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Cough persistence in adults with chronic cough: A 4-year retrospective cohort study

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HARQ, Hull Airway Reflux Questionnaire; FEV1, forced expiratory volume in 1 s; OR, odds ratio; CI, confidence interval; aOR, adjusted odds ratio; LCQ, Leicester Cough Questionnaire; GERD, gastroesophageal reflux disease

ABSTRACT

Background: There is very limited evidence regarding long-term prognosis of chronic cough. We examined longitudinal outcomes among patients with chronic cough, and explored predictors of cough persistence.

Methods: A retrospective cohort was constructed of adults who had newly visited a specialist cough clinic in 2012–2013. All had undergone systematic investigation for chronic cough. The Hull Airway Reflux Questionnaire (HARQ) was administered to assess reflux cough symptoms. A follow-up survey was conducted in 2016–2017 to assess cough persistence.

Results: From 418 candidates, 323 participated in the follow-up study; main analyses focused on patients with chronic persistent cough (n = 64; 19.8%) and remitted cough (n = 193; 59.8%). Compared with remitted cough group, chronic persistent cough group had more family history of chronic cough (17.2% vs. 4.7%, $p = 0.001$) and cold air-sensitive cough (62.5% vs. 44.6%, $p = 0.013$). The total HARQ score did not differ; however, two items *(cough with eating and cough with certain foods)* scored significantly higher in chronic persistent cough. In multivariate analyses, a family history of chronic cough (adjusted odds ratio 4.27 [95% confidence interval 1.35–9.89]), cold air-sensitive cough (2.01 [1.09–3.73]), and *cough with eating (1.22 [1.02–1.45])* were associated with chronic persistent cough at 4 years.

Conclusions: Cough persists in about 20% of patients after 4 years following systematic assessment and treatments. Several cough characteristics, such as family history, cold air-sensitivity, or reflux cough, may be associated with cough persistence. Larger cohort studies are warranted to further understand long-term prognosis and confirm predictors of persistence in patients with chronic cough.

Introduction

The cough reflex is a physiological mechanism for protecting the lower airways.[1] However, when dysregulated, cough becomes a pathologic condition. Cough is one of the most common symptoms that lead patients to seek a medical consultation.[2] In particular, chronic cough, usually defined as cough persisting for more than 8 weeks,[3,4] is a common problem in the general populations and is a major challenge for patients and clinicians in many clinical settings.[5,6] The impact of persistent cough on quality of life is not confined to the physical domain, but also encompasses psychosocial aspects, frequently leading to social isolation of the affected individuals.[7–9]

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Despite the importance of chronic cough, however, the long-term prognosis is largely unknown.[10] To our knowledge, only 2 studies so far have described longitudinal outcomes in patients in European countries.[11,12] However, given the heterogeneity of clinical characteristics and methodologies across studies, further studies are warranted to understand the long-term prognosis of chronic cough.

In this retrospective cohort study, we examined 4-year longitudinal outcomes in patients who were systematically managed according to anatomic diagnostic protocols at a tertiary cough clinic. Our outcomes of interest were: (1) the frequency of cough persistence, and (2) baseline predictors of cough persistence at 4 years after the first outpatient visit.

Methods

Baseline cohort description

A retrospective cohort was constructed with 418 adult patients with chronic cough who had visited a specialist cough clinic for the first time at a tertiary hospital in Seoul, Korea, between March 2012 and December 2013. All patients were assessed and managed according to anatomic diagnostic protocols in international guidelines for chronic cough.[3,4] In their initial visit, participants underwent investigation for a differential diagnosis, including chest X-rays, spirometry, methacholine bronchial challenges, or induced sputum analyses. Chest X-rays and spirometry were performed in all subjects, and other tests were selected at physician's discretion.

