



Persistence of chronic cough in a community-based population

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ABSTRACT Chronic cough causes significant impairment in the quality of life and is often immune to treatment. Previous studies about its persistence have focused on patients managed in special cough clinics. Little is known about the persistence of chronic cough in unselected populations. In this prospective follow-up study, we investigated factors that predict the persistence of cough at 12-month follow-up in a community-based study of subjects with chronic cough.

The first e-mail survey in 2017 included a questionnaire about current cough and its risk factors. The 264 subjects who reported chronic cough were sent a follow-up questionnaire 12 months later.

The response rate was 77.7% (205 subjects), of whom 165 subjects (80.5%) still had cough in 2018. In multivariate analysis, the following baseline factors predicted the persistence of cough at 12 months; gastro-oesophageal reflux disease (adjusted OR (aOR) 5.02 (95% CI 1.10–22.83)), presence of a chemical trigger (aOR 2.88 (95% CI (1.20–7.00))), duration of cough more than 1 year (aOR 2.80 (95% CI 1.27–6.22)), frequent somatic symptoms (aOR 1.31 (95% CI 1.07–1.59)), and low number of family members (aOR 0.71 (95% CI 0.52–0.98)).

In conclusion, most patients with chronic cough still suffer from cough 1 year later. The presence of gastro-oesophageal reflux disease is the main predictor for the persistence of cough.



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Introduction

Chronic cough is a troublesome disorder in many ways. Cough is the most common reason why people seek medical help [1, 2], it significantly decreases the quality of life [3] and individuals suffering from chronic cough feel debilitated [4]. Two previous studies reported that 50–60% of patients with chronic cough still suffer from the disorder 5 to 7 years after the initial evaluation [5, 6]. However, the majority of the patients in these studies had been recruited from specialised cough clinics. As only the most severe and long-standing forms of cough are usually managed in specialised cough clinics, these studies are prone to bias towards over-pessimism in the prognosis of chronic cough. To the best of our knowledge, there are no studies that have examined the persistence of chronic cough in a community-based sample.

Of the studies investigating the issue, only one could define the predictors of cough persistence. That study reported that the possible determinants of cough persistence were chronic rhinitis or reflux disease and mild responsiveness to histamine and severe cough responsiveness to hypertonic saline [5]. However, it is not clear whether these predictors also apply in a population-based sample without the possibility to special investigations like histamine and saline challenges.

In order to improve our understanding of chronic cough, it would be important to obtain up-to-date information about the persistence and risk factors of chronic cough in a nonselected population. In this study, we examined the factors that predicted the presence of cough at 12 months in a community-based sample of subjects reporting chronic cough.

Methods

Study design and population

This was a prospective, observational follow-up study conducted in public service employees of two middle-sized towns in central Finland (Kuopio and Jyväskylä; altogether 13 980 employees, mean 46.6 years of age, 79.2% of whom were females). An invitation to the study and the first questionnaire were sent *via* e-mail to the employees' e-mail addresses between March and April 2017. Answers were collected *via* an electronic reply form. One reminder was sent to the individuals who had not responded within 2 weeks. A total of 3695 subjects (26.4%) responded, out of whom 419 (11.3%) reported that they were suffering from chronic cough (>8 weeks duration). The second questionnaire was sent *via* e-mail in April 2018 to all of those participants who reported suffering from chronic cough in the first inquiry in 2017 and who had provided permission for follow-up (n=264, mean age 51.7 years (9.5), 83.0% females) (figure 1). One reminder message was sent if a subject had not responded within 2 weeks. One phone contact was made if a subject had still not answered within 2 weeks after the reminder message.

The study was approved by the Ethics Committee of Kuopio University Hospital (289/2015). Permission to conduct the study was obtained from town officials. An informed, written consent was obtained from all participants.

Questionnaires

The first questionnaire sent in 2017 included questions about the subject's household, pets, moisture damage both in their workplace and at home, family incomes, occupation, physical activity, smoking history, alcohol consumption, current medications, recent (within 1 month) somatic symptoms, as well as all disorders diagnosed by a physician and general health-related questions. The questions were mainly adapted from two previous studies, the Health Behaviour and Health Among the Finnish Adult Population study [7] and the Finnish National FINRISK study [8]. Asthma-, rhinosinusitis- and reflux-related symptoms were enquired by questions currently employed in epidemiological studies [9–11]. Depressive symptoms were assessed by utilising the Patient Health Questionnaire-2 [12]. The first questionnaire also included 23 detailed cough-related questions to be filled in by subjects reporting current cough, such as questions about the frequency of coughing bouts and cough duration, as well as the Leicester Cough Questionnaire, which was used to measure cough-related quality of life [13]. An English version of the Finnish questionnaire sent in 2017 is included as a supplementary file.

