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Validation of the Cough Phenotype TBQ among Elderly Finnish Subjects

Revision 1

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Take home -message

The previously described cough phenotypes TBQ (Triggers, Background disorders, Quality of life impairment) and the common cough phenotype could also be identified in elderly, retired subjects with current cough.

ABSTRACT

Background Phenotypes can be utilized in the clinical management of disorders. The approaches to phenotype disorders have evolved from subjective expert opinion to data-driven methodologies. A previous cluster analysis among working-age subjects with cough revealed a phenotype TBQ (Triggers, Background disorders, Quality of life impairment), which included 38 % of the subjects with cough. The present study was carried out to validate this phenotyping among elderly, retired subjects with cough.

Methods This was an observational, cross-sectional study conducted via email among the members of the Finnish Pensioners` Federation (N=26 205, 23.6% responded). The analysis included 1109 subjects with current cough (mean age 72.9 (SD 5.3) years) with 67.7 % females). All filled in a comprehensive 86-item questionnaire including the Leicester Cough Questionnaire. Phenotypes were identified utilizing K-means partitional clustering.

Results Two clusters were identified. The cluster A included 75.2 % and cluster B 24.8 % of the subjects. The three most important variables to separate the clusters were the number of cough triggers (mean 2.47 (2.34) vs. 7.08 (3.16), respectively, $p<0.001$), Leicester Cough Questionnaire physical domain (5.38 (0.68) vs. 4.21 (0.81), respectively, $p<0.001$), and the number of cough background disorders (0.82 (0.78) vs. 1.99 (0.89), respectively, $p<0.001$).

Conclusion The phenotype TBQ could be identified also among elderly, retired subjects with cough, thus validating the previous phenotyping among working-age subjects. The main underlying pathophysiological feature separating the phenotype TBQ from the common cough phenotype is probably hypersensitivity of the cough reflex arc.

Key words: Cough, chronic cough, phenotype, asthma, chronic rhinosinusitis, gastroesophageal reflux disease, cluster analysis

Introduction

Phenotype indicates a single or combination of disease attributes that describe differences between individuals [1]. Recently, approaches to phenotype disorders have evolved from subjective expert opinion to data-driven methodologies like clustering [2]. These methods explore the data through an unsupervised separation of a dataset with little or no ground truth, into a discrete set of hidden data structures [3]. This contrasts with the traditional methods based on human observation and testing of hypotheses using prior knowledge.

Cough is usually classified according to the length of the episode, to acute (<3 weeks), subacute (3–8 weeks), or chronic (>8 weeks) [4-12]. However, this classification is single-dimensional and not based on data-driven analyses. We recently performed a cluster analysis in 975 working-age subjects with cough [13]. Two clusters were identified. The smaller one was especially characterized by several Triggers of cough, many cough Background disorders, and poor cough-related Quality of life (TBQ). Those with the phenotype TBQ showed a high tendency for cough prolongation in the follow-up survey 12 months later [13]. The present study was carried out to validate that analysis in a different population, namely in aged, retired subjects, and under different conditions, namely in the middle of the covid-19 pandemic.

Material and methods

Study design, setting, and population

This was an observational, cross-sectional study conducted via email among the members of the Finnish Pensioners` Federation. The sample size assessment was based on the knowledge about the required sample size for cluster analysis, the response rates in email studies, and the prevalence of cough in Finland [14-16]. The 26 205 members (mean age 72.7 years, 63.5% females), who had an email address, were sent an invitation to participate along with information about the study. A pre-notification email was sent. The electronic questionnaires were sent as a hyperlink in an email in April 2021 and one reminder was sent two weeks later. The responses were recorded in an electronic datasheet.

The study was approved by the Ethics Committee of Kuopio University Hospital (289/2015). Permission to conduct the study was obtained from the Finnish Pensioners` Federation. The decision of the subject to reply was considered as an informed consent.

The questionnaire

The questionnaire was almost identical with the one used in our previous cluster analysis [13]. The 86 questions dealt with social background, lifestyle, general health, doctors` diagnoses and visits, and medications. Appropriate symptom questions for asthma, chronic rhinosinusitis, gastro-oesophageal reflux disease (GORD), obstructive sleep apnea (OSA), and depressive symptoms were included [17-21]. Respondents with current cough were asked to answer additional cough-related questions, including the Leicester Cough Questionnaire (LCQ). For the present study, new questions were added about symptoms of OSA, Covid-19 infection and vaccination, symptoms of flu at the beginning of the current cough episode, and recurrence of cough episodes. The list of potential cough triggers was completed by speaking, laughing, and deep inspiration. An English version of the questionnaire can be found as a supplementary file.

Definitions of variables derived from the raw data

Acute, subacute, and chronic cough were defined as suggested in international guidelines [4-12]. Current asthma was defined as doctor's diagnosis of asthma at any age and wheezing during the last 12 months [17]. 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 [18]. GORD was defined as heartburn and/or regurgitation on at least one day per week during the last three months [19]. OSA was defined as presence of two or more of the following features: Arterial hypertension, loud snoring, daytime somnolence or observed apneas [20]. These disorders, in addition to doctor's diagnoses of bronchiectasis and pulmonary fibrosis, were defined as cough background disorders. The number of cough background disorders was calculated by summing up them, giving a value from zero to six. Unexplained cough was defined as absence of any of these disorders. Autoimmune disorder was defined as presence of a doctor's diagnosis of hypothyroidism, rheumatoid arthritis, or other autoimmune disorders. Presence of depressive symptoms was defined as a Patient Health Questionnaire-2 score of three or more [21]. Symptom sum was calculated by summing up all reported symptoms except those associated with airway disorders, giving a value from zero to 15. Trigger sum was calculated by summing up all reported cough triggers, giving a value from zero to 15. Allergy was defined as a self-reported allergy to pollens, animals, or food. A family history of chronic cough was defined as the presence (now or in the past) of chronic (duration more than eight weeks) cough in parents, sisters, or brothers.

Statistical analysis

All questions of the questionnaire plus the derived variables were included in partitional clustering with K-means method [3] similarly to our previous cluster analysis [13]. Dimension reduction and cluster analysis steps were performed using R statistical software version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria) with diffusionMap, NbClust and cluster packages.

First, data were pre-processed to transform all variables to the same scale (0 – 1). Right skewed (skewness>1) variables were normalized with log(x+1) function since zero values cannot be log transformed. Ordinal and continuous variables were scaled into 0 - 1 interval. Variable's minimum value or the lowest class got value 0 and maximum value or the highest class 1. Binary variables remained unchanged. Value 0 indicated negative or 'no' alternative and value 1 positive or 'yes' alternative.

Second, clustering was applied. A distance matrix between observations with scaled variables were calculated using Manhattan distance function. Diffusion maps dimension reduction algorithm was applied to extract diffusion coordinates from distance matrix, using default settings of the software. The number of clusters was evaluated by the 24 criteria provided by the software. After that, the extracted diffusion map coordinates were clustered into groups with k-means method. To validate the clustering, the analyses were repeated by excluding those background variables with no plausible biological association with cough (like hometown, years of education, alcohol consumption *etc*.).

