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Subfreezing air as a cough trigger and multiple triggers are strongly associated with the presence of asthma in chronic cough

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A B S T R A C T

Background: Management of chronic cough relies on the recognition of cough background disorders. It is not known whether certain cough triggers are associated with specific background disorders.

Methods: This was an e-mail study to public service employees of two towns in Finland. The questionnaire included twelve triggers. Current asthma was defined as doctor's diagnosis of asthma and current wheezing. Chronic rhinosinusitis was defined as either nasal blockage or nasal discharge and either facial pain/pressure or reduction/loss of smell for more than three months. Gastroesophageal reflux disease was defined as heartburn and/or regurgitation on at least one day a week during the last three months. Idiopathic cough was defined as absence of any of them.

Results: There were 421 subjects with current cough that had lasted at least eight weeks. Subfreezing air as a cough trigger was associated with an adjusted odds ratio (aOR) of 7.27 (4.09–12.9), ($p < 0.001$), for current asthma. The number of cough triggers was largest in asthma, followed by chronic rhinosinusitis, gastroesophageal reflux, and idiopathic cough (7.05 (6.14–7.96), 4.94 (4.35–5.54), 4.60 (3.77–5.43), and 3.44 (3.02–3.86), respectively, $p < 0.001$). Presence of five or more triggers was associated with an aOR of 7.49 (3.96–14.2), ($p < 0.001$) for current asthma. Absence of any cough triggers increased the probability of idiopathic cough (aOR 2.71 (1.54–4.77), $p = 0.001$).

Conclusions: Subfreezing air as a cough trigger and multiple triggers are strongly associated with the presence of current asthma in chronic cough. Absence of any cough triggers increases the probability of idiopathic cough.

1. Introduction

Cough is the most common reason why people seek medical attention [1,2]. Chronic cough is considered a manifestation of cough hypersensitivity syndrome, a concept to describe a condition with long-standing hypersensitivity of vagal afferent nerves or an alteration of the central processing of their input regardless of the background disorder of the cough [3,4]. Effective medical therapy for this neuronal hypersensitivity is currently lacking and the management of chronic cough still relies on effective identification and management of the background disorders, usually asthma, chronic rhinosinusitis, and esophageal reflux disease [5]. The extremely high prevalence of chronic cough indicates that its management must usually take place in primary health care where the diagnostic resources are often limited. Therefore, new, simple methods to identify the cough background disorders would be of great value.

The typical manifestations of the cough hypersensitivity syndrome are the increased cough sensitivity to known tussigens, like exhaust fumes (hypertussia), and cough that is triggered in response to a nontussive stimulus, like exercise (allotussia) [6]. These triggers of cough are generally considered non-specific and are not utilized in current cough guidelines to identify cough background disorders [5]. However, there are some reports suggesting that certain cough triggers may be specifically associated with certain cough background disorders [7,8]. The present study was conducted to investigate this possibility in a large community-based sample of well-characterized subjects with chronic cough.

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; LCQ, Leicester Cough Questionnaire; LCQts, Leicester Cough Questionnaire total score; PHQ-2, Patient Health Questionnaire-2; Rs, Spearman's rank correlation coefficient; URI, Upper respiratory tract infection

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2. METHODS

2.1. Population

This was a cross-sectional study among all public service employees of two middle-sized towns in central Finland (Kuopio and Jyväskylä, altogether 13 980 employees, mean 46,6 years with 79.2% females). Details of the study have been described earlier [9]. Invitation to the study and the questionnaire were sent via e-mail to the employees' e-mail addresses in March–April 2017. Answers were collected via an electronic reply form. One reminding message was sent if a subject had not responded within two weeks. The study was approved by the Ethics Committee of Kuopio University Hospital (289/2015). Permission to conduct the study was obtained from the town officials. The invitation mail to participate the study included detailed information about the study. The decision of the subject to reply was considered as an informed consent. The analysis included all responders who reported of current cough, which had lasted at least eight weeks.

