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Original Research

Distribution of chronic cough phenotypes in the general population: A cross-sectional analysis of the LEAD cohort in Austria

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ABSTRACT

Rationale: Recent guidelines consider chronic cough to be a unique clinical entity with different phenotypes. We aimed to investigate them in a general population and to describe prevalence, distribution, and characteristics of these phenotypes within the Austrian general population.
Methods: From the LEAD study, a longitudinal observational population-based cohort, data from questionnaires and spirometry of 10,057 adult participants was analysed. Chronic cough was defined as coughing nearly every day during the last 12 months for at least 3 months (>12 weeks).
Results: The prevalence of chronic cough was 9% and increased with age. We found no sex predominance but a female preponderance (68%) in never smokers. A presumable cause was identified in 85% of which more than half (53.9%) had two phenotypes, 36.9% belonged to one only and 9.2% to three or more. Regarding the distribution of phenotypes, 40.8% were current smokers, 32.6% had an ACE inhibitor intake, 18.2% GERD, 17.6% asthmatic cough, 9.7% UACS and 28.3% other diseases associated with chronic cough. 15% had unexplained chronic cough with no identifiable phenotype. Current smoking, low socioeconomic status, obesity, COPD and obstructive sleep apnea were associated factors with chronic cough.
Conclusion: Chronic cough is common among adults in Austria and highly prevalent in the older population. Most participants can be phenotyped with simple questionnaire-based assessment and can therefore potentially receive specific treatment without intensive clinical workup.

1. Introduction

Chronic cough in adults is defined by clinical guidelines as cough lasting for ≥8 weeks [1–3] and is a common reason to seek medical attention worldwide [4] since it has a significant impact on daily life [5] and quality of life [6]. A systematic review and meta-analysis including more than 90 studies reported a global chronic cough prevalence of 9.6%, with a higher rate in Europe (12.7%) [7].

The concept of cough hypersensitivity has increasingly been suggested as the underlying mechanism for many of the multifactorial causes of chronic cough; indeed, the European Respiratory Society (ERS) guidelines proposed cough hypersensitivity syndrome as the overarching diagnosis. Within this umbrella term, new different phenotypes and groups are considered, specifically [1]: asthmatic cough/-eosinophilic bronchitis [2]; GERD (gastroesophageal reflux disease) cough [3]; postnasal drip syndrome/upper airway cough syndrome (UACS) [4]; angiotensin-converting enzyme -inhibitors (ACE inhibitor) [5]; chronic refractory cough (or unexplained/idiopathic chronic cough) [6]; chronic cough in other diseases; and [7], chronic cough related to tobacco and nicotine [1]. However, the prevalence and

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characteristics of these phenotypes in the general population are unknown. Our primary aim was to investigate these chronic cough phenotypes in 10,057 adult participants in the Lung, hEart, sociAl, boDy (LEAD) study, a population-based cohort that recruited a random sample of urban and rural Austrian inhabitants stratified by age and sex [8].

2. Methods

2.1. Study design and ethics

The LEAD study (ClinicalTrials.gov; NCT01727518; http://clinicaltrials.gov) is a longitudinal, observational, population-based study investigating a random sample recruited from the general population of Austria stratified by age, sex, and residential area (based on the inhabitants register). The LEAD cohort is representative of the Austrian population in terms of age and gender distribution and has a high external validity. Further details concerning study design, recruitment strategy, methodology, and external validity of the LEAD study has been described in detail elsewhere [8].

For the current analysis, we used cross-sectional baseline data from the study, captured between February 2012 and September 2016 in adults aged 18–80 years. The LEAD study is being conducted in accordance with the International Conference on Harmonisation notes for guidance on Good Clinical Practice and the principles of the Declaration of Helsinki. All participants signed informed consent, and no new consent was needed for the current analysis. The LEAD study has been approved by the Ethics Committee of Vienna (EK-11-117-0711).

2.2. Questionnaires

Assessment was performed at the LEAD study centre of the Ludwig Boltzmann Institute for Lung Health at the Clinic Penzing in Vienna, Austria, as detailed elsewhere [8]. Chronic cough was defined by a stepwise assessment based on two main questions: The first asked if the participant had cough daily within the last 12 months (independent of common cold). If this question was answered with “yes” the participant was asked whether the cough duration was 3 month or longer. If both questions were answered with ‘yes’, participants were defined as individuals with chronic cough. The assessment of different clinical diagnosis (eg. asthma, GERD, hypertension, etc) was also based on two questionnaires: a) if the participant has the diagnosis … and b) if this diagnosis was made by a general practitioner or specialist. If both questions were answered with “yes”, the clinical diagnosis was considered in the participant.