The second questionnaire, sent in 2018, included questions about current cough, current smoking, current moisture damage both in the workplace and at home, current pets, and current medications. Both questionnaires were initially tested in a preliminary sample of 25 subjects and slightly revised before the final study.

Definitions and outcomes based on questionnaires

Chronic cough was defined as cough that had lasted more than 8 weeks [14]. Wheezing was defined as wheezing occurring but not attributable to flu during the previous 12 months [15]. Chronic rhinosinusitis was present if there was either nasal blockage or nasal discharge (anterior or posterior nasal drip) and either facial pain/pressure or reduction/loss of smell for more than 3 months [10]. Gastro-oesophageal

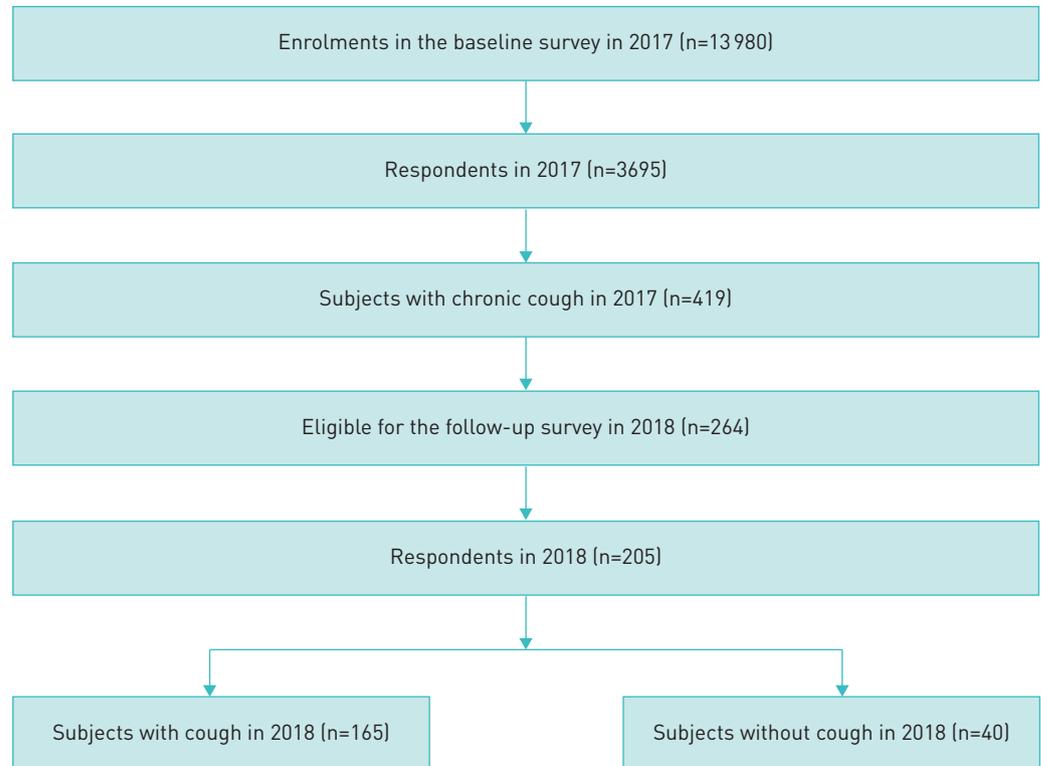


FIGURE 1 Flow chart of the study population.

reflux disease was present if the individual had experienced heartburn and/or regurgitation on at least 1 day per week during the last 3 months [11]. Depression was defined as a Patient Health Questionnaire-2 score of three or more [12]. The somatic symptom sum was calculated by summing all reported somatic symptoms except cough (including chest pain on exercise, arthralgia, back pain, toothache, leg oedema, varicose disorder, eczema, headache, sleeplessness, depression, other mental symptoms, constipation, diarrhoea or other gastro-intestinal symptoms, sciatica); it had a scale ranging from 0 to 14. The presence of a chemical trigger for cough was defined as the presence of one or more of the following triggers that would either cause or worsen the cough: exhaust fumes, poor indoor air, cigarette smoke, strong odours or strong smells. Trigger sum was calculated by summing all of the cough triggers (including the chemical triggers defined above, upper respiratory tract infection, subfreezing air, physical exercise, pollens, speaking (adopted from Leicester Cough Questionnaire) or a free choice) giving a value from 0 to 12. A family history of chronic cough was defined as the presence (now or in the past) of chronic (duration more than 8 weeks) cough in parents, sisters or brothers. The main outcome was the presence of cough in the past 2 weeks based on the questionnaire sent in 2018.