2.2. Questionnaire

The electronic questionnaire was created and the data entry performed utilizing the program "KYSELYT-järjestelmä" created by Istekki Ltd, Kuopio, Finland. The first part of the questionnaire was filled in by all subjects. It included 57 questions about the subject's household, pets, family incomes, occupation, physical activity, smoking history, alcohol consumption, general health-related questions, current medications, recent symptoms (chest pain, arthralgia, back pain, toothache, leg edema, varicose disorder, eczema, headache, sleeplessness, depression, other mental symptoms, constipation, diarrhea or other gastrointestinal symptoms, sciatica), as well as all disorders diagnosed by a doctor. Asthma-, rhinosinusitis- and esophageal reflux-related symptoms were further inquired by questions currently suggested for epidemiologic studies [10–12]. Depressive symptoms were asked utilising the Patient Health Questionnaire-2 (PHQ-2) [13]. Permission has been obtained for use of the PHQ-2. The second part consisted of 23 detailed cough-related questions to be filled by subjects reporting of current cough. It included questions about the cough bout frequency and cough duration, as well as the Leicester Cough Questionnaire (LCQ) to measure the cough-related quality of life [2]. Permission has been obtained for use of the LCQ. The subjects were asked whether they could define any external trigger for their cough (yes/no). If yes, they were inquired about the following triggers: Upper respiratory tract infection (URI), subfreezing air, physical exercise, exhaust fumes, poor indoor air, animals, pollens, cigarette smoke, perfumes and deodorants, paints and fumes, and a free choice. More than one choice was allowed. LCQ question number 18 was utilized for speaking as a cough trigger. The list of triggers was constructed based on the authors' clinical experience about typical cough triggers presented by patients in this geographical area.

2.3. Definitions

Chronic cough was defined as current cough that had lasted at least eight weeks. Current asthma was defined as a doctor's diagnosis of asthma and wheezing during the last 12 months. Chronic rhinosinusitis was defined as either nasal blockage or nasal discharge (anterior or posterior nasal drip) and either facial pain/pressure or reduction/loss of smell for more than three months [11]. Gastroesophageal reflux disease was defined as heartburn and/or regurgitation on at least one day a week during the last three months [12]. Idiopathic cough was defined as absence of any of them. Symptom sum was calculated by summing all reported symptoms except those associated with airway disorders, giving a value from zero to 14. Trigger sum was calculated by summing all reported cough triggers, giving a value from zero to 12. Depressive symptoms were defined as PHQ-2 score $\geq$ 3 [13]. Allergy was defined as a self-reported allergy to pollens, animals or food. Family history of chronic cough was defined as presence (now or in the past) of chronic (duration more than eight weeks) cough in parents, sisters or brothers.

2.4. Statistical analysis

Data are presented as percentages or as means and standard deviations or 95% confidence intervals (CI). Kruskal-Wallis test, Mann-Whitney test, Spearman's rank correlation coefficient (Rs), and chi-square test were applied when appropriate. Bonferroni correction was applied in multiple comparisons. A multivariate analysis utilizing binary logistic regression analysis with backward directed stepwise process was performed to investigate the association between cough triggers and specific background disorders. The following factors were considered as confounders: Age, gender, body mass index, depressive symptoms, LCQ total score (LCQts), and symptom sum. The factor was accepted as a confounder if it showed an association both with the cough triggers and the background disorders [14]. A p value less than 0.05 was accepted as the level of statistical significance. All analyses were performed using SPSS version 22 for the personal computer (SPSS, Inc. Chicago, Illinois, USA).

3. RESULTS

The response rate was 26,4% (3697 subjects, mean age 47,8 (10,8) years, 82.6% females). Among them, there were 421 subjects with chronic cough (Table 1). The prevalence of most cough triggers was highest among subjects with asthma, followed by subjects with chronic rhinosinusitis, subjects with gastroesophageal reflux, and subjects with idiopathic cough (Table 2). The most asthma-specific cough trigger was subfreezing air. Presence of this trigger showed the sensitivity of 82% and specificity of 62% to separate subjects with current asthma from other participants with chronic cough. The positive predictive value was 42% and the negative predictive value 92%. The associations between the cough triggers and specific background disorders can be seen more clearly in Table 3, in which subjects with multiple background disorders have been omitted.

