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Author contribution

M. Bizjak initiated, entitled and designed the COLD-CE study, collected data, performed data quality controls, and developed the manuscript. D. Terhorst-Molawi and M. Maurer contributed to study design and provided critical input to the manuscript. M. Bizjak and D. Terhorst-Molawi were principal investigators. M. Bizjak and D. Dinevski performed statistical analyses. All authors

contributed to acquisition of data, interpretation of data and manuscript development and approved it for publication.

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ABSTRACT

Background: Cold urticaria (ColdU), i.e. the occurrence of wheals or angioedema in response to cold exposure, is classified into typical and atypical forms. The diagnosis of typical ColdU relies on whealing in response to local cold stimulation testing (CST). It can also manifest with cold-induced anaphylaxis (ColdA). We aimed to determine risk factors for ColdA in typical ColdU.

Methods: An international, cross-sectional study COLD-CE was carried out at 32 urticaria centers of reference and excellence (UCAREs). Detailed history was taken and CST with an ice cube and/or TempTest® performed. ColdA was defined as an acute cold-induced involvement of the skin and/or visible mucosal tissue and at least one of: cardiovascular manifestations, difficulty breathing, or gastrointestinal symptoms.

Results: Of 551 ColdU patients, 75% (n=412) had a positive CST and ColdA occurred in 37% (n=151) of the latter. Cold-induced generalized wheals, angioedema, acral swelling, oropharyngeal/laryngeal symptoms, and itch of earlobes were identified as signs/symptoms of severe disease. ColdA was most commonly provoked by complete cold water immersion and ColdA caused by cold air was more common in countries with a warmer climate. Ten percent (n=40) of typical ColdU patients had a concomitant chronic spontaneous urticaria (CSU). They had a lower frequency of ColdA than those without CSU (4% vs 39%, $p=0.003$). We identified the following risk factors for cardiovascular manifestations: previous systemic reaction to a *Hymenoptera* sting, angioedema, oropharyngeal/laryngeal symptoms, and itchy earlobes.

Conclusion: ColdA is common in typical ColdU. High-risk patients require education about their condition and how to use an adrenaline autoinjector.

Keywords

adrenaline autoinjector, COLD-CE, cold urticaria, risk factors, systemic reactions

Abbreviations

aOR.....	adjusted odds ratio
BMI.....	body mass index
CIndU.....	chronic inducible urticaria
ColdA.....	cold-induced anaphylaxis
COLD-CE.....	comprehensive evaluation of cold urticaria and other cold-induced reactions, a study of the GA ² LEN UCARE network
ColdU.....	cold urticaria
CR(s).....	cold-induced reaction(s)
CST.....	cold stimulation testing
CSTT.....	critical stimulation time threshold
CSU.....	chronic spontaneous urticaria
CTT.....	critical temperature threshold
GA ² LEN.....	Global Allergy and Asthma European Network
IQR.....	interquartile range
OR.....	odds ratio
UCARE(s).....	Urticaria Center(s) of Reference and Excellence

INTRODUCTION

Cold urticaria (ColdU) is a subtype of chronic inducible urticaria (CIndU) where wheals, angioedema or both, with or without systemic signs or symptoms occur in response to cooling of the skin and/or mucosal tissue and/or the whole body.¹⁻³ Patients react to a wide range of triggers including cold air, contact with cold liquids, contact with cold solid surfaces, and the ingestion of cold food or drinks.^{2,3} ColdU is classified into typical and atypical forms.¹

The diagnosis of typical ColdU relies on immediate whealing at the tested skin site on the volar forearm in response to local cold stimulation testing (CST) with an ice cube and/or the thermoelectric device TempTest®.^{1,4} Both tests are endorsed by the 2016 EAACI/GA²LEN/EDF/UNEV consensus guidelines for CIndU.⁴ In atypical ColdU, local CST induces atypical responses (e.g., adjacent or delayed whealing) or specific provocation methods are needed to produce whealing (e.g., general body cooling). The pathophysiology underlying negative CST in atypical ColdU represents an enigma. Additionally, clinical features of atypical forms of ColdU are ill-characterized, and a better and clinically useful classification of ColdU needs to be developed.¹

The CST can also define the critical stimulation time threshold (CSTT) and the critical temperature threshold (CTT), i.e. the shortest contact time and the highest temperature that induce a wheal.^{1,3-6} TempTest® 4.0 has a single Peltier element (length: 350 mm, width: 2 mm) that provides a continuous gradient of temperatures from 4 to 44°C^{4,5} and the previous version 3.0 has 12 cold probes set at 2°C intervals from 4 to 26°C.⁷ CTT values obtained by both devices were shown to correlate.⁶

Anaphylaxis is a clinical emergency, and all healthcare professionals should be familiar with its recognition, treatment and prevention.⁸⁻¹⁰ Physical triggers such as cold and heat have been described to induce anaphylaxis.¹⁰⁻¹² The term cold-induced anaphylaxis (ColdA) has been used in a few prior studies of ColdU,^{3,13,14} but a consensus on its precise definition has not yet been established. ColdA is potentially life-threatening, although the fatality rate remains unknown.^{1,15} A delay in adrenaline administration is a risk factor for anaphylaxis-related death.¹⁶⁻¹⁸ Systemic reactions to cold exposure have been reported in 4 to 47% of ColdU patients (Table 1).^{3,13,14,19-30} Some clinical features linked to severe reactions were already described (i.e., positive local CST,²¹ shorter CSTTs,^{23,28} higher CTTs,²³ longer ColdU duration,²³ and oropharyngeal angioedema;²⁷ Table 1), but predictors for

ColdA remain ill defined. High-risk ColdU patients require an adrenaline autoinjector, but exactly which patients should carry it remains to be defined.³¹ Yee *et al*,²¹ Katsarou-Katsari *et al*,²⁵ and Alangari *et al*²⁶ suggested that all patients with ColdU should be provided with an adrenaline autoinjector, but this strategy could lead to high health care costs and trigger unnecessary anxiety in patients who have a low risk of life-threatening reactions.

To address these unmet needs, we investigated a large and diverse cohort of patients with typical ColdU for their rates of ColdA and their clinical characteristics. Most importantly, we investigated them for predictors of ColdA. The knowledge of risk factors of ColdA can help to better counsel patients with typical ColdU and help them to prevent ColdA.

PATIENTS AND METHODS

Study design

COLD-CE (i.e., comprehensive evaluation of ColdU and other cold-induced reactions)¹ is an international, cross sectional, observational study. The study was led by the University Clinic of Respiratory and Allergic Diseases Golnik, Slovenia and Charité – Universitätsmedizin Berlin, Germany and conducted in additional 30 GA²LEN (Global Allergy and Asthma European Network) UCAREs (Urticaria Centers of Reference and Excellence)³² from 17 countries between May 2019 and May 2021 (Table S1). The study was approved by the National Medical Ethics Committee of the Republic of Slovenia (KME0120-62/2019/4, 17.04.2019), Ethics Committee at Charité - Universitätsmedizin Berlin (EA1/069/19, 18.06.2019), and the responsible Ethics Committees of other participating institutions as required. Dated and signed written informed consent was obtained for all patients. Analyses of COLD-CE data are ongoing and additional results will be reported in further publications.

Study participants

This study included 551 ColdU patients who reported active ColdU during the 12 months prior to evaluation and were enrolled in COLD-CE during their routine clinical visits.

The association between cold-induced reactions and cold triggers

Patients were asked whether they had ever experienced the following cold-induced reactions (CRs): itch (CR1), localized wheals only (CR2), generalized wheals (CR3, Figure 1A), angioedema (CR4), swelling on acral body parts (CR5; i.e., fingertips, knuckles, or ears; Figures 1B and C), hypotension (i.e., RR<90/60 mmHg) or loss of consciousness (CR6), other signs or symptoms suggestive of hypotension (CR7; i.e., dizziness, sensation of fainting, weakness), difficulty breathing (CR8; i.e., dyspnoea, wheeze, stridor), or gastrointestinal symptoms (CR9). Secondly, they were asked whether the following cold triggers caused at least one CR: complete cold water immersion (T1), cold ambient air exposure (T2), transition from cold outdoors (<17°C) to warm indoors (T3), localized contact with cold liquids or ice (T4), and contact with cold surfaces (T5). Thirdly, we explored the link between CRs and triggers and analyzed additional reactions: oropharyngeal or laryngeal symptoms (i.e., indicating swelling of the tongue and pharynx, hoarseness) and itch of earlobes, but we did not collect data on triggers of the latter two reactions.

Comorbidity analysis

Patients were asked about the following comorbidities: (i) chronic spontaneous urticaria (CSU), (ii) asthma, (iii) atopic dermatitis and/or allergic rhinoconjunctivitis (we did not obtain data on frequency of atopic dermatitis and frequency of allergic rhinoconjunctivitis) data on individual comorbidity was not collected), (iv) previous systemic reaction to a *Hymenoptera* sting, and (v) thyroid disease.

Cold stimulation testing (CST)

Study participants discontinued H₁-antihistamines and systemic glucocorticoids at least 3 and 7 days before CST, respectively.⁴ A 5 minute stimulation was performed with an ice cube melting in a small amount of water in a non-latex medical glove (Figure 1D) or a plastic bag and/or with TempTest® 3.0 or 4.0 device (Figure 1G). TempTest® version 3.0 was used in 5 UCAREs and version 4.0 in 17 UCAREs. Skin responses were assessed 10 minutes after the end of stimulation. Tests were considered positive if whealing appeared at the tested skin site. In patients with a positive ice cube test, shorter stimulation (30 sec, 1 min, 2 min, 3 min, 4 min) was done to determine the CSTT (Figure 1E). Tested sites were observed for the presence of pseudopodial whealing indicating spreading of the wheal beyond the stimulated area (Figure 1F). In patients who tested positive with TempTest®, the

CTT and the maximal wheal diameter were measured (Figures 1H and 1I). Participants receiving omalizumab therapy (n=43) were excluded from analyses of these CST-parameters.

Categorization of patients

The diagnosis of typical ColdU was based on a positive CST at enrollment and/or in the past. We defined ColdA as an acute cold-induced involvement of the skin and/or visible mucosal tissue (CR1–5) and at least one of the following: cardiovascular manifestations (CR6 and/or CR7), difficulty breathing (CR8), or gastrointestinal symptoms (CR9).^{1,3,8,10,33} Cardiovascular manifestations, considered the most severe and reliable criterion for ColdA, were analyzed separately. We explored ColdA induced by: (i) at least one of triggers (T1–5), (ii) complete cold water immersion, (iii) cold air, (iv) transition from cold outdoors to warm indoors, and (v) localized contact with cold liquids, ice or surfaces. Patients were also categorized into residents of countries with a temperate, cold or tropical climate as shown in Table S1.

Statistical analyses

The data were analyzed using IBM SPSS software V25. Descriptive measures included frequencies, proportions, ranges, and medians with the first and third quartile range. Numerical variables were first assessed for normality distribution by visualization and tests of normality. Non-parametric statistic test (Mann-Whitney U test) was used given a non-normal distribution of all numerical variables. Categorical variables were assessed by the Fisher's Exact test. Univariate logistic regression analysis was done to assess the effect of these variables to 3 possible binary outcomes in typical ColdU. To control for possible confounder effects, we further assessed statistically significant variables by multivariate logistic regression analysis. A set of 7 independent variables was chosen in the final equation (i.e., multiple regression model with the highest Nagelkerke's R square coefficient of multiple determination) based on clinical reasoning, their odds ratio (OR) and forward and backward selection. The OR and adjusted OR (aOR) were reported with a 95% confidence interval (CI) and $p < 0.05$ was considered statistically significant (Figures 2A–C, Table S3).

RESULTS

Three of four patients with ColdU have typical ColdU.

Of 551 patients with ColdU, 75% (n=412) were diagnosed with typical ColdU. Among the latter, 70% (n=289) were females, 91% (n=374) adults, and 24% (n=99) had a pediatric onset of typical ColdU. Their median age was 36 years (IQR 26–48), age at onset of ColdU 29 years (IQR 18–42), and disease duration (i.e., time since first signs/symptoms) 42 months (IQR 17–108) (Table S2).

More than a third of patients with typical ColdU experience ColdA.

