

# Can sensation of cold hands predict Raynaud's phenomenon or paraesthesia?

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<b>Background</b>	Raynaud's phenomenon and neurosensory symptoms are common after hand-arm vibration exposure. Knowledge of early signs of vibration injuries is needed.
<b>Aims</b>	To investigate the risk of developing Raynaud's phenomenon and paraesthesia in relation to sensation of cold hands in a cohort of male employees at an engineering plant.
<b>Methods</b>	We followed a cohort of male manual and office workers at an engineering plant in Sweden for 21 years. At baseline (1987 and 1992) and each follow-up (1992, 1997, 2002, 2008), we assessed sensation of cold, Raynaud's phenomenon and paraesthesia in the hands using questionnaires and measured vibration exposure. We calculated risk estimates with univariate and multiple logistic regression analyses and adjusted for vibration exposure and tobacco usage.
<b>Results</b>	There were 241 study participants. During the study period, 21 individuals developed Raynaud's phenomenon and 43 developed paraesthesia. When adjusting the risk of developing Raynaud's phenomenon for vibration exposure and tobacco use, the odds ratios were between 6.0 and 6.3 (95% CI 2.2–17.0). We observed no increased risk for paraesthesia in relation to a sensation of cold hands.
<b>Conclusions</b>	A sensation of cold hands was a risk factor for Raynaud's phenomenon. At the individual level, reporting a sensation of cold hands did not appear to be useful information to predict future development of Raynaud's phenomenon given a weak to moderate predictive value. For paraesthesia, the sensation of cold was not a risk factor and there was no predictive value at the individual level.
<b>Key words</b>	Hand-arm vibration; hand-arm vibration syndrome; Raynaud's phenomenon; paraesthesia; sensation of cold.

## Introduction

Health hazards from prolonged exposure to hand-transmitted vibration (HTV) include vascular, neurosensory and musculoskeletal manifestations, collectively denoted hand-arm vibration syndrome (HAVS) [1]. The vascular component manifests as episodic attacks of clearly demarcated finger blanching triggered by exposure to cold or cooling conditions such as wind or damp conditions. This is a secondary form of Raynaud's phenomenon where the peripheral circulation in the fingers is severely impaired [1,2]. The neurosensory component includes positive, negative or inducible manifestations or a combination of these. Positive manifestations, such as paraesthesia (pins and needles, tingling, tickling) or pain, indicate spontaneous neuronal activation along the sensory pathway from skin receptors, along afferent

nerve fibres through the spinal cord to the sensory cortex [3]. These symptoms may severely affect quality of life and work ability [4,5]. There is no effective medical treatment, and symptoms are only partially reversible, particularly in more severe cases [6]. It is crucial to identify persons with early symptoms, so they can be more closely monitored and if necessary removed from exposure to prevent further progression. The pathogenesis of the vascular and neurosensory components of HAVS and their interconnection is not yet fully understood. Multifactorial pathogenesis has been suggested involving enhanced sympathetic activity and local abnormalities in the peripheral vascular and neurological systems [7,8]. Nerve fibre dysfunction in the vessel wall may initiate vasospasm or vice versa. Reduced peripheral circulation may cause intra-neural vessel damage, leading to loss of sensitivity or symptoms of paraesthesia [3]. Impairment

of peripheral circulation, manifested as a sensation of cold hands, may therefore be one of the first signs for disease progression towards Raynaud's phenomenon or neurosensory dysfunction [9]. Our hypothesis was that persons experiencing a sensation of cold in their hands were at higher risk of developing Raynaud's phenomenon and paraesthesia.

The aim of this study was to investigate the risk of developing Raynaud's phenomenon and paraesthesia in relation to a sensation of cold hands, in a cohort of male employees at an engineering plant.

