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Raynaud's phenomenon in Northern Sweden: a population-based nested case–control study

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Abstract

The aim of this study was to determine the association between individual and external exposure factors, and the reporting of Raynaud's phenomenon, with or without concomitant cold sensitivity. In a population-based nested case–control study, cases with Raynaud's phenomenon ($N=578$), and matched controls ($N=1156$), were asked to respond to a questionnaire focusing on different risk factors. Univariate and multiple conditional logistic regression were performed. Analyses were stratified according to whether the cases reported cold sensitivity or not. In total, 1400 out of 1734 study subjects answered the questionnaire (response rate 80.7%). In the final multiple model, the factor with the strongest association to Raynaud's phenomenon, with and without cold sensitivity, was previous frostbite affecting the hands (OR 12.44; 95% CI 5.84–26.52 and OR 4.01; 95% CI 1.78–9.01, respectively). Upper extremity nerve injury was associated to reporting Raynaud's phenomenon and cold sensitivity (OR 2.23; 95% CI 1.29–3.85), but not Raynaud's phenomenon alone. Reporting any exposure to hand-arm vibration or cumulative cold exposure was significant in univariate analyses for cases with both Raynaud's phenomenon and cold sensitivity, but not in the multiple model. Raynaud's phenomenon is strongly associated to previous cold injury, with a larger effect size among those who also report cold sensitivity. The fact that only upper extremity nerve injury differed significantly between case groups in our multiple model offers additional support to the neural basis for cold sensitivity.

Keywords Cold exposure · Hand · Frostbite · Epidemiology · Occupational exposure · Risk factors

Introduction

Raynaud's phenomenon

Raynaud's phenomenon (RP) is a common condition, characterized by attacks of peripheral blanching of digits, which can be triggered by exposure to cold, vibration, or emotional stress [1]. It occurs in a primary form (Raynaud's disease) that mostly affects younger women, and in a secondary form (Raynaud's syndrome) that is related to rheumatic disease, hematological conditions, occlusive arterial disease, hand-arm vibration (HAV) syndrome, as well as certain chemicals and therapeutic drugs [2]. The secondary form of RP has also been reported as a sequela to cold injury [3]. Having a severe manifestation of RP can affect the activities of daily living [4] and hinder outdoor leisure activities. Primary RP seldom progress to more severe stages of disease [5], while the prognosis of secondary RP is highly dependent on the treatment of the underlying cause. In a recent review, the prevalence of primary RP has been estimated to 0.8–6.5% of men and 2.1–15.8% of women [1]. In a previous study by

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our group, the prevalence of RP in Northern Sweden was 11.0% of men, and 14.0% of women [6]. We have also shown that RP overlaps heavily with another cold-related symptom, here denoted cold sensitivity (CS) [7].

Cold sensitivity

CS has been defined as a collection of acquired symptoms resulting in an abnormal aversion to cold with pain, sensory alterations, stiffness and/or color changes, which may occur after a traumatic injury [8]. Other terms such as cold intolerance and cold hypersensitivity have been used interchangeably. CS primarily affects the hands, and is often distinguished from RP by the fact that there is no clinically observable vasospasm present in CS, which is mandatory for a firm diagnosis of RP. CS has predominantly been studied in relation to different types of hand injuries, such as hand or digital amputation [9], nerve injury [10], arterial injury [11], or hand-arm vibration syndrome [12]. It has also been described in relation to certain systemic diseases, such as diabetes mellitus [13] and rheumatic disease [14]. However, the pathophysiological mechanism remains to be fully described. The clinical diagnosis of CS is most often based solely on the symptoms reported by the patient, and can be summarized by using the Cold Intolerance Symptom Severity (CISS) questionnaire [15]. Being sensitive to cold can have a profound impact on quality of life and work ability [9]. The literature on the prevalence of CS in the general population is scarce, and highly dependent upon the definition used. Recent Swedish studies have reported a prevalence between 4.9 and 14.4% in the general population [6, 12]. There is a need to establish common and separating factors for RP and CS to offer clues to the pathophysiological basis for the overlap between the conditions.

Objective

The objective of this study was to determine the association between individual and external exposure factors, and the reporting of RP. We also wanted to distinguish between RP cases who concomitantly reported CS from those who did not.

Methods

Study design

The present study was a nested case–control study on subjects reporting RP and matching controls. The cases were stratified according to the reporting of concomitant CS or not.

Setting

The study was carried out in the four northernmost counties in Sweden: Norrbotten; Västerbotten; Västernorrland; and Jämtland. The study region held a population of approximately 880,000 people, and is located between the 62°N and 69°N latitude, with a mixed subarctic and temperate climate.

Participants

The first data collection, here titled CHINS1, was initiated on the 5th of February and ended on the 5th of May, 2015. It consisted of a questionnaire-based study performed on a sample of men and women between ages 18 and 70 years living in the study area. The study sample was selected from the national Swedish population register. The data collection has previously been thoroughly described [6].