COPD was defined by spirometry values FEV1/FVC < LLN (lower limit of normal). Socioeconomic status (validated with Austrian Governmental population data and categorized in low, middle, and high) included data about income, education, and occupation. Smoking status was based on declarations from individuals as ‘never’, ‘former’ and ‘current smoking’. Obesity was calculated by body mass index according to the World Health Organization definition ($\geq$30 kg/m^2).

2.3. Phenotypes and categories

The ERS classification was taken into account for phenotyping [1]. Specifically, the following groups were considered [1]: ‘Asthmatic cough’, which included individuals with a diagnosis of bronchial asthma, asthmatic bronchitis or allergic bronchitis; however, we could not assess eosinophilic bronchitis due to lack of information on sputum eosinophilia [2]; ‘GERD’, that included individuals with a diagnosis or symptoms of reflux [3]; ‘UACS’, on the basis of presence of nasal polyps or a diagnosis of sinusitis [4]; ‘ACE inhibitor intake’, that included individuals with chronic cough receiving treatment with angiotensin converting enzyme (ACE) inhibitors [5]; ‘Other diseases’ which excluded individuals previously classified in any of the previous four groups but included individuals with chronic cough related to other respiratory diseases, including chronic airway diseases (chronic obstructive pulmonary disease [COPD], bronchitis, emphysema, bronchiectasis), interstitial lung disease, obstructive sleep apnea or tuberculosis [6]; chronic cough related to smoking; and finally [7], ‘unexplained chronic cough’ that included participants with chronic cough in whom no cough-related condition could be identified. Participants could be included in multiple phenotypes.

2.4. Statistical analysis

Results are presented as the means with standard deviation (SD), medians with range and quartiles, or absolute values with percentages and 95% confidence interval (CI), as appropriate. Data was not normally distributed so that differences between phenotypes and categories were assessed using the Kruskal-Wallis test. We then used the X^2 test to compare subgroups of categorical variables, and the students t-test or the Mann-Whitney-U-test for normally and non-normally distributed continuous variables, respectively. Binary logistic regression using a forced entry model for age, sex, socioeconomic and smoking status as well as reported comorbidities was used to identify factors associated with chronic cough. Statistical significance was considered at a p-value of $<$0.05. For multiple comparisons, p values were adjusted by Holm-Bonferroni correction. Analyses were performed using IBM SPSS Statistics version 25.

3. Results

3.1. Prevalence and characteristics of chronic cough

Among the 10,057 adult participants in LEAD, 9% had chronic cough. We did not identify any gender predominance of chronic cough in the entire LEAD cohort, but we observed a female predominance in never smokers (68.4%). The prevalence of chronic cough increased with age, both in males and females (Fig. 1). The median cough duration was 3 years, with more than 80% of participants with chronic cough having cough duration of more than one year, and 31.9% a cough duration of more than 5 years (Fig. 2). Almost 66% of chronic cough individuals were overweight or obese. Arterial hypertension was reported by 268 individuals (30.9%), 94.5% of whom were treated with an ACE inhibitor. The prevalence of chronic cough in all individuals taking an ACE inhibitor was 13.6%. Chronic cough was more common in current smokers; conversely more participants without chronic cough were never smokers (Table 1). Amongst the current smokers (n = 2402), 14.7% reported chronic cough, and in all chronic cough individuals, 40.8% were current smokers.

Participants with chronic cough had generally lower socioeconomic status, and more often suffered symptoms of dyspnoea, sputum production and wheezing. There were no differences between rural and urban populations (Table 1).

3.2. Distribution of chronic cough phenotypes

Fig. 3 shows that among the 868 participants with chronic cough, an associated condition was identified in 85% (735 individuals), who were classified according to the following phenotypes (individuals could be assigned to more than one group): 354 (40.8%) were current smokers, 283 (32.6%) had an ACE inhibitor intake, 158 (18.2%) GERD, 153 (17.6%) asthmatic cough, 84 (9.7%) UACS and 246 (28.3%) had other diseases associated with chronic cough. ACE inhibitor intake without any other phenotype was observed in 112 individuals (12.9%). From all chronic cough individuals, 12.7% (n = 110) had an airflow limitation. Looking at the distribution of airflow limitation, the highest proportion (28.1%) was found within the asthmatic phenotype, 23% within the ACE-inhibitor intake group, 16.7% in UACS and 14.6% in those with GERD.

