Effects of cold and hand-arm vibration on the peripheral neurosensory and vascular system
an occupational perspective

Daniel Carlsson
“As my artist’s statement explains, my work is utterly incomprehensible and is therefore full of deep significance”

- Calvin and Hobbes
# Table of Contents

Abstract ii  
Abbreviations iv  
Svensk sammanfattning v  
List of papers vii  
1 Introduction 1  
  1.1 Cold exposure 1  
  1.2 Hand-arm vibration exposure 2  
  1.3 Cold injuries 3  
  1.4 Hand arm vibration syndrome 4  
  1.5 Cold sensitivity 5  
  1.6 Sensation of cold 6  
  1.7 Rationale of the present thesis 6  
2 Purpose 7  
3 Methods 8  
  3.1 Study designs and overview 8  
  3.2 Subjects and study procedure 9  
  3.3 Cold exposure and cold injuries (Study I, II and IV) 12  
  3.4 Hand-arm vibration exposure (Study II-IV) 12  
  3.5 Other possible risk factors for cold sensitivity (Study IV) 13  
  3.6 Assessment of cold sensitivity 13  
  3.7 Quantitative sensory testing (Study I and II) 14  
  3.8 Assessment of Raynaud’s phenomenon (Study I -IV) 14  
  3.9 Assessment of paresthesia (Study III) 15  
  3.10 Assessment of finger systolic blood pressure after local cooling (Study II) 15  
  3.11 Statistical analysis 15  
4 Results 17  
  4.1 Effects of cold injuries (Study I) 17  
  4.2 Effects of cold exposure (Study II) 18  
  4.3 Sensation of cold, Raynaud’s phenomenon and paresthesia (Study III) 21  
  4.4 Risk factors for cold sensitivity (Study IV) 22  
5 Discussion 26  
  5.1 Effects of cold exposure and cold injury (Study I and II) 26  
  5.2 Risk factors or early signs of HAVS (study III) 26  
  5.3 Cold sensitivity (Study IV) 27  
  5.4 Implications in working life and future research 28  
  5.5 Methodological considerations 30  
6 Conclusions 33  
7 Acknowledgements 34  
8 References 35  
Original papers
Abstract

Background In Swedish working life, exposure to cold and exposure to hand-arm vibration (HAV) are two common health hazards. Health effects of HAV in the neurosensory, vascular and musculoskeletal systems are collectively denoted hand-arm vibration syndrome (HAVS), and have been thoroughly studied. Effects of cold exposure in terms of effects on the peripheral neurosensory and vascular system are on the contrary limited, especially in an occupational setting. Effects of cold exposure or cold injury have not previously been assessed with quantitative sensory testing (QST). Commonly reported symptoms after exposure to HAV and after cold injuries, includes cold sensitivity and sensation of cold. Cold sensitivity can also occur without previous exposure to vibration or cold and may have a major impact on quality of life. Other possible risk factors for cold sensitivity need to be assessed. Sensation of cold hands could theoretically imply an early manifestation of damage to the neurosensory or vascular system, and therefore be of importance to enable early detection of vascular and neurosensory HAVS. The purpose of this thesis was to increase the knowledge about health effects from cold and HAV on the peripheral neurosensory and vascular system, with an occupational perspective. The aims were: first, to identify and evaluate health effects and sequelae in the peripheral neurosensory and vascular system due to cold injury and cold exposure; second, to investigate if sensation of cold hands is a predictor for future onset of Raynaud's phenomenon or paresthesia; and third, to identify possible risk factors associated with cold sensitivity.

Methods A case series on 15 military conscripts with local cold injuries in the hands or feet, involving QST and symptom descriptions, was conducted to investigate the hypothesis that cold injuries can result in similar neurosensory and vascular impairments as in HAVS. To assess health effects of cold exposure, a cohort study on 54 military conscripts in cold winter military training, with cold exposure assessments, was conducted. Possible health effects were assessed after 14 months of military training, containing considerable cold exposure, by means of QST, Finger systolic blood pressure after local cooling (FSBP) and a questionnaire. To investigate if sensation of cold hands is a predictor for vascular or neurosensory HAVS we investigated a cohort of 178 employees at a manufacturing company where HAV was a common exposure. The cohort was followed during 21 years and both vibration exposure and health outcomes were assessed regularly. Questionnaire items were used to assess sensations of cold hands as well as signs of Raynaud’s phenomenon and paresthesia. To identify risk factors for cold sensitivity a case-control study was conducted involving 997...
participants from the general population in northern Sweden. The study was cross-sectional and explored possible risk factors for cold sensitivity.

**Results** Cold injuries and cold exposure were associated with reduced sensibility in QST and increase severity and prevalence of neurosensory and vascular symptoms. Our results did not show any impairment in peripheral blood flow due to cold exposure, detectable by FSBP. The risk of developing Raynaud’s phenomenon was increased for workers previously reporting sensation of cold hands (OR 6.3, 95% CI 2.3-17.0). No increased risk for paresthesia in relation to a sensation of cold hands was observed. The identified risk factors for cold sensitivity were frostbite in the hands, rheumatic disease, nerve injury in upper extremities or neck, migraine and vascular disease. When analysing women and men separately, women’s risk factors were frostbite in the hands, rheumatic disease, migraine and cold exposure. Men’s risk factors were frostbite in the hands, vibration exposure and nerve injury in upper extremities or neck. BMI > 25 was a protective factor for both men and women.

**Conclusion** Cold injury and cold exposure are associated with impairments in the neurosensory system, detectable by QST. Symptoms such as sensation of cold hands and white fingers indicate vascular involvement, even though no vascular impairments due to cold exposure could be detected by objective measurements. A sensation of cold hands is a risk factor for development of Raynaud’s phenomenon, but not for paresthesia. At the individual level, reporting cold hands does not appear to be useful information when considering the possibility of a future development of Raynaud’s phenomenon. Frostbite in the hands is a risk factor for cold sensitivity among both women and men. For women rheumatic disease, migraine and cold exposure are also independent risk factors, and for men, exposure to HAV. Being overweight is a protective factor for both women and men.
Abbreviations

BMI  Body mass index
CHINS  Cold and health in northern Sweden
CI  Confidence interval
CISS  Cold intolerance symptom severity
CPT  Cold perception threshold (CT in study II)
FSBP  Finger systolic blood pressure after local cooling
HAV  Hand-arm vibration
HAVS  Hand-arm vibration syndrome
Hz  Hertz
OR  Odds ratio
QST  Quantitative sensory testing
VPT  Vibrotactile perception threshold (VT in study II)
WPT  Warmth perception threshold (WT in study II)
Svensk sammanfattning


Syftet med avhandlingen var att öka kunskapen om hälsoeffekter på nerver och kärl, kopplade till exponering för kyla och handöverförda vibrationer, med fokus på arbetslivet.

Avhandlingen består av fyra delstudier. Syftet med studie 1 var att undersöka vilka hälsoeffekter som kan kopplas samman med en köldskada i hand eller fot. I studie 1 undersökt hälsoeffekter kopplade till nerver och kärl hos 15 väpnatala som drabbats av köldskador i händer eller fotter.

Syftet med studie 2 var att undersöka vilka hälsoeffekter som kan kopplas samman med långvarig exponering för kyla. I studie 2 undersökte samma hälsoeffekter som i studie 1, men den här gången gjordes hälsoundersökningar både före och efter väpnalt, för att undersöka hur olika hälsoparametrar kopplade till köldexponering förändrades hos varje individ. Hälsoundersökningarna i studie 1 och 2 utfördes på samma sätt som när man undersöker hälsoeffekter av vibrationer i arbetslivet. Detta för att rakt av kunna jämföra hälsoeffekter av kyla och vibrationer.

Syftet med studie 3 var att undersöka om köldkänsla i händerna kan förutså framtidiga symptom av s.k. ”vita fingrar” eller domningar. Vita fingrar, eller Raynaud’s phenomenon innebär att distinkt avskilda områden av ett eller flera fingrar tappar blodförsörjningen och vitnar när fingrarna utsätts för kontakt med kyla. I studie 3 undersöktes 178 anställda vid en tillverkningsindustri, där användning av handhållna vibrerande verktyg var vanligt förekommande. Deltagarna fick, i formulär, uppgift om de upplevde köldkänsla i händerna, hade vita fingrar eller hade domningar i fingrarna. Den här gruppen hade undersökt på samma sätt med jämna mellanrum sedan 1987 vilket gjorde att det gick att avgöra ifall köldkänslan uppkom före vita fingrar eller domningar.

