

Role and Impact of Chronic Cough in Individuals with Asthma From the General Population



Yunus Çolak, MD, PhD^{a,b}, Shoaib Afzal, MD, PhD, DMSc^{a,b}, Peter Lange, MD, DMSc^{b,c,d,e}, Lars C. Laursen, MD, DMSc^{d,e}, Børge G. Nordestgaard, MD, DMSc^{a,b,e}, and Morten Dahl, MD, PhD, DMSc^{b,e,f} Herlev, Copenhagen, and Køge, Denmark

What is already known about this topic? Cough is a well-recognized cardinal symptom in asthma, but the role and impact of chronic cough in individuals with asthma from the general population have not been described.

What does this article add to our knowledge? The study finds that among individuals with asthma, those with chronic cough versus those without have more often accompanying respiratory symptoms, health care utilizations, and severe airflow limitation with FEV₁ predicted value of less than 60% and higher levels of systemic inflammatory biomarkers in blood.

How does this study impact current management guidelines? The results indicate that chronic cough in individuals with asthma is associated with a more severe disease phenotype.

BACKGROUND: Cough is a well-recognized symptom in asthma, but the role and impact of chronic cough in individuals with asthma has not been described in the general population.

OBJECTIVE: We hypothesized that among individuals with asthma, those with chronic cough versus those without have a more severe disease phenotype.

METHODS: We identified individuals with asthma and chronic cough among 14,740 adults from the Copenhagen General Population Study, and investigated respiratory symptoms, health care utilizations, lung function, and biomarkers in blood.

RESULTS: A total of 855 (6%) individuals suffered from asthma, and 70 (8%) had chronic cough. Individuals with asthma and chronic cough had a Leicester Cough Questionnaire median total score of 16.8 (25th and 75th percentiles, 14.8–18.9), corresponding to 5.4 (4.6–6.0) for the physical domain, 5.7 (4.6–6.4) for the psychological domain, and 6.0 (5.3–6.8) for the social domain. Among individuals with asthma, those with chronic cough versus those without reported more often

wheezing (70% vs 54%), dyspnea (74% vs 49%), night-time dyspnea (27% vs 11%), sputum production (59% vs 14%), chest pain/tightness (14% vs 4%), acute bronchitis/pneumonia episodes, and general practitioner visits. Furthermore, these individuals had more often FEV₁ predicted value of less than 60% (14% vs 7%) and higher levels of neutrophils, leukocytes, and fibrinogen in blood, but there were no differences with regard to levels of high-sensitive C-reactive protein, eosinophils, and IgE in blood.

CONCLUSIONS: Chronic cough in individuals with asthma is associated with a more severe disease phenotype in terms of worse respiratory symptoms, greater health care utilizations, lower lung function, and higher levels of systemic inflammatory biomarkers in blood. © 2019 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;7:1783–92)

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^aDepartment of Clinical Biochemistry, Herlev and Gentofte Hospital, Copenhagen University Hospital, Herlev, Denmark

^bThe Copenhagen General Population Study, Herlev and Gentofte Hospital, Copenhagen University Hospital, Herlev, Denmark

^cDepartment of Public Health, Section of Epidemiology, University of Copenhagen, Copenhagen, Denmark

^dDepartment of Internal Medicine, Section of Respiratory Medicine, Herlev and Gentofte Hospital, Copenhagen University Hospital, Herlev, Denmark

^eDepartment of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

^fDepartment of Clinical Biochemistry, Zealand University Hospital, Køge, Denmark
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Conflicts of interest: Y. Çolak reports personal fees from AstraZeneca and Boehringer Ingelheim outside the submitted work. P. Lange reports grants from AstraZeneca and GlaxoSmithKline and personal fees from AstraZeneca, Boehringer Ingelheim, Novartis, and GlaxoSmithKline outside the submitted work. The rest of the authors declare that they have no relevant conflicts of interest.

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Corresponding author: Morten Dahl, MD, PhD, DMSc, Department of Clinical Biochemistry, Zealand University Hospital, Lykkebakvej 1, DK-4600 Køge, Denmark. E-mail: modah@regionsjaelland.dk.

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Abbreviations used
FVC-forced vital capacity

INTRODUCTION

Chronic cough, defined as a cough lasting more than 8 weeks,¹⁻³ has adverse impacts on quality of life in affected individuals and causes a substantial burden of disease worldwide.⁴⁻⁶ In asthma, chronic cough is a cardinal respiratory symptom that may suggest moderate to severe type of uncontrolled disease in some patients.⁷⁻¹⁰ However, the role and impact of chronic cough in individuals with asthma has not been described in the general population.

We hypothesized that among individuals with asthma, those with chronic cough versus those without have a more severe disease phenotype. For this purpose, we identified asthma and chronic cough among 14,740 adults from the Copenhagen General Population Study and investigated respiratory symptoms, health care utilizations, lung function, and biomarkers in blood.

METHODS

Study design and participants

The Copenhagen General Population Study is an epidemiological population-based cohort study in Denmark initiated in 2003 with ongoing enrollment.^{11,12} All individuals in Denmark are assigned a unique identification number at birth or immigration and recorded in the National Danish Civil Registration System. By using this number, individuals aged 20 to 100 years were randomly selected from the National Danish Civil Registration System to reflect the adult white Danish population. Since the initiation of the study, over a hundred thousand of individuals have been examined, of whom 14,740 individuals were asked consecutively from January 1, 2013, to January 1, 2015, about chronic cough. All participants completed a comprehensive questionnaire, underwent a physical health examination, and gave blood for biochemical analyses. Questionnaires were reviewed at the day of attendance by an investigator together with the participant. The study was approved by Herlev and Gentofte Hospital and a Danish ethical committee and was conducted according to the Declaration of Helsinki (identification no. H-KF-01-144/01). All participants provided written informed consent.

Definition of asthma and chronic cough

Asthma was defined as an affirmative response to the question: "Do you have asthma?"^{11,12} Subsequently, individuals with asthma were asked how many years they have had asthma. Individuals were also asked whether they used asthma medication, defined as taking any kind of medication for asthma/bronchitis (including sprays/dry powders) daily or almost daily. Chronic cough was defined as an affirmative response to the question "Do you have cough lasting more than 8 weeks?" in accordance with the clinical recommendations from the American College of Chest Physicians, the British Thoracic Society, and the European Respiratory Society.¹⁻³ The question was incorporated in the ongoing Copenhagen General Population Study from January 1, 2013.¹² Individuals identified with chronic cough completed the Leicester Cough Questionnaire, a validated and reproducible health-related quality-of-life

questionnaire specifically developed for patients with chronic cough, which also correlates well with objective measurements of cough.¹²⁻¹⁵

Clinical outcomes

Wheezing was whistling or wheezing while breathing. Dyspnea was shortness of breath during different levels of activity, at nighttime, and/or while seated/at rest. Sputum production was phlegm from the lungs in the morning and/or during the day for as long as 3 consecutive months each year. Chest pain/tightness was when hurrying or taking the stairs.

Episodes of acute bronchitis and/or pneumonias in the last 10 years and general practitioner visits in the past 12 months were self-reported. Hospitalizations for asthma (*International Classification of Diseases, Eighth Revision* code 493 and *International Classification of Diseases, Tenth Revision* codes J45-J46) and pneumonia (*International Classification of Diseases, Eighth Revision* codes 480-486 and *International Classification of Diseases, Tenth Revision* codes J12-J18) were defined as acute emergency department visits or hospital admissions with the mentioned primary discharge diagnosis, obtained from the national Danish Patient Registry, which covers all public and private Danish hospitals, as done previously.¹¹

Spirometry was performed with an EasyOne Spirometer (ndd Medical Technologies, Zurich, Switzerland) without investigator knowledge of disease status, and FEV₁ and forced vital capacity (FVC) were measured prebronchodilatory, as described previously.¹⁶ Spirometry was performed in a standing position without the use of a nose-clip under strict instructions from a trained investigator. FEV₁ and FVC were measured with at least 3 sets of values. A valid spirometry performance was based on at least 2 measurements differing by less than 5% and a correct visual inspection of the spirometry curves. Only the highest measurements of FEV₁ and FVC were used. Percentage of predicted values for FEV₁, FVC, and FEV₁/FVC were calculated using internally derived reference values based on healthy asymptomatic never-smokers with age and height as covariates and separately for men and women.¹¹ Airflow limitation was defined as FEV₁/FVC ratio of less than 0.70 and FEV₁/FVC ratio less than lower limit of normal, and the severity of airflow limitation was assessed using FEV₁ as percentage of predicted value and categorized into less than 60%, 60% to 79%, and 80% or more.¹¹

Systemic and allergic inflammatory biomarkers in blood were measured using standard hospital assays. Plasma high-sensitive C-reactive protein and fibrinogen and blood leucocytes and neutrophils were used as systemic inflammatory biomarkers, whereas blood eosinophils and plasma IgE were used as allergic inflammatory biomarkers; measurement of high-sensitive C-reactive protein was available in a subgroup of 12,469 participants.

