left hand	20	14	6	4
Clumsiness (difficulties in buttoning clothing)				
Right hand	29	20	9	4
Left hand	26	17	9	3

In the multivariate regression analysis, distal motor latency of the median nerve was associated with skin temperature (right/left hand) and age (left hand). Distal motor latency of the ulnar nerve was associated with skin temperature (right/left hand), and height (right/left hand). Neither the cumulative lifetime exposure nor the current daily exposure contributed to explaining the distal latencies in the multiple linear regression models.

Paired t-test for individual measurements between right and left hands in the median nerve gave a mean difference of 0.32 ms (SE 0.04, $p < 0.001$), and the corresponding figure for the ulnar nerve was 0.09 ms (SE 0.03, $p = 0.003$). Approximately the same figures apply when analysing data from exposed and unexposed workers separately. The right hands had the longer distal latency.

The skin temperature during motor conduction measurements of the median nerve was similar between unexposed (right hand 32.4°C ± 4.0, left hand 32.4°C ± 4.0) and exposed (right hand 32.2°C ± 3.3, left hand 32.5°C ± 3.2) subjects and corresponding skin temperature for the ulnar nerve was also similar between unexposed (right hand 32.3°C ± 3.8, left hand 32.5°C ± 3.9) and exposed (right hand 32.3°C ± 3.0, left hand 32.6°C ± 3.1) subjects. There were no significant differences in skin temperature between classes, with respect to cumulative lifetime exposure or current daily exposure.

Table 12. Nerve conduction measurements, study IV

		Exposed						Unexposed		Group difference (Exposed All–Unexposed) 95% CI	p-value[a]
		All		Formerly		Currently					
		Mean	SD	Mean	SD	Mean	SD	Mean	SD		
Motor examination											
Median nerve											
Velocity (m/s)	right	57.8	5.36	58.5	5.29	56.8	5.46	57.6	6.03	-1.96; 2.43	0.83
	left	60.4	6.08	61.0	6.16	59.8	5.68	61.1	7.02	-3.44; 2.01	0.60
Amplitude (wrist) (mV)	right	7.61	3.28	7.48	2.82	7.83	3.92	8.14	3.26	-1.74; 0.69	0.39
	left	8.95	3.42	8.94	3.38	8.80	3.52	7.70	3.40	-0.08; 2.57	0.06
Distal latency (ms)	right	4.42	0.73	4.40	0.67	4.41	0.83	4.28	0.65	-0.11; 0.39	0.28
	left	4.07	0.53	4.09	0.48	4.07	0.63	4.04	0.71	-0.23; 0.30	0.79
F-latency (ms)	right	25.9	2.08	25.7	1.87	26.2	2.37	26.5	2.11	-1.37; 0.23	0.16
	left	25.8	2.11	25.7	2.07	25.8	2.16	25.5	2.04	-0.50; 1.10	0.46
Ulnar nerve											
Velocity (m/s)	right	60.4	7.06	60.4	6.80	60.4	7.55	59.7	6.47	-1.83; 3.23	0.58
	left	64.0	6.52	63.8	6.82	64.2	6.19	63.5	6.39	-2.07; 2.97	0.72
Amplitude (wrist) (mV)	right	11.2	2.30	11.2	2.49	11.3	2.01	11.2	2.18	-0.81; 0.86	0.95
	left	10.4	1.99	10.4	2.04	10.3	1.94	10.4	2.20	-0.85; 0.82	0.98
Distal latency (ms)	right	3.36	0.46	3.35	0.43	3.37	0.51	3.38	0.41	-0.19; 0.13	0.73
	left	3.27	0.45	3.29	0.48	3.25	0.42	3.24	0.43	-0.14; 0.20	0.71
F-latency (ms)	right	26.9	2.26	26.9	2.08	26.9	2.54	27.3	1.81	-1.20; 0.25	0.20
	left	26.4	2.21	26.5	2.16	26.2	2.33	26.4	2.26	-0.93; 0.81	0.89
Sensory examination											
Median nerve											
Latency, dig. III-palm (ms)	right	1.74	0.20	1.72	0.21	1.75	0.20	1.78	0.23	-0.15; 0.06	0.36
	left	1.71	0.19	1.71	0.21	1.71	0.15	1.74	0.27	-0.15; 0.09	0.63
Amplitude (finger) (µV)	right	15.6	8.49	15.9	8.37	15.2	8.87	11.8	9.86	-0.56; 8.18	0.09
	left	17.8	10.5	18.6	11.5	16.9	9.38	15.8	9.07	-2.40; 6.43	0.36
Latency, palm-wrist (ms)	right	1.58	0.26	1.54	0.24	1.61	0.29	1.64	0.43	-0.25; 0.11	0.45
	left	1.50	0.23	1.45	0.21	1.54	0.25	1.48	0.18	-0.07; 0.11	0.67
Amplitude (wrist) (µV)	right	12.6	7.47	12.8	6.65	12.5	8.61	8.05	6.49	1.51; 7.60	0.004
	left	13.1	8.27	13.6	8.24	12.8	8.35	10.6	5.92	-0.58; 5.54	0.11

[a] p-value for difference between exposed (all) and unexposed subjects

4.4.2 Sensory conduction latencies

Median nerve, sensory latency, digit III-palm. There were no significant differences in sensory latencies in either arm between exposed and unexposed subjects (Table 12), or between classes with cumulative lifetime exposure (Figure 8a) or current daily exposure (Figure 8c).

In the multivariate regression analysis, the sensory latency of the median nerve (digit III-palm) was associated with skin temperature (right/left hand) and age (right/left hand). Neither cumulative lifetime exposure nor current daily exposure contributed to explaining the sensory latency in the multiple linear regression models.