Statistical analysis

Descriptive data are presented as means and 95% confidence interval. Mann–Whitney U-test and chi-squared test were applied when appropriate. T-tests or other parametric tests were not used because most of the variables were not continuous or normally distributed. Table 1 shows the difference in the number of family members between the groups utilising the Mann–Whitney U-test. The following predictors were considered based on plausible biological associations with cough [14, 16–18]: age, sex, body mass index, years of education, professional status, unemployment or being laid off, family income, number of family members, pet ownership, ownership of dog and cat, exposure to moisture damage in the home or in the workplace, smoking history, alcohol consumption (total doses per week), family history of chronic cough, acetylsalicylic acid intolerance, the somatic symptom sum, the presence of a cough chemical trigger, the trigger sum, the use of cough remedies, cough bout frequency, cough duration more than 1 year (this cut-off value was defined by the Youlden index), Leicester Cough Questionnaire total score, wheezing, chronic rhinosinusitis, and gastro-oesophageal reflux disease. Confounders present in fewer than 10 respondents were not considered. The variables showing at least a suggestive ($p < 0.1$) association with the outcome variables in the bivariate analyses were included in the multivariate analysis utilising binary logistic regression analysis with a backward-directed stepwise process. A p -value < 0.05 was

TABLE 1 Differences of baseline characteristics between subjects who presented cough and those who did not develop cough at the 12-month follow-up

Characteristic at baseline	Subjects with cough at follow-up (n=165)	Subjects without cough at follow-up (n=40)	p-value
Somatic symptom sum	3.89 [3.50–4.28]	2.38 [1.77–2.98]	<0.001
Duration of the cough episode median (range)	12–60 months (2 months to >10 years)	2–12 months (2 months to >10 years)	0.001
Trigger sum	5.60 [5.14–6.07]	4.05 [2.98–5.12]	0.003
Presence of a chemical trigger	84.8%	65.0%	0.004
Gastroesophageal reflux disease	22.4%	7.5%	0.033
Current daily smoking	10.3%	0%	0.034
Family members	1.58 [1.40–1.76]	2.00 [1.59–2.41]	0.051
Wheezing	52.1%	37.5%	0.097

Data are presented as mean (95% CI), unless otherwise stated. Characteristics with at least a suggestive association ($p < 0.10$) are presented and based on chi-squared and Mann–Whitney U-tests.

accepted as the level of statistical significance but results showing a suggestive association ($p < 0.1$) were also evaluated. All analyses were performed using SPSS version 22 for the personal computer (SPSS, Inc., Chicago, IL, USA).

Results

The response rate was 77.7% (205 subjects, mean age 52.1 years (9.0), 85.9% females, table 2). The proportion of missing values was less than 1%. In 2018, 165 subjects (80.5%) reported that they were still experiencing cough.

Table 1 presents the factors that predicted cough in 2018 in the bivariate analyses.

The following factors were associated with cough in the multivariate analyses: gastro-oesophageal reflux disease (adjusted OR (aOR) 5.02 (95% CI 1.10–22.83)), presence of a chemical trigger (aOR 2.88 (95% CI (1.20–7.00))), duration of cough more than 1 year (aOR 2.80 (95% CI 1.27–6.22)), frequent somatic symptoms (aOR 1.31 (95% CI 1.07–1.59)), and low number of family members (aOR 0.71 (95% CI 0.52–0.98)) (table 3).

From 2017 to 2018, the current daily smoking status had changed from 8.3% of subjects to 6.9% of subjects, current pet ownership from 39.7% to 41.9% of subjects and current moisture damage exposure status from 35.1% to 11.0% of subjects. Nonetheless, the inclusion of these factors into the multivariate analysis did not change the results.