Syftet studie 4 var att identifiera riskfaktorer kopplade till köldkänslighet hos den generella befolkningen. I studie 4 skickades ett frågeformulär ut till 35,144 slumpmässigt utvalda personer boende i något av Sveriges fyra
nordligaste län. Bland de ca 12,000 som besvarade enkäten identifierades till slut 374 personer som var köldkänsliga och 623 personer som inte var köldkänsliga. Dessa grupper kunde sedan jämföras med varandra för att identifiera faktorer som var vanligare hos dem med köldkänsla än dem utan köldkänsla.


List of papers

This thesis is based on the following papers referred to by their Roman numerals:


Reprints with the permissions of the Nordic Association of Occupational Safety and Health (NOROSH) and Taylor & Francis Group.
1 Introduction

1.1 Cold exposure
For people living near circumpolar areas or in areas at high altitude, cold exposure needs to be considered in everyday life (1). Winters are long, cold and dark, cold spells, where temperatures reaching well below freezing point, can come fast and last for long periods, and many people often need to work outdoor regardless of prevailing environmental conditions.

A definition of cold exposure, used in the international standard for ergonomics of the thermal environment ISO 15743 (2) is: conditions that cause uncomfortable sensations of cool or cold. In light physical work, these conditions can occur at 10 °C or below (2). The use of the word condition, and not temperature, in this definition is intentional to emphasize that temperature alone does not paint the full picture of cold exposure. The effects of cold on the body are dependent on several environmental factors such as ambient air temperature, contact cooling, air humidity, wind speed and mean radiant temperature (3-6). At temperatures below -5°C humidity and mean radiant temperature are practically neglectable (6).

Environmental factors, together with individual factors, determine the cold stress on the body. A simplified explanation is that the activity level determines the heat production and that clothing determines at what rate heat is transferred from the body to the environment (3, 7), but several other individual factors has to be considered as well, such as age, sex, anthropometry (including height and weight), and individual differences in thermoregulatory responses (1, 7).

Cold affects the body in several ways, partly depending on what area of the body that is being exposed. One distinction is made between whole body cooling and local cooling. Whole body cooling occurs when the body heat losses are greater than the heat production for long enough to result in decreased body core temperature. Local cooling mainly affects the hands, feet and exposed skin on the head (3) and may occur even though the body core temperature is maintained. Heat may be lost via convection, when exposed to high velocity wind, or conduction, when touching cold objects or surfaces, in combination with insufficient clothing (3, 7). The risk for local cooling increases when, during cold exposure, the body struggle to maintain core temperature by vasoconstricting vessels in the extremities, resulting in reduced local heat input to the hands and fingers (6). Another factor affecting the cold stress is cooling by contact with water or by wet clothing. Water has a thermal conductivity 24 times greater than air, meaning the heat is transferred from the body at a much higher rate if the tissue is submerged in water. In addition, wet clothing reduces the insulating capacity of most clothing materials.
Official statistics from 2015 show that 23% of all men and 14% of all women in Sweden reports being exposed to cold at work for more than 1/4 of their working hours (8). Occupations in the Nordic countries with high prevalence of cold exposure are the military, construction workers, work within forestry, agriculture and fishing industries, preschool teachers, mine workers and vehicle drivers as well as commuting to work (8-10).

1.2 Hand-arm vibration exposure
Vibrating tools or machinery are widely used in a variety of occupations and work tasks. Examples of vibrating tools are hand held power tools such as hammers, drills, grinders, reciprocating saws and chainsaws, driven by electricity, combustion engines, pneumatics or hydraulics. Vibration can also occur in a vehicle, originating either from the vibrating engine or from the uneven surface on which the vehicle travels. Vibration exposure is divided into two categories, depending on the way they are transferred to the body; whole body vibration, which are usually transferred to the operator via the driving chair or floor of a vibrating vehicle, and hand-arm vibration (HAV), which are transferred through the hands of the operator via grip handles of a vibrating tool or steering controls. This differentiation between HAV and whole body vibration is reasonable since they differ both in character and health effects on the human body. This thesis is limited to only include exposure and health effects of HAV.

Routines for assessment of health effects from HAV exposure are stipulated in the appendices in two international standards: ISO 5349-1 and ISO 5349-2 (11, 12). Several factors influence the way by which vibration may affect human health and four of these are incorporated in the standards: vibration frequency, vibration magnitude, daily exposure time and accumulated exposure time.(11, 12) The vibration frequency is the number of cycles per second, expressed in the SI unit Hertz (Hz). Human response to vibration is frequency dependent, and when measuring vibration, this is accounted for by frequency-weighting. The best practice for frequency weighting is a matter of debate (13). According to the present standards, the frequencies between 8 and 16 Hz are of the greatest importance for the calculated magnitude, with decreasing contribution from higher or lower frequencies, and frequencies below 5 Hz or above 1500 Hz do not generally make important contributions to the vibration magnitude (11, 12). The vibration magnitude is the root-mean-square, frequency-weighted acceleration, expressed in metres per second squared (m/s^2), according to the ISO standards. The health risk associated with vibration exposure is related to the weighted acceleration magnitude during one working day (11), although the exact nature of this association is not clear (14). The daily vibration exposure time, is the time, in hours and minutes, a person uses any hand-
held vibrating tool, and the accumulated exposure time, is the number of years a person has been exposed to vibration exposure (11).

Official statistics from 2015 show that 14% of all men and 3% of all women in Sweden reports being exposed to HAV at work for more than 1/4 of their working hours. Occupations in Sweden with high prevalence of HAV are, at large male-dominated, such as construction workers, mechanics and work within forestry, agriculture and fishing industries. (8)

In the European Union there are legislations, mandatory to enforce by each member country, proclaiming action and limit values of allowed vibration exposure, as well as legal duties imposed on employers at workplaces were vibration occurs. The maximum daily exposure limit, standardised to an eight-hour reference period, is set to 5 m/s² and the corresponding daily action value is 2.5 m/s². The employer shall assess possible vibration related risks at the workplace and ensure that workers who are exposed to such risks receive any necessary information and training. The employer shall also offer appropriate health surveillance of the workers, aimed at a rapid diagnosis of any health effects caused by vibration. (15)

1.3 Cold injuries

Health effects from cold may be classified based on the part of the body it affects: Hypothermia, affecting the entire body, by lowering the core temperature, cold related injuries to the respiratory system, and local cold injury, affecting a delimited area of the body, often in head or extremities. This thesis is limited to include only local cold injuries. Local cold injuries are divided into non-freezing cold injuries and freezing cold injuries.

Non-freezing cold injuries occur at temperatures just above 0°C, often in combination with wet conditions and local pressure. Non-freezing cold injury is historically reported mostly from warzones, where soldiers developed the condition from prolonged periods in wet trenches (trenchfoot) or in sunken ships (immersion foot) (16). The pathogenesis of non-freezing cold injury is not entirely understood, but it is suggested to primarily be caused by prolonged vasoconstriction, which in turn may cause injury to the vessels that supply blood to nerve, fat, and muscle cells (16).

Freezing cold injuries occur at temperatures below 0°C (17) and can further be classified according to severity. Frostnip is the mildest form of freezing cold injury. It is reversible within 30 minutes and is distinct from frostbite but may precede it (18). Frostbites are more severe and is most often classified in the same fashion as burns, with a scale from first degree being the most superficial and least severe, to fourth degree that affects all layers of skin as well as underlying muscle or bone tissue, being the most severe stage of frostbite (18). Several other classification systems has been
suggested, to better allow for classification at an early stage and to better predict likely outcome (19).

The lifetime prevalence of severe frostbite in Finland has been estimated at 11% of the entire population, with a higher figure among those in occupational groups exposed to cold (9). There are no comprehensive reliable data on the prevalence of cold injuries in Sweden. A population based study in northern Sweden, suggested a frostbite prevalence of 11% among men and 7% among women (10).

The exact pathogenesis of freezing cold injury is not fully understood but two main mechanisms for tissue damage have been suggested: direct cellular damage and progressive dermal ischemia (20). There are four phases a freezing injury goes through: prefreeze, freeze thaw, vascular stasis, and late ischemic phase (18).