Paired t-test for individual measurements between right and left hands gave a mean difference of 0.03 ms (SE 0.01, p = 0.09). The differential between right and left hands was approximately the same when analysing data from exposed and unexposed subjects separately, although the p-values were higher (exposed: mean difference 0.02 ms [SE 0.02 p = 0.18] and unexposed: mean difference 0.03 [SE 0.03, p = 0.31]). The right hands had the longer latency.

Median nerve, sensory latency, palm-wrist. There were no significant differences in sensory latencies in either arm between exposed and unexposed subjects (Table 12), or between classes with cumulative lifetime exposure (Figure 8b) or current daily exposure (Figure 8d).

In the multivariate regression analysis, the sensory latency of the median nerve (palm-wrist) was associated with skin temperature (right/left hand). Neither cumulative lifetime exposure nor current daily exposure contributed to explaining the sensory latency in the multiple linear regression models.

Paired t-test for individual measurements between right and left hands gave a mean difference of 0.08 ms (SE 0.03, p = 0.004). When analysing data from exposed and unexposed workers separately, the paired t-test between right and left hands of the exposed subjects gave a mean difference of 0.06 (SE 0.02, p = 0.006) and the corresponding figure for the unexposed subjects was 0.12 (SE 0.08, p = 0.14). The right hands had the longer distal latency.

Neuropathy of the median nerve at the carpal tunnel segment was considered to be present when the sensory latency from palm to wrist was greater than 1.73 ms at a distance of 60 mm (the cut-off point represents 3SD of the mean value of a normal material collected with similar plastic splint equipment in our laboratory). With this cut-off point, there were 15 right hands and 10 left hands with median nerve neuropathy in the exposed group. Corresponding numbers in the unexposed group were 6 and 2. There were 9 subjects with bilateral median nerve neuropathy. Among these 33 hands with median nerve neuropathy, there were 15 hands with one or several of the following symptoms: nocturnal numbness, pain in wrist or fingers, and difficulty in buttoning clothing, reported either in the questionnaire or during medical examination. There were 4 subjects with bilateral symptoms and bilateral median nerve pathology. Presence of median nerve neuropathy with or without symptoms was independent of exposure class (Table 13).

The skin temperature during sensory conduction measurements was similar between unexposed (right hand 31.6°C ± 4.3, left hand 31.5°C ± 4.4) and exposed (right hand 31.6°C ± 3.7, left hand 31.8°C ± 3.6) subjects. There were no significant differences in skin temperature between classes of cumulative lifetime exposure (Figure 8e) or current daily exposure.

In all the above-mentioned nerve conduction measurements, we have also separately analysed those subjects with current daily exposure (n = 46) and those with former exposure without current exposure (n = 70), in linear regression models. As the number of the subjects in each group was small, we used fewer predictive variables in the models (age, skin temperature, classes of exposure and 'years since last vibration exposure to date of test'). Neither the cumulative exposure nor the current daily exposure or 'years since last vibration exposure to date of test' contributed to explaining the nerve conduction measurements.

4.4.3 Other nerve conduction parameters

There were no differences in any other measured nerve conduction parameter (conduction velocities, amplitudes, and F-latencies) between unexposed and exposed groups, except for median nerve sensory amplitude at the wrist in the right hand (Table 12). The exposed group had higher amplitude than the unexposed group (12.6 [SD 7.5] µV versus 8.1 [SD 6.5] µV), but in the multivariate analysis, only age was associated with the amplitude. Neither cumulative lifetime exposure nor current daily exposure contributed to explaining the amplitude in the multiple linear regression models.

Table 13. Neuropathy of the median nerve at the carpal tunnel segment[a]

	Right hand		Left hand	
	Nerve conduction	Nerve conduction + symptoms[c]	Nerve conduction	Nerve conduction + symptoms[c]
	n	n	n	n
Cumulative lifetime exposure[b]				
Class 0	6 (23%)	3 (12%)	2 (8%)	1 (4%)
Class 1	2 (11%)	1 (5%)	1 (6%)	1 (6%)
Class 2	4 (19%)	0 (0%)	3 (16%)	1 (5%)
Class 3	3 (18%)	1 (6%)	3 (17%)	2 (11%)
Class 4	6 (31%)	3 (16%)	3 (17%)	2 (11%)
Current daily exposure[b]				
Class 0	6 (23%)	3 (12%)	2 (8%)	1 (4%)
Class 1	7 (16%)	2 (5%)	4 (10%)	3 (7%)
Class 2	2 (13%)	1 (7%)	2 (14%)	1 (7%)
Class 3	6 (33%)	2 (11%)	4 (23%)	2 (12%)

[a]Sensory latency from palm to wrist greater than 1.73 ms at a distance of 60 mm.
[b]Results are given as numbers and percentage of measured hands (in parentheses).
[c]Pain and/or nocturnal numbness and/or difficulty in buttoning clothing.

