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**The epidemiology of cough**

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## **ABSTRACT**

Cough is a common symptom that affects a large proportion of the general population, but has been somewhat neglected in the epidemiological literature in the recent years. Various types of coughs are described based on life-long epidemiological surveys. Using published and unpublished data from three epidemiological studies (the European Community Respiratory Health survey, the French Epidemiological study on the Genetics and environment of asthma (EGEA) and the French E3N study), some specific aspects are discussed in detail. Phenotypic heterogeneity according to chronicity, or its productive nature, or its daytime or nocturnal characteristics are discussed. The association of cough with asthma and gender is described, together with its evolution over a 12 year period. The potential for genetic studies of cough is discussed.

Key words: cough, epidemiology, gender, environment, genetics

## **1. Introduction**

There are several reasons to study the epidemiology of cough(s). The first one regards public health, as cough is a common symptom that affects a large proportion of the general population. The second one is that it is (seems) much more simple to try and understand symptoms of disease than the whole complex chronic respiratory diseases such as asthma and chronic obstructive pulmonary diseases of which cough may be an important component symptom. The third one is that it may be also that non-specific cough [1] may represent a specific disorder as such the cough hypersensitivity syndrome, an area of interest of many successive cough symposia. A key aspect in the current agenda in respiratory research is to address the phenotypic heterogeneity of patients in order to disentangle the complex network of aetiological factors, environmental and genetics of common diseases. There is increasing evidence for a role for supervised and unsupervised (without a priori hypotheses) analyses to understand phenotypic heterogeneity of asthma [2-3]. Therefore, addressing the heterogeneity of cough is a means to encompass research both for disease-related coughs (e.g. in asthma) and the unexplained chronic cough encountered in numerous patients attending cough clinics [4]. In the present paper, aspects regarding phenotypic aspects of cough (acute/chronic, day/night, female/male, triggered-related cough) will be discussed based on the epidemiological literature. Specific focus will be given to a life span approach to illustrate environmental determinants. Published and unpublished data from three large epidemiological studies (the European Community Respiratory Health survey, the French Epidemiological study on the Genetics and environment of asthma (EGEA) and the French E3N study) will be used to illustrate aspects regarding associations of cough with asthma, the longitudinal evolution of cough and gender differences. The potential of genetic studies to further understand cough will also be discussed.

## **2. Assessment of cough in epidemiology**

How cough is categorised in clinical practice and in epidemiological surveys differs. For example, in clinical practice, acute cough is often defined based on duration of less than 2 weeks, and chronic cough on a duration of more than 4 weeks for children and more than 8 weeks for adults [1]. It is beyond the topic of this paper to review clinical classifications presented elsewhere [1,4].

Epidemiological characterisation of cough is based on standardized questionnaires and thousands of individuals all over the world have already answered such questionnaires. The first type of questionnaire was developed for chronic bronchitis with emphasis on its two symptoms, cough and phlegm, all derived from the British Medical Research Council (BMRC) questionnaire issued in the late fifties. Then, these questions were incorporated in the European Coal and Steel community (ECSC) questionnaire and the American Thoracic Society questionnaire which were largely used in the sixties and seventies [5]. Chronicity was defined by symptoms occurring for at least 3 months of the year for two consecutive years (table 1).

Later, with the increase in asthma prevalence, asthma-oriented questionnaires have expanded the characterisation of respiratory symptoms and numerous studies have been based on the questionnaires set up for two large international surveys, the European Community Respiratory Survey (ECRHS) for adults and the International Study on Asthma and Allergy in children (ISAAC). The questions relating to cough in these surveys are reproduced in table 1. It is only in the asthma-oriented questionnaires that circadian aspects of cough are considered with information on nocturnal cough.

In a parallel area of research, more clinically oriented quality of life questionnaires have been designed and carefully standardized. They are now also largely used in epidemiology. In the Asthma quality of Life Questionnaire (AQLQ) [6], there is a specific question on cough (table 1). It is unusual however to perform analysis on specific items of quality of life questionnaires, because the initial validity of these questionnaires has been established on several global scores based on numerous items.