LCQts and the symptom sum were correlated with the trigger sum (Rs -0.34 ($p < 0.001$), and Rs 0.24 ($p < 0.001$). Because they both were associated also with the presence and number of background disorders, they were included as confounders in the multivariate analyses. Subfreezing air as a cough trigger was associated with an adjusted odds ratio (aOR) of 7.27 (4.09–12.9), ($p < 0.001$) for current asthma (Table 4, Fig. 1). Furthermore, several other triggers were associated with an increased probability of asthma and chronic rhinosinusitis, but not with esophageal reflux disease (Table 4). Absence of any cough triggers increased the probability of idiopathic cough (aOR 2.71 (1.54–4.77), $p = 0.001$).

Table 1
The basic characteristics of the 421 subjects with chronic cough. Figures are percentages or means and standard deviations.

Characteristic	Values
Age, years	50.5 ± 10.0
Female gender	82.6%
Body mass index, kg/m^2	27.9 ± 5.5
Current smokers	8.6%
Ever smokers	32.5%
Symptom sum	3.38 ± 2.32
Leicester Cough Questionnaire total score	14.6 ± 3.0
Trigger sum	4.97 ± 3.12
Subjects with current asthma[a]	24.6%
Subjects with chronic rhinosinusitis[a]	37.3%
Subjects with gastroesophageal reflux disease[a]	23.8%
Subjects with idiopathic cough	37.0%

[a] 81 subjects had more than one background disorder.

Table 2
Prevalence of reported cough triggers in the subgroups divided by the background disorder among 421 subjects with current chronic cough. Several subjects had more than one background disorder. The figures indicate percentages.

Trigger	Asthma N = 103	chronic rhinosinusitis N = 157	Esophageal reflux disease N = 100	Idiopathic N = 155	All subjects N = 421
Any	94.2	92.4	91.0	74.2	84.6
URI	82.5	80.9	74.0	61.9	71.7
Subfreezing air	82.5	56.1	54.0	34.8	48.9
Physical exercise	63.1	46.5	40.0	24.5	37.1
Exhaust fumes	64.1	45.9	47.0	20.0	38.0
Poor indoor air	87.4	80.3	72.0	55.5	68.9
Animals	39.8	23.6	23.0	9.0	19.5
Pollens	56.3	45.9	38.0	21.9	34.9
Cigarette smoke	61.2	41.4	47.0	25.8	38.7
Perfumes and deodorants	73.8	58.0	56.0	29.7	48.5
Paints and fumes	71.8	54.8	59.0	25.2	45.8
Speaking	43.7	37.6	33.0	24.7	32.9
Others	12.6	8.9	18.0	9.7	12.4

Table 3
Prevalence of reported cough triggers in the subgroups divided by the background disorder among subjects with current chronic cough. Subjects with more than one background disorder have been omitted (N = 338). The figures indicate percentages and the p value comparison between all four subgroups.

Trigger	Asthma N = 42	chronic rhinosinusitis N = 89	Esophageal reflux disease N = 52	Idiopathic N = 155	P value
Any	90.5	87.6	84.6	74.2	0.017
URI	81.0	77.5	65.4	61.9	0.021
Subfreezing air	78.6	40.4	34.6	34.8	< 0.001
Physical exercise	61.9	34.8	21.2	24.5	< 0.001
Exhaust fumes	59.5	38.2	40.4	20.0	< 0.001
Poor indoor air	83.3	75.3	57.7	55.5	0.001
Animals	33.3	18.0	15.4	9.0	0.001
Pollens	40.5	38.2	25.0	21.9	0.015
Cigarette smoke	61.9	33.7	40.4	25.8	< 0.001
Perfumes and deodorants	73.8	50.6	50.0	29.7	< 0.001
Paints and fumes	71.4	43.8	53.8	25.2	< 0.001
Speaking	45.2	33.7	36.0	24.7	0.053
Others	14.3	10.1	23.1	9.7	0.070

