Prognostic significance of chronic respiratory symptoms in individuals with normal spirometry

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Chronic respiratory symptoms are associated with respiratory hospitalisations and death in individuals with normal spirometry. Persistent symptoms should lead to further investigations for airway disease even with normal spirometry. http://bit.ly/2ZnnO3T

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ABSTRACT Normal spirometry is often used to preclude airway disease in individuals with unspecific respiratory symptoms. We tested the hypothesis that chronic respiratory symptoms are associated with respiratory hospitalisations and death in individuals with normal spirometry without known airway disease.

We included 108 246 randomly chosen individuals aged 20–100 years from a Danish population-based cohort study. Normal spirometry was defined as a pre-bronchodilator forced expiratory volume in 1 s/forced vital capacity ratio ⩾0.70. Chronic respiratory symptoms included dyspnoea, chronic mucus hypersecretion, wheezing and cough. Individuals with known airway disease, *i.e.* chronic obstructive pulmonary disease and/or asthma, were excluded (n=10 291). We assessed risk of hospitalisations due to exacerbations of airway disease and pneumonia, and respiratory and all-cause mortality, from 2003 through 2018.

52 999 individuals had normal spirometry without chronic respiratory symptoms and 30 890 individuals had normal spirometry with chronic respiratory symptoms. During follow-up, we observed 1037 hospitalisations with exacerbation of airway disease, 5743 hospitalisations with pneumonia and 8750 deaths, of which 463 were due to respiratory disease. Compared with individuals with normal spirometry without chronic respiratory symptoms, multivariable adjusted hazard ratios for individuals with normal spirometry with chronic respiratory symptoms were 1.62 (95% CI 1.20–2.18) for exacerbation hospitalisations, 1.26 (95% CI 1.17–1.37) for pneumonia hospitalisations, 1.59 (95% CI 1.22–2.06) for respiratory mortality and 1.19 (95% CI 1.13–1.25) for all-cause mortality. There was a positive dose–response relationship between number of symptoms and risk of outcomes. Results were similar after 2 years of follow-up, for never-smokers alone, and for each symptom separately.

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Introduction

Chronic obstructive pulmonary disease (COPD) is characterised by the presence of chronic respiratory symptoms and airflow limitation [1], and is one of the leading causes of morbidity and mortality in the world [2]. Since pulmonary function impairment in COPD usually develops slowly over time, patients often have progressive disease before a diagnosis is suspected and confirmed [3].

It was once believed that a prodromal phase of COPD, previously designated as Global Initiative for Chronic Obstructive Lung Disease (GOLD) Stage 0, could be used to identify high-risk populations mainly among smokers [4]. GOLD Stage 0 included individuals with chronic cough and phlegm but with normal spirometry. However, GOLD recommended that GOLD Stage 0 should no longer be included in the diagnosis and management of COPD as there was incomplete evidence that individuals with GOLD Stage 0 necessarily progress to GOLD Stage 1 or beyond [5]. Nonetheless, smokers with chronic respiratory symptoms and normal spirometry constitute a significant proportion of clinical consultations and may have increased risk of airway disease [6–10]. It has been speculated that these individuals may have early stages of COPD not yet evidenced by airflow limitation or a disease resembling COPD [5, 11].

We investigated the prognostic significance of chronic respiratory symptoms in individuals with normal spirometry without known airway disease by using a Danish contemporary population-based cohort study, including 108 246 randomly selected individuals irrespective of smoking status. We tested the hypothesis that chronic respiratory symptoms are associated with respiratory hospitalisations and death in individuals with normal spirometry without known airway disease.

Methods

Study design and population

We recruited individuals aged 20–100 years from the Copenhagen General Population Study, a Danish contemporary population-based cohort study initiated in November 26, 2003, with ongoing enrolment [12]. In the present study, we included 108 246 out of 108 928 individuals with complete information on lung function recruited up to April 28, 2015. In Denmark, all individuals are assigned a unique identification number at birth or immigration and recorded in the national Danish Civil Registration System. Individuals living in the Capital Region of Denmark were randomly invited from the national Danish Civil Registration System to reflect the adult Danish population (response rate 43%). All participants completed a comprehensive questionnaire, underwent a physical health examination and provided blood for biochemical analyses. Questionnaires were reviewed on the day of attendance by a healthcare professional together with the participant. The study was approved by Herlev and Gentofte Hospital (Herlev, Denmark) and the regional ethics committee (approval H-KF-01-144/01), and was conducted according to the Declaration of Helsinki. All participants provided written informed consent.

Lung function and chronic respiratory symptoms

Pre-bronchodilator forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC) were measured at the physical health examination using spirometry. Spirometry use in the Copenhagen General Population Study has previously undergone a rigorous validation process [13]. Predicted values were calculated using internally derived reference values based on a subsample of 11 288 healthy asymptomatic never-smoking individuals with age and height as covariates separately for males and females [13]. Normal spirometry was defined as $FEV_1/FVC \geqslant 0.70$ and airflow limitation was below this cut-off. Information on chronic respiratory symptoms was obtained from the questionnaire, and included data on dyspnoea, chronic mucus hypersecretion, wheezing and cough. There was no reference to a specific time horizon of the present symptoms nor were more detailed questionnaires used to characterise and quantify symptoms. Detailed descriptions of lung function procedures and chronic respiratory symptoms can be found in the supplementary material. Individuals were subsequently assigned into one of four mutually exclusive subgroups: normal spirometry without chronic respiratory symptoms, normal spirometry with chronic respiratory symptoms, airflow limitation without chronic respiratory symptoms and airflow limitation with chronic respiratory symptoms (supplementary figure S1).