Other relevant information

Allergy was defined in those participants reporting asthma, hay fever, or eczema as a reaction to food, medication, grass, flower, animal hair, or other allergens. No objective measurement for allergy was available. Familial predisposition for asthma was having at least 1 first-degree relative (father, mother, and/or sibling) with asthma. Childhood allergy was asthma, hay fever, or eczema in childhood. Smoking status was determined using information on tobacco smoking, including age of onset, duration, and daily amount of consumption (reported as number of daily consumed cigarettes, cheroots, and cigars and grams of weekly consumed pipe tobacco). Cumulative tobacco consumption was calculated in pack years: 1

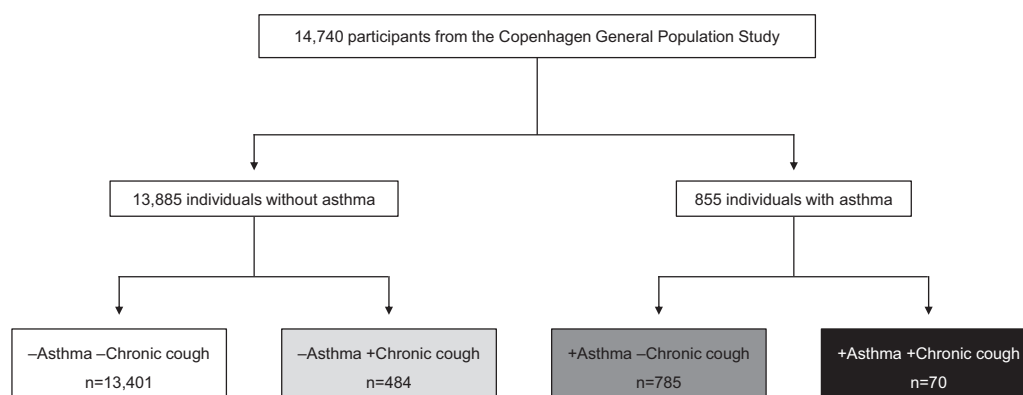


FIGURE 1. Flowchart for selection of study participants from the Copenhagen General Population Study.

pack year was 20 cigarettes or equivalent, for example, cheroots, cigars, or pipe, smoked daily for 1 year (a single cheroot = 0.8 g of tobacco and a single cigar = 5 g of tobacco; 1 cigarette = 1 g of tobacco). Occupational exposure to dust/fumes and daily exposure to passive smoking was self-reported. Body mass index was measured weight divided by measured height squared (kg/m^2). Education was reported as years attending school, and income was reported as annual household income. Physical activity was reported according to hours per week and degree of activity in leisure-time.

Statistical analyses

All statistical analyses were performed using STATA/SE 13.1 for Windows (StataCorp, College Station, Texas) and a 2-sided P value of less than .05 was considered significant. Wilcoxon rank-sum test was used for continuous data, and Pearson chi-square test or Fischer exact test was used for categorical data. Inflammatory biomarkers in blood were depicted using geometric means by using multiple linear regression models allowing for age and sex as covariates. Logistic regression was used to determine risk of hospitalization for asthma and pneumonia. Ordered logistic regression was used to determine risk of frequent hospitalizations (≥ 2 hospitalizations). Logistic regression models were multivariable adjusted for potential confounders. We performed multiple imputation using chained equations to fill out the missing values for some potential confounders; however, results were similar without the use of imputation.

RESULTS

Among 14,740 individuals from the general population, 855 (6%) had asthma, and 70 (8%) of these had chronic cough (Figure 1). Among 13,885 individuals without asthma, 484 (3%) of these had chronic cough. Individuals with asthma used more often asthma medication (67% and 79% vs 2%) and reported more often familial predisposition for asthma (41% and 37% vs 15%), allergy (79% and 74% vs 26%), and childhood allergy (46% and 44% vs 14%) compared with individuals without asthma or chronic cough (Table 1, all P values < .005). Individuals without asthma but with chronic cough were characterized by being old, more often active smokers with a higher tobacco consumption, and 7% of them reported asthma medication use, 21% familial predisposition for asthma, 28% allergy, and 13% childhood allergy.

Among individuals with asthma, those with chronic cough versus those without were older, but there were no differences

with regard to use of asthma medication, duration of asthma, presence of allergy, smoking habits, and tobacco consumption. Because some of these comparisons comprise few individuals, these results should be interpreted with care. The Leicester Cough Questionnaire showed that individuals with asthma and chronic cough had a median total score of 16.8 (25th and 75th percentiles, 14.8-18.9), corresponding to 5.4 (4.6-6.0) for the physical domain, 5.7 (4.6-6.4) for the psychological domain, and 6.0 (5.3-6.8) for the social domain. Corresponding values for individuals without asthma but with chronic cough were 17.4 (15.4-18.9), 5.8 (5.1-6.3), 5.6 (4.6-6.3), and 6.3 (5.5-6.8), respectively.

Respiratory symptoms and health care utilizations

Individuals with asthma and chronic cough had more often wheezing (70% vs 54%; $P < .05$), dyspnea (74% vs 49%; $P < .005$), night-time dyspnea (27% vs 11%; $P < .005$), sputum production (59% vs 14%; $P < .005$), and chest pain/tightness (14% vs 4%; $P < .005$) compared with individuals with asthma but without chronic cough (Figure 2). Individuals with asthma had more often respiratory symptoms compared with those without asthma; however, no differences could be observed between individuals with asthma without chronic cough and individuals without asthma with chronic cough with regard to dyspnea and chest pain/tightness, and the latter group had more often sputum production.

Among individuals with asthma, those with chronic cough versus those without had more often 6 or more episodes of acute bronchitis and/or pneumonia in the last 10 years (21% vs 10%; $P < .005$) and 3 or more visits to a general practitioner in the past 12 months (60% vs 45%; $P < .05$) (Figure 3). As would be expected, individuals with asthma reported more often health care utilizations compared with those without asthma but the differences were small or diminished after comparing with individuals without asthma but with chronic cough.

Compared with individuals without asthma or chronic cough, individuals with asthma had an increased risk of hospitalizations for asthma, regardless of the presence of chronic cough, but there were no differences with regard to hospitalizations for pneumonia (Figure 4). In contrast, individuals without asthma but with chronic cough had an increased risk of hospitalizations for pneumonia but did not differ with regard to hospitalizations for asthma.