From the collected baseline data, cases with RP were identified through the use of a single questionnaire item: "Does one or more of your fingers turn white (as shown on picture) when exposed to moisture or cold?", that was supported by a standardized color chart, which previously has been shown to increase the accuracy in RP diagnosis [16]. Those who answered yes fulfilled the case definition.

In the group that had reported RP, we also investigated whether these subjects simultaneously fulfilled our definition of CS [7], which was based on two questionnaire items:

1. "I am oversensitive to cold" to which the study participant could answer on a fixed numerical scale ranging from 1 ("do not agree") to 10 ("agree completely"). An answer of 4 or more was considered a positive response.
2. "I experience pain/discomfort when fingers/hands are exposed to cold" to which the study participant could answer on a four-grade scale, in the form of "none", "insignificant", "somewhat" or "a lot". Answering "a lot" was considered a positive response.

A positive response on both questions fulfilled our definition for CS.

All subjects that reported both RP and CS were invited to a second data collection, here titled CHINS2. We also invited a similarly sized group of randomly selected subjects which had reported RP but negated CS. This approach was used to be able to stratify cases reporting RP on the basis of concomitant CS, to establish any distinguishing factors.

Controls were randomly selected with a ratio of 2:1 among study subjects from the CHINS1 cohort according to the following inclusion criteria:

1. No reported RP;

2. No reported CS;
3. Matching the case with regard to geographical area, sex, and age (±2 years).

The second, CHINS2 study, was initiated on the 10th of October, 2015, and ended on the 10th of March, 2016. Cases and controls received the same questionnaire. A flowchart of the data collection is presented in Fig. 1.

The study protocol was approved by the Regional Ethical Review Board situated at Umeå University (DNR 2015-24-31M and 2014-286-31M).

Variables

The study questionnaire collected data on place of livelihood, sex, age, height, and weight. Geographical location was determined by postal code and subsequently categorized into three groups: coastal, inland, and alpine. The occupations of the study participants were coded in accordance with the International Standard Classification of Occupations [17].

To quantify the severity of CS, we added a 100 mm visual analogue scale (VAS) [18], where the study participants were asked to mark the extent of problems with their hands they experience when exposed to cold climate. We also included the Swedish version of the Cold Intolerance Symptom Severity (CISS) questionnaire [15]. This inventory scores subjective problems with ambient cold exposure on a scale ranging from 4 to 100, where a value exceeding 50 has been suggested to indicate abnormal CS [19].

Frostbite affecting the hands was categorized as first degree (white spots), second degree (blisters), or third degree (blood-filled blisters) according to a previous definition [20]. Other questions asked if the study participants had been diagnosed by a physician for any of the following: hypertension; angina pectoris; myocardial infarction; stroke; diabetes mellitus; joint disease; or migraines. Questions were also posed about the presence of rheumatic disease, upper extremity nerve injury, polyneuropathy, carpal tunnel syndrome, and peripheral vascular disease, and the study participants were asked to specify the condition in detail (in free text). The rheumatic diseases included were systemic sclerosis, CREST syndrome, rheumatoid arthritis, juvenile rheumatoid arthritis, reactive arthritis, unspecified arthritis, systemic lupus erythematosus, psoriatic arthritis, ankylosing spondylitis, Sjögren's syndrome, Ehlers–Danlos