Outcomes

Hospitalisations due to exacerbations of airway disease, *i.e.* COPD and asthma (International Classification of Diseases 10th Revision (ICD-10): J41–J46), and pneumonias (ICD-10: J12–J18) included all acute emergency department visits and hospital admissions with the mentioned primary diagnosis. Information was obtained from the national Danish Patient Registry, which covers all public and private hospitals in Denmark, recorded until April 19, 2018.

Information on vital status was obtained from the national Danish Civil Registration System, which contains date of death for all individuals resident in Denmark, recorded until April 19, 2018. Information

on cause of death was obtained from the national Danish Causes of Death Registry, which contains data on causes of death for all individuals resident in Denmark, recorded until December 31, 2016. Death due to respiratory disease (ICD-10: J00–J99) was based on the underlying cause of death. Since the national Danish Causes of Death Registry lags the national Danish Civil Registration System by ∼1 year, not all deaths could be classified by cause. As follow-up was done using the aforementioned register linkage based on the unique identification number provided to everyone at birth or immigration, no person was lost to follow-up; individuals who emigrated were censored at the date of emigration (n=457). All diagnoses recorded in the registries are strictly made by a medical doctor according to national Danish laws using the World Health Organization ICD codes.

Statistical analyses

Wilcoxon rank-sum and Pearson Chi-squared tests were used for group comparisons. Cox proportional regression models were used to determine prognoses. For hospitalisations with exacerbation and pneumonia, we carried out multiple failure-time analysis using the Andersen–Gill approach [14]. Otherwise, an approach with single failure-time analysis was used. To avoid counting a single event multiple times, we chose that hospitalised individuals during follow-up had to be clinically stable for at least 4 weeks after discharge before they were at risk for a subsequent event, in accordance with previous methodological recommendations [15–17]. We used analyses with left truncation and age as the underlying timescale. Competing risk analyses to estimate cumulative incidences used the Fine–Gray method [18], with competing events being all-cause mortality and emigration. Since an approach with multiple failure-time analysis does not work using the Fine–Gray method, we instead used an approach with single failure-time analysis for hospitalisations with exacerbation and pneumonia. Kaplan–Meier analysis was used to determine cumulative incidence for all-cause mortality. Analyses were adjusted for

TABLE 1 Characteristics according to lung function and chronic respiratory symptoms in individuals in the Copenhagen General Population Study without known airway disease[#]

	$FEV_1/FVC \geqslant 0.70$		$FEV_1/FVC < 0.70$	
	No symptoms	**Symptoms**	**No symptoms**	**Symptoms**
Subjects	52 999	30 890	7076	6990
At baseline examination				
Age years	55 (47–65)	58 (48–67)[+]	66 (57–73)[+]	67 (58–75)[+]
Male	25 239 (48)	12 482 (40)[+]	3467 (49)[+]	3322 (48)
FEV_1 % pred	101 (92–109)	96 (86–105)[+]	90 (80–100)[+]	81 (68–92)[+]
FVC % pred	101 (93–110)	96 (87–106)[+]	107 (96–118)[+]	98 (84–110)[+]
FEV_1/FVC	0.79 (0.76–0.83)	0.79 (0.75–0.82)[+]	0.67 (0.63–0.69)[+]	0.66 (0.61–0.68)[+]
FEV_1/FVC <LLN	563 (1)	446 (1)[+]	5318 (75)[+]	5479 (78)[+]
Current smoker	5663 (11)	6926 (22)[+]	1344 (19)[+]	2570 (37)[+]
Ex-smoker	20 869 (39)	12 322 (40)	3262 (46)[+]	3021 (43)[+]
Tobacco consumption pack-years[¶]	11.3 (4.5–22.5)	18.0 (7.5–31.8)[+]	19.1 (8.0–33.6)[+]	30.0 (15.0–44.2)[+]
Occupational exposure	3462 (7)	4149 (13)[+]	481 (7)	1069 (15)[+]
Environmental tobacco smoke	7768 (15)	6483 (21)[+]	859 (12)[+]	1231 (18)[+]
Fever or infection within the past 4 weeks	1287 (2)	1539 (5)[+]	188 (3)	397 (6)[+]
Body mass index $kg \cdot m^{-2}$	25.0 (22.8–27.5)	26.9 (24.2–30.3)[+]	24.5 (22.5–26.8)[+]	25.6 (23.2–28.6)[+]
Plasma cholesterol $mmol \cdot L^{-1}$	5.5 (4.8–6.2)	5.6 (4.9–6.3)[+]	5.6 (4.9–6.3)[+]	5.5 (4.8–6.3)
Systolic blood pressure mmHg	138 (125–153)	140 (127–155)[+]	143 (129–159)[+]	144 (130–160)[+]
Diastolic blood pressure mmHg	84 (76–91)	84 (77–92)[+]	84 (76–91)	84 (76–91)
Alcohol $units \cdot week^{-1}$	8 (4–14)	7 (3–15)[+]	9 (4–16)[+]	9 (3–17)[+]
Cardiovascular disease	3534 (7)	4030 (13)[+]	850 (12)[+]	1407 (20)[+]
Diabetes	1572 (3)	1711 (6)[+]	277 (4)[+]	446 (6)[+]
Cancer	2968 (6)	2163 (7)[+]	611 (9)[+]	834 (12)[+]
During follow-up				
Exacerbation hospitalisations	129 (<1)	280 (1)	112 (2)	516 (7)
Pneumonia hospitalisations	1908 (4)	2071 (7)	577 (8)	1187 (17)
Respiratory deaths	94 (<1)	163 (<1)	56 (<1)	150 (2)
Deaths	3009 (6)	3254 (11)	897 (13)	1590 (23)