TABLE I. Characteristics of individuals with asthma and chronic cough

Characteristic	– Asthma – Chronic cough (n = 13,401)	– Asthma + Chronic cough (n = 484)	+ Asthma – Chronic cough (n = 785)	+ Asthma + Chronic cough (n = 70)
Age (y)	58 (49-68)	64 (54-70)*	57 (48-68)†	63 (54-72)*†
Sex: female (%)	54	56	61*	67*
BMI (kg/m ²)	25 (23-28)	26 (23-29)*	26 (23-29)*	27 (24-30)*
FEV ₁ % predicted	97 (88-107)	92 (81-103)*	89 (77-99)*†	86 (69-98)*†
FVC % predicted	98 (89-107)	95 (85-104)*	94 (84-103)*	92 (82-100)*†
FEV ₁ /FVC	0.76 (0.72-0.80)	0.74 (0.68-0.79)*	0.73 (0.66-0.77)*†	0.72 (0.64-0.76)*†
Smoking status (%)				
Never-smokers	46	35*	45†	39
Former smokers	43	41	46	51
Current smokers	10	24*	9†	10†
Cumulative tobacco consumption (pack years)§	13 (5-25)	20 (9-35)*	13 (5-27)†	15 (4-22)†
Familial predisposition for asthma (%)	15	21*	41*†	37*†
Childhood allergy (%)	14	13	46*†	44*†
Occupational exposure to dust and/or fumes (%)	7	13*	9*†	11
Daily exposure to passive smoking (%)	7	8	9	7
Low education (%)	15	23*	15†	23
Low income (%)	7	9	10*	16*
Physically inactive (%)	5	7*	7*	6
Allergy (%)	26	28	79*†	74*†
Use of asthma medication (%)	2	7*	67*†	79*†
Duration of asthma (y)	NA	NA	20 (10-33)	16 (5-30)
Leicester Cough Questionnaire				
Physical domain	NA	5.8 (5.1-6.3)	NA	5.4 (4.6-6.0)†
Psychological domain	NA	5.6 (4.6-6.3)	NA	5.7 (4.6-6.4)
Social domain	NA	6.3 (5.5-6.8)	NA	6.0 (5.3-6.8)
Total score	NA	17.4 (15.4-18.9)	NA	16.8 (14.8-18.9)
Airflow limitation according to FEV ₁ /FVC < 0.70 (%)	19	34*	39*	40*
Airflow limitation according to FEV ₁ /FVC < LLN (%)	10	21*	28*†	31*†

BMI, Body mass index; LLN, lower limit of normal; NA, not applicable.

Data are presented as median and 25th and 75th percentiles, or percent.

* $P < .05$ for comparison with individuals without asthma or chronic cough, calculated using Wilcoxon rank-sum test or Pearson χ^2 or Fischer exact test.

† $P < .05$ for comparison with individuals without asthma but with chronic cough, calculated using Wilcoxon rank-sum test or Pearson χ^2 or Fischer exact test.

‡ $P < .05$ for comparison with individuals with asthma but without chronic cough, calculated using Wilcoxon rank-sum test or Pearson χ^2 or Fischer exact test.

§Included only former and current smokers.

Lung function and inflammatory biomarkers in blood

Individuals with asthma had lower lung function and more often airflow limitation compared with those without asthma or chronic cough (Table I). Among individuals with asthma, those with chronic cough versus those without showed a trend to lower lung function and had more severe airflow limitation with FEV₁ predicted value of less than 60% (Table I and Figure 5). Interestingly, individuals without asthma but with chronic cough had lower lung function and more severe airflow limitation compared with those without asthma or chronic cough but not compared with those with asthma.

Individuals with asthma and chronic cough versus those without had higher levels of blood neutrophils, blood leukocytes, and plasma fibrinogen, but there were no differences with regard to levels of plasma high-sensitive C-reactive protein, blood eosinophils, or plasma IgE (Figure 6). Individuals without asthma

but with chronic cough had higher levels of both systemic and allergic inflammatory biomarkers in blood compared with those without asthma or chronic cough. In contrast, compared with those with asthma, these individuals did not differ overall in levels of systemic inflammatory biomarkers in blood, but they had lower levels of blood eosinophils and plasma IgE.

Sensitivity and subgroup analyses

Results were similar after using different definitions for asthma, that is, including individuals reporting asthma and/or asthma as a reaction to food, medication, grass, flower, animal hair, or other allergens (see Tables E1-E3 in this article's Online Repository at www.jaci-inpractice.org) and including individuals reporting asthma of minimum 2 years of duration and to be in treatment with asthma medication (see Tables E4-E6 in this article's Online Repository at www.jaci-inpractice.org). When

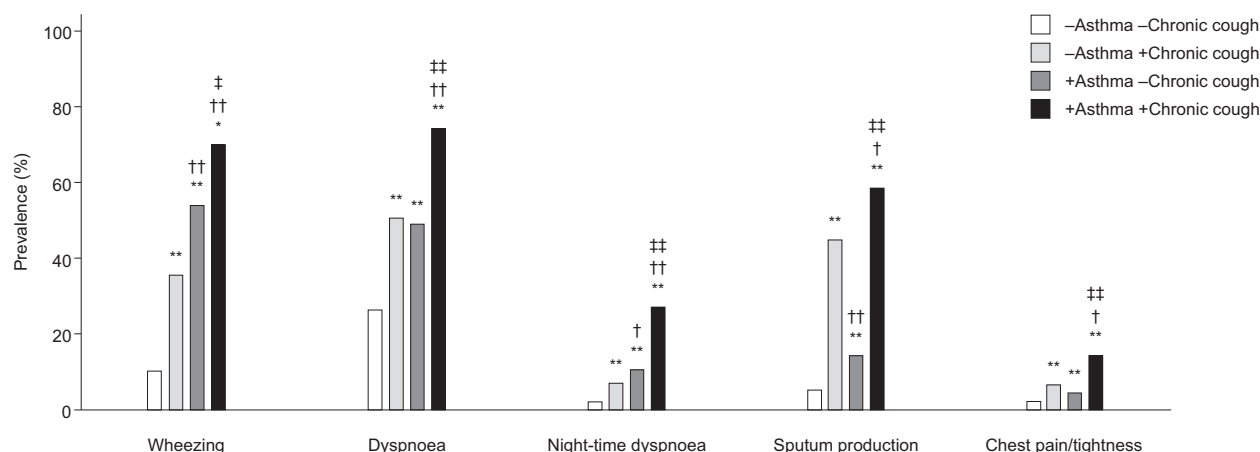


FIGURE 2. Respiratory symptoms in individuals with asthma and chronic cough. * $P < .05$ and ** $P < .005$ for comparison with individuals without asthma or chronic cough. † $P < .05$ and †† $P < .005$ for comparison with individuals without asthma but with chronic cough. ‡ $P < .05$ and ‡‡ $P < .005$ for comparison with individuals with asthma but without chronic cough. P values calculated using Pearson χ^2 or Fischer exact test.

stratifying according to presence of chronic cough and sputum production, individuals with asthma having both these conditions seemed to have more severe disease compared with those having only one (see Tables E7-E9 in this article's Online Repository at www.jaci-inpractice.org). When stratifying according to presence of chronic cough and level of blood eosinophils, having low or high blood eosinophils did not seem to matter for disease severity in individuals with asthma and chronic cough; however, the latter group seemed to have higher levels of IgE (see Tables E10-E12 in this article's Online Repository at www.jaci-inpractice.org). Because of the small size of the subgroups analyses, results should be interpreted with care.

DISCUSSION

In this study of the Danish general population, we found that 8% of individuals with asthma had chronic cough. Among individuals with asthma, those with chronic cough versus those without had more often accompanying respiratory symptoms, episodes of acute bronchitis and/or pneumonia, and visits to the general practitioner. In addition, these individuals had more severe airflow limitation, with FEV₁ predicted value of less than 60% and higher levels of systemic inflammatory biomarkers in blood. No differences were observed for risk of hospitalizations due to asthma or pneumonia or levels of plasma high-sensitive C-reactive protein or allergic inflammatory biomarkers in blood. To our knowledge, this is the first study assessing the role and impact of chronic cough in individuals with asthma using a general population setting.

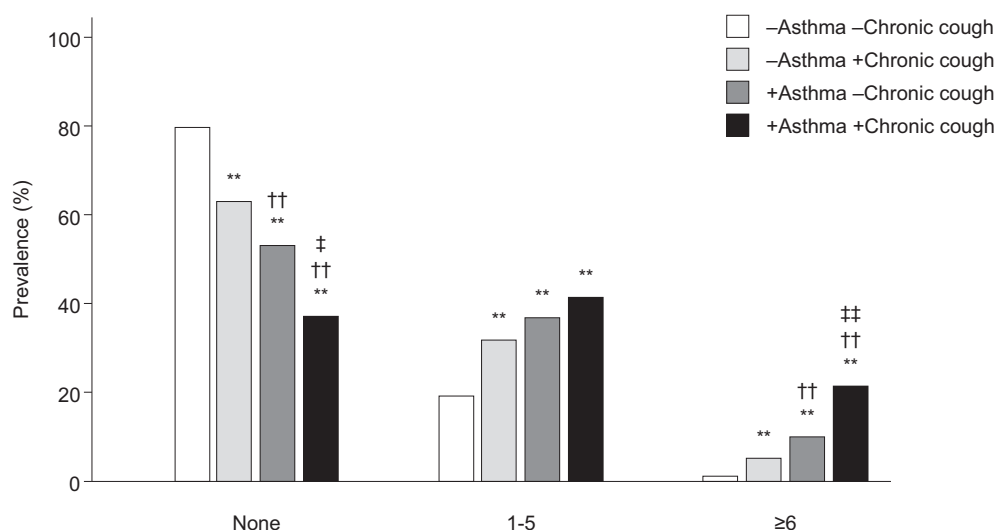
In individuals with asthma, unspecific cough usually combined with mucus hypersecretion has been associated with uncontrolled asthma, especially in individuals treated with inhaled corticosteroids.^{7,10,17} Also, patients with asthma often consider cough to be more troublesome compared with other respiratory symptoms.^{8,18} Chronic cough is known to have adverse impacts on quality of life, affecting different aspects of health, including physical, psychological, and social areas, equivalent to other chronic respiratory diseases.⁴⁻⁶ Thus, a combination of

uncontrolled asthma and impaired quality of life in individuals with concomitant chronic cough may lead to increased disability and health care utilizations, as observed in the present study.