Discussion

In the present sample consisting of a community-based subjects with chronic cough, as many as 80.5% still were suffering from cough when assessed 12 months later. In the multivariate analysis, the five factors

TABLE 2 The characteristics at baseline of the 205 subjects who responded to the follow-up survey in 2018

Age years mean\pmsd	52.1 \pm 9.0
Female sex	176 (85.9%)
Body mass index kg·m⁻² mean\pmsd	28.1 \pm 5.6
Current smokers	17 (8.3%)
Ex-smokers	51 (24.9%)
Pet ownership	81 (39.5%)
Moisture damage in workplace or at home	72 (35.1%)
Presence of gastro-oesophageal reflux disease with proton-pump inhibitors	40 (19.5%)
Patients receiving medication	25 (62.5%)
Presence of doctor diagnosed asthma with asthma medication	62 (30.2%)
Patients receiving medication	60 (96.8%)
Presence of chronic rhinitis treated with any kind of nasal sprays	82 (40.0%)
Patients receiving medication	50 (61.0%)

Data are presented as n (%), unless otherwise stated.

TABLE 3 Multivariate adjusted odds ratios (aOR) between characteristics at baseline in 2017 and the presence of cough at the 12-month follow-up

Characteristic at baseline	aOR (95% CI)	p-value
Gastro-oesophageal reflux disease	5.02 (1.10–22.83)	0.037
Presence of a chemical trigger	2.88 (1.20–7.00)	0.018
Duration of cough more than 1 year	2.80 (1.27–6.22)	0.011
Somatic symptom sum[#]	1.31 (1.07–1.59)	0.008
Number of family members[¶]	0.71 (0.52–0.98)	0.034

[#]: per individual somatic symptom; [¶]: per number of family members other than the respondent.

at baseline that predicted cough at 12 months were 1) gastro-oesophageal reflux disease, 2) the presence of a chemical trigger, 3) duration of cough more than 1 year, 4) number of somatic symptoms, and 5) a low number of family members.

Gastro-oesophageal reflux disease was the most important predictor for persistent cough at 12 months after the initial evaluation among patients with chronic cough. The relationship between chronic cough and gastro-oesophageal reflux disease is rather complex and the exact pathophysiological mechanism underpinning this relationship remains unclear [19]. In patients with chronic cough, the passage of acid into the distal oesophagus increases the frequency of coughing [20] and elevates the cough reflex sensitivity to capsaicin [21]. Furthermore, it has been claimed that the major determinants of the cough seem to be the volume of the refluxate and the duration of the reflux episode rather than the acidity of the refluxate [22]. These findings could explain why acid-suppressive therapy has proven to be ineffective in reducing cough frequency in many placebo-controlled trials [23]. Given the fact that reflux seems to be a strong predictor for a poor prognosis in chronic cough, its proper treatment is of fundamental importance. According to the latest guidelines [19], the treatment of chronic cough due to gastro-oesophageal reflux should consist of diet modification to promote weight loss in overweight or obese patients, head-of-bed elevation and avoidance of meals 3 h before going to bed. Proton-pump inhibitors, H₂-receptor antagonists or antacid therapy are recommended for patients who report heartburn and regurgitation. Those patients whose cough has been refractory to a 3-month trial of lifestyle and medical anti-reflux therapy and who are being evaluated for surgical management, should undergo a 24-h oesophageal manometry and pH-metry monitoring and if peristalsis is adequate and oesophageal acid exposure is abnormal, anti-reflux surgery should be considered as a way of treating their chronic cough.

One may think that the under-medication of reflux in the population might explain the predictive value of reflux symptoms. Indeed, just 25 out of 40 subjects with symptomatic reflux used proton-pump inhibitors. However, it has been shown that the effect of any medical therapy is poor in reflux-associated cough. Therefore, it is unlikely that under-medication of reflux symptoms explains the association between reflux symptoms and the persistence of cough.

It should be noted that many patients with chronic cough possibly due to gastro-oesophageal reflux disease do not have the typical symptoms associated with gastro-oesophageal reflux disease (*i.e.* heartburn and regurgitation) [24]. In this study, we asked about the presence of gastro-oesophageal reflux disease based on validated symptoms [11]. This raises the following questions: what is the prevalence of gastro-oesophageal disease among chronic cough patients with atypical or absent reflux symptoms and should 24-h oesophageal manometry and pH-metry be performed in all patients complaining of unexplained chronic cough?