During the prefreeze phase the tissue temperature is still above freezing temperature but tissue cooling leads to vasoconstriction and thereby reduced blood flow and local ischemia. In the freeze thaw phase, intra or extra cellular ice crystals are formed. It is in this phase, the direct cellular damage occurs by several proposed mechanisms, including mechanical cell destruction, cell membrane damage, resulting in cellular dehydration, and cellular electrolyte shifts, initiating cell death. Intermittent thawing and freezing during this phase is common and further aggravates the damage. During vascular stasis, vessels may alternate between constriction and dilation, causing blood to leak from vessels or coagulate within them. In the late ischemic phase, the second suggested mechanism for damage sets in; progressive dermal ischemia. The ischemia is caused by several proposed mechanisms, including inflammation response, local emboli and thrombus formation, intermittent constriction of arterioles and venules, and a continued reperfusion injury. (18, 20, 21)

1.4 Hand arm vibration syndrome

Prolonged exposure to HAV is a known cause of health problems, entailing vascular, neurosensory and musculoskeletal manifestations, collectively denoted hand-arm vibration syndrome (HAVS) (14). The vascular component of HAVS is represented by a secondary form of Raynaud’s phenomenon, known as vibration-induced white fingers. The neurosensory component is characterised by a peripheral, diffusely distributed neurosensory malfunction with predominantly sensory manifestations of unknown topology (22). The neurosensory malfunction manifests as either a loss of sensation (negative manifestation), the occurrence of positive manifestations, such as pain or "needles and pins" (positive manifestations) or as increased sensitivity to provocation (provocative manifestations) (22). The musculoskeletal component of HAVS is the least precisely described (23) and includes degenerative changes in the
bones and joints of the upper extremities, mainly in the wrists and elbows. An increased risk for upper limb muscle and tendon disorders, as well as for nerve trunk entrapment syndromes, has also been reported in workers who use hand-held vibrating tools (24). This thesis will focus on the vascular and neurosensory effects.

1.4.1 Raynaud's phenomenon
The medical term Raynaud's phenomenon describes a transient attack of disturbed circulation in a local area of the skin, during which the skin is experienced as dead and cold (white fingers). The manifestation occurs as a result of an increased spasm of the small peripheral blood vessels in the skin of the fingers, when cooled. The affected area has reduced sensitivity and fine motor ability under the attack. After an attack with "white fingers", the skin goes through a triphasic color change, where the affected area turns blue, as a result of tissue hypoxia and before it regains normal colour and temperature the skin turns red, as blood flow is reintroduced (25). Raynaud's phenomenon can be either primary or secondary. Primary Raynaud's phenomenon occurs in absence of associated disorders or exposures, and secondary Raynaud's phenomenon can be associated with an underlying disorder or exposure (25).

1.5 Cold sensitivity
An increased sensitivity to cold could be represented by a single or a combination of the following:
(1) A high perceptual sensitivity to a cold stimulus, resulting in a cold detection threshold at low cold stimulus strength.
(2) A steepened increased sensation magnitude in relation to cold stimulus strength, compared to normative values (cold hyperesthesia).
(3) A qualitative aberration of cold perception, where cold exposure is perceived as pain (cold alldynia) or discomfort.
(4) An increased vasomotor response to cold, resulting in a reduced peripheral blood flow (Raynuuds phenomenon). (26)

The concept "cold sensitivity" as used in this thesis is defined as a sense of pain or discomfort when exposed to cold and can be referred to the third option stated above.

An increased sensitivity to cold is commonly reported among patients with hand injuries or diseases (27) and has been described in populations with nerve injuries (28), fractures (29), carpal tunnel syndrome (30) and HAVS (31), to mention a few.

In current research and clinical setting, a questionnaire called “Cold Intolerance Symptom Severity” (CISS) is used to help diagnose patients with cold sensitivity following nerve injury (32). This inventory investigates the subjective discomfort and problems regarding ambient cold temperature on
a score from 4 to 100. Cut-off value to distinguish between normal and abnormal cold sensitivity are 30 for the English version of CISS (33) and 50 for the Swedish version (34).

1.6 Sensation of cold
The perception of cold in the hands or fingers could be either a true sensation of a hand with impaired peripheral circulation or a false perception of a hand with normal circulation but with a sensory malfunction.

The terminology for this symptom is not strictly defined. Possibly, distinctions could be made between perception and sensation, and finger coldness has also previously been used (35). The term “sensation of cold” is used in this thesis to harmonise with previous research in the field (36, 37).

The pathogenesis is not fully understood, but the origin has been suggested to be either vascular, neurosensory or a combination of both (35, 38). Sensation of cold hands, described by Yamada et al., as subjective reports of finger coldness, has been proposed to be an early stage in a typical clinical course of vascular and neurosensory HAVS (39). Suggested mechanisms, common for vascular and neurosensory HAVS, are either that damage to the intraneural vessels causes impaired blood supply to peripheral nerves, causing sensory loss, paresthesia, numbness and other neurosensory symptoms, or that the vasospasm is initiated by damage to nerve fibres in the vessel wall (38). If perception of cold is a step in the clinical course of vascular and neurosensory HAVS the same mechanisms should apply to sensation of cold hands.

Sensation of cold hands has been reported after both pronounced cold exposure accompanied by tissue damage (37, 40) and prolonged exposure to HAV (35).

1.7 Rationale of the present thesis
In Swedish working life, exposure to HAV and cold are two common health hazards. Health effects of HAV have been thoroughly studied, though effects of cold exposure, in terms of effects on the peripheral neurosensory and vascular system, are on the contrary limited, especially in an occupational setting.
2 Purpose

The purpose of this thesis was to increase the knowledge about health effects from cold and HAV on the peripheral neurosensory and vascular system, with an occupational perspective.

2.1 Aims

- To identify and evaluate health effects and sequelae in the peripheral neurosensory and vascular system, due to cold injury and cold exposure (Study I and II).

- To investigate if sensation of cold hands is a predictor for future onset of Raynaud's phenomenon or paresthesia (Study III).

- To identify possible risk factors associated with cold sensitivity (Study IV).
3 Methods

3.1 Study designs and overview
In the present thesis different study designs have been used and an overview is presented in table 1. An overview of risk factors and outcomes assessed in the different studies is presented in figure 1.

<table>
<thead>
<tr>
<th>Study</th>
<th>Topic</th>
<th>Study design</th>
<th>Study population</th>
<th>Study period</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Effects of cold injury</td>
<td>Case series with prospective follow-up</td>
<td>Healthy young men (n=15)</td>
<td>4y</td>
</tr>
<tr>
<td>II</td>
<td>Effects of cold exposure</td>
<td>Cohort (prospective)</td>
<td>Healthy young men (n=54)</td>
<td>14m</td>
</tr>
<tr>
<td>III</td>
<td>Early sign of Raynaud's phenomenon and paresthesia</td>
<td>Cohort (prospective)</td>
<td>Men older than 18y (n=178)</td>
<td>21y</td>
</tr>
<tr>
<td>IV</td>
<td>Risk factors for cold sensitivity</td>
<td>Nested case-control (cross-sectional)</td>
<td>General population (n=997)</td>
<td>-</td>
</tr>
</tbody>
</table>

y, Years; m, Months
Figure 1. Overview on how the different study designs covered risk factors and outcomes. BMI, body mass index; HAV, hand-arm vibration; QSR, quantitative sensory testing; FSBP, finger systolic blood pressure after local cooling.

3.2 Subjects and study procedure

**Study I and II**
For study I and II, the subjects were military conscripts enlisted for 14 months ranger training in the north of Sweden (Arvidsjaur, the “Norrbotten Regiment I19”) in 2007 and 2009. All subjects were males, aged between 19 and 21 years old. The ranger training in Arvidsjaur was considered one of the toughest and most prestigious military trainings in Sweden demanding healthy, physically fit and highly motivated conscripts.

