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Prevalence, incidence, and characteristics of chronic cough among adults from the Canadian Longitudinal Study on Ageing (CLSA)

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KEY WORDS: chronic cough, prevalence, incidence, epidemiology, CLSA

ABBREVIATIONS:

AMI; acute myocardial infarction, BMI; body mass index, CLSA; Canadian Longitudinal Study of Ageing, COPD; chronic obstructive pulmonary disease, CHF; congestive heart failure, FEV1; forced expiratory volume in 1 second, FVC; forced vital capacity, LLN; lower limit of normal,

ABSTRACT

The global prevalence of chronic cough(CC) is highly variable ranging from 2-18%. There is a lack of data on the prevalence and incidence of CC from the general population. The objective of this study was to investigate the prevalence and incidence of CC in a sample of Canadian adults, and how these influenced by age, sex, smoking, respiratory symptoms, medical co-morbidities, and lung function.

Participants with chronic cough were identified from the Canadian Longitudinal Study on Ageing (CLSA) based on a self-reported daily cough in the last 12 months. This is a prospective, nationally generalizable, stratified random sample of adults aged 45-85 at baseline recruited between 2011-2015, and followed-up 3 years later. The prevalence and incidence per-100-person-years are described, with adjustments for age, sex and smoking.

Of the 30,097 participants, 29,972 completed the CC question at baseline and 26,701 at follow-up. The prevalence of CC was 15.8% at baseline and 17.6% at follow-up with 10.4%-17.1% variation across 7 provinces included in the CLSA comprehensive sample. Prevalence increased with age, current smoking, and was higher in males(15.2%), Caucasians(14%), and those born in North America, Europe or Oceania(14%). The incidence of CC adjusted for age, sex and smoking was higher in males, underweight and obese. Respiratory symptoms, airways diseases,lower FEV1 %predicted, cardio-vascular diseases, psychological disorders, diabetes and chronic pain had a higher incidence of CC.

The prevalence and incidence of CC is high in the CLSA sample with geographic, ethnic and gender differences which is influence by a number of medical co-morbidities.

INTRODUCTION

Chronic cough defined as a daily cough lasting greater than eight weeks is a prevalent condition associated with poor quality of life[1-4]. The estimated 10% of adults globally with chronic cough report adverse psychosocial and physical effects such as exhaustion, depression, and disruptions to social interactions, sleep, and work[5-8]. Chronic cough is one of the most common reasons for referral to a specialist in secondary care, representing a significant burden on the health care system[9,10]. Quantitative assessments of the prevalence, incidence and characteristics features of chronic cough help to identify at risk populations, potentially causative factors, and reflects the burden of chronic cough in the general population.

The global prevalence of chronic cough is highly variable by geographic region, ranging between 2-18% in a systematic review and meta-analysis of 90 studies[5]. The differences by region persisted after adjustment for smoking and highlight the importance of country-specific estimates of the prevalence of chronic cough. The majority of the studies did not include chronic cough as a primary outcome and therefore did not examine the prevalence of cough stratified by demographic, physiological and clinical variables. These can influence the prevalence and incidence of chronic cough. There is also a lack of data describing the incidence of chronic cough from large nationwide study.

The objective of this study was to estimate the prevalence and incidence of chronic cough in a national sample of adults from the Canadian Longitudinal Study on Ageing (CLSA) who were between the ages of 45 and 85 at the baseline and to assess how prevalence and incidence differs by age, sex, smoking, respiratory symptoms, co-morbidities, and lung function.

STUDY DESIGN AND METHODS

Study Design and Population

The Canadian Longitudinal Study on Ageing (CLSA) is a large, nationally generalizable, stratified random sample of 51,338 Canadian men and women aged 45 to 85 years at baseline (2011-2015) from the 10 Canadian provinces[11]. Eligible participants had to be physically and

cognitively able to participate on their own and not living in institutions such as long-term care facilities. Participants were recruited in the tracking cohort (n = 21 241) and the comprehensive cohort (n = 30 097). Tracking cohort participants were randomly selected from the 10 provinces and completed interviews by phone. Participants in the comprehensive cohort were randomly selected from within 25–50 km of 11 data collection sites, which are located in seven provinces(n=30,097). In addition to completing interviews in-person, the comprehensive participants completed in-depth physical assessments and provided blood and urine samples. Details on the study design have been described elsewhere.[12] Each participant is followed every three years for 20 years or until death. The first follow-up was conducted between 2015 and 2018 with a retention rate of 95%. The comprehensive data from baseline and follow-up one were included in the current analyses. This study was approved by the Hamilton integrated Research Ethics Board and by the CLSA scientific advisory board (Project ID: 1909024).

Chronic Cough definitions

Participants who self-identified as having coughed most days within the last 12 months were categorized as having a chronic cough at baseline and at follow up. Chronic cough was further classified as a productive cough if participants reported bringing up phlegm in the morning or most days during the year. Participants who did not report the presence of phlegm were categorized as having a dry cough. Questionnaires were available in both English and French.