Although individuals with asthma reported more allergy and had higher levels of blood eosinophils and plasma IgE, no differences were observed between those with and without chronic cough among individuals with asthma. However, individuals with both asthma and chronic cough had higher levels of blood neutrophils, suggesting that these individuals may have both eosinophilic and neutrophilic type of inflammatory response.¹⁹ In individuals with asthma, the neutrophilic type of inflammation seems to be more refractory to treatment with inhaled corticosteroids.²⁰ Unfortunately, we did not have information on dosage and type of airway medication use. Thus, future studies of dosage and type of treatment used for individuals with asthma with concomitant chronic cough therefore seem warranted. Also, it is not totally clear whether neutrophilic inflammation is accompanied by eosinophilic inflammation,²¹⁻²³ or whether it is merely a consequence of mechanical stimulation from coughing.^{24,25} Yet, as reflected by higher levels of plasma fibrinogen and blood leukocytes, individuals with asthma and chronic cough may have some sort of systemic inflammatory response.

Asthma is a heterogeneous disease entity and chronic cough may help to differentiate between different phenotypes of asthma. Cough-variant asthma is characterized by airway hyperresponsiveness, presence of chronic cough, and absence of other respiratory symptoms.^{26,27} Individuals with cough-variant asthma typically have normal or near-normal lung function and a degree of eosinophilic airway inflammation corresponding to classical asthma, indicating possible similarity in the site and type of inflammation.^{28,29} Furthermore, it has been shown that some patients with cough-variant asthma later develop classical asthma, and that early treatment with inhaled corticosteroids may prevent this progression.^{26,30-33} In the present study, 90% of individuals with asthma with concomitant chronic cough reported accompanying respiratory symptoms, which thereby precludes cough-variant asthma and instead suggests uncontrolled asthma. Nevertheless, there is still the possibility that

Episodes of acute bronchitis/pneumonias in the last 10 years



General practitioner visits in the past 12 months

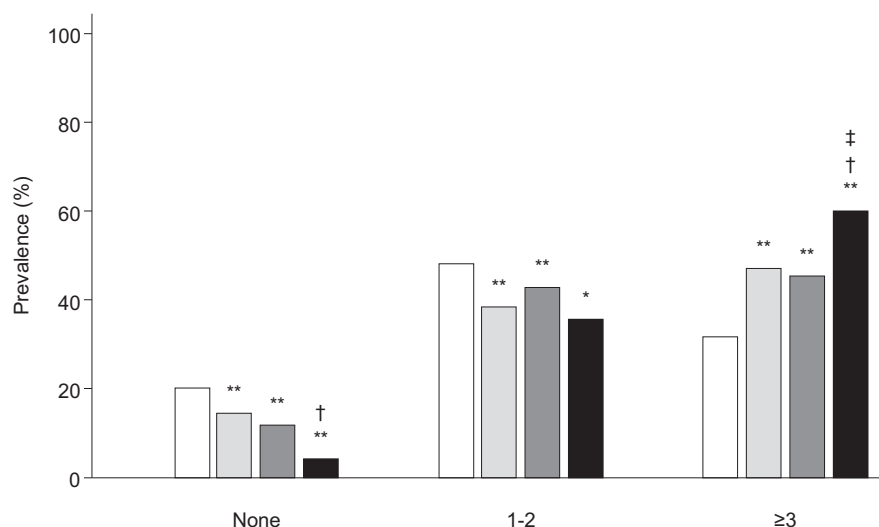


FIGURE 3. Lung infection and health care use in individuals with asthma and chronic cough. * $P < .05$ and ** $P < .005$ for comparison with individuals without asthma or chronic cough. † $P < .05$ and †† $P < .005$ for comparison with individuals without asthma but with chronic cough. ‡ $P < .05$ and ‡‡ $P < .005$ for comparison with individuals with asthma but without chronic cough. P values calculated using Pearson χ^2 or Fischer exact test.

some of the individuals with asthma with chronic cough suffer from end-stages of cough-variant asthma characterized by chronic cough with typical clinical features of asthma, including accompanying respiratory symptoms, airflow limitation, and neutrophilic type of inflammation, refractory to treatment with inhaled corticosteroids.³⁴ In addition, emerging evidence suggest heightened cough response in patients with asthma due to neuronal dysfunction, which seems to be most pronounced among those with a nonatopic form of asthma, and that the response may be modified by degree of bronchoconstriction.^{35,36}

Until now, we mainly knew how chronic cough affected quality of life, as measured with the Leicester Cough Questionnaire, in

individuals with asthma followed in specialized clinics. This is problematic, because individuals with asthma from specialized clinics are often selected toward severe disease and may not be representative for individuals with asthma from the general population, which obviously comprises the majority. To our knowledge, this is the first study reporting Leicester Cough Questionnaire score for randomly selected individuals with asthma from a general population setting, thereby presenting an opportunity to put results in context with other previous reports from specialized clinics. According to a single clinical study comprising patients with asthma from specialized clinics, a median total score of 17.8 was observed, corresponding to 5.5 for the physical

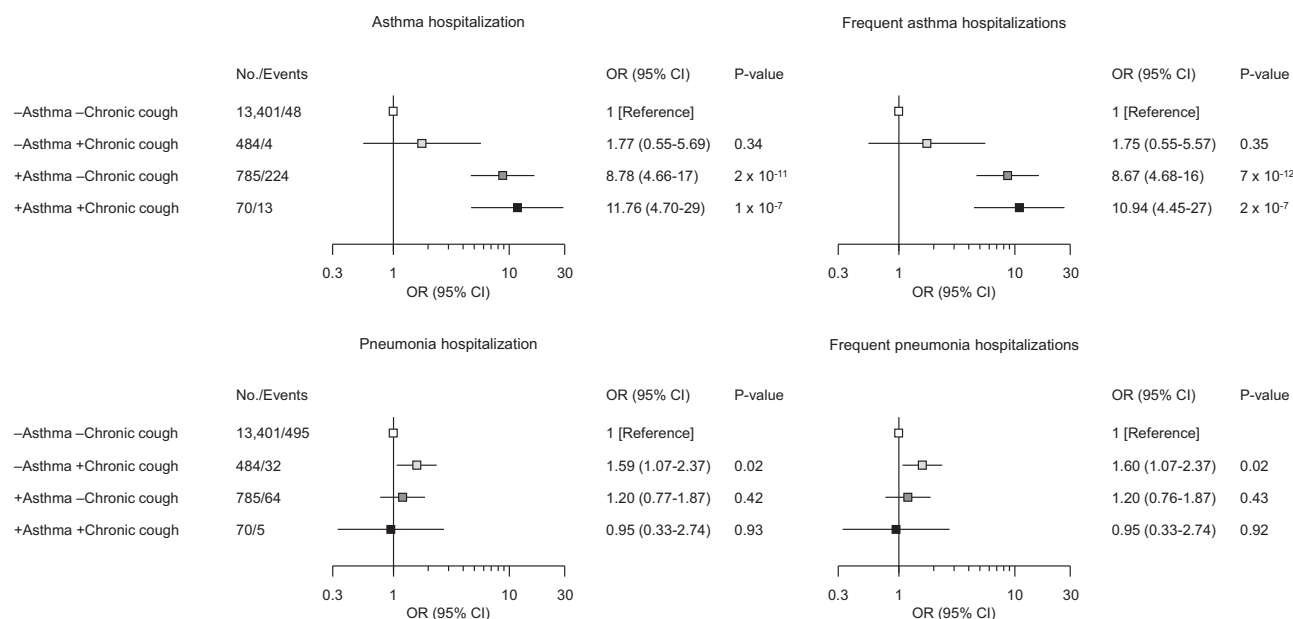


FIGURE 4. Risk of hospitalizations for asthma and pneumonia in individuals with asthma and chronic cough. Risk estimates were multivariable adjusted for age, sex, body mass index, smoking status, cumulative tobacco consumption (pack-years), familial predisposition for asthma, childhood allergy, occupational exposure to dust/fumes, daily exposure to passive smoking, education, income, physical activity, allergy, and use of medication. Frequent asthma/pneumonia hospitalizations included 2 or more hospitalizations. OR, Odds ratio.