**Study I**
At the end of their military service in northern Sweden, 34 military conscripts were assessed by personnel at the clinics of occupational and environmental medicine in northern Sweden (Sundsvall and Umeå), at the request from the military health service on site. The intention was to assess and document possible health effects linked to cold injuries that several
conscripts had suffered from during their winter training. Approximately four months after initial cold injury, the conscripts were medically examined, assessed by laboratory testing and they answered a questionnaire, all focusing on vascular and neurosensory function, signs and symptoms. Fifteen conscripts were included in the study, out of a group of 34 conscripts that had reported a cold injury to the military health service team. To be included, the conscript must had developed a freezing cold injury in the hands or feet during their military training. The medical journals from these conscripts were analyzed and used to describe a series of 15 cases of cold injured patients. The severity of the cold injuries, according to the conventional classification system (18), was not clearly stated in the journals, but by interpreting findings described in the journals, we could not find any descriptions of injuries equivalent to third degree frostbite or worse. The cold injuries were most likely equivalent to first or second degree frostbite or frostnip. Four years after their military training the conscripts was again given the same questionnaire, to assess possible long-term effects. As reference values, data from two different, healthy, male, age-matched populations were used. One were the baseline data from the population in study II (n=81). Those participants were of the same age and had passed the same military recruitment procedures, and were therefor considered to be comparable to the study population in most aspects. The other set of reference values were data from 15 healthy male volunteers, with a mean age of 26 years (range 16 – 32). They had been invited to participate as reference population in previous research studies at the Department of clinical neurosciences, division of Clinical neurophysiology at the University of Umeå in Sweden.

**Study II**

To analyze the effects of cold exposure, a company (military unit) with 81 military conscripts were followed for 14 months of military training in north of Sweden. All 81 conscripts in the company volunteered to participate, of which 54 of those remained in military service throughout the 14 months and fulfilled a follow-up and were included in the study. None of the participants reported previous cold injury, or had been exposed to substantial HAV prior to the study. Participants were medically examined, assessed by laboratory testing and they answered a questionnaire, all focusing on vascular and neurosensory function, signs and symptoms, before and after their military training. During the cold period of the year, the participants carried a body-worn temperature logger to record ambient temperature. Comparisons between test values at baseline, before military training, and at follow-up, after military training, were used to analyze vascular and neurosensory effects of cold exposure.
Study III
The analyses in study III is based on data from the SUNDS-cohort (41), which has been followed since 1987. The original study population consisted of 241 male office and manual workers, all full-time employees at an engineering plant, manufacturing pulp and paper machinery. The manufacturing process involved a considerable amount of exposure to HAV compared to the general population. The cohort was followed every fifth year through medical examinations, QST assessments and questionnaires, as well as with additional methods not included in study III. To secure accurate estimates of the vibration exposure in the cohort, a combination of technical measurements, diaries, interviews, and questionnaires was used. The group was an open cohort, with new participants recruited at several occasions, although in study III, only participants recruited in 1987 and 1992 were included. Two final study populations were formed; one to analyse the risk of Raynaud’s phenomenon (n= 178) and one to analyse the risk of paresthesias (n=168). Participants were included in one of the study populations if they were healthy at baseline, attended at least one follow-up evaluation, and did not report their first sensation of cold hands at the same follow-up as their first report of Raynaud’s phenomenon or paresthesias.

Study IV
In early 2015, a research project called Cold and Health in Northern Sweden (CHINS) was launched, with the purpose of investigating cold-related health effects in the general population in northern Sweden. The project was conducted in the four northernmost counties in Sweden. The first data collection, here titled CHINS1 (10), was a large questionnaire-based study, performed on a randomly selected sample of 35,144 men and women between 18 and 70 years of age from the general population. From the responders in CHINS1 (n=12,627), 502 cases that fulfilled our criterion for cold sensitivity were identified. This cold sensitivity criterion was positive answers to both of the two questionnaire items: “I am oversensitive to cold” and “I experience pain/discomfort when fingers/hands are exposed to cold”. Controls from the same study population (CHINS1) were matched to cases regarding geographical area, sex and age (±2 years). The identified cases and matched controls were sent another questionnaire, CHINS2, focusing on possible risk factors for cold sensitivity. One hundred and five cases and 340 controls did not respond to the second questionnaire and 23 cases and 41 controls were excluded since they were missing a matched control or case. The final study population consisted of 374 cases with cold sensitivity and 623 matching controls. Mean age was 50.5 years, mean BMI 25.4 and 63% of the participants were women. The risk of developing cold sensitivity was analyzed for several possible risk factors with a nested case-control study design.
3.3  Cold exposure and cold injuries (Study I, II and IV)
For participants in study I and II the 14 months ranger training in Arvidsjaur comprised cold winter conditions and included prolonged periods spent in field with no indoor possibilities, full body water immersion in ice-covered waters, outdoor shooting, and physical exercise in cold temperature.

In study I, a cold injury was considered present if the participant had reported a cold injury in the hands or feet to the military health service team during their military training and if this was clearly described in their medical records. Cold exposure measurements in study I were obtained from official data from the National Swedish Meteorological and Hydrological Institute, recorded at the local weather station in Arvidsjaur (42).

In study II, previous cold injuries were asked for in the baseline questionnaire to make sure no participant had suffered from a cold injury before the study. At follow-up the participants reported if they had suffered from a cold injury in their hands or feet during their military training. Cold injuries in other areas were disregarded in this study. A cold injury was defined as answering yes to the question “Have you developed frostbite during your military training?” and reporting hand and/or feet as the site of injury. To measure ambient temperature in study II, all participants wore a temperature logger (EL-USB-1, Lascar Electronics, Whiteparish, UK) exposed to outdoor air. The temperature logger recorded the temperature continuously every 30th minute during 200 days from November to May. All recordings <0 °C were considered as cold exposure. The participants were categorized into three groups based on the 33rd and 66th percentiles for cold exposure.

In study IV, information on frostbites was gathered via questionnaire questions, where participants stated if they had ever had a frostbite, and if so, when and at what severity. Frostbite was categorized according to location (hands, feet or face) and as first degree (white spots), second degree (blisters), or third degree (blood-filled blisters). The ambient and contact cold exposures in study IV were assessed through several questions, adapted from the Potential Work Exposure Scale (43). Four different measurements were used in the analyses: Occupational and Leisure-time cold exposure, where study participants were asked to what extent they spent time in cold environment at work and at leisure time (numeric rating scale from 1-10), cumulative cold exposure, which was a calculated measurement equal to the sum of occupational and leisure-time cold exposure, and contact cooling where participants were asked if their work required them to manually handle objects with a temperature near or below freezing (yes or no).

3.4  Hand-arm vibration exposure (Study II-IV)
In study II, all participants were asked if they had been exposed to HAV prior to the study or during the study period. If a considerable vibration
exposure was reported, the participant would have been excluded from the study. This was made to eliminate the risk that possible health effects seen in the study were due to vibration exposure instead of cold injury or cold exposure. In study II, no considerable amount of vibration exposure was reported.

In study III, assessments of individual vibration exposure, from primarily pneumatic grinders and hammers, were made with a combination of technical measurements and subjective assessments of duration. The technical measurements were conducted according to the appendixes to ISO standard 5349-1 and 5349-2 (11, 12) during normal working conditions. Duration was estimated by use of diaries, questionnaires and interviews, where the participants stated which type of tool they used, what type of work they performed, the time in minutes each tool was used during the day, and the number of years with such exposure. Data on leisure time exposure to HAV was collected using interviews.

In study IV, exposure to HAV was reported with questionnaire questions. The participants reported if they were recurrently exposed to HAV at work. They also stated which type of tools they had used: Impact tools, high frequency tools, forestry and gardening equipment, heavily vibrating tools or vehicles with vibrating controls. Several examples were given as guidance for each type of vibration.

### 3.5 Other possible risk factors for cold sensitivity (Study IV)

Apart from cold injury, cold exposure and vibration exposure, a number of other possible risk factors for cold sensitivity were investigated in study IV: Individual factors such as height and weight, diseases linked to upper extremity nerve and vascular system, such as diabetes, rheumatic disease, polyneuropathy and carpal tunnel syndrome, and traumatic upper extremity nerve injury, tobacco use, medications and heredity. The participants were asked to answer a self administered questionnaire. Height, weight and medications were collected as text, and all other from yes or no questions.

### 3.6 Assessment of cold sensitivity

In study I and II regarding the effects of cold injury and cold exposure, there was one question much in line with the concept of cold sensitivity, which was interpreted as an indication of cold sensitivity: “Do you experience pain/discomfort when fingers/hands are exposed to cold?” to which the study participant could answer on a four-grade scale, consisting of “none”, “insignificant”, “somewhat” and “a lot”.

From the collected baseline data in study IV, cases with cold sensitivity were identified through the use of two questionnaire items:
“I am oversensitive to cold”, to which the study participant could answer on a fixed numerical scale ranging from 1 (“do not agree”) to 10 (“agree completely”). An answer of 4 or more was considered a positive response.