Respiratory symptoms and chronic conditions

Self-reported presence of respiratory symptoms including chest pain, shortness of breath upon exertion, and wheezing were assessed. Participants were asked “Do you wheeze with mild to moderate exertion? Do you become short of breath climbing stairs or walking up a small hill? and “Do you get chest pain or discomfort when you walk uphill or hurry?

Disease definitions were based on self-reported physician diagnosis on direct questioning of participants by trained research assistants at baseline and at each follow-up. Participants were asked if they had ever been diagnosed with a list of respiratory, cardio-vascular, metabolic,

neurological, musculoskeletal, and mental health disorders. A history of infectious disease such as pneumonia or influenza in the last 12 months was also surveyed.

Spirometry

Lung function was measured with the TruFlow Easy-On Air Spirometer (ndd Medical Technologies, Switzerland) and categorized based on the American Thoracic Society requirements and criteria. Participants screened positive for major contra-indications were excluded.[21] The highest FEV_1 and FVC from 3 acceptable maximal efforts were selected. Only grades A and B were accepted for analysis. The forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), and the ratio of FEV_1/FVC was recorded without bronchodilator therapy.

Chronic Airflow Obstruction (CAO) was defined as a FEV1/FVC ratio of <0.7 as well as using the lower limit of normal (LLN). Age, height, and sex were used to develop a CLSA specific prediction reference values for this total population. These were based on standard allometric principles, FEV1 and FVC increase in a positively accelerating manner with height ($y=k*HeightK1$) there was a proportionate increase in males relative to females at the same height ($y=k*HeightK_1* (1+K_2*Males(1))$; and decreasing by a constant proportion with age ($y=k*HeightK_1* (1+K_2*Males(1)*(1-K_3*(Age)))$). Grade A and B spirometry data was available in 22,547 participants.

Statistical Analysis

Descriptive statistics for demographic and health variables stratified by chronic cough status were reported as means and standard errors for continuous variables and frequencies and percentages for categorical variables. The prevalence of chronic cough was assessed by age group, sex, smoking status, respiratory symptoms, FEV1% predicted categories, chronic airway obstruction, and by the presence of asthma, COPD, or both asthma and COPD. The incidence of chronic cough per 100 person years was calculated (incidence=(new cases/total follow up years)*100) in the 22,547 participants who did not report the presence of chronic cough at baseline and provided chronic cough information at follow up time (FUT). Incidence rates were stratified by the same variables used to assess the prevalence of chronic cough as well as body

mass index categories, the presence of common cardio-respiratory, vascular, gastro-intestinal, metabolic, neurological and mental health disorders.

The CLSA provided inflation weights which were used for all analyses (CLSA Sample Weight Version 1.2). The inflation weights are proportional to the reciprocal of the individual inclusion probabilities and are re-calibrated to the Canadian population within strata of sex, age, and geographic area[13]. Using the inflation weights allows the results to be generalizable to the catchment areas of the 11 data collection sites located in seven provinces (CLSA Methodology Working Group 2017). The survey analysis procedure in SAS was used to account for the stratified sampling technique. All analyses were conducted using SAS version 9.4.

RESULTS

Study Population and Demographics

The comprehensive cohort included 30,097 participants. A total of 29,972 completed the chronic cough question at baseline (Table 1) and 26,701 at follow-up. Of these, 4,739 (15.8%) participants reported chronic cough at baseline and 4,694 (17.6%) at follow up. The mean age of participants reporting cough was 61.5 years with more males than females reporting chronic cough at baseline (15.2% vs 12.7%) and at follow up (16.2% and 14.4%). The majority of participants with and without cough were overweight at baseline. The prevalence of chronic cough was greatest in the underweight (19.6%) and obese (17.0%) categories. There were 2,558 (8.5%) current smokers at baseline and participants with chronic cough had a 2-fold higher smoking pack-year history (mean 6.7 pack years vs. 13.2) with a prevalence of chronic cough of 34% in current smokers.

Differences across Canadian provinces, ethnic origin and country of birth

There were provincial differences in the prevalence of chronic cough across Canada (Table 1). Participants from Manitoba (17.1%) had the highest prevalence of chronic cough and Quebec the lowest prevalence at baseline (10.4%). Over 90% of the CLSA participants were white with smaller representation from other ethnic backgrounds. Participants from a white background

had the highest prevalence (14.0%), whilst black, South Asian, Asian, Arab ranged from 5-8%. Approximately 84% were born in Canada and the USA and along with those born in Europe and Oceania, all demonstrated a similar prevalence of approximately 14%.

Effects of ageing, sex, and smoking on the prevalence of chronic cough at baseline

The prevalence of chronic cough was greatest in current smokers ranging from 27-44% and was lower in former (7-21%) or non-smokers (6-15%) (Figure 1). The prevalence of chronic cough increased with age, was higher in males, and was highest in current smokers in both sexes across all age groups.