In clinical practice, in particular in the asthma field, triggers of attacks are recorded. Less often, triggers of specific symptoms are recorded, although not systematically. They are specifically useful to assess the relevance of desensitization regarding allergen triggers or to evaluate hypersensitivity syndromes in more general terms such as discussed under the airway sensory hyperreactivity syndrome [7]. In the French Epidemiological Study on the Genetics of Asthma, which aims at a precise phenotyping of subjects (recruited as members of asthmatic families from chest clinics and population-based controls) both BMRC/ECSC and ECRHS questions are included. Furthermore, symptoms (including fits of coughing) induced by known triggers have been recorded using a self-completed questionnaire (table 1). All questionnaires cited above are openly accessible [8-10]. In order to compare results from country to country

for a given survey, or from various surveys, or from one survey to a follow-up survey, it is essential to use standardized respiratory symptom questionnaires.

### **3. From birth to old age with a specific interest on environment**

Not a lot of studies have addressed the epidemiology of cough and very few considered various types of cough in the same study. Often, it was studied in relation with another symptom such as in chronic bronchitis, or in association with wheeze. This can be illustrated by several life-long studies on environmental determinants. Besides changes over age, there are cohort effects occurring in the study of environmental factors. For example, air pollution at the time of the London fog in the fifties is different from contemporary air pollution, which is traffic-related, and from occupational irritants which can induce coughs have evolved in the last decades.

In a recent paper primarily focused on understanding the effect of components of air pollution, Patel et al. observed the expected seasonal variation of cough, among New York city babies over the first 24 months of age [11]. Interestingly, they studied how small particulate matter (PM<sub>2.5</sub>) of nickel (Ni), vanadium (V), zinc (Zn) and elemental carbon (EC) may induce different types of symptoms and different types of coughs, and they stratified their analysis according to the cold/flu season. They provided evidence for early effects of EC in cold/flu season on cough among very young children. These results should not be over-interpreted, but it raises the issue of interaction of cold/flu season with environmental exposure amongst the determinants of cough.

In the Tucson Children's Respiratory Study, Wright et al. investigated factors influencing gender differences in diagnosis and treatment of asthma in childhood, among 533 boys and 556 girls [12]. They looked at the sex ratio of cough according to age (from 2 years till 18 years) using prospective data and reported that the childhood sex ratio (more males with cough) reversed at age 16. This result is related to the issue of asthma and puberty, and it underlined that the change in sex ratio is also related to cough. To our knowledge, no studies have been conducted regarding cough in relation to puberty, a topic that should be analysed in more detail.

In college undergraduates (18-24 years), a very high perception of cough and sore throat was reported (62%) along with a strong association in relation to cigarette use was reported, which may be used for preventive programs, but the results of this

large study (n=6,053) conducted through internet should be considered with caution because of a low response rate (26%)[13].

Based on the standardized questionnaire of ECRHS, Potts et al. in a semi-rural area in Chile investigated the effects of indoor risk factors including smoking, on different types of cough and on cough and wheeze, among 1,232 men and women aged 22-28 years [14]. They reported gender differences and associations with environmental factors, some of which mainly occurring in countries with low economic status. Nocturnal cough and dry cough were more prevalent in women than in men (40.9% vs. 31.7%, and 11.8% vs. 16.9, respectively nocturnal and dry), but productive cough was more prevalent in men (25.4% vs. 17.2%). In a multivariate analysis, they assessed the association between nocturnal, dry and productive coughs and some new environmental factors such as ventilation in winter, coal heating or the type of housing (solid house vs. ramshackle dwelling). They reported an association of coal heating with dry cough (odds ratio (95% confidence interval)=3.40 (1.41-8.21)), and borderline associations of no ventilation and ramshackle dwelling with productive cough (OR (95% CI)=1.74 (0.97-3.09); 3.37 (0.98-11.61), respectively for windows not opened in winter as compared to always opened, and for ramshackle dwelling as compared to wooden house with at least 3 rooms. Results suggest that cough in developing countries may be related to other factors than in others, and that a global perspective of this very common disorder is very important.

