

# Risk of hearing loss from combined exposure to hand-arm vibrations and noise

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*“If you only read the books that everyone else is reading, you can only think what everyone else is thinking.” – Haruki Murakami*



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# Abstract

Hearing loss from noise exposure is one of the most common occupational injuries, and exposure to vibrations may increase the risk of noise-induced hearing loss. Earlier cross-sectional and longitudinal studies found an increased risk of noise-induced hearing loss among workers with vibration-induced white fingers (VWF) symptoms compared to workers without such symptoms. It has been suggested that vibrations to the hand stimulate the sympathetic nervous system and cause vasoconstriction in both the exposed hand and the ears and that this contributes to noise-induced hearing loss. The overall aim of this thesis was to examine how hand-arm vibrations (HAV) interact with noise in the development of noise-induced hearing loss.

The experimental study in this thesis examined the effects of HAV and noise, both separately and combined, on the temporary threshold shift (TTS) in hearing in 22 healthy male and female subjects. The two longitudinal studies in this thesis were based on a cohort of 189 male workers at a heavy engineering workshop. The first cohort study examined the risk of noise-induced hearing loss from long-term exposure to HAV and noise. The second cohort study examined if workers with VWF had an increased risk of noise-induced hearing loss compared to workers without such symptoms. Finally, the questionnaire study in this thesis examined the occurrence of Raynaud's phenomenon among 133 men and women with noise-induced hearing loss in relation to exposure to vibrations.

In the experimental study, no differences in TTS in hearing were observed after combined exposure to HAV and noise compared to exposure to only noise. In the first cohort study, there was an increased risk of noise-induced hearing loss with increased exposure to HAV in a noisy environment. In the second cohort study, it was found that workers with VWF had an increased risk of noise-induced hearing loss compared to workers without VWF. In the questionnaire study, many men and women with noise-induced hearing loss had used hand-held vibrating machines suggesting that vibrations might contribute to noise-induced hearing loss. A high prevalence of Raynaud's phenomenon was found among men.

This thesis demonstrated that there was a long-term effect on noise-induced hearing loss from combined exposure to noise and HAV, but no short-term effect, and that having Raynaud's phenomenon may also increase the risk of noise-induced hearing loss.

# Sammanfattning

Många arbetare använder sig av handhållna vibrerande verktyg. Det utsätter dem för höga nivåer av både buller och vibrationer. Människor som utsätts för höga bullernivåer under lång tid kan skada sin hörsel. Risken för hörselnedsättning orsakad av buller kan eventuellt öka om personen samtidigt är utsatt för vibrationer från handhållna vibrerande verktyg. Syftet med avhandlingen var att studera om vibrationer i kombination med buller ökar risken för hörselnedsättning.

Avhandlingen består av fyra studier. Den första studien är en experimentell studie med 22 friska deltagare med god hörsel. Denna studie undersökte hur hörseln tillfälligt påverkas av buller och vibrationer, separat och i kombination. Den andra och tredje studien bygger på en population bestående av 189 verkstadsarbetare i Sundsvall som följts regelbundet sedan 1987. Den andra studien undersökte om det finns en ökad risk för hörselnedsättning för arbetare som utsätts för buller och vibrationer under lång tid. Den tredje studien undersökte om arbetare med vita fingrar har en ökad risk för hörselnedsättning än arbetare utan vita fingrar. *Vita fingrar* är en kärlskada orsakad av vibrationer som gör att fingrarna reagerar onormalt snabbt på kyla. Fingrarna blir vita när blodtillförseln till dem stryps. Den fjärde studien är en enkätstudie med 342 kvinnor och män som har en bekräftad hörselnedsättning orsakad av buller. Studien undersökte hur många ur denna grupp som utsätts för vibrationer samt har vita fingrar.

Resultaten från studierna visar att det inte finns någon skillnad i hörselpåverkan från buller och vibrationer i kombination jämfört med enbart buller under kort tid. De som utsätts för vibrationer från handhållna vibrerande verktyg i en bullrig miljö under lång tid har en ökad risk för hörselnedsättning. Arbetare med vita fingrar har en högre risk för hörselnedsättning än de utan. En hög andel av de med hörselnedsättning orsakad av buller använder sig av handhållna vibrerande verktyg. I studien fanns även en hög andel med vita fingrar.

Sammanfattningsvis visar resultaten att det finns en långtidseffekt av buller och vibrationer på hörselnedsättning men inte någon korttidseffekt, och att vita fingrar kan påverka risken för hörselnedsättning.

# Abbreviations

|          |   |
|----------|---|
| ANS      | Autonomic nervous system  |
| CI       | Confidence interval   |
| dB       | Decibel   |
| dB(A)    | Decibel with A-weighted filter  |
| dB(C)    | Decibel with C-weighted filter  |
| dBHL     | Decibel hearing threshold level   |
| HAV      | Hand-arm vibrations   |
| HAVS     | Hand-arm vibration syndrome   |
| Hz       | Hertz   |
| OR       | Odds ratio  |
| Pa       | Pascal  |
| PNS      | Parasympathetic nervous system  |
| Rms      | Root mean square  |
| RR       | Relative risk   |
| SNS      | Sympathetic nervous system  |
| SPL      | Sound pressure level  |
| SWS      | Stockholm workshop scale  |
| Time     | The lifetime exposure to HAV  |
| TimeAcc  | The lifetime exposure to HAV multiplied by the HAV acceleration           |
| TimeAcc2 | The lifetime exposure to HAV multiplied by square of the HAV acceleration |
| TTS      | Temporary threshold shift   |
| VWF      | Vibration-induced white fingers   |
| WF       | White fingers   |

# List of papers

This thesis is based on the following papers:

- I. Pettersson H, Burström L, Nilsson T. The effect on the temporary threshold shift in hearing acuity from combined exposure to authentic noise and hand-arm vibration. *International Archives of Occupational and Environmental Health* 2011; 84(8):951-7.
- II. Pettersson H, Burström L, Hagberg M, Lundström R, Nilsson T. Noise and hand-arm vibration exposure in relation to the risk of hearing loss. *Noise & Health* 2012; 14(59):159-65.
- III. Pettersson H, Burström L, Hagberg M, Lundström R, Nilsson T. Risk of hearing loss in relation to vibration-induced white fingers among workers using hand-held vibrating tools. To be submitted.
- IV. Pettersson H, Burström L, Nilsson T. Raynaud's phenomenon among men and women with noise-induced hearing loss in relation to vibration exposure. To be submitted.

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# **Background**

## **Exposures**

### ***Noise***

Sound or sound waves represent waves of pressure variations that propagate through solids, fluids, and gas. In this thesis only sound that propagate through air was studied. Sound can be quantified in terms of both its amplitude and frequency. The amplitude depends on the sound pressure described as Pascal (Pa). Amplitude is measured on the logarithmic decibel scale (dB) that describes the pressure changes relative to a reference pressure. Frequency is measured in Hertz (Hz) and is the number of changes in air pressure per second. The intensity of a sound is also called the sound pressure level (SPL). Sound waves set the ear drum in motion by way of pressure changes inside the ear, and the human ear is sensitive to sound depending on its frequency [1]. Noise is physically characterized as a complex sound signal with little or no periodicity. Psychologically, it is an uninformative, annoying and unwanted sound [2]. In this thesis I will use the term noise for the sound waves workers are exposed for. The SPL of noise can be attenuated with frequency filters that account for the ear's different sensitivities to various frequencies. Commonly used filters are the A-filter, for continuous noise, and C-filters, for impact noises. The A-filter varies with the ear's sensitivity to different frequencies, and the C-filter is adapted for impact noises that are so fast that the ear is not able to hear how high it really is. Noise measured with the A-filter is measured in dB(A) and with C-filter its measured in dB(C). Noise measurement follows international standards [3], and noise exposure limits for workers are described in the European directive on noise [4]. Exposure limits have been implemented in Swedish law and are defined as an 8-hour equivalent exposure of 85 dB(A). The 8-hour equivalent noise exposure is the average noise exposure for an 8-hour working day. There are also noise exposure limits on the peak sound pressure measured with the A-filter and C-filter. The peak exposure limit measured with the C-filter is set to 135 dB(C) and the maximum value limit measured with the A-filter is set to 115 dB(A) [5].

### ***Vibrations***

When an object moves around an equilibrium point, it is said to be vibrating. The magnitude of the vibration is commonly measured as the root mean square (rms) value of the accelerations in  $m/s^2$ . The frequency is measured in Hz, which describes the number of oscillations per second around the

equilibrium point. Vibrations affecting humans are commonly divided into whole-body vibrations and hand-arm vibrations (HAV). HAV affect the hands and arms and are often associated with the use of hand-held vibrating tools such as grinders, drills, and chainsaws. Measurements of HAV are defined by international standards [6, 7] and usually fall in the range of 5 to 1500 Hz. The body has different sensitivities to HAV depending on the vibration frequency, and the measurement of HAV is weighted to reflect these differences [6]. The European Union has issued a directive that limits the amount of HAV that workers can be exposed to [8]. When implemented into Swedish law, the 8-hour equivalent action value was set to  $2.5 \text{ m/s}^2$  and the maximum exposure limit was set to  $5 \text{ m/s}^2$  [9]. The 8-hour equivalent value is calculated as the average exposure to the duration and acceleration level during an 8-hour working day.

## **The ear**

The human ear can hear sounds in the frequency range of 20–20 000 Hz, with sound pressures ranging from 20  $\mu\text{Pa}$  to 20 Pa. These sound pressures are much lower than the atmospheric pressure, which is 101 000 Pa. The hearing threshold varies with frequency, and the human ear is most sensitive at 2000–5000 Hz, which includes frequencies used in speech [1].

The main function of the ear is to gather sounds from the surroundings and convert them into nerve signals that propagate into the brain for further analysis [1]. The external ear gathers sound waves that travel into the ear canal and activate the tympanic membrane (ear drum). The tympanic membrane is connected to three small bones called the malleus, incus, and stapes. The eardrum and these bones (the ossicles) constitute the middle ear. The role of the middle ear is to transmit the sound waves into the fluid-filled cochlea through mechanical vibration of the ossicles [1, 10]. The stapedius muscle is connected to the stapes, and noise exposure can contract the stapedius muscle (acoustic reflex) causing stiffness in the ossicle chain. This dampens the oscillations travelling through the middle ear especially at low frequencies [1].