ColdA occurred in 37% (n=151) of patients with typical ColdU (Table 2). The most common triggers were complete cold water immersion, in 27% (n=112) of patients, and cold ambient air exposure, in 13% (n=54) of typical ColdU patients (n=412). Additional reported triggers of ColdA were transition from cold outdoors to warm indoors (n=11), localized contact with cold liquids or ice (n=8), and contact with cold surfaces (n=2).

Comorbid CSU is linked to a decreased frequency of ColdA reactions.

Ten percent (n=40) of typical ColdU patients had a concomitant CSU (Table 2). Comorbid CSU was linked to a lower frequency of ColdA and cardiovascular manifestations caused by at least one of triggers (T1–5; Table 2) and by complete cold water immersion (Table S4). Further analyses were done in typical ColdU patients without CSU (n=372; Tables 2 and 3).

Cold-induced generalized wheals, angioedema and acral swelling are signs of severe ColdU.

Patients with generalized wheals (n=231) and angioedema (n=184) had a higher frequency of ColdA provoked by complete cold water immersion or cold air than those without (Table 3, Tables S4 and S5A). Acral swelling (n=126) was linked to a higher frequency of ColdA provoked by cold air (Table 3, Table S5A), and it was more common in patients with angioedema caused by at least one of triggers (T1–5) than those without (69% vs 31%, $p<0.001$).

Oropharyngeal/laryngeal symptoms and itch of earlobes are symptoms of severe typical ColdU.

A history of oropharyngeal/laryngeal symptoms (n=117) and itchy earlobes (n=146) were associated with a higher frequency of ColdA induced by complete cold water immersion or cold air (Table 3, Table S4 and S5A). Oropharyngeal/laryngeal symptoms were more common in patients with angioedema caused by at least one of triggers (T1–5) than those without (40% vs 23%, $p<0.001$).

ColdA induced by exposure to cold air is more common in countries with a tropical climate.

Residents of tropical countries had: (i) a higher frequency of ColdA (including cardiovascular manifestations, difficulty breathing, and gastrointestinal symptoms) induced by cold air and (ii) a lower frequency of ColdA (including cardiovascular manifestations) induced by complete cold water immersion than residents of temperate or cold climate countries (Table 3, Table S1).

ColdA induced by complete cold water immersion is linked to clinical characteristics of patients living in temperate climates.

Residents of temperate regions had a higher frequency of ColdA (including cardiovascular manifestations and difficulty breathing) induced by complete cold water immersion than residents of cold climate countries (Table 3). Patients living in temperate regions, who experienced ColdA induced by complete cold water immersion (n=94), had significantly: (i) longer disease duration, (ii) higher frequency of generalized wheals, angioedema, oropharyngeal/laryngeal symptoms, and itchy earlobes, (iii) shorter CSTTs, and (iv) larger TempTest[®]-induced wheal diameters than those without this ColdA phenotype (Table 3). Two of them also had aquagenic urticaria. Additionally, patients living in temperate regions, who experienced cardiovascular manifestations induced by complete cold water immersion (n=80), had a higher frequency of pseudopodial whealing than those without (Table 3).

Pediatric onset of typical ColdU was linked to severe systemic reactions.

Hypotension and/or loss of consciousness induced by complete cold water immersion was linked to a pediatric onset of typical ColdU. Patients with these reactions also had a higher frequency of angioedema and previous systemic reactions to *Hymenoptera* stings (Table 3, Table S4).

The features of ColdA induced by transition from cold outdoors to warm indoors are similar to those of ColdA induced by cold air.

ColdA induced by transition from cold outdoors to warm indoors was rare (n=11). It was more common in patients who had also experienced ColdA triggered by cold air exposure than those without (13% vs 1%, $p<0.001$), and both phenotypes had similar clinical features (Table S6).

ColdA induced by localized contact with cold liquids/ice/surfaces occurred only in colder countries.

ColdA induced by localized contact with ice, cold liquids or surfaces was reported only in countries with a temperate climate (n=9) and a country with a cold climate (n=1). Of these 10 patients, 50% (n=5) had cardiovascular manifestations and 70% (n=7) difficulty breathing. Patients with locally triggered ColdA also had shorter CSTTs than those without this ColdA phenotype (median [IQR]: 60 [45–60] vs 300 [120–300] sec, $p=0.015$).

Five independent risk factors are associated with ColdA in typical ColdU.

Of 16 analyzed categorical variables (Table 2), 7 were risk factors for ColdA based on univariate logistic regression analysis (Table S3). Further multivariate logistic regression analysis identified the following 5 independent risk factors for ColdA: a previous systemic reaction to a *Hymenoptera* sting (aOR=3.30, CI: 1.24–8.79, $p=0.017$), angioedema (aOR=2.38, CI: 1.47–3.86, $p<0.001$), oropharyngeal/laryngeal symptoms (aOR=2.28, CI: 1.39–3.75, $p=0.001$), concomitant asthma (aOR=2.11, CI: 1.15–3.85, $p=0.015$), and itchy earlobes (aOR=2.00, CI: 1.24–3.23, $p=0.005$) (Figure 2A, Table S3).

Four factors increase the risk for cardiovascular manifestations.

We identified four independent risk factors for cardiovascular manifestations: a previous systemic reaction to a *Hymenoptera* sting (aOR=3.11, CI: 1.21–7.97, $p=0.018$), angioedema (aOR=2.12, CI: 1.29–3.49, $p=0.003$), oropharyngeal/laryngeal symptoms (aOR=2.03, CI: 1.23–3.34, $p=0.006$), and itchy earlobes (aOR=1.85, CI: 1.13–3.03, $p=0.014$) (Figure 2B, Table S3).

Comorbid asthma is linked to a higher frequency of ColdA induced by cold air.

Analysis of patients with typical ColdU (n=372) showed that ColdA induced by cold air was more prevalent in patients with comorbid asthma than those without (25% vs 12%, p=0.009; Table S7). Asthma patients did not express unique features of their ColdU when compared to non-asthma patients (Tables S7 and S8).

Three factors increase the risk for difficulty breathing in patients without asthma.

Regression analysis of risk factors for difficulty breathing was done on a subgroup of patients without asthma (n=309, Table 2). Pediatric onset of typical ColdU was associated with a 2.4 fold increased risk of cold-induced difficulty breathing (CI: 1.17–4.96, p=0.018). Oropharyngeal/laryngeal symptoms and itchy earlobes were also predictors and increased the risk of difficulty breathing by 4.9 and 2.1 fold (CI: 2.55–9.56, p<0.001; CI: 1.08–4.08, p=0.030, respectively; Figure 2C, Table S3).

DISCUSSION

This study demonstrates, in a large and multicenter patient cohort, that more than a third of patients with typical ColdU develop ColdA, which is within a range of previous reports.^{3,14,20-30} We identified clinical features linked to ColdA, characterized the triggers that prompt it, and present predictors for its occurrence. ColdA was mostly caused by complete cold water immersion, and this is also consistent with previous studies.^{14,21,23,26,27,30} Our report is the first to characterize trigger-based ColdA phenotypes.

Differences in clinical features between typical ColdU patients who do or do not have comorbid CSU have not been described before. Interestingly, concomitant CSU was linked to a lower frequency of ColdA. It is important to assess typical ColdU patients for comorbid CSU.

Our ColdA patients had a significantly longer duration of ColdU than the ones without ColdA. This is consistent with the study by Deza *et al*²³ who also reported the association between longer ColdU duration and its higher severity. By contrast, duration was not correlated with patient-related disease severity in a study by Jain *et al*.¹⁴

Cold-induced generalized wheals have previously been recognized as a feature of severe typical ColdU.^{20,21,23,25,26,28} In a French study of 35 patients, angioedema after eating cold food was predictive of the risk of ColdA provoked by complete cold water immersion, but statistical significance of this finding was not reported.²⁷ Our study showed that both angioedema and oropharyngeal/laryngeal symptoms present independent risk factors for ColdA, including cardiovascular manifestations. Acral swelling and itchy earlobes, which were also linked to severe reactions, present a novel described sign/symptom in ColdU.

We found that shorter CSTTs as determined by CST are associated with a higher frequency of ColdA induced by complete cold water immersion. In a study of 50 ColdU patients, Wanderer *et al* made a more general (i.e., not trigger-specific) conclusion that CSTT of ≤ 180 sec was associated with a higher incidence of severe systemic reactions.²⁸ In a study of 74 ColdU patients by Deza *et al*, shorter CSTTs were likewise significantly related to systemic reactions.²³ Neittaanmäki reported that 14% of patients with a 30 sec CSTT had a severe type of ColdU.³⁰ TempTest[®] has been used in many studies to confirm typical ColdU and to measure the CTT. Deza *et al*²³ and Mlynek *et al*³⁴ reported the association between higher CTT and higher ColdU severity, but CTTs in our study were not

associated with increased likelihood of ColdA. On the other hand, larger TempTest®-induced wheal diameters were associated with an increased frequency of ColdA and cardiovascular manifestations induced by complete cold water immersion. In a study by Yee and coworkers, the median diameter of wheals induced by an ice cube (a non standardized method) was higher in patients with ColdA than in those without, but the difference did not reach significance.²¹ Since TempTest® testing has been validated for identifying CTTs, further studies are needed to evaluate its usefulness in wheal-diameter assessment.

We identified a higher frequency of ColdA induced by cold air in countries with a tropical climate. Cold tolerance induction by repeated exposures to cold temperatures (e.g., cold baths or showers) has been used to achieve temporary cold desensitization in ColdU.³⁵⁻⁴⁰ It remains unknown whether typical ColdU patients residing in colder countries develop tolerance to cold ambient air exposure or whether ColdA in residents of tropical countries is triggered by different mechanisms.

Ten patients had severe cold sensitivity with ColdA provoked by localized contact with ice, cold liquids or surfaces in real life, which is an important reminder that caution is needed during CST. The mechanism for the occurrence of a systemic reaction after a local cold stimulation remains unknown. Interestingly, it has been described that systemic symptoms in ColdU have been prevented when venous return from the exposed site was obstructed with a tourniquet.⁴¹

COLD-CE has several strengths. The study was conducted in several certified UCAREs by physicians specialized in urticaria, with a robust protocol, with well-defined data collection tools and provocation testing, and in a sizable cohort of more than 500 patients. The limitations of our study are inherent in the cross-sectional study design, lacking prospective evaluations of risk factors for ColdA. Further studies are needed to confirm their relevance and to establish their predictive values including their specificity and sensitivity. Additionally, the frequency of cold-induced cardiovascular reactions and systemic reactions to venoms were determined based on patient history data collected by physicians. It remains unknown how many of these patients had proper tests required for the diagnosis of IgE-mediated allergy to venoms or systemic mastocytosis. Patient- or physician-reported “venom allergy” without a proper allergological work-up might overestimate the real prevalence of venom allergy and the relevance of this feature as a risk factor for ColdA. We assume that ColdA patients need to be tested for underlying mastocytosis similarly to patients with *Hymenoptera* venom-triggered

anaphylaxis.⁴²⁻⁴⁴ Bizjak *et al* recently reported a patient in whom a clonal mast cell disorder was suspected (and confirmed) only based on clinical features of severe ColdU.³ Potential limitation of our study may also arise from the fact that patients with mild ColdU or with ColdA that resolved without treatment, may not seek medical advice, and our data may over-represent severe ColdU compared to that occurring in the community. Our study provides novel insights into ColdU characteristics in tropical, temperate and cold climates, significantly extending previous observations.^{20,30,45} However, the climate-based comparison of ColdU has limitations which need to be assessed in future studies taking into account the latitude of the patient's residence and behaviour patterns regarding swimming in open waters and other risk taking behaviors.

The results of our study imply changes in clinical practice. For the first time, we propose the criteria for adrenaline autoinjector prescription for patients with typical ColdU, as shown in Figure 3. ColdU patients with risk factors for ColdA need to be educated on the avoidance of relevant cold triggers and recognition of the onset of severe reactions. High-risk ColdU patients need to carry an adrenaline autoinjector and know how and when to self-inject and follow-up with a specialist if ColdA occurs.

Table 1. Previous studies that assessed severe systemic reactions in ColdU.