The trigger sum was largest among subjects with asthma, followed by subjects with chronic rhinosinusitis, subjects with gastroesophageal reflux, and subjects with idiopathic cough (7.05 (6.14–7.96), 4.94 (4.35–5.54), 4.60 (3.77–5.43), and 3.44 (3.02–3.86), $p < 0.001$), respectively, among subjects with not more than one background disorder, Fig. 2). Trigger sum ≥ 5 was associated with aOR of 7.49 (3.96–14.2), ($p < 0.001$) for current asthma among all subjects with chronic cough. Presence of trigger sum ≥ 5 showed the sensitivity of 87% and specificity of 58% to separate subjects with current asthma from other participants with chronic cough. The positive predictive value was 40% and the negative predictive value 93%.

All analyses were repeated in a combined group of subjects with subacute (3–8 weeks' duration) and chronic (> 8 weeks' duration) current cough (N = 593). All main results were similar (data not shown).

Table 4
Association with various cough triggers with background disorders among 421 subjects with chronic cough. The figures indicate adjusted odds ratios and 95% confidence intervals, adjusted with the Leicester Cough Questionnaire total score and the symptom sum. In each trigger, the control group was those without that trigger. *p < 0.05, **p < 0.01, ***p < 0.001.

Trigger	Asthma, N = 103	chronic rhinosinusitis, N = 157	Esophageal reflux disease, N = 100
Any	2.95 (1.20–7.22)*	2.52 (1.28–4.96)**	1.83 (0.86–3.89)
URI	1.90 (1.06–3.40)*	1.94 (1.19–3.15)**	1.06 (0.63–1.77)
Subfreezing air	7.27 (4.09–12.9)***	1.36 (0.90–2.05)	1.19 (0.75–1.90)
Physical exercise	3.53 (2.17–5.73)***	1.57 (1.03–2.40)*	1.12 (0.69–1.81)
Exhaust fumes	3.67 (2.26–5.97)***	1.43 (0.94–2.18)	1.49 (0.93–2.39)
Poor indoor air	3.13 (1.65–5.94)***	2.01 (1.24–3.25)**	1.18 (0.70–1.99)
Animals	3.94 (2.30–6.74)***	1.24 (0.75–2.07)	1.24 (0.71–2.16)
Pollens	2.84 (1.76–4.59)***	1.84 (1.20–2.83)**	1.06 (0.65–1.72)
Cigarette smoke	3.10 (1.92–5.01)***	1.02 (0.67–1.55)	1.44 (0.90–2.29)
Perfumes, deodorants	3.39 (2.03–5.66)***	1.51 (0.99–2.29)	1.27 (0.79–2.05)
Paints, fumes	3.52 (2.13–5.82)***	1.47 (0.97–2.22)	1.89 (1.17–3.03)**
Others	0.88 (0.43–1.80)	0.49 (0.25–0.97)*	1.67 (0.88–3.17)

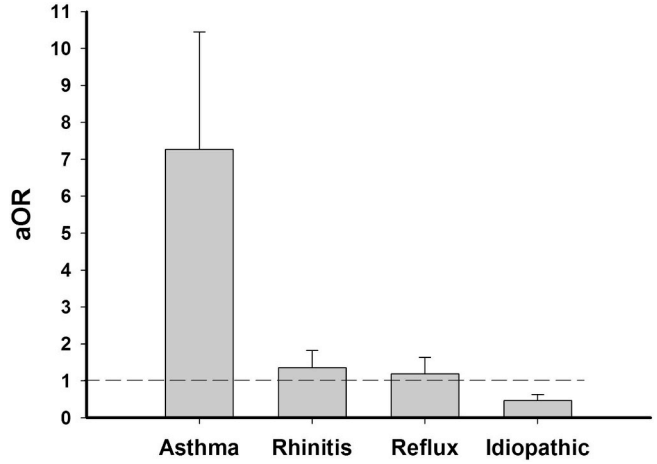

Fig. 1. The association of subfreezing air as a cough trigger with various background disorders among 421 subjects with chronic cough. The columns indicate adjusted odds ratios (aOR) with 95% confidence intervals. The dashed line indicates aOR of 1.