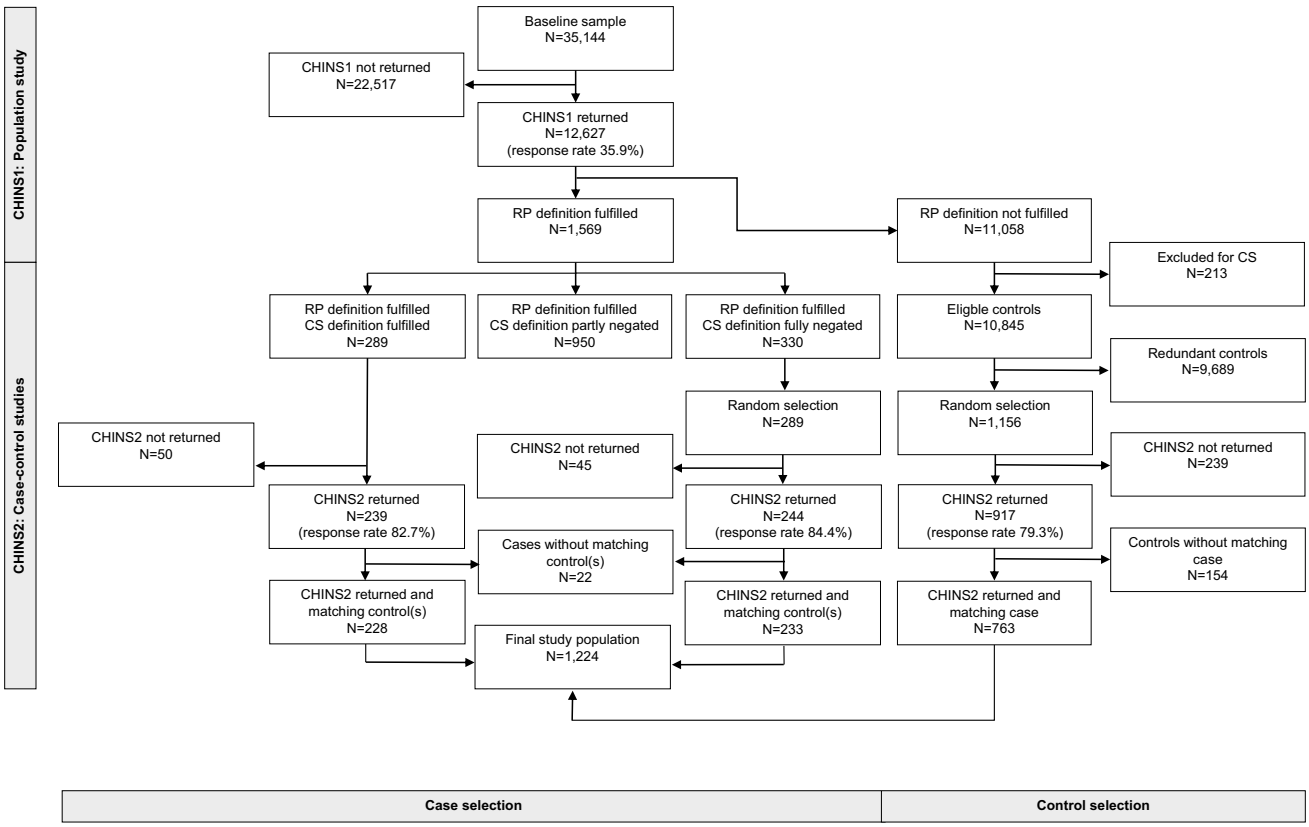

Fig. 1 Data collection for the CHINS1 and CHINS2 studies. The number of study subjects in each step of the data collection process is illustrated, and the response rates are shown in parentheses. *CHINS1* the first, population-based, data collection, *CHINS2* the second, case-based, data collection, *RP* Raynaud's phenomenon, *CS* cold sensitivity

syndrome, fibromyalgia, gout, polymyositis, dermatomyositis, Dercum's disease, and mixed connective tissue disease.

The use of therapeutic drugs was collected in free text, and coded by one of the study physicians (AS) into two broad categories based on whether the substance has a documented negative effect on either peripheral nerves [21] or circulation [22]. Beta-adrenergic antagonists, as well as oral contraceptives and hormone replacement therapies, were also analyzed separately.

Ambient cold exposure was investigated with several questions, partly rephrased from the Potential Work Exposure Scale [23]. For example, study participants were asked if their work required them to manually handle objects with a temperature near or below freezing. They were also asked to grade their occupational and leisure-time cold exposure on a fixed numerical rating scale (NRS) ranging from 1 to 10, respectively. The two scales were subsequently added together to form a cumulative measurement of cold exposure ranging from 2 to 20, as has been done earlier [7]. For HAV, the study participants were asked to specify if they had recurrent occupational exposure to impact tools, high-frequency tools, forestry and gardening equipment, vibrating tools, heavily vibrating tools, or operating vehicles with vibrating controls.

Statistical methods

Cases reporting RP were stratified on the basis of reporting concomitant CS, and analyzed separately with matching controls as reference. Characteristics for cases and controls were described as means and standard deviation (SD) for continuous variables, and as numbers and percentages for categorical variables. Missing data were excluded from all analyses. Numerical rating scales for occupational and leisure-time, as well as for cumulative cold exposure, were dichotomized into high or low exposure based on the 50th percentile.

The statistical association for each candidate factor was assessed separately using univariate conditional logistic regression, and presented as an odds ratio (OR) with 95% confidence interval (95% CI) for reporting RP (Tables 2, 3). In these analyses, p values less than 0.05 were considered statistically significant. Sex-specific subgroup analyses were also conducted. Thereafter, multiple conditional logistic regression was used to investigate the relationships between and identify the most important associated factors using a manual forward stepwise procedure. For this model, all factors with a p value less than 0.25 in the univariate analyses were tested. In each step, the associated factor with the lowest p value when entered into the model was included, and the remaining factors that had not been included were all tested again in the next step. The procedure was stopped when no factor with a p value less than 0.25 when added to the model remained available. Variables with missing data > 15% were not eligible for the multiple model.

Results

Participants

The CHINS2 questionnaire was sent out to 289 cases reporting RP and CS, of which 239 were returned (response rate 82.7%). An additional 289 cases that had only reported RP also received the same questionnaire, and 244 responded (84.4%). For the matched controls, 1156 subjects were asked to participate, and 917 returned the questionnaire (79.3%). From both groups of cases, 11 subjects were excluded for lacking at least one responding matching control. Also, 154 controls were excluded for lacking a matching case. Therefore, the final study population consisted of 1224 subjects, of which 228 were cases reporting RP and CS, 233 cases reporting only RP, and 763 matching controls (Fig. 1). The amount of missing data varied between 0.8 and 5.1% between questionnaire items, except for the free text question regarding therapeutic drug use, which had a larger proportion (25.0%).