Chest X-rays were interpreted by radiologists and classified as abnormal in this study, if any of the following conditions were reported: pulmonary tuberculosis, pneumonia, emphysema, bronchiectasis, pulmonary nodules, lung cancer, mediastinal disease, or other lung parenchymal diseases. Methacholine bronchial challenge tests assessed airway hyper-responsiveness, using the modified protocol by Chai *et al.*[13]; each individual inhaled 5 inspiratory capacity breaths while increasing the methacholine concentration from 0.5 to 16 mg/mL. The methacholine challenge test was considered positive if 16 mg/mL or lower concentration of methacholine caused a 20% fall in forced expiratory volume in 1 s (FEV1) from the baseline.[14] Induced sputum analyses were performed according to European Respiratory Society/American Thoracic Society working group report protocols[15]; sputum eosinophilia was defined by sputum eosinophils $\geq$3%.[16] Skin prick tests were performed with 55 common inhalant allergens in Korea[17]; a wheal response with $\geq$3 mm to any inhalant allergen compared with negative controls was considered positive. Capsaicin cough challenge tests were performed to assess cough sensitivity, as previously described.[18] The subjects inhaled 0.5–64 μM of nebulized capsaicin. The number of coughs within 1 min after each dose was counted. Capsaicin cough sensitivity was described as the lowest capsaicin concentration (μM) to provoke 2 (C2) and 5 (C5) consecutive coughs after the inhalation.

Following outcomes were assessed using structured questionnaires. Cold air-sensitive cough was defined by a positive response to "Is your cough triggered when you inhale cold air?" Family history of chronic cough was defined by at least 1 parent or sibling ever having chronic cough. The Korean version of the Hull Airway Reflux Questionnaire (HARQ) was administered to assess airway reflux symptoms, which consists of 14 items with a maximum total score of 70.[19]

Follow-up study

A follow-up study was conducted between October 2016 and March 2017. Multiple choice questions were utilized to assess cough activity and persistence as the following: Q1: "How was your cough during the last month, compared to the initial outpatient visit?" (not troublesome; similarly troublesome; or worse); Q2: "How long did you suffer from cough during the last 1 year?" (not troublesome; less than 25%; 25–50%; or more than 50% of the year); and Q3: "In the last 1 month, have you taken medication to control your cough?" (yes or no) (Fig. 1). Based on the responses, participants were classified as having "chronic persistent cough" if they had current troublesome cough (similarly troublesome or worse cough as in Q1) that is persistent for longer than 25% of the last 1 year (Q2). Participants were classified as having "remitted cough" if they had no trouble with their cough during the last 1 year (Q1, Q2), with no current needs for medication to control their cough (Q3). Other patients were classified as "intermediate cough" subgroups, based on different responses to Q1-Q3. Main analyses focused on the comparison between chronic persistent cough and remitted cough patient groups.

In-person interviews were conducted for patients who were regularly attending the clinic. However, for those who were not regularly visiting the clinic, a telephone interview was conducted using the same questionnaire. All interviews were conducted by an experienced research nurse. Electronic medical records were reviewed to retrieve cough durations at the baseline visit. All participants gave written informed consent (verbal informed consent in the case of telephone interviews) and the study protocol was approved by the institutional review board (IRB No. 1605-050-760).

Statistical analysis

Differences between the 2 main groups (chronic persistent cough vs. remitted cough) were evaluated by Student's t-test for continuous variables and by the Chi-squared test for categorical variables. Capsaicin cough responses as continuous parameters (C2 or C5) were compared after $\log_2$ transformation, as they are not normally distributed. Univariate and multivariate logistic regression analyses were performed to explore predictors for chronic persistent cough (vs. remitted cough); multivariate logistic regression analyses were conducted for parameters with p values less than 0.1 in the univariate analyses. All statistical analyses were performed using SPSS version 18.0 (SPSS Inc., Chicago, IL, USA). Two-sided p values less than 0.05 were considered statistically significant.