Data are presented as n, median (interquartile range) or n (%). FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; LLN: lower limit of normal. [#]: symptoms included dyspnoea, chronic mucus hypersecretion, wheezing and cough; [¶]: only for current smokers and ex-smokers; [+]: $p<0.05$ for comparison with individuals with $FEV_1/FVC \geqslant 0.70$ and no symptoms at baseline examination, obtained from Wilcoxon rank-sum or Pearson Chi-squared tests.

potential confounders of pulmonary and nonpulmonary diseases obtained at the baseline examination, including age (as timescale), sex, smoking status, cumulative tobacco consumption, FEV_1 % pred, occupational exposure, environmental tobacco smoke, fever or infection within the past 4 weeks, body mass index, plasma cholesterol, blood pressure, alcohol consumption, cardiovascular disease (ischaemic heart disease, stroke, heart failure and atrial fibrillation), diabetes and cancer (including, among others, lung cancer). Detailed descriptions of potential confounders can be found in the supplementary material. Some individuals lacked information on some of the potential confounders and we performed multivariate imputation using chained equations to fill out missing values; however, results were similar without imputation. Analyses were performed using Stata/SE version 13.1 for Windows (StataCorp, College Station, TX, USA) and a two-sided p-value <0.05 was considered significant.

Results

Among 108 246 individuals from the Copenhagen General Population Study, 10 291 (10%) were excluded due to known airway disease, *i.e.* COPD and/or asthma, based on previous inpatient and outpatient hospital contacts obtained from the national Danish Patient Registry and/or self-reported disease and treatment with airway medication (supplementary figure S1). Among the remaining 97 955 individuals, 52 999 (54%) had normal spirometry without chronic respiratory symptoms, 30 890 (32%) had normal spirometry with chronic respiratory symptoms, 7076 (7%) had airflow limitation without chronic respiratory symptoms and 6990 (7%) had airflow limitation with chronic respiratory symptoms.

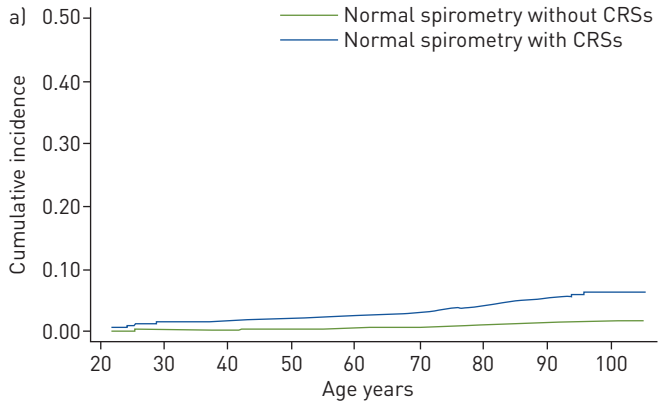
Clinical characteristics

Compared with individuals with normal spirometry and without chronic respiratory symptoms, individuals with chronic respiratory symptoms and/or airflow limitation were older, had lower lung function, were more often smokers with a higher tobacco consumption and more often had nonpulmonary diseases (table 1 and supplementary table S1). Furthermore, these individuals had greater healthcare use with frequent episodes of acute bronchitis and/or pneumonia and visits to the physician's office (supplementary table S2). Among individuals with chronic respiratory symptoms, dyspnoea and wheezing were the most prevalent symptoms, and the distribution of symptoms was comparable between individuals with normal spirometry and those with airflow limitation (supplementary table S1). Excluded individuals with known airway disease had lower lung function and higher prevalence of symptoms compared with those without known airway disease, otherwise there were no overall differences in clinical characteristics (supplementary tables S3 and S4).

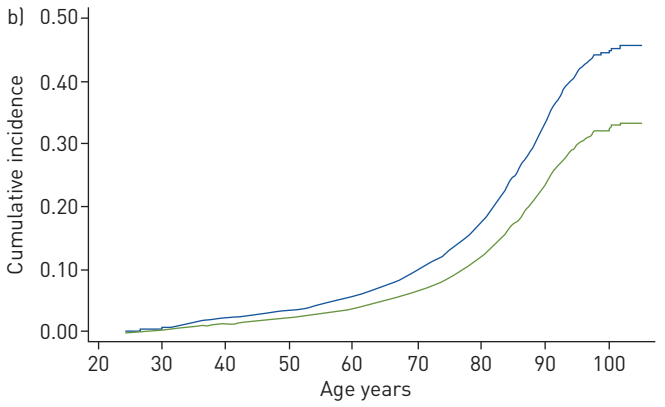
Chronic respiratory symptoms and prognosis