Study population characteristics (Table 1)

There was a predominance of women among cases reporting both RP and CS ($N = 138$; 60.5%), and cases reporting only RP ($N = 143$; 61.4%). The mean age was 52.5 years (SD 12.5) for cases reporting both RP and CS and 55.8 years (SD 11.4) for cases only reporting RP. The mean age at which attacks of RP debuted was 31.0 years (SD 15.5; range 4–69) in the group reporting both RP and CS, and 33.0 years (SD 14.6; range 4–66) in the group reporting only RP. The CISS score was generally higher among cases reporting both RP and CS (mean 50.2; SD 15.9) compared to cases only reporting RP (mean 23.8; SD 11.1) and controls (mean 21.3; SD 14.3). For the VAS rating, cases reporting RP and CS had a higher value (mean 80.6 mm; SD 17.4) compared to cases with only RP (mean 41.1 mm; SD 25.2), which in turn was higher than among controls (mean 28.0 mm; SD 27.0).

Univariate analyses (Tables 2, 3)

In the univariate conditional logistic regression analyses, heredity for RP was significantly associated with reporting RP and CS (OR 3.90; 95% CI 2.49–6.11), as well as only reporting RP (OR 5.03; 95% CI 3.11–8.15), compared to controls. Previous frostbite was also significantly associated with reporting RP and CS (OR 13.13; 95% CI 6.79–25.40), and only RP (OR 4.26; 95% CI 2.23–8.12). A high BMI (≥ 25 kg/m^2) showed an inverse relationship to reporting

Table 1 Descriptive data on study participants, presented as numbers (*N*) and column percentages (%)

	RP cases with CS		RP cases without CS		Controls	
	N	%	*N*	%	*N*	%
Responders	228		233		763	
Sex						
Men	90	39.5	90	38.6	308	40.4
Women	138	60.5	143	61.4	455	59.6
Age group						
18–29	16	7.0	7	3.0	32	4.2
30–39	16	7.0	15	6.4	50	6.6
40–49	52	22.8	41	17.6	147	19.3
50–59	70	30.7	64	27.5	212	27.8
60–70	74	32.5	106	45.5	322	42.2
Geographical region						
Alpine	51	22.4	51	21.9	165	21.6
Inland	67	29.4	54	23.2	206	27.0
Coastal	110	48.2	128	54.9	392	51.4
Cold sensitivity measures						
CISS > 50	96	50.3	4	2.1	33	5.9
CISS ≤ 50	95	49.7	185	97.9	526	94.1
VAS > 50	211	95.5	91	41.6	166	22.7
VAS ≤ 50	10	4.5	128	58.4	566	77.3
Occupation						
Managers	6	2.8	11	4.8	27	3.6
Professionals	46	21.1	44	19.4	115	15.4
Technicians and associate professionals	21	9.6	31	13.7	75	10.1
Clerical support workers	22	10.1	20	8.8	68	9.1
Service and sales workers	29	13.3	23	10.1	115	15.4
Skilled agricultural, forestry, and fishery workers	3	1.4	3	1.3	13	1.7
Crafts and related trades workers	10	4.6	11	4.8	26	3.5
Plant and machine operators and assemblers	19	8.7	11	4.8	43	5.8
Elementary occupations	2	0.9	4	1.8	15	2.0
Armed forces occupations	2	0.9	0	0.0	2	0.3
Self-employed	5	2.3	5	2.2	14	1.9
Students	5	2.3	4	1.8	11	1.5
Unemployed	2	0.9	2	0.9	15	2.0
Parental leave	0	0.0	0	0.0	2	0.3
Sick leave	5	2.3	2	0.9	13	1.7
Retired	41	18.8	56	24.7	192	25.7

RP Raynaud's phenomenon, *CS* cold sensitivity, *CISS* cold intolerance symptom severity score, *VAS* visual analogue scale

RP and CS (OR 0.37; 0.25–0.54), and only RP (OR 0.50; 0.35–0.71).

Diseases and injuries that were statistically significant among cases reporting RP and CS were: vascular disease (OR 1.79; 95% CI 1.01–3.19); migraines (OR 1.96; 95% CI 1.14–3.36); polyneuropathy (OR 5.58; 95% CI 1.12–27.79); and upper extremity nerve injury (OR 2.09; 95% CI 1.42–3.09); none of these variables were significant among cases reporting only RP. The use of therapeutic drugs with negative effects on peripheral nerves or circulation did not show any significant association to reporting of RP; nor did beta-adrenergic antagonists, or oral contraceptives and hormone replacement therapies, when analyzed separately (data not shown).