Region	Total cases (n)	Study design	Age group	Systemic reactions			Frequency of typical ColdU	Authors, y
				Description/definition (cited)	Frequency	Indicators [†]		
Slovenia	36	P	Adult	ColdA – sudden cold-induced onset of at least 2 of the following: involvement of the skin and/or mucosal tissue, respiratory involvement, reduced blood pressure or associated symptoms, or gastrointestinal symptoms.	33% (12/36)	NP	61% (22/36)	Bizjak <i>et al</i> , 2021 ³
Germany	49	P	Pediatric/adult	ColdA (description NP)	47% (23/49)	NP	69% (34/49)	Ginter <i>et al</i> , 2021 ¹³
Portugal	52	R	Pediatric/adult	Systemic symptoms (with respiratory and/or cardiovascular compromise)	33% (17/52)	NP	83% (43/52)	Paulino <i>et al</i> , 2021 ¹⁹
Thailand	27	R	Adult	Anaphylaxis (one patient had dyspnoea and collapsed)	4% (1/27)	NP	100% (27/27)	Kulthanan <i>et al</i> , 2019 ²⁰
United States	415	R	Pediatric	Anaphylaxis (grade 3) – severe systemic reactions consisting of urticaria and/or angioedema associated with airway, respiratory and/or abdominal symptoms and/or cardiovascular or neurologic symptoms suggestive of hypotension including dizziness, lethargy, sensation fainting, disorientation or shock /or symptoms of shock.	19% (77/415)	Positive local CST	70% (179/256)	Yee <i>et al</i> , 2019 ²¹
Canada	59	R	Pediatric/adult	ColdA (description NP)	4% (2/50)	NP	85% (50/59)	Stepaniuk <i>et al</i> , 2018 ²²
Australia	99	R, P	Pediatric/adult	Anaphylaxis – respiratory symptoms of noisy or difficulty breathing (dyspnoea, bronchospasm/wheeze, cyanosis/hypoxia) and/or cardiovascular compromise (loss of consciousness or reported presyncope).	28% (28/99)	NP	NP	Jain and Mullins, 2016 ¹⁴
Spain	74	R	NP	Type III – severe systemic reactions with episodes suggestive of hypotension (ie, dizziness, sensation of fainting, disorientation, or shock) or respiratory distress (eg, shortness of breath or wheezing).	19% (14/74)	Shorter CSTT Higher CTT Longer ColdU duration	72% (53/74)	Deza <i>et al</i> , 2016 ²³
Germany	30	P	Adult	A: dizziness/difficulty swallowing/circulation disorders/dyspnoea	A: 33% (10/30)	NP	100% (30/30)	Siebenhaar <i>et al</i> ,

				B: unconsciousness/shock	B: 13% (4/30)			2009 ²⁴
Greece	62	P	Adult	Type III – severe systemic reactions with one or more episodes of generalized urticaria or angioedema associated with hypotension (dizziness, fainting, disorientation, shock).	29% (18/62)	NP	84% (46/55)	Katsarou-Katsari <i>et al</i> , 2008 ²⁵
United States	30	R	Pediatric	Type III – severe systemic reactions with ≥ 1 episodes suggestive of respiratory distress (such as wheezing or shortness of breath) or hypotension (ie, dizziness, sensation of fainting, disorientation, or shock) A: respiratory distress B: decrease in the level of consciousness (dizziness, faintness, or hypotension)	Type III: 37% (11/30) A: 17% (5/30) B: 27% (8/30)	NP	59% (17/29)	Alangari <i>et al</i> , 2004 ²⁶
France	35	P	NP	Shocklike reactions concurrently with hypotension, dizziness, and fainting.	34% (12/35)	Oropharyngeal angioedema	100% (35/35)	Mathelier-Fusade <i>et al</i> , 1998 ²⁷
United States	50	P	NP	Type III – severe systemic reactions with one or more episodes of generalized urticaria and/or angioedema associated with episodes suggestive of hypotension, i.e., dizziness, sensation of fainting, disorientation, or shock.	38% (19/50)	CSTT ≤ 3 min	80% (40/50)	Wanderer <i>et al</i> , 1986 ²⁸
Netherlands	39	R, P	Pediatric/adult	A: collapse B: dyspnoea	A: 36% (14/39) B: 8% (3/39)	NP	92% (36/39)	Doeglas <i>et al</i> , 1986 ²⁹
Finland	220	R, P	NP	A: fainting or shock B: dyspnoea	A: 7% (16/220) B: 14% (31/220)	NP	94% (207/220)	Neittaanmäki, 1985 ³⁰

Table 1.

†Patient-related features linked to systemic reactions.

Abbreviations: ColdA, cold-induced anaphylaxis; ColdU, cold urticaria; CST, cold stimulation testing; CSTT, critical stimulation time threshold; CTT, critical temperature threshold; NP, not provided; P, prospective study; R, retrospective study; y, year.

Table 2. Characteristics of typical ColdU patients stratified by the presence of ColdA, cardiovascular manifestations, and difficulty breathing caused by at least one of triggers (T1–5).

		ColdA – broad definition ^{†§}				Cardiovascular manifestations (CR6 and/or CR7) [§]			Difficulty breathing (CR8) [§] , no asthma			
All typical ColdU patients		Total, n=412	Yes, n=151	No, n=261	p-value	Yes, n=120	No, n=292	p-value	Total, n=343	Yes, n=59	No, n=284	p-value
Comorbid CSU		40 (10%)	6 (4%)	34 (13%)	0.003	4 (3%)	36 (12%)	0.005	34 (10%)	2 (3%)	32 (11%)	0.091
Typical ColdU patients without CSU		Total, n=372	Yes, n=145	No, n=227	p-value	Yes, n=116	No, n=256	p-value	Total, n=309	Yes, n=57	No, n=252	p-value
Demographics and baseline characteristics	Female gender	258 (69%)	102 (70%)	156 (69%)	0.818	81 (70%)	177 (69%)	1.000	210 (68%)	40 (70%)	170 (68%)	0.755
	Age at study enrollment (y)	36 (26–48)	36 (26–49)	36 (26–48)	0.897	36 (25–48)	36 (26–48)	0.730	36 (26–50)	35 (24–48)	37 (26–50)	0.465
	Age ≥18 y at study enrollment	338 (91%)	135 (93%)	203 (89%)	0.271	106 (91%)	232 (91%)	1.000	283 (92%)	54 (95%)	229 (91%)	0.437
	Age at onset of ColdU (y)	30 (18–42)	30 (16–40)	29 (19–44)	0.287	30 (16–39)	29 (19–44)	0.284	30 (18–44)	24 (15–39)	30 (20–44)	0.072
	Pediatric onset of ColdU (<18 y)	90 (24%)	40 (28%)	50 (22%)	0.264	32 (28%)	58 (23%)	0.360	70 (23%)	18 (32%)	52 (21%)	0.082
	ColdU duration (months)	41 (17–99)	60 (24–129)	36 (13–80)	0.001	56 (24–120)	36 (14–84)	0.041	48 (17–108)	60 (26–132)	41 (14–108)	0.046
	BMI	24 (22–28)	25 (22–28)	24 (22–28)	0.773	24 (22–27)	24 (22–28)	0.789	24 (22–28)	24 (22–28)	24 (22–28)	0.852
Cold-induced reactions	Itch [§]	356 (96%)	139 (96%)	217 (96%)	1.000	111 (96%)	245 (96%)	1.000	294 (95%)	54 (95%)	240 (95%)	0.745
	Wheals [§]	360 (97%)	140 (97%)	220 (97%)	1.000	113 (97%)	247 (97%)	0.761	300 (97%)	56 (98%)	244 (97%)	1.000
	Localized wheals only [§]	126 (34%)	33 (23%)	93 (41%)	<0.001	27 (23%)	99 (39%)	0.004	107 (35%)	13 (23%)	94 (37%)	0.045
	Generalized wheals [§]	231 (62%)	106 (73%)	125 (55%)	<0.001	85 (73%)	146 (57%)	0.003	190 (62%)	43 (75%)	147 (58%)	0.016
	Angioedema, unknown/any location [§]	184 (50%)	97 (67%)	87 (38%)	<0.001	78 (67%)	106 (41%)	<0.001	154 (50%)	40 (70%)	114 (45%)	0.001
	Acral swelling [§]	126 (34%)	63 (43%)	63 (28%)	0.002	56 (48%)	70 (27%)	<0.001	101 (33%)	25 (44%)	76 (30%)	0.060
	Oropharyngeal/laryngeal symptoms	117 (32%)	68 (47%)	49 (22%)	<0.001	55 (47%)	62 (24%)	<0.001	93 (30%)	36 (63%)	57 (23%)	<0.001
Comorbidities	Itchy earlobes	146 (39%)	77 (53%)	69 (30%)	<0.001	62 (53%)	84 (33%)	<0.001	116 (38%)	33 (58%)	83 (33%)	0.001
	At least one of asthma, AD or AR	144 (39%)	60 (41%)	84 (37%)	0.445	47 (41%)	97 (38%)	0.647	81 (26%)	17 (30%)	64 (25%)	0.507
	Asthma	63 (17%)	34 (23%)	29 (13%)	0.010	26 (22%)	37 (15%)	0.073	NA	NA	NA	NA
	Systemic reaction to <i>Hymenoptera</i>	22 (6%)	14 (10%)	8 (4%)	0.022	12 (10%)	10 (4%)	0.030	20 (7%)	6 (11%)	14 (6%)	0.227
CS	Thyroid disease	58 (16%)	22 (15%)	36 (16%)	0.885	16 (14%)	42 (16%)	0.644	49 (16%)	11 (19%)	38 (15%)	0.426
	IC ₅₀ CSTT (sec)	300	180 (60–300),	300	0.098	180 (60–300),	300	0.011	300 (60–300),	240 (60–300),	300 (120–300),	0.507

T _{res}	cub _e		(120–300), n=206	n=66	(120–300), n=140		n=47	(120–300), n=159		n=170	n=28	n=142	
		Pseudopodial whealing	31 (9%), n=337	15 (12%), n=125	16 (8%), n=212	0.178	15 (15%), n=98	16 (7%), n=239	0.021	27 (10%), n=279	4 (9%), n=45	23 (10%), n=234	1.000
	TempTest®	CTT (°C)	18 (14–24), n=200	18 (14–24), n=81	18 (14–24), n=119	0.689	20 (14–24), n=66	18 (14–24), n=134	0.420	19 (14–24), n=170	20 (14–24), n=27	18 (14–24), n=143	0.514
		Maximal TempTest® 4.0- wheal diameter (mm)	9 (5–13), n=146	10 (6–14), n=65	8 (5–12), n=81	0.114	10 (6–15), n=53	8 (5–12), n=93	0.012	10 (6–13), n=121	10 (5–13), n=24	10 (6–13), n=97	0.700

Table 2.

Data are given as no. (%) and median (IQR). If not obtained in all patients, patient numbers are displayed as “n”. Statistical significance of differences between patient groups was calculated by Fisher’s Exact test and Mann-Whitney U test. Statistically significant values ($p < 0.05$) are in bold.

†ColdA was defined as an acute cold-induced involvement of the skin and/or visible mucosal tissue and at least one of the following: cardiovascular manifestations (CR6 and/or CR7), difficulty breathing (CR8), or gastrointestinal symptoms (CR9). Cardiovascular manifestations were defined as hypotension or loss of consciousness (CR6) and/or other signs or symptoms suggestive of hypotension (i.e., dizziness, sensation of fainting, weakness; CR7). Difficulty breathing (CR8) was defined as dyspnoea, wheeze or stridor.

§Induced by at least one of triggers (T1–5): complete cold water immersion (T1; CWI), cold ambient air exposure (T2), transition from cold outdoors to warm indoors (T3), local contact with cold liquids or ice (T4), and contact with cold surfaces (T5).

Abbreviations: AD, atopic dermatitis; AR, allergic rhinoconjunctivitis; BMI, body mass index; ColdA, cold-induced anaphylaxis; ColdU, cold urticaria; CR, cold-induced reaction; CST, cold stimulation testing; CSTT, critical stimulation time threshold; CSU, chronic spontaneous urticaria; CTT, critical temperature threshold; CWI, complete cold water immersion; IQR, interquartile range; n, number of patients; y, year(s).

Table 3. Characteristics of systemic reactions caused by at least one of triggers (T1–5), complete cold water immersion or cold ambient air exposure in all patients with typical ColdU and residents of countries with temperate, cold and tropical climate.