Interesting results were reported by Janson et al. on various types of cough (nocturnal only, dry and productive only) among 18,277 adults (20-48 years) coming from 16 countries from the ECRHS study [15]. Figure 1 represents the geographical heterogeneity of cough between countries and between centres from individual countries. Very few coughed in Erfurt-Germany (5.3% nocturnal only, 13.1% dry, 6.8% productive only). For nocturnal cough, the highest prevalence was reported for Göteborg-Sweden (28.4%) and the lowest for Erfurt-Germany (5.3%). For dry cough, the highest prevalence was in Bordeaux-France (16%) and the lowest in Umeå-Sweden (5.5%). Finally, for productive cough only, the highest prevalence was in Dublin-Ireland (27.4%) and the lowest in Cambridge-UK (3.8%). Figure 1 also shows that the ratio of productive and non productive cough was not the same amongst countries. The geographical heterogeneity of cough could suggest hypotheses regarding potential determinants of cough. The multivariate analyses showed that nocturnal and dry coughs

were related to female gender (OR (95% CI)=2.08 (1.89-2.29); 1.27 (1.12-1.45), respectively for nocturnal and dry coughs)), while all three types of cough were related to asthma, tobacco smoking, exposure to ETS and obesity.

Among 3,883 adults from Leeds and Bradford (UK) aged 40-49 years, Ford et al. have investigated the relationship between self-reported cough severity and frequency, and factors known to be related to the aetiology of chronic cough, in particular symptoms of gastrointestinal disease [16]. Two variables of cough have been studied: cough frequency in the previous two months, and a marker of severity, "interference with normal activities of daily living in the previous two months", which was indeed an indicator of quality of life. Cough frequency in the previous 2 months was reported as never by 59%, less than monthly by 20%, between monthly and weekly by 9%, between weekly and daily by 7%, and daily by 5%. Cough severity was reported as occurring never in 78%, less than monthly in 11%, between monthly and weekly in 4%, between weekly and daily in 4%, and daily in 3%. Multivariate analysis showed that cough ( $\geq 1$ /week in the last 2 months) increased with age (OR (95% CI)=1.05 (1.00-1.10)), and smoking (OR (95% CI)= 1.61 (1.18-2.19)), and was significantly associated with regurgitation (OR (95% CI)= 1.71 (1.20-2.45)) and poor social class (OR (95% CI)= 1.63 (1.04-2.57)), with an association with obesity of borderline significance (OR (95% CI)= 1.34 (0.93-1.91)).

Among 2,104 elderly aged  $\geq 65$  years from the 3C study in France, Bentayeb et al. investigated the association between cough and proximity air quality [17]. They reported that usual cough was associated with SO<sub>2</sub> both in men (OR (95% CI)=1.76 (1.20-2.58)) and women (OR (95% CI)=1.54 (1.06-2.23)), whereas no association were reported for NO<sub>2</sub> and PM<sub>10</sub>.

In conclusion, a variety of environmental factors are associated with coughs over the lifespan.

#### **4. Coughs and asthma**

Data regarding the association between various types of cough and asthma are scarce. Using data from the French EGEA study (Epidemiological study on the genetics and environment of asthma) [18] and the French E3N study (Etude épidémiologique auprès des femmes de la Mutuelle Générale de l'Education Nationale) [19], we assessed the association between various types of cough and asthma (table 2). Briefly, EGEA is a



case-control and a family study on asthma (asthmatic families in chest clinics, pediatric and adult), including roughly 2,000 subjects. Approximately 12 years later, this population was reexamined (EGEA2) [20]. The associations of asthma with morning, day or night, usual, chronic, chronic productive, nocturnal, nocturnal and usual, cough to any trigger were all highly significant ( $p < 0.001$ ), and odds ratio varied from 2.6 to 6.8 (table 2). Odds ratios of coughs with asthma were higher than the one reported in the ECRHS [15], likely related to the greater severity of asthmatics in EGEA, a large proportion of whom were recruited in chest clinics. The highest OR was observed for chronic productive cough, i.e. the definition of chronic bronchitis. Nocturnal cough is the most typical asthma-like cough, but the high prevalence of the symptom, usually recorded as ever in the last 12 months (without detailing further its frequency), is a concern that needs further understanding.