The function of the inner ear is to transform the oscillations from the ossicles into nerve signals inside the cochlea [1]. Vibrating ossicles transmit the oscillations to the oval window, which is attached to the fluid-filled cochlea. When the oval window oscillates, it causes pressure changes inside the cochlea. These pressure changes travel through the three fluid-filled cavities inside the cochlea causing oscillation of the hair cells inside the middle cavity (scala media). The hair cells consist of a cell body that is attached at one end to a sensory nerve ending and at the other end to small tubes (the

stereocilia). Changes in pressure will cause the hair cells to move relative to the tectorial membrane located above the hair cells and make the stereocilia bend against it. This causes a hyperpolarisation of the hair cell followed by a depolarisation. A neuroactive substance will then be released into the hair cell that causes the hair cell to transmit a signal to the hair cell's sensory nerve ending and onward to the cochlear nerve [1]. There is one row of inner hair cells and three rows of outer hair cells, and all four rows of hair cells are located throughout the entire cochlea. There are about 3500 inner hair cells and 12 000 outer hair cells [1]. The hair cells that respond to high-frequency sounds are located at the basal end of the cochlea where the oval window is located. At the opposite, or apical end, are hair cells that respond to low-frequency sounds [1]. The functions of the inner and outer hair cells are not fully understood. The majority of inner hair cells sends nerve signals to the cochlear nerve and are connected to more sensory nerves than outer hair cells. The outer hair cells have a majority of connections that receives nerve signals from the cochlear nerve and the outer hair cells might control the sensitivity of the ear [1].

### ***Regulation of the blood supply to the cochlea***

The cochlear artery (spiral modiolar artery) is the main blood vessel of the cochlea. The smooth muscles that control the blood flow inside the blood vessels throughout the body are regulated by the sympathetic nervous system (SNS), part of the autonomic nervous system (ANS) [10, 11]. The SNS in the cochlea also provides connections to the cochlear nerve fibres and the hair cells of the cochlea [12, 13], and the SNS is believed to control the auto-regulation of cochlear blood flow [14-16].

### **Autonomic nervous system**

The nervous system allows the human body to respond to its external and internal stimuli [10]. The nervous system consists of two major independent systems, the central and peripheral systems that interact with each other. The central nervous system consists of the brain and the spinal cord, and the peripheral nervous system consists of nerves that connect the central nervous system with the muscles, glands, and sensory organs. Within the peripheral nervous system is the ANS whose main function is to control and maintain a stable environment within the body [10]. The neurons of the ANS innervate the smooth muscles, which are part of the blood vessels. It also innervates the heart, glands, and the gastrointestinal tract [11]. The ANS itself can be further divided into two subsystems known as the SNS and the parasympathetic nervous system (PNS). The SNS and PNS interact and coordinate their activities with each other. The SNS and PNS can have

opposite effects on an organ so that if one system increases in activity then the other system usually decreases in activity [10, 11]. Not all organs connected to the ANS are innervated by both the SNS and PNS. For example, most blood vessels have smooth muscles that are only innervated by the SNS. The SNS can regulate the blood flow and cause restriction of blood flow inside the blood vessels through the process of vasoconstriction [10]. Smooth muscles and glands in the skin are also only innervated by the SNS [10].

### **Regulation of the blood supply to the fingers**

The velocity of fluid in a blood vessel follows Poiseuille's Law, which states that the velocity of a fluid in a cylinder depends on three factors [17]. In the case of blood flow, these factors are the pressure of the blood in the vessel (the perfusion pressure), the radius of the capillary (the luminal radius), and the blood viscosity. Both the perfusion pressure and the luminal radius are controlled by the SNS [17].

The blood in the hands and fingers is transported by the main palmar arteries, the ulnar and radial arteries, and the relative contribution of these two arteries varies between individuals. Both the ulnar and radial arteries are connected to the deep and superficial palmar arteries. Blood in the little, ring, and middle fingers is supplied by the superficial arteries that are mainly supplied by the ulnar artery. The thumb and index finger get their blood supply from the deep arteries, which are supplied by the radial artery. The radius of the arteries in the skin is controlled by the sympathetic vasoconstriction or vasodilator nerves. Only sympathetic vasoconstrictor nerves are part of the hairless skin on the fingers [17].

The blood supply to the fingers can be constricted referred to as Raynaud's phenomenon, which is an overreaction to cold that causes vasoconstriction of the peripheral blood vessels of the fingers [17, 18]. The vasoconstriction in the fingers causes colour changes to the skin such as finger blanching or white fingers (WF). The finger blanching usually occurs when the body is cooled in cold, windy, or damp conditions or when the body experiences emotional stress. Low oxygen levels in the skin will turn it blue then red when the blood eventually returns [17, 18]. The occurrence of Raynaud's phenomenon is more common in colder climates [19-21] and is more common among women than men. The first finger blanching attacks usually occur before the age of 45. Both hands are usually affected and in some cases also the toes and, to a lesser degree, the nose and ears [18]. Raynaud's phenomenon is commonly classified as either primary or secondary Raynaud's phenomenon. Primary Raynaud's phenomenon is idiopathic with no apparent cause [17] and may have a genetic component. Secondary

Raynaud's phenomenon is caused by several factors, including trauma from exposure to HAV, frostbite, diseases such as diabetes, scleroderma, and rheumatoid arthritis, the use of hypertension drugs, and the occurrence of carpal tunnel syndrome. [17, 18].

## **Effects of exposures**

### ***Noise-induced hearing loss***

Intensive noise exposure may at first cause a temporary threshold shift (TTS) in hearing. If exposure to high levels of noise continues for a longer period, the ear can develop permanent noise-induced hearing loss [1, 22]. TTS in hearing and noise-induced hearing loss are often accompanied by tinnitus, a ringing sound in the ears, that itself can be temporary or permanent. The risk for TTS in hearing or noise-induced hearing loss depends on the frequency distribution, level, and duration of the noise as well as individual susceptibility. TTS in hearing and noise-induced hearing loss usually occur in the range of 3000 –6000 Hz with 4000 Hz being the most commonly affected frequency [1, 22].

### ***Mechanism behind noise-induced hearing loss***

The mechanism behind noise-induced hearing loss is still not fully understood. Hair cell damage might come from mechanical injury such as that suffered from firing a rifle. Damage of hair cells might also come from metabolic changes or reduced blood supply in the cochlea from continuous noise exposure [2, 14, 16]. Impact noise with an intense sound level can cause a pressure increase in the cochlear fluid that can break the stereocilia or hair cells and cause noise-induced hearing loss [1, 17]. Oxygen metabolism in a normally functioning cochlea produces reactive oxygen species (ROS) such as free radicals, oxygen ions, and peroxides that are important for cell signalling [2]. Excessive noise exposure can cause metabolic changes that lead to an overproduction of ROS. Animal studies support the hypothesis that ROS, and free radicals in particular, can damage cells in the cochlea and lead to hearing loss [2, 14]. Noise exposure also increases the demand for oxygen and glucose in the cochlea cells [16] while at the same time these metabolic changes in the cochlea from noise exposure may cause a reduction in the blood supply to the cochlea [2, 14, 16, 23]. Less intense noise can still cause mild metabolic changes in the cochlea that can lead to a TTS in hearing [1, 2].

### ***Effect of noise on the SNS connected to the cochlea***

How noise exposure may affect the SNS nerves connected to the cochlea is not clear. Because the SNS nerves innervates the cochlea and provides connections to the hair cells and auditory nerve, it has been suggested that the SNS could be stimulated by noise exposure [12, 13, 24]. In some animal studies, the SNS connection to the cochlea has been severed prior to noise exposure but whether this provides a protective effect on hearing is not conclusive [24-27]. The noise exposure may trigger SNS activity that causes a vasoconstriction in the cochlea, and this vasoconstriction might be harmful to the hair cells. By removing the influence of the SNS on the cochlea, the vasoconstriction from an activated SNS might be avoided [24, 27]. However, Wada et al. [25] electrically stimulated the SNS in the cochlea and found a protective effect of the stimulated SNS during moderate-intensity noise exposure.

### ***Interaction of noise exposure and age on noise-induced hearing loss***

Age-related hearing loss must be considered in any analysis of noise exposures effect on hearing. The interaction between noise exposure and aging is complicated, but it might be an additive effect. Age-related hearing loss increases with age, but the effects of noise-induced hearing loss begin to decrease after about 10–12 years of exposure. Thus noise-induced hearing loss do not increase to the same extent in older persons as younger persons because older persons already have age-related hearing loss. Age will have a limited effect, however, on noise-induced hearing loss for frequencies that have already suffered severe hearing loss [17, 28]. Hair cell death in the cochlea increases with age. Higher frequencies are affected first, but hair cell death will spread and eventually affect all frequencies to some degree. Other parts of the hearing apparatus might also be affected with age, including the auditory nerve, and there are also likely to be losses in cognitive functions. [17, 28].

### ***Hand-arm vibration syndrome***

The use of hand-held vibrating tools for long durations can cause injuries to the neurological, vascular, and musculoskeletal systems. These injuries are collectively known as hand-arm vibration syndrome (HAVS) [17, 18]. The vascular and sensorineural components in HAVS can develop independently, but they usually occur simultaneously. Neural damage causes reduced sensation in the form of numbness and reduced sensitivity to temperature and pressure but can also lead to tingling sensations, pain, and

hypersensitivity [17, 18]. The most common problem associated with HAVS is difficulty in enduring cold conditions. Cold can provoke, or act as a confounder for, the vascular constriction that leads to finger blanching. The vascular component of HAVS is a form of secondary Raynaud's phenomenon that is referred to as vibration-induced white fingers (VWF). Workers who have long-term exposures to hand-held vibrating tools may experience symptoms in the form of episodic attacks with clearly marked finger-blanching areas. The attacks are provoked by cooling of the body from cold produced by windy or damp conditions as well as by exposure to vibrations and emotional stress. The first symptoms occur in the outer phalanges and may expand towards the phalanges closer to the palm. The vascular and sensorineural components of HAVS are classified separately in the Stockholm workshop scale (SWS) [17, 29, 30].