		ColdA - broad definition ^{††}			Cardiovascular manifestations (CR6 and/or CR7) [‡]			Hypotension and/or loss of consciousness (CR6) [‡]			Difficulty breathing (CR8), no asthma [¶]			Gastrointestinal symptoms (CR9) [‡]		
Trigger		Any [§]	CWI	Air	Any [§]	CWI	Air	Any [§]	CWI	Air	Any [§]	CWI	Air	Any [§]	CWI	Air
		T1–5	T1	T2	T1–5	T1	T2	T1–5	T1	T2	T1–5	T1	T2	T1–5	T1	T2
All patients	Yes (n=372 [‡] , n=309 [¶])	145	107	53	116	88	31	48	41	10	57	40	26	39	23	20
Δ○	% within yes	39%	29%	14%	31%	24%	8%	13%	11%	3%	18%	13%	8%	11%	6%	5%
Temperate	Yes (n=264 [‡] , n=220 [¶])	115	94	32	95	80	18	38	35	3	43	35	14	24	19	8
▲●	% within yes	44%	36%	12%	36%	30%	7%	14%	13%	1%	20%	16%	6%	9%	7%	3%
Cold	Yes (n=75 [‡] , n=64 [¶])	16	10	9	9	7	2	3	3	1	5	3	3	4	3	2
▲●	% within yes	21%	13%	12%	12%	9%	3%	4%	4%	1%	8%	5%	5%	5%	4%	3%
Tropical	Yes (n=33 [‡] , n=25 [¶])	14	3	12	12	1	11	7	3	6	9	2	9	11	1	10
▲●	% within yes	42%	9%	36%	36%	3%	33%	21%	9%	18%	36%	8%	36%	33%	3%	30%
Tropical vs temperate or cold (p-value)		0.710	0.008	0.001	0.556	0.002	<0.001	0.168	1.000	<0.001	0.029	0.754	<0.001	<0.001	0.708	<0.001
Tropical vs temperate (p-value)		1.000	0.001	0.001	1.000	<0.001	<0.001	0.306	0.781	<0.001	0.070	0.388	<0.001	<0.001	0.710	<0.001
Tropical vs cold (p-value)		0.035	0.750	0.007	0.007	0.430	<0.001	0.009	0.367	0.003	0.002	0.617	<0.001	<0.001	1.000	<0.001
Temperate vs cold (p-value)		<0.001	<0.001	1.000	<0.001	<0.001	0.267	0.015	0.023	1.000	0.036	0.021	0.771	0.352	0.431	1.000
Pediatric onset of ColdU (<18 y)								○●	○							
↑ ColdU duration		Δ●	○●	○●	○●		○			○	○					
↑ BMI		●					○									
Generalized wheals [§]		Δ▲	○●	Δ●	○●●	●	Δ●	○●		○	○		○	●		
Angioedema, unknown/any location [§]		Δ▲●●	Δ●	Δ●●●	Δ▲●	○●	Δ●	○●	○●	Δ	Δ●	○●	○	○		○

Acral swelling [§]	○●●●	●	△●●	△▲●●	●	△▲●	○●		△●	●		○●●	○●●		△●
Oropharyngeal/laryngeal symptoms	△▲▲	△●	△●▲	△●▲	○●	△▲	●		○●	△▲▲	△▲	△▲	○▲		△▲
Itchy earlobes	△▲▲	○▲	△▲	△●▲	○●	○▲	○●		●	△●●		△●	○▲		○▲
Asthma	○●		○●												
Systemic reaction to <i>Hymenoptera</i>	○●		●	○●			○●	○●							
↓ CSTT	●	○●		○●	△▲										
Pseudopodial whealing				○	○●										
↑ TempTest® 4.0-wheal diameter		○●		○	○●								○	○●	

Table 3.

Statistical significance of differences between patient groups was calculated by Fisher's Exact test and Mann-Whitney U test. Statistically significant results are shown as $\Delta\blacktriangle\blacktriangle\blacktriangle$ for $p\leq 0.001$ and $\circ\bullet\bullet\bullet$ for $p<0.05$. Analogous symbols of different colors are used for 4 patient groups: $\Delta\circ$ for all patients with typical ColdU (detailed results are provided in Tables S5A–E), $\blacktriangle\bullet$ for residents of countries with a temperate climate, $\blacktriangle\bullet$ for residents of countries with a cold climate, and $\blacktriangle\bullet$ for residents of countries with a tropical climate (Table S1).

†ColdA was defined as an acute cold-induced involvement of the skin and/or visible mucosal tissue and at least one of the following: cardiovascular manifestations (CR6 and/or CR7), difficulty breathing (CR8), or gastrointestinal symptoms (CR9). Cardiovascular manifestations were defined as hypotension or loss of consciousness (CR6) and/or other signs or symptoms suggestive of hypotension (i.e., dizziness, sensation of fainting, weakness; CR7). Difficulty breathing (CR8) was defined as dyspnoea, wheeze or stridor.

‡Analysis of typical ColdU patients without CSU (n=372).

¶Analysis of typical ColdU patients without CSU and without asthma (n=309).

§Induced by at least one of triggers (T1–5): complete cold water immersion (T1; CWI), cold ambient air exposure (T2), transition from cold outdoors to warm indoors (T3), local contact with cold liquids or ice (T4), and contact with cold surfaces (T5).

Abbreviations: BMI, body mass index; ColdA, cold-induced anaphylaxis; ColdU, cold urticaria; CR, cold-induced reaction; CSTT, critical stimulation time threshold; CWI, complete cold water immersion; y, year(s).

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Figure legends

Figure 1. Characteristics linked to systemic reactions in typical ColdU.

Patients were asked whether they had ever experienced cold-induced generalized wheals (A), swelling on acral body parts (B and C), and itchy earlobes (C). CST with an ice cube melting in a small amount of water (D) was done and CSTT determined (E). The tested sites were also observed for the presence of pseudopodia (F). TempTest®-testing (G) was used to determine a maximal wheal diameter and CTT (H and I). The photos are a courtesy of Dr Mojca Bizjak.

Abbreviations: ColdU, cold urticaria; CST, cold stimulation testing; CSTT, critical stimulation time threshold; CTT, critical temperature threshold.

Figure 2. Risk factors for ColdA, cardiovascular manifestations, and difficulty breathing caused by at least one of triggers (T1–5).

Statistically significant ($p < 0.05$) results of the univariate (OR) and multivariate (aOR) logistic regression analysis for 3 binary outcomes in typical ColdU are shown. Panel A shows risk factors for ColdA in 372 patients with a typical ColdU ($R^2 = 0.238$), Panel B risk factors for cardiovascular manifestations in 372 patients with a typical ColdU ($R^2 = 0.184$), and Panel C risk factors for difficulty breathing in 309 patients with a typical ColdU and no asthma ($R^2 = 0.246$). Results are also shown in Table S3.

ColdA was defined as an acute cold-induced involvement of the skin and/or visible mucosal tissue and at least one of the following: cardiovascular manifestations (CR6 and/or CR7), difficulty breathing (CR8), or gastrointestinal symptoms (CR9). Cardiovascular manifestations were defined as hypotension or loss of consciousness (CR6) and/or other signs or symptoms suggestive of hypotension (i.e., dizziness, sensation of fainting, weakness; CR7). Difficulty breathing (CR8) was defined as dyspnoea, wheeze or stridor.

Abbreviations: aOR, adjusted odds ratio; ColdU, cold urticaria; ColdA, cold-induced anaphylaxis; R^2 , Nagelkerge's R Square.

Figure 3. Proposed criteria for adrenaline autoinjector prescription in ColdU patients.

Abbreviations: ColdA, cold-induced anaphylaxis; ColdU, cold urticaria; CST, cold stimulation testing; CSTT, critical stimulation time threshold.

Supporting information

Additional Supporting Information may be found in the online version of this article:

Table S1. List of participating UCARE centers and their classification into climate groups.

Table S2. Demographics and baseline characteristics of typical and atypical ColdU patients.

Table S3. Risk factors for ColdA, cardiovascular manifestations, and difficulty breathing in typical ColdU.

Table S4. Characteristics of typical ColdU patients stratified by the presence of ColdA, cardiovascular manifestations, and difficulty breathing caused by complete cold water immersion.

Tables S5A–E. Characteristics of typical ColdU patients significantly linked to ColdA and specific systemic reactions (also shown in Table 3).

Table S6. Characteristics of systemic reactions caused by cold ambient air exposure and/or transition from cold outdoors to warm indoors in all patients with typical ColdU and in residents of countries with a temperate, cold and tropical climate.

Table S7. Characteristics of systemic reactions caused by at least one of triggers (T1–5), complete cold water immersion or cold ambient air exposure in: (i) all patients with typical ColdU, (ii) those without asthma, and (iii) those with asthma.

Table S8. Characteristics of systemic reactions caused by cold ambient air exposure or transition from cold outdoors to warm indoors in: (i) all patients with typical ColdU, (ii) those without asthma, and (iii) those with asthma.

Conflict of interest

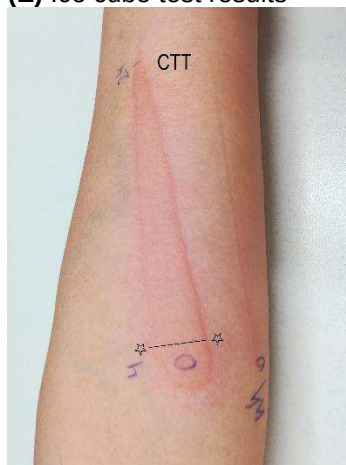
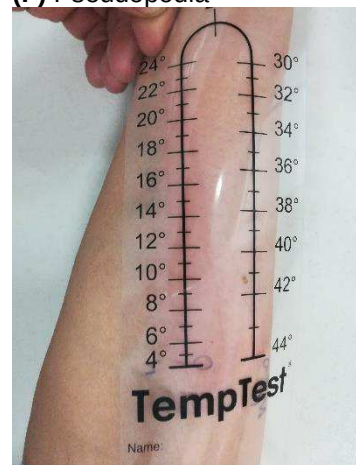
M. Bizjak has been a speaker and served on advisory boards for Novartis, outside the submitted work. S.F. Thomsen reports grants and non-financial support from Novartis, Sanofi, UCB, LEO Pharma, and Janssen, outside the submitted work. D. Fomina received honoraria from Novartis, Shire, Behring CSL and Sanofi, outside the submitted work. E. Borzova received honoraria for educational lectures from Novartis and Sanofi and research funding from GSK, outside the submitted work. R. Meshkova received honoraria from Novartis, outside the submitted work. S. Altrichter reports grants and personal fees from AstraZeneca, grants from Allakos, personal fees from Novartis, non-financial support from Moxie, grants from CSL Behring, grants from LEO Pharma, outside the submitted work. A. Bauer reports grants, personal fees and other from Novartis, personal fees and other from LEO Pharma, grants, personal fees and other from Sanofi/Regeneron, other from Amgen, other from Lilly, other from AbbVie, personal fees from Takeda, other from Pharvaris, outside the submitted work. C. Costa reports personal fees from Novartis, AstraZeneca, Menarini, Leti and Bial, outside the submitted work. R. Fachini Criado reports personal fees from Novartis, Takeda, Abbvie and Sanofi, outside the submitted work. L.F. Felipe Ensina reports personal fees from Novartis, Sanofi, Abbvie and Takeda, outside the submitted work. A.M. Giménez-Arnau reports grants and personal fees from Uriach, other from Genentech, grants, personal fees and other from Novartis, grants and personal fees from GSK, personal fees from Sanofi/Regeneron, personal fees from Amgen, personal fees from Thermo Fisher, grants from Instituto Carlos III, personal fees from LEO Pharma, personal fees from Almirall and personal fees from Avene, outside the submitted work. M. Gonçalo has been a speaker and/or advisor for Abbvie, LEO Pharma, Lilly, Novartis, Pfizer, Sanofi and Takeda, outside the submitted work. J.G. Holm has been a speaker for Novartis, outside the submitted work. E. Kocatürk reports personal fees from Novartis, Sanofi and Menarini, outside the submitted work. M. Makris reports personal fees from Novartis, Chiesi Hellas, AstraZeneca, Pfizer, GSK and Menarini, outside the submitted work. P. Xepapadaki reports personal fees from Uriach, Novartis, Nestle and Nutricia, outside the submitted work. Ma. Mauer is or recently was a speaker and/or advisor for and/or has received research funding from Allakos, Aralez, ArgenX, AstraZeneca, Celldex, Centogene, CSL Behring, FAES, Genentech, GIInnovation, Innate Pharma, Kyowa Kirin, LEO Pharma, Lilly, Menarini, Moxie, MSD, Novartis, Roche, Sanofi/Regeneron, Third HarmonicBio, UCB, and Uriach,