## Methods

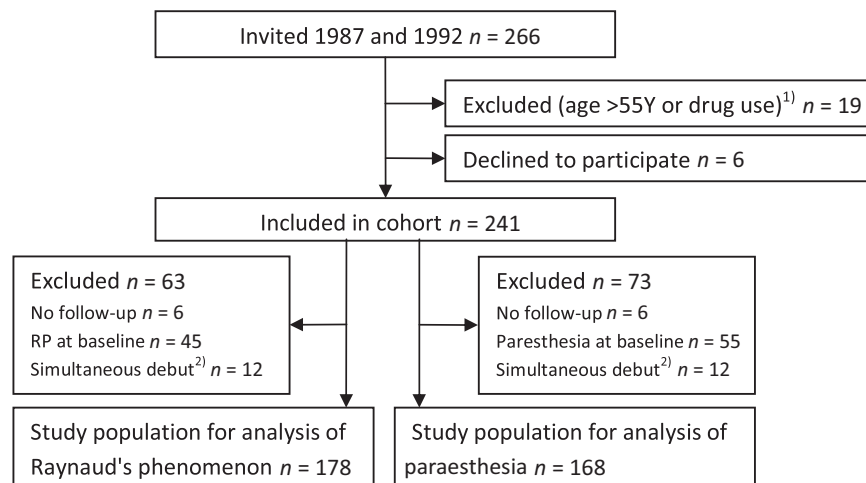
We undertook a prospective longitudinal dynamic cohort study. The cohort included male office and manual workers, all full-time employees at an engineering plant in Sundsvall, Sweden, manufacturing paper and pulp machinery [10]. We invited employees to participate in 1987 and 1992. All participants signed written informed consent. We excluded participants who: (i) did not attend any follow-up, (ii) reported symptoms (Raynaud's phenomenon or paraesthesia) at baseline and (iii) reported first sensation of cold hands and first onset of symptoms (Raynaud's phenomenon or paraesthesia) at the same follow-up. The number of participants excluded with each criterion is presented in Figure 1. Since exclusion criteria 2 and 3 comprised the outcome measure of interest, we formed two different, but largely overlapping study populations to analyse the two different outcome measures: Raynaud's phenomenon and paraesthesia.

We conducted follow-ups in 1992 (for those recruited in 1987) and again in 1997, 2002 and 2008. The participants answered a questionnaire at baseline and all follow-ups, covering sensation of cold hands, Raynaud's phenomenon, paraesthesia and individual characteristics

such as age, height and weight. We performed a medical examination for each of the participants. We did all baseline and follow-up investigations during the same season, when snow and temperatures below zero prevailed in Sundsvall, Sweden, where we conducted the study.

To define the presence of sensation of cold hands, Raynaud's phenomenon and paraesthesia, we used three questionnaire items from a self-designed and piloted questionnaire. We used two questions to define the presence of tobacco use and a set of variables to establish the vibration exposure. We considered a sensation of cold present, if the participant answered positively to the question 'Do you have a sensation of cold in your hands/fingers?'. We defined Raynaud's phenomenon as a positive answer to the question 'Do you have white (pale) fingers of the type that appears when exposed to damp or cold weather?'. These questions were followed by a four category response scale, comprising: 'no', 'insignificant', 'somewhat' and 'quite a lot'. Answering 'somewhat' or 'quite a lot' was regarded as a positive answer. For the neurosensory component, we asked: 'If you suffer from paraesthesia in the hands, for how long have you been suffering from paraesthesia?' We considered paraesthesia present if the participant reported any period of time in response to this question. We defined tobacco users as participants responding positively to one or both of the questions: 'Do you smoke?' and 'Do you use snuff?' in 1987 or 1992. Response options were either 'yes' or 'no'.

We assessed vibration exposure during normal working conditions combining technical measurements of tools and subjective assessments of daily exposure time [11]. We measured vibration acceleration of a large number of tools according to ISO standard 5349, Part 1 and Part 2 [12,13], primarily pneumatic grinders and slag hammers. We collected subjective assessments of daily exposure time by diary, questionnaire and interview.



**Figure 1.** Study sample and exclusion process for the original cohort as well as for the two study populations in this study. RP, Raynaud's phenomenon; Y, years. <sup>1</sup>Exclusion criteria were age >55 years old and use of drugs with the potential to affect the nerve system. <sup>2</sup>Reported first onset of Raynaud's phenomenon or paraesthesia and first sensation of cold hands at same follow-up.

We calculated hand-arm vibration dose as the product of self-reported exposure hours and the HTV exposure acceleration value for each tool used. This procedure is recommended when evaluating effects of HTV [14]. We also included leisure time exposure (hobbies, snowmobiling, motorcycling, etc.) in this measure, based on interviews. For example, a welder using a grinder 3 h per day and a chisel hammer 30 min per day for 7 years at exposure values of 6 and 9 m/s<sup>2</sup>, respectively, received a dose of 7 years × 220 days × 3 h × 6 m/s<sup>2</sup> = 27 720 h × m/s<sup>2</sup> + 7 years × 220 days × 0.5 h × 9 m/s<sup>2</sup> = 6930 h × m/s<sup>2</sup>, thus the total dose of 34 650 h·m/s<sup>2</sup>. We used two measures of HTV dose in this study: study period vibration dose, defined as the vibration dose from baseline to symptom onset (year of follow-up questionnaire) or to being censored (last follow-up without symptoms), and lifetime vibration dose, defined as the vibration dose during participant's lifetime up to 2008. When dichotomized, we defined a vibration dose >0 h·m/s<sup>2</sup> as exposed to HTV.