Third, cluster membership was added to original data to compare the clusters, utilizing Mann-Whitney U test or chi-square test. The interrelationships of the variables were analysed by the Spearman's correlation coefficient (r_s) using SPSS software version 22.0 (IBM SPSS Statistics for Windows. Armonk, NY, USA). Receiver operating characteristic curves (ROC) and the Youden index were utilized to define the cut-off values. The

values are expressed by either means and standard deviations, medians and interquartile ranges, or percentages. A p value less than 0.05 was accepted as the level of statistical significance.

Results

23.6% of the subjects responded (6189 respondents, mean (SD) age 72.2 (5.5), 66.4% female, (figure 1)). 206 respondents were excluded from the analyses because of age less than 64 years. Of the remaining 5983, 1109 subjects suffered from current cough. They formed the population in which the clustering was applied. Their mean age was 72.9 years (5.3) and 67.7 % were females. The proportion of missing values was less than 2.5%, except for the two OSA-related questions (3.1–3.7%).

Nine of the criteria provided by the R statistical software suggested two as the best number of clusters, five suggested three clusters, three suggested five clusters, one criterion suggested seven, eight, nine, eleven, or fourteen clusters, and two suggested fifteen clusters. Therefore, the extracted diffusion map coordinates were clustered into two groups, called cluster A (834 subjects (75.2 %)) and cluster B (275 subjects (24.8 %)).

The distribution of the clusters in acute, subacute, and chronic cough is presented in table 1. Cluster B was represented in all subtypes, though its proportion was largest in chronic cough.

Table 2 presents those 10 variables that most strongly separated the clusters, according to the p value between the clusters, as well as 23 other variables of interest. The cluster B was especially characterized by several cough triggers, many cough background disorders, and low LCQ scores (figures 2 and 3). Of the various cough triggers, paints and fumes most strongly separated the clusters. Of the cough background disorders, asthma most strongly separated the clusters. Of the three LCQ domains, the physical domain most strongly separated the clusters.

Table 3 presents the best cut-off values for the ten most important variables to identify the cluster B and their sensitivity, specificity, and area under the ROC values. After that, a ROC curve was constructed to evaluate the best number of the main determinants (trigger sum $\geq$ 5, LCQ physical domain $\leq$ 4.9, at least one cough background disorder) to separate the clusters (figure 4). The presence of at least 2 main determinants gave the best Youden index with the sensitivity of 0.96 and specificity of 0.72. The presence of all three main determinants gave the sensitivity of 0.61 and the specificity of 0.97.

Belonging to cluster B increased the likelihood of at least one doctor's visit due to cough in the last 12 months (OR 3.39 (95 % CI 2.53 – 4.55)) and the likelihood of having used cough medicines in the last 12 months (OR 1.88 (1.41 – 2.50)). The population was also divided according to the length of the cough episode. Presence of chronic (> 8 weeks' duration) cough slightly increased the likelihood of doctors' visits (OR 1.91 (1.36 – 2.70)) but decreased the likelihood of using cough medicines (OR 0.66 (0.50 – 0.89)).

The validation analysis by excluding those background variables with no plausible biological association with cough gave almost identical results. The five most important variables in that analysis were trigger sum, LCQ physical domain, number of cough background disorders, LCQ question 9 (paints or fumes as a cough trigger), and dyspnea with wheezing (data not shown).

There were significant interrelationships between the most important variables: The number of cough triggers was associated with the number of cough background disorders and the LCQ physical domain (r_s = 0.28, p <

0.001, and rs = −0.34, p < 0.001, respectively), and the number of cough background disorders was associated with the LCQ physical domain (rs = −0.40, p < 0.001).

Discussion

This clustering, which was performed in the middle of Covid-19 pandemic among 1109 elderly, retired subjects with current cough, validates our previous clustering among working-age, employed subjects [13]. Again, two clusters were found. The cluster B, consisting of 24.8 % of the subjects, was especially characterized by several cough triggers, many cough background disorders, and poor cough-related quality of life. These features fit to the cough phenotype TBQ, which was identified in our previous study. The cluster A, lacking these features, may be called as the 'common' cough phenotype.

Clustering is a task of grouping subjects in such a way that subjects in the same group (cluster) are more like each other than to those in other groups. This is achieved by measuring the distances between the subjects with respect to each variable. These distances are summed and placed on a two-dimensional table representing every possible pair of subjects, called the distance matrix. Different algorithms can then be applied to recognise the clusters of subjects with small distances to each other. Dimension reduction is often necessary to improve the observation to variable ratios, which makes the analysis more reliable.

Both cluster analyses identified the number of cough triggers as the most important variable to separate the phenotypes. Both analyses also identified the chemical triggers like paints, fumes, and strong scents as the most important types of triggers [13]. Several studies have shown that subjects with lower airway symptoms induced by chemical irritants are especially sensitive to the cough-provocation test with capsaicin [22-31]. Therefore, we hypothesize that the main underlying pathophysiological feature separating the phenotype TBQ from the common phenotype is hypersensitivity of the cough reflex. Thus, this phenotype might also represent a distinct endotype. Subjects with TBQ phenotype might especially benefit from medication that can decrease the sensitivity of the cough reflex. If that is the case, the phenotype TBQ could also provide a treatable trait. To investigate whether the phenotype TBQ is a distinct cough genotype, studies applying genome analyses should be performed. Of note, family history of chronic cough was far more common in the phenotype TBQ than in the common phenotype.

The common cough phenotype seems to be less associated with the cough reflex hypersensitivity than the phenotype TBQ. Other mechanisms, like excessive mucus production, may be more important in that phenotype [32].

The phenotype TBQ was more strongly associated with doctor's visits due to cough and the use of cough medicines than the presence of chronic cough. Furthermore, our previous study showed a strong tendency for cough prolongation in the phenotype TBQ [13]. Since the phenotype TBQ is related to clinically meaningful outcomes, it fulfils the criteria for clinical phenotype [1]. Identification of it may serve as an indication for prompt and comprehensive clinical evaluation regardless of the duration of the cough episode.

The phenotype TBQ resembles the concept 'cough hypersensitivity syndrome', introduced by experienced clinicians [33]. Both emphasize the enhanced response to cough triggers. However, there seems to be two major discrepancies between the entities. First, 'cough hypersensitivity syndrome' has been connected to chronic cough [33] but the present study shows that features of cough hypersensitivity can be present in acute

and subacute cough as well. Second, it has been postulated that the 'cough hypersensitivity syndrome' is present in the majority of subjects with chronic cough [33-35] whereas in the present analysis just 27.4 % of subjects with chronic cough showed the features of the phenotype TBQ. These discrepancies may be best explained by the fact that 'cough hypersensitivity syndrome' has been described among subjects attending special cough clinics [33] whereas our cluster analyses are based on community-based populations. Given the documented high tendency of the subjects with the phenotype TBQ to seek medical attention, they are probably overrepresented in the population attending special cough clinics. Despite the above-mentioned differences, it is remarkable that unsupervised, data-driven analyses lead to similar conclusions to those drawn from clinical experience.