“I experience pain/discomfort when fingers/hands are exposed to cold”, to which the study participant could answer on a four-grade scale, in the form of “none”, “insignificant”, “somewhat” or “a lot”. Answering “a lot” was considered a positive response. A positive response on both questions fulfilled our case definition for cold sensitivity.

### 3.7 Quantitative sensory testing (Study I and II)

Cold perception thresholds (CPT), cold pain perception thresholds, warmth perception thresholds (WPT), warmth pain perception thresholds and vibrotactile perception thresholds (VPT) in the hands and feet, were assessed using three different methods of Quantitative sensory testing (QST). Quantitative sensory testing is a non-invasive semi-objective psychophysiological method for assessment of sensory perception thresholds (44, 45).

When assessing thermal perception thresholds, heating and cooling stimuli were delivered with a 2.5 x 5.0 cm stimulation probe of Peltier-type (Thermostest®, v. 01-S, Somedic AB, Hörby, Sweden). A VibroSense Meter (VibroSense Dynamics AB, Malmö, Sweden) was used to assess VPT.

The thermal perception thresholds were assessed at four test sites in study I; the combined surfaces of the distal phalanges of dig 2 and dig 3 in both hands and the dorsal surface of the foot arc in both feet. In study II, six sites were assessed; the palmar surfaces of the distal phalange of dig 2 and dig 5 bilaterally and the plantar surface of the distal phalange of the first toe bilaterally. The tests were conducted according to the method of limits (46, 47), following standard test procedure (48). The test sites assessed for VPT were the palmar surface of the distal phalanges of dig 2 and dig 5 bilaterally and the plantar surface of the distal phalange of the first toe bilaterally. Vibration perception thresholds were determined for four frequencies: 8, 32, 125 and 500 Hz, following standard procedure as stipulated in ISO 13091-1 (49). Touch perception thresholds were only assessed in study II. The test sites were the palmar surface of the distal phalanges of dig 2 and dig 5 bilaterally and the plantar surface of the distal phalange of the first toe bilaterally. Assessments were following standard procedure (50).

### 3.8 Assessment of Raynaud’s phenomenon (Study I -IV)

In study I to III, The participants answered the question: “Do you have white (pale) fingers of the type that appear when exposed to damp and cold weather?” in a self administered questionnaire, supplied with a four-grade response options: “none”, “insignificant”, “somewhat” or “quite a lot”. This question was considered to address an indication of Raynaud’s phenomenon.
In study I and II the response options were used as a four stage ordinal scale, and in study III the options “somewhat” or “quite a lot” were considered a positive answer. Raynaud's phenomenon was defined as having a positive answer to that question.

In study IV, one questionnaire item addressed Raynaud's phenomenon: “Does one or more of your fingers turn white (as shown on picture) when exposed to moisture or cold?”, and was accompanied by a standardized color chart and the response options “yes” or “no”. Usage of a color chart has previously been shown to increase the diagnostic specificity (51).

### 3.9 Assessment of paresthesia (Study III)

The participants answered the question: “If you suffer from paresthesia, for how long have you suffered from these symptoms?” Paresthesia was considered present if the participant reported any period of time in this question. This question was considered to address an indication of the neurosensory component in HAVS.

### 3.10 Assessment of finger systolic blood pressure after local cooling (Study II)

The equipment used when assessing finger systolic blood pressure after local cooling (FSBP) was a strain gauge plethysmography (HV Lab Multi–Channel Plethysmograph, IVSR, University of Southampton, UK).

The FSBP of the distal phalanges of dig 1-5 was assessed according with International Standard ISO 14835-2 (2005) (52). The testing procedure stipulates sessions of pressurization to a suprasystolic level and cooling of the fingers to 30°C, 20°C and 10°C followed by release of pressure and aborted cooling between every session. The systolic blood pressure needed for a rapid return of blood circulation in the assessed finger, was measured.

### 3.11 Statistical analysis

All statistical analyses were performed with IBM SPSS Statistics for Windows (version 23.0, IBM Corp, Armonk. NY, USA). P-values less than or equal to 0.05, and odds ratios (OR) with the 95% confidence interval (CI) greater than one or lower than one, were considered statistically significant.

In study I, when a test value was compared to a reference value, a difference that exceeded two standard deviations from the reference value was considered abnormal.

In study II, all differences in test values between baseline and follow-up were controlled for normality. Paired t-test was used to analyze changes in mean values between baseline and follow-up for variables meeting normality and Wilcoxon signed-rank tests were used for non-normal distributed variables and ordinal categorical variables. One-way ANOVA was used to
analyze possible impact from a third variable (cold exposure, tobacco use or cold injury) on test-retest results.

In study III, descriptive participant data was presented in two groups, with and without cold sensation in the hands. All descriptive data was controlled for normality and means between the groups were compared using independent sample t-test for normally distributed data and Wilcoxon signed rank test for non-normal distributed data. Analyses were presented as p-values for continuous data and as OR with 95% CI for dichotomous data. Univariate logistic regression was used to calculate OR (95% CI) between the dependent variables and each independent variable. Multiple logistic regression analysis was used to calculate risk to develop disease, adjusting for vibration exposure and tobacco use. Positive and negative likelihood ratio and the Youden index were calculated to estimate the predictive value.

In study IV, associations between cold sensitivity and risk factors was assessed separately using conditional logistic regression and presented as an OR of cold sensitivity comparing exposed and non-exposed. Multiple logistic regressions were also used to identify the most important risk factors using a forward stepwise procedure where, in each step, the risk factor with the lowest p-value was added to the model.
4 Results

4.1 Effects of cold injuries (Study I)

During the study period, 46 days with temperatures below -10°C were recorded and the lowest temperature recorded was -28°C.

All modalities of QST measures; VPT, WPT and CPT, were affected at some extent after a cold injury. Six out of ten patients had significantly impaired sensibility for vibrotactile stimuli (VPT) in at least one of the measurement points in any of the injured hands, when compared to a reference population. Four out of ten had impaired sensibility for warmth (WPT) and one out of ten had impaired sensibility for cold (CPT). The measurements in the feet showed similar results (Fig 2).

![Graph showing number of patients with abnormal quantitative sensory testing findings in hands or feet. Red symbol represents patient with abnormal findings. Vibration perception threshold (VPT), warmth perception threshold (WPT) and cold perception threshold (CPT).](image)

**Figure 2.** Number of patients with abnormal (impaired) quantitative sensory testing findings in hands or feet. Red symbol represents patient with abnormal findings. Vibration perception threshold (VPT), warmth perception threshold (WPT) and cold perception threshold (CPT).

The most prominent neurosensory or vascular symptom after a cold injury was pain/discomfort when exposed to cold. Among the patients that
remained in the study for the 4-year follow-up, all six with a cold injury in the hands reported the highest or second highest severity of symptom after four months and still after four years. Seven out of eight patients with a cold injury in the feet reported the highest or second highest severity of symptom four years after the injury. Four patients reported the highest or second highest severity of white fingers after four months. This was reduced to one patient after four years. The equivalent results for sensation of cold in the hands were four patients after four months, which increased to five patients after four years (Fig 3). All eight patients with a cold injury in the feet reported the highest or second highest severity of sensation of cold feet and white toes after four years.

**Figure 3.** Reported neurosensory and vascular symptoms in the hands four months (4m) and in the hands and feet four years (4y) after initial cold injury.

### 4.2 Effects of cold exposure (Study II)

Mean thermal perception thresholds, assessed with QST, were compared between baseline and follow-up. One winter passed by between baseline and follow-up, thus a period of prolonged cold exposure for the military conscripts. Perception thresholds were elevated at all test sites for both cold and warm stimuli (Fig 4), indicating reduced sensibility to detect both temperature rise and temperature fall. For thermal pain perception thresholds there were no consistent pattern in changes between baseline and follow-up (not included in the figure).
Figure 4. Perception thresholds for warmth, and cold in the hands at baseline and follow-up presented as the mean difference with standard deviation bars, in degrees Celsius from neutral temperature to detection temperature.

* p<0.05

When testing VPT the perception thresholds were elevated at all test sites except for the second digit at the right hand where no statistically significant difference could be found. This indicated a reduced sensibility for vibrotactile stimuli.

All neurosensory and vascular symptoms in both hands and feet were significantly more severe in the follow-up, compared to baseline. The results for the feet are presented in figure 5. Results for the hands are of the same amplitude and follow the same pattern.

