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CLINICAL FORUM

Chronic cough and phlegm in young adults

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ABSTRACT: The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines underline that the presence of chronic cough and sputum production before airflow obstruction offers a unique opportunity to identify subjects at risk of chronic obstructive pulmonary disease for an early intervention. Current epidemiological data on these subjects are scant.

Between 1998–2000, the authors evaluated the prevalence and characteristics of these symptoms by a multicentre cross-sectional survey of Italian people aged between 20–44 yrs from the general population (Italian Study on Asthma in Young Adults (ISAYA)). Besides the questions on asthma, more than 18,000 subjects answered the question: "Have you had cough and phlegm on most days for as much as 3 months per year and for at least two successive years?"

The adjusted prevalence of subjects with chronic cough and phlegm was 11.9%, being 11.8% in males and 12.0% in females. From these subjects ~20% reported coexisting asthma and ~30%, predominately females, were nonsmokers. The survey showed that sex (female), smoking and low socioeconomic status were significantly and independently associated with chronic cough and phlegm, current smoking playing the major role.

The prevalence of subjects with chronic cough and phlegm is startlingly high among young adults. Further follow-up studies are needed to establish how many of them will go on to develop chronic obstructive pulmonary disease.
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The enormous cost of chronic obstructive pulmonary disease (COPD) and its increase over the foreseeable future are constant reminders that the disease is not adequately managed [1, 2]. In previous years strong epidemiological evidence has shown chronic cough and phlegm production are significantly related to COPD death [3–5], excess FEV_1 decline [6, 7], and increased risk of subsequent hospitalisation because of COPD [6]. This information overturned the beliefs, based on classical epidemiological studies conducted in the 1960s, that mucus hypersecretion and airflow obstruction are largely independent disease processes [8, 9]. The recently published guidelines of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) underline that the presence of chronic cough and sputum production before airflow obstruction offers a unique opportunity to identify subjects at risk for COPD (GOLD stage 0) for an early intervention [10]. In a recent study VESTBO and LANGE [11] tried to validate this staging approach, retrospectively, using data from three surveys in the Copenhagen City Heart Study. This study examined a sample taken from the general population, at baseline and after 5 and 15 yrs, by taking spirometric readings at each stage. The authors concluded that GOLD stage 0 is of little help in identifying subjects at risk for COPD. This statement is a key point that requires further investigation as it could profoundly influence future strategies for the early detection and prevention of COPD [12].

Current epidemiological data on subjects with chronic cough and phlegm are scant. Rapid changes in environmental, behavioural (particularly smoking habits) and socioeconomic conditions in the last few decades throughout the world [13], mean that *ad hoc* population-based studies are needed [14]. The Italian Study on Asthma in Young Adults (ISAYA) provided the present authors the opportunity to assess the prevalence of subjects with chronic cough and phlegm in the youngest age classes and to evaluate these subjects' main characteristics and risk factors.

Methods

Study design and subjects

The ISAYA was a multicentre, cross-sectional survey of the young adult population, specifically aimed at assessing the

variations of asthma and the current management of asthmatics in Italy [15–17]. The survey was carried out between 1998 and 2000 in nine Italian centres, of these six were in northern Italy (Udine, Pavia, Turin, Verona, Sassuolo, and Ferrara), and three were in central/southern Italy (Pisa, Sassari and Siracusa).

The design of the study was the same as that used in stage I of the European Community Respiratory Health Survey (ECRHS) [18]. Each centre selected an up-to-date sampling frame of the residents of the target area, from which a random sample of about 3,000 people aged between 20–44 yrs (male:female, 1:1) was chosen. A screening questionnaire was sent by post to each subject up to three times in the case of no response; finally the questionnaire was administered by phone to the remaining nonresponders. The questionnaire used has been published elsewhere and tested in a pilot study in 1998 [19], it contains validated questions, mostly taken from the ECRHS questionnaire.

There were 25,969 eligible subjects. The overall response rate to the screening questionnaire was 72.7% (18,873 subjects). From the respondents, 18,645 subjects answered the question on chronic cough and phlegm.