Results

Cohort characteristics

From a total of 418 candidates, 323 patients responded to the follow-up study invitation (overall response rate: 77.3%). Among 53 patients with regular follow-ups to the outpatient clinic, 45 responded to a request for an in-person interview. Among 365 patients without regular follow-ups to the clinic, 278 responded to a telephone interview survey (Fig. 1). Overall, non-respondents had significantly more cold air-sensitive cough and chest X-ray abnormalities at baseline than respondents; however, there were no differences in age, sex, body mass index, cough duration, and other clinical parameters (Supplementary Table 1). The average duration of follow-ups in the respondents was 3.6 ± 0.5 years.

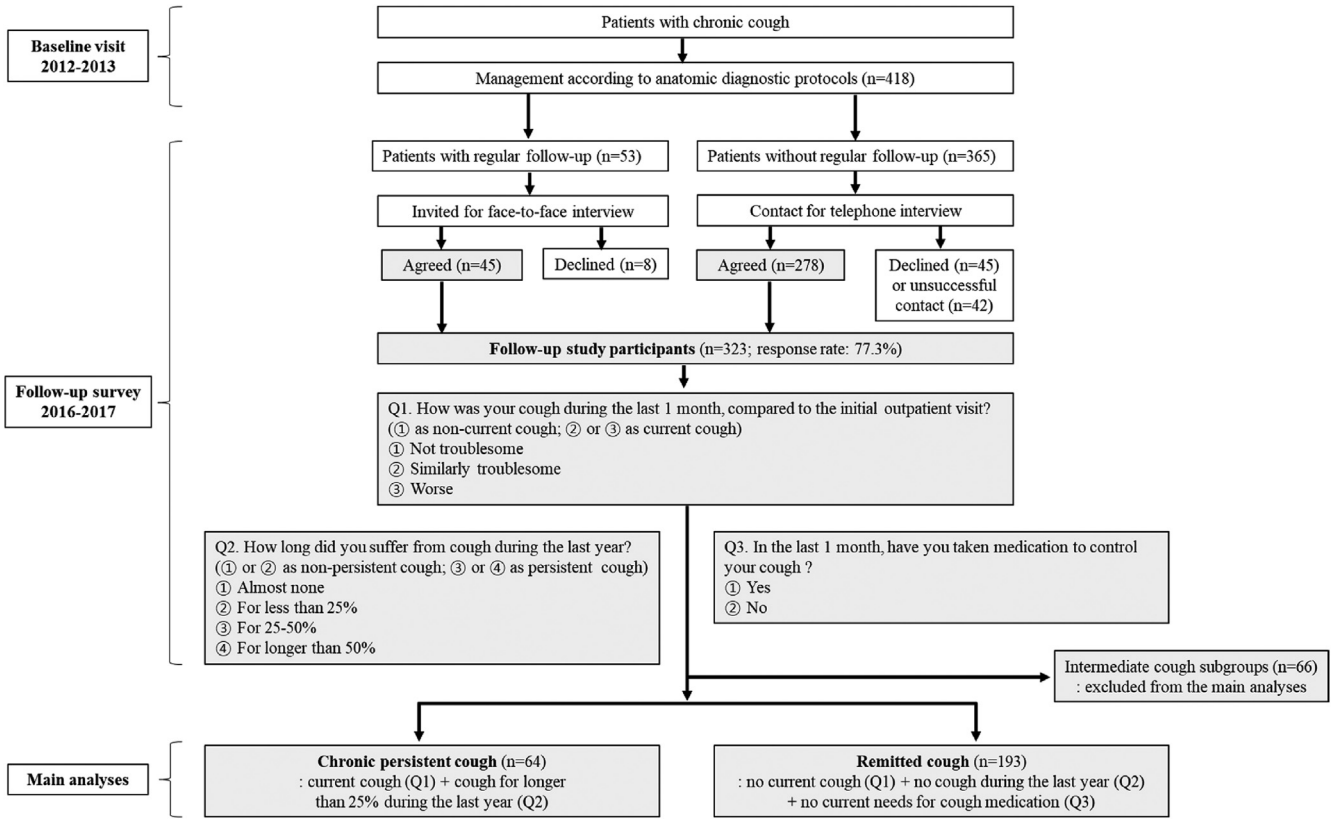

Fig 1. Flow of patient selection.