A recent study from Australia supports the present analysis. In that study, two clusters could be identified among subjects with various respiratory symptoms. The smaller cluster was characterized by symptoms of laryngeal hypersensitivity and a strong cough response to mannitol [36]. The characteristics of that cluster resemble those of the phenotype TBQ.

For clinical purposes, we calculated the best cut-off values for the most important variables to separate the clusters. They were almost identical to those reported in our previous cluster analysis [13]. Presence of at least two of the three main TBQ determinants gave the largest sum of sensitivity + specificity and is thus the most suitable clinical criterion for the cough phenotype TBQ. Reliable clinical demonstration of the phenotype TBQ requires that a comprehensive list of triggers is presented to the patient in a written form since patients often forget some triggers when asked openly. The list of the 15 triggers asked in the present study can be found in the questionnaire (Supplementary file).

There were slight differences in the questionnaires between the present and the previous study [13], which did not affect the main results. It has been shown that there are more cough background disorders in elderly than in younger subjects [37-39]. Therefore, bronchiectasis, pulmonary fibrosis, and OSA were added to the variable 'number of cough background disorders '. Questions about Covid-19 infection and vaccination, and symptoms of flu at the beginning of the current cough episode were added due to the current pandemic. We also asked how many cough episodes the subject had had in the last 12 months. This number was significantly higher in the phenotype TBQ than in the common phenotype. Of note, the number of the cough episodes was more strongly associated with the phenotype TBQ than the length of the current cough episode.

The present study has several limitations. The participation rate was relatively low, which is typical for academical e-mail surveys [15] and of similar magnitude to our previous cluster analysis [13]. However, the age and gender distribution of the responders did not differ significantly from the original population. High age of the population may have hindered the use of e-mail in some individuals. It is possible that patients with severe cough have been more willing to participate than patients with mild cough. This may have led to an over-representation of the TBQ phenotype. The proportion of current smokers was small, which may have reduced the impact of smoking on the analysis. The prevalence of short, infection-associated cough subtypes was low in the present population, probably due to personal protective and social measures that were recommended during the pandemic era [39]. Finally, the analysis was based on the questionnaire data only; spirometry, laboratory, and x-ray data were missing.

The strengths of the present study included a large population, which was missing in our previous cluster analysis: Elderly, retired subjects [13]. The survey was not limited to cough patients but to a community-based population. Therefore, even those coughing subjects who would never complain their cough to doctors were also included. The questionnaire was originally planned and further completed to investigate cough and associated conditions. It included a comprehensive list of cough triggers with both external triggers and those representing allotussia [40]. The interindividual variation in how subjects recognise and report symptoms was controlled by the variable 'symptom sum'. Furthermore, the symptom questions to define important background disorders were those recommended for epidemiologic studies. All raw data plus the derived variables were included in the cluster analysis without hypotheses using prior knowledge. By this way, all relevant features of cough and even undiagnosed but symptomatic background disorders were equally considered in the analysis.

Conclusions

The phenotypes TBQ and the common phenotype could be identified among elderly, retired subjects with cough, thus validating the previous phenotyping among working-age subjects [13]. The phenotype TBQ was associated with frequent doctor's visits due to cough, use of cough medicines, and a high tendency for cough prolongation [1,13]. Clinical evaluation of a patient with cough should probably focus on the presence of cough triggers, background disorders, and the quality of life rather than on the length of the cough episode.

List of abbreviations

GORD: Gastro-oesophageal reflux disease

LCQ: Leicester cough questionnaire

OSA: Obstructive sleep apnea

TBQ: Triggers, Background disorders, Quality of life impairment

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Table 1. Distribution of the clusters in acute (duration < 3 weeks), subacute (3 – 8 weeks), and chronic (> 8 weeks) cough. 23 subjects could not define the length of the cough episode.

	Acute cough (N = 207)	**Subacute cough (N = 70)**	**Chronic cough (N = 809)**
Cluster A (the 'common' phenotype)	169 (81.6 %)	57 (81.4 %)	587 (72.6 %)
Cluster B (the phenotype TBQ)	38 (18.4 %)	13 (18.6 %)	222 (27.4 %)

TBQ: Triggers, Background disorders, Quality of life impairment.

Table 2. The clusters and their defining variables among 1109 subjects with current cough. The ten most important variables and 23 variables of special interest expressed, in order of importance. The order was defined by the p value obtained by Mann-Whitney U test or chi-square test between the clusters. The values are expressed by either means (standard deviations) or percentages, unless stated otherwise.

Order	Variable	Cluster A (N = 834)	Cluster B (N = 275)	P value
1	Trigger sum	2.47 (2.34)	7.08 (3.16)	2.39E-78
2	LCQ physical domain	5.38 (0.68)	4.21 (0.81)	1.02E-75
3	Number of cough background disorders	0.82 (0.78)	1.99 (0.89)	9.09E-65
4	LCQ total score	16.1 (2.48)	12.5 (2.79)	7.12E-64
5	Dyspnea with wheezing	8.4 %	55.0 %	3.38E-61
6	Paints or fumes as a cough trigger	19.2 %	70.5 %	5.03E-56
7	Current asthma	6.4 %	46.5 %	2.36E-53
8	LCQ social domain	5.63 (1.00)	4.38 (1.12)	1.47E-52
9	Automobile exhaust fumes as a cough trigger	13.4 %	59.3 %	4.37E-52
10	LCQ question 3 (tired because of cough)[1]	5.93 (1.07)	4.57 (1.36)	2.36E-48
23	Symptom sum	2.32 (1.71)	4.13 (2.17)	9.67E-35
30	LCQ question 2 (sputum production when coughing)[a]	4.86 (1.84)	3.29 (1.78)	2.20E-30
40	Unexplained cough	38.0 %	4.0 %	1.93E-26
46	Chronic rhinosinusitis	13.9 %	41.8 %	1.15E-22
47	Allergy	9.1 %	33.1 %	1.37E-21
51	Number of doctor's visits due to cough in the last 12 months	0.40 (1.15)	1.24 (2.19)	4.49E-19
53	Presence of any trigger for cough	71.8 %	96.7 %	1.11E-17
56	Speaking as a cough trigger	16.4 %	40.4 %	2.98E-16
61	Family history of chronic cough	31.8 %	58.0 %	2.03E-14
70	Gastro-oesophageal reflux disease	22.3 %	43.8 %	8.87E-12
77	Sleep apnea	39.9 %	63.4 %	4.20E-11
85	Symptoms of flu at the beginning of the current cough	13.9 %	30.7 %	6.65E-10
86	Number of cough episodes in the last 12 months	4.92 (7.90)	7.39 (8.98)	1.03E-09
105	Duration of the cough episode (median, (interquartile range))	1 – 5 years (2 to 12 months – 1 to 5 years)	1 – 5 years (1 to 5 years – 5 to 10 years	1.29E-05
107	Use of cough medicines in the last 12 months	28.2 %	42.4 %	1.82E-05
114	Female gender	64.7 %	76.7 %	0.0003
115	Autoimmune disorder	18.2 %	28.0 %	0.0007
121	Chronic obstructive pulmonary disease	2.3 %	6.2 %	0.0029
124	Bronchiectasis	1.3 %	4.4 %	0.0046
138	Body mass index (kg/m^2)	27.7 (4.5)	28.2 (5.4)	0.19
146	Pulmonary fibrosis	0.8 %	1.8 %	0.30
149	Age (years)	72.8 (5.2)	73.1 ((5.4)	0.36
150	Current smoking	1.8 %	2.9 %	0.38

[a] Leicester Cough Questionnaire (LCQ) questions have 7-step scales from 1 = all of the time to 7 = none of the time.