Chronic cough associated respiratory airways diseases, symptoms and physiology

In participants who complained of chronic cough, dry cough was reported by 51%, while 43% had cough with phlegm (6% did not report if phlegm was present or not). Participants reporting respiratory symptoms at baseline, lower FEV1% predicted, airflow obstruction (both FEV1/FVC ratio <0.7 or <LLN) or the presence of COPD, asthma or both, had a higher prevalence of chronic cough at baseline (Figure 2). A FEV1 %predicted of <50%, combined asthma and COPD or COPD alone, and wheeze had the highest prevalence. The prevalence of chronic cough in COPD was almost twice that of asthma.

Factors affecting the incidence of chronic cough

There were 26701 participants who attended for follow-up 1 (3271 lost to follow-up), and 2506 participants developed chronic cough between baseline and follow-up. The yearly incidence rate per 100 person-years of chronic cough increased from the youngest age group[45 to 54 years; 2.60 (95%C.I. 2.33-2.86)] to the oldest age group [75 to 85 years; 4.50 (4.05-4.95)], was higher in males than in females, in current smokers compared with former smokers or never smokers, and was highest in underweight and obese participants (Table 2). After adjustment for age, sex and smoking, the same patterns were observed.

Adjusted incidence rates per 100 person-years of chronic cough were highest in the presence of wheezing (7.0), combined asthma/COPD (9.2), COPD (8.0) or asthma alone (5.7), airflow obstruction [either FEV1/FVC ratio <0.7, (5.8) or <LLN, (6.2)], and lower FEV1 % predicted

(Figure 3). Adjusted incidence rates were higher in those who had a prior history of stroke (6.8), anxiety (6.2), acute myocardial infarction (6.2), pneumonia (6.4) or influenza (5.8) in the past year, mood disturbance (5.8), current depression (5.7), chronic pain (5.5), migraine (5.5), diabetes (5.5), heart failure (5.6) and history of allergies (5.2) (Figure 4). A history of stomach or intestinal ulcers, bowel disorders did not significantly increase the adjusted incidence rates.

DISCUSSION

This is the largest population based study to date describing the prevalence, incidence and characteristics of chronic cough in older adults across a whole country. About 30,000 participants were randomly selected and nearly 27,000 were followed up 3 years later. This study demonstrated a high prevalence of chronic cough at baseline and follow-up of 16% and 18% respectively in the older adult population (>45), with variations across centres located in seven provinces in Canada. Prevalence increased with age, current smoking and was highest in males, whites, and those born in Canada, USA, Europe and Oceania. The presence of co-existing respiratory symptoms, particularly wheeze, worsening FEV1% predicted, airflow obstruction, COPD and asthma were all associated with a higher prevalence. The incidence of chronic cough adjusted for age, sex and smoking status was higher with increasing age, current smokers, and being underweight or obese. Incidence rates were also highest with wheeze, FEV1 50-80% predicted, airflow obstruction, airway diseases (asthma/COPD) and a history of pneumonia or influenza in the past year. A history of cardio-vascular diseases, mental health and mood disorders, chronic pain and diabetes were all associated with a higher incidence of chronic cough.

A prevalence of 16-18% in CLSA sample is one of the highest globally. A meta-analysis of 90 studies showed global prevalence estimates to be 18% for Australia, 13% for Europe, 11% for the United States, 7% for Asia, and 2% for Africa[5]. The reasons for these large variations are unclear, but 19 different chronic cough definitions were identified. The most common definition was ‘cough ≥ 3 months’ or ‘cough ≥ 3 months for 2 successive years’ or ‘cough and phlegm ≥ 3 months for 2 consecutive years. To our knowledge, 6 studies have used the current

8 week definition: UK (12%)[14], Finland (7.2%)[15], Copenhagen (4%)[16], South Korea (2.6%)[17], Japan (2.2%)[18], Nigeria (1.1%)[19]. The CLSA recruited participants were between 45 and 85 at baseline which could have influenced the high prevalence compared to the UK, Europe and the USA.

The incidence of chronic cough is also much higher in CLSA compared with the Rotterdam study[20]. The adjusted incidence rate ranged from 3.58-5.70 per 100 person years with increasing age, which is 3-4 times the overall incidence of 1.16 from the Rotterdam study. This was despite the fact there were more current smokers in the Rotterdam study (15.5%) compared with the CLSA (8.5%) and the cohort was slightly older (67.8 vs 61.5yrs, respectively). A possible explanation for this difference is that the Rotterdam study had a 28.6% attrition rate (due to death or loss to follow-up) compared to approximately 10% in the CLSA, and the former used the chronic bronchitis definition for chronic cough.