Of the 735 individuals with chronic cough, 271 (36.9%) belonged to

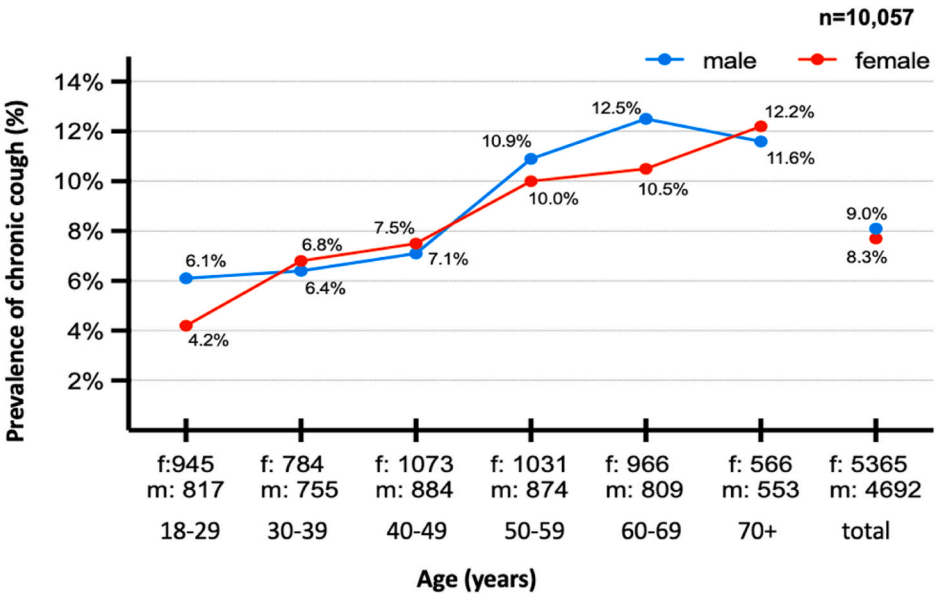

Fig. 1. Proportion of participants in the LEAD study with chronic cough stratified by age and gender. For further explanations, see text.

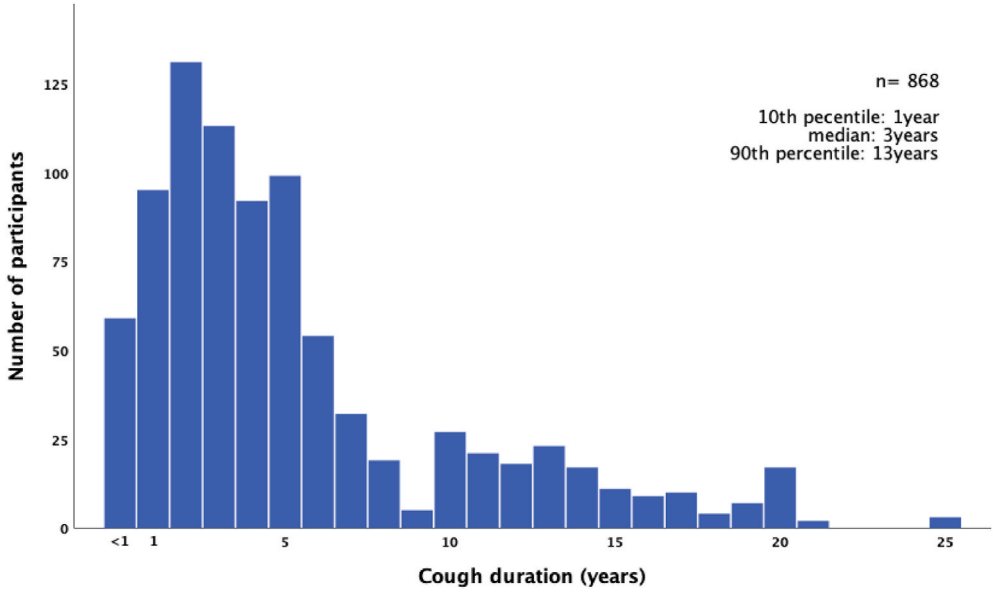

Fig. 2. Proportion of participants in the LEAD study with chronic cough by cough duration. For further explanations, see text.

one phenotype only, 396 (53.9%) to two and 68 (9.2%) to three or more phenotypes. Further we investigated the prevalence of inhalation therapy within chronic cough. We report 48% of the asthmatic phenotype and 51% of those with COPD being on inhalation treatment (agent not specified).