Patients were categorized into “chronic persistent cough”, “remitted cough”, and “intermediate subgroups”, as described in Methods. Among a total of 323 respondents, 64 patients (19.8%) were classified as having “chronic persistent cough” and 193 patients (59.8%) were classified as having “remitted cough” (Fig. 1). “Intermediate cough” subgroups (n = 66; 20.4%) included: “current non-persistent cough” (n = 23; current troublesome cough in Q1 but lasting for less than 25% of the last year in Q2); “past non-persistent cough” (n = 38; no current troublesome cough in Q1 and cough but lasting for less than 25% of the last year in Q2); and “past persistent cough” (n = 5; no current troublesome cough in Q1 but cough lasting for longer than 25% of the last year in Q2). Subsequent analyses were focused on the comparison between chronic persistent cough and remitted cough patient groups. The flow of participant selection and classification is summarized in Figure 1.

Comparison between chronic persistent cough and remitted cough

Baseline characteristics of the 2 patient groups are summarized in Table 1. Middle-aged female predominance was commonly observed in both groups. Compared with patients with remitted cough, patients with chronic persistent cough had more family history of chronic cough (17.2% vs. 4.7%; $p = 0.001$), and cold air-sensitive cough (62.5% vs. 44.6%; $p = 0.013$). Patients with chronic persistent cough showed trends toward longer cough duration (70.1 ± 106.1 vs. 44.6 ± 72.7 months; $p = 0.080$). However, there were no significant differences in other parameters, such as body mass index, smoking history, chest X-ray abnormality, spirometry parameters, methacholine airway hyper-responsiveness, capsaicin cough sensitivity (C2 and C5), sputum eosinophilia, or inhalant allergen skin prick test responses between the 2 groups at baseline.

Table 1
Comparison of baseline characteristics in patients with chronic persistent cough and remitted cough patients.

	Chronic persistent cough (n = 64)	Remitted cough (n = 193)	*p* value
Age (years)	54.2 ± 15.0	51.2 ± 15.0	0.17
Sex (female, %)	70.3	69.9	0.96
Body mass index (kg/m^2)	24.3 ± 4.1	23.9 ± 3.4	0.50
Smoking status (%)			0.87
Non-smoker	75.0	74.6	
Ex-smoker	18.8	18.1	
Current smoker	6.3	7.3	
Cough duration (months)	70.1 ± 106.1	44.6 ± 72.7	0.080
Family history of chronic cough (%)	17.2	4.7	0.001
Cold air-sensitive cough (%)	62.5	44.6	0.013
Chest x-ray abnormality (%)	3.1	2.6	1.00
FEV1, % predicted	99.1 ± 18.7	101.0 ± 16.0	0.45
FVC, % predicted	99.1 ± 15.1	101.2 ± 12.6	0.28
Inhalant allergen skin prick test positivity (%)	53.3	45.9	0.32
Rhinosinusitis symptoms (%)	62.5	56.0	0.36
Methacholine airway hyper-responsiveness (%)[†]	11.3	6.9	0.28
Log$_2$ capsaicin C2 (μM) [‡]	Median 3 (IQR 2–4)	Median 3 (IQR 2–4)	0.29
Log$_2$ capsaicin C5 (μM) [‡]	Median 5 (IQR 4–7)	Median 5 (IQR 3–7)	0.81
Sputum eosinophilia (≥3%) (%)	54.0	46.9	0.39

FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; IQR, interquartile range.

[†] Positive airway hyperresponsiveness was defined if the subject had methacholine PC20 (the provocative concentration of methacholine that results in a 20% drop in FEV1) < 16 mg/mL.

[‡] C2 (or C5) was defined by the lowest capsaicin concentration to provoke 2 (or 5) consecutive coughs within 1 min after inhalation.

