Cold Intolerance and Associated Factors: A Population Study

Alireza Khabbazi (dr.khabazi@gmail.com)
Tabriz University of Medical Sciences
Rojin Farzaneh
Tabriz University of Medical Sciences
Maryam Mahmoudi
Tabriz University of Medical Sciences
Mohammad Shahi
Tabriz University of Medical Sciences
Amirreza Jabbaripour Sarmadian
Tabriz University of Medical Sciences
Elaheh Babapour
Tabriz University of Medical Sciences
Leila Alizadeh
Tabriz University of Medical Sciences
Raha Khabbazi
Tabriz University of Medical Sciences
Masoud Nouri-Vaskeh
Tabriz University of Medical Sciences

Research Article

Keywords: Cold intolerance, cold sensitivity, Cold Intolerance Symptom Severity (CISS) questionnaire

Posted Date: February 15th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1323589/v1

Abstract

Cold intolerance has been defined as a set of symptoms including pain, tingling, numbness, chills, stiffness, weakness, swelling or skin color changes on exposure to cold. Cold intolerance may have a profound effect on health-related quality of life. In this cross-sectional study, we investigated the prevalence of cold intolerance and associated factors in the general population of Tabriz. Simple random sampling of individuals aged ≥18 was performed from the population covered by Emamieh health center under the supervision of Tabriz University of Medical Sciences. A telephone interview was conducted with the participants by the general physician of that center. In participants with a positive response to each of two questions "I am oversensitive to cold" and "I experience pain or discomfort when exposed to cold" a Cold Intolerance Symptom Severity (CISS) questionnaire was filled. We used a cut off value 50 for defining cold intolerance. Of the 353 person who received telephone calls, 322 answered questions. Cold related symptoms and cold intolerance were reported in 144 (44.7%) and 38 (11.1%) persons, respectively. Being female and having fibromyalgia, upper limb disease and history of upper limb surgery were independent risk factors for predicting cold intolerance. Cold intolerance disturbed job in 27 (8.4%) and led to a change in job in 6 (1.9%) persons. Cold intolerance is a common problem in the general population that may lead to job disruption and even job change.

Introduction

Cold intolerance or cold sensitivity has been defined as a set of symptoms including pain, tingling, numbness, chills, stiffness, weakness, swelling or skin color changes on exposure to cold. Neurovascular, humoral and endocrine factors play role in the pathogenesis of cold intolerance[1]. Recently, the role of genetic factors in determining the severity of cold induced pain in different people has been considered. Soeda et al. reported an association between cold induced pain sensitivity and the rs2243057 polymorphism of the protease-activated receptor 2 and rs12992084 polymorphism of the transient receptor potential melastatin 8 genes. These receptors are involved in the sensation of pain[2]. Cold intolerance has been reported in many conditions including upper extremity injuries and surgeries, fibromyalgia, anemia, hypothyroidism, atherosclerosis, Raynaud's disease, diabetes, low body weight, vitamin B12 deficiency, Fabry disease, side effects of medications, hypothalamus diseases, paroxysmal cold hemoglobinuria and Waldenstrom's macroglobulinemia[1,3,4]. Carlsson et al. reported cold intolerance in 45% of person with history of traumatic hand injuries[5]. Novak et al. reported cold intolerance in 30% of patients with hand related traumatic and non-traumatic pathologies[6]. Klocker et al. reported cold intolerance in 41% of patients underwent repair of upper limb arterial injuries[7].

Cold intolerance may have a profound effect on health-related quality of life[5]. Cold intolerance is one of the main reasons of disability after hand injuries or surgeries[7–11]. Despite many studies that reported the frequency of cold intolerance after upper limb surgeries, the literature on the prevalence of cold intolerance in the general population is scarce. In this cross-sectional study, we investigated the prevalence of cold intolerance and associated factors in the general population of Tabriz.

Results

Of the 353 person who received telephone calls, 322 answered questions. Demographic characteristics of participants were shown in Table 2. Cold related symptoms were reported in 144 (44.7%) persons. Pain was the most common symptom when exposed to cold. Pain severity was 6.53 ± 2.47. Frequency of symptoms in exposure to cold were shown in Table 1. The mean CISS in the 144 subjects measured was 36.9 ± 18.6. Cold intolerance according CISS ≥50 was reported in 38 (11.1%) patients. Cold intolerance was started during childhood or adolescence in 19 (50.0%) patients. In the other cases, it started at the ages of 18-30, 30-50 and ≥50 in 6 (15.7%), 9 (23.7%) and 9 (23.7%) cases, respectively. Cold intolerance disturbed job in 27 (8.4%) and led to a change in job in 6 (1.9%) persons.