Table 3. Sensitivity and specificity of the ten main variables to identify cluster B, utilizing the cut-off values giving the best sum of sensitivity and specificity (The Youden index).

Variable	**Cut-off value**	**Sensitivity**	**Specificity**	**aROC**
Trigger sum	≥ 5	0.80	0.81	0.87
LCQ physical domain	≤ 4.9	0.75	0.81	0.87
Number of cough background disorders	≥ 1	0.72	0.82	0.82
LCQ total score	≤ 14.7	0.76	0.76	0.84
Dyspnea with wheezing	Yes/No	0.55	0.92	NA
Paints or fumes as a cough trigger	Yes/No	0.70	0.81	NA
Current asthma	Yes/No	0.46	0.94	NA
LCQ social domain	≤ 5.6	0.57	0.90	0.81
Automobile exhaust fumes as a cough trigger	Yes/no	0.59	0.87	NA
LCQ question 3 (tired because of cough)[a]	≤ 5	0.73	0.70	0.78

[a] Leicester Cough Questionnaire (LCQ) questions have 7-step scales from 1 = all of the time to 7 = none of the time. aROC = Area under the receiver operator characteristic curve. NA = not applicable

REFERENCES

1. Han MK, Agusti A, Calverley PM, et al. Chronic obstructive pulmonary disease phenotypes: the future of COPD. Am J Respir Crit Care Med 2010; 182: 598-604.

2. Deliu M, Sperrin M, Belgrave D, et al. Identification of Asthma Subtypes Using Clustering Methodologies. Pulm Ther 2016; 2: 19-41.

3. Xu R, Wunsch DC. Clustering algorithms in biomedical research: a review. IEEE Rev Biomed Eng 2010; 3: 120-154.

4. Morice AH, Millqvist E, Bieksiene K, et al. ERS guidelines on the diagnosis and treatment of chronic cough in adults and children. Eur Respir J 2020; 55: 1901136.

5. Morice AH, McGarvey L, Pavord I, et al. Recommendations for the management of cough in adults. Thorax 2006; 61 Suppl 1: i1-i24.

6. Irwin RS, French CL, Chang AB, et al. Classification of Cough as a Symptom in Adults and Management Algorithms: CHEST Guideline and Expert Panel Report. Chest 2018; 153: 196-209.

7. Shankar PS, Korukonda K, Bendre S, et al. Diagnoses and management of adult cough: An Indian Environmental Medical Association (EMA) position paper. Respir Med 2020; 168: 105949.

8. Song DJ, Song WJ, Kwon JW, et al. KAAACI Evidence-Based Clinical Practice Guidelines for Chronic Cough in Adults and Children in Korea. Allergy Asthma Immunol Res 2018; 10: 591-613.

9. Gibson PG, Chang AB, Glasgow NJ, et al. CICADA: Cough in Children and Adults: Diagnosis and Assessment. Australian cough guidelines summary statement. Med J Aust 2010; 192: 265-271.

10. Kardos P, Dinh QT, Fuchs K-, et al. [Guidelines of the German Respiratory Society for Diagnosis and Treatment of Adults Suffering from Acute, Subacute and Chronic Cough]. Pneumologie 2019; 73: 143-180.

11. Lai K, Shen H, Zhou X, et al. Clinical Practice Guidelines for Diagnosis and Management of Cough-Chinese Thoracic Society (CTS) Asthma Consortium. J Thorac Dis 2018; 10: 6314-6351.

12. Mukae H, Kaneko T, Obase Y, et al. The Japanese respiratory society guidelines for the management of cough and sputum (digest edition). Respir Investig 2021; 59: 270-290.

13. Koskela HO, Selander TA, Lätti AM. Cluster analysis in 975 patients with current cough identifies a phenotype with several cough triggers, many background disorders, and low quality of life. Respir Res 2020; 21: 219.

14. Dalmaijer ES, Nord CL, Astle DE. Statistical power for cluster analysis. BMC Bioinformatics 2022; 23: 205.

15. Sheehan KB. E-mail Survey Response Rates: a Review. JCMC 2001; 6. https://doi.org/10.1111/j.1083-6101.2001.tb00117.x

16. Lätti AM, Pekkanen J, Koskela HO. Defining the risk factors for acute, subacute and chronic cough: a cross-sectional study in a Finnish adult employee population. BMJ Open 2018; 8: e022950.

17. Sa-Sousa A, Jacinto T, Azevedo LF, et al. Operational definitions of asthma in recent epidemiological studies are inconsistent. Clin Transl Allergy 2014; 4: 24-24.

18. Fokkens WJ, Lund VJ, Mullol J, et al. European Position Paper on Rhinosinusitis and Nasal Polyps 2012. Rhinol Suppl 2012; 50: 1-298.

19. El-Serag HB, Sweet S, Winchester CC, et al. Update on the epidemiology of gastro-oesophageal reflux disease: a systematic review. Gut 2014; 63: 871-880.

20. Chung F, Yegneswaran B, Liao P, et al. STOP questionnaire: a tool to screen patients for obstructive sleep apnea. Anesthesiology 2008; 108: 812-821.

21. Kroenke K, Spitzer RL, Williams JB. The Patient Health Questionnaire-2: validity of a two-item depression screener. Med Care 2003; 41: 1284-1292.

22. Millqvist E, Bende M, Löwhagen O. Sensory hyperreactivity--a possible mechanism underlying cough and asthma-like symptoms. Allergy 1998; 53: 1208-1212.

23. Millqvist E, Löwhagen O, Bende M. Quality of life and capsaicin sensitivity in patients with sensory airway hyperreactivity. Allergy 2000; 55: 540-545.

24. Johansson A, Löwhagen O, Millqvist E, et al. Capsaicin inhalation test for identification of sensory hyperreactivity. Respir Med 2002; 96: 731-735.

25. Ternesten-Hasséus E, Farbrot A, Löwhagen O, et al. Sensitivity to methacholine and capsaicin in patients with unclear respiratory symptoms. Allergy 2002; 57: 501-507.

26. Millqvist E, Johansson A, Bende M. Relationship of airway symptoms from chemicals to capsaicin cough sensitivity in atopic subjects. Clin Exp Allergy 2004; 34: 619-623.