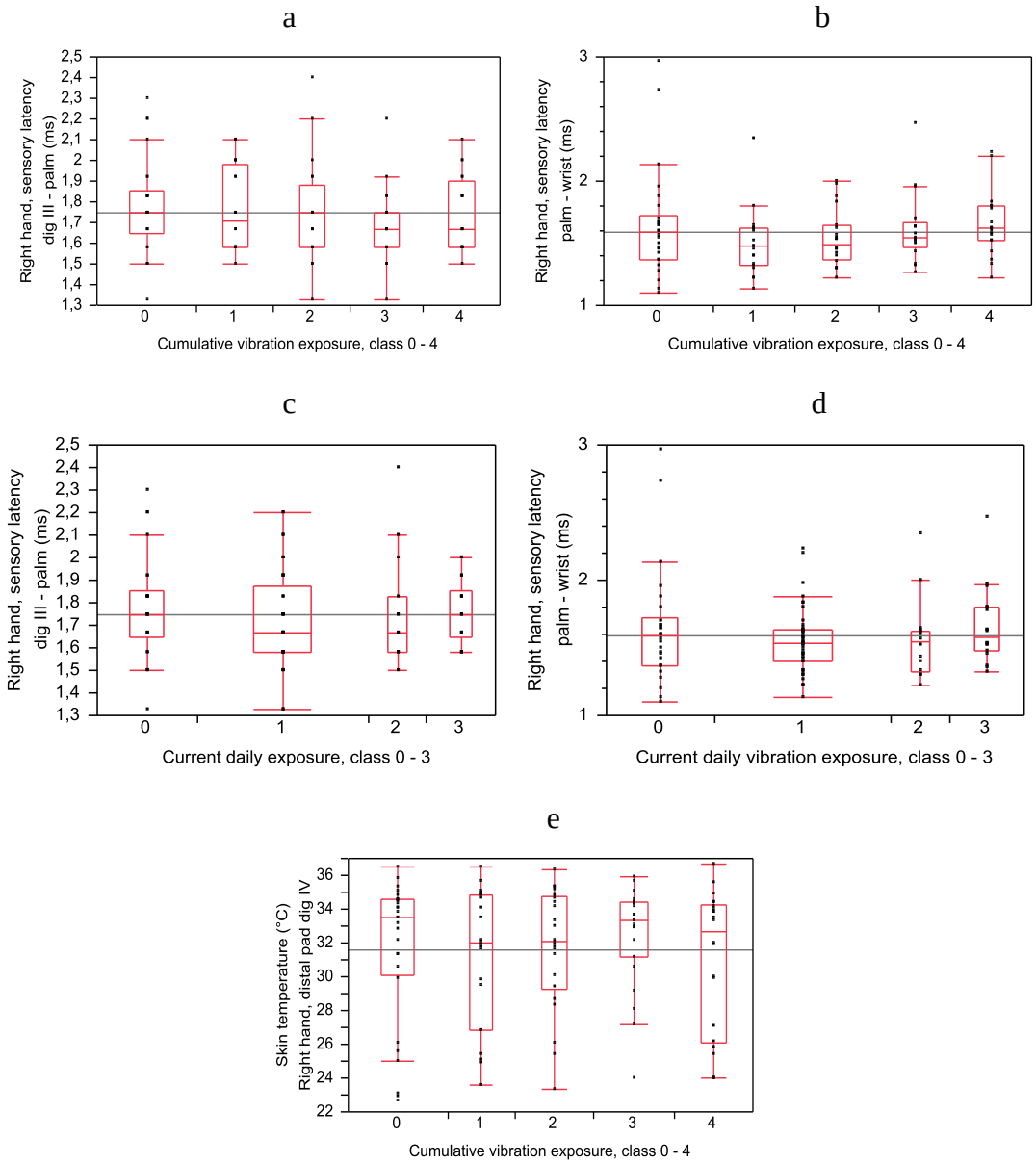

Figure 8a–e. Nerve conduction and skin temperature in different classes of vibration exposure. Median values (-) are presented within the interquartile box. The difference between the quartiles is the interquartile range (Q3–Q1). The whiskers extend to the farthest point that is still within 1.5 interquartile ranges from the quartiles. Grand mean is presented with a line.

5 Discussion

5.1 Non-positive studies

Epidemiological studies are important in order to identify and evaluate potential risk factors in the work environment, and Hill [91] has suggested well-known criteria for scrutinizing the results. A negative study may be defined as presenting a result that significantly goes against a hypothesis of risk [92]. Studies with differences between groups above, but close to zero, with a confidence interval including zero, should be taken as non-positive [92]. In this thesis there are several non-positive findings and it should be of equal importance to evaluate these studies. In all epidemiological studies there could be *random errors* and *systematic errors* [93].

5.1.1 Random errors

If the study sample is small, the random variation of the difference between groups is often large, meaning that in another sample the difference between groups could have been very different. With a large sample, the random variation decreases (the confidence interval becomes more narrow). The power is the probability that the statistical test will signal a significant difference, if there indeed is a difference in the underlying population. Power calculations are made for specified differences (e.g. a specific value of difference to detect) and often the difference is chosen in connection with a clinically relevant difference. Thus, if a study is optimized to detect a difference of 0.17 ms in sensory latency of the carpal segment, the probability of the statistical test being significant is high, if the difference is actually 0.17 ms between the exposed and unexposed population. But if the difference is in fact only 0.05 ms, the power of detection is low. A test can be non-significant as a result of a difference close to null (e.g. CI -0.1 ms; 0.1 ms) or as a result of a large variation (e.g. CI -2.0 ms; 1.5 ms). In the former case the interval indicates a small difference (if any) and in the latter case the large random error prevents us from detecting a difference. This distinction cannot be made from two p-values, so by presenting confidence intervals, it is possible to judge if the non-significant result is likely due to there being no difference (differences in fact close to 0) or to random variation (which may be helped by a larger sample). In order for a study to indicate that an exposure has no effect on the risk of the disease, it is necessary that the confidence interval is narrow and located around the null value. In the findings in studies II and IV the differences in outcome were fairly close to the null value. This indicates that the vibrotactile perception thresholds and the outcome of the nerve conduction measurements are approximately the same, independent of whether the measured exposure is low or high.

5.1.2 Systematic errors

Exposure misclassification can, for example, lead to greater contrast between groups than actually exists. The result will be dilution, and the difference in outcome will be pulled towards the null value [93, 94].