We analysed participants' descriptive data at baseline in two groups, with and without sensation of cold hands and we analysed associations between the groups for each characteristic. For continuous data, we used the Shapiro–Wilk test and histogram to control for normality and independent sample *t*-test for normally distributed variables. To analyse variables not normally distributed, we used Wilcoxon signed-rank test. We calculated *P* values for continuous data and odds ratios (ORs) with 95% confidence interval (95% CIs) for dichotomous data. We used univariate logistic regression to calculate OR (95% CI) between the dependent variables Raynaud's phenomenon and paraesthesia, respectively, and each independent variable: sensation of cold, vibration exposure and tobacco use. We used multiple logistic regression analysis to calculate the risk to develop Raynaud's phenomenon or paraesthesia, respectively, if a sensation of cold was previously reported, adjusted for vibration exposure and tobacco use. We presented risk estimate from the multiple logistic regression analysis as OR with 95% CI. To rule out a strong association between any of the independent variables we used a chi-square test (not presented). We calculated positive and negative likelihood ratio and the Youden index [15] to estimate the predictive value of a sensation of cold hands as a screening question. The Youden index is a single statistic combined measurement of a test's sensitivity and specificity. All statistical analyses were performed with IBM SPSS Statistics for Windows (version 23.0, IBM Corp, Armonk, NY, USA). *P* values <0.05 and OR with the lower 95% CI >1 or the higher 95% CI <1 were considered statistically significant.

The Regional Ethical Review Board for Medical Research in Umeå, Sweden, approved the study.

## Results

We invited 266 employees to participate. Nineteen were excluded due to age >55 years (1987) or use of drugs with the potential to affect the nervous system. Six employees declined to participate. The final cohort included 241 participants. After exclusion, we included 178 participants for Raynaud's phenomenon and 168 for paraesthesia in the analysis (Figure 1). Participant characteristics of the Raynaud's phenomenon and the paraesthesia study populations are shown in Tables 1 and 2, respectively.

In the Raynaud's phenomenon study population, there were no statistically significant differences in height, weight, body mass index (BMI) or tobacco use between workers reporting a sensation of cold or not. For vibration exposure, there was a significantly higher exposure dose and a larger proportion of participants exposed to vibrations among those reporting a sensation of cold. For the paraesthesia study population, the only statistically significant observation was a lower BMI for participants with a sensation of cold.

Among the participants with cold sensations in their hands, 14 (29%) developed Raynaud's phenomenon during the study period compared with seven (5%) in the group who did not suffer from cold sensations in their hands. The OR of developing Raynaud's phenomenon for participants with a sensation of cold was 7.0 (95% CI 2.6–18.6) (Table 3). When adjusted for study period, vibration exposure dose and tobacco use, the OR was 6.0 (95% CI 2.2–16.4), and slightly higher when adjusted for lifetime dose instead of study period dose.

Of the participants with cold sensations in the hands, 9 (32%) developed paraesthesia during the study period compared with 34 (24%) in the group who did not suffer from cold sensations in the hands. The OR of developing paraesthesia for participants with a sensation of cold was 1.5 (95% CI 0.6–3.6) (Table 3) and unchanged when adjusted for vibration exposure dose and tobacco.

The predictive values of sensation of cold to rule in (positive likelihood ratio) or rule out (negative likelihood ratio), future development of Raynaud's phenomenon and paraesthesia are presented in Table 4. The positive likelihood ratio for the sensation of cold to be a predictor for Raynaud's phenomenon was 3. Between 2 and 5 is considered to represent a small probability to predict disease. The negative likelihood ratio for Raynaud's phenomenon was 0.4 where 0.2–0.5 represents a small probability to rule out disease. The positive and negative likelihood ratios to predict paraesthesia were 1.3 and 0.9, respectively, which is of no predictive value. The Youden index for a sensation of cold as a predictor for Raynaud's phenomenon was 44% and for paraesthesia 6%, where >50% is preferred and 100% ideal for a test to be useful to a specific patient [16].