The distribution of time spent below 0 °C, between the groups was 26.3–39.1 days (low cold exposure group), 39.8–44.6 days (medium cold exposure group) and 45.3–58.0 days (high cold exposure group).
Figure 5. Neurosensory and vascular symptoms in the feet at baseline (BL) and follow-up (FU).
4.3 Sensation of cold, Raynaud's phenomenon and paresthesia (Study III)

Two study populations were formed to investigate the risk of Raynaud's phenomenon and paresthesia respectively, if previously reported sensation of cold hands. Descriptive data for the study populations at baseline included a median age of 37 years (range 19-58 years), a median height of 180 cm (range 165-198 cm), a median weight of 77 kg (range 60-108 kg) and a median body mass index (BMI) of 24.3 (range 16.6-31.7). 92% used tobacco, 29% were exposed to HAV during the study period and 70% had been exposed to HAV during their lifetime. In the corresponding study populations, 21 out of 178 developed Raynaud's phenomenon and 43 out of 168 developed paresthesia.

Sensation of cold hands was a significant risk factor (OR 7) for developing Raynaud's phenomenon but not for developing paresthesia. The results persisted when adjusting for tobacco and vibration exposure (Table 2).

Table 2. Risk of developing Raynaud's phenomenon or paresthesia if previously experienced a sensation of cold hands.

<table>
<thead>
<tr>
<th></th>
<th>OR  95% CI</th>
<th>OR  95% CI</th>
<th>OR  95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raynaud's phenomenon</td>
<td>7.0 2.6-18.6</td>
<td>6.0 2.2-16.4</td>
<td>6.3 2.3-17.0</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>1.5 0.6-3.6</td>
<td>1.5 0.6-3.6</td>
<td>1.5 0.6-3.6</td>
</tr>
</tbody>
</table>

OR, Odds ratio; CI, Confidence interval

1 Adjusting for tobacco use and study period vibration exposure dose
2 Adjusting for tobacco use and lifetime vibration exposure dose

With a positive likelihood ratio of 3.0 and a negative likelihood ratio of 0.4, sensation of cold hands has a small probability to both rule in and rule out future development of Raynaud’s phenomenon. The likelihood ratios are even weaker, with no probability to predict development of paresthesia.
4.4  **Risk factors for cold sensitivity (Study IV)**

Occupational exposure to hand-held vibrating tools was more common among men than women, 54% and 7% respectively. An increased risk (OR 2.8, 95% CI 1.7-4.6) was found for male cases working with impact tools such as chipping hammers, rotary hammers, rock drills, impact drills, nailers and impact wrenches.

Cases reported higher exposure to cold during work, compared to controls and there was also a tendency of an exposure-response association with higher risks for highly exposed, compared to those less exposed (Table 3). Exposure to manual handling of cold objects during work was associated to cold sensitivity among both men and women (Table 3).

Cases had a higher prevalence of previous frostbite affecting hands, than controls, with a risk of OR 10.2 (95% CI 6.0-17.2). Cases also reported a higher prevalence of vascular disease with a risk of OR 1.8 (95% CI 1.3-2.6). Other diseases associated with cold sensitivity were migraine, rheumatic diseases, polyneuropathy, upper extremity nerve injury and peripheral vascular disease. Daily tobacco use was more common among the cases but a high BMI (≥25 kg/m²) was associated with a lower reported frequency of cold sensitivity.
Table 3. Univariate odds ratios for occupational and leisure-time risk factors for cold sensitivity. Presented as odds ratios with 95% confidence intervals (95% CI).

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Occupational cold exposure</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(NRS 1-10) <strong>1</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1 (-)</td>
<td>1 (-)</td>
<td>1 (-)</td>
</tr>
<tr>
<td>Low</td>
<td>1.3 (0.9-1.8)</td>
<td>1.2 (0.6-2.1)</td>
<td>1.3 (0.8-2.1)</td>
</tr>
<tr>
<td>Medium</td>
<td>1.5 (0.98-2.2)</td>
<td>1.1 (0.6-2.0)</td>
<td>2.0 (1.1-3.4)</td>
</tr>
<tr>
<td>High</td>
<td>1.8 (1.1-2.8)</td>
<td>1.9 (0.96-3.8)</td>
<td>1.5 (0.8-2.8)</td>
</tr>
<tr>
<td><strong>Handling cold objects during work</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2.6 (1.9-3.6)</td>
<td>2.8 (1.8-4.5)</td>
<td>2.4 (1.5-3.9)</td>
</tr>
<tr>
<td>No</td>
<td>1 (-)</td>
<td>1 (-)</td>
<td>1 (-)</td>
</tr>
<tr>
<td><strong>Leisure-time cold exposure</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(NRS 1-10) <strong>2</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1 (-)</td>
<td>1 (-)</td>
<td>1 (-)</td>
</tr>
<tr>
<td>Low</td>
<td>1.3 (0.8-2.2)</td>
<td>1.2 (0.5-3.1)</td>
<td>1.3 (0.7-2.5)</td>
</tr>
<tr>
<td>Medium</td>
<td>1.2 (0.7-1.9)</td>
<td>0.8 (0.3-1.9)</td>
<td>1.4 (0.8-2.6)</td>
</tr>
<tr>
<td>High</td>
<td>1.6 (0.99-2.7)</td>
<td>1.2 (0.5-2.8)</td>
<td>1.9 (1.0-3.5)</td>
</tr>
<tr>
<td><strong>Cumulative cold exposure</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(NRS 2-20) <strong>3</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High (&gt;8)</td>
<td>1.6 (1.2-2.1)</td>
<td>1.2 (0.7-1.9)</td>
<td>1.8 (1.3-2.6)</td>
</tr>
<tr>
<td>Low (≤8)</td>
<td>1 (-)</td>
<td>1 (-)</td>
<td>1 (-)</td>
</tr>
<tr>
<td><strong>Impact tools</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2.4 (1.5-3.9)</td>
<td>2.8 (1.7-4.6)</td>
<td>1.3 (0.4-4.0)</td>
</tr>
<tr>
<td>No</td>
<td>1 (-)</td>
<td>1 (-)</td>
<td>1 (-)</td>
</tr>
<tr>
<td><strong>Fast rotating tools</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.9 (0.9-4.2)</td>
<td>2.3 (0.9-6.0)</td>
<td>1.3 (0.3-5.3)</td>
</tr>
<tr>
<td>No</td>
<td>1 (-)</td>
<td>1 (-)</td>
<td>1 (-)</td>
</tr>
<tr>
<td><strong>Forestry/gardening tools</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.4 (0.9-2.2)</td>
<td>1.4 (0.9-2.4)</td>
<td>1.3 (0.4-4.0)</td>
</tr>
<tr>
<td>No</td>
<td>1 (-)</td>
<td>1 (-)</td>
<td>1 (-)</td>
</tr>
<tr>
<td><strong>Vibrating tools</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.9 (1.2-2.9)</td>
<td>2.0 (1.2-3.2)</td>
<td>1.5 (0.5-4.2)</td>
</tr>
<tr>
<td>No</td>
<td>1 (-)</td>
<td>1 (-)</td>
<td>1 (-)</td>
</tr>
<tr>
<td><strong>Heavily vibrating tools</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2.4 (1.5-3.9)</td>
<td>2.5 (1.5-4.1)</td>
<td>1.6 (0.3-8.1)</td>
</tr>
<tr>
<td>No</td>
<td>1 (-)</td>
<td>1 (-)</td>
<td>1 (-)</td>
</tr>
<tr>
<td><strong>Vehicles with vibrating controls</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.5 (0.95-2.3)</td>
<td>1.5 (0.9-2.4)</td>
<td>1.6 (0.6-4.2)</td>
</tr>
<tr>
<td>No</td>
<td>1 (-)</td>
<td>1 (-)</td>
<td>1 (-)</td>
</tr>
<tr>
<td><strong>Any HAV exposure</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2.1 (1.4-3.0)</td>
<td>2.6 (1.6-4.3)</td>
<td>1.4 (0.8-2.6)</td>
</tr>
<tr>
<td>No</td>
<td>1 (-)</td>
<td>1 (-)</td>
<td>1 (-)</td>
</tr>
</tbody>
</table>

NRS, Numeric rating scale; HAV, Hand-arm vibration

1. None = NRS 1; Low = NRS 2-4; Medium = NRS 5-7; High = NRS 8-10
2. Summation of occupational and leisure-time cold exposure
3. Any occupational use of impact tools, fast rotating tools, forestry and gardening tools, vibrating tools, heavily vibrating tools and/or vehicles with vibrating controls
In the final multiple model, frostbite in the hands, rheumatic disease, nerve injury in upper extremities or neck, migraine and vascular disease were included. When analysing women and men separately, women’s risk factors were frostbite in the hands, rheumatic disease, migraine and cumulative cold exposure. Men’s risk factors were frostbite in the hands, vibration exposure and nerve injury in upper extremities or neck. BMI > 25 was a protective factor for both men and women.