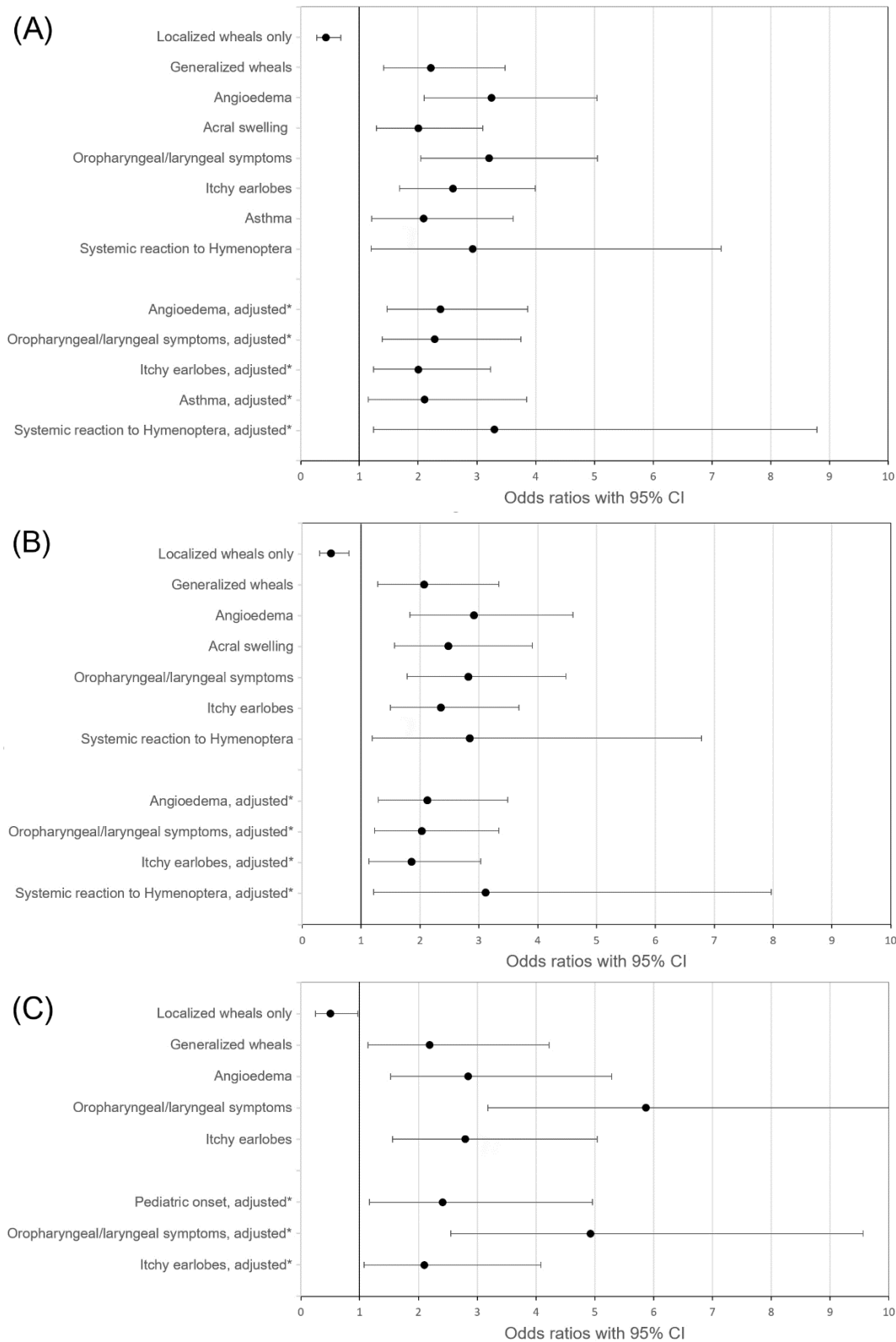
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**(A)** Generalized wheals**(B)** Acral swelling**(C)** Acral swelling and itch**(D)** CST using an ice cube**(E)** Ice cube test results**(F)** Pseudopodia**(G)** CST using a TempTest® 4.0**(H)** TempTest®-testing results**(I)** CTT reading



Proposed criteria for adrenaline autoinjector prescription in typical cold urticaria:

- previous cold-induced anaphylaxis (ColdA)
- no previous ColdA, but the patient reports cold-induced:
 - angioedema
 - oropharyngeal/laryngeal symptoms
 - itchy earlobes

Attention also to:

- long disease duration
- pediatric onset
- generalized wheals
- acral swelling
- short critical stimulation time thresholds (CSTTs)
- large wheals with pseudopodia seen at cold stimulation testing

Table S1. List of participating UCARE centers and their classification into climate groups.

Country (n=19)	Location (n=32)	Total, n=372*	Data from the Köppen-Geiger climate map ¹					
			Classification	1st symbol (climate)	2nd symbol (precipitation)	3rd symbol (temperature)	Average annual temperature (°C) [†]	The coldest monthly average (°C) [‡]
Argentina	Buenos Aires (n=2)	7	Cfa	Temperate	Without dry season	Hot summer	17.44	10.89
Brazil	São Paulo (n=2)	6	Cfa	Temperate	Without dry season	Hot summer	19.45	15.98
China	Guangzhou (n=2)	16	Cfa	Temperate	Without dry season	Hot summer	22.00	13.64
Georgia	Tbilisi	9	Cfa	Temperate	Without dry season	Hot summer	13.44	-0.51
Germany	Berlin	70	Cfa	Temperate	Without dry season	Hot summer	8.32	-1.57
Germany	Dresden	7	Cfa	Temperate	Without dry season	Hot summer	8.99	-0.03
Germany	Erlangen	5	Cfa	Temperate	Without dry season	Hot summer	7.61 [‡]	-1.68 [‡]
Greece	Athens (n=2)	33	Csa	Temperate	Dry summer	Hot summer	17.46	8.55
Iran	Mashhad	4	BSk	Temperate, arid	Steppe	Cold	13.89	1.26
Japan	Yokohama	2	Cfa	Temperate	Without dry season	Hot summer	15.28	4.98
Portugal	Coimbra	11	Csa	Temperate	Dry summer	Hot summer	15.06	9.45
Portugal	Lisbon	18	Csa	Temperate	Dry summer	Hot summer	16.49	10.82
Slovenia	Golnik	25	Cfb	Temperate	Without dry season	Warm summer	10.28 [‡]	-0.59 [‡]
South Africa	Cape Town	8	Csb	Temperate	Dry summer	Warm summer	21.52	17.87
Spain	Barcelona	19	Csa	Temperate	Dry summer	Hot summer	15.76	8.77
Turkey	Istanbul (n=2)	19	Csa	Temperate	Dry summer	Hot summer	14.43	5.72
United Kingdom	London	5	Cfb	Temperate	Without dry season	Warm summer	10.11	4.39
China	Beijing	1	Dwa	Cold	Dry winter	Hot summer	13.09	-3.91
Denmark	Copenhagen	18	Dfb	Cold	Without dry season	Warm summer	7.97	-0.35
Poland	Zabrze	13	Dfb	Cold	Without dry season	Warm summer	8.11 [‡]	-2.69 [‡]
Russian Federation	Kazan	5	Dfb	Cold	Without dry season	Warm summer	2.72	-13.91
Russian Federation	Moscow	21	Dfb	Cold	Without dry season	Warm summer	7.82	-3.00
Russian Federation	Smolensk	17	Dfb	Cold	Without dry season	Warm summer	3.99	-8.79
Brazil	Minas Gerais	11	Aw	Tropical	Savannah	/	21.33 [‡]	18.26 [‡]
Brazil	Rio de Janeiro	7	Af	Tropical	Rainforest	/	23.10	20.51
Kuwait	Safat	10	BWh	Tropical, arid	Desert	Hot	25.87 [‡]	12.79 [‡]
Thailand	Bangkok	5	Aw	Tropical	Savannah	/	28.11	25.49

*Patients with typical cold urticaria.

[†]Values obtained from the Supplementary material of the Peel *et al* manuscript.¹

[‡]Value obtained for the closest city.

Table S2. Demographics and baseline characteristics of typical and atypical ColdU patients.

	Typical ColdU (n=412)	Atypical ColdU (n=139)
Female gender	289 (70%)	96 (69%)
Age at study enrollment (y)	36 (26–48)	32 (21–46)
Age ≥18 y at study enrollment	374 (91%)	122 (88%)
Age at onset of ColdU (y)	29 (18–42)	22 (13–37)
Pediatric onset of ColdU (<18 y)	99 (24%)	47 (34%)
ColdU duration (months)	42 (17–108)	48 (15–144)
BMI	24 (22–28)	24 (21–28)

Data are given as no. (%) and median (IQR).

Abbreviations: BMI, body mass index; ColdU, cold urticaria; IQR, interquartile range; n, number of patients; y, year(s).

Table S3. Risk factors for ColdA, cardiovascular manifestations, and difficulty breathing in typical ColdU.

	ColdA – broad definition ^{†§} Figure 2A				Cardiovascular manifestations (CR6 and/or CR7) [§] Figure 2B			Difficulty breathing (CR8), no asthma [§] Figure 2C				
Univariate LR analysis	OR	95% CI		p-value [‡]	OR	95% CI		p-value [‡]	OR	95% CI		p-value [‡]
Pediatric onset	1.35	0.83	2.18	0.264	1.30	0.79	2.15	0.360	1.78	0.94	3.35	0.082
Localized wheals only [§]	0.43	0.27	0.68	<0.001	0.48	0.29	0.79	0.004	0.50	0.25	0.97	0.045
Generalized wheals [§]	2.22	1.41	3.48	<0.001	2.07	1.28	3.34	0.003	2.19	1.14	4.22	0.016
Angioedema, unknown/any location [§]	3.25	2.10	5.04	<0.001	2.91	1.83	4.60	<0.001	2.85	1.53	5.29	0.001
Acral swelling [§]	2.00	1.29	3.10	0.002	2.48	1.57	3.91	<0.001	1.81	1.01	3.26	0.060
Oropharyngeal/laryngeal symptoms	3.21	2.04	5.05	<0.001	2.82	1.78	4.48	<0.001	5.87	3.18	10.83	<0.001
Itchy earlobes	2.59	1.68	3.99	<0.001	2.35	1.50	3.68	<0.001	2.80	1.56	5.04	0.001
Asthma	2.09	1.21	3.62	0.010	1.71	0.98	2.99	0.073	NA	NA	NA	NA
Systemic reaction to <i>Hymenoptera</i>	2.93	1.20	7.16	0.022	2.84	1.19	6.78	0.030	2.00	0.73	5.45	0.227
Multivariate LR analysis	R ² = 0.238				R ² =0.184			R ² = 0.246				
	aOR	95% CI		p-value	aOR	95% CI		p-value	aOR	95% CI		p-value
Pediatric onset	1.50	0.87	2.57	0.143	1.43	0.83	2.47	0.202	2.41	1.17	4.96	0.018
Generalized wheals [§]	1.62	0.98	2.69	0.063	1.55	0.92	2.63	0.103	1.31	0.63	2.72	0.477
Angioedema, unknown/any location [§]	2.38	1.47	3.86	<0.001	2.12	1.29	3.49	0.003	1.84	0.92	3.67	0.084
Oropharyngeal/laryngeal symptoms	2.28	1.39	3.75	0.001	2.03	1.23	3.34	0.006	4.93	2.55	9.56	<0.001
Itchy earlobes	2.00	1.24	3.23	0.005	1.85	1.13	3.03	0.014	2.10	1.08	4.08	0.030
Asthma	2.11	1.15	3.85	0.015	1.66	0.91	3.04	0.099	NA	NA	NA	NA
Systemic reaction to <i>Hymenoptera</i>	3.30	1.24	8.79	0.017	3.11	1.21	7.97	0.018	1.67	0.53	5.30	0.381

Statistically significant (p<0.05) risk factors (OR>1, adjusted OR>1) are in bold and are also shown in Figures 2A–C.