As mentioned previously, the mechanisms behind the restricted blood supply in the capillaries are related to Poiseuille's Law that states that blood flow depends upon the perfusion pressure, the luminal radius, and the blood viscosity. Both the perfusion pressure and the luminal radius are controlled by the SNS [17].

The restriction of the blood supply during bouts of VWF could be from an unbalanced ANS in which the SNS is overstimulated by vibrations [31]. Long-term exposure to HAV might decrease PNS activity [32], and patients with HAVS also have lower PNS activity [33]. There are also studies that suggest that patients with HAVS have a more sensitive SNS [34, 35].

Studies have shown that vibrations of different frequencies and continuous versus intermittent exposures have differing effects on the blood flow in the fingers [36-38]. Vibrations have also been shown to alter the blood flow in the non-exposed hand [38, 39] as well as cause restriction in blood supply to the toes. A commonly suggested mechanism for this is that stimulation of the SNS in the exposed hand causes a global restriction in blood supply to all of the extremities [39-41], and studies on VWF patients have found pathological changes in the toes and fingers [42-44].

Other sources leading to abnormal function of vasodilators that increase blood flow in the blood vessels and vasoconstriction reflexes in the fingers are injuries caused by trauma to the nerves in the hand, Dupuytren's disease, and carpal tunnel syndrome [17].

### ***Effects on hearing from combined exposure to HAV and noise***

Vibration exposure occurs in a number of industries such as manufacturing, construction, and engineering. Many workers in these industries use hand-held vibrating machines and are, therefore, exposed to hazardous noise and HAV levels. Combined exposure to HAV and noise is common for workers using hand-held vibrating tools such as grinders, hammers, and chainsaws. In the Swedish directive on noise there is a recommendation for using hearing protection at lower noise levels when the noise occurs along with exposure to HAV. In Swedish law there are no action or limit values for noise exposure that depend on the level of HAV [5].

Vibration as an interacting factor in noise-induced hearing loss is supported by studies on workers with VWF. The risk of noise-induced hearing loss among workers with VWF is increased compared to workers with similar age and noise exposure but without VWF [45-49].

There are few studies available on the combined exposure to HAV and noise and the relationship of this combination to noise-induced hearing loss. Experimental animal studies have found that exposure to noise and HAV increases noise-induced hearing loss compared to exposure to noise alone [50]. Experimental studies on humans have had conflicting results. Zhu et al. found an increased TTS in hearing after combined exposure to noise and HAV as opposed to noise-only exposure, but Miyakita et al. did not find any such differences [51, 52]. Longitudinal studies on combined exposure to HAV and noise have not found any increased risk of noise-induced hearing loss when HAV were present along with noise exposure [45, 53].

As mentioned earlier, VWF might increase the risk of noise-induced hearing loss. WF that occurs for reasons other than exposure to vibrations might also indicate an increased risk for noise-induced hearing loss. Palmer et al. [54] found that there was an increased risk of hearing loss for men and women with finger blanching who had not been extensively exposed to HAV or noise. Raynaud's phenomenon is more common among women than men and women might, therefore, be at a higher risk for hearing loss [18, 55-57].

Workers with VWF might have an increased risk of noise-induced hearing loss. What causes the possible interacting effect of HAV on noise-induced hearing loss has not been fully explored. One possible cause could be that the SNS is involved. Vibrations from hand-held vibrating tools might activate SNS in the fingers, and the SNS could then restrict blood supply to the

fingers, as well as to the cochlea, resulting in noise-induced hearing loss [47, 58].

# Aims

The overall aim of this thesis was to explore how hand-arm vibration interacts with noise-induced hearing loss. The specific aims were:

- To study the short-term effect of hand-arm vibration and noise exposure, separately or combined, on temporary threshold shifts in hearing (Paper I).
- To examine the possible association between long-term combined exposure to hand-arm vibration and noise in relation to the risk of noise-induced hearing loss (Paper II).
- To examine the risk of noise-induced hearing loss for workers with VWF who use hand-held vibrating machines (Paper III).
- To study the occurrence of Raynaud's phenomenon among men and women with noise-induced hearing loss (Paper IV).
- To examine the possible modifying effect of gender on noise-induced hearing loss (Paper I and IV).

# **Data collection and Methods**

## **Study design**

An experimental design was used for Paper I. The participants were exposed to three different conditions in a randomized order. The three exposure conditions were noise, HAV, and a combination of HAV and noise. The outcome was a TTS in hearing for the right ear. The hearing threshold was measured just before and after the exposures.

Papers II and III were cohort studies. The outcomes from both of these studies were noise-induced hearing loss among workers at a heavy engineering production workshop that constructed paper and pulp-mill machinery in Sweden. Most of the workers in the cohort were welders and grinders. The focus of Paper II was on the risk of noise-induced hearing loss in the left ear after exposure to HAV and noise from hand-held vibrating tools. Paper III examined the risk of noise-induced hearing loss in both ears for workers with VWF in either hand that uses hand-held vibrating machines.

Paper IV was a questionnaire study. The occurrence of Raynaud's phenomenon and the exposure to HAV was examined among men and women with noise-induced hearing loss.

## **Subjects**

In Paper I, 22 healthy subjects (11 men and 11 women) were recruited through an advertisement. Their mean age was 22 years (range 18–31).

All participants in Paper II and III were men and were recruited from a Swedish cohort that started in 1987 and were followed-up in 1992, 1997, 2002, and 2008. In Paper II the participants were 18-64 years, 20 – 69 years in Paper III. Each participant in Paper II had a record of both hearing status and specified use of hand-held vibrating machines for at least one of the follow-up years. The summarized years with completed records (hearing status and use of hand-held vibrating machines) were 1077 for the 189 participants who met the inclusion criteria in Paper II. To be included in Paper III, participants must have used hand-held vibrating tools. All participants had a record of hearing status, the duration and acceleration of hand-held vibrating machines, categorized in terms of VWF symptoms according to the SWS, and smoking habits for at least one of the follow-up

years. A total of 184 male workers had a completed record with 1066 summarized years.

In Paper IV, all 342 men and women of the study sample had reported and received financial benefits from AFA insurance in Sweden for work-related noise-induced hearing loss between 1995 and 2004. They were all ages between 18 and 55 years. The men were randomly chosen but because there were only a few women who had a confirmed work-related noise-induced hearing loss, we chose to invite all such women for Paper IV. Eighteen of the study participants' addresses could not be found so the final study group consisted of 324 participants (246 men and 78 women) who received a questionnaire. If they did not answer the first time, a reminder was sent to them.

### **Definition of noise-induced hearing loss and audiometric measurement**

In Paper I the fixed frequency von Bekesy method (up-and-down method) with pure tone for 30s per frequency was used for all audiometric measurements. The average value of the 30s measurements at each frequency was used as the hearing acuity threshold. The audiometer was set up in a computer based system (Diagnostic audiometer model AD229) with audiometric headset (TDH39) in a semi-isolated chamber at room temperature. The background noise level were according to ISO 8253-1 [59]. Eleven frequencies from 500 Hz up to 8000 Hz were tested for 30 seconds at each frequency. All subjects had hearing acuity thresholds of at most 10 dB hearing threshold level (dBHL) for each frequency and in both ears. For the analysis of TTS in hearing only 1000, 4000, and 8000 Hz was used. The subjects' hearing thresholds at 1000, 4000, and 8000 Hz were measured immediately before and directly after the exposures. The hearing thresholds were then measured at 0.5, 3, 5.5, 8, 10.5, 13, 20, and 30 minutes after the exposure had ended. The TTS in hearing was defined as the hearing acuity threshold after exposure subtracted with the hearing acuity threshold before exposure. Before each exposure the subjects were asked not to be exposed to loud music or HAV and to avoid tobacco and caffeine. There were at least 24 hours between each exposure so that each subject's hearing could be fully recovered.

For Paper II and III, 476 audiograms were obtained from 1987 to 2008 in cooperation with the Occupational Health Service and County Council's central archive in Härnösand. Screening of pure-tone audiometry was performed in a soundproof booth at the heavy engineering workshop at which the study participants worked. The shortened ascending method was

used in 5 dB steps and the threshold was determined by two out of three responses [59]. The same operator educated in audiometry was used from 2001 to 2008.

The audiograms for the left and right ear were classified as having normal hearing or noise-induced hearing loss by the Klockhoff method [60]. The definition of normal hearing by this method was hearing threshold levels that did not exceed 30 dB at 500 Hz and 25 dB at 1000, 2000, 3000, 4000, and 6000 Hz. If the noise-induced hearing loss exceeds one or more of these limits then the ear was classified as having noise-induced hearing loss. Hearing losses not related to age or noise exposure were also classified by the Klockhoff method and were excluded in these studies.

In Paper IV all participant had a work-related noise-induced hearing loss defined and graded by AFA insurance. Information was gathered on their degree of disability from AFA insurance.

### **Experimental exposure**

All subjects in Paper I had good hearing in both ears and normal thermal and tactile perceptions in both hands. The subjects completed a questionnaire concerning their previous experience of loud noise and HAV levels, general health, medication, and basic individual data.

The exposures lasted for 20 min and for all exposure settings the subjects were sitting down and held two handles in a semi-isolated chamber. They also wore headphones for noise exposures or hearing protectors when only vibrations were used. Both noise and vibrations were recorded from an angular grinder that is typically used in industry (Hitachi G23UB, 6,600 rpm). HAV exposures came from the two handles in an up down direction with an acceleration of 6.7 m/s<sup>2</sup> rms, which corresponds to an eight-hour equivalent acceleration exposure of 1.4 m/s<sup>2</sup>. The noise exposure level inside the headphones was 99 dB(A) and corresponded to an eight-hour equivalent noise exposure of 85 dB(A).