The frequency of nocturnal cough was assessed in the context of a respiratory survey in a subsample of the E3N cohort, a prospective investigation of major chronic diseases among members from the Mutuelle Générale de l'Éducation Nationale, a national health insurance plan covering mostly teachers [19]. Similar figures regarding the prevalence of various types of cough according to ever asthma were observed in E3N and in EGEA, whereas E3N included only women, older than the EGEA population (table 2). The associations between coughs and asthma were all highly significant too ( $p < 0.001$ ). Regarding the frequency of nocturnal cough, approximately half of the women who coughed during the night, reported a frequency of at least once per week (46.4%). Further studies are needed to understand nocturnal and daytime coughs.

Gender is in fact an important aspect differentiating nocturnal and daytime coughs. Data from the EGEA study (figure 2) show that morning and chronic productive coughs were more prevalent in men than in women. Day/night, usual and chronic cough were similar among men and women. Nocturnal cough (nocturnal only, nocturnal and usual, and nocturnal in the last 3 days) as well as cough in response to any stimuli were more prevalent in women than in men. To summarise, men cough during the day and women during the night. More research is needed to better understand gender differences in coughs.

Epidemiological studies on coughs are usually cross-sectional. Cough is in fact extremely variable as evidenced by longitudinal observations over 12 years for coughs in the EGEA study. Participants were classified according to never cough (no cough both

at both surveys), persistent cough (cough at both surveys), incident cough (cough at follow-up without cough at baseline) and remittent cough (cough at baseline without cough at follow-up). Persistent cough varied from 2% for productive cough to 21% for nocturnal cough. As shown in table 3, coughs at both surveys were highly related, with odds ratios varying from 2.8 to 10.9 ( $p < 0.001$ ). Variability in coughs was strong and expressed by figures regarding incident and remittent symptoms. Incidence varied from 3% (productive cough) to 25% (nocturnal cough), and the remission was greater than 42% for all types of coughs. The high remission for cough is coherent with the overall clinical improvement of the population where part of these subjects was recruited in chest clinics, where they got treatment. Overall, kappas, measure of concordance, were around 0.30 which is quite low.

More research is needed taking into account the frequency of coughs (in particular for nocturnal cough) and the pattern of evolution assessed through longitudinal surveys.

## 5. Coughs and genetics

Geneticists have proposed the term candidate genes to infer there was a specific hypothesis, usually regarding the function of the gene, justifying its study for a given disease, whereas genome wide comparisons have been called "agnostic", which etymologically means without knowledge. In a similar way, it is logical to name candidate gene-environment interaction when known pathological/physiological function of a gene/pathway and/or the role of a given environmental factor is at the origin of the research [21].

New hypotheses are emerging regarding the role of air pollutants (see above), and also regarding occupational hazards. There is increasing evidence of the role of exposures encountered in cleaning activities [22]. Such exposures include those to a lot of irritants. Besides RADS, an acute onset of asthma related to unique massive exposure [23], it is currently being proposed that repeated acute exposure to irritants, not necessary to a high level exposure, may lead to asthma [22,24]. Transient receptor potential cation channels genes (*TRPs*) are candidate genes for irritant-induced chronic cough [25] and *TRP* x irritant is a candidate interaction for cough, and in particular cough-related asthma. It has recently been shown that a functional *TRPV1* variant was associated with a lower risk of cough and wheezing among children with asthma [26].

Preliminary results from EGEA have suggested potential interactions with *TRPV* polymorphisms with occupational irritants exposures in relation to adult asthma [27], an observation which needs replication. Further genetic steps could be to look at other *TRPs*, such as *TRPA1*, to consider agnostic approaches, possibly performing genome wide associations studies (GWAS) on various types of coughs.

The field of genetics has changed with the availability of GWAS analyses, which do need very large samples. GWAS can indicate new hypotheses, such as the role of genes involved in the 17q for childhood onset asthma [28]. They also allow one to question the classical pathways. For example, recent results from the Gabriel consortium, have shown that genes associated with asthma are different from those associated to total IgE, thus leading to reconsideration of the role of allergy in the occurrence of asthma [29]. Agnostic approaches, such as GWAS, can also provide evidence of the pleiotropic effects of genes on various diseases. It is possible that genes associated with cough may also relate to neurological diseases. The next period will probably provide new insights regarding the genetic determinants of various types of cough. Proper phenotyping and large sample size is a requisite for such endeavour.