27. Millqvist E, Ternesten-Hasséus E, Ståhl A, et al. Changes in levels of nerve growth factor in nasal secretions after capsaicin inhalation in patients with airway symptoms from scents and chemicals. Environ Health Perspect 2005; 113: 849-852.

28. Ternesten-Hasseus E, Johansson K, Lowhagen O, et al. Inhalation method determines outcome of capsaicin inhalation in patients with chronic cough due to sensory hyperreactivity. Pulm Pharmacol Ther 2006; 19: 172-178.

29. Elberling J, Dirksen A, Johansen JD, et al. The capsaicin cough reflex in eczema patients with respiratory symptoms elicited by perfume. Contact Derm 2006; 54: 158-164.

30. Holst H, Arendt-Nielsen L, Mosbech H, et al. The capsaicin cough reflex in patients with symptoms elicited by odorous chemicals. Int J Hyg Environ Health 2010; 213: 66-71.

31. Pullerits T, Ternesten-Hasseus E, Johansson EL, et al. Capsaicin cough threshold test in diagnostics. Respir Med 2014; 108: 1371-1376.

32. Koskela HO, Nurmi HM, Birring SS. Utility of Cough Provocation Tests in Chronic Cough and Respiratory Diseases: A Comprehensive Review and Introduction of New Reference Ranges for the Capsaicin Test. Allergy Asthma Immunol Res 2021; 13: 833-849.

33. Morice AH, Millqvist E, Belvisi MG, et al. Expert opinion on the cough hypersensitivity syndrome in respiratory medicine. Eur Respir J 2014; 44: 1132-1148.

34. Chung KF. Chronic 'cough hypersensitivity syndrome': a more precise label for chronic cough. Pulm Pharmacol Ther 2011; 24: 267-271.

35. Morice AH. Chronic cough hypersensitivity syndrome. Cough 2013; 9: 14.

36. Lee JW, Tay TR, Borg BM, et al. Laryngeal hypersensitivity and abnormal cough response during mannitol bronchoprovocation challenge. Respirology 2022; 27: 48-55.

37. Song W, Morice AH, Kim M, et al. Cough in the elderly population: relationships with multiple comorbidity. PLoS One 2013; 8: e78081.

38. Wei W, Yu L, Lu H, et al. Comparison of cause distribution between elderly and non-elderly patients with chronic cough. Respiration 2009; 77: 259-264.

39. Kaulamo JT, Lätti AM, Koskela HO. Cough in the Elderly During the COVID-19 Pandemic. Lung 2022; 200: 161-168.

40. Mazzone SB, McGarvey L. Mechanisms and Rationale for Targeted Therapies in Refractory and Unexplained Chronic Cough. Clin Pharmacol Ther 2021; 109: 619-636.

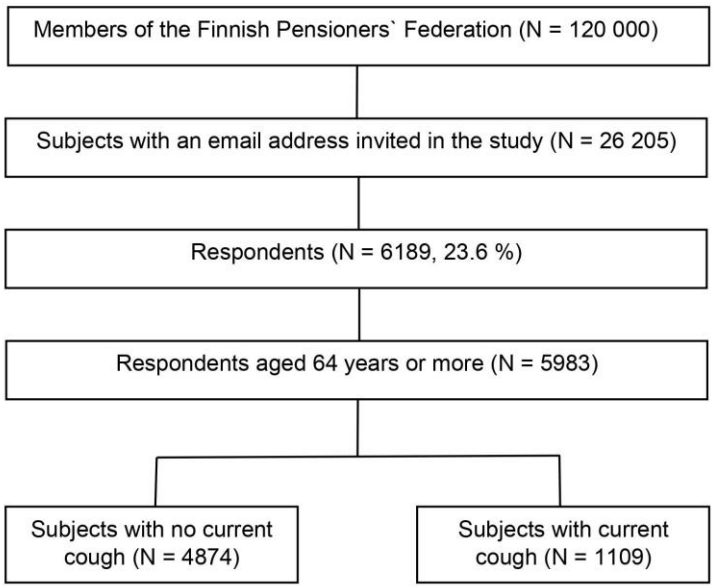
FIGURE LEGENDS

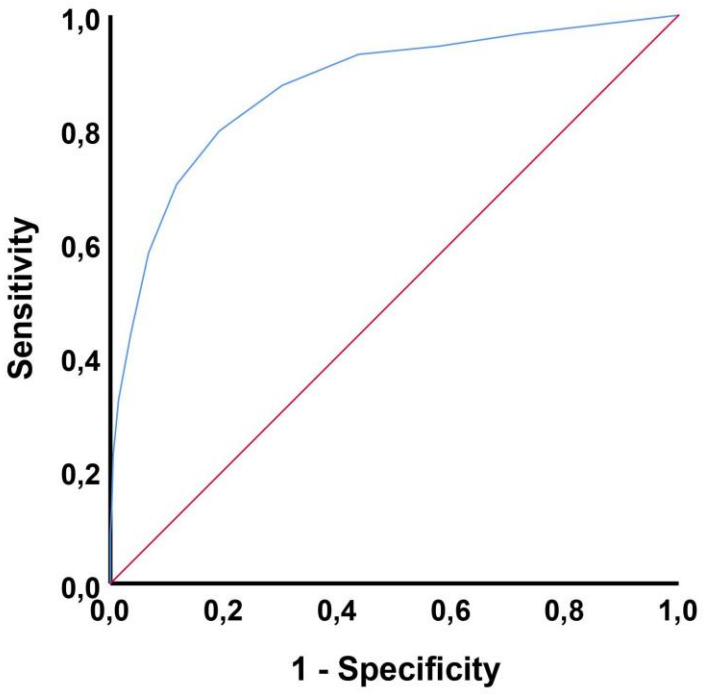
Figure 1. The flow chart.

Figure 2. A receiver operating characteristic curve (ROC) constructed to demonstrate the separation of the two clusters by the number of cough triggers. Area under the ROC curve is 0.87 (95 % CI 0.85 – 0.90).

Figure 3. Each subject of the cluster A (N = 834, blue color) and cluster B (N = 275, green color) represented in a 3-dimensional scatterplot. The number of the cough triggers is represented in the vertical axis, the number of the cough background disorders in the horizontal axis, and the Leicester Cough Questionnaire (LCQ) physical domain in the axis pointing to the observer. The marker of every subject is connected to the cluster mean value by a spike. Most of the subjects aggregate close to the cluster mean value where the markers of each subject are difficult to distinguish. The distances between the individuals are shorter within the cluster than those between the clusters.

Figure 4. A receiver operating characteristic curve (ROC) constructed to demonstrate the separation of the two clusters by the number of the three main determinants (trigger sum $\geq$ 5, LCQ physical domain $\leq$ 4.9, at least one cough background disorder). Area under the ROC curve is 0.92 (95 % CI 0.90 – 0.93).