### **Exposure assessment**

In Papers II and III, the lifetime use or cumulative duration of hand-held vibrating tools by each participant was collected from a questionnaire distributed during each follow-up period. The participants subjectively estimated how many minutes each working day they used different hand-held vibrating machines. They also specified for how many months and years they had used each vibrating machine. The cumulative time each participant

had used hand-held vibrating machines was then calculated in hours. On average the mean duration of the use of hand-held vibrating tools had decreased from 108 min in 1987 down to 52 min in 2008.

The vibration acceleration for 306 hand-held vibrating tools in total were randomly selected and measured during the 21-year follow up study. For every follow up period, 50–90% of all the hand-held vibrating tools were gathered and measured under normal working conditions. Hammers and grinders were the most commonly used type of vibrating tools. The mean frequency-weighted acceleration decreased between 1987 and 2008 for both hammers and grinders. In 1987 the mean frequency-weighted acceleration for grinders was  $11.0 \text{ m/s}^2$  and decreased to  $7.6 \text{ m/s}^2$  in 2008. During the same period, the mean frequency-weighted acceleration for hammers decreased from  $5.8$  to  $4.5 \text{ m/s}^2$ .

Noise exposure measurements were gathered in 2008 but were lacking from earlier follow-up periods. Personal noise exposure measurements were taken from a selection of workers (welders/grinders or supervisors) at the company ( $n = 15$ ). The randomly selected hammers and grinders in 2008 ( $n = 78$ ) had a mean noise exposure of 95 dB(A) with a range of 77–109 dB(A). The background noise exposure level at the company in 2008 was 85 dB(A) with a range of 75–88 dB(A). The calculated average eight-hour equivalent noise level in 2008 was 88 dB(A) with a range of 75–99 dB(A).

Some of the hammer and grinder models used at the company in 1987 and 2008 had been measured for their noise emission levels by the manufacturers of these machines. The mean noise emission levels from hammer and grinder models used at the company increased from 76 dB(A) in 1987 up to 79 dB(A) in 2008.

Participants in Paper IV subjectively assessed their exposures to noise and HAV at the time when they discovered they had noise-induced hearing loss. They estimated how many minutes of their working day they used hand-held vibrating machines or they were in a noisy environment where they had to raise their voice to be heard. The participants were also asked for how many years they had worked in the same occupation or with hand-held vibrating machines. The cumulative noise exposure durations were calculated by multiplying the minutes per day in a noisy environment by 220 workdays each year and multiplying that number by the number of years they had worked at the current noisy occupation. The cumulative HAV duration exposure was calculated by multiplying the total number of years they had used hand-held vibrating machines by 220 workdays each year and by the number of minutes each day they were exposed to HAV.

## **Primary and secondary Raynaud's phenomenon assessment**

Papers II and III were based on a Swedish cohort, and a questionnaire was distributed to each participant at each follow-up period. The questionnaire included questions on the symptoms of VWF including the question: "*Do you have white (pale) fingers of the type that appears when exposed to damp and cold weather?*" If participants answered 'yes' to this question, they were also asked to define which phalanges of both hands were affected. From the information provided on the hand diagrams, both hands were classified according to the vascular part of the SWS [17, 29].

In Paper IV the questionnaire also included the question "*Do you have white (pale) fingers of the type that appears when exposed to damp and cold weather?*" Participants who answered 'yes' to this question were classified as having WF. To be classified as having possible primary or secondary Raynaud's phenomenon, the participant must not have had frostbite on either hand, carpal tunnel syndrome, or hospitalization following an accident. Nor could they have had sicknesses or discomfort relating to blood circulation such as diabetes, hypertension, heart disease or rheumatic diseases. They could not have used any medication for migraines or heart or cardiovascular problems. Those who did not use any hand-held vibrating machines and who had WF with no apparent cause were classified as possibly having primary Raynaud's phenomenon. Participants who used hand-held vibrating machines and had WF with no apparent cause other than HAV exposure were classified as possibly having secondary Raynaud's phenomenon.

Participants with WF specified for how many years they experienced discomfort with WF, all participant specified if they smoked or used snuff daily or alcohol weekly in the questionnaire. Women were also asked if they had been pregnant or used hormones at the time when they first discovered their noise-induced hearing loss.

## **Statistics**

All analyses were performed with PASW statistics software version 18.0 (SPSS Inc., Chicago, Illinois) or IBM SPSS Statistics for Windows, Version 20.0.

In Paper I the TTS in hearing was calculated by subtracting the hearing acuity threshold level after exposure with the hearing acuity threshold level before the exposure to noise of 1000, 4000, and 8000 Hz. The use of Q-Q plots and histograms allowed the determination of whether the post-

exposure hearing threshold measurement had a normal distribution. The TTS in hearing after exposure to HAV, noise, and a combination of both was tested with paired Student's t-test. An independent Student's t-test was used to determine if there were any statistically significant differences in TTS after the exposure in relation to gender. Both the paired and independent t-tests were adjusted according to Holm's method.

To further study how exposure, time, and the interaction between them affected TTS in hearing, the repeated measurement ANOVA method was used. This method included all eight post-exposure hearing threshold measurements. Mauchly's sphericity test was used to determine if sphericity was violated. If sphericity was violated, the Huynh-Feldt correction was used. TTS in relation to gender was also analysed with repeated measurement ANOVA by study exposure, time, gender, and the interaction between them. For analysis with paired and independent t-tests as well as repeated measurement ANOVA, a  $p$  value of  $<0.05$  was considered significant.

In Paper II and III, the HAV and noise exposures from hand-held vibrating machines were estimated by the duration and acceleration from these vibrating machines. The noise exposure level was not included because there was a lack of noise exposure level measurements prior to 2008. The mean noise exposure difference between the use of hand-held vibrating machines and the background level indicate a more hazardous noise exposure level from the vibrating machines. The noise exposure was, therefore, estimated as the lifetime use of hand-held vibrating tools.

In Paper II three exposure estimates were calculated. The first estimate was the lifetime exposure to HAV from hand-held vibrating machines for each participant. This value was calculated as the cumulative duration of exposure to HAV (Time). By multiplying cumulative duration of exposure to HAV with acceleration, the possible effect of HAV on noise-induced hearing loss could be studied further. The second exposure estimate was the cumulative duration of exposure to HAV multiplied by the acceleration (TimeAcc), and the third estimate was the cumulative duration of exposure to HAV multiplied by the square of the acceleration (TimeAcc2). Time and TimeAcc were also used in Paper III.

Both Paper II and III included the binary outcome of hearing status and used logistic regression with the general estimation equation because there were repeated measurements in the data. The first order autoregressive correlation structure was used because the data collected within a short period of time between data collections were assumed to be more related than data collected over a wider time span.

In Paper II the three exposure estimates and age (in years) were the explanatory variables. The exposure measurements were both continuous and divided into exposure quartiles. The number of years each participant had normal hearing or noise-induced hearing loss were grouped into exposure quartiles for each of the three exposure estimates. Further analysis of the continuous exposure estimates was performed by dividing the mean value of TimeAcc and TimeAcc2 by the mean value of Time. The calculated ratios were then used to normalize the exposure data by dividing each individual's exposure data for TimeAcc and TimeAcc2 with the calculated ratio. The result was the odds ratios (OR) with a 95% confidence interval (95% CI) for the risk of noise-induced hearing loss with increased exposure to hand-held vibrating machines (exposure estimates) adjusted for age. In the analysis with exposure quartiles the first (lowest) exposure quartile was the reference.

Three different analyses were performed for Paper III. The first analysis was on the left ear and left hand, the second analysis was on the right ear and right hand, and the third analysis was on the ear with the worst hearing status and the hand with worst degree of VWF according to the SWS. For the left ear and hand there were 146 participants with 655 years of complete records (hearing status, categorized VWF, exposure estimates, and smoking habits), for the right ear and hand there were 174 participants with 588 years of complete records, and for the ear with worst hearing status and the hand with worst SWS categorization there were 184 participants with 1066 years of complete records.

In Paper III the explanatory variables were categorized VWF according to the SWS, exposure estimates (Time, TimeAcc), age, and smoking habits. Each hand was categorized as normal or as having VWF. Both Time and TimeAcc were divided into a higher and lower exposure group. Age was divided into those 40 years or older and those younger than 40 years old. Smoking habits were grouped into smokers and non-smokers. The analysis included main effects and interactions between the explanatory variables, and separate analyses were performed for Time and TimeAcc. Only two-way and main effects were analysed because there were not enough data for a three- or four-way analysis. Interactions with a  $p$ -value of less than 0.1 were removed through regression analysis. All main effects that were significant ( $p$ -value above 0.05) or part of an interaction effect were kept, and the rest of the main effects were removed. The result of this analysis was the OR with 95% CI for the risk of noise-induced hearing loss for workers with VWF compared to workers without VWF.