Cases were more prone than controls to stay inside even in relatively mild ambient temperatures (Fig 6) and experience more symptoms (Fig 7). The symptoms occurs at least once a week for 63% of the cases.

**Figure 6.** Proportion of cases (N=394) and controls (N=616) that reported refraining from outdoor leisure time activities at the given temperature intervals.
In study IV there was a high prevalence of Raynaud’s phenomenon among cases. Fifty eight percent of the men and 67.2% of the women reported white fingers. Thus, cold sensitivity and Raynaud’s phenomenon seem to be partly overlapping conditions that may share pathophysiological mechanisms (53).
5 Discussion

5.1 Effects of cold exposure and cold injury (Study I and II)
Cold injuries and cold exposure are associated with measurable effects in the vascular and neurosensory system. This was shown in study I by abnormally elevated perception thresholds, measured by QST in 11 out of 15 patients four months after cold injury, as well as reports of cold sensitivity, cold sensation and white fingers, still four years after the cold injury. In study II, QST measures as well as vascular and neurosensory symptoms changed after one winter of considerable cold exposure. This was shown by elevated perception thresholds and increased severity and prevalence of cold sensitivity, sensation of cold and white fingers.

Health effects of freezing cold injuries have been studied as long as wars have been fought in areas cold enough to cause a substantial loss of soldiers or loss of soldiers’ ability to continue the warfare. The latest reviews on cold injuries (54-56) consistently report cold sensitivity, altered peripheral circulation and altered perception of temperature as some of the health effects related to cold injury. The symptoms cold sensitivity, sensation of cold and white fingers, found in study I and II, supports these findings. Our observation of long term sequelae after cold injury supports previous studies reporting sequelae between six months and 30 years after injury occurrence (55, 57-61). The cold injuries in our study were most likely superficial, of first or second degree. This supports the findings in previous research that such relatively modest cold injuries can cause prolonged sequelae (58, 60).

There is not as much research comparable to study II, investigating health effects of cold exposure. There are studies describing acute effects on muscular performance described in a review from 2002 (62). Several studies investigate work related musculoskeletal disorders, but mostly by cross-sectional study design, not allowing analysing for causality and not focusing on vascular or neurosensory effects. These studies, up to 2002 have been summarised in a review by Pienimäki (63). To our knowledge, study II in this thesis, is the first prospective study investigating sustained neurosensory and vascular effects in hands and feet, caused by cold exposure. In comparison to studies on cold injuries, cold sensitivity was the most prominent neurovascular symptom found in study II and that is also a reoccurring manifestation described in several studies on cold injury (57, 59, 60, 64).

5.2 Risk factors or early signs of HAVS (study III)
When looking at the results from study III, that investigated if sensation of cold hands affected the risk of developing symptoms of Raynaud’s phenomenon or paresthesia, the results were interpreted in two ways: at
group level and at individual level. At group level, the risk of developing Raynaud’s phenomenon was increased. This was not the case for paresthesia. At individual level, the use of self-reported sensation of cold hands was not an efficient method to rule in or rule out future onset of Raynaud’s phenomenon or paresthesia.

Gerhardsson et al. (65) investigated young vibrating machine operators with only a few years of vibration exposure and found elevated VT and pathologic TT but no increased rates of neurosensory symptoms like tingling or numbness. The author’s concluded that neurosensory effects can appear after short term vibration exposure. The study was limited to neurosensory symptoms and effects, thus not including the symptom sensation of cold hands, making it difficult to compare the results to study III.

Sakakibara et al. (66) and Ishitake et al. (35) both found associations between reported finger coldness and the severity of Raynaud’s phenomena. Both studies used a cross-sectional design so they could not determine if finger coldness developed before, after or simultaneously with Raynaud’s phenomenon. Ishitake suggests that coldness in the fingers may be a good warning signal of potential problems in peripheral circulatory function. The findings in study III support the association between finger coldness (sensation of cold hands) and Raynaud’s phenomenon found by Sakakibara and Ishitake, and can confirm Ishitakes suggestion that finger coldness preceeds indications of Raynaud’s phenomenon.

5.3 Cold sensitivity (Study IV)
Cold sensitivity was associated with several inherent factors on a population level. The risk factors were modified by sex. The greatest risk factor was frostbite in the hand, both for women and men. High BMI (>25) was negatively associated to cold sensitivity for both women and men, that is to say, a protective factor. Cold exposure, migraine and rheumatic disease were significantly associated to cold sensitivity among women but not men while HAV exposure was significantly associated to cold sensitivity among men and not women.

In the latest reviews on cold injuries by Golant et al. (54) And Hutchison (56) it was concluded that cold sensitivity is a commonly reported sequelae after cold injury, which is supported by the results in study IV. Other risk factors for cold sensitivity, identified in study IV, that are supported by previous research are HAV (31) and upper extremity nerve injury (31, 67-69). Some authors have even argued that nerve injury is the main determinant of cold sensitivity (70) while others have argued that a multifactorial etiology should be considered where vascular, neural, humoral and bony components could be associated with cold sensitivity (71). Among female cases, cold exposure, rheumatic disease and migraine, were significaly more common than among controls. Cold sensitivity has previously been reported a
common complaint among patients with rheumatic disease (72). Several rheumatic diseases are associated with Raynaud's phenomenon (73) and given the high prevalence of Raynaud's phenomenon among the cases in study IV, it is not surprising that an association between cold sensitivity and rheumatic disease was found. Association between migraine and cold sensitivity has to our knowledge not previously been investigated. That exposure to HAV was a significant risk factor for men but not for woman was probably because there were too few exposed woman for the analysis to gain sufficient power for a significant result. That there would be sex related differences in risk factors for cold sensitivity was not entirely unexpected. Previous studies have found diversities between prevalence of chronic pain conditions and in sensitivity across multiple sensory domains between women and men (74). The underlying mechanisms for this are still not clear but since women and men appear to differ in other sensory perceptions, differences in cold sensitivity may also be expected. The results could also be affected by prevalence differences between women and men within the different risk factors, where risk factors with low prevalence of any of the sexes are less likely to reach a level of statistical significance.

5.4 Implications in working life and future research
Cold temperature is one of many physical hazards, affecting risk of occupational illness, disease or symptoms. Other common physical hazards that are of relevance to occupational health problems, are for example warm temperature, vibration and noise (75). As stated in the introduction, there are provisions under the Swedish Work Environment Authority’s Statute Book (AFS) for HAV and also for work in extreme warmth and for noise. For work in cold however, there is no provision.

As we have shown, cold exposure can affect both the vascular and the neurosensory system, shown by symptoms such as Raynaud’s phenomenon and paresthesia, and by elevated perception thresholds for cold, warmth and vibration assessed by QST. These findings are similar to the vascular and neurosensory effects caused by HAV. One example is a study by Hagberg (41) where they used the exact same questionnaire item, describing symptoms of white fingers, and found a dose response relationship between HAV and white fingers. Symptoms of cold sensitivity and sensation of cold hands have also been confirmed as health effects of HAV (31, 35, 66). The elevated perception thresholds for cold, warmth and vibration, detected by QST are also common findings in HAVS patients (76).

The results in this thesis, show that there are effects of cold exposure that are comparable to effects of HAV, but our studies are small and further research is needed to confirm the parts of the results that are unique to this thesis, and to our knowledge, never has been shown before. That is the results of impaired sensibility for thermal and vibrotactile stimuli assessed
with QST, as well as neurosensory and vascular impairments, signs and symptoms, shown with a longitudinal study design. Further research is also needed to establish more precise estimates regarding the magnitude of the association between cold exposure and vascular and neurosensory effects, comparable to what have recently been done for HAV (14). Based on the current knowledge it would be reasonable with similar protective regulations for cold exposure, as the current regulations for HAV. Or at least clear recommendations on how to handle exposure to cold in the occupational setting.