Although speciality chronic cough clinics show female predominance by approximately 2:1[4,21,22], the same pattern is not observed in population based studies. In the current study, there were more males with prevalent chronic cough (53%), and the proportion of all males compared with females who had chronic cough was also higher (15.2% vs 12.7%). This is in contrast to the Copenhagan[16] and Rotterdam[20] studies which demonstrated a slight female predominance. In this study, after adjusting for age, sex and smoking status the incidence of chronic cough was still slightly higher in males but the magnitude of the difference was small. Interestingly, this is consistent with studies from South Korea[17] and China[21,23,24], where there is also no female predominance of chronic cough. We also speculate that the reasons for the female predominance in cough clinics and in clinical trials may be due to greater cough frequency, intensity, disruption and impact on quality of life in females than males[3,25,26]. Furthermore, socio-economic factors such as being in full-time employment or co-morbid anxiety, depression and mood disorders may influence referral to speciality clinics.

Smoking is a well-known causative factor of chronic cough[16,20,27], but the fact that former smokers and never smokers have similar prevalence of chronic cough at each age group is re-assuring and suggests smoking cessation should be the foremost target for intervention in all clinical encounters in primary and secondary care[28-30]. This study also extends the harmful

respiratory manifestations of smoking by demonstrating that airflow obstruction, COPD and a lower FEV1% predicted are all associated with a higher prevalence of chronic cough. This is consistent with findings from the Copenhagan General Population Study[31].

Canada is a large geographical country with different, often extreme climates and environmental exposures. The variations in the prevalence of chronic cough throughout the different urban centers suggests the possibility that weather, changes in temperature, and air pollution could influence chronic cough. It is well known that airway nerves responsible for cough express transient receptor (TRP) channels which are temperature sensitive[32,33], and patients in clinical practice often complain of worsening cough due to changes in temperature[34]. This neuronal dysfunction is supported by heightened and exaggerated capsaicin evoked cough responses in chronic cough, COPD and asthma[35-37]. These provincial differences require further exploration.

The majority of participants in the CLSA are white Caucasian, but there are nearly 1000 non-whites, and their prevalence is almost half of whites. Likewise, participants born in N.America/Europe/Oceania have almost double the prevalence of chronic cough. The reasons for this are unclear. Studies investigating cough reflex sensitivity have no difference between Caucasian, Indian and Chinese healthy controls[38]. There may be genetic, socio-economic, cultural or occupational exposures which are yet to be explored.

Understanding chronic cough at a population level can also provide a different perspective and may identify other associated risk factors, for example, occupational exposure to dust/fumes[16] and chronic pain[39]. This study showed many other cardio-vascular and mental health conditions that were associated with a higher incidence of chronic cough in a population. A potential common factor linking cerebrovascular accidents, hypertension, acute myocardial infarct, and diabetes is that ACE-Inhibitors are used in all these conditions and is the commonest medication to cause chronic cough as a side effect[40]. Stroke can also result in swallowing difficulties with an increased risk of aspiration. Anxiety and depression are well known associated risk factors in speciality clinics, but we have now shown this in a population based study. There may also exist a shared mechanistic pathology between chronic pain and chronic

cough where an impairment in descending inhibitory neurons has been described in both conditions[41,42]. What type of mood disorders increases the risk of chronic cough is unknown but may help in the clinical assessment and treatment of patients with chronic cough.

There are limitations to this study. Firstly, the CLSA used a 12 month definition of chronic cough rather than 8 weeks. The 8 week cut-off is arbitrary and although useful to initiate investigations for a cause, has no inherent diagnostic or prognostic value. Recent clinical trials of chronic cough have an inclusion criteria of chronic cough more than 12 months[43,44]. An amendment to the CLSA was made in 2018 to ask participants whether daily cough is >8 weeks, >1 year or >5 years. This data will be collected in future follow up visits and help to reduce any recall bias. Second, there are currently no questions on heartburn, indigestion, nasal congestion, runny nose or a physician diagnosis of gastro-esophageal reflux disease (GERD) or chronic rhinosinusitis (CRS). This does not allow identification of other potential associated conditions of chronic cough. Third, medication data such as inhaler therapy, proton pump inhibitors (PPI), nasal steroids and ACE inhibitors are currently not available to identify those with potentially refractory chronic cough (RCC). Fourth, the CLSA sample represents the population living 25 to 50 km around the 11 data collection sites across 7 provinces and hence not representative of the whole country. However, sites were across the provinces. Fifth, individuals visiting speciality clinics for chronic cough likely have more severe symptoms or are experiencing more negative outcomes than those that do not attend speciality clinics[10,21]. Thus, population based studies may not be generalizable to patients in chronic cough clinics.

Conclusions

The prevalence of chronic cough in Canada is high at 16%-18% with geographic and ethnic differences. The prevalence increases with age, is more common in males, and in current smokers. After adjusting for age, sex and smoking, the incidence of chronic cough is higher in males, increases with age, and being underweight or obese. The presence of respiratory, cardio-vascular, mental health disorders, chronic pain and diabetes were all associated with a higher incidence of chronic cough.