**Table 1.** Descriptive data on participants in the Raynaud's phenomenon study population

	Total ( <i>n</i> = 178)	Sensation of cold ( <i>n</i> = 49)	No sensation of cold ( <i>n</i> = 129)		
	Mean	Mean	Mean	<i>P</i>	
Height (cm)	179.6	180.2	179.4	NS	
Weight (kg)	78.4	78.2	78.5	NS	
BMI (kg/m <sup>2</sup> )	24.3	24.1	24.4	NS	
Age (years)	35.9	34.8	36.3	NS	
Study period vibration exposure dose <sup>a</sup>	4166	6114	3426	NS	
Lifetime vibration exposure dose <sup>a</sup>	24 104	35 870	19 636	**	
	<i>n</i> (%)	<i>n</i> (%)	<i>n</i> (%)	OR	95% CI
Study period vibration exposure dose <sup>b</sup>	51 (29)	20 (41)	31 (24)	2.2	1.1–4.4
Lifetime vibration exposure dose <sup>b</sup>	125 (70)	40 (82)	85 (66)	2.3	1.0–5.2
Tobacco users	164 (92)	47 (96)	117 (91)	2.4	0.5–11.2
Raynaud's phenomenon	21 (12)	14 (29)	7 (5)	7.0	2.6–18.6

Associations of participant characteristics between participants with and without a sensation of cold in the hands. NS, not significant.

<sup>a</sup>Vibration dose presented as the product of exposure hours and the hand-arm vibration exposure value (h·m/s<sup>2</sup>).

<sup>b</sup>Number of participants with a vibration dose >0 h·m/s<sup>2</sup>.

\*\**P* < 0.01.

**Table 2.** Descriptive data on participants in the paraesthesia study population

	Total ( <i>n</i> = 168)	Sensation of cold ( <i>n</i> = 28)	No sensation of cold ( <i>n</i> = 140)		
	Mean	Mean	Mean	<i>P</i>	
Height (cm)	179.7	181.5	179.3	NS	
Weight (kg)	77.9	76.4	78.3	NS	
BMI	24.1	23.2	24.3	*	
Age (years)	35.4	33.5	35.8	NS	
Study period vibration exposure dose <sup>a</sup>	3488	6171	2952	NS	
Lifetime vibration exposure dose <sup>a</sup>	22 244	27 715	21 149	NS	
	<i>n</i> (%)	<i>n</i> (%)	<i>n</i> (%)	OR	95% CI
Study period vibration exposure dose <sup>b</sup>	41 (24)	10 (36)	31 (22)	2.0	0.8–4.7
Lifetime vibration exposure dose <sup>b</sup>	118 (70)	21 (75)	97 (69)	1.3	0.5–3.4
Tobacco users	154 (92)	27 (96)	127 (91)	2.8	0.3–22.0
Paraesthesia	43 (26)	9 (32)	34 (24)	1.5	0.6–3.6

Associations of participant characteristics between participants with and without a sensation of cold in the hands. OR with 95% CI for nominal values. NS, not significant.

<sup>a</sup>Vibration dose presented as the product of exposure hours and the hand-arm vibration exposure value (h·m/s<sup>2</sup>).

<sup>b</sup>Number of participants with a vibration dose >0 h·m/s<sup>2</sup>.

\**P* < 0.05.

## Discussion

At group level, the risk of developing Raynaud's phenomenon was significantly increased among those with a previous sensation of cold hands. This was not the case for symptoms of paraesthesia. As a predictor for disease at the individual level, previous experience of a sensation of cold hands showed a small increase in the likelihood of developing Raynaud's phenomenon and no increased likelihood of developing symptoms of paraesthesia.

The prospective study design, the long interval from baseline to latest follow-up (21 years), and minimal attrition, were strengths of this study. The prospective approach allows assessment of causality by observing

risk factors occurring before symptoms arise. We made no separate analyses of those who declined to participate (*n* = 6) or that did not attend any follow-up (*n* = 6). We considered them too few (7%), to significantly affect the representativeness of our sample. The definition of Raynaud's phenomenon and paraesthesia in this study was limited to one question for each condition in a self-administered questionnaire. We chose these questions because they have been used in previous studies within this area of research [10,17–19]. Information bias, shown as an over reporting of Raynaud's phenomenon, is a probable effect of this limitation. We have no reason to believe this information bias differed between participants with

**Table 3.** Risk of developing Raynaud's phenomenon or paraesthesia if previously experienced a sensation of cold hands

	OR	95% CI	Adj. OR	95% CI <sup>a</sup>	Adj. OR	95% CI <sup>b</sup>
Raynaud's phenomenon	7.0	2.6–18.6	6.0	2.2–16.4	6.3	2.3–17.0
Paraesthesia	1.5	0.6–3.6	1.5	0.6–3.6	1.5	0.6–3.6

<sup>a</sup>Adjusting for tobacco use and study period vibration exposure dose.

<sup>b</sup>Adjusting for tobacco use and lifetime vibration exposure dose.