Palmer et al. found that workers overestimated their duration of hand-arm vibration exposure in self-administered questionnaires, particularly when the exposure was intermittent and for short periods [95]. In a study of Burström et al. [96], the vibration exposure times were assessed by subjective assessments and by objective measurements, and there were no statistical relationships between the different evaluation methods on an individual basis, probably due to diversified work. The results showed that there was some agreement between the subjective assessment and the objective measurements of the average exposure time. Nilsson et al. [97] showed the same tendency of large individual deviation, but also some evidence for a good concordance between estimated and measured exposure time at group level. Barregård [98] examined the daily exposure times to hand-arm vibration in Swedish car mechanics and revealed that the mechanics' self-estimates were close to the daily exposure times estimated by observing intermittently. When estimating the daily exposure time by subjective assessment many years back in time, there is probably a greater risk of recall bias.

In study IV we have tried to minimize exposure misclassification by calculating the cumulative hand-arm vibration dose as the product of self-reported occupational exposure, as collected by questionnaire and interviews, and the measured or estimated hand-arm vibration exposure in 1987, 1992, 1997, 2002, and 2008. In the questionnaire, the workers were asked to estimate the amount of time (minutes per day) they were exposed to vibration while using the different types of hand-held vibrating tools during their most recent working day and in the calculations, the exposure during the periods between the investigations was estimated based on values from the latest study.

In study II the exposure assessment was made by self-reports using questionnaires. A study regarding agreement by self-reported questionnaire and observer-rated physical exposure to the hands and wrist showed the best agreement between self-reported and observed values in a clerical/technical work group, and there was no effect of symptoms on exposure reporting [99]. At the time of studies I–III in 1999–2000, we invited nurses at hospital departments that had not yet adopted computers in their ordinary nursing work, and we also knew that the secretaries' main work task was to write medical records using a computer keyboard. Hence, there was probably a true substantial difference in exposure regarding computer work between the groups. However, there could be other occupational risk factors for peripheral neuropathy in nursing. To our knowledge, there is only one study on the issue, which presented sentinel clusters of CTS in female nurse anaesthetists compared with operating room nurses, possible due to rigid laryngoscopes [100]. We had three nurse anaesthetists in our study, and when analysing the results from VPT and NCT without these nurses, there were still no differences between the occupational groups.

Diagnostic misclassification may be due to low specificity, which leads to inclusion of disease in the unexposed groups. This could give rise to a dilution, and consequently, to an underestimation of the differences between groups. The sensitivity and specificity of our methods are discussed in the introduction. We have tried to optimize the reliability and validity of our outcome measurements by having only one trained assistant making the measurements. Furthermore, she was blinded both to the group of subjects and to the preceding examinations. In study IV, some of the subjects were wearing their ordinary work clothes, which allowed the assistant to guess the group of the subject. We were also trying to minimize the source of errors in the nerve conduction by using the bicycle ergometer test as a warming method and by using plastic splints with a fixed distance during sensory measurements. A limitation of our studies is that we have not made our own test of reliability in either nerve conduction or vibration threshold test. However, the vibration threshold test was performed twice in each subject and paired t-test revealed that the changes in vibrotactile perception thresholds after 4 h of work were small, went in both directions, and did not differ significantly between the chronic pain (all) group and the controls (study III) or between computer users and nurses (study II). When analysing all subjects (studies II–III), there were a small decrease in VPT between the first and second tests at the distal pad within the territory of the median nerve. The index finger was the first finger to be measured in the vibration threshold test and we hypothesized that the decrease could be due to a learning effect.

Uncontrolled confounding is often a concern when an excess risk is found in a study, but it can also obscure an effect, either when the confounding risk factor tends to be more common in absence of the exposure or when there is a protective factor occurring among the exposed subjects [92]. We have reasonably good information about the frequency and magnitude of potential confounding factors and we used multivariate multiple regression models to control for such factors, but there is always a risk of unknown confounding.

Health-related selection, that is, workers who develop symptoms of CTS or other peripheral neuropathy (in part because they are exposed) leave their jobs and are not selected for future studies of working populations. This type of selection problem will probably lead to a negative bias in the estimation of the effect of physical work exposure on neuropathy in cross-sectional studies. However, our studies had a fairly large sample in a working population where the workforce turnover, to our knowledge, was low, and the study population had no extreme work disability rate.

In study IV, the original study base included randomly selected office workers and nearly all manual workers in 1987/1992. In 2008 there was only 18% loss to follow-up and the study group consisted of 197 subjects. All 197 were invited to participate in nerve conduction and 163 finally attended. The most common reason for not attending the nerve conduction measurements were that the subjects had retired or moved away from the area, but there is always a risk that the subjects were lost to follow-up due to health-related departures.

Sampling bias. In studies I–III the female subjects who entered the study were invited via personnel notice boards. The invitation referred to working women (secretaries or nurses) with and without chronic upper limb pain. It would have been better if the participants had been randomly selected. We do not know if there was a selection bias. It may be that the workers with more symptoms are more prone to participate than others, or it may be the opposite. Most likely is that the phenomenon is the same in both occupational groups, although the symptoms may be of different kind and different aetiology. If the secretaries with no symptoms of the upper limb were more prone to participate in the study, and/or the nurses with symptoms of the upper limb were more prone to participate, there would be a dilution and the difference in outcome would be pulled towards the null value in study II. It may also be that subjects entering the study for some reason are more prone not to report mild chronic pain, although they actually have chronic pain, or the opposite, and then again there would be a dilution and the difference in outcome would be pulled towards the null in study III.

5.2 Bicycle ergometer test (Study I)

A bicycle ergometer test proved to be a simple and effective method of raising hand temperature. For a large number of test subjects, the finger temperature increased 7ºC or more in just over 15 minutes and the level remained constant throughout an examination with duration of approximately 25 minutes. Thus, temperature as a source of error was minimized in studies II and III. The fact that the temperature remained constant is an important advantage compared to local warming procedures; with local warming the temperature usually starts to decrease as soon as the lamp or the hot pack is removed. Our precaution of covering the subjects with an electrically heated blanket after the end of the exercise may not have been necessary: Kenny et al. [101] found that skin temperature remained at an elevated level for approximately 25 minutes after the end of the exercise.