Baseline total HARQ score did not significantly differ (30.2 ± 13.5 vs. 28.1 ± 13.6; $p = 0.279$); however, 2 items (Q9: "Cough with eating" [during or soon after meals] and Q10: "Cough with certain foods") scored significantly higher in the chronic persistent cough group than in the remitted cough group (Q9: 2.3 ± 1.8 vs. 1.7 ± 1.6; $p = 0.025$, and Q10: 1.7 ± 1.9 vs. 1.1 ± 1.5; $p = 0.021$) (Table 2).

Exploration of predictors of chronic persistent cough

Univariable logistic regression analyses were conducted to explore potential predictors of chronic persistent cough (vs. remitted cough) (Supplementary Table 2). In univariate analyses, cough duration (year) (odds ratio [OR]: 1.003; [95% confidence interval [CI]: 1.000–1.006]), family history of chronic cough (OR: 4.24; [95% CI 1.67–10.78]), cold air-sensitive cough (OR: 2.07; [95% CI: 1.16–3.70]), HARQ Q9 (cough with eating) score (OR: 1.23; [95% CI: 1.04–1.46]) and Q10 (cough with certain foods) score (OR: 1.24; [95% CI: 1.05–1.45]) were positively associated with chronic persistent cough. In multivariate logistic regression analyses (vs. remitted cough; please see Methods for covariate selection), we found significant associations between chronic persistent cough and the following baseline parameters: a family history of chronic cough (adjusted odds ratio [aOR]: 4.27; [95% CI: 1.35–9.89]), cold air-sensitive cough (aOR: 2.01; [95% CI: 1.09–3.73]) and HARQ Q9 (cough with eating) score (aOR: 1.22; [95% CI: 1.02–1.45]) (Fig. 2).

Discussion

The present retrospective cohort study found that about 20% of patients had chronic persistent cough about 4 years after systematic assessment and management at a tertiary cough clinic. Several cough characteristics, such as family history of chronic cough, cold air-sensitive cough, or cough with eating, were positively associated with cough persistence, suggesting that specific cough characteristics may predict the natural course of chronic cough. These findings suggest that prospective studies are warranted to confirm predictors for cough persistence in patients with chronic cough.

In the literature, there are only 2 studies on longitudinal outcomes and predictors for cough persistence in patients with chronic cough. Yousaf *et al.*[11] followed up 45 patients with unexplained chronic cough diagnosed over 7 years at a UK cough clinic; complete resolution was observed in 14% of the patients, whereas 60% had worsening or no improvement of cough over time. In a postal questionnaire study by Koskela *et al.*,[12] a 5-year prognosis was examined in 68 unselected patients with chronic cough in Finland; and the proportion of continuing impairment in cough-specific quality of life (defined as less than 1.3 points' improvement in the Leicester Cough Questionnaire [LCQ] scores) was 47%.[12] We found that cough persisted in about 20% of patients with chronic cough after 4 years of observation following systematic assessment and treatments, which is lower than the persistence rates reported in these 2 studies.[11,12] These findings are not comparable to each other, because patients characteristics and endpoint definitions were different. However, they altogether suggest that cough may persist for several years in a considerable proportion of patients with chronic cough, even after systematic management at specialist clinics. Therefore, further cohort investigation is warranted for more precisely understanding longitudinal outcomes in patients with chronic cough.

Predictors for cough persistence in patients with chronic cough are largely unknown. The UK study did not aim to examine baseline predictors for the cough persistence.[11] In the Finnish study,[12] continuing regular cough was significantly associated with the presence of chronic rhinitis, gastroesophageal reflux disease (GERD), and mild histamine airway hyper-responsiveness, but also with cough responsiveness to hypertonic saline at baseline, suggesting a patient's clinical trait may predict the persistence of cough. In the present study, several cough characteristics, such as a family history of chronic cough, cold air-sensitive cough, or reflux-associated cough, were found as potential predictors for cough persistence. Although all above-mentioned findings are not conclusive because the baseline measurements were heterogeneous between studies, these findings suggest that cough should be more characterized in further cohort studies of cough.