[†]ColdA was defined as an acute cold-induced involvement of the skin, visible mucosal tissue, or both and at least one of the following: cardiovascular manifestations (CR6 and/or CR7), difficulty breathing (CR8), or gastrointestinal symptoms (CR9). Cardiovascular manifestations were defined as hypotension or loss of consciousness (CR6) and/or other signs or symptoms suggestive of hypotension (i.e., dizziness, sensation of fainting, weakness; CR7). Difficulty breathing (CR8) was defined as dyspnoea, wheeze or stridor.

[‡]Fisher's Exact test result (Table 2).

[§]Induced by at least one of triggers (T1–5): complete cold water immersion (T1; CWI), cold ambient air exposure (T2), transition from cold outdoors to warm indoors (T3), local contact with cold liquids or ice (T4), and contact with cold surfaces (T5).

Abbreviations: aOR, adjusted odds ratio; ColdA, cold-induced anaphylaxis; ColdU, typical cold urticaria; CI, confidence interval; CR, cold-induced reaction; LR, logistic regression; OR, odds ratio; R², Nagelkerke's R Square.

Table S4. Characteristics of typical ColdU patients stratified by the presence of ColdA, cardiovascular manifestations, and difficulty breathing caused by complete cold water immersion.

			ColdA - broad definition [†] , CWI			Cardiovascular manifestations (CR6 and/or CR7), CWI			Hypotension and/or loss of consciousness (CR6), CWI			
All typical ColdU patients			Total, n=412	Yes, n=112	No, n=300	p-value	Yes, n=92	No, n=320	p-value	Yes, n=42	No, n=370	p-value
Comorbid CSU			40 (10%)	5 (5%)	35 (12%)	0.038	4 (4%)	36 (11%)	0.048	1 (2%)	39 (11%)	0.103
Typical ColdU patients without CSU			Total, n=372	Yes, n=107	No, n=265	p-value	Yes, n=88	No, n=284	p-value	Yes, n=41	No, n=331	p-value
Demographics and baseline characteristics	Female gender		258 (69%)	75 (70%)	183 (69%)	0.901	60 (68%)	198 (70%)	0.792	28 (68%)	230 (70%)	0.859
	Age at study enrollment (y)		36 (26–48)	35 (24–50)	36 (26–48)	0.876	36 (23–50)	36 (26–48)	0.898	33 (20–50)	36 (26–48)	0.373
	Age ≥18 y at study enrollment		338 (91%)	98 (92%)	240 (91%)	0.844	79 (90%)	259 (91%)	0.675	35 (85%)	303 (92%)	0.244
	Age at onset of ColdU (y)		30 (18–42)	30 (16–41)	29 (19–43)	0.366	30 (16–51)	29 (19–43)	0.552	23 (12–42)	30 (19–43)	0.149
	Pediatric onset of ColdU (<18 y)		90 (24%)	32 (30%)	58 (22%)	0.110	26 (30%)	64 (23%)	0.200	16 (39%)	74 (22%)	0.032
	ColdU duration (months)		41 (17–99)	60 (24–120)	36 (14–84)	0.008	56 (24–117)	36 (15–96)	0.088	41 (19–120)	40 (17–96)	0.543
	BMI		24 (22–28)	24 (22–27)	25 (22–28)	0.160	24 (21–27)	25 (22–28)	0.088	23 (21–27)	25 (22–28)	0.219
Cold-induced reactions	Itch [§]		356 (96%)	102 (95%)	254 (96%)	0.783	83 (94%)	273 (96%)	0.547	38 (93%)	318 (96%)	0.401
	Wheals [§]		360 (97%)	103 (96%)	257 (97%)	0.749	85 (97%)	275 (97%)	1.000	40 (98%)	320 (97%)	1.000
	Localized wheals only [§]		126 (34%)	26 (24%)	100 (38%)	0.015	22 (25%)	104 (37%)	0.053	9 (22%)	117 (35%)	0.115
	Generalized wheals [§]		231 (62%)	76 (71%)	155 (59%)	0.025	62 (71%)	169 (60%)	0.078	31 (76%)	200 (60%)	0.062
	Angioedema, unknown/any location [§]		184 (50%)	67 (63%)	117 (44%)	0.001	55 (63%)	129 (45%)	0.007	27 (66%)	157 (47%)	0.031
	Acral swelling [§]		126 (34%)	40 (37%)	86 (33%)	0.397	34 (39%)	92 (32%)	0.303	17 (42%)	109 (33%)	0.296
	Oropharyngeal/laryngeal symptoms		117 (32%)	49 (46%)	68 (26%)	<0.001	37 (42%)	80 (28%)	0.018	15 (37%)	102 (31%)	0.478
	Itchy earlobes		146 (39%)	55 (51%)	91 (34%)	0.003	44 (50%)	102 (36%)	0.024	22 (54%)	124 (38%)	0.061
Comorbidities	At least one of asthma, AD or AR		144 (39%)	43 (40%)	101 (38%)	0.725	35 (40%)	109 (38%)	0.900	21 (51%)	123 (37%)	0.091
	Asthma		63 (17%)	23 (22%)	40 (15%)	0.169	17 (19%)	46 (16%)	0.517	11 (27%)	52 (16%)	0.080
	Systemic reaction to <i>Hymenoptera</i>		22 (6%)	9 (8%)	13 (5%)	0.225	9 (10%)	13 (5%)	0.067	6 (15%)	16 (5%)	0.024
	Thyroid disease		58 (16%)	16 (15%)	42 (16%)	0.876	13 (15%)	45 (16%)	0.868	5 (12%)	53 (16%)	0.652
CST results	Ice cube	CSTT (sec)	300 (120–300), n=206	180 (60–300), n=41	300 (120–300), n=165	0.006	180 (60–180), n=31	300 (120–300), n=175	<0.001	180 (53–300), n=14	300 (120–300), n=192	0.118
		Pseudopodial whealing	31 (9%), n=337	13 (14%), n=90	18 (7%), n=247	0.055	13 (18%), n=74	18 (7%), n=263	0.010	5 (14%), n=36	26 (9%), n=301	0.354
	TempTest [®]	CTT (°C)	18 (14–24), n=200	20 (14–25), n=66	18 (14–24), n=134	0.385	20 (14–25), n=57	18 (14–24), n=143	0.146	23 (11–25), n=26	18 (14–24), n=174	0.424
		Maximal TempTest [®] 4.0-wheal diameter (mm)	9 (5–13), n=146	10 (6–15), n=55	8 (5–11), n=91	0.014	11 (6–15), n=48	9 (5–11), n=98	0.004	10 (6–15), n=20	9 (5–12), n=126	0.421

Data are given as no. (%) and median (IQR). If not obtained in all patients, patient numbers are displayed as “n”. Statistical significance of differences between patient groups was calculated by Fisher’s Exact test and Mann-Whitney U test. Statistically significant values ($p < 0.05$) are in bold.

†ColdA was defined as an acute cold-induced involvement of the skin, visible mucosal tissue, or both and at least one of the following: cardiovascular manifestations (CR6 and/or CR7), difficulty breathing (CR8), or gastrointestinal symptoms (CR9). Cardiovascular manifestations were defined as hypotension or loss of consciousness (CR6) and/or other signs or symptoms suggestive of hypotension (i.e., dizziness, sensation of fainting, weakness; CR7). Difficulty breathing (CR8) was defined as dyspnoea, wheeze or stridor.

§Induced by at least one of triggers (T1–5): complete cold water immersion (T1; CWI), cold ambient air exposure (T2), transition from cold outdoors to warm indoors (T3), local contact with cold liquids or ice (T4), and contact with cold surfaces (T5).

Abbreviations: AD, atopic dermatitis; AR, allergic rhinoconjunctivitis; BMI, body mass index; ColdA, cold-induced anaphylaxis; ColdU, cold urticaria; CR, cold-induced reaction; CST, cold stimulation testing; CSTT, critical stimulation time threshold; CSU, chronic spontaneous urticaria; CTT, critical temperature threshold; CWI, complete cold water immersion; IQR, interquartile range; n, number of patients; y, year(s).

Tables S5A–E. Characteristics of typical ColdU patients significantly linked to ColdA and specific systemic reactions (also shown in Table 3).

Table A	ColdA - broad definition†			
Trigger	At least one of triggers (T1–5) [§]	Complete cold water immersion (T1)	Cold ambient air exposure (T2)	Out/in (T3)
No. (% of total, n=372)	145 (39%)	107 (29%)	53 (14%)	11 (3%)
	yes vs no	yes vs no	yes vs no	yes vs no
Pediatric onset of ColdU (<18 y)	28% vs 22%, p=0.264	30% vs 22%, p=0.110	30% vs 23%, p=0.299	18% vs 24%, p=1.000
ColdU duration	60 (24–129) vs 36 (13–80), p=0.001	60 (24–120) vs 36 (14–84), p=0.008	72 (32–134) vs 36 (14–94), p=0.002	78 (36–132) vs 40 (16–96), p=0.151
BMI	25 (22–28) vs 24 (22–28), p=0.773	24 (22–27) vs 25 (22–28), p=0.160	26 (23–29) vs 24 (22–27), p=0.074	29 (21–29) vs 24 (22–27), p=0.207
Generalized wheals [§]	73% vs 55%, p<0.001	71% vs 59%, p=0.025	85% vs 58%, p<0.001	73% vs 62%, p=0.544
Angioedema, unknown/any location [§]	67% vs 38%, p<0.001	63% vs 44%, p=0.001	77% vs 45%, p<0.001	82% vs 49%, p=0.034
Acral swelling [§]	43% vs 28%, p=0.002	37% vs 33%, p=0.397	59% vs 30%, p<0.001	100% vs 32%, p<0.001
Oropharyngeal/laryngeal symptoms	47% vs 22%, p<0.001	46% vs 26%, p<0.001	59% vs 27%, p<0.001	82% vs 30%, p=0.001
Itchy earlobes	53% vs 30%, p<0.001	51% vs 34%, p=0.003	60% vs 36%, p=0.001	91% vs 38%, p=0.001
Asthma	23% vs 13%, p=0.010	22% vs 15%, p=0.169	30% vs 15%, p=0.009	27% vs 17%, p=0.406
Systemic reaction to <i>Hymenoptera</i>	10% vs 4%, p=0.022	8% vs 5%, p=0.225	9% vs 5%, p=0.220	9% vs 6%, p=0.493
CSTT	180 (60–300), n=66 vs 300 (120–300), n=140, p=0.098	180 (60–300), n=41 vs 300 (120–300), n=165, p=0.006	300 (180–300), n=29 vs 300 (60–300), n=177, p=0.075	300 (53– 300), n=6 vs 300 (120– 300), n=200, p=0.837
Pseudopodial whealing	12%, n=125 vs 8%, n=212, p=0.178	14%, n=90 vs 7%, n=247, p=0.055	7%, n=43 vs 10%, n=294, p=0.780	0%, n=8 vs 9%, n=329, p=1.000
Maximal TempTest [®] 4.0-wheal diameter (mm)	10 (6–14), n=65 vs 8 (5–12), n=81, p=0.114	10 (6–15), n=55 vs 8 (5–11), n=91, p=0.014	10 (5–13), n=11 vs 9 (5–12), n=135, p=0.911	8 (5–12), n=6 vs 9 (5–13), n=140, p=0.533