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Guarantor Statement: P.R. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Table 1: Demographics of Chronic Cough at Baseline

		Baseline (29972)			
		No Chronic cough		Chronic cough	
Baseline		**N=25233**	**Mean/% (SE)**	**N=4739**	**Mean/% (SE)**
Age (years)		25233	59.2 (0.04)	4739	61.5 (0.18)
	Male	12184	84.8 (0.37)	2526	15.2 (0.37)
	Female	13049	87.3 (0.31)	2213	12.7 (0.31)
Body mass index		25139	27.7 (0.04)	4701	28.6 (0.11)
BMI Category (kg/m^2)	Under Weight (<20)	171	80.4 (3.24)	42	19.6 (3.24)
	Normal (20-25)	7644	88.0 (0.41)	1190	12.0 (0.41)
	Overweight (25-30)	10221	86.7 (0.37)	1815	13.3 (0.37)
	Obese (>30)	7103	83.0 (0.49)	1654	17.0 (0.49)
Smoking Status	Never	13729	89.1 (0.30)	1953	10.9 (0.30)
	Former	9755	86.5 (0.38)	1803	13.5 (0.38)
	Current	1605	65.8 (1.17)	953	34.2 (1.17)
Smoking Packs per year		24952	6.7 (0.10)	4680	13.2 (0.35)
Provinces	Alberta	2445	85.7 (0.76)	493	14.3 (0.76)
	British Columbia	5147	84.2 (0.51)	1075	15.8 (0.51)
	Manitoba	2548	82.9 (0.75)	552	17.1 (0.75)
	Newfoundland and Labrador	1880	86.0 (0.80)	331	14.0 (0.80)
	Nova Scotia	2547	84.7 (0.70)	511	15.3 (0.70)
	Ontario	5320	84.2 (0.49)	1087	15.8 (0.49)
	Quebec	5346	89.6 (0.42)	690	10.4 (0.42)
Ethnicity	White only	22948	86.0 (0.25)	4359	14.0 (0.25)
	Black only	186	94.5 (1.58)	17	5.5 (1.58)
	Asian (East+West)	355	91.7 (1.87)	31	8.3 (1.87)
	South Asian	245	92.0 (1.84)	25	8.0 (1.84)
	Arab	79	93.0 (3.15)	8	7.0 (3.15)
	Others	1213	83.2 (1.22)	254	16.8 (1.22)
Country of Birth	Canada	20579	85.5 (0.27)	3980	14.5 (0.27)
	USA	568	86.4 (1.48)	116	13.6 (1.48)
	South, Central America and Caribbean	378	92.0 (1.49)	41	8.0 (1.49)
	Europe/Oceania	2846	86.6 (0.69)	522	13.4 (0.69)
	Africa	257	92.3 (1.71)	27	7.7 (1.71)
	Asia	601	93.2 (1.22)	52	6.8 (1.22)

Table 2: Incidence of Chronic Cough at Follow-Up 1 based on age, sex, smoking status and BMI (Unadjusted and adjusted). Mean and 95% Confidence Intervals shown.

Variable	Category	Incidence rate/100 person years	
		Unadjusted	Adjusted with age-sex and smoking
Age categories	45-54	2.60 (2.33,2.86)	3.58 (3.20,3.96)
	55-64	3.55 (3.28,3.82)	4.54 (4.17,4.92)
	65-74	4.20 (3.86,4.54)	5.32 (4.89,5.75)
	75-85	4.50 (4.05,4.95)	5.70 (5.17,6.23)
Sex	Male	3.61 (3.37,3.85)	5.09 (4.72,5.45)
	Female	3.06 (2.85,3.27)	4.48 (4.13,4.83)
Smoker	Non-Smoker	2.86 (2.66,3.06)	3.37 (3.15,3.58)
	Former Smoker	3.50 (3.25,3.76)	3.80 (3.53,4.06)
	Current Smoker	6.53 (5.65,7.42)	7.20 (6.31,8.08)
BMI (kg/m^2)	Under Weight	5.03 (1.83,8.23)	5.99 (5.97,6.01)
	Normal	2.53 (2.29,2.77)	4.09 (4.07,4.11)
	Overweight	3.41 (3.16,3.67)	4.80 (4.78,4.82)
	Obese	4.14 (3.81,4.47)	5.60 (5.55,5.65)

Figure 1: Prevalence of Chronic Cough based on Age, Sex and Smoking Status at baseline