In study IV we also increased the skin temperature before the nerve conduction measurements by using the bicycle ergometer test, but our effort to raise the temperature in fingertips failed in some cases. The study population was older and the most common reasons were inability to perform the bicycle ergometer test because of musculoskeletal pain in the hip or knee, lung disease, or contraindications such as cardiovascular disease. Another reason was that the subjects went through a digital critical opening pressure (COP) test just before cycling, with the result that it was probably more difficult to raise the temperature in the fingertip after the cooling in the COP.

The main application of the bicycle exercise test will probably be in scientific studies on healthy subjects where this method of warming will ensure that the whole material achieves stable, high temperatures, as well as reduced interindividual variations. In clinical practice the usefulness may be more limited; in many patients underlying disease, old age, and poor general condition will make them unable to perform an adequate bicycle test. However, in certain conditions, for example, a

suspected carpal tunnel syndrome, it may be a rapid and practical way of attaining optimal thermal conditions also in patients whose fingers are very cold.

There are some limitations of the study. First, skin temperature was measured using a thermistor taped to the tip of digit IV during the whole bicycle ergometer test and during all the nerve conduction measurements, but we did not store the results during the bicycle test, and therefore, we cannot present at what time during the test the temperature was raised. Hence, we do not know if it was a slowly continuous rise of the temperature or a quick rise during the test period.

Second, we did not measure the skin temperature at the wrist or the temperature near the nerve, and the temperature at the carpal segment is important when measuring latency at the carpal segment. Most likely, the temperature at the wrist was at least the same or higher than in the fingertip, but it would have been interesting to see the actual difference and whether the difference between the finger and wrist decreased after the test. It would also have been valuable to have measured the core temperature in order to compare the central and peripheral temperatures.

Third, we do not know if the heated blankets were necessary, as we have not studied what would happen to the skin temperature without using the electrically heated blankets. Fourth, the study population in studies I–III consisted only of females. In study IV, the study population consisted of males, but we did not store the figures for the skin temperature before the bicycle ergometer test, so we cannot analyse the pre/post test differences. However, there are no obvious reasons to believe that men react differently. Finally, we had no restrictions regarding smoking just before the test, so we do not know if smoking influenced the results.

5.3 Computer work (Study II)

Study II showed no difference in vibrotactile perception thresholds between female computer users and non-users, which is in contrast to the findings of Greening and Lynn [24], who reported significantly raised vibrotactile perception thresholds within the territory of the median nerve in a group of computer keyboard workers. Possible reasons for the discrepancy could be a difference in frequency of upper extremity symptoms/disorders, a difference in keyboard exposure or differences of intensity, workstation design, or equipment. Although we had a higher power to detect differences between computer users and non-users (n = 117 in our study compared with n = 56 in the study of Greening and Lynn), there is still a chance of a ‘true’ difference between users and non-users. We had only women in our study group, and although they were a minority, Greening and Lynn had also men in their study group. We do not know if men react differently. It is unclear whether our care in performing the study using only one assistant, who was fully blinded to the occupation of the subjects and to the preceding examination, can account for the difference in outcome.

In this study we also attempted to control for cumulative exposure, and found no differences between the two occupational groups. There were some nurses who used

a computer at work, and therefore, we also grouped the subjects into classes of daily keyboard computer use, and still there were no differences between groups.

Our results are in line with the results of a study in which no differences in fingertip vibrotactile perception threshold were found between the non-symptomatic group of computer users and the control group [42].

The lack of difference in vibrotactile perception thresholds between computer users and non-users agrees with our results from the nerve conduction measurements: there was no difference in any parameter between the groups. This is in contrast to the results of Murata et al. [23], who found reduced SCV in subjects using visual display computer terminals compared to a control group. Whether the different conclusion in the study by Murata et al. depends on difference in methods or exposure is unclear.

Several epidemiological occupational studies have now been published on this issue and the results from this study are in line with the conclusions from a systematic review by Thomsen et al. in 2008, who found that there is insufficient evidence that computer work causes CTS [25]. They also concluded that experiments on the effect of the position of fingers, wrists, and forearms, comparable to the positions common in computer work, have shown that the carpal tunnel pressure increases, but not to levels generally believed to be harmful [25]. A Swedish population-based study, using clinical examination and nerve conduction tests to establish the diagnosis of CTS, revealed that persons who reported intensive keyboard use were less likely to be diagnosed as having CTS than those who reported little keyboard use [26].

There are some limitations of the study. First, as mentioned above, the participants were not randomly selected and we do not know if there was a sampling bias. Second, this is a cross-sectional study and there is always a risk of underestimating an existing risk due to health-related selection. Third, exposure assessment was made by self-reports using questionnaires. There are no objective measurements. Finally, we did not measure the skin temperature before the vibration threshold test. Low temperatures might affect the Pacinian corpuscles and result in increased thresholds [61].

5.4 Chronic pain (Study III)

The main findings in the study of subjects with chronic diffuse upper limb pain were (a) perceived stress and energy did not influence the VPT; (b) there was a small influence of chronic diffuse upper limb pain on VPTs, with increased thresholds seen in the territory of the ulnar and radial nerve in female workers with normal nerve conduction; and (c) there was no difference in conduction velocity between the groups.

The findings from the mood adjective list revealed that the group with chronic diffuse upper limb pain and VAS ≥ 5 had significantly higher stress scores compared to the control group. There was no significant difference in energy between groups. Neither perceived stress nor perceived energy appeared to influence the VPT in our

study groups. It is not clear whether perceived stress and energy influence the subject's attention, concentration, and/or motivation during vibration threshold testing. The vibration threshold test is a psychophysical test, and our study does not support the theory that the increased VPT in subjects with chronic pain is due to mood. To our knowledge, there has been no previous clinical study on the influence of mood in vibration threshold measurements.