Among external exposures, variables that were statistically significant among cases reporting RP and CS were: cumulative cold exposure above the 50th percentile (OR 1.47; 95% CI 1.03–2.09); handling cold objects during

Table 2 Univariate conditional logistic regression of individual factors suggested to be associated with Raynaud's phenomenon and cold sensitivity, including body mass index, heredity, tobacco use, therapeutic drug use, diseases, and injuries

Factor	Exposure level	RP cases with CS ($N=228$)				Controls ($N=379$)		RP cases without CS ($N=233$)				Controls ($N=384$)	
		N	%	OR	95% CI	*N*	%	*N*	%	OR	95% CI	*N*	%
BMI	BMI < 18.5	2	0.9	0.99	0.16–6.02	3	0.8	1	0.4	0.35	0.03–3.59	3	0.8
	18.5 ≤ BMI < 25	144	64.0	1	–	155	41.8	125	54.8	1	–	143	38.4
	BMI ≥ 25	79	35.1	**0.37***	**0.25–0.54**	213	57.4	102	44.7	**0.50***	**0.35–0.71**	226	60.8
Heredity													
Raynaud's phenomenon[a]	Yes	75	33.8	**3.90***	**2.49–6.11**	41	11.2	83	37.4	**5.03***	**3.11–8.15**	41	11.1
	No	147	66.2	1	–	324	88.8	139	62.6	1	–	329	88.9
Tobacco use													
Daily tobacco use	Yes	52	22.8	1.40	0.93–2.11	66	17.5	59	25.5	1.45	0.97–2.17	81	21.6
	No	176	77.2	1	–	311	82.5	172	74.5	1	–	294	78.4
Therapeutic drug use													
Affecting peripheral nerves[b]	Yes	23	12.6	0.92	0.46–1.84	37	13.9	24	14.3	0.72	0.41–1.27	56	19.9
	No	160	87.4	1	–	230	86.1	144	85.7	1	–	226	80.1
Affecting peripheral circulation[c]	Yes	41	22.9	1.53	0.88–2.67	54	20.8	30	18.2	1.23	0.69–2.22	48	17.1
	No	138	77.1	1	–	206	79.2	135	81.8	1	–	232	82.9
Diseases and injuries													
Vascular disease[d]	Yes	27	12.9	**1.79***	**1.01–3.19**	28	7.7	26	11.4	1.49	0.81–2.74	31	8.5
	No	183	87.1	1	–	336	92.3	202	88.6	1	–	334	91.5
Diabetes mellitus	Yes	8	3.6	0.77	0.33–1.78	19	5.1	6	2.6	0.48	0.19–1.24	22	5.8
	No	217	96.4	1	–	354	94.9	225	97.4	1	–	355	94.2
Migraines	Yes	32	14.3	**1.96***	**1.14–3.36**	30	8.1	16	7.0	0.67	0.37–1.21	39	10.4
	No	192	85.7	1	–	341	91.9	211	93.0	1	–	335	89.6
Rheumatic disease[e]	Yes	15	7.1	2.05	0.99–4.25	14	3.8	6	2.6	1.08	0.51–2.29	10	2.7
	No	196	92.9	1	–	351	96.2	216	97.3	1	–	362	97.3
Carpal tunnel syndrome	Yes	22	10.0	1.24	0.67–2.30	31	8.4	20	8.7	1.40	0.74–2.64	26	6.9
	No	198	90.0	1	–	339	91.6	209	91.3	1	–	350	93.1
Polyneuropathy	Yes	7	3.2	**5.58***	**1.12–27.79**	3	0.8	0	0	0.03	0.00–18.71	7	1.8
	No	215	96.8	1	–	362	99.2	225	100.0	1	–	374	98.2
Upper extremity nerve injury	Yes	73	32.7	**2.09***	**1.42–3.09**	72	19.4	46	20.4	1.17	0.77–1.79	65	17.1
	No	150	67.3	1	–	300	80.6	180	79.6	1	–	316	82.9
Frostbite hands[f]	Yes	89	39.2	**13.13***	**6.79–25.40**	23	6.1	36	15.6	**4.26***	**2.23–8.12***	15	4.0
	No	138	60.8	1	–	354	93.9	195	84.4	1	–	364	96.0

OR odds ratio, *95% CI* 95% confidence interval, *RP* Raynaud's phenomenon, *CS* cold sensitivity, *BMI* body mass index

*Bold values indicate odds ratios with significant 95% confidence intervals

[a]First-degree relative (parent, sibling or child) with Raynauds phenomenon, indicating a positive family history

[b]Statins, antibiotics, immunosuppressive drugs, antineoplastic agents, amiodarone, dapsone, phenytoin and/or hydralazine

[c]Beta-adrenergic antagonists, interferons, oral contraceptives and hormone replacement therapies, antineoplastic agents, sympathomimetics drugs, lithium, clonidine, and/or ergotamine

[d]Hypertension, angina pectoris, myocardial infarction, stroke, and/or peripheral vascular disease

[e]Systemic sclerosis, CREST syndrome, rheumatoid arthritis, juvenile rheumatoid arthritis, reactive arthritis, unspecified arthritis, systemic lupus erythematosus, psoriatic arthritis, ankylosing spondylitis, Sjögren's syndrome, Ehlers–Danlos syndrome, fibromyalgia, gout, polymyositis, dermatomyositis, Dercum's disease, and/or mixed connective tissue disease

[f]The majority (> 94.0%) reported first degree injuries

work (OR 3.06; 95% CI 1.92–4.90); being exposed to extreme cold, wind or cooling moisture during work (OR 2.41; 95% CI 1.53–3.79); and being exposed to any type of occupational HAV (OR 1.98; 95% CI 1.23–3.19); none of these variables were significant among cases reporting only RP.