## **6. Conclusion**

The heterogeneity of coughs needs to be better understood. Multidisciplinary research is needed involving refined phenotyping, large sample size, detailed environmental characterisation, and incorporating genetics and biology. More collaboration between epidemiologists, who master issues at the population level, and those involved in functional studies, who master issues at a cellular level - is needed. Such collaboration would better substantiate scientific evidence, and likely lead to new findings. Such multidisciplinary research could ultimately lead to more efficient prevention and therapy.

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Figure 1 - Distribution of various coughs in the European Community Respiratory Health Survey. After Janson et al. [15].

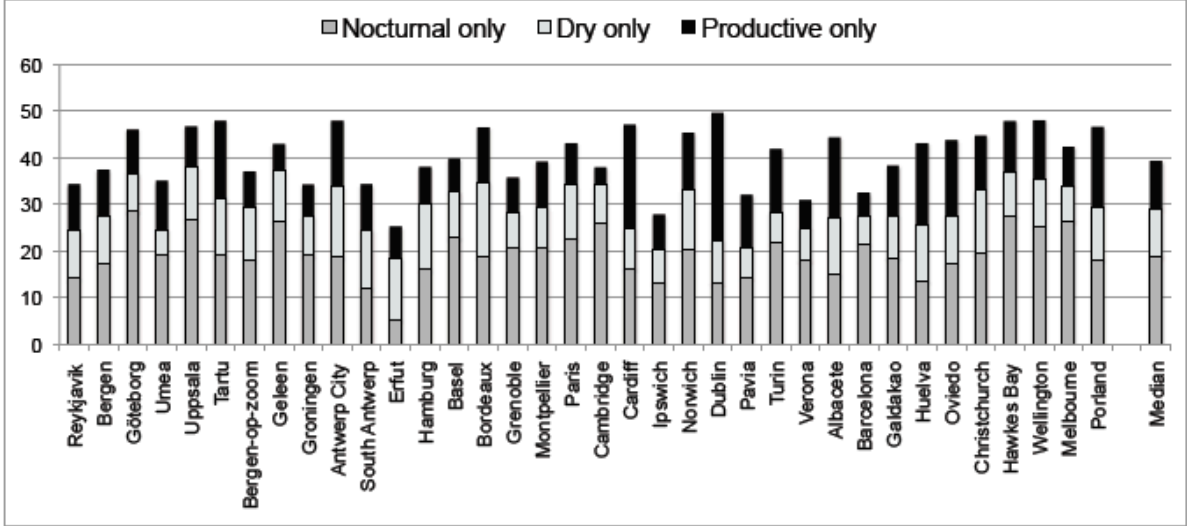




Figure 2 - Coughs and gender among 1,866 men and women from the Epidemiological Study on the Genetics and Environment of Asthma (EGEA).

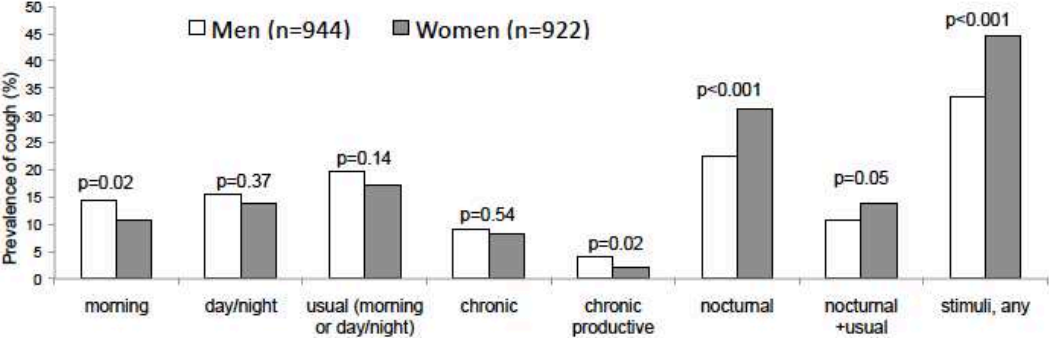


Table 1 - Questionnaires used in epidemiological surveys to assess coughs

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**60's « Classic BMRC/ECSC questions » - Chronic bronchitis**

1. Do you usually cough first thing in the morning in the winter?
2. Do you usually cough during the day, or at night, in the winter?