During a median follow-up time of 8.8 years (range up to 14.4 years), we observed 1037 hospitalisations due to exacerbation, 5743 hospitalisations due to pneumonia and 8750 deaths, of which 463 were due to respiratory disease (table 1). Among individuals with normal spirometry, those with chronic respiratory symptoms compared with those without had an increased risk of hospitalisations due to exacerbation and pneumonia, and of respiratory and all-cause mortality, including in competing risk analyses and after adjustment for potential confounders of pulmonary and nonpulmonary diseases (figures 1 and 2, and supplementary figure S2). Risk estimates were attenuated after adjustment for potential confounders of pulmonary rather than nonpulmonary diseases (figure 2 and supplementary figure S3). Compared with individuals with normal spirometry without chronic respiratory symptoms, fully adjusted hazard ratios for individuals with normal spirometry with chronic respiratory symptoms were 1.62 (95% CI 1.20–2.18) for hospitalisations due to exacerbation, 1.26 (95% CI 1.17–1.37) for hospitalisations due to pneumonia, 1.59 (95% CI 1.22–2.06) for respiratory mortality and 1.19 (95% CI 1.13–1.25) for all-cause mortality (figure 2, right panel). Increased risks could already be observed after 2 years of follow-up, and risk estimates seemed robust throughout the whole follow-up period (figure 3). Results were similar in never-smokers and ever-smokers separately; however, the risk estimate was reduced and overlapped with 1 in never-smokers for risk of respiratory mortality due to the small number of events (figure 4). All types of chronic respiratory symptoms were associated with all outcomes with comparable risk estimates in individuals with normal spirometry (figure 5). There was also a clear dose–response relationship with number of chronic respiratory symptoms, *i.e.* higher risk estimates with higher number of symptoms (figure 5). Results were similar after exclusion of individuals with interstitial lung disease from the analyses (supplementary figure S4). Results were also similar after inclusion of individuals with known airway disease in the analyses (supplementary figure S5) and also when adjusting for type of spirometer during the survey (supplementary figure S6).

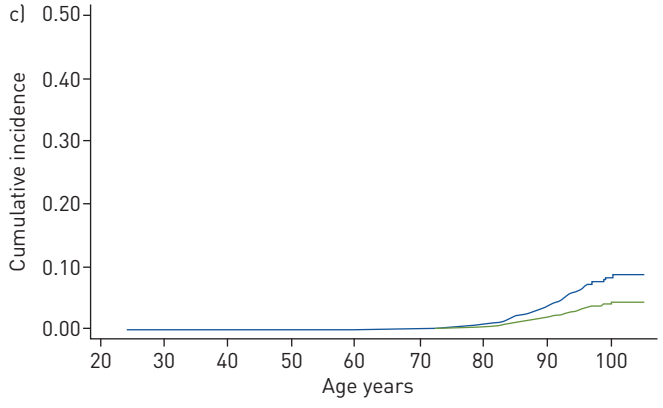
Individuals with airflow limitation had increased risk of respiratory hospitalisations and death compared with individuals with normal spirometry and without chronic respiratory symptoms; however, after adjustment for potential confounders, those without symptoms only had increased risk of hospitalisations



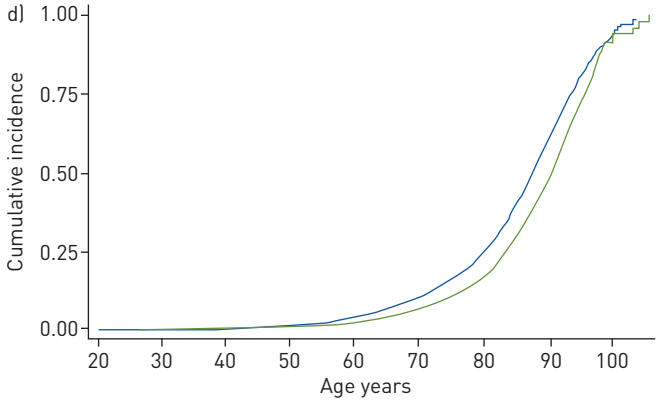
	Individuals n/ events n	SHR (95% CI)	p-value
Normal spirometry without CRSs	52 999/97	1 (reference)	
Normal spirometry with CRSs	30 890/203	3.21 (2.52–4.09)	<0.001



	Individuals n/ events n	SHR (95% CI)	p-value
Normal spirometry without CRSs	52 999/1604	1 (reference)	
Normal spirometry with CRSs	30 890/1713	1.50 (1.40–1.61)	<0.001



	Individuals n/ events n	SHR (95% CI)	p-value
Normal spirometry without CRSs	52 999/94	1 (reference)	
Normal spirometry with CRSs	30 890/163	2.04 (1.57–2.64)	<0.001



	Individuals n/ events n	HR (95% CI)	p-value
Normal spirometry without CRSs	52 999/3009	1 (reference)	
Normal spirometry with CRSs	30 890/3254	1.43 (1.36–1.50)	<0.001

FIGURE 1 Cumulative incidence and risk of a) hospitalisations due to exacerbation, b) hospitalisations due to pneumonia, c) respiratory mortality and d) all-cause mortality according to chronic respiratory symptoms (CRSs) in individuals with normal spirometry without known airway disease. SHR: subhazard ratio; HR: hazard ratio. Symptoms included dyspnoea, chronic mucus hypersecretion, wheezing and cough. For a) hospitalisations due to exacerbation, b) hospitalisations due to pneumonia and c) respiratory mortality, cumulative incidences and SHRs with 95% confidence intervals were obtained from competing risk analyses using the Fine–Gray regression model, with competing events being all-cause mortality and emigration. For d) all-cause mortality, cumulative incidences were obtained from Kaplan–Meier analysis and HRs with 95% confidence intervals were obtained from the Cox proportional regression model. p-values were from Wald's test. Analyses were automatically adjusted for age by using left truncation with age as the underlying timescale.

due to exacerbation, whereas those with symptoms still had increased risk of hospitalisations due to exacerbation and pneumonia, and of death due to respiratory disease (figure 2).