Data management and statistical analysis

Cases were identified on the basis of a positive response to the question: "Have you had cough and phlegm on most days for as much as three months per year and for at least two successive years?" A subgroup of subjects with coexisting asthma was identified according to the positive answer to any of the questions: "Have you had an attack of asthma at any time in the last twelve months?", "Are you currently taking any medicines (including inhalers, aerosols or tablets) for asthma?", "Have you ever had asthma?"

Subjects were classified according to smoking habits as current smokers (0–14 pack-yrs "light smokers", $\geqslant$15 pack-yrs "moderate-heavy smokers"), past smokers, or nonsmokers. Socioeconomic status was classified into four classes according to the type of occupation; these were as follows: managers, entrepreneurs, businessmen, clerks; retired people, students and housewives; unemployed and finally blue-collar workers.

As the centres had different final cumulative response rates, obtained with different percentages of telephone interviews, for the sake of comparison the prevalence rates were adjusted for cumulative response rate and type of contact (telephone *versus* postal), and for age and sex also. For this purpose, each subject was attributed the median of the cumulative response rate of the contact to which he/she had answered (first, second, third postal contact and telephone interview) and a dummy indicator of the type of interview (telephone *versus* postal). Adjusted prevalence rates were then obtained through a logistic regression model, considering the variable of interest as the dependent variable and sex, age (categorised in 5-yr classes), cumulative response rate and type of interview as the covariates. The prevalence in each centre was estimated setting the distribution of age, sex and type of contact equal to the average distribution, and the cumulative response rate to the overall mean. Prevalence rates with their 95% confidence intervals (CIs) were obtained.

Chi-squared tests, two-sample unpaired t-tests and median tests were used when needed. A multilevel binary response model [20], with subjects nested within centres, was used to assess the independent effect of sex, smoking habits and socioeconomic status on the prevalence of chronic cough and phlegm according to the presence of coexisting asthma, considering the absence of chronic cough and phlegm as the reference category. Odds ratios (ORs) were also adjusted for season of response, cumulative response rate and type of interview. The model had a random intercept term at the level of the centre and all predictor variables as fixed effects.

Results

The overall prevalence of subjects with chronic cough and phlegm was 11.9% (95% CI: 11.4–12.4), of which the prevalence of subjects with chronic cough and phlegm without coexisting asthma was 9.5% (9.1–10) and the prevalence of those with coexisting asthma was 2.2% (2.0–2.4). The prevalence was not significantly different between males and females either in the whole group of subjects with chronic cough and phlegm or in those with and without coexisting asthma (table 1).

The prevalence of current smokers was 33.3% (32.5–34.0) and varied significantly according to sex: 37.1% (36.1–38.1) in males and 29.9% (29–30.8) in females ($p<0.001$). The prevalence of past smokers was 13.1% (12.6–13.6), 13.9% (13.2–14.6) in males and 12.4% (11.7–13.1) in females ($p=0.001$). The median (95% CI) number of pack-yrs was significantly higher among males than among females 10.2 (9.7–10.6) *versus* 7.5 (7.0–7.8) pack-yrs ($p<0.001$) and, on average, males started smoking significantly earlier than females ($p<0.001$). According to the authors classification, the percentage of moderate-heavy smokers was higher in males than in females (33.1% *versus* 22.9%; $p<0.001$).

Subjects with chronic cough and phlegm included a larger proportion of current smokers (53.5% *versus* 30.7%, $p<0.001$), in particular moderate-heavy smokers (22.4% *versus* 7.7%), than those without chronic cough and phlegm. The prevalence of subjects with chronic cough and phlegm progressively increased from among nonsmokers to among moderate-heavy smokers (fig. 1) and from among people of the higher socioeconomic classes to among the unemployed and workers (fig. 2). About 30% of subjects with chronic cough and phlegm were nonsmokers. In comparison with current smokers, they were significantly younger, there were significantly more females, and more subjects with coexisting asthma and nasal allergies. The socioeconomic status of this subgroup was also different, as it contained more housewives and fewer workers (table 2).