4. Discussion

The present study among employed, working age subjects with chronic cough showed that a large number of reported cough triggers may suggest the presence of asthma, and an absence of any triggers may suggest idiopathic cough. The trigger profiles of chronic rhinosinusitis and esophageal reflux disease were between these extremities. Of the specific cough triggers, subfreezing air showed the strongest association with asthma, increasing its likelihood by sevenfold.

The association of the cold air as a cough trigger and asthma is supported by two previous Japanese studies. Matsumoto et al. analyzed the presence of 18 cough triggers among 194 subjects with prolonged (> 3 weeks' duration) cough [7]. Cold air was reported by 51% of subjects with cough predominant asthma, 49% of subjects with cough variant asthma, and 26% of the subjects with non-asthmatic cough ($p = 0.027$). Fatigue/stress was the only other symptom separating the groups. Kanemitsu et al. studied 163 patients with prolonged (> 3 weeks' duration) cough [8]. Of the 18 possible triggers of cough, cold air was the only trigger with a statistically significant difference between subjects with cough-variant asthma and non-cough-variant asthma (prevalences 40 and 24%, respectively, $p = 0.03$). The

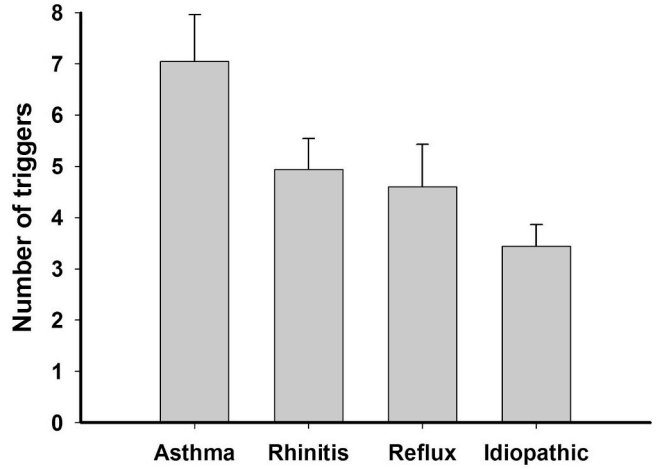

Fig. 2. The number of reported triggers of cough in various background disorders. Subjects with more than one background disorder have been omitted (N = 338). The columns indicate mean values and 95% confidence intervals. $p < 0.001$ between the disorders.

population in the present study was larger than those of the two Japanese studies together. This and the comprehensive information about various subject characteristics allowed us to perform multivariate analyses about the associations. They confirmed the strong association between subfreezing air as a cough trigger and a doctor's diagnosis of asthma.

In the present study, the questionnaire indeed included subfreezing air, not cold air, reflecting the very cold climate in Finland. Subfreezing air is always dry, containing virtually no water. Thus, the stimulus of subfreezing air is cooling and drying of the airways, leading to hyperosmolarity of the airway lining fluid, especially at high ventilation levels induced by physical exercise [15]. Of note, exercise as a cough trigger also strongly increased the likelihood of asthma in the present study. We have shown before that asthmatic subjects are hypersensitive to the cough-provoking effect of isocapnic hyperpnea of dry air [16]. They are also hypersensitive to the cough-provoking effect of hypertonic aerosols like mannitol, hypertonic histamine, and hypertonic saline [17–19]. In summary, we propose that the association between cold air as a cough trigger and asthma can be best explained by the special hypersensitivity of the asthmatic airways to sudden rise in airway lining fluid osmolarity.