Discussion

In a large sample from a Danish contemporary population-based cohort study, we investigated the prognostic significance of chronic respiratory symptoms in individuals with normal spirometry without known airway disease. We found that chronic respiratory symptoms are associated with respiratory hospitalisations and death in individuals with normal spirometry without known airway disease. These are novel findings.

Among individuals with normal spirometry without known airway disease, 32% were reported to have chronic respiratory symptoms. Even after adjustment for pulmonary and nonpulmonary disease-related risk factors, these individuals still had an increased risk of exacerbation of airway disease, pneumonia and

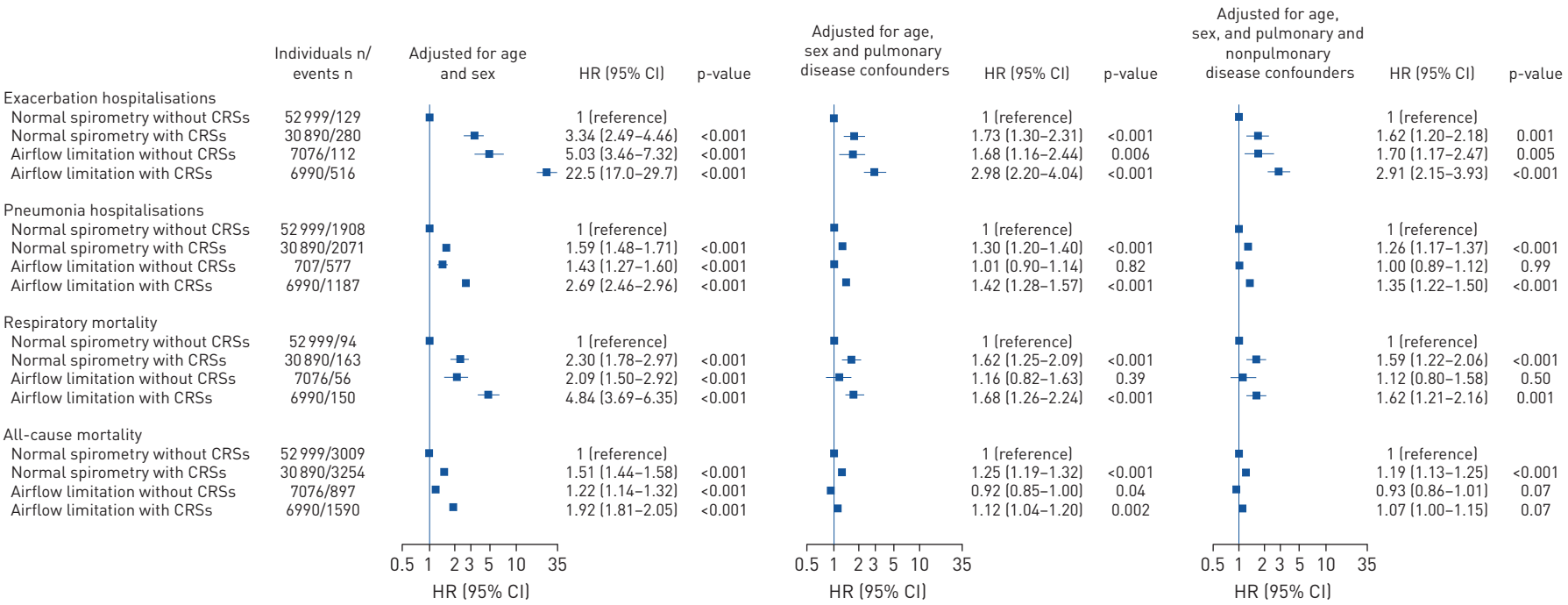


FIGURE 2 Risk of hospitalisations due to exacerbation, hospitalisations due to pneumonia, respiratory mortality and all-cause mortality according to lung function and chronic respiratory symptoms (CRSs) in individuals without known airway disease. HR: hazard ratio. Symptoms included dyspnoea, chronic mucus hypersecretion, wheezing and cough. HRs with 95% confidence intervals were obtained from the Cox proportional regression model. p-values were from Wald's test. Analyses were automatically adjusted for age by using left truncation with age as the underlying timescale. Pulmonary disease-related confounders included smoking status, cumulative tobacco consumption, forced expiratory volume in 1 s % pred, occupational exposure and environmental tobacco smoke. Nonpulmonary disease-related confounders included smoking status, cumulative tobacco consumption, fever or infection within the past 4 weeks, body mass index, plasma cholesterol, blood pressure, alcohol consumption, cardiovascular disease (ischaemic heart disease, stroke, heart failure and atrial fibrillation), diabetes and cancer.