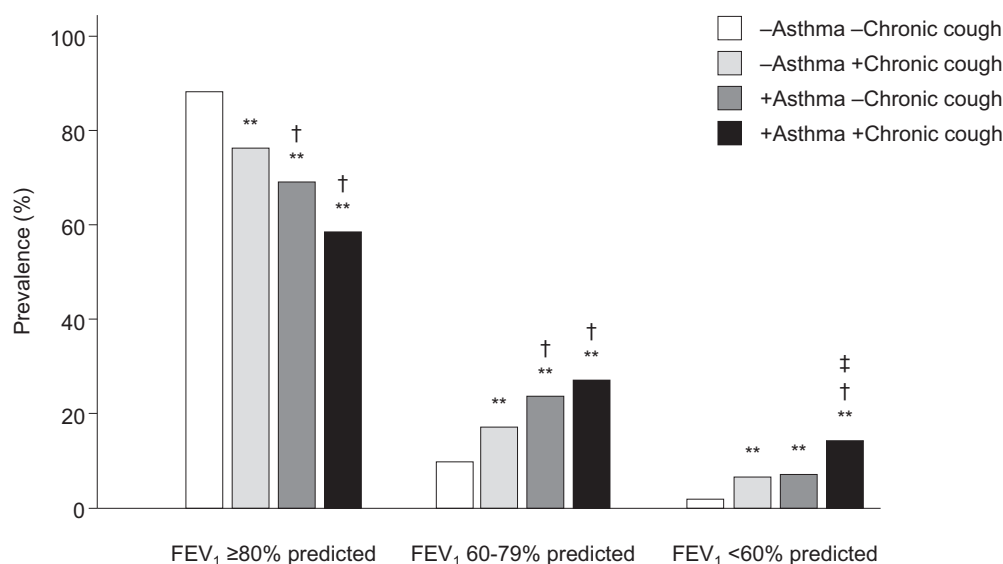


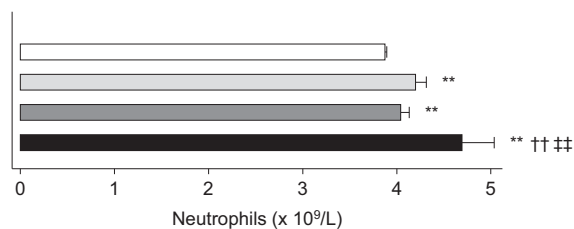
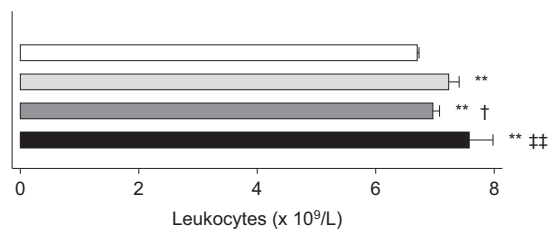
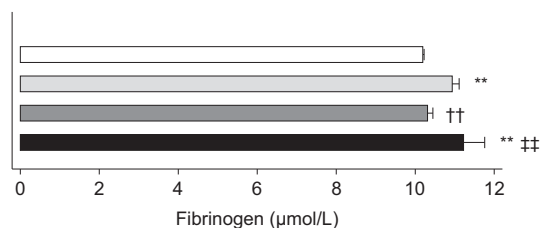
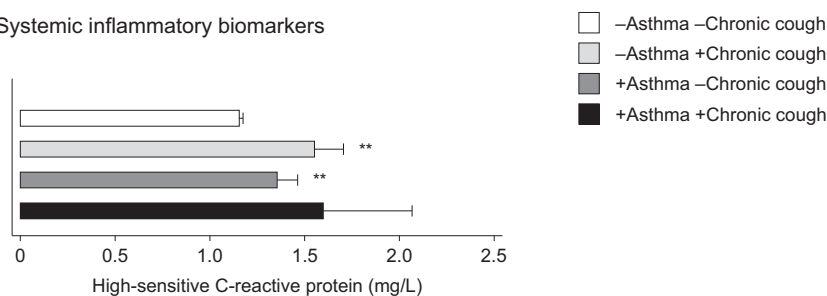
FIGURE 5. Severity of airflow limitation in individuals with asthma and chronic cough. * $P < .05$ and ** $P < .005$ for comparison with individuals without asthma or chronic cough. † $P < .05$ and †† $P < .005$ for comparison with individuals without asthma but with chronic cough. ‡ $P < .05$ and ‡‡ $P < .005$ for comparison with individuals with asthma but without chronic cough. P values calculated using Pearson χ^2 or Fischer exact test.

domain, 6.3 for the psychological domain, and 6.5 for the social domain,³⁷ which seem to be comparable to the observed scores in the present study. However, according to other clinical studies comprising patients with chronic cough from specialized clinics, much lower scores were observed.^{5,14,38} It would be expected that severity of chronic cough depends on the setting that is being

studied; individuals with chronic cough from specialized clinics will be more disabled and are therefore expected to have lower scores than individuals with chronic cough from a general population setting.

Strengths of the present study include a large sample of individuals randomly selected from the general population, and the

Systemic inflammatory biomarkers



Allergic inflammatory biomarkers

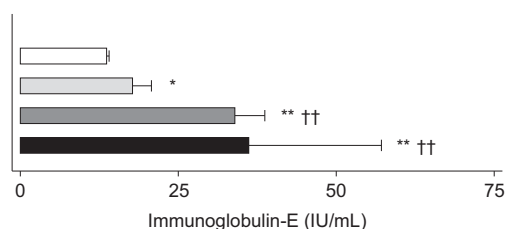
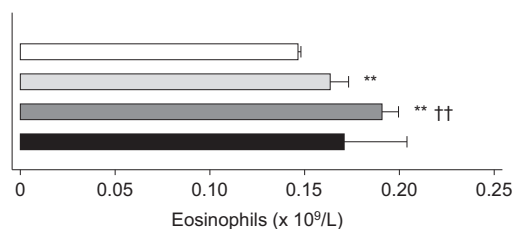


FIGURE 6. Levels of systemic and allergic inflammatory biomarkers in blood in individuals with asthma and chronic cough. Data are presented as geometric mean and 95% CI. Data were adjusted for age and sex using multiple linear regression models. * $P < .05$ and ** $P < .005$ for comparison with individuals without asthma or chronic cough. † $P < .05$ and †† $P < .005$ for comparison with individuals without asthma but with chronic cough. ‡ $P < .05$ and ‡‡ $P < .005$ for comparison with individuals with asthma but without chronic cough. P values were obtained from the Wald tests.

diagnosis of chronic cough using a standard definition as recommended.¹⁻³ Bias caused by investigator knowledge of disease or risk factor status seems unlikely because our sample was randomly selected from the general population and because clinical outcomes were collected without investigator knowledge of disease status.

A potential limitation of our study includes the diagnosis of asthma, which was self-reported and not defined according to presence of reversible or variable airflow limitation and/or airway hyperresponsiveness.²⁰ Unfortunately, clinical approaches to diagnose diseases in large-scale population-based studies are not feasible. Although self-reported asthma has previously been evaluated and displays high specificity and sensitivity in population-based studies,³⁹⁻⁴¹ the prevalence of asthma can still be underestimated depending on type and definition of self-reported asthma. To increase the reliability of the asthma diagnosis, we used a broader and a more stricter definition of asthma and have observed similar results. Furthermore, individuals with asthma had more often typical asthmatic clinical attributes compared with individuals without asthma irrespective of chronic cough, for example, in terms of wheezing, high levels of blood eosinophils and plasma IgE, and increased risk of asthma-related hospitalizations. Thus, we do not think that potential misclassification substantially influenced the results. If misclassification was present, it would most likely tend to bias the results toward the null hypothesis and dilute a true association, thereby not explaining the positive results observed in the present study.