If yes to 1 or 2:

Do you cough like this on most days for as much as three months each year?

**90's – « Asthma-like »**

(ECRHS) – Adults

ECRHS1 - Have you been woken by an attack of coughing at any time in the last 12 months?

ECRHS 2 – (At the time of lung function tests - acute events) Have you been woken by an attack of coughing in the last 3 days?

(Quality of life AQLQ Item) How much discomfort or distress have you felt over the past two weeks as a result of coughing? 1-7 (very great, great, good deal, moderate amount, some, very little, no)

(Isaac) - Children

In the past 12 months, has your child had a dry cough at night apart from a cough associated with a cold or chest infection?

**Triggers of cough**

(EGEA) Situations which usually induce the following symptoms (., fits of coughing, ...) (last 12 months) : smoky room, contact with cold air, physical effort, hay/cut flowers, animals, dust, occupational exposure, air pollution, weather, emotion, wine/alcohol, aspirin

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Table 2 - Coughs and asthma in adults of various ages.

	EGEA*		E3N†	
	Asthma	No asthma	Asthma	No asthma
N	818	1048	364	377
Age, m ± SD (range)	38.3 ± 16.1 (16.1-81.4)	45.6 ± 16.1 (16.1-81.4)	68.5 ± 6.2 (59.5-84.0)	68.7 ± 6.7 (59.5-84.0)
Women, %	45.2	52.7	100.0	100.0
<b>Coughs</b>				
Morning, %	18.4	8.2	17.2	7.2
Day/night, %	21.7	9.2	25.6	11.2
Usual (morning or day/night), %	26.5	12.2	30.8	13.9
Chronic, %	12.3	5.7	12.6	5.6
Productive (chronic), %	5.0	1.5	6.9	2.0
Nocturnal, %	35.5	19.9	35.9	15.3
Nocturnal + usual, %	17.8	8.2	16.9	5.1
Any trigger, %	49.9	30.8	54.1	31.2

The same questionnaires were used in both surveys.

All associations were statistically significant ( $p < 0.001$ ).

\* EGEA (French Epidemiological Study on the Genetics and Environment of Asthma), second survey (EGEA2-2003/2007), n=1,866 adults (1,048 never asthmatics, 818 ever asthmatics) [18,20]

† E3N study (Etude épidémiologique auprès des femmes de la Mutuelle Générale de l'Education Nationale, n=98,995 women aged 40-65 years in 1990), randomly selected sub-sample of ever asthmatics and never asthmatics (conducted in 2009/2010), n=741 adult women (377 never asthmatics, 364 ever asthmatics).

Table 3 – Twelve-year change in various coughs among 531 adults with asthma from the Epidemiological Study on the Genetics and Environment of Asthma (EGEA)

	Never (%)*	Persistent (%)*	Incident (%)†	Remittent (%)**	Odds ratio	Kappa
Morning	66	9	14	60	4.3	0.28
Day/night	64	11	17	55	4.2	0.29
Usual	54	14	23	51	3.2	0.25
Chronic	76	6	10	63	5.5	0.29
Productive (chronic)	89	2	3	73	10.9	0.29
Nocturnal	44	21	25	51	2.8	0.24
Triggered						
- Smoking	54	17	23	42	4.8	0.34
- Effort	65	8	14	68	2.8	0.19
- Dust	71	7	12	63	4.3	0.27

531 asthmatics were adults ( $\geq 16$  years) at both surveys (EGEA1 and EGEA2).

\* Among all the asthmatics with data on coughs at both surveys.

† Among those without coughs at the first survey.

\*\* Among those with coughs at the first survey.