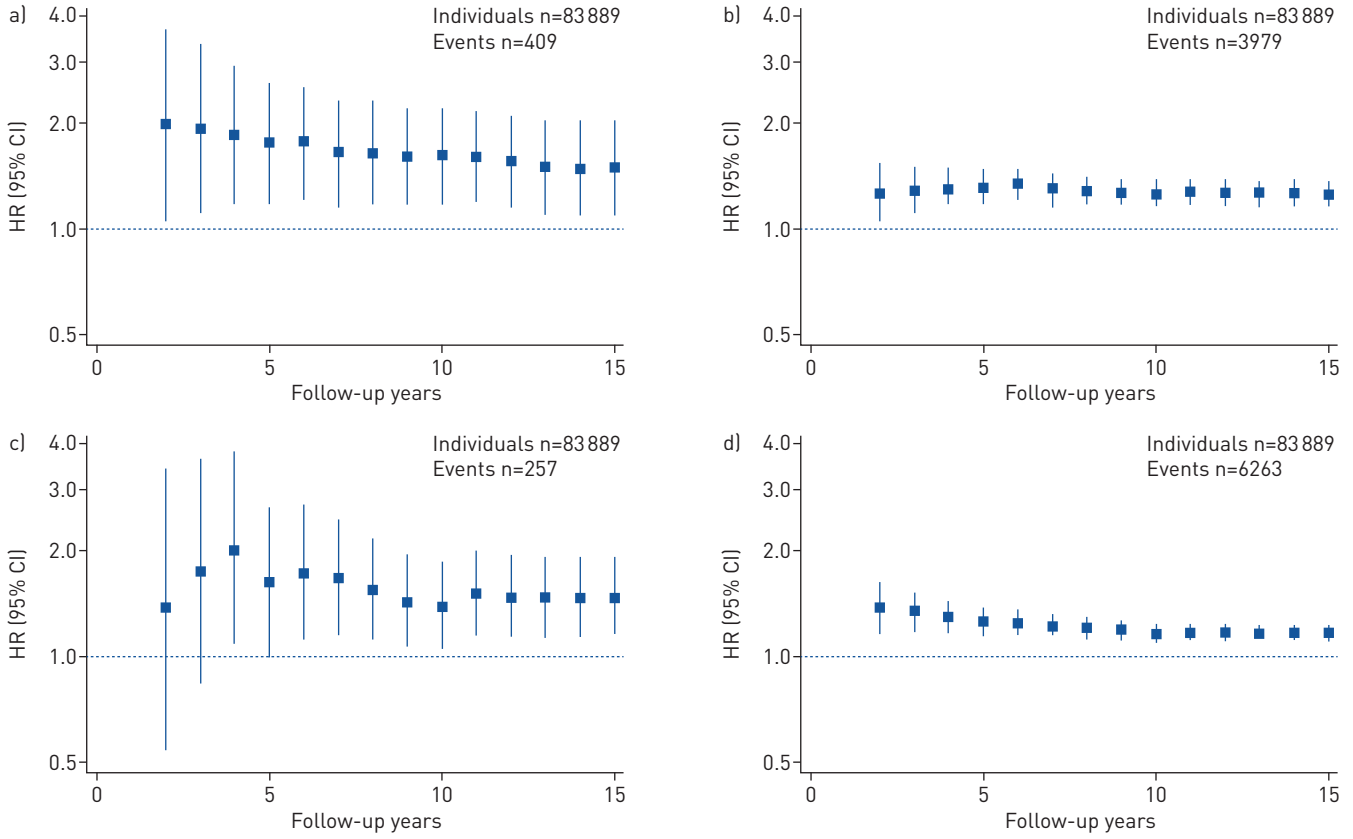


FIGURE 3 Follow-up time and risk of a) hospitalisations due to exacerbation, b) hospitalisations due to pneumonia, c) respiratory mortality and d) all-cause mortality according to with *versus* without chronic respiratory symptoms in individuals with normal spirometry without known airway disease. HR: hazard ratio. Symptoms included dyspnoea, chronic mucus hypersecretion, wheezing and cough. HRs with 95% confidence intervals were obtained from the Cox proportional regression model. Analyses were adjusted for age (not as timescale), sex, and pulmonary and nonpulmonary disease-related confounders, including smoking status, cumulative tobacco consumption, forced expiratory volume in 1 s % pred, occupational exposure, environmental tobacco smoke, fever or infection within the past 4 weeks, body mass index, plasma cholesterol, blood pressure, alcohol consumption, cardiovascular disease (ischaemic heart disease, stroke, heart failure and atrial fibrillation), diabetes and cancer.

death, including deaths from respiratory disease. Although the prognosis of this group resembles that for COPD, increased risks could already be observed after 2 years of follow-up. Thus, it is unlikely that these individuals during this short follow-up time developed airflow limitation, even though respiratory symptoms are associated with increased lung function decline and development of chronic airflow limitation [19–28]. It is therefore debatable whether we are observing true exacerbations or merely exacerbation-like respiratory complications [29, 30]. Nonetheless, other studies suggest that individuals with normal spirometry and chronic respiratory symptoms seem to have evidence of airway disease, including increased airway wall thickness, pulmonary emphysema, gas trapping and abnormal diffusing capacity [6, 8, 31–35], which are well-known clinical characteristics of COPD. Therefore, it has been speculated whether these individuals have early COPD not yet evidenced by airflow limitation [5, 11]. However, it seems that only a small proportion of such individuals progress over time from having chronic respiratory symptoms alone to comorbid chronic airflow limitation [27]. Whether COPD should be redefined and include other diagnostic criteria besides chronic airflow limitation or whether these individuals have another presently undefined disease seems to elude consensus [5]. In addition, by only including pre-bronchodilator FEV_1 and FVC, we will likely overlook individuals with a certain degree of reversibility in lung function despite absence of airflow limitation. Thus, it could be speculated that some of these symptomatic individuals with normal spirometry have reversibility, *i.e.* undiagnosed asthma. However, based on previous analyses of individuals with COPD or asthma in the same cohort [12, 36], the pattern of prognosis we observe is more akin to COPD than asthma.