The mean differences in VPT between the chronic pain (VAS ≥ 5) group and the controls in our study were small; 0.61 μm vs. 0.46 μm for the radial nerve and 0.64 μm vs. 0.49 μm for the ulnar nerve/metacarpal. We excluded subjects who had CTS. If those subjects were included in the calculation, there would still be approximately the same differences between the groups. The difference between our chronic pain (all) group and the controls was smaller than the difference between the chronic pain (VAS ≥ 5) group and the controls. Thus, in our study, chronic moderate and severe pain had a greater influence on VPTs than did chronic mild pain. Furthermore, the mean of the VPTs from the territory of all three nerves was significantly higher in the chronic pain (all) group.

In the present study, all nerve conduction velocities and hand temperatures were similar in the chronic pain (all) and the control groups, and therefore, the increased VPTs in the chronic pain (all) group are unlikely to have been related to dysfunction or entrapment of large myelinated peripheral nerve fibres at the wrist. However, one must bear in mind that only the fastest of the large myelinated fibres, and thus a limited proportion of the whole nerve fibre population, are examined in nerve conduction studies. Consequently, it is theoretically conceivable that a subgroup of myelinated fibres may be afflicted in spite of normal nerve conduction. Fibre types other than large myelinated fibres, such as small myelinated and unmyelinated fibres, may also be involved in chronic diffuse upper limb pain. The function of the smaller fibres that convey sensations of pain and temperature can be assessed by measurements of the psychophysical thresholds of those sensations.

The findings regarding VPT are partly in line with earlier studies, which showed increased VPT within the territories of the ulnar and median nerves, but not the radial nerve, in patients with non-specific arm pain [24, 41, 42]. On the other hand, Johnston et al. [102] found increased VPT not only within median and ulnar areas but also in the radial nerve territory in office workers who experienced neck pain with and without arm pain. This is compatible with peripheral nerve dysfunction at a proximal (e.g. brachial plexus) level, and/or altered sensory processing due to central inhibition. Laursen et al. [103] found raised vibrotactile perception thresholds in the contralateral limb in patients with upper limb disorders, supporting the theory of central nervous alteration. Tucker et al. [104] found global elevation of VPTs in subjects with carpal tunnel syndrome or upper limb disorders, and concluded that this is consistent with a physiological inhibitory mechanism, common to both conditions, which appears to be related to central nervous system perception of chronic pain, rather than a specific peripheral pathology.

Based on the results of our study and those of the previous studies mentioned above, we find it reasonable to propose that pain may lead to a global increase of upper limb VPTs. This does not exclude the possibility that pain sometimes is due to a peripheral nerve affliction, but rather that central and peripheral mechanisms may be involved at the same time and contribute (in varying proportions) to both the pain and the increase in VPTs. The gate control theory of pain suggests that concurring tactile stimuli may decrease the perception of pain [105]. However, Apkarian et al. [106] have proposed the opposite; that is, that there is an inhibitory effect of nociceptive input on the perception of touch via a thalamic 'touch gate'. The touch gate theory is supported by findings of decreased sensitivity to light touch in experimentally induced pain in healthy subjects in the area of referred pain [107]. Moreover, improved sensitivity to light touch has been reported following relief of pain in patients with chronic pain [108].

To our knowledge, little information is available regarding the optimal sites for determination of VPTs in the hand. The fingertips and the palm have higher receptor density than the dorsum of the hand [3, 109, 110]. In our study, we found increased VPT only at the dorsum of the 5th metacarpal bone and the dorsum of the 2nd metacarpal bone, and not in the fingertips or the palm. We hypothesize that the reason for these results is that there is a delicate balance in the thalamic 'touch gate' between the excitatory input from somatosensory receptors and inhibition from nociceptive stimuli. Because of the higher receptor density in the fingertips and the palm compared to the dorsum of the hand, the sensory input from fingertips and palm may be able to outbalance the inhibition from the pain, and therefore VPT is normal in these areas. In contrast, the sensory input from the dorsum of the hand is weaker, and therefore, the VPT increases in this area.

There are some limitations of the study. First, the non-positive finding of a relationship between mood and VPT may be due to a lack of variability in mood. However, the variability in perceived stress is of the same magnitude as described for female workers in a production system [72]. Second, lack of power could be the reason we found no significant difference in VPT between the chronic pain (all) group and the controls within the territory of the median nerve. Third, the menstrual phase was not addressed. Whether physiological changes accompanying menstrual cycles can change sensory perception thresholds has been unclear; however, a study of menstrual phase and current perception thresholds could not see any changes across the menstrual cycle [111]. Finally, we did not measure the skin temperature before the vibration threshold test.

5.5 Hand-transmitted vibration (Study IV)

In our electrophysiological study of hand-arm vibration-exposed and unexposed subjects, there were no differences between the groups in either the sensory conduction latencies of the median nerve or in the motor conduction latencies of the median and ulnar nerves. Specifically, exposure to hand-arm vibration was not

associated with a decrease of peripheral nerve conduction and we saw no signs of increased slowing in large myelinated fibres.

The strength of study IV lies in our careful assessment of subjects' exposure and the consequent reduction of recall bias. To our knowledge, there has been no other study with similar exposure assessment over a period of 21 years. In a recent report, Burström et al. concluded that regular surveillance of the exposure and health have significantly reduced the exposure to vibration in this study population [82].