From the total of 2,318 subjects with chronic cough and phlegm, 455 (19.8%) (204 males and 251 females) reported coexisting asthma. These subjects were significantly younger than subjects reporting only chronic cough and phlegm (31.9 *versus* 33.4 yrs, $p<0.001$), and more often reported wheezing

Table 1. – Prevalence of subjects with chronic cough and phlegm and of those with and without coexisting asthma according to sex

	Chronic cough and phlegm	Without coexisting asthma	With coexisting asthma
Males	11.8 (11.1–12.5)	9.6 (9.0–10.2)	2.0 (1.7–2.3)
Females	12.0 (11.4–12.7)	9.5 (8.9–10.1)	2.3 (2.1–2.7)

All data are presented as % (95% confidence interval). The prevalences were adjusted for age, cumulative response rate and type of contact (telephone *versus* mail).

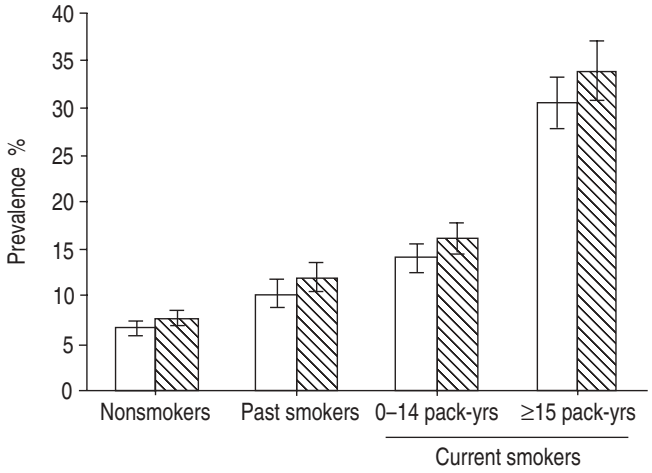

Fig. 1. – Prevalence (95% confidence interval) of chronic cough and phlegm plotted by sex (□: males; ▨: females) and smoking habits. The prevalence is adjusted for age, cumulative response rate and type of contact (telephone *versus* mail).

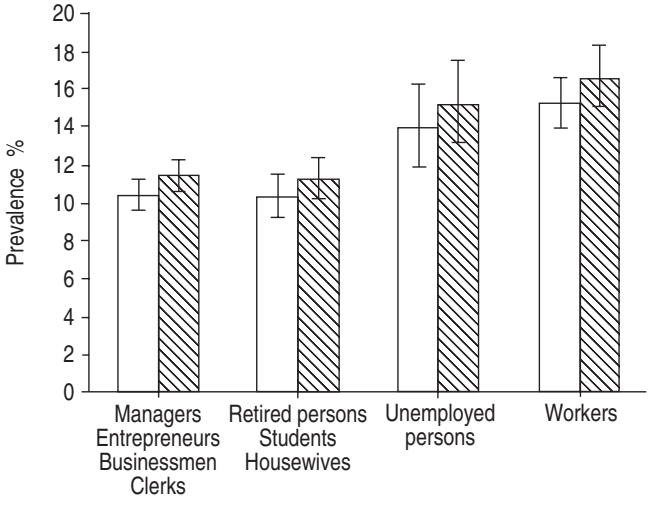

Fig. 2. – Prevalence (95% confidence interval) of chronic cough and phlegm plotted by sex (□: males; ▨: females) and socioeconomic status. Adjusted for age, cumulative response rate and type of contact (telephone *versus* mail).

(71.0% *versus* 29.4%, p<0.001) and nasal allergies (64.1% *versus* 31.1%, p<0.001). Moreover, these subjects were characterised by a significantly lower percentage of current smokers (40.5% *versus* 56.7%, p<0.001) and a lower cumulative consumption of cigarettes (8.4 *versus* 13.4 pack-yrs) than subjects reporting only chronic cough and phlegm. Anyway, the percentage of current smokers in subjects with chronic cough and phlegm with coexisting asthma was higher than that of the population as a whole.