Another potential limitation is the relatively small sample size of the group with asthma and chronic cough ($n = 70$), which could limit comparisons in some subgroup analyses due to insufficient statistical power; however, results were consistent throughout, supporting the conclusion that those with asthma with chronic cough have a more severe disease phenotype.

A potential limitation is how treatment was defined, because it does not provide adequate granularity, that is, level of care as suggested by the Global Initiative for Asthma, to allow reliable comparison between asthma groups.²⁰

Although chronic cough was defined using a standard recommended definition, a potential limitation is that we did not ask about the exact duration of their cough, which prevents us from investigating the stability of this trait.

Finally, another potential limitation is the cross-sectional study design used, and thus future studies of chronic cough in asthma using a prospective study design are warranted.

In conclusion, among individuals with asthma, those with chronic cough versus those without had worse respiratory symptoms, greater health care utilizations, lower lung function, and higher levels of systemic inflammatory biomarkers in blood. The results show that chronic cough in individuals with asthma is associated with a more severe disease phenotype.

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ONLINE REPOSITORY

TABLE E1. Clinical outcomes in individuals with asthma and chronic cough

Outcome	– Asthma – Chronic cough (n = 13,169)	– Asthma + Chronic cough (n = 471)	+ Asthma – Chronic cough (n = 1,017)	+ Asthma + Chronic cough (n = 83)
Respiratory symptoms				
Wheezing	10	34*	48*†	71*†‡
Dyspnea	26	50*	46*	76*†‡
Night-time dyspnea	2	7*	9*	24*†‡
Sputum production	5	45*	13*†	57*†‡
Chest pain/tightness	2	7*	4*	12*†‡
Episodes of acute bronchitis/pneumonias in the last 10 y				
None	80	63*	56*†	42*†‡
1-5	19	32*	36*	39*
≥6	1	5*	8*†	19*†‡
General practitioner visits in the past 12 mo				
None	20	15*	13*	4*†‡
1-2	48	39*	44*†	35*
≥3	32	47*	43*	61*†‡
Severity of airflow limitation				
FEV ₁ ≥ 80% predicted	88	76*	72*	61*†
FEV ₁ 60%-79% predicted	10	17*	22*†	25*
FEV ₁ < 60% predicted	2	7*	6*	13*†‡
Systemic inflammatory biomarkers				
High-sensitive C-reactive protein (mg/dL)	1.16 (1.14-1.18)	1.54 (1.40-1.69)*	1.30 (1.21-1.38)*	1.66 (1.30-2.12)*
Fibrinogen (μmol/L)	10.2 (10.2-10.2)	10.9 (10.8-11.1)*	10.2 (10.1-10.4)†	11.3 (10.8-11.8)*†‡
Leukocytes (×10 ⁹ /L)	6.7 (6.7-6.7)	7.2 (7.0-7.4)*	6.9 (6.8-7.0)*†	7.6 (7.3-8.0)*†‡
Neutrophils (×10 ⁹ /L)	3.9 (3.9-3.9)	4.2 (4.1-4.3)*	4.0 (3.9-4.1)*†	4.7 (4.4-5.0)*†‡
Allergic inflammatory biomarkers				
Eosinophils (×10 ⁹ /L)	0.15 (0.14-0.15)	0.16 (0.15-0.17)*	0.19 (0.18-0.20)*†	0.18 (0.15-0.21)*
IgE (IU/mL)	13 (13-14)	17 (15-20)*	35 (31-39)*†	38 (26-56)*†

Individuals with asthma include those reporting asthma and/or asthma as a reaction to food, medication, grass, flower, animal hair, or other allergens. Data are presented as percent. Data for inflammatory biomarkers in blood are presented as geometric mean with 95% CI, adjusted for age and sex using multiple linear regression models. Numbers may not add up because of rounding.

* $P < .05$ for comparison with individuals without asthma or chronic cough, calculated using Pearson χ^2 or Fischer exact test. For inflammatory biomarkers, comparisons were performed using Wald test from multiple linear regression models adjusted for age and sex.

† $P < .05$ for comparison with individuals without asthma but with chronic cough, calculated using Pearson χ^2 or Fischer exact test. For inflammatory biomarkers, comparisons were performed using Wald test multiple linear regression models adjusted for age and sex.

‡ $P < .05$ for comparison with individuals with asthma but without chronic cough, calculated using Pearson χ^2 or Fischer exact test. For inflammatory biomarkers, comparisons were performed using Wald test multiple linear regression models adjusted for age and sex.

TABLE E2. Risk of hospitalizations for asthma in individuals with asthma and chronic cough

Study subjects	No./events	OR (95% CI), <i>P</i> value	
		Asthma hospitalization	Frequent asthma hospitalizations
–Asthma–Chronic cough	13,169/35	1 (Reference)	1 (Reference)
–Asthma+Chronic cough	471/2	0.86 (0.11-6.5), <i>P</i> = .88	0.86 (0.11-6.5), <i>P</i> = .89
+Asthma–Chronic cough	1,017/237	13 (6.9-23), <i>P</i> = 8×10^{-17}	12 (6.9-23), <i>P</i> = 6×10^{-17}
+Asthma+Chronic cough	83/15	18 (7.9-42), <i>P</i> = 1×10^{-11}	17 (7.5-39), <i>P</i> = 2×10^{-11}

OR, Odds ratio.

Individuals with asthma include those reporting asthma and/or asthma as a reaction to food, medication, grass, flower, animal hair, or other allergens. Risk estimates were multivariable adjusted for age, sex, body mass index, smoking status, cumulative tobacco consumption (pack years), familial predisposition for asthma, childhood allergy, occupational exposure to dust/fumes, daily exposure to passive smoking, education, income, physical activity, allergy, and use of medication. Frequent asthma hospitalizations included ≥ 2 hospitalizations.

TABLE E3. Risk of hospitalizations for pneumonia in individuals with asthma and chronic cough

Study subjects	No./events	OR (95% CI), <i>P</i> value	
		Pneumonia hospitalization	Frequent pneumonia hospitalizations
–Asthma–Chronic cough	13,169/484	1 (Reference)	1 (Reference)
–Asthma+Chronic cough	471/30	1.54 (1.03-2.32), <i>P</i> = .04	1.55 (1.03-2.32), <i>P</i> = .04
+Asthma–Chronic cough	1,017/75	1.30 (0.86-1.95), <i>P</i> = .22	1.29 (0.85-1.96), <i>P</i> = .23
+Asthma+Chronic cough	83/7	1.37 (0.54-3.46), <i>P</i> = .51	1.36 (0.54-3.44), <i>P</i> = .52

OR, Odds ratio.

Individuals with asthma include those reporting asthma and/or asthma as a reaction to food, medication, grass, flower, animal hair, or other allergens. Risk estimates were multivariable adjusted for age, sex, body mass index, smoking status, cumulative tobacco consumption (pack years), familial predisposition for asthma, childhood allergy, occupational exposure to dust/fumes, daily exposure to passive smoking, education, income, physical activity, allergy, and use of medication. Frequent pneumonia hospitalizations included ≥ 2 hospitalizations.