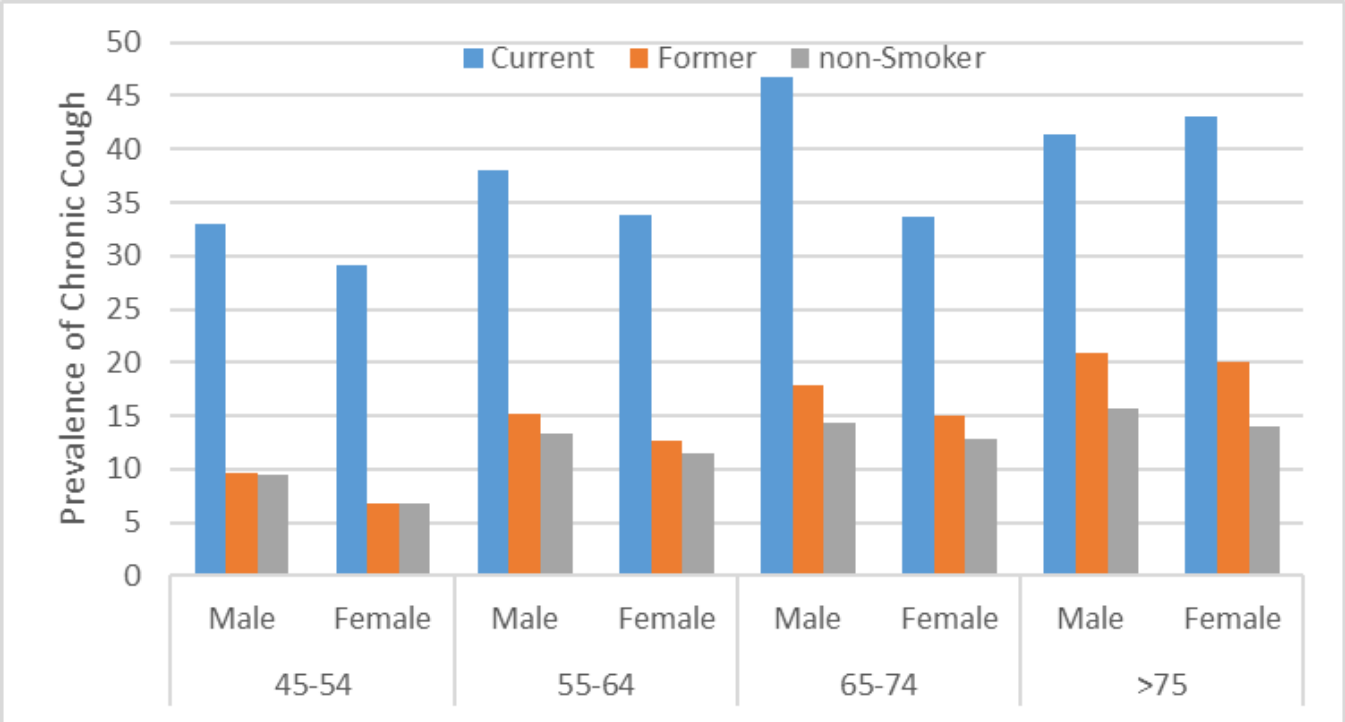


Figure 2: The associations of symptoms, lung Function, airflow obstruction and airways diseases on the prevalence of chronic cough at baseline. Mean and 95% C.I. shown. FEV1; forced expiratory volume in 1 second, CAO; chronic airflow obstruction, LLN; lower limit of normal, SOB; shortness of breath going uphill, COPD; chronic obstructive pulmonary disease.