Members of the Finnish Pensioners` Federation (N = 120 000)
Subjects with an email address invited in the study (N = 26 205)
Respondents (N = 6189, 23.6 %)
Respondents aged 64 years or more (N = 5983)
Subjects with no current cough (N = 4874)
Subjects with current cough (N = 1109)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Sensitivity
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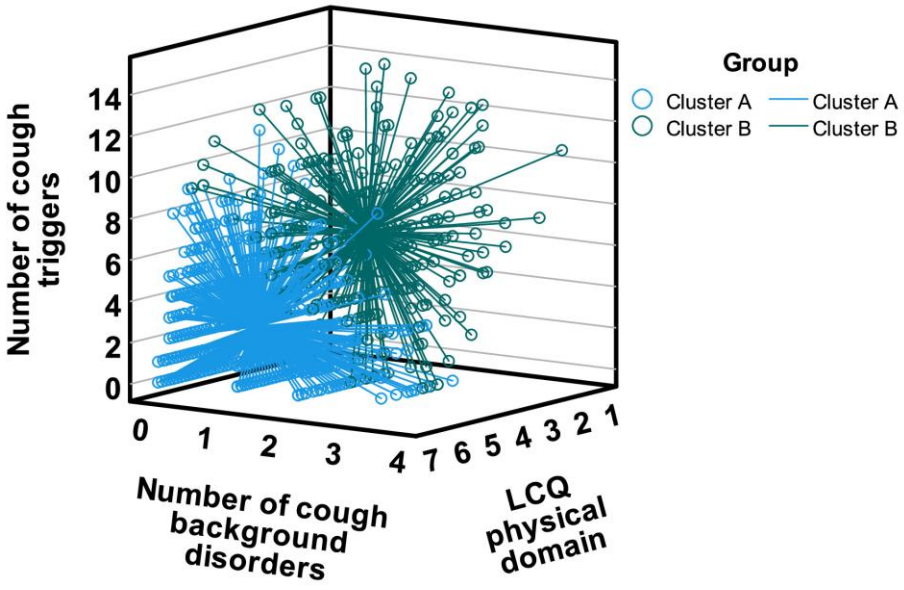
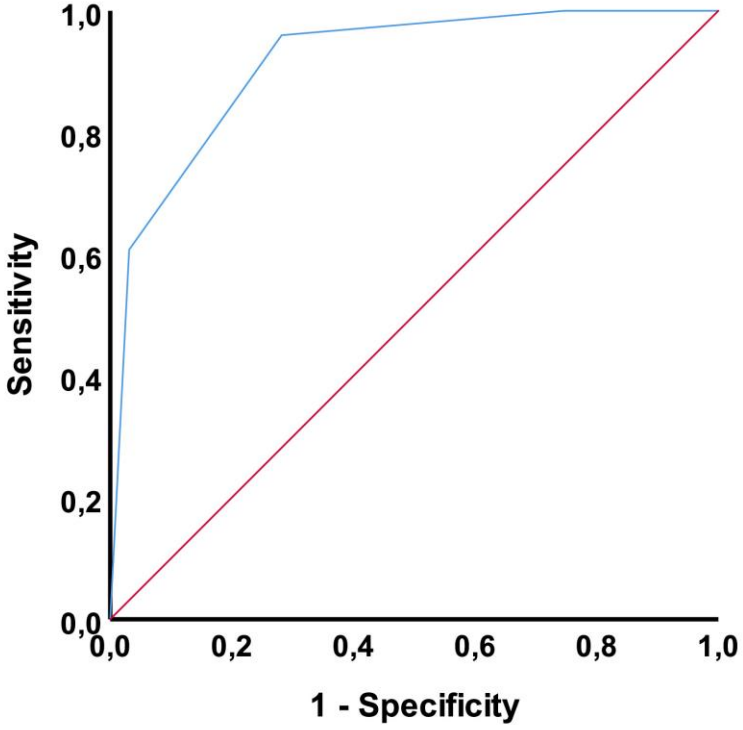
1 - Specificity


Group
Cluster A
Cluster B
Cluster A
Cluster B
Number of cough triggers
0
2
4
6
8
10
12
14
Number of cough background disorders
0
1
2
3
4
LCQ physical domain
7
6
5
4
3
2
1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COUGH IN SAVO AND CENTRAL FINLAND

THE QUESTIONNAIRE

GENERAL QUESTIONS

1. Gender

1 male
0 female

2. Year of birth_____

3. Place of birth_____

4. Residence at the moment_____

5. Marital status

1 married/ in a registered relationship/ common-law marriage
2 unmarried
3 separated or divorced
4 widow/widower
5 can not define

6. How many years of full-time education have you had?
Please include both primary and secondary schooling

_____years

7. In addition to yourself, how many people live in your household?

_____individuals

8. At present, do you have any pets (also include farm animals if you live on a farm)?

0 no (please proceed to question 10)
1 yes

9. Do you have any of the following pets?

	no	yes
Dog…….	0…..	1
Cat……	0….	1
Rodent (mouse, hamster, guinea pig etc.)……..	0…..	1
Some other furry animal……..……..	0….	1
Farm animals (cows, pigs etc.)……...	0….	1
Some other animal…...……..	0….	1

10. During the past 12 months has moisture damage been identified in your home?

0 no
1 yes

11. How large is your household's yearly income (before tax and other deductions) adding the income of all of its members together?

1 less than 15 000 e
2 15 000- 40 000 e
3 40 000 – 70 000 e
4. 70 000 – 120 000 e
5. More than 120 000 e

12. What was your most recent employment status?

1 employer, entrepreneur
2 farmer, farmer's wife
3 senior white collar worker
4 lower white collar worker
5 skilled blue collar worker (vocational college degree)
6 unskilled blue collar worker
7 I have not been employed outside the home

YOUR USE OF HEALTH SERVICES AND YOUR HEALTH CONDITION

13. How many times in the past year (12 months) have you visited a doctor for any symptom whatsoever?
If you have not visited a doctor at all in the past year, please write 0

_times

.
14. During the past year (12 months) have you had any of the following illnesses either diagnosed or treated by a doctor?

yes
asthma 1
chronic rhinitis……..... 1
allergy (foods, pollen or to animals)…….....1
chronic obstructive pulmonary disease (= COPD)..... 1
bronchiectasis……1
fibrosing lung disease……...1
sarcoidosis…….1
tuberculosis in the lungs..……1
gastric distress (gastritis, gastric ulcer)……..... 1
esophageal reflux disease (heartburn, gastroesophageal reflux)……..1
sleep apnea……..…1
Parkinson's disease……1
depression 1
other mental health problems 1
rheumatoid arthritis……. 1
other connective tissue disorders (Sjögren's syndrome etc.)……....1
hypothyreosis……..……..1
arterial hypertension 1

elevated blood cholesterol 1
diabetes.....1
myocardial infarction…….....1
coronary artery disease, angina pectoris ……..... 1
cancer 1
spinal disc problems, other back disease……...1
prostate hyperplasia……1

15. Have you had any of the following symptoms or illnesses in the past month?

yes
chest pain on exertion 1
aching joints 1
back problems, back pain 1
toothache 1
swollen feet 1
varicose veins 1
eczema 1
headache 1
insomnia 1
depressive symptoms.....1
other mental health problems 1
constipation 1
other gut problems (flatulence, diarrhoea) 1
sciatica (back pain that radiates to the leg) 1
urination disorders……1