Table 3 shows the adjusted ORs for the association between the presence of chronic cough and phlegm and sex, smoking habit and socioeconomic status for subjects with chronic cough and phlegm divided according to whether or not they also had asthma. All the three factors were significantly and independently associated with chronic cough and phlegm in both groups. The effect of smoking habits was much less evident in those with coexisting asthma, and not apparently related to the number of cigarettes smoked.

Table 2. – Characteristics of subjects with chronic cough and phlegm according to smoking habits

	Nonsmokers	Current smokers	p-value
Subjects n	754	1233	
Female %	58.9	47.4	<0.001
Age mean±SD	31.8±6.8	33.3±7.0	<0.001
Socioeconomic status %			<0.001
Manager, entrepreneur, businessman, clerk	51.5	50.4	
Retired, student, housewife	25.2	15.8	
Unemployed	6.9	8.4	
Blue-collar worker	16.4	25.4	
Asthma %	26.4	15.1	<0.001
Nasal allergies %	44.5	22.1	<0.001

Discussion

The prevalence of subjects with chronic cough and phlegm is startlingly high among young adults without difference between sex. Alongside smoking, which is already well known for playing a major role, sex and low socioeconomic status were significantly and independently associated with chronic cough and phlegm. Even considering chronic respiratory symptoms in many of these subjects may be reversible or attributable to diseases not resulting in COPD, this data suggests how large the bottom of the COPD iceberg is.

Estimates in past decades showed chronic cough and phlegm were more prevalent among males than females, a finding attributed to higher smoking rates and more frequent occupational exposure for males [21, 22]. According to other studies [13, 23, 24], particularly those with data collected more recently, the authors found that the prevalence of chronic cough and phlegm among females has already reached that among males and that to be female has an effect on chronic cough and phlegm independently from smoking. Even if studies of a sex-related effect of smoking on respiratory outcomes have not been conclusive, there is increasing evidence of a higher prevalence of smoking and long-term cumulative effect of smoking among women after the 1970s. Some studies had suggested a possibly greater susceptibility to the adverse pulmonary effects of smoking [13, 25]. However, it is difficult to control for all the circumstances of exposure and the effects of smoking in females could be underestimated, since males not only smoke more than females, but they have often started earlier as observed in the present study and have a higher rate of inhalation than females [26].

Although smoking was the major risk factor, the authors observed that a considerable proportion of symptomatic subjects were nonsmokers. These subjects were predominantly females, and frequently reported coexisting asthma and nasal allergies. Epidemiological studies have already shown that 5–12% of patients with a diagnosis of COPD have never smoked and there is evidence of an increasing incidence with increasing age [27]; these subjects were predominantly females and there was an association with lower income [28]. Therefore it should be considered that, at least in some of the subjects with chronic cough and phlegm, particularly the nonsmokers, a different pathogenesis such as asthma, chronic rhinosinusitis or gastroesophageal reflux could be involved. These patients could have a different disease evolution and may not go on to develop bronchial obstruction in the future, particularly if properly diagnosed and treated.

In the present study sample, 20% of subjects with chronic cough and phlegm also reported asthma. It is well recognised that there is an overlap between asthma and COPD in some

Table 3. – The association between chronic cough and phlegm and sex, smoking habits and socioeconomic status according to the presence of asthma

	Chronic cough and phlegm	
	Without asthma	With asthma
Sex		
Female *versus* male	1.22 (1.10–1.36)**	1.27 (1.04–1.55)*
Smoking habits		
Past smoker *versus* nonsmoker	1.59 (1.35–1.86)**	1.36 (1.04–1.79)*
Current smoker (0–14 pack-yrs) *versus* nonsmoker	2.56 (2.26–2.91)**	1.85 (1.48–2.31)**
Current smoker ($\geqslant$15 pack-yrs) *versus* nonsmoker	6.57 (5.70–7.58)**	1.84 (1.31–2.58)**
Socioeconomic status		
Retired person, student, housewife *versus* manager, entrepreneur, businessman, clerk	1.03 (0.89–1.18)	1.19 (0.93–1.52)
Unemployed person *versus* manager, entrepreneur, businessman, clerk	1.24 (1.01–1.52)*	1.63 (1.15–2.32)*
Blue-collar worker *versus* manager, entrepreneur, businessman, clerk	1.35 (1.18–1.54)**	1.48 (1.14–1.92)*