A possible explanation for the non-positive result in study IV could be that the exposed population is mixed with currently and formerly exposed manual workers, and if there exists a recovery factor, the mixed population would contribute to diluting the difference between the exposed and the unexposed groups. However, there was no difference in nerve conduction between currently exposed and formerly exposed subjects, and the attempt to adjust for a recovery time factor in the regression model by using 'years since last vibration exposure to date of test' as a predictor did not contribute to explaining the results of the nerve conduction measurements.

When comparing each individual's right and left hand, the right hand had longer distal latency in the motor conduction of the median and ulnar nerves and also slightly longer latency in the sensory conduction of the median nerve over the carpal segment. However, although not significant, the latency difference over the carpal segment was larger in the unexposed subjects. The right hand is generally more exposed to hand-arm vibration in this cohort [97]. The majority is right-handed and the ergonomic load in the workplace and at home is probably higher on this side [112]. Nathan et al. [113] reported slowing in the dominant hand in a prospective study of median nerve sensory conduction in industrial workers, but could not reveal any correlation with occupational hand use.

Seven subjects (9%) and 11 hands (7%) of those who underwent sensory nerve conduction measurements in the exposed group had both pathological sensory nerve conduction at the wrist and symptoms suggestive of carpal tunnel syndrome (CTS); the corresponding numbers in the unexposed group were 3 (12%) and 4 (8%). There was no significant difference between groups. We excluded subjects who had had surgery for carpal tunnel syndrome. If those subjects were included in the calculation, there would still be no difference between exposed and unexposed subjects. The overall prevalence of CTS in the present study is higher than that reported among men in an epidemiological study of the general population in Sweden (2.1%) [11]. A review of occupational populations showed a wide range in the prevalence of CTS (0.6%–61%) [114]. In the present study there were also a high proportion of pathological nerve conduction velocities in the palm-wrist segment in subjects without symptoms. Among those subjects, there were still no differences between exposed and unexposed. This has also been reported in other studies [11] [115, 116]. Atroshi et al. [11] found abnormal nerve conduction without symptoms to be more common among older subjects. The mean age of the subjects with abnormal nerve conduction in the present cohort was 56 years (range 39–71).

Cherniack et al. [36], reported that the significant differences in digital sensory conduction velocities between vibration-exposed and unexposed workers, which had been observed after segmental cutaneous warming, were eliminated after systemic warming with a bicycle ergometer test. Our effort to raise the skin temperature before the nerve conduction measurements by using the bicycle ergometer test failed in some cases. Hence, we had a number of subjects with skin temperatures at the fingertip below 32°C. However, the skin temperature was only measured at the fingertip of digit IV and it is possible that the skin temperature was higher at the wrist. On the other hand, there were no differences in mean skin temperature between the exposed and unexposed subjects or between classes with cumulative lifetime exposure or current daily exposure. There are mathematical formulas for temperature corrections at low temperatures, but those are based on skin temperature at the wrist and are probably not reliable for skin temperature at the fingertip. We chose to control for temperature in the multiple linear regression model, and it did not alter the fact that vibration exposure was not a predictor of nerve conduction variables in the equation. We also conducted an analysis after excluding all subjects with fingertip temperature under 32°C and there were still no differences in skin temperature or nerve conduction between classes of vibration exposure.

At baseline in 1987 the present cohort was investigated with nerve conduction measurements in a cross-sectional study; Nilsson et al. [117] reported impaired nerve conduction in the exposed group. The risk was not proportional to the vibration exposure. They concluded that the contributions from vibration and ergonomic factors to the impaired nerve conduction were inseparable. We do not know why the difference between unexposed and exposed is not detectable 21 years later. One possible reason could be recovery due to retirement, job transfer, use of fewer or less-vibrating tools, and/or decreased daily exposure time; another possible reason is that different methods were used in the two studies for measuring nerve conduction velocity, for example, in the present study we used a systemic warming method to eliminate the temperature as a source of error. A third possibility is that those who had impaired nerve conduction in 1987 are among those we have not been able to follow up, and finally, a fourth reason could be lack of power to detect a small difference in nerve conduction.

Our results, with no differences in nerve conduction velocity between hand-arm vibration-exposed and unexposed subjects differ from the results of several other epidemiological studies. Most of the studies that demonstrate an association between vibration exposure and nerve conduction impairment come from case-control studies where the vibration-exposed workers have been selected either from a population of patients, subjects with suspected hand-arm vibration syndrome disorders [31, 33, 118], or from job categories entailing a well-recognized exposure to vibration [119-121]. In our present study, the majority of the sample does not have severe neurological symptoms and most subjects have not been referred to a clinic.

There are some limitations of the study. Although there appears to be little difference between the 197 invited subjects and the final study group, the reduction in our

sample size weakens the statistical power of our analyses, that is, the ability to reject the null hypothesis of no differences. Thus, we would caution that a relationship between hand-arm vibration exposure and peripheral neuropathy may exist, but has not been detected in this study. Secondly, there is a risk of healthy worker effect. However, our study sample was from a working population where the workforce turnover, to our knowledge, was low, and the study population had no extreme disability rate. Finally, epidemiological studies have indicated an association of carpal tunnel syndrome and ergonomic factors such as high requirements for hand force, prolonged work with extended wrist, high repetitiveness, and their combination. In this study we did not control for these factors.

5.6 Considerations for the future

Temperature is an important source of error in all nerve conduction studies. For nerves in the upper limp, this error can be reduced by systemic warming in a bicycle ergometer test. This finding should be taken into account when past studies are evaluated and future studies are designed. It would be useful if the technique of systemic warming with a bicycle ergometer test is applicable also to studies of other nerves, especially those of the lower limb, and in particular, the sural nerve. This remains to be shown. Furthermore, it would be interesting to investigate whether this method of increasing extremity temperature is equally effective in patients as in healthy subjects. For example, would the time course of the increase of skin temperature differ between controls and patients with autonomic neuropathies and impaired circulatory control? There is a need for future studies on this issue. It could also be valuable to examine how other sorts of physical activity affect the finger skin temperature. Perhaps there are alternatives that require less equipment, for example, a step-up board.