**Table 4.** Likelihood ratios and Youden index for the sensation of cold hands as a predictor for Raynaud's phenomenon and Paraesthesia

	Raynaud's phenomenon		Paraesthesia	
	Likelihood ratio	95% CI	Likelihood ratio	95% CI
Likelihood ratio +	3.0	2.0–4.6	1.4	0.7–2.8
Likelihood ratio –	0.4	0.2–0.8	0.9	0.8–1.1
Youden index	44%		6%	

and without a sensation of cold hands, so the calculated risk should not be affected. The relatively small sample size ( $n = 168$ ,  $n = 178$ ) limited statistical power, resulting in a large spread of 95% CI and limited the possible confounders that were adjusted for in the logistic regression model. We adjusted for tobacco use and vibration exposure, leaving out important risk factors such as diabetes, and peripheral nerve disease. We only included male participants in the study, limiting generalization of the results. A strength of the study design is that participants were included well after retirement, after a job change, or if they quit work for medical reasons. Thus, interpretations of the results are not limited to healthy males in working ages, but rather to the male population as a whole, and the risk for selection bias, such as healthy worker effect is minimized. We did not include some important risk factors for Raynaud's phenomenon or paraesthesia, such as cold exposure [18], previous cold injuries [17] and migraine [20] in the original questionnaire, and therefore we could not analyse them.

We have not found other studies assessing possible early signs or predictors of Raynaud's phenomenon, paraesthesia, HAVS or any neurosensory defect in the extremities. Sensation of cold has merely been described as one of many symptoms in HAVS [21]. Gerhardsson *et al.* assessed early signs of HAVS in a cross-sectional study [22] and found no increase in neurosensory symptoms. Early signs in this study meant signs after a relatively short period of exposure, in contrast to our study where early signs meant signs at an early stage in the progression of a disease. Thus, a comparison of the results from the two studies is of limited value. Ishitake and Ando found a positive correlation between subjective symptoms of finger coldness and measured skin temperature in patients

with HAVS [9]. The results strengthen the theory that a sensation of cold is a sign of vascular dysfunction and is coherent with the association we found between sensation of cold and Raynaud's phenomenon. An earlier study by Sakakibara *et al.* found a correlation between the degree of finger coldness and the severity of their vibration induced white fingers [23] which also supports our results. The longitudinal design of our study allowed us to draw conclusions of the causality between sensation of cold and Raynaud's phenomenon. We found no study to confirm or reject the causality aspect of our results since we found no longitudinal studies with comparable variables.

Our hypothesis initially assumed simplified mechanisms suggesting that a sensation of cold hands could be an early sign of either disease progression towards Raynaud's phenomenon or towards paraesthesia, caused by defects in the vascular or the neurological system. If we assume the origin is a sensitized sympathetic nerve system, or locally damaged endothelium releasing vasoconstricting substances into surrounding tissues, the consequence would be vasospastic attacks in the digital arteries already at low levels of cold exposure or a constant low level vasoconstriction, causing impaired peripheral circulation. A possible early manifestation would then be sensation of cold hands [9] and if left unattended there would be an increased risk of developing Raynaud's phenomenon as suggested by our results. According to our study, a sensation of cold hands does not seem to indicate an incipient impairment of the skin receptors or afferent nerve fibres, ultimately leading to paraesthesia.

The question 'Do you have a sensation of cold in your hands/fingers?' can be used in screening to identify persons at risk of developing Raynaud's phenomenon. However, the predictive strength of the question alone does not justify any expensive intervention on individual level, such as removal of vibration exposure, since the positive likelihood ratio is low. It could, however, be used to identify groups that need to be better informed concerning health-related issues regarding hand-arm vibration and more strictly monitored in the future to identify early stages of disease. More longitudinal research in this area is needed to identify early signs of HAVS, such as vascular or neurological symptoms, or objective findings like biomarkers. Future research should assess if there is a model including one or several signs combined that can reliably predict a future onset of HAVS. If this is achieved, a screening procedure that works in a clinical

setting at individual level should be the ultimate goal. To strengthen the clinical value of future research, the vascular component needs to be assessed according to international consensus [24], possibly in combination with objective assessments, and additional neurosensory symptoms need to be included apart from paraesthesia.

### Key points

- In this study, a sensation of cold hands was shown to be a risk factor for Raynaud's phenomenon but not for paraesthesia.
- Sensation of cold hands should be considered to be included in the future development of a screening procedure to identify persons at risk for secondary Raynaud's phenomenon.
- The predictive value for sensation of cold hands as a single, stand-alone screening question is too low to justify any extensive preventive measure at the individual level.

### Competing interests

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.

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