TABLE E4. Clinical outcomes in individuals with asthma and chronic cough

Outcome	– Asthma – Chronic cough (n = 13,401)	– Asthma + Chronic cough (n = 484)	+ Asthma – Chronic cough (n = 507)	+ Asthma + Chronic cough (n = 51)
Respiratory symptoms				
Wheezing	10	36*	58*†	78*†‡
Dyspnea	26	51*	54*	82*†‡
Night-time dyspnea	2	7*	11*†	27*†‡
Sputum production	5	45*	18*†	65*†‡
pain/tightness	2	7*	4*	16*†‡
Episodes of acute bronchitis/pneumonias in the last 10 y				
None	80	63*	45*†	33*†
1-5	19	32*	42*†	47*†
≥6	1	5*	13*†	20*†
General practitioner visits in the past 12 mo				
None	20	14*	8*†	6*
1-2	48	38*	43*	31*
≥3	32	47*	49*	63*†
Severity of airflow limitation				
FEV ₁ ≥80% predicted	88	76*	63*†	57*†
FEV ₁ 60%-79% predicted	10	17*	26*†	27*
FEV ₁ <60% predicted	2	7*	10*†	16*†
Systemic inflammatory biomarkers				
High-sensitive C-reactive protein (mg/dL)	1.15 (1.13-1.18)	1.55 (1.41-1.71)*	1.50 (1.35-1.65)*	1.60 (1.18-2.19)
Fibrinogen (μmol/L)	10.2 (10.2-10.2)	10.9 (10.8-11.1)*	10.5 (10.3-10.7)*†	11.5 (10.8-12.1)*†‡
Leukocytes (×10 ⁹ /L)	6.7 (6.7-6.7)	7.2 (7.1-7.4)*	7.0 (6.9-7.2)*	7.6 (7.2-8.1)*†
Neutrophils (×10 ⁹ /L)	3.9 (3.9-3.9)	4.2 (4.1-4.3)*	4.1 (4.0-4.2)*	4.8 (4.4-5.2)*†‡
Allergic inflammatory biomarkers				
Eosinophils (×10 ⁹ /L)	0.15 (0.14-0.15)	0.16 (0.15-0.17)*	0.20 (0.18-0.21)*†	0.17 (0.13-0.21)
IgE (IU/mL)	14 (13-14)	18 (15-21)*	38 (32-45)*†	38 (22-67)*†

Individuals with asthma include those reporting asthma of minimum 2 y of duration and to be in treatment with asthma medication. Data are presented as percent. Data for inflammatory biomarkers in blood are presented as geometric mean with 95% CI, adjusted for age and sex using multiple linear regression models. Numbers may not add up because of rounding.

* $P < .05$ for comparison with individuals without asthma or chronic cough, calculated using Pearson χ^2 or Fischer exact test. For inflammatory biomarkers, comparisons were performed using Wald test from multiple linear regression models adjusted for age and sex.

† $P < .05$ for comparison with individuals without asthma but with chronic cough, calculated using Pearson χ^2 or Fischer exact test. For inflammatory biomarkers, comparisons were performed using Wald test from multiple linear regression models adjusted for age and sex.

‡ $P < .05$ for comparison with individuals with asthma but without chronic cough, calculated using Pearson χ^2 or Fischer exact test. For inflammatory biomarkers, comparisons were performed using Wald test from multiple linear regression models adjusted for age and sex.

TABLE E5. Risk of hospitalizations for asthma in individuals with asthma and chronic cough

Study subjects	No./events	OR (95% CI), <i>P</i> value	
		Asthma hospitalization	Frequent asthma hospitalizations
–Asthma–Chronic cough	13,401/48	1 (Reference)	1 (Reference)
–Asthma+Chronic cough	484/4	1.54 (0.46-5.15), <i>P</i> = .49	1.53 (0.46-5.06), <i>P</i> = .49
+Asthma–Chronic cough	507/207	5.43 (2.21-13), <i>P</i> = 2×10^{-4}	5.70 (2.32-14), <i>P</i> = 1×10^{-4}
+Asthma+Chronic cough	51/11	7.00 (2.33-21), <i>P</i> = .001	6.87 (2.31-20), <i>P</i> = .001

OR, Odds ratio.

Individuals with asthma include those reporting asthma of minimum 2 y of duration and to be in treatment with asthma medication. Risk estimates were multivariable adjusted for age, sex, body mass index, smoking status, cumulative tobacco consumption (pack years), familial predisposition for asthma, childhood allergy, occupational exposure to dust/fumes, daily exposure to passive smoking, education, income, physical activity, allergy, and use of medication. Frequent asthma hospitalizations included ≥ 2 hospitalizations.

TABLE E6. Risk of hospitalizations for pneumonia in individuals with asthma and chronic cough

Study subjects	No./events	OR (95% CI), <i>P</i> value	
		Pneumonia hospitalization	Frequent pneumonia hospitalizations
–Asthma–Chronic cough	13,401/495	1 (Reference)	1 (Reference)
–Asthma+Chronic cough	484/32	1.59 (1.07-2.36), <i>P</i> = .02	1.59 (1.07-2.36), <i>P</i> = .02
+Asthma–Chronic cough	507/52	1.24 (0.70-2.20), <i>P</i> = .46	1.23 (0.69-2.19), <i>P</i> = .49
+Asthma+Chronic cough	51/5	1.22 (0.40-3.74), <i>P</i> = .73	1.20 (0.39-3.72), <i>P</i> = .75

OR, Odds ratio.

Individuals with asthma include those reporting asthma of minimum 2 y of duration and to be in treatment with asthma medication. Risk estimates were multivariable adjusted for age, sex, body mass index, smoking status, cumulative tobacco consumption (pack years), familial predisposition for asthma, childhood allergy, occupational exposure to dust/fumes, daily exposure to passive smoking, education, income, physical activity, allergy, and use of medication. Frequent pneumonia hospitalizations included ≥ 2 hospitalizations.

TABLE E7. Clinical outcomes in individuals with asthma and chronic cough according to sputum production

Outcome	+ Asthma – Chronic cough – Sputum (n = 673)	+ Asthma – Chronic cough + Sputum (n = 112)	+ Asthma + Chronic cough – Sputum (n = 29)	+ Asthma + Chronic cough + Sputum (n = 41)
Respiratory symptoms				
Wheezing	51	72*	55	80*†‡
Dyspnea	46	67*	66*	80*
Night-time dyspnea	9	21*	14	37*†‡
Chest pain/tightness	3	16*	3	22*†‡
Episodes of acute bronchitis/pneumonias in the last 10 y				
None	56	38*	52	27*†‡
1-5	37	35	34	46
≥6	7	28*	14	27*
General practitioner visits in the past 12 mo				
None	12	8	7	2
1-2	43	41	41	32
≥3	44	51	52	66*
Severity of airflow limitation				
FEV ₁ ≥ 80% predicted	71	59*	69	51*
FEV ₁ 60%-79% predicted	23	25	17	34
FEV ₁ < 60% predicted	6	16*	14	15*
Systemic inflammatory biomarkers				
High-sensitive C-reactive protein (mg/dL)	1.30 (1.20-1.41)	1.69 (1.36-2.11)	1.31 (0.90-1.91)	1.85 (1.31-2.62)
Fibrinogen (μmol/L)	10.2 (10.1-10.4)	10.9 (10.6-11.4)*	11.2 (10.5-11.9)	11.2 (10.5-12.0)*
Leukocytes (×10 ⁹ /L)	6.9 (6.8-7.1)	7.2 (6.9-7.5)	7.0 (6.6-7.5)	8.0 (7.5-8.6)*†‡
Neutrophils (×10 ⁹ /L)	4.0 (3.9-4.1)	4.3 (4.1-4.6)*	4.2 (3.8-4.6)	5.1 (4.7-5.6)*†‡
Allergic inflammatory biomarkers				
Eosinophils (×10 ⁹ /L)	0.19 (0.18-0.20)	0.20 (0.17-0.23)	0.19 (0.16-0.24)	0.16 (0.12-0.20)
IgE (IU/mL)	34 (30-40)	31 (22-44)	61 (30-127)	25 (14-43)

Data are presented as percent. Data for inflammatory biomarkers in blood are presented as geometric mean with 95% CI, adjusted for age and sex using multiple linear regression models. Numbers may not add up because of rounding.

* $P < .05$ for comparison with individuals with asthma but without chronic cough or sputum, calculated using Pearson χ^2 or Fischer exact test. For inflammatory biomarkers, comparisons were performed using Wald test from multiple linear regression models adjusted for age and sex.

† $P < .05$ for comparison with individuals with asthma and sputum but without chronic cough, calculated using Pearson χ^2 or Fischer exact test. For inflammatory biomarkers, comparisons were performed using Wald test from multiple linear regression models adjusted for age and sex.

‡ $P < .05$ for comparison with individuals with asthma and chronic cough but without sputum, calculated using Pearson χ^2 or Fischer exact test. For inflammatory biomarkers, comparisons were performed using Wald test from multiple linear regression models adjusted for age and sex.