In this study, some parameters related to reflux cough, such as cough with eating or cough with certain foods, scored significantly higher in patients with chronic persistent cough than in patients with remitted cough (Table 2). Our findings should be carefully interpreted, as reflux-associated cough was merely evaluated by the questionnaire but not by objective tests. However, we speculate that esophageal diseases such as dysmotility or airway reflux might underlie the cough persistence,[20–22] and proper identification and control of the condition could be clinically useful. In a recent study of 312 patients with subacute or chronic cough in Japan, about half of the patients had GERD symptoms as measured by the Frequency Scale for Symptoms of Gastroesophageal reflux, and the presence of GERD was significantly associated with a lower rate of treatment response, longer cough duration, more time until cough alleviation, and also poorer cough-specific quality of life.[23] In a study of 172 patients with cough variant asthma, gastroesophageal dysmotility

Table 2
Comparison of the HARQ scores between chronic persistent cough and remitted cough groups.

Within the last month, how did the following problems affect you?	Chronic persistent cough	Remitted cough	*p* value
Q1. Hoarseness or a problem with your voice	1.7 ± 1.7	1.8 ± 1.7	0.62
Q2. Clearing your throat	3.1 ± 1.5	2.9 ± 1.6	0.39
Q3. The feeling of something dripping down the back of your nose or throat	1.9 ± 1.9	2.1 ± 1.8	0.48
Q4. Retching or vomiting when you cough	1.8 ± 1.7	1.7 ± 1.7	0.70
Q5. Cough on first lying down or bending over	1.7 ± 1.8	1.7 ± 1.7	0.94
Q6. Chest tightness or wheeze when coughing	2.3 ± 2.0	2.0 ± 1.5	0.22
Q7. Heartburn, indigestion, stomach acid coming up	2.0 ± 1.9	2.0 ± 1.5	0.66
Q8. A tickle in your throat, or a lump in your throat	3.1 ± 1.7	3.0 ± 1.6	0.91
Q9. Cough with eating (during or soon after meals)	2.3 ± 1.8	1.7 ± 1.6	0.025
Q10. Cough with certain foods	1.7 ± 1.9	1.1 ± 1.5	0.021
Q11. Cough when you get out of bed in the morning	1.9 ± 1.7	2.0 ± 1.8	0.85
Q12. Cough brought on by singing or speaking	2.8 ± 1.9	2.5 ± 1.7	0.14
Q13. Coughing more when awake rather than asleep	2.8 ± 1.8	2.9 ± 1.7	0.89
Q14. A strange taste in your mouth	1.1 ± 1.5	0.9 ± 1.5	0.44
Total HARQ score	30.2 ± 13.5	28.1 ± 13.6	0.28

HARQ, Hull Airway Reflux Questionnaire.
Each item in the HARQ is scored between 0 and 5 (0 = no problem; 5 = severe/frequent problems), with total score of 0–70 (from 14 items).