16. Have you used any of the following drugs in the past month?

yes
cough medicines 1
drugs for asthma……..1
drugs for rhinitis…….....1
drugs to treat allergies (for example, antihistamines).……1
antacids (drugs to treat heartburn)……..1
antihypertensives (drugs to treat high blood pressure).....1
cholesterol lowering drugs.....1
thyroid hormone (Thyroxine)……..1
insulin 1
drugs to treat diabetes 1
analgesics (pain medicines) 1
contraceptives..... ……1
tranquilizers ..... ……..1
sedatives (sleeping pills) 1
antidepressants 1
vitamins or mineral supplements 1
hormone drugs to treat menopausal
or post-menopausal symptoms (for women) 1
potency medicines (for men) 1

17. Are you usually able to do the following physical actions?

	no	yes
walking for about half a kilometer without stopping to rest	0	1
running for a short distance (about 100 meters)	0	1
running for a longer distance (more than half a kilometer)	0	1

18. At present, do you feel that your state of health is in general:

1 good
2 quite good
3 about average
4 quite bad
5 bad

19. How tall are you?

_____ cm

20. How much do you weigh? (wearing light clothing)

_____ kg

EXERCISE

21. How often do you undertake either leisure-time physical activity or the equivalent while commuting to work that lasts for at least half an hour and which makes you at least slightly out of breath or sweaty?

1 every day
2 4–6 times a week
3 3 times a week
4 2 times a week
5 once a week
6 2–3 times a month
7 a few times in a year or even less
8 I have a handicap or illness that makes it impossible for me to exercise

22. How would you rate your present physical condition?

1 very good
2 quite good
3 satisfactory
4 quite bad
5 very bad
6 I do not know

SMOKING HABITS

23. Have you ever smoked at any time in your life?

0 no (proceed directly to question 29)
1 yes

24. During your life have you smoked at least 100 times?
(cigarettes, cigars or pipes)
0 no
1 yes

25. Have you ever smoked on a daily basis for at least one year? For how many years altogether?

0 I have never smoked on a daily basis
1 I have smoked on a daily basis for ____ years

26. Are you currently a smoker?
(cigarettes, cigars, pipes or electronic cigarrettes)

1 yes, on a daily basis
2 occasionally
3 I am no longer a smoker

27. When did you last smoke?
If you are a regular smoker, please mark 1

1 yesterday or today
2 between 2 days and a month ago
3 between one and six months ago
4 between six months and a year ago
5 between one to five years ago
6 between five to ten years ago
7 more than 10 years ago

28. On average, how much do you smoke now on a daily basis or did you smoke before you quit smoking?
Please answer every point. Put 0, if you have never smoked that type of tobacco product at all

About _____ manufactured cigarettes every day
About _____self-rolled cigarettes every day
About_____ pipefuls every day
About_____ cigars every day
About_____doses of electronic cigarettes every day

29. Is there anyone who currently smokes either inside your home or in your workplace?
0 no
1 yes

ALCOHOL CONSUMPTION

30. In the past year (12 months) have you ever drank any alcoholic beverages (e.g. beer, wine, cider or strong alcoholic drinks)?

0 I have not consumed any (please proceed to question 32)
1 yes

33. How many glasses (counted as usual restaurant-sized glasses) or bottles of the following alcoholic beverages have you drank in the past week: if you have not drank any of the particular type of beverage, please mark 0 in that line

About ____bottles (1/3 l) of medium strength or strong beer
About ____bottles (1/3 l) of alcopops /long drinks
About ____glasses of strong alcohol (restaurant sized glasses)
About____glasses of wine or alcohol of similar strength (alcohol content over 5%)
About ____glasses of cider or low-strength wine (alcohol content about 5%)

SYMPTOMS OF DISEASES OR ILLNESSES

32. In the past year (12 months), have you experienced wheezing or a whistling sound when you breathe
0 no (please proceed to question 39)
1 yes

33. Have you experienced a wheezing or whistling sound when you breathe at times other than when you are suffering from a flu or an upper respiratory tract infection?
0 no
1 yes

34. Have you experienced a shortness of breath at the same time when your breathing is wheezy or whistling?

0 no
1 yes

35. Has the wheezing or whistling sound when you are breathing disturbed your sleep in the past year (12 months)?
0 no
1 yes

36. In the past year (12 months) have you ever woken up due to an attack of a shortness of breath?
0 no
1 yes

37. In the past year (12 months) have you ever woken up due to a coughing fit?
0 no
1 yes

38. In the past year (12 months) have you experienced any of the following rhinitis-related symptoms?
You can mark ”yes” to more than one option

	no	yes
nasal discharge (anterior or posterior nasal drip)……..	0……	1
nasal blockage…….....	0	1
facial pain or pressure…….....	0	1
reduction/loss of smell …….	0……	1

39. In the past year (12 months) have you experienced any of the following rhinitis-related symptoms in a prolonged fashion, for at least three months?
You can mark ”yes” to more than one option

	no	yes
nasal discharge (anterior or posterior nasal drip)……..	0……	1
nasal blockage…….....	0	1
facial pain or pressure…….....	0	1
reduction/loss of smell …….	0……	1

40. Are you supersensitive to pain killing drugs (causing skin rash, swelling of your face, feelings of shortness of breath)?

0 no
1 yes

41. In the past 12 months have you suffered from heartburn and/or regurgitation?

0 no (please proceed to question 44)
1 yes

42. In the past 3 months have you suffered from heartburn and/or regurgitation?

0 no (please proceed to question 44)
1 yes

43. How often in the past 3 months have you suffered from heartburn and/or regurgitation?

1 less often than once a month
2 at least once a month
3 at least once a week
4 every day

44. Do you snore loudly (louder than talking or loud enough to be heard through closed doors)?

0 no
1 yes

45. Do you often feel tired, fatigued, or sleepy during daytime?

0 no
1 yes

46. Has anyone observed you stop breathing during your sleep?

0 no
1 yes

47. Have you had a covid-19 (coronavirus) infection?

0 no (please proceed to question 49)
1 yes, how many weeks ago did the symptoms start?_____

48. If you have had a covid-19 (coronavirus) infection, were you hospitalised for at least overnight?

0 no
1 yes

49. Have you been vaccinated against covid-19 (coronavirus) infection?

0 no

1 yes, how many weeks ago did you get the latest vaccination?_____

YOUR MOOD

How often in the past two weeks have you been troubled by the following problems?

50. Little interest or pleasure in doing things?

0 not at all
1 several days
2 more than half the days
3 nearly every day

51. Feeling down, depressed, or hopeless?

0 not at all
1 several days
2 more than half the days
3 nearly every day

QUESTIONS CONCENTRATING ON COUGH

52. Do you have any close family members (father, mother, sisters, brothers) who are now suffering or have suffered from prolonged cough which has lasted over two months? (include also family members who have already passed away)

0 no
1 yes

53. Have you suffered from a phlegmy cough on most days or nights for at least three months yearly?
0 no
1 yes

54. In past 12 months, have you had a cough?
choose only one option

0 not at all (please proceed to the last page)
1 yes

55. In the past 12 months, have you suffered from episodes of cough, which have lasted for at least one week and during which you have coughed daily?