3.3. Unexplained chronic cough

A total of 133 (15.3% of the chronic cough cohort) individuals had unexplained cough, almost half of whom (45.1%) had a past smoking history. Regarding smoking frequency, significant differences were found in individuals with over 20 pack years, the highest impact in those with 30+ pack years (no chronic cough 10.6% vs chronic cough 27%; $p < 0.001$). Compared to the general chronic cough population, those with unexplained chronic cough were younger, with a higher proportion of females and reported less respiratory symptoms of dyspnoea, wheezing and sputum production.

3.4. Factors associated with chronic cough

In addition to asthma, GERD, COPD and UACS, older age, current, but not former, smoking, low socioeconomic status, obesity, and obstructive sleep apnea were other associated factors with chronic cough (Table 2).

4. Discussion

The main findings of this study are: (1) the prevalence of chronic cough in a large (n = 10,057), adult general population cohort in Austria was 9%, with no sex differences but an increase with age; (2) 85% of participants with chronic cough had at least one condition associated with chronic cough, and (3) current (but not former) smoking, low socioeconomic status, obesity and obstructive sleep apnea were factors associated with chronic cough, with current smoking (over 20 pack years) being the greatest factor. Finally, 15% of participants with

Table 1
Characteristics of participants with and without chronic cough.

		No chronic cough (n = 9189)	Chronic cough (n = 868)
Age	Mean ± SD	48.4 ± 15.0	53.8 ± 15.8
Gender	Male	4269 (46,5%)	420 (48,4%)
	Female	4920 (53,5%)	448 (51,6%)
BMI	Low	184 (2%)	21 (2,4%)
	Normal	4187 (45,6%)	291 (33,5%)
	Overweight	3183 (34,6%)	339 (39,1%)*
	Obese	1635 (17,8%)	217 (25%)*
Socioeconomic status	Low	652 (7,1%)	95 (10,9%)*
	Normal	5127 (55,8%)	534 (61,5%)*
	High	3409 (37,1%)	239 (27,5%)
Smoking status	Never smoker	4158 (45,2%)	263 (30,3%)
	Former smoker	2981 (32,4%)	251 (28,9%)
	Current smoker	2048 (22,3%)	354 (40,8%)*
Residence area	Urban	7680 (83,6%)	726 (83,6%)
	Rural	1509 (16,4%)	142 (16,4%)
Conditions	Asthmatic	798 (8,7%)	153 (17,6%)*
	GERD	816 (8,9%)	158 (18,2%)*
	UACS	327 (3,6%)	84 (9,7%)*
	ACE inhibitor intake	1869 (20,3%)	283 (32,6%)*
	Arterial hypertension	1706 (18,6%)	268 (30,9%)*
	COPD	408 (4,4%)	110 (12,7%)*
	OSA	174 (1,9%)	47 (5,4%)*
	Tuberculosis	164 (1,8%)	20 (2,3%)
	Bronchiectasis	4 (0%)	4 (0,5%)*
	Emphysema	54 (0,6%)	21 (2,4%)*
	ILD	23 (0,3%)	9 (1%)
Symptoms	Dyspnoea	284 (3,1%)	130 (15%)+
	Wheezing	703 (7,7%)	342 (39,4%)*
	Sputum	652 (7,1%)	524 (60,4%)*

* significant at level $p < 0.05$ SD, standard deviation.
BMI, body mass index.
GERD, gastroesophageal reflux disease.
UACS, upper airway cough syndrome.
ACE inhibitor, angiotensin-converting enzyme -inhibitor.
OSA, obstructive sleep apnea.
ILD, interstitial lung disease.

chronic cough belong to the unexplained cough phenotype.

The prevalence of chronic cough in our study (9%) is consistent with previous studies, in which prevalence ranged between 4% and 13% [5,9–15]. We did not find any impact of sex on chronic cough prevalence, in contrast with previous reports where there was a higher prevalence of chronic cough in females attending cough clinics [16,17], although our data agree with several population based studies in the UK [18], Denmark [9] and the Netherlands [13]. Finally, we observed that the prevalence of chronic cough increased with age in both sexes (Fig. 1), consistent with other reports [13,16]. We found that more than 80% of participants with chronic cough in LEAD had experienced chronic cough for more than one year, and that about 30% had it for more than 5 years. Again, this is in keeping with previous reports indicating that chronic cough can persist for many years [19–22].