The presence of a chemical trigger (either exhaust fumes, poor indoor air, cigarette smoke, strong odours or strong smells) was also a crucial predictor for persistence of cough. TERNESTEN-HASSÉUS *et al.* [30] have previously shown that chemical-sensitive patients coughed significantly more on inhaling capsaicin, and had significantly more other airway symptoms compared to those in the nonsensitive group. These findings fit to the concept of cough hypersensitivity syndrome [25], hence presence of a chemical trigger suggests a diagnosis of cough hypersensitivity syndrome. We think that the presence of a chemical trigger is an important part of the anamnesis of a patient suffering chronic cough.

In this study, a duration of cough lasting more than 1 year predicted the prolongation of chronic cough almost as strongly as the presence of a chemical trigger. The mechanism behind this finding might be central sensitisation, such as in chronic pain. As with chronic pain, continued stimulation may result in increased neuronal responsivity and sensitisation [26]. Given the fact that chronic cough is difficult to treat [4–6], careful diagnostic and therapeutic management should be done in the early phase of cough.

The number of somatic symptoms predicted the presence of cough at 12 months. It seems likely that there are individual differences in the ways in which individuals recognise and report their symptoms, a phenomenon called somatisation. In the present study, somatisation was taken into account by calculating the somatic symptom sum. Previously it has been reported that there is a good association between somatisation symptoms and asthma symptoms [27]. A lower number of family members also predicted cough at 12 months. This is an interesting finding because the hygiene hypothesis has been proposed to lie behind atopy and atopic disease (*i.e.* family size is negatively associated with atopy and atopic disease) [28] but to the best of our knowledge, not previously with chronic cough. The protective effect of large families in atopy and allergic diseases is considered to be explained by the greater exposure to microbes in members of these families. The same mechanism does not necessarily explain our finding about the protective effect of larger family size.

Interesting negative findings are that neither asthma nor chronic rhinitis predicted cough at 12 months. These diseases had been quite well medically treated, similarly to gastro-oesophageal reflux disease (table 2). It can be postulated that asthma and chronic rhinitis are conditions that respond better to medical treatment in contrast to gastro-oesophageal disease, which requires lifestyle modifications rather than simply acid-suppressive therapy to effectively treat chronic cough. In addition, asthma and chronic rhinitis tend to be seasonal and this may have influenced the failure to detect a relationship with chronic cough.

Furthermore, the Leicester Cough Questionnaire did not predict cough prolongation, suggesting that severity of cough is not predictive for its prolongation. This is an important message to patients with chronic cough and also to doctors treating them. There is no reason for pessimism on the basis of cough severity at the initial evaluation.

There are several limitations to this study. The population consisted of working-age, public service employees, so the generalizability of the study may be somewhat limited. Individuals in the lower social classes and older persons are therefore underrepresented, and this may also partly explain the low smoking rate. Thus, the role of smoking in cough prolongation cannot be determined in this population. It should also be taken into account that all the data in this study are based on self-reported symptoms. Subjects also self-reported clinical diagnoses and medications and these were not rechecked from the electronic patient record system. Many patients with gastro-oesophageal reflux disease did not use proton-pump inhibitors, which may have affected the results. A single year is also a rather short time in the follow-up of chronic cough; in fact, we are well aware that the majority of cough patients may have suffered from cough for several years [4, 29]. On the other hand, from the point of view of the patients, even suffering from this irritating disorder for 1 year is already a long time.

The strengths of the study include the community-based sample; the previous two studies that have examined the prognosis of chronic cough were conducted in a selected population (*i.e.* patients being treated in specialised cough clinics). In addition, this study includes more patients than the previous two studies combined [5, 6]. The strength of this study is also its prospective, follow-up design. It is recognised that causal inference between risk factors and cough prolongation can be better investigated in a prospective, follow-up study than in one with a cross-sectional design. The baseline questionnaire was originally developed to investigate the risk factors of cough. Nonetheless, this questionnaire was comprehensive, the collection of risk factors was systematic, and the response rate was good (77.7%).

In conclusion, this study is the first that has investigated the persistence of chronic cough and its risk factors in a community-based sample. It was found that the vast majority (*i.e.* 80%) of patients still have cough at the 1-year follow-up, even though asthma and chronic rhinitis had been mainly adequately medically treated. Gastro-oesophageal reflux disease is the main indicator for cough persistence in chronic cough. Physicians should take a careful patient history about the presence of gastro-oesophageal reflux disease in a patient suffering from chronic cough. Treatment should be started, especially focusing on lifestyle modifications as well as anti-reflux therapy if needed. The presence of a chemical trigger, the duration of cough and the presence of other somatic symptoms should also be considered to get a proper assessment of the risk factors of prolongation of chronic cough.

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