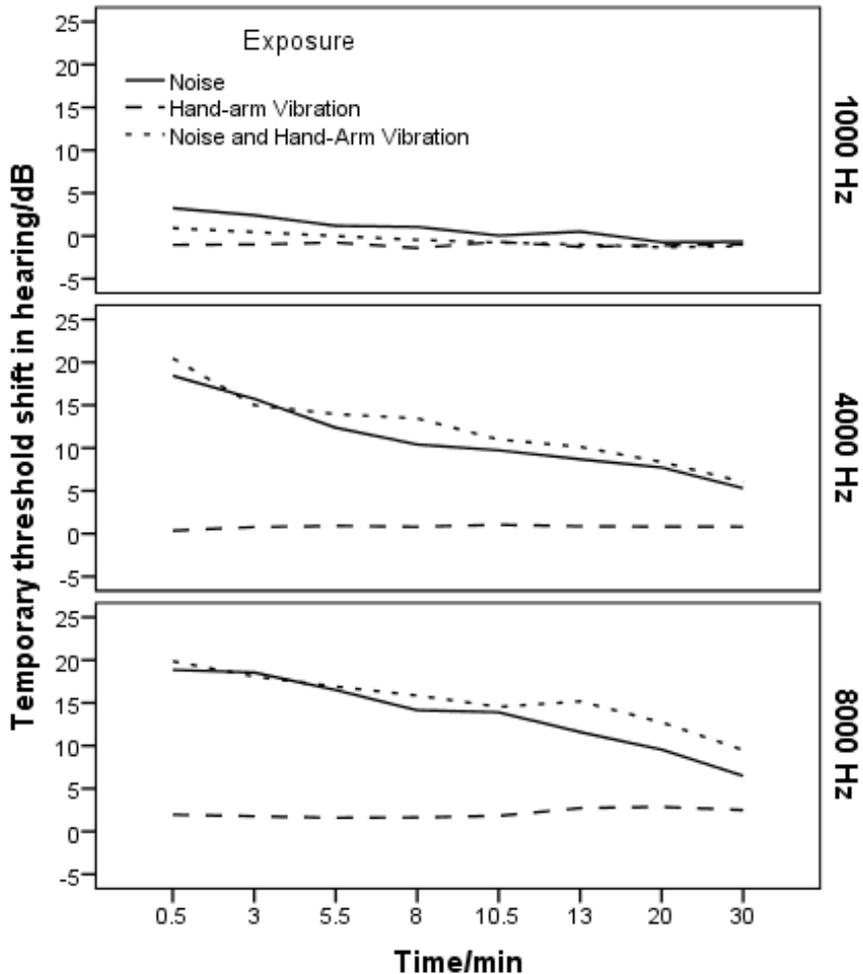
In Paper IV the prevalence of WF and possible primary and secondary Raynaud's phenomenon among men and women was calculated for those who used or did not use hand-held vibrating machines. The relative risk (RR) with 95% CI of WF was calculated as the prevalence of WF among those exposed to HAV divided by the prevalence of WF among those not exposed to HAV.

# Results

## Paper I

HAV exposure alone did not significantly change the TTS in hearing at the measured frequencies of 1000, 4000, or 8000 Hz ( $p = 0.66 - 0.97$ ) (Figure 1). The noise exposure alone increased the TTS in hearing at 1000 Hz significantly more than after only HAV exposure ( $p < 0.041$ ). There was no significant difference between the TTS in hearing at 1000 Hz after noise exposure compared to the combination of exposure to HAV and noise ( $p = 0.11$ ).

The mean values of TTS in hearing were very similar after exposure to only noise and after combined exposure to HAV and noise, at the measured frequencies 4000 and 8000 Hz (Figure 1). Exposure to noise with or without HAV exposure created a larger mean TTS in hearing compared to after only HAV exposure, at 4000 and 8000 Hz ( $p < 0.001$ ) (Figure 1). The TTS in hearing did not differ significantly after combined exposure to HAV and noise compared to exposure to only noise, at 4000 and 8000 Hz ( $p = 0.12 - 0.18$ ).



**Figure 1.** The mean TTS in hearing after exposure to hand-arm vibration (HAV) alone or to noise or a combination of both at 1000, 4000, and 8000 Hz.

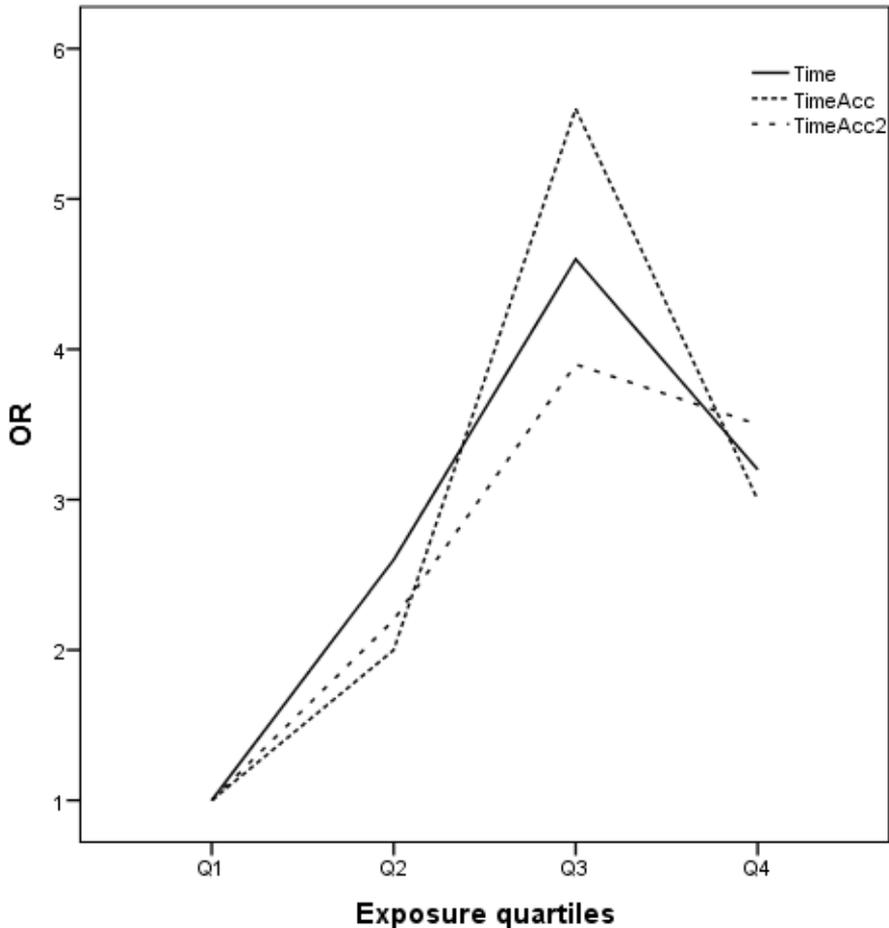
For both men and women, the TTS in hearing after HAV exposure alone was close to 0 dB and was constant over time at 1000, 4000, and 8000 Hz.

After exposure to noise with or without HAV, the TTS in hearing was not significantly different in relation to gender ( $p = 0.15\text{--}0.92$ ) at any of the test frequencies.

## **Paper II**

With an accumulation of 1000 hours of lifetime exposure to hand-held vibrating machines, the OR (95% CI) for noise-induced hearing loss was 1.12 (1.02–1.23). The OR (95% CI) for noise-induced hearing loss for every 1000-unit increase in TimeAcc and TimeAcc2 were 1.01 (1.00–1.03) and 1.00 (1.00–1.00), respectively. Normalized TimeAcc and TimeAcc2 had an OR (95% CI) for noise-induced hearing loss of 1.09 (1.00–1.19) and 1.08 (1.00–1.16) for every 1000-unit increase in exposure.

Analysis with exposure quartiles found an increased OR for noise-induced hearing loss with increasing exposure quartile for all three exposure estimates. At the fourth quartile the OR decreased compared to the third quartile for all exposure estimates (Figure 2).



**Figure 2.** The odds ratios (OR) for the risk of noise-induced hearing loss among workers exposed to hand-held vibrating machines grouped into exposure quartiles (Q1–4) adjusted for age. The exposure estimates are the lifetime exposure to HAV from hand-held vibrating machines (Time), the exposure estimate Time multiplied by the acceleration (TimeAcc), or Time multiplied by the square of the acceleration (TimeAcc2).

The only significantly increased risk of noise-induced hearing loss at the second exposure quartile was for Time with an OR (95% CI) of 2.6 (1.0-6.9). For the third exposure quartile the OR from all three exposure estimates were 3.9 – 5.6 with a 95% CI greater than one. At the fourth quartile the OR for all three exposure estimates decreased to 3.0 – 3.5 with a 95% CI greater than one (Table 1).

**Table 1.** The risk of noise-induced hearing loss expressed as the odds ratio (OR) with a 95% confidence interval (95% CI) for the three exposure estimates grouped into exposure quartiles (Q1-4) adjusted for age. The exposure estimates are the lifetime exposure to HAV from hand-held vibrating machines (Time), the exposure estimate Time multiplied by the acceleration (TimeAcc), and Time multiplied by the square of the acceleration (TimeAcc2).

| <b>Exposure Estimates</b> | <b>Exposure Quartiles</b> |               |                  |               |
|---------------------------|---------------------------|---------------|------------------|---------------|
|                           | <b>Q1</b>                 | <b>Q2</b>     | <b>Q3</b>        | <b>Q4</b>     |
| <b>OR (95% CI)</b>        |                           |               |                  |               |
| Time                      | 1.0                       | 2.6 (1.0-6.9) | 4.6 (1.9 – 11.0) | 3.2 (1.4-7.5) |
| TimeAcc                   | 1.0                       | 2.0 (0.7-5.1) | 5.6 (2.2 – 14.0) | 3.0 (1.2-7.4) |
| TimeAcc2                  | 1.0                       | 2.2 (0.9-5.4) | 3.9 (1.6 – 9.1)  | 3.5 (1.4-8.7) |

### **Paper III**

The OR (95% CI) for the risk of noise-induced hearing loss in the right ear among workers with VWF in the right hand compared to workers without VWF in the right hand was 2.3 (1.4–3.9) when the exposure estimate Time was included in the analysis. The analysis with the exposure estimate TimeAcc found an OR (95% CI) for noise-induced hearing loss in the right ear for workers with VWF in their right hand of 2.2 (1.3–3.7).

In the analysis of the risk of noise-induced hearing loss in the left ear for workers with VWF in the left hand, the explanatory variables Time and TimeAcc interacted with categorized VWF. Workers in the low-exposure group of the explanatory variable Time who had VWF in the left hand had an OR (95% CI) of 4.7 (1.4–15.7) for noise-induced hearing loss compared to workers without VWF in the left hand. In the low-exposure group using TimeAcc, the OR (95% CI) for noise-induced hearing loss in the left ear for workers with VWF in the left hand was 7.1 (1.8–27.6). Workers with VWF in the left hand in the high-exposure group using Time had an OR (95% CI) of 0.9 (0.6–1.6) and when using TimeAcc they had an OR (95% CI) of 0.9 (0.5–1.6) for the risk of noise-induced hearing loss.

The risk of noise-induced hearing loss for the ear with worst hearing status was not significantly increased for workers with VWF on the hand with worst SWS categorization compared to workers without VWF.