Interestingly, we found similar results for analyses restricted to never-smokers, suggesting that we are not only observing some form of smoking-related disease. Recently, it was shown that approximately half of the cases with COPD develop through a trajectory with accelerated lung function decline, while the other half follows a trajectory with low maximal attained lung function in early adulthood [3]. Surprisingly, 74%

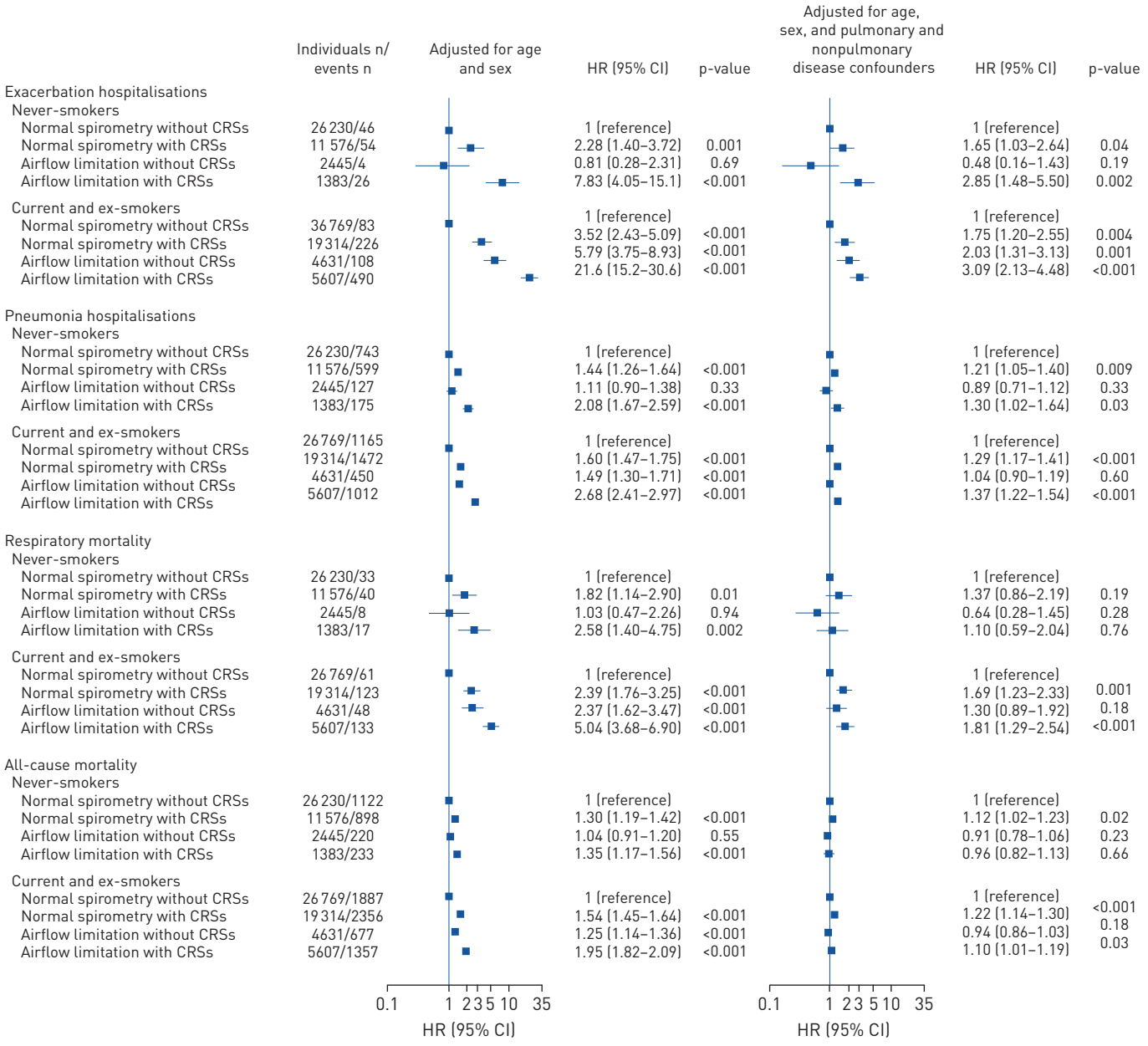


FIGURE 4 Smoking habits and risk of hospitalisations due to exacerbation, hospitalisations due to pneumonia, respiratory mortality and all-cause mortality according to lung function and chronic respiratory symptoms (CRSs) in individuals without known airway disease. HR: hazard ratio. Symptoms included dyspnoea, chronic mucus hypersecretion, wheezing and cough. HRs with 95% confidence intervals were obtained from the Cox proportional regression model. p-values were from Wald's test. Analyses were automatically adjusted for age by using left truncation with age as the underlying timescale. Pulmonary and nonpulmonary disease-related confounders included smoking status, cumulative tobacco consumption, forced expiratory volume in 1 s % pred, occupational exposure, environmental tobacco smoke, fever or infection within the past 4 weeks, body mass index, plasma cholesterol, blood pressure, alcohol consumption, cardiovascular disease (ischaemic heart disease, stroke, heart failure and atrial fibrillation), diabetes and cancer.

of never-smokers with COPD follow the latter trajectory. Additionally, while never-smokers with COPD have milder disease compared with smokers with COPD, they still have a poor prognosis with an increased risk of exacerbation and pneumonia [37]. Thus, our findings indicate that symptomatic never-smokers with normal spirometry could have either early COPD or another underlying respiratory disease.