TABLE E8. Risk of hospitalizations for asthma in individuals with asthma and chronic cough according to sputum production

Study subjects	No./events	OR (95% CI), <i>P</i> value	
		Asthma hospitalization	Frequent asthma hospitalizations
+Asthma–Chronic cough–Sputum	673/167	1 (Reference)	1 (Reference)
+Asthma–Chronic cough +Sputum	112/57	1.42 (0.78-2.59), <i>P</i> = .25	1.49 (0.81-2.75), <i>P</i> = .20
+Asthma+Chronic cough–Sputum	29/3	1.17 (0.33-4.11), <i>P</i> = .80	1.10 (0.33-3.68), <i>P</i> = .87
+Asthma+Chronic cough+Sputum	41/10	1.52 (0.66-3.52), <i>P</i> = .33	1.45 (0.63-3.30), <i>P</i> = .38

OR, Odds ratio.

Risk estimates were multivariable adjusted for age, sex, body mass index, smoking status, cumulative tobacco consumption (pack years), familial predisposition for asthma, childhood allergy, occupational exposure to dust/fumes, daily exposure to passive smoking, education, income, physical activity, allergy, and use of medication. Frequent asthma hospitalizations included ≥ 2 hospitalizations.

TABLE E9. Risk of hospitalizations for pneumonia in individuals with asthma and chronic cough according to sputum production

Study subjects	No./events	OR (95% CI), <i>P</i> value	
		Pneumonia hospitalization	Frequent pneumonia hospitalizations
+Asthma–Chronic cough Sputum	673/45	1 (Reference)	1 (Reference)
+Asthma–Chronic cough +Sputum	112/19	1.71 (0.83-3.55), <i>P</i> = .15	1.74 (0.85-3.57), <i>P</i> = .13
+Asthma+Chronic cough–Sputum	29/2	1.04 (0.27-4.08), <i>P</i> = .95	1.03 (0.28-3.77), <i>P</i> = .97
+Asthma+Chronic cough+Sputum	41/3	0.74 (0.15-3.61), <i>P</i> = .71	0.74 (0.15-3.59), <i>P</i> = .71

OR, Odds ratio.

Risk estimates were multivariable adjusted for age, sex, body mass index, smoking status, cumulative tobacco consumption (pack years), familial predisposition for asthma, childhood allergy, occupational exposure to dust/fumes, daily exposure to passive smoking, education, income, physical activity, allergy, and use of medication. Frequent pneumonia hospitalizations included ≥ 2 hospitalizations.

TABLE E10. Clinical outcomes in individuals with asthma and chronic cough according to levels of blood eosinophils

Outcome	+ Asthma – Chronic cough Blood eosinophils <0.30 × 10 ⁹ /L (n = 587)	+ Asthma – Chronic cough Blood eosinophils ≥0.30 × 10 ⁹ /L (n = 195)	+ Asthma + Chronic cough Blood eosinophils <0.30 × 10 ⁹ /L (n = 54)	+ Asthma + Chronic cough Blood eosinophils ≥0.30 × 10 ⁹ /L (n = 14)
Respiratory symptoms				
Wheezing	51	64*	70*	71
Dyspnea	50	46	74*†	71
Night-time dyspnea	10	11	24*†	36*†
Sputum production	13	18	59*†	57*†
Chest pain/tightness	4	5	17*†	7
Episodes of acute bronchitis/pneumonias in the last 10 y				
None	53	53	33*†	57
1-5	36	37	44	29
≥6	10	10	22*†	14
General practitioner visits in the past 12 mo				
None	12	12	4	7
1-2	42	46	41	14†
≥3	46	43	56	79*†
Severity of airflow limitation				
FEV ₁ ≥ 80% predicted	70	66	61	50
FEV ₁ 60%-79% predicted	24	22	26	36
FEV ₁ < 60% predicted	6	11	13	14
Systemic inflammatory biomarkers				
High-sensitive C-reactive protein (mg/dL)	1.38 (1.27-1.51)	1.27 (1.08-1.48)	1.53 (1.15-2.05)	1.89 (1.10-3.23)
Fibrinogen (μmol/L)	10.3 (10.1-10.5)	10.4 (10.1-10.7)	11.2 (10.6-11.9)	11.2 (10.5-12.3)
Leukocytes (×10 ⁹ /L)	6.8 (6.7-6.9)	7.5 (7.2-7.7)*	7.7 (7.2-8.1)*	7.3 (6.5-8.2)
Neutrophils (×10 ⁹ /L)	4.0 (3.9-4.1)	4.2 (4.0-4.4)	4.8 (4.4-5.2)*†	4.4 (3.8-5.1)
Allergic inflammatory biomarkers				
IgE (IU/mL)	27 (23-31)	67 (52-87)*	30 (18-50)†	81 (32-206)*

Data are presented as percent. Data for inflammatory biomarkers are presented as geometric mean with 95% CI, adjusted for age and sex using multiple linear regression models. Numbers may not add up because of rounding.

* $P < .05$ for comparison with individuals with asthma but without chronic cough and blood eosinophils <0.30 × 10⁹/L, calculated using Pearson χ^2 or Fischer exact test. For inflammatory biomarkers, comparisons were performed using Wald test from multiple linear regression models adjusted for age and sex.

† $P < .05$ for comparison with individuals with asthma but without chronic cough and with blood eosinophils ≥0.30 × 10⁹/L, calculated using Pearson χ^2 or Fischer exact test. For inflammatory biomarkers, comparisons were performed using Wald test from multiple linear regression models adjusted for age and sex.

TABLE E11. Risk of hospitalizations for asthma in individuals with asthma and chronic cough according to levels of blood eosinophils

Study subjects	No./events	OR (95% CI), <i>P</i> value	
		Asthma hospitalization	Frequent asthma hospitalizations
+Asthma—Chronic cough Blood eosinophils $<0.30 \times 10^9/L$	587/113	1 (Reference)	1 (Reference)
+Asthma—Chronic cough Blood eosinophils $\geq 0.30 \times 10^9/L$	195/109	1.48 (0.89-2.46), <i>P</i> = .13	1.57 (0.94-2.61), <i>P</i> = .08
+Asthma+Chronic cough Blood eosinophils $<0.30 \times 10^9/L$	54/10	1.41 (0.61-3.29), <i>P</i> = .42	1.42 (0.61-3.33), <i>P</i> = .42
+Asthma+Chronic cough Blood eosinophils $\geq 0.30 \times 10^9/L$	14/3	1.89 (0.56-6.42), <i>P</i> = .31	1.57 (0.54-4.58), <i>P</i> = .41

OR, Odds ratio.

Risk estimates were multivariable adjusted for age, sex, body mass index, smoking status, cumulative tobacco consumption (pack years), familial predisposition for asthma, childhood allergy, occupational exposure to dust/fumes, daily exposure to passive smoking, education, income, physical activity, allergy, and use of medication. Frequent asthma hospitalizations included ≥ 2 hospitalizations.

TABLE E12. Risk of hospitalizations for pneumonia in individuals with asthma and chronic cough according to levels of blood eosinophils

Study subjects	No./events	OR (95% CI), <i>P</i> value	
		Pneumonia hospitalization	Frequent pneumonia hospitalizations
+Asthma—Chronic cough Blood eosinophils $<0.30 \times 10^9/L$	587/49	1 (Reference)	1 (Reference)
+Asthma—Chronic cough Blood eosinophils $\geq 0.30 \times 10^9/L$	195/15	1.24 (0.65-2.39), <i>P</i> = .52	1.26 (0.66-2.41), <i>P</i> = .48
+Asthma+Chronic cough Blood eosinophils $<0.30 \times 10^9/L$	54/5	1.10 (0.37-3.30), <i>P</i> = .87	1.08 (0.37-3.19), <i>P</i> = .88
+Asthma+Chronic cough Blood eosinophils $\geq 0.30 \times 10^9/L$	14/0	—	—

OR, Odds ratio.

Risk estimates were multivariable adjusted for age, sex, body mass index, smoking status, cumulative tobacco consumption (pack years), familial predisposition for asthma, childhood allergy, occupational exposure to dust/fumes, daily exposure to passive smoking, education, income, physical activity, allergy, and use of medication. Frequent pneumonia hospitalizations included ≥ 2 hospitalizations.

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