Table 1
Comparison of studied population and Tabriz population characteristics.

Parameters	Tabriz (n=1558693)							Study population (n=322)						
	18-29 (%)	30-39 (%)	40-49 (%)	50-59 (%)	60-69 (%)	>70 (%)	Total (%)	18-29 (%)	30-39 (%)	40-49 (%)	50-59 (%)	60-69 (%)	≥70 (%)	Total (%)
Gender														
Female	22.1	27.5	20.1	14.9	9.0	6.4	100	23.8	26.8	20.7	13.4	9.8	5.5	100
Male	22.8	278	19.7	14.8	8.7	6.3	100	23.4	25.9	19.6	15.2	10.1	5.7	100
Education level														
Illiterate	1.7	3.4	10.5	24.6	39.8	62.9	10.1	1.3	4.0	4.6	7.8	9.0	60.0	12.1
Primary	5.9	11.4	22.5	24.8	27.1	22.2	23.3	2.6	17.3	47.7	39.2	28.9	33.3	25.5
Highschool	48.2	52.5	45.1	36.1	21.7	9.0	43.9	70.5	44.0	29.2	33.3	5.3	6.7	37.9
University	44.2	32.7	21.9	14.5	11.4	5.9	22.6	25.6	34.7	18.5	19.6	15.8	0	24.5
n, number														

Table 2
Demographic and health characteristics of participants (n=322)

Parameters	n (%)
Female (%)	164 (50.9)
Age	
18-29 (%)	76 (23.6)
30-39 (%)	85 (26.4)
40-49 (%)	65 (20.2)
50-59 (%)	46 (14.3)
60-69 (%)	32 (9.9)
≥ 70 (%)	18 (5.6)
BMI (mean ± SD)	26.2 ± 4.2
Smoker (%)	32 (9.9)
Education	
Illiterate (%)	39 (12.1)
Primary school (%)	82 (25.5)
Highschool (%)	122 (37.9)
University (%)	79 (24.5)
Comorbidities (%)	88 (27.3)
Hypertension (%)	35 (10.9)
Diabetes (%)	30 (9.3)
Anemia (%)	6 (1.9)
Thyroid disorders	16 (5.0)
Hypertension (%)	46 (10.9)
Fibromyalgia (%)	21 (6.5)
Peripheral vascular diseases (%)	5 (1.6)
Upper limb trauma (%)	13 (4.0)
Upper limb diseases (%)	12 (3.7)
Upper limb surgery (%)	12 (3.7)
Rheumatic diseases (%)	4 (1.2)
Cold related symptoms (%)	144 (44.7)
Pain (%)	78 (54.2)
Numbness (%)	39 (27.1)
Shivering (%)	33 (22.9)

n, number; BMI, body mass index; SD, standard deviation

Parameters	n (%)
Skin color change (%)	19 (13.2)
Weakness (%)	14 (9.7)
Stiffness (%)	4 (2.8)
Swelling (%)	4 (2.8)
Cold intolerance (%)	38 (11.8)
n, number; BMI, body mass index; SD, standard deviation	

Demographic and clinical characteristics of participants with and without cold intolerance were shown in Table 3. Being female and having fibromyalgia, upper limb disease and history of upper limb surgery were independent risk factors for predicting cold intolerance (Table 4).

Table 3
Frequency of cold intolerance in different groups

Parameters	CISS ≥ 50 (N=38)	CISS < 50 (N=284)
Age	7 (18.4)	71 (25.0)
18-29 (%)	7 (18.4)	68 (23.9)
30-39 (%)	7 (18.4)	58 (20.4)
40-49 (%)	10 (26.3)	41 (14.4)
50-59 (%)	7 (18.4)	46 (16.2)
≥ 60 (%)		
Female (%)	27 (71.1)	137 (48.2)
Obesity (%)	7 (18.9)	49 (17.3)
Smoking (%)	3 (7.9)	29 (10.2)
Familial history of cold intolerance (%)	14 (36.8)	59 (20.8)
Comorbidities		
Hypertension (%)	8 (21.1)	27 (9.5)
Diabetes (%)	7 (18.4)	23 (8.1)
Anemia (%)	4 (10.5)	2 (0.7)
Hypothyroidism (%)	3 (7.9)	13 (4.6)
Fibromyalgia (%)	11 (28.9)	10 (3.5)
Upper limb trauma (%)	4 (10.5)	9 (3.2)
Upper limb disease (%)	7 (18.4)	5 (1.8)
Upper limb surgery (%)	5 (13.2)	7 (2.5)
Peripheral vascular diseases (%)	1 (2.6)	4 (1.4)
Hypothalamic disorders (%)	0	0
Rheumatic diseases (%)	0	4 (1.4)
Medications		
Beta blockers (%)	2 (5.3)	14 (4.9)
Alfa blockers (%)	0	1 (0.4)
Levothyroxine (%)	4 (10.5)	14 (4.9)
Statins (%)	4 (10.5)	13 (4.6)
Psychoactive medications (%)	4 (10.6)	17 (6.0)
Calcium blockers (%)	0	4 (1.4)
Antihypertensive agents (%)	6 (15.8)	27 (9.5)