0 No
1 Yes

56. How many such episodes you have had in the past 12 months? (If none, please write 0)

_____ episodes

57. Do you think that there is some outside trigger or stimulus which makes you cough or worsens an existing cough?

0 no (please proceed to question 60)
1 yes

58. Which of the following triggers make you cough or worsens an existing cough?
You can select more than one option

	yes
Upper respiratory tract infection (”’flu”)…….	1
Subfreezing air……....	1
Physical exercise……..	1
Automobile exhaust fumes……..	1
Poor indoor air quality…….	1
Proximity to animals……	1
Pollens……..	1
Cigarette smoke……...……	1
Strong scents (perfumes, deodorants etc.)……	1
Strong paints or fumes……..…	1
Speaking……...	1
Eating or drinking (during or soon after it)……..	1
Laughing……...	1
Deep inspiration……	1
Something else……...…...	1

59. If you chose the alternative ‘something else’, please define the trigger

_____
_____

60. In the past 12 months, have you used cough medicines?
(Both those purchased from a pharmacy and herbal remedies)

0 no
1 yes

61. How many times in the past year (12 months) have you visited the doctor because of your cough?
If you have not made any visits, then please mark 0

_____times

62. In the past two weeks, have you had a cough?

0 no
1 yes

The last part of this questionnaire is intended only for those people who have had a cough in the past two weeks i.e. those people who responded “yes” to question 62. Others can proceed to the last page of the questionnaire.

THE FOLLOWING QUESTIONS ARE ONLY TO BE ANSWERED BY THOSE WHO HAVE BEEN SUFFERING FROM COUGH IN THE PAST TWO WEEKS

63. Did you have symptoms of 'flu' when your current cough began (fever, throat ache, rhinitis, muscle pain or arthralgia, headache)?

0 No
1 Yes
2 Do not remember or can not define

64. How often has your current cough been bothering you?

1. Several times a day
2. Every day at least once a day
3. Four to six days in a week
4. Two or three times a week
5. At least once every week
6. Less than weekly

65. For how long have you been troubled by your current cough?

1. Less than one week
2. Longer than one week, but less than three weeks
3. More than three weeks, but less than two months
4. More than two months, but less than one year
5. More than one year, but less than five years
6. More than five years, but less than ten years
7. More than ten years

66. Have you considered being examined by a doctor because of your current cough?

0 no
1 yes

67. How many times have you visited a doctor because of your current cough?
Answer 0, if you have not visited a doctor due to your cough

_____times

The next questions are designed to assess the impact of cough on various aspects of your life. Read each question carefully and answer by choosing the response that best applies to you. Please answer all questions, as honestly as you can.

68. In the last 2 weeks, have you had chest or stomach pains as a result of your cough?

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

69. In the last 2 weeks, have you been bothered by sputum (phlegm) production when you cough?

1. Every time

2. Most times
3. Several times
4. Some times
5. Occasionally
6. Rarely
7. Never

70. During the past two weeks, have you been tired because of your cough?

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

71. In the last 2 weeks, have you felt in control of your cough?

1. None of the time
2. Hardly any of the time
3. A little of the time
4. Some of the time
5. A good bit of the time
6. Most of the time
7. All of the time

72. How often during the last 2 weeks have you felt embarrassed by your coughing?

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

73. In the last 2 weeks, my cough has made me feel anxious.

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

74. In the last 2 weeks, my cough has interfered with my job, or other daily tasks.

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time

7. None of the time

75. In the last 2 weeks, I felt that my cough interfered with the overall enjoyment of my life.

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

76. In the last 2 weeks, exposure to paints or fumes has made me cough.

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

77. In the last 2 weeks, has your cough disturbed your sleep?

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

78. In the last 2 weeks, how many times a day have you had coughing bouts?

1. All the time (continuously)
2. Most times of during the day
3. Several times during the day
4. Some times during the day
5. Occasionally through the day
6. Rarely
7. None

79. In the last 2 weeks, my cough has made me feel frustrated.

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

80. In the last 2 weeks, my cough has made me feel fed up.

1. All of the time

2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

81. In the last 2 weeks, have you suffered from a hoarse voice as a result of your cough?

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

82. In the last 2 weeks, have you had a lot of energy?

1. None of the time
2. Hardly any of the time
3. A little of the time
4. Some of the time
5. A good bit of the time
6. Most of the time
7. All of the time

83. In the last 2 weeks, have you worried that your cough may indicate a serious illness?

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

84. In the last 2 weeks, have you been concerned that other people think something is wrong with you, because of your cough?

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

85. In the last 2 weeks, my cough interrupted conversation or telephone calls.

1. Every time
2. Most times
3. A good bit of the time
4. Some of the time
5. A little of the time

6. Hardly any of the time
7. None of the time

86. In the last 2 weeks, I feel that my cough has annoyed my partner, family or friends.

1. Every time I cough
2. Most times when I cough
3. Several times when I cough
4. Some times when I cough
5. Occasionally when I cough
6. Rarely
7. Never

CONSENT TO USE MY DATA, WHICH HAS BEEN CATHERED IN MEDICAL REGISTERS

You are able to participate in this questionnaire survey also without giving your personal identification data.

Can my data in medical registers (Statistics Finland, the Cancer Registry, and the National Institute for Health and Welfare) be utilised in association with the present study?

1 no. You can now submit the questionnaire without filling in the next sections – please click here___
2 yes. In that case, we ask you to fill in the next sections:

Cough in Savo and Central Finland
Unit for Medicine and Clinical Research, Pulmonary Division, Kuopio University Hospital, Kuopio,

I have been requested to participate in the above research project, which is intended to determine cough prevalence and to clarify factors that influence the prevalence and the consequences of cough in the population living in Eastern and Central Finland. I have read and understood the written information I have received about this research project. I have been given the opportunity to contact the researchers should I wish to receive further information. The information that I have received has given me a satisfactory understanding about this research project and about the way in which the data in the project will be gathered, handled and distributed. I was given a sufficient amount of time to consider whether or not I would participate in this project. I have been provided with sufficient information about my rights, the goals of this research project, how it will be implemented as well as the advantages and risks associated with this research project. I have not been coerced nor given any incentives to participate in this research project.

I understand that my participation is voluntary. I am aware that I can withdraw my permission to participate in this research project at any time and without giving any reason for my withdrawal. I am aware that my responses will be handled confidentially and not provided to any outside parties. I am aware that should I decide to interrupt or withdraw my permission to participate in this research project, any data which has been collected prior to my withdrawal/ refusal to continue can be included in the project's research material.

Name of the participant _____
Identity number of the participant_____
Address of the participant_____
Telephone number of the paricipant_____
Date_____

You can now submit your responses by clicking here: ____