Table 3 Univariate conditional logistic regression of external exposure factors suggested to be associated with Raynaud's phenomenon and cold sensitivity, including cold exposure and hand-arm vibration measures

Factor	Exposure level	RP cases with CS (*N* = 228)				Controls (N = 379)		RP cases without CS (N = 233)				Controls (*N* = 384)	
		N	%	OR	95% CI	*N*	%	*N*	%	OR	95% CI	*N*	%
Cold exposure measures													
Occupational cold exposure[a] (NRS 1–10)	High (NRS > 1)	110	50.7	1.44	0.995–2.09	144	40.1	84	37.7	1.15	0.78–1.71	131	36.1
	Low (NRS 1)	107	49.3	1	–	215	59.9	139	62.3	1	–	232	63.9
Leisure-time cold exposure[b] (NRS 1–10)	High (NRS > 5)	120	54.1	1.11	0.79–1.57	185	49.6	127	56.2	**1.48***	**1.04–2.12**	177	47.3
	Low (NRS ≤ 5)	102	45.9	1	–	188	50.4	99	43.8	1	–	197	52.7
Cumulative cold exposure[c] (NRS 2–20)	High (NRS > 8)	123	57.5	**1.47***	**1.03–2.09**	160	44.9	96	43.4	1.12	0.77–1.64	149	41.3
	Low (NRS ≤ 8)	91	42.5	1	–	196	55.1	125	56.6	1	–	212	58.7
Handling cold objects during work	Yes	74	33.3	**3.06***	**1.92–4.90**	61	16.4	45	19.7	1.09	0.70–1.72	70	18.5
	No	148	66.7	1	–	311	83.6	184	80.3	1	–	308	81.5
Extreme cold, wind or cooling moisture during work	Yes	81	36.2	**2.41***	**1.53–3.79**	88	23.7	55	23.9	0.94	0.62–1.43	93	24.6
	No	143	63.8	1	–	284	76.3	175	76.1	1	–	285	75.4
Occupational HAV exposure measures													
Impact tools	Yes	39	17.4	**2.60***	**1.49–4.54**	28	7.5	30	13.1	1.49	0.86–2.58	34	9.0
	No	185	82.6	1	–	344	92.5	199	86.9	1	–	344	91.0
Rapidly rotating tools	Yes	7	3.2	2.00	0.62–6.41	5	1.3	8	3.5	1.13	0.43–3.02	10	2.7
	No	215	96.8	1	–	366	98.7	219	96.5	1	–	366	97.3
Forestry/gardening tools	Yes	35	15.8	1.40	0.80–2.45	50	13.5	33	14.7	1.18	0.69–2.04	48	12.7
	No	187	84.2	1	–	321	86.5	192	85.3	1	–	329	87.3
Vibrating tools	Yes	44	19.6	**2.21***	**1.29–3.76**	40	10.8	39	17.0	1.49	0.91–2.44	46	12.3
	No	180	80.4	1	–	330	89.2	190	83.0	1	–	329	87.7
Heavily vibrating tools	Yes	39	17.5	**2.81***	**1.52–5.19**	32	8.6	34	14.8	**2.13***	**1.21–3.74**	29	7.7
	No	184	82.5	1	–	338	91.4	196	85.2	1	–	348	92.3
Vehicles with vibrating controls	Yes	34	15.2	**1.94***	**1.11–3.38**	36	9.7	28	12.2	1.21	0.68–2.16	39	10.4
	No	189	84.8	1	–	336	90.3	201	87.8	1	–	335	89.6
Any HAV exposure[d]	Yes	67	31.0	**1.98***	**1.23–3.19**	79	21.5	54	24.1	1.19	0.76–1.86	78	21.1
	No	149	69.0	1	–	289	78.5	170	75.9	1	–	291	78.9

OR odds ratio, *95% CI* 95% confidence interval, *RP* Raynaud's phenomenon, *CS* cold sensitivity, *BMI* body mass index, *NRS* numerical rating scale, *HAV* hand-arm vibration

*Bold values indicate odds ratios with significant 95% confidence intervals

[a]Self-estimated occupational cold exposure, reported on a ten-point numerical rating scales (NRS), where a value above the 50th percentile (NRS > 1) was denoted high, while a value below (NRS 1) was denoted low