## Paper IV

In the study group of men and women with noise-induced hearing loss, 133 answered the questionnaire (participation rate 41%). Among those who answered there were 94 men and 39 women. One hundred twenty (84 men and 35 women) of the participants specified if they did or did not have WF and if they had used any hand-held vibrating machines. Of these 120 men and women, 41% had used hand-held vibrating machines (Table 2) and 18% used these types of machines for at least 2 hours each working day. The most commonly used hand-held vibrating tools among the participants were grinders, drills, and screwdrivers. The most typical occupations among the participants were teachers (15), military personnel (13), and welders (4).

There were 29 cases of WF (Table 2). The mean ages for participants in the four groups were 40–43 years and the mean noise exposure durations varied from 9400 to 12 000 hours. A higher prevalence of WF was observed among those exposed to HAV compared to those not exposed to HAV. Participants with WF had on average 11 years of WF symptoms while HAV-exposed participants had on average 6 years of WF symptoms (Table 2).

**Table 2.** The prevalence (%) of white fingers (WF) among participants exposed and not exposed to hand-arm vibration (HAV), and the mean (SD) age, WF symptoms in years, and duration of noise exposure.

|          | Age |           | WF      | WF        | Noise                   |
|----------|-----|-----------|---------|-----------|-------------------------|
|          | No. | Mean (SD) | No. (%) | Mean (SD) | duration**<br>Mean (SD) |
| Exposure |     |           |         |           |                         |
| HAV      | 49  | 41 (10)   | 18 (37) | 6 (8)     | 10 (13)                 |
| No HAV   | 71  | 41 (9)    | 11 (15) | 12 (14)   | 10 (11)                 |
| Symptom  |     |           |         |           |                         |
| WF       | 29  | 43 (11)   | -       | 11 (11)   | 12 (15)                 |
| No WF    | 91  | 40 (9)    | -       | -         | 9.4 (11)                |

\*in years, \*\*in 1000 hours.

Among participants who did not use hand-held vibrating machines, the prevalence of WF was 20% for men and 10% for women (Table 3). The prevalence for possible primary Raynaud's phenomenon was 13% for men and 6% for women (Table 3). For participants using hand-held vibrating

machines, the prevalence of WF was 34% for men and 20% were classified as possible secondary Raynaud's phenomenon. Three out of the five women who had used hand-held vibrating machines also had WF and one had possible secondary Raynaud's phenomenon (Table 3).

**Table 3.** The prevalence (%) of white fingers (WF) and possible primary and secondary Raynaud's phenomenon among men and women divided into those who were exposed to HAV and those who were not.

| <b>Exposure</b> |           | <b>Men</b> |            | <b>Women</b> |            | <b>Both</b> |            |
|-----------------|-----------|------------|------------|--------------|------------|-------------|------------|
|                 |           | <b>NO.</b> | <b>(%)</b> | <b>No.</b>   | <b>(%)</b> | <b>No.</b>  | <b>(%)</b> |
| No HAV          | All       | 40         |            | 31           |            | 71          |            |
|                 | WF        | 8          | 20         | 3            | 10         | 11          | 15         |
|                 | Primary   | 5          | 13         | 2            | 6          | 7           | 10         |
| HAV             | All       | 44         |            | 5            |            | 49          |            |
|                 | WF        | 15         | 34         | 3            | 60         | 18          | 37         |
|                 | Secondary | 8          | 20         | 1            | 20         | 9           | 18         |

For those with WF, six had suffered from frostbite, two had operations for carpal tunnel syndrome, two had been hospitalized after an accident, and four had taken cardiac medication for hypertension or vascular spasms.

The average noise exposure for men not exposed to HAV with WF or possible primary Raynaud's phenomenon was less than for men without WF (Table 4).

**Table 4.** The mean (SD) duration of noise exposure among men and women with or without white fingers (WF) and the average (range) use of hearing protectors during noise exposure.

|                      |            | <b>Noise<br/>duration**</b> | <b>Hearing<br/>protection†</b> | <b>WF<br/>duration*</b> |
|----------------------|------------|-----------------------------|--------------------------------|-------------------------|
|                      | <b>No.</b> | <b>Mean (SD)</b>            | <b>Mean (Range)</b>            | <b>Mean (SD)</b>        |
| <b>Men</b>           |            |                             |                                |                         |
| WF                   | 8          | 1.4 (2.1)                   | 38 (0-100)                     | 15 (15)                 |
| Primary              | 5          | 1.6 (2.3)                   | 91 (0-100)                     | 19 (17)                 |
| No WF                | 32         | 7.3 (9.8)                   | 58 (0-100)                     |                         |
| <b>Women</b>         |            |                             |                                |                         |
| WF                   | 3          | 26 (90)                     | 33 (0-100)                     | 20 (-)                  |
| Primary              | 2          | 28 (11)                     | 0 (0)                          | 20 (-)                  |
| No WF                | 28         | 12 (12)                     | 35 (0-100)                     |                         |
| <b>Men and women</b> |            |                             |                                |                         |
| WF                   | 11         | 9.5 (13)                    | 37 (0-100)                     | 16 (13)                 |
| Primary              | 7          | 10 (15)                     | 61 (0-100)                     | 19 (15)                 |
| No WF                | 60         | 9.6 (11)                    | 47 (0-100)                     |                         |

\*in years, \*\*in 1000 hours, †% of noise exposure.

The average noise exposure duration was higher for those who used hand-held vibrating machines than for those who did not use these types of machines (Tables 4 and 5). The average noise exposure duration for all participants or only men with WF compared to men without WF, who used hand-held vibrating machines, was about the same (Table 5). Among all participants or just men who used hand-held vibrating machines there was, on average, more use of hearing protection during a working day than among those without HAV exposure except for those with possible primary Raynaud's phenomenon (Tables 4 and 5). Those who were not exposed to HAV but had WF had longer periods with WF symptoms before the

discovery of noise-induced hearing loss than among participants who used hand-held vibrating machines (Tables 4 and 5).

**Table 5** The mean (SD) duration of noise and hand-arm vibration (HAV) exposure among men and women with or without white fingers (WF) who were exposed to HAV. The average (range) use of hearing protectors during noise exposure is also shown.

|                      |    | Noise duration** |            | Hearing protection† | WF duration* | HAV duration** |
|----------------------|----|------------------|------------|---------------------|--------------|----------------|
|                      |    | No.              | Mean (SD)  | Mean (Range)        | Mean (SD)    | Mean (SD)      |
| <b>Men</b>           |    |                  |            |                     |              |                |
| WF                   | 15 | 11 (16)          | 88 (0-100) | 7.5 (9.0)           | 9.9 (14)     |                |
| Secondary            | 8  | 11 (13)          | 75 (0-100) | 4.3 (3.9)           | 6.9 (6.0)    |                |
| No WF                | 29 | 9.3 (12)         | 72 (0-100) |                     | 7.5 (9.7)    |                |
| <b>Women</b>         |    |                  |            |                     |              |                |
| WF                   | 3  | 26 (19)          | 62 (0-100) | 8 (-)               | 4.4 (-)      |                |
| Secondary            | 1  | 13 (-)           | 85 (0)     | -                   | -            |                |
| No WF                | 2  | 4 (-)            | 30 (10-50) |                     | 15 (-)       |                |
| <b>Men and women</b> |    |                  |            |                     |              |                |
| WF                   | 18 | 13 (17)          | 83 (0-100) | 7.5 (8.5)           | 9.5 (13)     |                |
| Secondary            | 9  | 12 (13)          | 76 (0-100) | 4.3 (3.9)           | 6.9 (6.0)    |                |
| No WF                | 31 | 9.1 (11)         | 69 (0-100) |                     | 7.8 (9.6)    |                |

\*in years, \*\*in 1000 hours, †% of noise exposure.

## Discussion

This thesis examined the short- and long-term effects of combined exposure to HAV and noise on TTS in hearing and on noise-induced hearing loss. The effect of VWF in male workers using hand-held vibrating tools on noise-induced hearing loss, and the occurrence of Raynaud's phenomenon among men and women with noise-induced hearing loss were also examined.

In the experimental study, short-term exposure to HAV did not change the hearing threshold, but exposure to noise, whether with or without HAV, increased the TTS in hearing. There was no difference in TTS in hearing after combined exposure to HAV and noise compare to after noise exposure alone. There were no differences observed in terms of TTS in hearing in relation to gender.

Two of the studies presented in this thesis were prospective studies based on a cohort of workers at a heavy engineering workshop in Sweden. In the first cohort study, an increased risk of noise-induced hearing loss was found with increased exposure to both noise and HAV for all three exposure estimates (Time, TimeAcc, and TimeAcc2). For the third and fourth exposure quartiles the ORs from all three exposure estimates were between 3.0 and 5.6 with 95% CIs greater than one. This result indicates an association between exposure to HAV from hand-held vibrating tools in a noisy environment and an increased risk of noise-induced hearing loss.

In the second cohort study, it was found that workers with VWF in the right hand had a significant risk of noise-induced hearing loss in the right ear (OR 2.2–2.3). Workers with VWF in the left hand also had a significant risk of noise-induced hearing loss in the left ear in the low exposure group (OR 4.7–7.1). This result supports an association between workers with VWF who use hand-held vibrating machines and an increased risk of noise-induced hearing loss.

In the questionnaire study, many of the men and women with noise-induced hearing loss had used hand-held vibrating machines. There was a high prevalence of Raynaud's phenomenon among men with or without exposure to HAV but whom all had noise-induced hearing loss. The prevalence of Raynaud's phenomenon was higher among men than women.