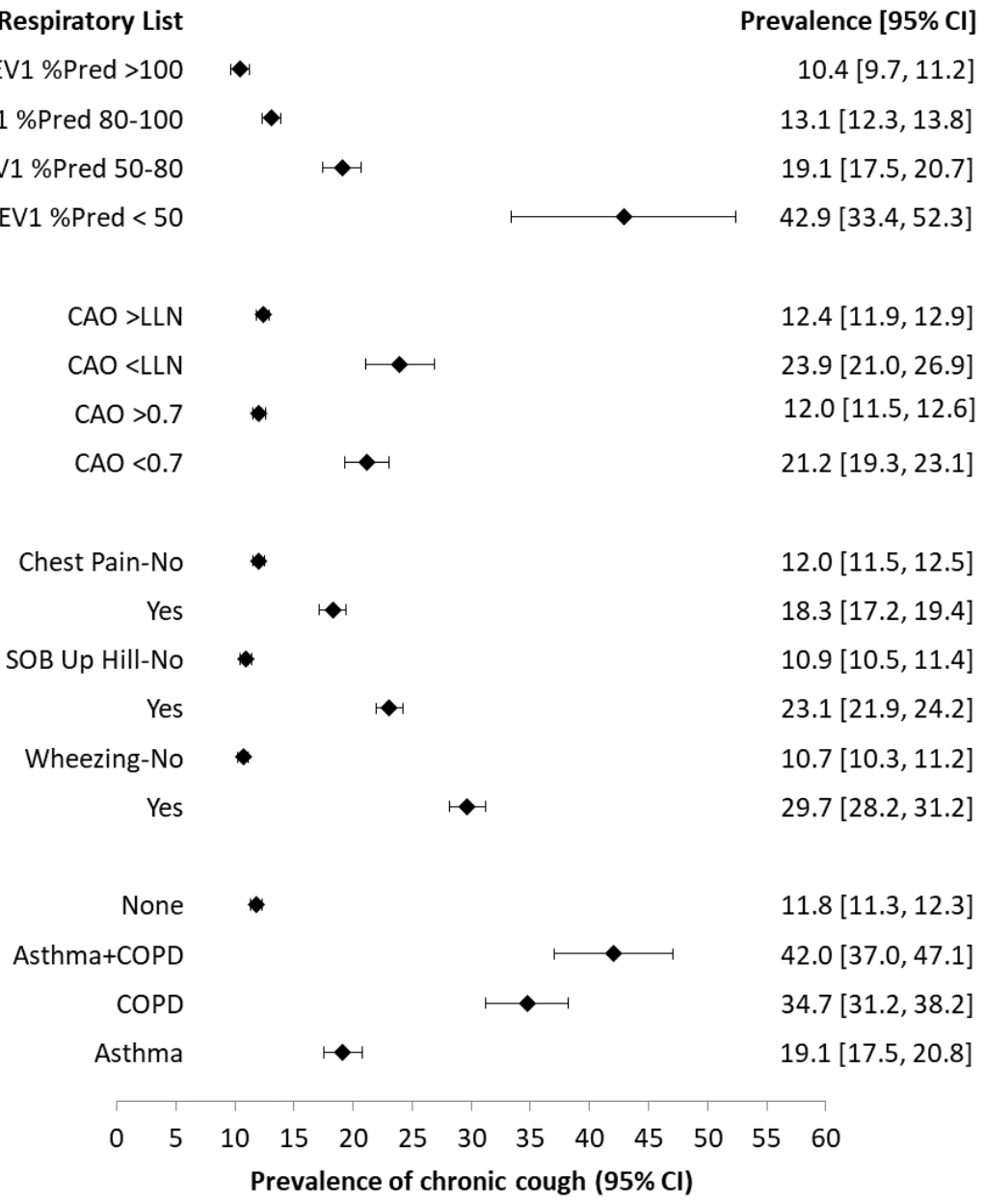


Figure 3: Adjusted (age, sex, smoking) incidence rates of chronic cough for respiratory symptoms, airways diseases, lung function, airflow obstruction. Mean and 95% C.I. shown. FEV1; forced expiratory volume in 1 second, CAO; chronic airflow obstruction, LLN; lower limit of normal, SOB; shortness of breath going uphill, COPD; chronic obstructive pulmonary disease.