Furthermore, these results are important when considering secondary preventive actions. Traditionally in occupational medicine QST is mostly used to assess patients exposed to HAV that are suspected to have developed some level of neurosensory impairments. According to our results, possible QST findings, previously interpreted as the vascular component of HAVS, caused by exposure to HAV, could in fact be a result from cold exposure. Occupations like construction workers, mechanics and workers within forestry, agriculture and fishing industries are often exposed to both cold and vibration and since symptoms not always appear in direct connection with the exposure, it is plausible that both patient and physician will suspect the most well known exposure to be the cause. If preventive measures only aims at reducing the vibration exposure and not consider cold exposure, there is a risk of only taking care of half the problem.

Cold sensitivity has previously been found to have a profound impact on work capacity, leisure time activities, disability and quality of life (31, 77). This was shown in study IV by more severe symptoms (Fig 7) and avoidance of cold temperature outdoor activities (Fig 6) among persons with cold sensitivity, compared to healthy controls. This shows some true consequences of cold sensitivity. It is not all about pain and discomfort. People tend to avoid what is unpleasant and this could be devastating for people living in areas where hunting, fishing, skiing or snow mobile driving can be a large part of persons’ identity and social life.

A goal should be to prevent the onset of cold sensitivity in occupations with known risk factors for the disorder. From study IV it is known that HAV, and cold exposure are potential risk factors for cold sensitivity as well as frostbite in the hands, which is strongly associated with cold exposure. These risk factors are common in many industries in the working life, therefore focus should be to target these industries, with the intention to reduce exposure to both cold and HAV. Further research need to address if there is a causal relationship between our found risk factors and cold sensitivity, by studies with well designed longitudinal approach. If such relationship is found, it should be possible to identify persons at risk of developing cold sensitivity, by screening all workers with a questionnaire containing question on all risk factors of relevance.
For sensation of cold as a risk factor for Raynaud's phenomenon, the results from study III suggested that there is an association, and that sensation of cold appears before Raynaud’s phenomenon. Groups with an increased risk of Raynaud's phenomenon can easily be identified by a simple questionnaire asking for sensation of cold hands. These groups should be given information about HAVS and what preventive measures they can take, and have their work organisation examined for possibilities to reduce exposure to HAV and cold exposure. In this field, future research needs to focus on identifying more risk factors or early signs of both the vascular and neurosensory component of HAVS and for that, use a more specific definition of Raynaud's phenomenon than in study III. With more identified risk factors or early signs, it should be possible to build a model from multiple screening questions, which reliably can be used to identify persons at risk of vascular or neurosensory HAVS, with a predictive value, satisfying enough to be used at the individual level. An even more important focus for future research is to study the effects from preventive measures. We already have lots of reliable knowledge on the risks, now is the time to start reducing risks and reduce disease.

5.5 Methodological considerations
Study I was a case series, with relatively few participants, designed to use a wide approach to, in detail, understand what health effects cold injuries may have. The small number of participants had the advantage of allowing us to use a wider range of time consuming assessment tools, than would have been possible with a larger study population. The main limitation of our study design is limited generalisability to other populations since our results are derived from only 15 selected young male patients. However the intention with study I was not to obtain general results applicable to the general population but to investigate a hypothesis; that health effects of local freezing cold injuries are comparable to those of HAV exposure. The case series design allowed us to investigate the hypothesis. The results from this thesis shows that it is possible for cold injury victims to obtain these types of health effects, but we could not make any conclusions regarding the magnitude of the risk or if the findings are applicable to other populations.

Study II and III has a cohort design with the advantage to allow analysis on causal relationships within a population between the exposure of interest (vibration exposure or cold exposure) and multiple related health outcomes.

The most considerable limitation in study II was the difficulties to connect the outcomes to the exposure of interest, namely cold exposure. We had reliable data on cold exposure by ambient air temperature measurements at the individual level but we did not assess other possible exposures, such as vast amounts of physical activity and periods without adequate sleep. The military training is intensive and conscripts were without doubt exposed to
numerous stressors apart from cold during their 14 months in Arvidsjaur. Some of the most obvious could be adjusted for, like HAV and tobacco but there were too few participants to adjust for additional factors without losing too much power in the study. There were probably also unknown exposures that can’t be accounted for unless they are identified. Most of these issues would have been solved by the use of an appropriate control group.

A strength in study III is that we followed participants even after they retired, after a job change, or if they quit work for medical reasons. The interpretations of the results are thereby generalisable to the male population as a whole, and the risk of selection bias such as healthy worker effect is minimised. Study III has limitations in the definition of the outcome symptoms, which are Raynaud’s phenomenon and paresthesia. They are defined as a positive answer to only one questionnaire item each. Optimal would have been a more specific definition of Raynaud’s phenomenon by combining questionnaire items, colour chart, results from the medical assessment and possibly even objective measures like FSBP. This introduces an information bias where we risk to not measure what we intended to measure. It is however a non-differential misclassification in the sense that both groups (with and without sensation of cold) are subject to the misclassification. To conclude: the risk estimate was not affected by bias but there is a risk that we didn’t measure exactly what was intended to be measured.

Study IV has a nested case-control design which allowed us to study a broader variety of possible risk factors than would have been possible in a cohort study, because of the relatively low incidence of cold sensitivity in the general population. The cross-sectional design did not provide any information on if risk factors appeared before onset of cold sensitivity, not allowing for analyses of causality between found relationships. There was also a low response rate (35.9 %) in the initial questionnaire that made up the study base for this study. This makes it possible that a selection bias is introduced where responders differ from the general population, making our results less generalisable, however the anthropometric data, tobacco use, and disease spectrum corresponded with other recent Swedish investigations (78), which indicates that a representative sample of the population was included. One limitation at the core of study IV is the relatively large overlap with Raynaud’s phenomenon among cases (58.2% of men and 67.2% of women reporting white fingers). This makes it difficult to know for sure to what extent the risk factors we found are risk factors for cold sensitivity and Raynaud’s phenomenon respectively.

When using QST, there is a need for reliable reference values. This was not an issue in study II where the participants were their own controls, but in study I, the QST results completely rely on adequate reference values. The findings that more patients had elevated vibrotactile thresholds than
elevated thermal threshold were rather surprising. If considering that
sensation of warmth is transmitted by small unmyelinated C-fibers and
sensation of vibration is transmitted by larger myelinated A-beta fibers, the
warmth perception should be expected to be more severely affected than the
vibrotactile sensibility. This might be a consequence of limitations in the
reference data. The reference data was gathered using a slightly different
method (larger probe contact area) with the possible results being an
underestimation of the measured effects.
6 Conclusions

Cold injury and cold exposure are associated with impairments detectable by QST in the neurosensory system. Symptoms such as sensation of cold hands and white fingers indicate vascular involvement, even though no vascular impairments due to cold exposure could be detected by objective measurements.

A sensation of cold hands is a risk factor for development of Raynaud’s phenomenon but not for paresthesia. At the individual level, a report of sensation of cold hands does not appear to be useful information when considering the possibility of a future development of Raynaud’s phenomenon.

Frostbite in the hands is a risk factor for cold sensitivity among both women and men. For women rheumatic disease, migraine and cold exposure are also independent risk factors, and for men, exposure to HAV. Being overweight (BMI >25) is a protective factor for both women and men.
7 Acknowledgements

I would like express my gratitude to:

My supervisor Jens Wahlström and assistant supervisors Tohr Nilsson, Hans Pettersson and Erik Nordh. You have been my mentors, advisors, friends, and at crucial moments my therapists throughout this journey.

My co-writers Lage Burström, Victoria Heldestad Lilliesköld, Mats Hagberg, Ronnie Lundström, Albin Stjernbrandt and Ingrid Liljelind. Your support has been invaluable, both in work, out of work and after work.

My beloved wife Matilda. You encouraged me all the way through and carried a heavy burden during the final weeks, enabling me to focus on my work.

I am also grateful for the generous cooperation of the participating military conscripts, officers and staff at the Norrbotten Regiment in Arvidsjaur, workers in the SUNDS-cohort and the people that spent time and effort answering the CHINS questionnaires.

Financial support was provided through regional agreement between Umeå University and the County Councils of Västerbotten and Västernorrland on cooperation in the field of Medicine, Odontology and Health.
8 References


57. Ervasti E. Late sequela of the frostbites of the lower extremities (the State Accident Office, Helsinki, the Central Hospital, University of Helsinki and the Kainuu Central Hospital, Finland). Acta Sociomed Scand Suppl, 1972. Suppl 6: p. 269-71.