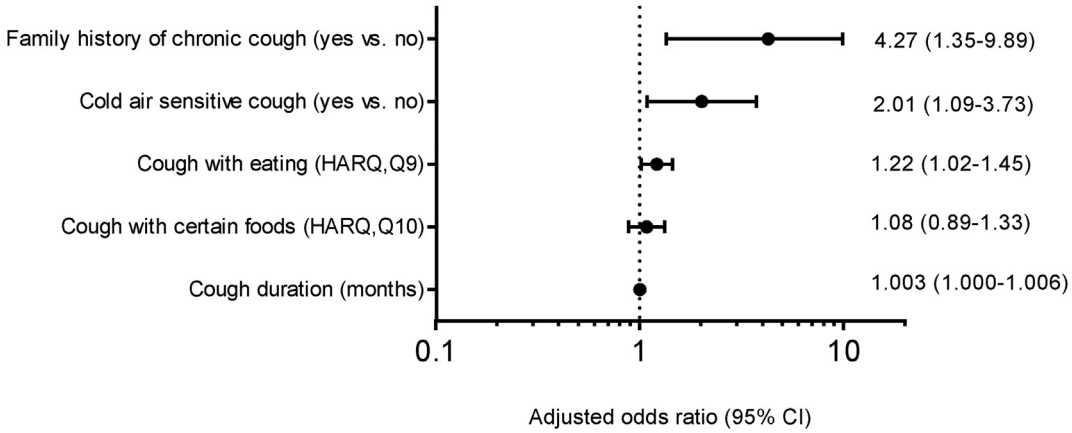

Fig 2. Potential predictors for chronic persistent cough (vs. remitted cough) in patients with chronic cough. Adjusted odds ratios (95% confidence interval (CI)) for chronic persistent cough (vs. remitted cough) were calculated in multivariate logistic regression analyses with adjustment for parameters with *p* values less than 0.1 in univariate analyses. HARQ, Hull Airway Reflux Questionnaire.

symptoms domain, but not acid reflux symptoms, was the significant predictor of impaired cough-specific quality of life.[24] These findings suggest that more attention should be paid to reflux-associated cough in patients with persistent cough.

Potential relevance of a cough trigger or hypersensitivity pattern has been suggested in several studies of patients with chronic cough. In studies of patients with prolonged or chronic cough in Japan, cold air, as a cough trigger, was significantly associated with the diagnosis of cough variant asthma, or its biomarkers such as methacholine airway responsiveness and fractional exhaled nitric oxide levels.[25,26] Similarly, in a Finnish community population-based study of 421 subjects with current cough, subfreezing air as a cough trigger predicted current asthma-associated cough.[27] Meanwhile, in a cross-sectional study in Sweden, the number of chemical sensitivity (as a cough trigger) was positively associated with poorer quality of life in patients with chronic cough.[28] In a recent multi-center study of Korean patients, the number of cough triggers was significantly higher in patients with chronic refractory cough than those with unselected chronic cough.[29] However, none of previous studies have examined the relevance of a cough trigger or hypersensitivity pattern in relation to longitudinal persistence of cough.

The present study also indicates that there may be a familial association with persistence in cough (aOR: 4.27 [95% CI: 1.35–9.89]; Fig. 2). Interestingly, in a Finnish community population study by Lätti *et al.*, family history of chronic cough was significantly associated with current daily cough (*vs.* no current cough).[30] Although it is rare, a genetic inheritance was reported for Australian families with chronic cough and GERD.[31] These findings altogether suggest a potential role for genetic inheritance, or common environmental factors in rendering cough more persistent, which warrant further investigation.

In the present study, several baseline indicators for common cough-associated conditions, such as rhinosinusitis symptoms, methacholine airway hyper-responsiveness, or sputum eosinophilia,[4] were not significantly associated with cough persistence. However, our findings do not refute the clinical relevance of these cough-associated conditions, because all study participants had undergone systematic assessment and treatment according to the anatomic diagnostic protocols.[3,4]

This study mainly focused on the comparison between chronic persistent cough and remitted cough patient groups. However, there were "intermediate cough" subgroups (20.4% of the participants), as described in Results, which did not clearly fit into any of 2 main groups. Due to small numbers of patients per each subgroup, they were arbitrarily classified as a single intermediate group, and then compared with chronic persistent cough and remitted cough groups. Four baseline parameters significantly differed among 3 groups, including family history of chronic cough, cold air-sensitive cough, cough with eating, and cough with certain foods, but also