CISS, Cold Intolerance Symptom Severity

Table 4
Predictors of cold intolerance in different groups.

Predictors	Univariate		Multivariate	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Age ≥ 50 (%)	1.8 (0.9-1.8)	**0.084**	1.5 (0.7-3.3)	0.351
Female (%)	2.6 (1.3-5.5)	**0.010**	2.7 (1.2-6.2)	**0.016**
Obesity (%)	1.1 (0.5-2.7)	0.809		
Smoking (%)	0.6 (0.1-4.4)	0.586		
Familial history of cold intolerance (%)	2.3 (1.1-4.8)	**0.023**	1.5 (0.6-3.5)	0.352
Comorbidities				
Hypertension (%)	2.5 (1.1-6.1)	**0.037**	1.1 (0.3-3.6)	0.849
Diabetes (%)	2.6 (1.1-6.5)	**0.046**	2.2 (0.8-6.6)	0.145
Anemia (%)	5.3 (1.5-18.9)	**0.002**	1.5 (0.3-7.6)	0.122
Hypothyroidism (%)	1.5 (0.5-4.7)	0.441		
Fibromyalgia (%)	11.2 (4.3-28.6)	**0.001**	7.3 (2.6-20.5)	**0.001**
Peripheral vascular diseases	1.9 (0.2-17.4)	0.573		
Upper limb trauma (%)	3.6 (1.1-12.3)	**0.042**	0.6 (0.1-5.9)	0.696
Upper limb diseases (%)	12.6 (3.8-42.1)	**0.001**	6.1 (1.5-24.7)	**0.012**
Upper limb surgeries (%)	5.9 (1.8-19.9)	**0.004**	7.1 (1.9-26.4)	**0.003**
Medications				
Beta blockers (%)	1.1 (0.2-4.9)	0.929		
Levothyroxine (%)	2.1 (0.7-5.8)	0.162		
Statins (%)	2.4 (0.8-7.9)	0.135		
Psychoactive medications (%)	1.8 (0.6-5.8)	0.294		
Antihypertensive agents (%)	1.8 (0.7-4.7)	0.236		
CI, confidence interval; OR, odds ratio				

Discussion

In our study cold related symptoms and cold intolerance were reported in 44.7 and 11.1 present of studied population. The demographic characteristics of studied population shows that it can be considered as a representative of the general population of Tabriz. Despite numerous studies on the frequency of cold intolerance in patients with upper limb surgeries and injuries, a few studies exist about the frequency of cold intolerance in general population. Carlsson et al. reported frequency of self-reported cold intolerance in 5% of normal population in Sweden[5]. In another study Stjernbrandt et al. reported cold intolerance in 9.7% of men and 14.4% of women in Sweden[4]. They found a positive correlation between cumulative cold exposure and cold intolerance[4].

In our studied cases fibromyalgia (OR 7.3), upper limb surgeries (OR 7.1), upper limb diseases (OR 6.1) and being female (OR 2.7) were the independent risk factors of cold intolerance. We could not find associations between cold intolerance and age,

body mass index (BMI), medications and underlying diseases like diabetes and hypertension. There were differences between our results and previous studies. Stjernbrandt et al. reported that frostbite affecting the hands (OR 10.3) is the strongest risk factor for cold intolerance[12]. In addition, upper extremity nerve injury (OR 2.0), and having rheumatic disease (OR 3.1), migraines (OR 2.4) and vascular disease (OR 1.9) were associated with cold sensitivity[12]. Unlike our results, a BMI ≥ 25 was a negative risk factor for cold intolerance[12]. In a study on 198 patients with traumatic and non-traumatic hand pathologies, there was no difference in the prevalence of cold-induced symptoms between men and women[6]. Collins et al. in a study on 50 patients with upper-extremity peripheral nerve injuries did not report association between cold sensitivity with age and smoking[13]. Similarly, Ruijs et al. did not report association between cold sensitivity with age in general population[14]. In another study on patients with arterial repair in upper extremity injuries no association was reported between sex and age with cold intolerance[7].