All data are presented as adjusted OR (95% CI). The ORs were calculated by multilevel binary response models with random intercept at the level of the centre and all predictor variables as fixed effects. The ORs were also adjusted for season of response, cumulative response rate and type of contact (telephone *versus* mail). *: $p<0.05$, **$p<0.001$ value using the Wald test for the main factors.

patients but it cannot be excluded that chronic cough and phlegm are purely expressions of asthma. The earlier onset of symptoms in these patients, the association with nasal allergies, as a marker of atopy, wheezing and the minor role of current smoking in these subjects seem to suggest that many of them have only asthma.

Even if only some of the subjects with chronic cough and phlegm will go on to develop chronic airflow obstruction, all subjects with chronic cough and phlegm should be carefully evaluated, presumably mainly in the primary care context but in any setting that they are first recognised. The GOLD guidelines stated that spirometry should be undertaken for any patients who have chronic cough and sputum production even if they do not have dyspnoea. All the moderate-heavy smokers should also undergo spirometry because they could be more motivated to stop smoking if they realise that their respiratory problems are caused by smoking and that they are at risk of developing COPD [29]. Smoking cessation has been proven to be capable of reversing the steep decline in lung function [30] and, at present, it is the only intervention able to do so. Recent results of the Lung Health Study showed that males and females who quit smoking at the beginning of the study and were still abstaining after 11 yrs had almost halved the decline of FEV1 per year as compared to those who continued to smoke throughout the 11 yrs. At 11 yrs, 38% of individuals who continued to smoke had a FEV1 <60% of the predicted normal value, as compared with 10% in the individuals who stopped smoking permanently. ANTHONISEN *et al* [31] concluded that the loss of lung function among continuing smokers is more rapid than previously suspected. It is particularly important to study young adults, as the present authors did, because there is evidence suggesting that the benefits of smoking cessation are greatest at younger ages, usually before 45 yrs [32].

In a recent study VESTBO and LANGE [11] raised an important point, showing that chronic cough and phlegm are not stable features since, in their retrospective study, ~40% of subjects who reported chronic respiratory symptoms no longer did so after 5 yrs. Smoking cessation was found to predict the subsequent absence of chronic symptoms. The present authors' interpretation on finding that disappearance of chronic mucus hypersecretion is associated with young age and smoking cessation differs from that of VESTBO and LANGE [11] as it indicates the opportunity for early detection of these subjects in order to promote smoking cessation [12].

The strengths of this present epidemiological study are its large sample size, robust study design and statistical analysis. In particular, differently from other studies, the present study sample was selected from young adults, allowing the authors to estimate how large the bottom of the COPD iceberg is; in fact, during the course of such a chronic disease, patients are supposed to move from low stages upwards.

The limitations of this present study are the use of a simple screening questionnaire that does not allow deep investigation on the specific characteristics of the subjects and the absence of spirometry. In the authors' previous international study, which focused on subjects of the same age range, the prevalence of airflow obstruction in young adults with chronic cough and phlegm was only 8.4% [33].

In conclusion, the impressively high prevalence of subjects with chronic cough and phlegm among young adults, although only some of them will develop chronic obstructive pulmonary disease, supports the projections of a remarkable increase of chronic obstructive pulmonary disease over the foreseeable future. The final message is that subjects with chronic cough and phlegm should be carefully evaluated in the primary care context or in any other setting as soon as these symptoms are first recognised and should have access to spirometry. Unfortunately, the present cross-sectional study does not answer the inevitable question surrounding the progression from cough and sputum to airflow obstruction or indeed whether intervention can prevent the inevitable. Prospective population-based studies are needed, particularly in the youngest age ranges, to validate the predictive value of chronic cough and phlegm in the development of chronic obstructive pulmonary disease.

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