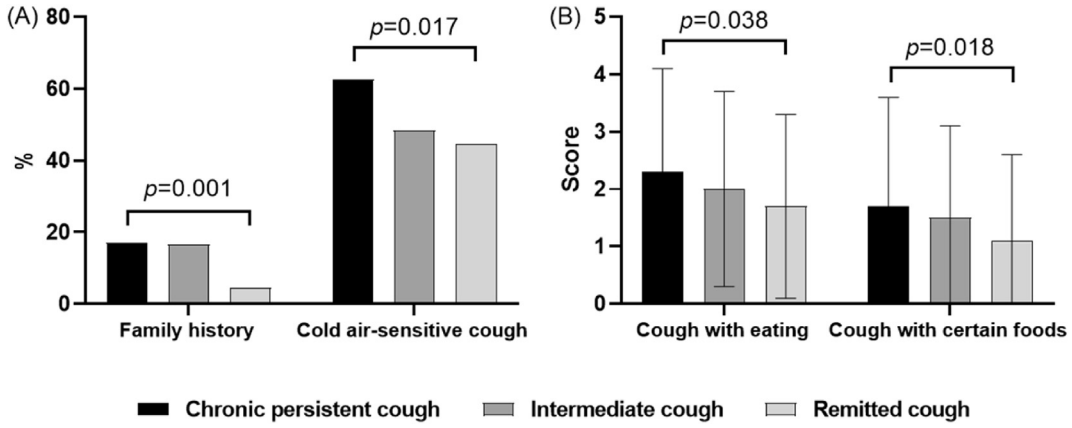

Fig. 3. Potential predictors for chronic persistent cough (vs. intermittent cough and remitted cough) in patients with chronic cough **(A)** Proportions of family history of chronic cough (left) and cold air-sensitive cough (right) **(B)** Scores for 'Cough with eating' (left) and 'Cough with certain foods' (right) in the Hull Airway Reflux Questionnaire. Values are presented as percentage, or mean with standard deviation. *p* values were determined by Chi-squared test or 1-way ANOVA.

with slightly different patterns in between-group differences (Fig. 3A, B; Supplementary Table 3, 4), suggesting potentially different roles of each parameter in cough persistence. However, larger cohort studies are warranted to clarify their relevance.

There are several limitations that should be considered when interpreting our findings. First, the persistence of cough was self-reported, which may be prone to a recall bias. Second, although we employed structured questionnaires to define cough persistence, an approach utilizing validated scales, such as the LCQ, may have been more appropriate, as the minimal important difference is known as 1.3 points.[32] However, it is unknown whether the LCQ holds its original validity when utilized in a telephone interview. Third, we could not fully obtain treatment details and reasons to continue (or stop) their medications over 4 years. Finally, we could not assess longitudinal changes in baseline clinical parameters, and thus the possibility should not be overlooked that causative factors of cough (such as GERD, eosinophilic bronchitis, or atopic cough) may remain uncontrolled at the time of follow-up survey. We found several baseline parameters that were significantly associated with cough persistence at 4 years, but their causal relationships warrant confirmation in prospective longitudinal cohort studies.

The strength of our present study includes a relatively high response rate (77.3%), enabling a follow-up of 323 patients at 4 years, which is much larger than previous studies.[11,12] Our findings are valuable addition to the literature on longitudinal epidemiology of chronic cough, and suggest clues for further investigations

In conclusion, cough may persist in about 20% of patients after 4 years of observation following systematic assessment and treatments. Several cough characteristics, such as a family history of chronic cough, cough trigger pattern, or reflux cough may be potentially associated with cough persistence. Larger prospective cohort studies are warranted to further understand the long-term prognosis and confirm predictors of persistence in patients with chronic cough.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.alit.2020.03.012.

Conflict of interest

The authors have no conflict of interest to declare.

Authors' contributions

SYK and WJS designed the study, collected the data, performed the statistical analysis, interpreted the data, wrote the first draft of the manuscript, and critically reviewed the manuscript. HKW, SJC, JYK, HWP and SHC collected and interpreted the data. AHM and SHC interpreted the data, and critically reviewed the manuscript. All authors approved the final version of the manuscript.

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