In our studied population cold intolerance led to disturbance in job in 8.4% and a change in job in 1.9%. In Collin et al. report on patients who were followed after upper-extremity peripheral nerve injuries no association was observed between the presence or absence of cold intolerance and job change[15]. Carlsson et al. reported disturbance in job in 27% of patients with traumatic hand injuries or hand-arm vibration syndrome, and also higher CISS scores [66 (21-86)] in patients who changed jobs than those who remained in their previous jobs [45 (7-85)][5].

This study for the first time reported the frequency of cold intolerance in Iran. Population based design of the study and high rate of participation were the advantage of our study. Important limitations of the study were the relatively small sample size that did not provide a sufficient number of cases in some subgroups.

Methods

This cross-sectional study was conducted from October 13 to November 13, 2021 in Tabriz. The city of Tabriz is the largest city in northwestern Iran with a population of more than 1.5 million people. Tabriz has a Continental climate with regular seasons bordering cold semi-arid climate. Simple random sampling of individuals aged ≥18 was performed from the population covered by Emamieh health center under the supervision of Tabriz University of Medical Sciences. Comparison of age distribution, sex and educational level of participants with Tabriz population aged ≥ 18 showed that study population is reliably representative of Tabriz population (Table 1)[16]. A telephone interview was conducted with the participants by the general physician of that center. Due to the fact that the population covered by this health center was closely followed, the participation rate was more than 90%. A questionnaire contained questions about age, sex, weight, height, job, smoking, family history of cold intolerance, current medications, underlying diseases, history of frostbite, history of hand injuries and surgeries, cold intolerance symptoms and effect of cold intolerance on job was filled out during interview and completed and rechecked by their medical records. In participants with a positive response to each of the two questions “I am oversensitive to cold” and “I experience pain or discomfort when exposed to cold” a Cold Intolerance Symptom Severity (CISS) questionnaire was filled. The CISS score evaluates 6 domains with various subsets of questions[14]. Scores range from 4 to 100, and higher scores indicate worse symptoms[14]. We used a cut off value 50 for defining cold intolerance[12]. Severity of cold sensitivity in exposure to cold weather was assessed using a 100 mm visual analogue scale (VAS). The study was conducted in accordance with the Declaration of Helsinki and its protocol was approved by the Ethics Committee of Tabriz University of Medical Sciences. Informed consent has been obtained from all participants.

Statistical analysis

Statistical analyses were conducted using the SPSS statistical package (SPSS Inc., version 16). Qualitative and quantitative variables were displayed as numbers (percentages) and means ± standard deviation (SD), respectively.

The parameters associated with cold intolerance were subjected to univariate analysis. The predictive factors for cold intolerance with P-values of <0.1 in univariate analysis were included in a Binary logistic regression analysis with cold intolerance as a dependent factor and variables with significant differences in univariate analysis as covariates to calculate

odds ratios with 95% confidence intervals (OR, 95% CI). Variable selection was performed using a backward stepwise method based on P-value. We evaluated accuracy of the model using Hosmer and Lemeshow test. *P*-value less than 0.05 was considered significant.

Conclusion

Cold intolerance is a common problem in the general population that may lead to job disruption and even job change. Being female and having fibromyalgia, upper limb disease and history of upper limb surgery are independent risk factors.

Declarations

Funding Information

This research was supported by the Connective Tissue Diseases Research Center.

Conflicts of interest

We declare, we have no potential conflict of interest.

We declare that no part of the review is copied or published elsewhere.

Acknowledgements

We would like to express our thanks to Leila Khabazi for editing the text.

Contributions

Conceptualization and designing the study: RF, LA and AK

Data acquisition: MM, MS, AJ, RK, EB and MN

Data analysis: AK

Drafting the manuscript: RF and AK

Data Availability Statements

Data available on request.

The data underlying this article will be shared on reasonable request to the corresponding author.