## **Short-term exposure**

In the experimental study, there was no difference in TTS in hearing after combined exposure to HAV and noise compare to after noise exposure alone. This result agrees with the results obtained by Miyakita et al. [52] experimental study but differs from those of Zhu et al. [51] experimental study. Zhu et al. [51] found an increased TTS in hearing after combined exposure to both HAV and noise. The discrepancies between the studies are probably due to the fact that different experimental techniques, conditions, and subjects were used. In Paper I and the work by Miyakita et al. [52], authentic HAV and noise exposures were used. In Paper I, vibration and noise exposures came from an angular grinder of a type commonly used in industry, and in the experimental study by Miyakita et al. [52] the subjects operated a chainsaw. In the study by Zhu et al. [51], however, white noise and a continuous 60 Hz sinusoidal vibration were used as the exposures. Continuous exposures for 20 minutes were used in Paper I, but previous experimental studies exposed subjects for 10–15 min with interrupted exposure intervals. The noise exposure levels varied between 90 dB(A) to 105 dB(A) between Paper I and earlier studies, and the frequency-weighted acceleration levels varied between 4.0 m/s<sup>2</sup> and 7.7 m/s<sup>2</sup> [51, 52]. In Paper I the same eight-hour equivalent acceleration level was used as in the study by Zhu et al. [51]. In Paper I, the eight-hour equivalent noise exposure level was 85 dB(A) and the eight-hour frequency weighted acceleration was 1.4 m/s<sup>2</sup>, both of which are comparable to the noise and HAV exposure levels found in a variety of different occupations.

The subjects in earlier experimental studies consisted only of men or of a majority of men, but in Paper I an equal number of men and women were included. In that study, no differences in regards to gender were seen in TTS in hearing after short-term exposure to HAV and noise separately or combined. Experimental studies on exposure to noise alone have found some differences in TTS in hearing in relation to gender, but their results have been inconclusive [61-64]. The results from Paper I are the first that we know of in regards to potential gender differences in TTS in hearing upon exposure to a combination of noise and HAV.

## **Long-term exposure**

In Paper II, an increased risk of noise-induced hearing loss was found upon increasing exposure to HAV and noise for all three exposure estimates. This result indicates an association between combined long-term exposure to both HAV and noise and the risk of noise-induced hearing loss. In Paper II, the exposure estimates were analysed both as continuous data and divided

into exposure quartiles. Based on the continuous exposure estimates, it was assumed that the same increase in exposure level for each of the three exposure estimates had the same increased risk of noise-induced hearing loss for the entire exposure range. The analysis with exposure quartiles, however, found that this was not true. The OR for the risk of noise-induced hearing loss decreased in the fourth quartile compared to the third quartile for all three exposure estimates. The cause of the decline in OR for the fourth quartile could be from a healthy workers effect. Workers that had injuries may have ended their employment and only healthy workers were left in the high-exposure group.

Earlier longitudinal studies on the risk of noise-induced hearing loss from long-term exposure to a combination of HAV and noise did not find any increased risk of noise-induced hearing loss when HAV were present [45, 53]. The study in Paper II had the advantage of being a long-term prospective study that included more detailed data on the use of hand-held vibrating machines compared to the earlier longitudinal studies. The previous longitudinal studies tried to predict every individual's hearing using noise exposure duration and level, and the differences between measured hearing levels and the calculated hearing levels were then related to HAV exposure [45, 53]. In Paper II there was a lack of extensive noise exposure data before 2008, but because the noise exposure level from hand-held vibrating tools are more hazardous than the background noise exposure level, the length of time the subject had used hand-held vibrating tools was used as the measure of noise exposure. The lifetime or cumulative exposure to HAV used in Paper II also included the lifetime exposure to noise from the hand-held vibrating machines because noise and HAV exposure both have a common source. By multiplying the lifetime exposure to HAV by the acceleration of the vibrations, the possible effect of HAV on noise-induced hearing loss could be studied further.

Unlike earlier longitudinal studies, all audiograms in Paper II were classified according to Klockhoff categories [60]. This classification scheme uses information on the hearing threshold level from several frequencies. Changes for individual frequencies could not be analysed because only data on hearing thresholds from 10–20 dBHL and were available. Previous longitudinal studies analysed individual frequencies [45, 53]. Measurements from the left ear were used in Paper II as well as in the study by Pyykko et al. [45] study, but Starck et al. [53] used the average hearing level of both ears. Thus there could be difficulties in comparing the hearing threshold levels of the left ear with the average of both ears. Experimental and epidemiological noise exposure studies has found an asymmetry in noise-induced hearing loss between the ears with the left ear suffering worse noise-induced hearing

loss than the right ear. This asymmetry was observed even after adjustment for handedness and the use of firearms [65-68]. By using the left ear instead of the right ear, the noise-induced hearing loss would not be underestimated.

### **Vibration-induced white fingers**

In Paper III, workers using hand-held vibrating machines with VWF had an increased risk of noise-induced hearing loss compared to workers without VWF. The result support earlier longitudinal and cross-sectional studies who also found that workers with VWF have a greater noise-induced hearing loss compared to workers without VWF [45-49].

Workers in Paper III with VWF in the left hand had an increased risk of noise-induced hearing loss in the left ear and workers with VWF in the right hand had an increased risk of noise-induced hearing loss in the right ear. The same result was found by House et al. [48]. However, in Paper III there was an interaction between the variable of categorized VWF symptoms in the left hand and exposure estimates (Time, TimeAcc). Workers with VWF in the left hand who were in the low exposure group had an increase risk of noise-induced hearing loss in the left ear compared to workers with VWF in the left hand in the high exposure group. This result might be because workers who had been injured earlier were not part of the cohort. The only workers left with high exposure were the healthy workers. There was also an analysis on the risk of noise-induced hearing loss in the ear with worst hearing status with the hand with worst SWS categorization. It was found that workers with VWF in either the left or right hand had no increased risk of noise-induced hearing loss in either the left or right ear compared to workers without VWF. Earlier longitudinal studies found that workers with a history of VWF on any hand had an increase risk of noise-induced hearing loss in the left ear [45-47].

Paper III had some differences compared to previous studies. As mentioned earlier, the audiograms were categorized in this study while earlier longitudinal and cross-sectional studies used individual frequencies [45-49]. House et al. [48] cross-sectional study used both individual frequencies as well as all frequencies combined. The noise exposure level and duration were used in some earlier longitudinal and cross-sectional studies while other studies used the noise exposure duration from hand-held vibrating tools or years working in a noisy environment [45-49]. In Paper III the duration of used hand-held vibrating tools were used as an estimation of noise exposure duration. This study used data of exposure, VWF, and audiograms gathered by a 21-year follow-up cohort. Previous longitudinal and cross-sectional studies had shorter follow-up periods [45-49]. Longer prospective studies

have the advantage of more detailed exposure data and data on the development of noise-induced hearing loss and VWF.

### **Raynaud's phenomenon**

The study sample in Paper IV consisted of men and women with a confirmed noise-induced hearing loss. Their hearing disabilities were graded as 1–15% where 15% corresponded to a total loss of hearing in one ear. There were 84 men and 36 women included in the study who specified if they had WF or not and also specified if they had used hand-held vibrating machines or not. Eighteen per cent of the subjects had used hand-held vibrating tools at least 2 hours each working day. Among all workers in Sweden, 9% use hand-held vibrating tools at least 2 hours of each workday [69]. In paper IV there was a higher prevalence of the use of hand-held vibrating tools among participants with noise-induced hearing loss compared to all workers in Sweden. One source for the noise-induced hearing loss in this study could be from the noise exposure produced by the hand-held vibrating tools, and HAV could be an interacting factor with noise exposure on the risk of noise-induced hearing loss as suggested in Paper II.

Among the participants in this study, 23 men and 6 women specified that they had WF. Among the men with noise-induced hearing loss who had been exposed to HAV, 34% had WF and 20% had possible secondary Raynaud's phenomenon. This is a higher prevalence of WF compared to the 13% prevalence of WF among Swedish male construction workers [21]. Both Paper III and earlier longitudinal and cross-sectional studies found an increased risk of noise-induced hearing loss for workers with VWF compared to workers without VWF [45-49]. One could, therefore, speculate that WF from exposure to HAV might increase the risk of noise-induced hearing loss. Among men who were not exposed to HAV, 20% had WF and 13% had possible primary Raynaud's phenomenon. Male Swedish office workers not exposed to HAV have a prevalence of WF of 8.4% [21], and an earlier cross-sectional study by Palmer et al. [54] found that men and women with finger blanching had an increased risk of hearing loss even if they had no extensive exposure to noise or HAV. Therefore, it might be that having WF, not exposure to HAV, increases the risk of noise-induced hearing loss.

Sixteen per cent of women in a cross-sectional study of the female population in the city of Västerås in Sweden suffer from Raynaud's phenomenon regardless of whether or not they have been exposed to HAV [70], and in Paper IV the prevalence of Raynaud's phenomenon among women with or without HAV exposure was 17%. Thus the prevalence of Raynaud's phenomenon among women with noise-induced hearing loss was

about the same as for Swedish women in the general population. WF among women with or without exposure to HAV might not increase the risk of noise-induced hearing loss, but Palmer et al. [54] found an increased risk of hearing loss among women with finger blanching.

In Paper IV a higher prevalence of Raynaud's phenomenon was observed among men compared to women in subjects with noise-induced hearing loss. Earlier cross-sectional studies on general populations indicated that there was a higher prevalence of Raynaud's phenomenon among women compared to men [18, 55-57]. Men with WF, with or without exposure to HAV, might have a higher risk for noise-induced hearing loss compared to women with WF. It is not clear what kinds of mechanisms could account for such a difference, and it is possible that this result is a simple statistical anomaly because fewer women than men were available for the study in Paper IV.

In Paper IV, men with WF who were not exposed to HAV developed noise-induced hearing loss with shorter exposures to noise than men with WF who were exposed to HAV. WF from HAV exposure might, therefore, affect the risk of noise-induced hearing loss differently than WF that is not from HAV exposure.

### **Mechanism behind the possible relation of hand-arm vibration and noise-induced hearing loss**

Earlier longitudinal studies suggested that vibrations might stimulate the SNS and lead to vasoconstriction in the hand and in the cochlea. Noise exposure increases the demand for oxygen in the cochlea, and if the blood supply to the cochlea was simultaneously restricted because of an overstimulated SNS then there might be an increased risk for hair cell death and noise-induced hearing loss [47, 58]. As mentioned earlier, the SNS has been suggested to control the cochlear blood flow [14-16] because the SNS controls the smooth muscles that regulate the blood flow in blood vessels [10, 11]. If vibrations stimulate the SNS, then it might be possible that the blood circulation in the cochleae and fingers will be affected. An overstimulated SNS could also be the cause of an unbalanced ANS that restricts blood circulation in VWF patients and also causes blood restriction in the vibration-exposed and non-exposed hand [31, 39-41]. It is not clear, however, if the SNS response to noise exposure has a protective or harmful effect on the cochlea [24-27].