We classified chronic cough phenotypes according to published guidelines, and our analyses therefore provide real life information about phenotyping individuals with chronic cough in a general population. While most participants (85%) had at least one known condition that is associated with chronic cough, of particular note is a high prevalence of chronic cough related to smoking. This finding was significant for individuals with over 20 pack years. Although we adopted current smoking as an individual phenotype in our analysis, there was a high proportion of current smokers in all phenotypes, with a prevalence of at least 30% in every other group. The impact of current smoking in chronic cough is evidenced by the finding that from all current smokers (n = 2,402) in our study, 14.7% reported chronic cough. Conversely, from all chronic cough individuals, 40.8% were current smokers. These results were statistically significant and underline the substantial role of tobacco smoke in chronic cough. In addition, we did not identify any

Table 2
Logistic regression model for associated factors with chronic cough.

	Forced entry model	
	p	OR (95% CI)
Gender	0.644	1.0 (0.9–1.2)
Age groups	<0.001	1.2 (1.1–1.3)
Smoking status		
former smoker	0.440	1.1 (0.9–1.3)
current smoker	<0.001	2.8 (2.3–3.3)
Socioeconomic status categories		
low	<0.001	1.6 (1.2–2.0)
high	0.004	0.8 (0.7–0.9)
Residence area	0.860	1.0 (0.8–1.2)
Asthma	<0.001	2.1 (1.7–2.5)
GERD	<0.001	1.9 (1.5–2.3)
UACS	<0.001	2.4 (1.9–3.2)
Obesity	0.014	1.2 (1.0–1.5)
Obstructive sleep apnea	<0.001	2.1 (1.4–2.9)
COPD	<0.001	2.2 (1.8–2.7)
Omnibus test	<0.001	
Nagelkerkes R square	0.112	
Hosmer-Lemeshow test	0.441	

UACS, upper airway cough syndrome.

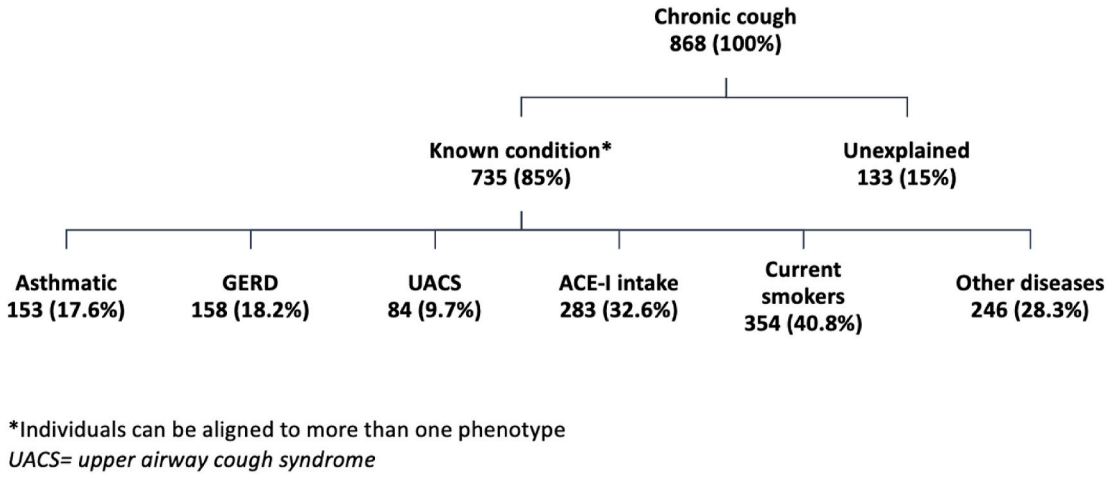

Fig. 3. Distribution of chronic cough in the LEAD study. For further explanations, see text.

gender difference, but we observed a female predominance (68.4%) when current and former smokers were excluded.