[b]Self-estimated leisure-time cold exposure, reported on a ten-point numerical rating scales (NRS), where a value above the 50th percentile (NRS > 5) was denoted high, while a value below (NRS ≤ 5) was denoted low

[c]Self-estimated occupational and leisure-time cold exposure, reported on two separate ten-point numerical rating scales (NRS), were added together to form a cumulative measurement of cold exposure ranging from 2 to 20, and a value above the 50th percentile (NRS > 8) was denoted high, while a value below (NRS ≤ 8) was denoted low

[d]Any recurrent occupational hand-arm vibration (HAV) exposure, including use of impact tools, rapidly rotating tools, forestry and gardening tools, vibrating tools, heavily vibrating tools, and/or vehicles with vibrating controls

Multiple model

In the final multiple model for cases reporting RP and CS, the following factors remained, reported in the same sequence as added to the model: frostbite affecting the hand (OR 12.44; 95% CI 5.84–26.52); heredity for RP (OR 4.03; 95% CI 2.17–7.46); BMI ≥ 25 kg/m^2 (OR 0.27; 95% CI 0.16–0.45); upper extremity nerve injury (OR 2.23; 95% CI 1.29–3.85); and work with cold objects (OR 1.73; 95% CI 0.91–3.31). For cases reporting only RP, the final multiple model included the following factors: frostbite affecting the hands (OR 4.01; 95% CI 1.78–9.01); heredity for RP (OR 5.08; 95% CI 2.82–9.17); BMI ≥ 25 kg/m^2 (OR 0.54; 95% CI 0.36–0.83); daily tobacco use (OR 1.57; 95% CI 0.96–2.57); heavily vibrating tools (OR 1.45; 95% CI 0.72–2.93); leisure-time cold exposure above the 50th percentile (OR 1.32; 95% CI 0.85–2.07); migraines (OR 0.56; 95% CI 0.25–1.22); and heredity for migraines (OR 1.35; 95% CI 0.83–2.20).

Analyses stratified by sex (Electronic supplementary material)

There were only minor differences when univariate analyses were stratified for sex for cases with RP and CS: vascular disease and migraines was only significant for men (OR 2.57; 95% CI 1.15–5.73 and OR 3.90; 95% CI 1.19–12.79, respectively), and rheumatic disease only for women (OR 2.75; 95% CI 1.05–7.25). Cumulative cold exposure was only significant for women (OR 1.63; 95% CI 1.04–2.56), and any HAV exposure only for men (OR 2.71; 95% CI 1.46–5.03).

Discussion

Key results

In the univariate analyses, those with RP and simultaneous CS showed associations to certain diseases and injuries (vascular disease; migraines; polyneuropathy; upper extremity nerve injury) and external factors (cold and occupational HAV exposure) that were not present among cases only reporting RP. In the multiple model, frostbite, heredity for RP and high BMI (protective) remained in both case groups, but upper extremity nerve injury only remained in the group reporting RP and CS. When comparing effect sizes in the multiple model, the odds ratio for frostbite was much higher among those reporting RP and CS compared to the other group (OR 12.44 and 4.01, respectively). Also, the effect of BMI seemed stronger in the RP and CS group compared to RP only (OR 0.27 and 0.54, respectively).

Interpretation and comparison

In our univariate analyses of the group reporting both RP and CS, there was a greater occurrence of diseases and injuries that are normally regarded as causes for secondary RP, such as vascular disease, cold injury and HAV syndrome [2, 3]. A number of these diseases and injuries have previously been reported in conjunction to CS alone, such as vascular disease [24], nerve injury [10], cold injury [25] and HAV syndrome [12]. Thus, it seems that CS and secondary RP share several common denominators, which suggest that CS is an acquired condition primarily arising as a result of peripheral neural or vascular injury. The peripheral nerves are supported by the vasa nervorum, a network of small blood vessels that provide perfusion from adjacent arteries, and this offers an explanation as to how vascular pathology could lead to neural injury. The basis for vascular pathology can be structural, such as in atherosclerotic disease, or functional as a result of vasospasm. In an angiographic study of 103 men and women suffering from bilateral RP without any established secondary cause, about half of them had obvious atherosclerotic changes and the other half vasospasm, showing that both can be present and contribute to the clinical picture [26]. However, apart from ischemic effects on nerves, it is also likely that a proportion of subjects may have autonomic neuropathy of other cause, which can predispose to vascular phenomena. An attack of RP is commonly associated with neurosensory symptoms, such as pain or paresthesia, and this has been described as a result of sensory nerve ischemia [27]. Research on cold injury, where CS is a prevalent sequelae, indicate that ischemic nerve injury from hypoperfusion may also play an important role in the etiology of CS [20]. We hypothesize that frequent ischemic episodes due to RP attacks, possibly in conjunction with other peripheral vascular and neural disease, can cause a long-lasting dysfunction in the peripheral sensory nerves of the hands, giving rise to the reporting of CS. The fact that upper extremity nerve injury was the only remaining factor that differed between case groups in our multiple model, offers additional support to the neural basis for CS.