Table B	Cardiovascular manifestations (CR6 and/or CR7)			
Trigger	At least one of triggers (T1–5) [§]	Complete cold water immersion (T1)	Cold ambient air exposure (T2)	Out/in (T3)
No. (% of total, n=372)	116 (31%)	88 (24%)	31 (8%)	6 (2%)
	yes vs no	yes vs no	yes vs no	yes vs no
Pediatric onset of ColdU (<18 y)	28% vs 2%, p=0.360	30% vs 23%, p=0.200	29% vs 24%, p=0.514	33% vs 24%, p=0.635
ColdU duration	56 (24–120) vs 36 (14–84), p=0.041	56 (24–117) vs 36 (15–96), p=0.088	70 (24–132) vs 38 (15–96), p=0.047	69 (16–156) vs 40 (17–97), p=0.469
BMI	24 (22–27) vs 24 (22–28), p=0.789	24 (21–27) vs 25 (22–28), p=0.088	27 (24–29) vs 24 (22–27), p=0.012	27 (21–33) vs 24 (22–28), p=0.407
Generalized wheals [§]	73% vs 57%, p=0.003	71% vs 60%, p=0.078	90% vs 60%, p<0.001	67% vs 62%, p=1.000
Angioedema, unknown/any location [§]	67% vs 41%, p<0.001	63% vs 45%, p=0.007	84% vs 46%, p<0.001	67% vs 49%, p=0.445
Acral swelling [§]	48% vs 27%, p<0.001	39% vs 32%, p=0.303	77% vs 30%, p<0.001	100% vs 33%, p=0.001
Oropharyngeal/laryngeal symptoms	47% vs 24%, p<0.001	42% vs 28%, p=0.018	68% vs 28%, p<0.001	67% vs 31%, p=0.081
Itchy earlobes	53% vs 33%, p<0.001	50% vs 36%, p=0.024	65% vs 37%, p=0.004	83% vs 39%, p=0.036
Asthma	22% vs 15%, p=0.073	19% vs 16%, p=0.517	26% vs 16%, p=0.207	33% vs 17%, p=0.269
Systemic reaction to <i>Hymenoptera</i>	10% vs 4%, p=0.030	10% vs 5%, p=0.067	7% vs 6%, p=0.704	17% vs 6%, p=0.308
CSTT	180 (60–300), n=47 vs 300 (120–300), n=159, p=0.011	180 (60–180), n=31 vs 300 (120–300), n=175, p<0.001	300 (150–300), n=17 vs 30 (90–300), n=189, p=0.391	60 (45–180), n=3 vs 300 (120–300), n=203, p=0.228
Pseudopodial whealing	15%, n=98 vs 7%, n=239, p=0.021	18%, n=74 vs 7%, n=263, p=0.010	13%, n=23 vs 9%, n=314, p=0.456	0%, n=4 vs 9%, n=333, p=1.000
Maximal TempTest [®] 4.0-wheal diameter (mm)	10 (6–15), n=53 vs 8 (5–12), n=93, p=0.012	11 (6–15), n=48 vs 9 (5–11), n=98, p=0.004	6 (4–25), n=5 vs 9 (5–13), n=141, p=0.560	6 (4–11), n=5 vs 9 (5–13), n=141, p=0.268

Table C	Hypotension and/or loss of consciousness (CR6)			
Trigger	At least one of triggers (T1–5) [§]	Complete cold water immersion (T1)	Cold ambient air exposure (T2)	Out/in (T3)
No. (% of total, n=372)	48 (13%)	41 (11%)	10 (3%)	0
	yes vs no	yes vs no	yes vs no	yes vs no
Pediatric onset of ColdU (<18 y)	40% vs 22%, p=0.011	39% vs 22%, p=0.032	40% vs 24%, p=0.263	NA
ColdU duration	22 (12–40) vs 30 (19–43), p=0.217	41 (19–120) vs 40 (17–96), p=0.543	90 (33–192) vs 40 (16–96), p=0.049	NA
BMI	24 (22–27) vs 25 (22–28), p=0.586	23 (21–27) vs 25 (22–28), p=0.219	28 (24–31) vs 24 (22–27), p=0.094	NA
Generalized wheals [§]	79% vs 60%, p=0.010	76% vs 60%, p=0.062	100% vs 61%, p=0.016	NA
Angioedema, unknown/any location [§]	71% vs 46%, p=0.002	66% vs 47%, p=0.031	100% vs 48%, p=0.001	NA
Acral swelling [§]	50% vs 32%, p=0.014	42% vs 33%, p=0.296	100% vs 32%, p<0.001	NA
Oropharyngeal/laryngeal symptoms	42% vs 30%, p=0.133	37% vs 31%, p=0.478	80% vs 30%, p=0.002	NA
Itchy earlobes	54% vs 37%, p=0.027	54% vs 68%, p=0.061	70% vs 38%, p=0.053	NA
Asthma	27% vs 15%, p=0.061	27% vs 16%, p=0.080	30% vs 17%, p=0.383	NA
Systemic reaction to <i>Hymenoptera</i>	13% vs 5%, p=0.049	15% vs 5%, p=0.024	0% vs 6%, p=1.000	NA
CSTT	180 (60–300), n=18 vs 300 (120–300), n=188, p=0.288	180 (53–300), n=14 vs 300 (120–300), n=192, p=0.118	300 (240–300), n=6 vs 300 (120–300), n=200, p=0.207	NA
Pseudopodial whealing	13%, n=40 vs 9%, n=297, p=0.392	14%, n=36 vs 9%, n=301, p=0.354	0%, n=6 vs 9%, n=331, p=1.000	NA
Maximal TempTest® 4.0-wheal diameter (mm)	10 (6–15), n=21 vs 9 (5–12), n=125, p=0.671	10 (6–15), n=20 vs 9 (5–12), n=126, p=0.421	5 (3–5), n=3 vs 10 (5–13), n=143, p=0.116	NA

Table D	Difficulty breathing (CR8), no asthma			
Trigger	At least one of triggers (T1–5) [§]	Complete cold water immersion (T1)	Cold ambient air exposure (T2)	Out/in (T3)
No. (% of total, n=309)	57 (18%)	40 (13%)	26 (8%)	2 (1%)
	yes vs no	yes vs no	yes vs no	yes vs no
Pediatric onset of ColdU (<18 y)	32% vs 21%, p=0.082	35% vs 21%, p=0.666	27% vs 22%, p=0.625	50% vs 23%, p=0.402
ColdU duration	60 (26–132) vs 41 (14–108), p=0.046	60 (25–135) vs 42 (14–108), p=0.118	60 (34–114) vs 42 (14–108), p=0.081	189 (78–300) vs 48 (17–108), p=0.129
BMI	24 (22–28) vs 24 (22–28), p=0.852	24 (22–28) vs 24 (22–28), p=0.937	24 (22–29) vs 24 (22–28), p=0.706	31 (21–40) vs 24 (22–28), p=0.665
Generalized wheals [§]	76% vs 58%, p=0.016	73% vs 60%, p=0.163	85% vs 59%, p=0.011	100% vs 61%, p=0.525
Angioedema, unknown/any location [§]	70% vs 45%, p=0.001	68% vs 47%, p=0.018	73% vs 48%, p=0.014	100% vs 50%, p=0.248
Acral swelling [§]	44% vs 30%, p=0.060	38% vs 32%, p=0.476	58% vs 30%, p=0.008	100% vs 32%, p=0.106
Oropharyngeal/laryngeal symptoms	63% vs 23%, p<0.001	58% vs 26%, p<0.001	65% vs 27%, p<0.001	100% vs 30%, p=0.090
Itchy earlobes	58% vs 33%, p=0.001	53% vs 35%, p=0.053	69% vs 35%, p=0.001	100% vs 37%, p=0.140
Systemic reaction to <i>Hymenoptera</i>	11% vs 6%, p=0.227	10% vs 6%, p=0.307	8% vs 6%, p=0.680	0% vs 7%, p=1.000
CSTT	240 (60–300), n=28 vs 300 (120–300), n=142, p=0.507	150 (60–300), n=16 vs 300 (120–300), n=154, p=0.091	300 (270–300), n=14 vs 300 (60–300), n=156, p=0.050	60, n=1 vs 300 (120–300), n=169, p=0.365
Pseudopodial whealing	9%, n=45 vs 10%, n=234, p=1.000	13%, n=30 vs 9%, n=249, p=0.509	0%, n=20 vs 10%, n=259, p=0.235	0%, n=1 vs 10%, n=278 p=1.000
Maximal TempTest [®] 4.0-wheal diameter (mm)	10 (5–13), n=24 vs 10 (6–13), n=97, p=0.700	10 (6–13), n=19 vs 10 (6–13), n=102, p=0.647	9 (5–15), n=6 vs 10 (6–13), n=115, p=0.914	6 (5–6), n=2 vs 10 (6–13), n=119, p=0.208

Table E	Gastrointestinal symptoms (CR9)			
Trigger	At least one of triggers (T1–5) [§]	Complete cold water immersion (T1)	Cold ambient air exposure (T2)	Out/in (T3)
No. (% of total, n=372)	39 (11%)	23 (6%)	20 (5%)	4 (1%)
	yes vs no	yes vs no	yes vs no	yes vs no
Pediatric onset of ColdU (<18 y)	35% vs 24%, p=0.217	25% vs 24%, p=1.000	0% vs 25%, p=0.576	31% vs 23%, p=0.325
ColdU duration	52 (36–120) vs 37 (16–98), p=0.257	60 (27–125) vs 40 (15–96), p=0.156	114 (51–159) vs 40 (16–96), p=0.120	52 (30–120) vs 37 (15–96), p=0.124
BMI	25 (22–27) vs 24 (22–28), p=0.820	26 (23–29) vs 24 (22–28), p=0.343	29 (21–29) vs 24 (22–28), p=0.341	25 (22–27) vs 24 (22–28), p=0.982
Generalized wheals [§]	65% vs 62%, p=0.827	80% vs 61%, p=0.102	75% vs 62%, p=1.000	74% vs 61%, p=0.117
Angioedema, unknown/any location [§]	72% vs 47%, p=0.004	61% vs 49%, p=0.288	80% vs 48%, p=0.005	100% vs 49%, p=0.059
Acral swelling [§]	56% vs 31%, p=0.002	39% vs 34%, p=0.650	75% vs 32%, p<0.001	100% vs 33%, p=0.013
Oropharyngeal/laryngeal symptoms	54% vs 29%, p=0.003	48% vs 30%, p=0.103	70% vs 39%, p<0.001	100% vs 31%, p=0.009
Itchy earlobes	56% vs 37%, p=0.024	48% vs 39%, p=0.387	65% vs 38%, p=0.019	100% vs 39%, p=0.023
Asthma	28% vs 16%, p=0.068	17% vs 17%, p=1.000	35% vs 16%, p=0.058	0% vs 17%, p=1.000
Systemic reaction to <i>Hymenoptera</i>	5% vs 6%, p=1.000	9% vs 6%, p=0.637	0% vs 6%, p=0.620	0% vs 6%, p=1.000
CSTT	300 (180–300), n=22 vs 300 (75–300), n=184, p=0.123	180 (45–300), n=9 vs 300 (120–300), n=197, p=0.143	300, n=13 vs. 300 (60–300), n=193, p=0.001	300, n=2 vs 300 (120–300), n=204, p=0.223
Pseudopodial whealing	9%, n=34 vs 9%, n=303, p=1.000	10%, n=20 vs 9%, n=317, p=0.705	6%, n=16 vs 9%, n=321, p=1.000	0%, n=3 vs 9%, n=334, p=1.000
Maximal TempTest® 4.0-wheal diameter (mm)	13 (8–15), n=13 vs 9 (5–12), n=133, p=0.047	14 (11–15), n=11 vs 9 (5–12), n=135, p=0.005	6 (5–10), n=3 vs 9 (5–13), n=143, p=0.459	13, n=1 vs 9 (5–13), n=145, p=0.347

Tables S5A–E. Data are given as yes (%) vs no (%) and median (IQR). If not obtained in all patients, patient numbers are displayed as “n” next to results. Statistical significance of differences between patient groups was calculated by Fisher’s Exact test and Mann-Whitney U test. Statistically significant p-values are in bold.

†ColdA was defined as an acute cold-induced involvement of the skin, visible mucous tissue, or both (CR1–5) and at least one of the following: cardiovascular manifestations (CR6 and/or CR7), difficulty breathing (CR8), or gastrointestinal symptoms (CR9). Cardiovascular manifestations were defined as hypotension (RR<90/60) or loss of consciousness (CR6) and/or other signs or symptoms suggestive of hypotension (i.e., dizziness, sensation of fainting, weakness; CR7). Difficulty breathing (CR8) was defined as dyspnoea, wheeze or stridor.

§Induced by at least one of triggers (T1–5): complete cold water immersion (T1), cold ambient air (T2), transition from cold outdoors to warm indoors (T3), local contact with cold liquids or ice (T4), and contact with cold surfaces (T5).

Abbreviations: BMI, body mass index; ColdA, cold-induced anaphylaxis; ColdU, cold urticaria; CR, cold-induced reaction; CSTT, critical stimulation time threshold; CWI, complete cold water immersion; NA, not applicable.