References

1. Stjernbrandt, A., Carlsson, D., Pettersson, H., Liljelind, I., Nilsson, T. & Wahlström, J. Cold sensitivity and associated factors: a nested case-control study performed in Northern Sweden. Int. Arch. Occup. Environ. Health. **91**:785–797. https://doi.org/10.1007/s00420-018-1327-2 (2018).
2. Soeda, M., Ohka, S., Nishizawa, D., Hasegawa, J., Nakayama, K., Ebata, Y., Ichinohe, T., Fukuda, K.I. & Ikeda, K. Cold pain sensitivity is associated with single-nucleotide polymorphisms of PAR2/F2RL1 and TRPM8. <background-color:#CCFF99;bidirection:ltr;>Mol. Pai.</background-color:#CCFF99;bidirection:ltr;> **17**, 17448069211002009. https://10.1177/17448069211002009 (2021).
3. U.S. National Library of Medicine: https://medlineplus.gov/ency/article/003095.htm; Accessed 10 Jan 2022.
4. Stjernbrandt, A., Pettersson, H., Liljelind, I., Nilsson, T. & Wahlström, J. Raynaud's phenomenon in Northern Sweden: a population-based nested case–control study. Rheumatol. Int. **39**, 265–275. https://doi.org/ 10.1007/s00296-018-4133-y

(2019).

5. Carlsson, I.K., Rosén, B. & Dahlin, L.B. Self-reported cold sensitivity in normal subjects and in patients with traumatic hand injuries or hand-arm vibration syndrome. *BMC. Musculoskeletal. Disorders*<bi>.</bi> **11**, 89. https://doi.org/10.1186/1471-2474-11-89 (2010).
6. Novak, C.B. & McCabe, S.J. Prevalence of cold sensitivity in patients with hand pathology. <bi>Hand (N Y)</bi> **10**, 173-6. https://doi.org/ 10.1007/s11552-014-9694-y (2015).
7. Klocker, J., Peter, T., Pellegrini, L., Mattesich, M., Loescher, W., Sieb, M., Klein-Weigel, P. & Fraedrich, G. Incidence and predisposing factors of cold intolerance after arterial repair in upper extremity injuries. J. Vasc. Surg. **56**, 410–4. https://doi.org/10.1016/j.jvs.2012.01.060 (2012).
8. Koman, L.A., Slone, S.A., Smith, B.P., Ruch, D.S. & Poehling, G.G. Significance of cold intolerance in upper extremity disorders. J. South. Orthop. Assoc. **7**, 192–197 (1988).
9. Rosen, B. Recovery of sensory and motor function after nerve repair. A rationale for evaluation. J. Hand. Ther. **9**, 315–327. https://doi.org/10.1016/s0894-1130(96)80037-8 (1996).
10. Lithell, M., Backman, C. & Nystrom, A. Cold intolerance is not more common or disabling after digital replantation than after other treatment of compound digital injuries. Ann. Plast. Surg. **40**, 256–259. https://doi.org/10.1097/00000637-199803000-00010 (1998)
11. Irwin, M.S., Gilbert, S.E., Terenghi, G., Smith, R.W. & Green, C.J. Cold intolerance following peripheral nerve injury. Natural history and factors predicting severity of symptoms. J. Hand. Surg. Br. **22**, 308–16. https://doi.org/10.1016/s0266-7681(97)80392-0 (1997).
12. Statistical Center of Iran: https://www.amar.org.ir/Portals/0/News/1397/n-koli-95.pdf. Updated 19 Jan 2022.
13. Ruijs, A.C.J., Jaquet, J-B., Daanen, H.A.M., Hovius, & S.E.R. Cold intolerance of the hand measured by the CISS questionnaire in a normative study population. J Hand Surg Br. 2006;31:533–6.
14. Carlsson, IK, Nilsson, JA, Dahlin, LB. Cut-off value for self-reported abnormal cold sensitivity and predictors for abnormality and severity in hand injuries. J. Hand. Surg. Eur. **35**, 409–16. https://doi.org/10.1177/1753193409354184 (2010.)
15. Stjernbrandt, A., Carlsson, D., Pettersson, H., Liljelind, I., Nilsson, T. & Wahlström, J. Cold sensitivity and associated factors: a nested case-control study performed in Northern Sweden. <bi>Int. Arch. Occup. Environ. Health.</bi> **91**, 785-797. https://doi.org/0.1007/s00420-018-1327-2 (2018).
16. Collins, E.D., Novak, C.B., Mackinnon, S.E. & Weisenborn, S.A. Long-term follow-up evaluation of cold sensitivity following nerve injury. J. Hand. Surg. Am. **21**, 1078–85. https://doi.org/ 10.1016/S0363-5023(96)80319-4 (1996).