The fact that migraines was only associated with RP with CS in the univariate analyses, and not with subjects only reporting RP, is a novel finding. A recent review [1] showed a strong association between migraines and primary RP (pooled OR 4.02; 95% CI 2.62–6.17) and the authors concluded that the pathophysiological background for migraines includes both vascular and neural events, with a paroxysmal nature similar to other vasospastic conditions, such as RP and variant angina, which have previously been shown to be associated to migraines [28]. Other

authors have suggested that all three conditions may share a common underlying defect and could be characterized as a clinical syndrome of generalized arterial vasospasm [29, 30]. However, the role of vasoregulatory dysfunction in migraines has recently been downplayed, and a distinct mechanistic link is lacking [31]. Thus, the neural hypothesis in both CS and migraines, and their possible interplay, is a subject for further study.

Our data showed that being overweight was inversely related to reporting RP, while being underweight did not show any significant relation to our studied outcome, the latter most likely due to insufficient statistical power. Several previous studies have documented an inverse relationship between BMI and RP [24, 32, 33], and this finding could be explained by an increased amount of body fat having an insulating effect, maintaining both core and peripheral temperature.

Previous authors have reported smoking as a risk factor for RP [1], but this was not confirmed in our study. We investigated the current daily use of cigarettes or snuff, and it is likely that subjects suffering from RP would be encouraged by health care professionals to diminish or discontinue their use of tobacco, leading to an underestimation of the contribution of tobacco to the development of RP, and possibly CS, in our study. Neither could we establish an association between RP and the use of therapeutic drugs, including beta-adrenergic antagonists, oral contraceptives and hormone replacement therapies, which have previously been suggested as risk factors [1, 34]. However, we had a large amount of missing data (25.0%) in our questionnaire item about therapeutic drugs, which we believe was not missing at random since there were no checkbox for declaring no use, and this could have affected the reliability of analyses.

In our univariate analyses, a high cold exposure or handling of cold objects was significantly associated with reporting RP and CS, but not to only reporting RP. A previous French cross-sectional study showed that working in an environment with an ambient temperature below 15 °C for > 4 h per day, and handling cold objects and hand tools, was strongly associated with reporting RP [32]. Unfortunately, CS was not investigated in that study. Other studies have shown that patients with RP show a decreased perfusion of fingers during cold exposure [35] and have an increased risk of contracting cold injuries [36]. As described above, ischemic effects on peripheral nerves might then serve as an explanation for CS in heavily cold-exposed subjects with RP. However, whether cold exposure is a cause or mere trigger of RP, remains controversial [20].

Some authors have argued that epidemiologic studies on risk factors for RP should preferably be performed with men and women analyzed separately, since the pattern of risk factors may differ between the sexes [37]. However, the main purpose of this study was to distinguish between subjects with both RP and CS from those with only RP, rather than highlighting sex differences. For fullness, we provided supplemental sex-specific analyses in Online Appendix.

Strengths

This study represents a large population-based sample that explores a broad range of possible risk factors and introduces several interesting concepts regarding the background for RP and CS. Even though CS lacks a standardized definition, the clear difference in CISS and VAS results between cases with CS and other study participants support that our definition and inclusion criteria for CS were relevant. Since the questionnaires were administered during the cold winter period, the risk of recall bias regarding cold exposure was considered low.

Limits

One of the major limits of this study is that the nested case–control study design cannot be used to establish causal relations between individual and exposure factors and the disease states studied. However, it would be difficult to perform a longitudinal study with sufficient sample size and follow-up time. Another issue is that both RP and CS diagnoses were based on self-assessment, which limits the accuracy. Since our study does not investigate the reporting of CS in isolation, without concomitant RP, it is hard to distinguish which factors would be relevant only to the reporting of CS. However, an attempt to characterize CS more closely has previously been made on subjects selected from the same population [7]. The fact that the multiple model showed few remaining differences between the groups is suspected to be partly due to the covariance between the studied factors, for instance, that subjects who report previous frostbite could also be heavily exposed to ambient and contact cold. Further studies entailing longitudinal risk factor assessment, as well as objective evaluations of CS, are encouraged. Clinicians could benefit from separating CS from RP, since the etiology as well as the need for medical investigation may differ.

Conclusion

Raynaud's phenomenon is strongly associated to previous cold injury, with a larger effect size among those who also report cold sensitivity. The fact that only upper extremity nerve injury differed significantly between case groups in our multiple model offers additional support to the neural basis for cold sensitivity.

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Compliance with ethical standards

Conflict of interest Albin Stjernbrandt, Hans Pettersson, Ingrid Liljelind, Tohr Nilsson and Jens Wahlström declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study protocol was approved by the Regional Ethical Review Board situated at Umeå University (DNR 2015-24-31M and 2014-286-31M).

Informed consent Informed consent was obtained from all individual participants included in the study.

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