Table S6. Characteristics of systemic reactions caused by cold ambient air exposure and/or transition from cold outdoors to warm indoors in all patients with typical ColdU and in residents of countries with a temperate, cold and tropical climate.

		ColdA - broad definition ^{†‡}		Cardiovascular manifestations (CR6 and/or CR7) [‡]		Difficulty breathing (CR8), no asthma [†]		Gastrointestinal symptoms (CR9) [‡]	
Trigger		Air	Out/ in	Air	Out/ in	Air	Out/ in	Air	Out/ in
		T2	T3	T2	T3	T2	T3	T2	T3
All patients	Yes (n=372 [‡] , n=309 [†])	53	11	31	6	26	2	20	4
Δ○	% within yes	14%	3%	8%	2%	8%	1%	5%	1%
Temperate	Yes (n=264 [‡] , n=220 [†])	32	3	18	3	14	1	8	0
▲●	% within yes	12%	1%	7%	1%	6%	1%	3%	0
Cold	Yes (n=75 [‡] , n=64 [†])	9	3	2	2	3	1	2	1
▲●	% within yes	12%	4%	3%	3%	5%	2%	3%	1%
Tropical	Yes (n=33 [‡] , n=25 [†])	12	5	11	1	9	0	10	3
▲●	% within yes	36%	15%	33%	3%	36%	0	30%	9%
Tropical vs temperate or cold (p-value)		0.001	0.001	<0.001	0.430	<0.001	1.000	<0.001	0.002
Tropical vs temperate (p-value)		0.001	0.001	<0.001	0.377	<0.001	1.000	<0.001	0.001
Tropical vs cold (p-value)		0.007	0.055	<0.001	1.000	<0.001	1.000	<0.001	0.084
Temperate vs cold (p-value)		1.000	0.125	0.267	0.306	0.771	0.401	1.000	0.221
Pediatric onset of ColdU (<18 y)									
↑ ColdU duration		○●		○					
↑ BMI				○					
Generalized wheals [§]		Δ●		Δ●		○			
Angioedema, unknown/any location [§]		Δ●●●	○	Δ●		○		○	
Acral swelling [§]		Δ●●	Δ●	Δ▲●	Δ●	○●●		Δ●	○
Oropharyngeal/laryngeal symptoms		Δ●▲	Δ●	Δ▲	●	Δ▲		Δ▲	○
Itchy earlobes		Δ▲	Δ	○▲	○	Δ●		○▲	○
Asthma		○●							
Systemic reaction to <i>Hymenoptera</i>		●							
↓ CSTT									
Pseudopodial whealing									
↑ TempTest [®] 4.0-wheal diameter									

Statistical significance of differences between patient groups was calculated by Fisher's Exact test and Mann-Whitney U test. Statistically significant results are shown as $\Delta \blacktriangle \blacktriangle \blacktriangle$ for $p \leq 0.001$ and $\circ \bullet \bullet \bullet$ for $p < 0.05$. Analogous symbols of different colors are used for 4 patient groups: $\Delta \circ$ for all patients with typical ColdU (detailed results are provided in Tables S5A–E), $\blacktriangle \bullet$ for residents of countries with a temperate climate, $\blacktriangle \bullet$ for residents of countries with a cold climate, and $\blacktriangle \bullet$ for residents of countries with a tropical climate (Table S1).

†ColdA was defined as an acute cold-induced involvement of the skin, visible mucosal tissue, or both and at least one of the following: cardiovascular manifestations (CR6 and/or CR7), difficulty breathing (CR8), or gastrointestinal symptoms (CR9). Cardiovascular manifestations were defined as hypotension or loss of consciousness (CR6) and/or other signs or symptoms suggestive of hypotension (i.e., dizziness, sensation of fainting, weakness; CR7). Difficulty breathing (CR8) was defined as dyspnoea, wheeze or stridor.

‡Analysis of typical ColdU patients without CSU (n=372).

¶Analysis of typical ColdU patients without CSU and without asthma (n=309).

§Induced by at least one of triggers (T1–5): complete cold water immersion (T1; CWI), cold ambient air exposure (T2), transition from cold outdoors to warm indoors (T3), local contact with cold liquids or ice (T4), and contact with cold surfaces (T5).

Abbreviations: BMI, body mass index; ColdA, cold-induced anaphylaxis; ColdU, cold urticaria; CR, cold-induced reaction; CSTT, critical stimulation time threshold; CWI, complete cold water immersion; y, year(s).

Table S7. Characteristics of systemic reactions caused by at least one of triggers (T1–5), complete cold water immersion or cold ambient air exposure in: (i) all patients with typical ColdU, (ii) those without asthma, and (iii) those with asthma.

		ColdA - broad definition [†]			Cardiovascular manifestations (CR6 and/or CR7)			Hypotension and/or loss of consciousness (CR6)			Difficulty breathing (CR8)			Gastrointestinal symptoms (CR9)		
Trigger		Any [†]	CWI	Air	Any [†]	CWI	Air	Any [†]	CWI	Air	Any [†]	CWI	Air	Any [†]	CWI	Air
		T1–5	T1	T2	T1–5	T1	T2	T1–5	T1	T2	T1–5	T1	T2	T1–5	T1	T2
All patients Δ○	Yes (n=372)	145	107	53	116	88	31	48	41	10	82	53	42	39	23	20
	% within yes	39%	29%	14%	31%	24%	8%	13%	11%	3%	22%	14%	11%	11%	6%	5%
No asthma ▲●	Yes (n=309)	111	84	37	90	71	23	35	30	7	57	40	26	28	19	13
	% within yes	36%	27%	12%	29%	23%	7%	11%	10%	2%	18%	13%	8%	9%	6%	4%
Asthma ▲●	Yes (n=63)	34	23	16	26	17	8	13	11	3	25	13	16	11	4	7
	% within yes	54%	37%	25%	41%	27%	13%	21%	18%	5%	40%	21%	25%	18%	6%	11%
Asthma vs no asthma (p-value)		0.010	0.169	0.009	0.073	0.517	0.207	0.061	0.080	0.383	0.001	0.116	0.001	0.068	1.000	0.058
Pediatric onset of ColdU (<18 y)								○	○		○	○				
↑ ColdU duration		Δ●	○●	○●●	○●		○			○	○●		○			
↑ BMI							○●									
Generalized wheals [§]		Δ▲	○	Δ●●	○▲		Δ●	○▲	●	○●	○●	○	Δ●●			
Angioedema, unknown/any location [§]		Δ▲●	Δ▲	Δ▲●	Δ▲	○●	Δ▲●	○●	○●	Δ●	Δ▲▲	○●	Δ●●	○●●		○●
Acral swelling [§]		○●		Δ▲●	Δ▲		Δ▲●	○●		Δ▲	○		Δ●●	○●		Δ●●
Oropharyngeal/laryngeal symptoms		Δ▲●	Δ▲	Δ▲	Δ▲●	○●	Δ●●			○●	Δ▲●	Δ▲	Δ▲	○●		Δ▲
Itchy earlobes		Δ▲	○▲	Δ▲	Δ●	○●	○●	○			Δ▲	○	○▲	○		○
Systemic reaction to <i>Hymenoptera</i>		○●			○●	●		○●	○●							
↓ CSTT		●	○●		○●	Δ●										●
Pseudopodial whealing					○●	○●●										
↑ TempTest® 4.0-wheal diameter			○●		○●	○●								○▲	○▲	

Table S7.

Statistical significance of differences between patient groups was calculated by Fisher's Exact test and Mann-Whitney U test. Statistically significant results are shown as Δ▲▲ for $p \leq 0.001$ and ○●● for $p < 0.05$. Analogous symbols of different colors are used for 3 patient groups: Δ○ for all typical ColdU patients, ▲● for those without asthma, and ▲● for those with asthma.

†ColdA was defined as an acute cold-induced involvement of the skin, visible mucosal tissue, or both and at least one of the following: cardiovascular manifestations (CR6 and/or CR7), difficulty breathing (CR8), or gastrointestinal symptoms (CR9). Cardiovascular manifestations were defined as hypotension or loss of consciousness (CR6) and/or other signs or symptoms suggestive of hypotension (i.e., dizziness, sensation of fainting, weakness; CR7). Difficulty breathing (CR8) was defined as dyspnoea, wheeze or stridor.

§Induced by at least one of triggers (T1–5): complete cold water immersion (T1; CWI), cold ambient air exposure (T2), transition from cold outdoors to warm indoors (T3), local contact with cold liquids or ice (T4), and contact with cold surfaces (T5).

Abbreviations: BMI, body mass index; ColdA, cold-induced anaphylaxis; ColdU, cold urticaria; CR, cold-induced reaction; CSTT, critical stimulation time threshold; CWI, complete cold water immersion; y, year(s).

Table S8. Characteristics of systemic reactions caused by cold ambient air exposure or transition from cold outdoors to warm indoors in: (i) all patients with typical ColdU, (ii) those without asthma, and (iii) those with asthma.

		ColdA - broad definition [†]		Cardiovascular manifestations (CR6 and/or CR7)		Difficulty breathing (CR8)		Gastrointestinal symptoms (CR9)	
Trigger		Air	Out/ in	Air	Out/ in	Air	Out/ in	Air	Out/ in
		T2	T3	T2	T3	T2	T3	T2	T3
All patients	Yes (n=372)	53	11	31	6	42	5	20	4
Δ○	% within yes	14%	3%	8%	2%	11%	1%	5%	1%
No asthma	Yes (n=309)	37	8	23	4	26	2	13	4
▲●	% within yes	12%	3%	7%	1%	8%	1%	4%	1%
Asthma	Yes (n=63)	16	3	8	2	16	3	7	0
▲●	% within yes	25%	5%	13%	3%	25%	5%	11%	0
Asthma vs no asthma (p-value)		0.009	0.406	0.207	0.269	0.001	0.036	0.058	1.000
Pediatric onset of ColdU (<18 y)									
↑ ColdU duration		○●●	●	○		○			
↑ BMI				○●					
Generalized wheals [§]		Δ●●		Δ●		Δ●●			
Angioedema, unknown/any location [§]		Δ▲●	○●	Δ▲●		Δ●●		○●	
Acral swelling [§]		Δ▲●	Δ▲	Δ▲●	Δ●	Δ●●	○	○●●	○●
Oropharyngeal/laryngeal symptoms		Δ▲	Δ▲	Δ●●		Δ▲	○	○▲	○●
Itchy earlobes		Δ▲	Δ●	○●	○	○▲	○	○	○●
Systemic reaction to <i>Hymenoptera</i>									
↓ CSTT								●	
Pseudopodial whealing									
↑ Maximal TempTest [®] 4.0-wheal diameter									

Table S8.

Statistical significance of differences between patient groups was calculated by Fisher's Exact test and Mann-Whitney U test. Statistically significant results are shown as Δ▲▲ for p≤0.001 and ○●● for p<0.05. Analogous symbols of different colors are used for 3 patient groups: Δ○ for all typical ColdU patients, ▲● for those without asthma, and ▲● for those with asthma.

[†]ColdA was defined as an acute cold-induced involvement of the skin, visible mucosal tissue, or both and at least one of the following: cardiovascular manifestations (CR6 and/or CR7), difficulty breathing (CR8), or gastrointestinal symptoms (CR9). Cardiovascular manifestations were defined as hypotension or loss of consciousness (CR6) and/or other signs or symptoms suggestive of hypotension (i.e., dizziness, sensation of fainting, weakness; CR7). Difficulty breathing (CR8) was defined as dyspnoea, wheeze or stridor.

[§]Induced by at least one of triggers (T1–5): complete cold water immersion (T1; CWI), cold ambient air exposure (T2), transition from cold outdoors to

warm indoors (T3), local contact with cold liquids or ice (T4), and contact with cold surfaces (T5).

Abbreviations: BMI, body mass index; ColdA, cold-induced anaphylaxis; ColdU, cold urticaria; CR, cold-induced reaction; CSTT, critical stimulation time threshold; CWI, complete cold water immersion; y, year(s).

Reference:

1. Peel MC FB, McMahon TA. Updated world map of the Köppen-Geiger climate classification. *Hydrol Earth Syst Sci.* 2007;11:1633–1644.