Another possible mechanism for the increased risk of noise-induced hearing loss from combined exposure to HAV and noise could be the transmission of vibrations through the bones. However, vibrations from the hand through

the bones up to the cochlea are highly dampened [58]. Also, if bone transmission were the mechanism then the workers with VWF should have had the same risk of noise-induced hearing loss as workers without VWF. This was not found to be the case, however, in earlier longitudinal and cross-sectional studies that compared workers with VWF to workers without VWF who had similar noise and HAV exposures [45-49] or in Paper III.

In Paper I, no significant difference was found in the TTS in hearing after exposure to noise alone or after combined exposure to HAV and noise. Results from previous experimental studies on the ANS suggest that a 20-min exposure to HAV and noise separately or in combination can have an acute effect on the SNS and PNS. Vibrations with or without simultaneous noise exposure might decrease PNS activity while noise exposure alone might increase the sympathetic activity [32, 71, 72]. Although our experimental study did not show an increase in TTS after combined exposure compared to only noise exposure, it is possible that both the SNS and PNS were affected by the exposures. In Paper I there were also no differences in the TTS in hearing found in relation to gender after exposure to HAV, noise, or both. Bjoer et al. [71] did not find any difference in the acute effects on the SNS or PNS after exposure to HAV, noise, or both in relation to gender. Therefore, there are likely no gender-based differences in the PNS or SNS upon short-term exposure to HAV and noise.

Workers with long-term exposure to HAV might have a decrease in PNS activity [32], and decreased PNS activity has been seen in patients with HAVS [33]. Studies on patients with HAVS also indicate a greater SNS sensitivity [34, 35]. These studies suggest that long-term exposure to HAV by workers with or without HAVS affects the ANS, and suggest that an unbalanced ANS may be involved in the increased risk of noise-induced hearing loss for workers exposed to long-term HAV. The result from Paper II suggested an association between long-term combined exposure to HAV and noise and noise-induced hearing loss. In Paper III workers with VWF who were exposed to HAV and noise had an increased risk of noise-induced hearing loss compared to workers without VWF. This result is supported by earlier longitudinal and cross-sectional studies [45-49].

The men and women with noise-induced hearing loss studied in Paper IV who were not exposed to HAV had a high prevalence of Raynaud's phenomenon. The cross-sectional study by Palmer et al. [54] indicated that men and women with finger blanching had an increased risk of hearing loss, even if they had not been importantly exposed to noise or never exposed to HAV. These men and women did not have a stimulated SNS from vibrations, and further studies are required to determine if Raynaud's phenomenon

from sources other than vibrations could increase the risk of noise-induced hearing loss.

This thesis has examined whether combined exposure to HAV and noise with or without VWF could increase the risk of noise-induced hearing loss. However, noise exposure might also affect the risk of developing VWF. As mentioned earlier, both HAV and noise influence the SNS and PNS [32, 71, 72]. Vibrations could influence the metabolism of the cochlea by stimulating the SNS and, conversely, noise may influence the SNS and affect the blood circulation in the fingers. An experimental study found that skin temperature decreased more after exposure to a combination of noise and HAV as opposed to exposure to HAV alone [49], but whether noise exposure might affect the risk of VWF could not be studied in this thesis.

### **Methodological considerations**

In Paper I, the TTS in hearing was used because it is the most practical and observable test for the effect of noise exposure on hearing acuity threshold in experimental human studies [22]. The outcome of the study may be biased, however, by the use of young and healthy subjects with very good hearing. To be included in Paper I, the subjects had to have very good hearing with hearing threshold levels better than 10 dBHL. Normal hearing, however, can be defined by hearing thresholds up to 25 dBHL [60]. Healthy young people might be at less risk of developing noise-induced hearing loss from the experimental exposures than elderly people. The subjects also had normal thermal and tactile thresholds in the fingers, and healthy subjects with very good hearing may be less influenced by exposure to noise and HAV. Hearing threshold levels could change day to day, but the outcome in Paper I was the relative change in hearing threshold and not the absolute threshold. All subjects had time to examine the audiometric test method so that errors due to misunderstanding of the audiometric measurements were limited. Because there was no examination of the subject's ears with an otoscope, there was no information as to whether any had lesions in the outer or middle sections of the ear that could have influenced the results. The experimental exposure levels of noise and HAV were comparable to levels possible in a variety of different occupations. The noise exposure level were at the eight-hour equivalent exposure limit of 85 dB(A), and the HAV corresponded to an eight-hour equivalent acceleration exposure of 1.4 m/s<sup>2</sup>, much less than the exposure action value. The short exposure duration of 20 min exposed the subjects to low eight-hour frequency-weighted acceleration and might have been too low to affect the hearing threshold level in combination with noise.

Only young and healthy subjects were used in Paper I, and they had no history of regular exposure to noise or HAV. The results from this study must, therefore, be interpreted with caution when generalizing to elderly subjects with extensive exposure to noise and HAV. Elderly subjects with more extensive noise and HAV exposures were included in Papers II, III, and IV. The participants were 18–64 years old in Paper II, 20–69 years old in Paper III, and 19–55 years old in Paper IV. In Papers II and III the majority of participants had been regularly exposed to noise and HAV. In Paper IV less than half of the subjects had been exposed to HAV, but all had a history of noise exposure. The results of Paper II, III, and IV might, therefore, be more generally applicable than those from Paper I.

The cohort used in Papers II and III only had extensive noise exposure level measurements taken during 2008, and it was found that the hand-held vibrating machines used at the company had considerably higher noise levels than the background noise level. Some noise level data from 1987 was obtained from the manufacturers of the hand-held vibrating tools used at the company, and the noise exposure levels appeared to be more or less the same in 1987 and 2008. The change in duration of the use of hand-held vibrating tools and the small changes in noise exposure levels from these types of tools suggested that the eight-hour equivalent noise levels were almost the same in 1987 as in 2008. In Papers II, III, and IV there was no information on whether the noise exposures were continuous or impulsive.

Klockhoff categories were used in Papers II and III [60], but there are other categorisations of normal hearing and noise-induced hearing loss that use fewer frequencies [73, 74]. In Papers II and III the levels of hearing were categorized as either normal hearing or noise-induced hearing loss. With more categories of noise-induced hearing loss, more information on the progress of noise-induced hearing loss in relation to combined exposure to HAV and noise or VWF could have been gained. A few audiograms from workers in Papers II and III did not meet the criteria for normal hearing or noise-induced hearing loss and were, therefore, excluded from the analysis.

Information on hearing protection used by the subjects in Papers II and III was only available for 2008, and even a small reduction in the use of hearing protection could lead to a significant increase in the risk of noise-induced hearing loss. In Paper IV, those who used hand-held vibrating machines also used hearing protectors more on average during the working day than those without HAV exposure, except for those with possible primary Raynaud's phenomenon.

In Papers II, III, and IV the duration of noise and HAV exposure were subjectively estimated by answers to a questionnaire. However, people tend to overestimate their exposures when using hand-held vibrating tools and this could bias a possible relationship between exposure to HAV and noise and noise-induced hearing loss [75, 76]. Recall bias may have been a particular problem in paper IV. All of the subjects in that study had a confirmed case of noise-induced hearing loss between 1995 and 2004 but they were sent the questionnaire in 2011/2012. The long time period between confirmation of their noise-induced hearing loss and their receiving the questionnaire may have made it more difficult to recall and estimate their exposures and health status during that time.

In Paper IV the participation rate was 38% for men and 50% for women with a total of 41% for both men and women. It is not clear why more women than men answered the questionnaire. One cause for the low participation rate could be due to difficulties remembering exposure duration of noise and HAV. At least seven years had past from their discovery of noise-induced hearing loss until they received the questionnaire although we had limited the participant's age to be no older than 55 years at the time of confirmed noise-induced hearing loss. Among those who answered the questionnaire, the mean (SD) age was 39 (10) years for men, 46 (8) for women, and 41 (9) for both men and women. The mean age (SD) for those who did not answer the questionnaire was 40 (9) years for men, 44 (7) for women, and 41 (9) for both men and women. There is no difference in mean age between those who answered and those who did not.

Information on smoking was used in Papers III and IV. Earlier longitudinal studies on exposure to a combination of HAV and noise on the risk of noise-induced hearing loss did not find any increased risk for smokers [45]. Smoking's effect on VWF is not consistent [77-79], but some studies suggest an increased risk of noise-induced hearing loss upon noise exposure among smokers [80, 81]. Smoking might also have an effect on noise-induced hearing loss in workers with VWF who are exposed to noise [82].

The extensive questionnaire in paper IV covered several illnesses, discomforts, and medications that might affect blood circulation. This information made it possible to exclude some of the possible causes of WF other than primary or secondary Raynaud's phenomenon. There was a lack of information, however, on when the participants acquired their sicknesses, discomforts, or injuries, or when they began taking medications.

## **Conclusions**

The studies in this thesis demonstrate that:

- Short-term exposure to noise and HAV did not change the TTS in hearing differently than short-term exposure to noise alone.
- Long-term exposure to HAV and noise increases the risk of noise-induced hearing loss for workers using hand-held vibrating machines in a noisy environment.
- Workers with VWF who use hand-held vibrating machines have an increased risk of noise-induced hearing loss compared to workers without VWF.
- A large percentage of men and women with confirmed noise-induced hearing loss had used hand-held vibrating tools extensively in their work
- Raynaud's phenomenon is common among men with noise-induced hearing loss.
- The prevalence of Raynaud's phenomenon is higher among men compared to women with noise-induced hearing loss.
- The possible various interactions between noise and HAV should be studied further.

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