For ACE inhibitor intake, we focused on the class effect of ACE inhibitors, which is known to induce cough in patients treated with these agents [23]. Given chronic cough from drug treatment is frequently unrecognised [1] the high percentage of ACE inhibitor intake (32.6%) also deserves to be mentioned. Of note, only 112 individuals with chronic cough (12.9%) had ACE inhibitor intake without any other chronic cough phenotype. Almost all participants (94.5%) with hypertension in the LEAD study were being treated with an ACE inhibitor intake, 13.6% of whom reported chronic cough, consistent with the estimated 15% prevalence of chronic cough in these individuals [1]. Looking at chronic cough individuals with an asthmatic phenotype or COPD, about 50% were on inhalation treatment.

In 15% of the individuals with chronic cough we were not able to identify any chronic cough associated condition, and so we considered them to have unexplained chronic cough. These individuals were more likely to be female which is in line with the current literature [24].

The majority of participants with chronic cough had at least one condition that is associated with chronic cough. This clearly highlights the importance of a careful medical history to not only identify, but also phenotype those individuals, so that they can receive guideline-recommended, targeted treatment.

Asthma, GERD and UACS were not surprisingly associated factors previously included in the phenotypes of chronic cough. Logistic regression identified other several factors including current but not former, smoking, older age, low socioeconomic status, obstructive sleep apnea and obesity. These observations are consistent with previous studies [9,11,25,26]. Current smoking had the highest association with chronic cough (OR 3.0, 95% CI 2.5–3.6; $p < 0.001$). Importantly, all these factors can be identified by careful clinical examination; some, including smoking, obesity, and obstructive sleep apnea, are amenable to specific therapy or lifestyle changes. Obesity as an associated condition is considered in recent guidelines. Not only obesity, but a BMI reading of overweight was also significantly higher in chronic cough individuals. As underlying mechanisms, it is postulated that obese individuals show more severe symptoms of cough associated conditions like asthma and GERD. In our cohort obese individuals with chronic cough had more COPD, asthma, GERD, UACS and accompanying respiratory symptoms like dyspnoea, sputum and wheezing. This is in line with recent findings in the Copenhagen general population study which described this relationship and postulated GERD as the most common mediator factor of the increased risk of chronic cough in obese individuals [27]. Further from other studies we know that obstructive sleep apnea may also be involved in the development of chronic cough in obese patients [9,11,25,26].

We do acknowledge some potential limitations. First, as a general population study we did not perform an extensive diagnostic work-up towards chronic cough and did not use cough specific questionnaires, such as the Leicester Cough Questionnaire or the Chronic Cough Impact Questionnaire [28,29]. Second, the ACE inhibitor intake and unexplained phenotypes may be prone to overestimation, given we did not perform an ACE inhibitor or smoking withdrawal trial, and we did not collect information on prior withdrawal trials. Furthermore, since our phenotype stratification was based on a general study self-reported questionnaire, we did not collect data on cough-specific therapeutic trials or to conclude chronic cough was refractory. Still, it allowed detecting the spectrum of phenotypes with simple questionnaire-based assessment. Third, we did not conduct treatment trials to assess any causality of the reported conditions in term of cough hypersensitivity as the underlying feature of all phenotypes. Fourth, although chronic cough is generally defined by clinical guidelines as cough lasting for at least 8 weeks [1], we used the 3 month duration definition proposed by a previous systematic analysis that included all available literature published during the last three decades on chronic cough, and in which the majority of epidemiological studies utilised a 3 month cut-off [7]. Still, it is likely that the real burden of chronic cough may be underestimated by our used threshold.

This population-based study shows that chronic cough is a prevalent medical condition (9%), particularly in older individuals. The majority of individuals with chronic cough (85%) can be assigned to a specific phenotype by a simple questionnaire-based assessment and can therefore potentially receive specific treatment. 15% belong to the unexplained cough phenotype.

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CRediT authorship contribution statement

H. Abozid: Writing – original draft, Writing – review & editing, Conceptualization, Methodology, Formal analysis. **C.A. Baxter:** Writing – review & editing, Funding acquisition, Conceptualization. **S. Hartl:** Project administration, Writing – review & editing, Supervision. **E. Braun:** Writing – review & editing, Funding acquisition. **S. Salomonsson:** Writing – review & editing, Funding acquisition. **R. Breyer-Kohansal:** Writing – review & editing, Project administration. **M.K. Breyer:** Writing – review & editing, Project administration. **E.F.M. Wouters:** Supervision, Conceptualization, Methodology, Writing – review & editing. **A. Agusti:** Writing – review & editing. **O.C. Burghuber:** Supervision, Conceptualization, Methodology, Project administration, Writing – review & editing.

Declaration of competing interest

Conflicts of interest were disclosed.

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