Nerve conduction test may not be a sufficiently sensitive method for detecting small hand-arm vibration-related pathological changes in peripheral nerves.

Slight variations in mood do not appear to affect the result in the vibration threshold test. However, in future studies of vibrotactile perception thresholds, the presence of pain must be taken into account, since the results may be affected by the subjects' pain.

6 Conclusions

Nerve conduction measurements revealed no signs of early neural deficits of large myelinated fibres measured in the upper limbs of either women who intensively use computer keyboard equipment or hand-arm vibration-exposed male manual workers, or female workers with chronic diffuse upper limb pain. In the present studies, the majority of the subjects did not have severe neurological symptoms and most subjects had not been referred to a clinic.

Vibration threshold test revealed no signs of deficits in computer users. In females with chronic pain there was a small elevation of vibrotactile perception thresholds, and perceived stress and energy before the test did not influence the thresholds. Although a peripheral mechanism cannot be excluded, the findings support the idea that increased vibration perception thresholds in chronic diffuse upper limb pain may be secondary to pain.

Study I: Adequate control of tissue temperature is a crucial factor in nerve conduction studies and a bicycle ergometer test proved to be a simple and effective method of raising hand temperature. Moreover, the interindividual temperature variation in the hand was reduced.

Study II: Nerve conduction measurements of peripheral hand nerves and vibrotactile perception thresholds in the hands revealed no signs of early neural deficits of large sensory fibres in the upper limbs of women who intensively use computer keyboard equipment.

Study III: Nerve conduction measurements of peripheral hand nerves and vibrotactile perception thresholds in the hands in subjects with chronic pain revealed that chronic diffuse upper limb pain is associated with a small elevation of vibrotactile perception thresholds in the territories of the ulnar and radial nerves, but we saw no deterioration in nerve conduction measurements. Perceived stress and energy before the vibration threshold testing did not influence the thresholds.

Study IV: Nerve conduction measurements of peripheral hand nerves revealed no exposure-response association between hand-arm vibration exposure and distal neuropathy of the large myelinated fibres in a cohort of male office and manual workers.

7 Sammanfattning

Smärta och funktionshinder i arm och hand är vanligt, särskilt i den arbetande befolkningen. Avhandlingens övergripande syfte var att undersöka perifer nervfunktion i övre extremiteten genom att mäta känseltrösklar för vibration och nervledingshastigheter i hand och arm hos kvinnliga datorarbetare, manliga hand-arm vibrationsexponerade verkstadsarbetare samt yrkesarbetande kvinnor med kronisk värk. Studierna är tvärsnittstudier avseende mätningar av perifer nervfunktion. Exponeringsbedömning vad gäller datorarbete gjordes med hjälp av frågeformulär i samband med undersökningarna. För vibrationer beräknades den kumulativa exponeringen utifrån enkäter, intervjuer och den uppskattade eller uppmätta vibrationsexponeringen 1987, 1992, 1997 och 2008.

Vibrationströskelmätning kräver uppmärksamhet och koncentration hos försökspersonen. Vi undersökte om upplevd stress- och energinivå innan testet kunde påverka känseltrösklarna för vibration. För att mäta de två dimensionerna stress och energi använde vi ett Stress-Energi-formulär som är ett självskattningsformulär och består av en adjektivlista.

Vid studier av nervledningshastigheter är det viktigt att man har god kontroll på temperaturen i handen. Vid låga temperaturer får man sämre nervledning. För att undvika falskt låga värden bör därför mätning av nervledningshastighet göras under standardiserade temperaturförhållanden. Vår ambition var att via en ny metodik, submaximalt cykelergometertest, försöka minimera temperaturskillnader mellan individer och om möjligt få en fingertemperatur på 34°C. Cykelergometertest är ett standardiserat submaximalt konditionstest och det visade sig vara en enkel och effektiv metod att höja handtemperaturen. Hos ett stort antal individer ökade fingertemperaturen 7°C eller mer på knappa 15 minuter och temperaturen låg kvar på i stort sett oförändrad nivå under hela den efterföljande nervledningsundersökningen. Risken för temperaturrelaterade felkällor har därmed reducerats kraftigt.

Nervledningshastighetsmätningar visade inga tidiga tecken på nervpåverkan av de grova nervtrådarna i övre extremiteten hos kvinnor som ofta använder dator eller hos män som exponerats för hand-armvibrationer och inte heller hos yrkesarbetande kvinnor med kronisk värk. I våra studier hade majoriteten av deltagarna inte några svåra neurologiska symtom och de flesta hade inte sökt läkare för de symtom som förekom.

Vid mätning av känseltrösklar för vibration i handen såg vi inte några tidiga tecken på störningar hos kvinnor som ofta använder dator. Däremot hade arbetande kvinnor med kronisk diffus värk i övre extremiteten lätt förhöjda trösklar i nervus ulnaris och nervus radialis utbredningsområden på handen. Upplevd stress och energi före vibrationströskelmätningen tycktes inte påverka känseltröskeln för vibration. Även om vi inte kan utesluta perifera mekanismer så stödjer fynden teorin att förhöjda känseltrösklar för vibration i handen kan vara sekundära till kronisk smärta.

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”Sammanfattningsvis skulle man kunna säga att det är positivt att resultatet är så ickepositivt att det nästan är negativt vilket i stort är positivt, även om det för forskningsområdets utveckling möjligtvis är negativt eller i alla fall icke-positivt. Dock fanns det vissa resultat som var så icke-negativa att de faktiskt var positiva vilket ju var negativt, men som borde kunna leda till ny positiv forskning om negativa konsekvenser av såväl tangentbordsanvändning som positivhalning”

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