Asthma was also associated with a largest number of reported cough triggers. Presence of ≥ 5 triggers was associated with aOR of 7.05 for current asthma in the present population. This finding is supported by the previously mentioned Japanese study among 194 subjects with prolonged cough [7]. In that study, the number of reported cough triggers was 3.9 in subjects with cough predominant asthma, 3.3 in cough variant asthma, and 3.0 in non-asthmatic cough patients ($p = 0.024$). The much larger Nagahama Cohort Study showed that the prevalence of several cough triggers were higher in asthmatic subjects with prolonged cough than in non-asthmatic subjects with prolonged cough [20]. Assuming that the number of identifiable cough triggers associates with the degree of the hypersensitivity of the cough reflex arch, these findings suggest that asthma is associated with severe hypersensitivity of the cough reflex arch.

Among all subjects with chronic cough, 15% denied any external triggers for their cough and the corresponding number was as high as 26% among the subjects with idiopathic chronic cough. Absence of triggers increased the likelihood of idiopathic cough threefold. These findings show that presence of cough triggers is not a uniform feature of chronic cough. Assuming that the presence of identifiable cough triggers is a marker of an abnormally functioning cough reflex arch, the present findings may challenge the current concept of chronic cough hypersensitivity syndrome [3,4]. In a proportion of subjects with chronic cough the cough seems to be an automatic, self-functioning phenomenon unrelated to external conditions.

This study has several limitations. The list of triggers may not be comprehensive. Especially, triggers associated with certain foods or with eating in general are lacking. Indeed, Everett et al. investigated 47 subjects with gastroesophageal disease-associated cough and found that speaking, rising, throat clearing, and certain foods were the commonest triggers [21]. Lack of subjects with other cough background disorders limits the differential diagnostic value of these findings. In our population, speaking as a cough trigger was most prevalent in subjects with asthma, similarly to almost all cough triggers. We also had the free choice option as a trigger. Especially the subjects with gastroesophageal reflux disease crossed this option. Unfortunately, we did not ask the participants to define this option in more detail. It is known that a significant number of patients can have cough secondary to asymptomatic or silent gastroesophageal reflux. Defining gastrooesophageal reflux based on symptoms alone was likely to underestimate the number of patients with reflux. One possible cause for chronic cough is eosinophilic bronchitis. It could not be identified in this kind of questionnaire study. The response rate was rather low in the present survey, which is common in electronic surveys. However, it is unlikely that this could affect the associations between various triggers and background

disorders. There were no elderly and unemployed subjects in the present population, which may decrease the generalizability of the results. Finland has very cold climate and one may doubt whether the association between cold air and asthma apply to countries with warmer climates. However, the two pre-mentioned Japanese studies, which reported of similar associations, were performed in Kyoto [7,8]. It has much more temperate climate than central Finland with average lowest temperatures well above zero year around. Finally, all of the information used in the present analyses are based on self-reports in a cross-sectional design with the associated problems of biased reporting and lack of possibility to separate associations from causality.

The strengths of the present study include the large and well-characterized sample. The background disorders were clearly defined. Especially, the doctor's diagnosis of asthma in Finland is always based on objective evidence of variable airway obstruction [22]. The definitions of chronic rhinosinusitis and gastroesophageal reflux disease were those currently suggested for epidemiological surveys [11,12]. The multivariate analyses could be confounded adequately. Not surprisingly, reporting of cough triggers was strongly associated with reporting of various non-specific somatic symptoms, i.e., the degree of somatization [23]. Even this could be taken into account in the present analyses.

In conclusion, subfreezing air as a cough trigger is strongly suggestive of current asthma in chronic cough. This association can be best explained by the special hypersensitivity of the asthmatic airways to the sudden rise in airway lining fluid osmolarity. In addition, large number of reported cough triggers may also suggest asthma. Absence of any cough triggers increases the possibility of idiopathic cough. These findings may help in the clinical management of chronic cough, which relies on the identification of the most probable cough background disorder. Prospective studies are now needed to test the validity of these conclusions.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.rmed.2019.05.004.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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