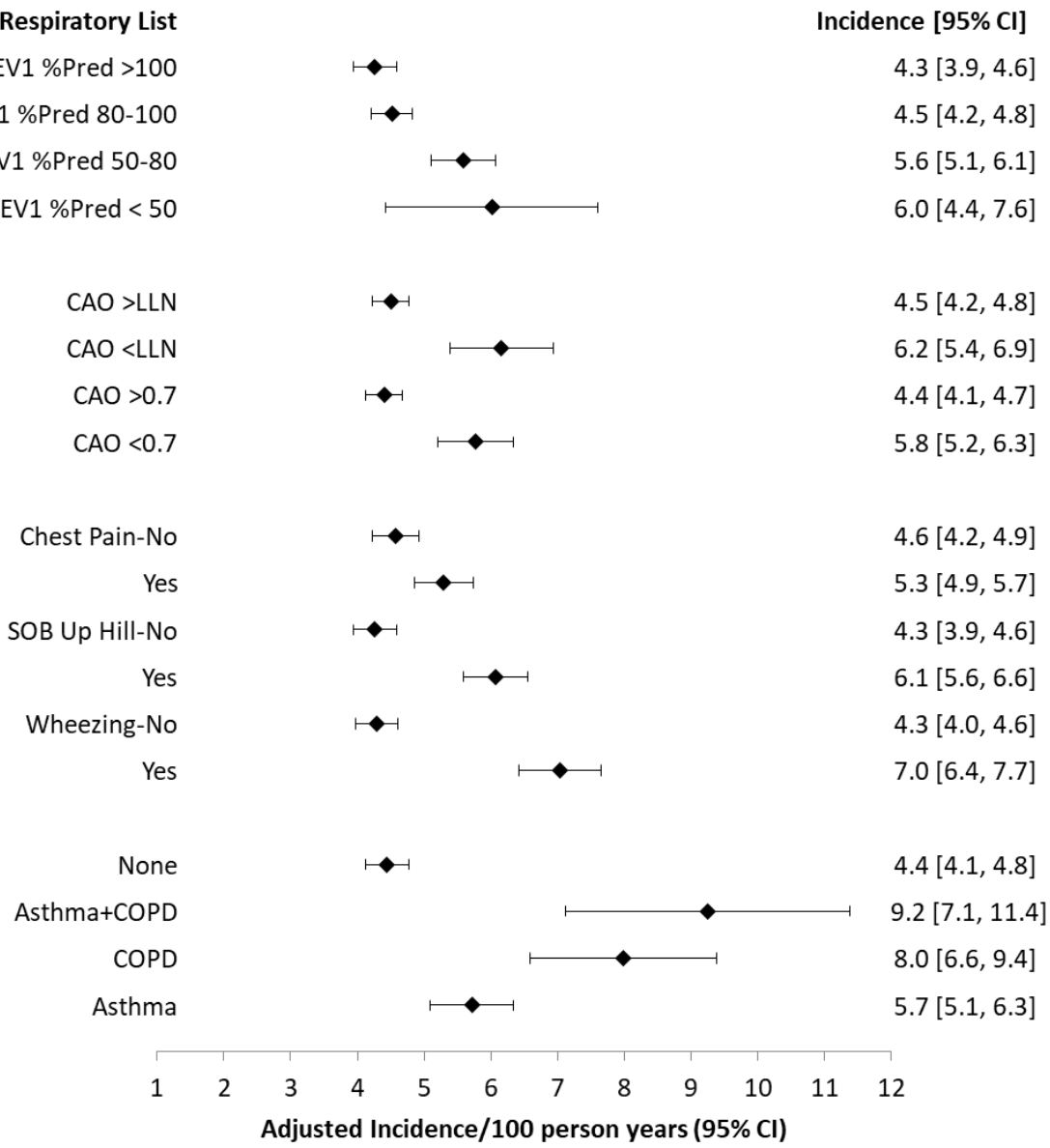
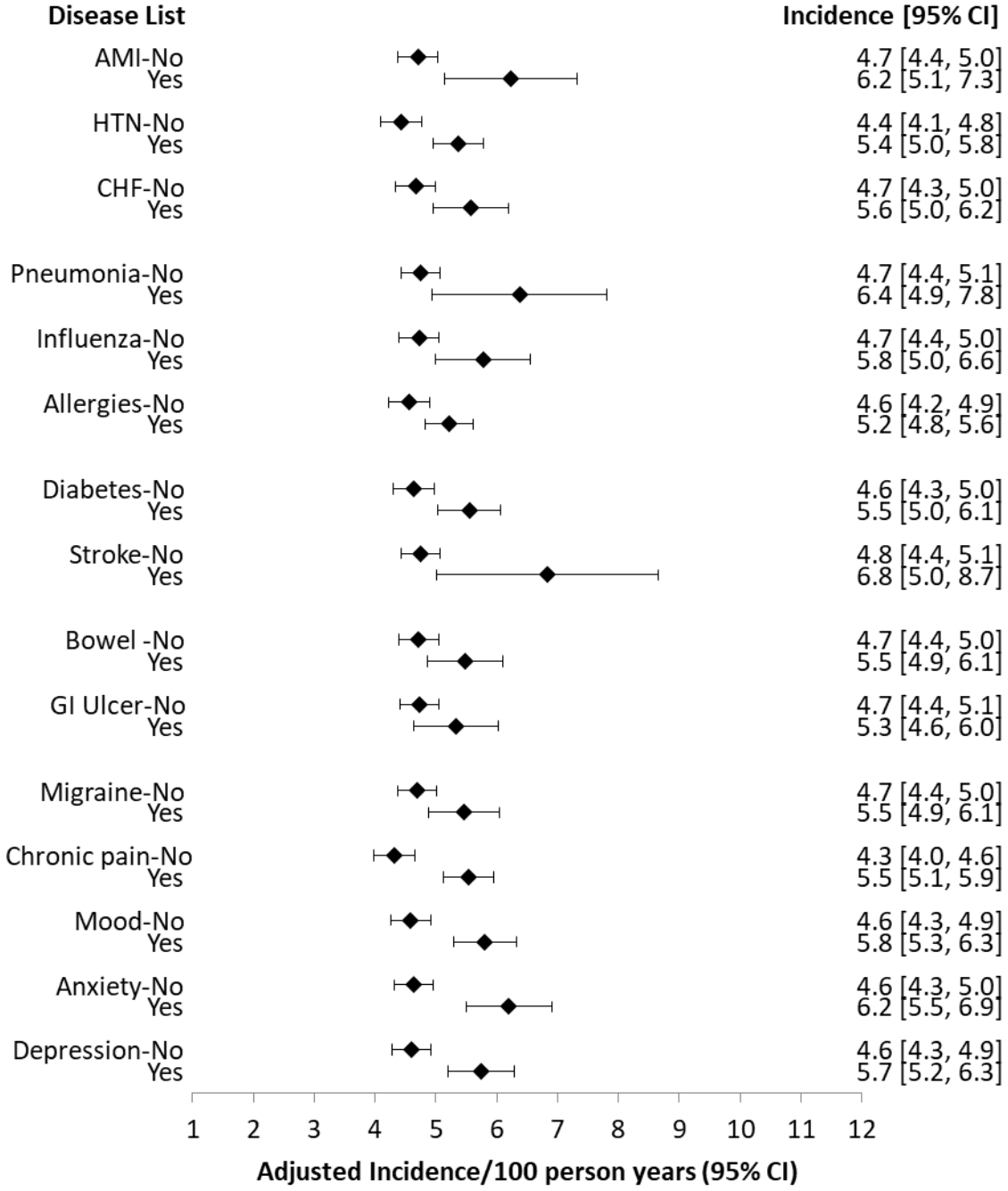


Figure 4: Adjusted (age, sex, smoking) incidence rates of chronic cough in the presence of other medical co-morbidities. Mean and 95% C.I. shown. AMI; acute myocardial infarction, HTN; hypertension, CHF; congestive heart failure, GI; gastrointestinal.



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