Previous studies have also reported exacerbation-like events in individuals with normal spirometry [7–10]. In a selected cohort of current smokers and ex-smokers, those reporting severe symptoms compared with those reporting mild symptoms had an increased risk of COPD-related exacerbations among individuals with normal spirometry [6]. In addition, symptoms, primarily in the form of chronic cough and phlegm,

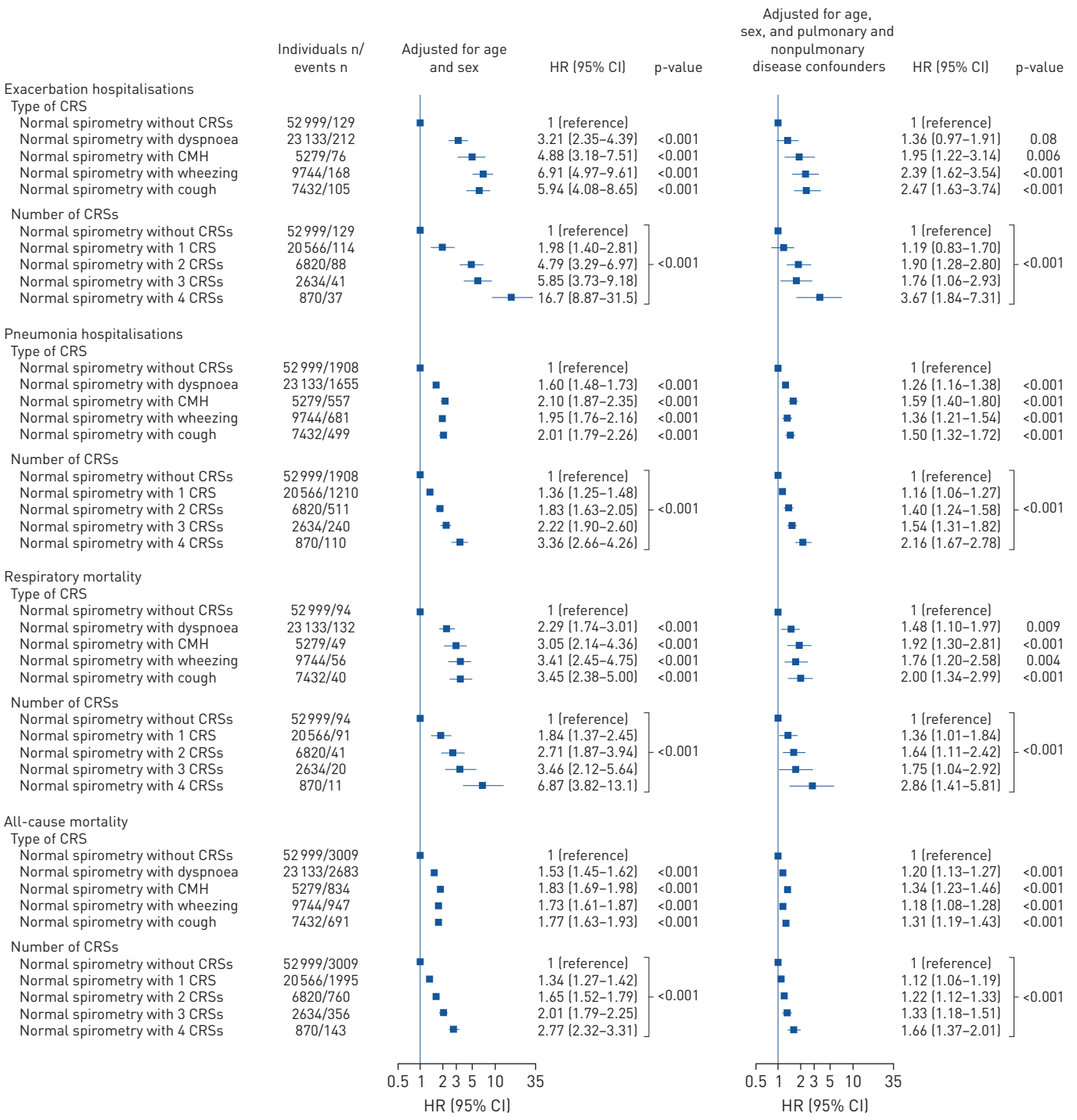


FIGURE 5 Risk of hospitalisations due to exacerbation, hospitalisations due to pneumonia, respiratory mortality and all-cause mortality according to type and number of chronic respiratory symptoms (CRSs) in individuals with normal spirometry without known airway disease. HR: hazard ratio. Symptoms included dyspnoea, chronic mucus hypersecretion (CMH), wheezing and cough. HRs with 95% confidence intervals were obtained from the Cox proportional regression model. p-values were from Wald's test. Analyses were automatically adjusted for age by using left truncation with age as the underlying timescale. Pulmonary and nonpulmonary disease-related confounders included smoking status, cumulative tobacco consumption, forced expiratory volume in 1 s % pred, occupational exposure, environmental tobacco smoke, fever or infection within the past 4 weeks, body mass index, plasma cholesterol, blood pressure, alcohol consumption, cardiovascular disease (ischaemic heart disease, stroke, heart failure and atrial fibrillation) diabetes and cancer.

have been associated with increased risk of death in individuals with normal spirometry [38–42]. In contrast to most of these previous studies that have mainly focused on smokers or populations selected on other criteria, we investigated the prognostic significance of chronic respiratory symptoms in a general

population setting. We likewise observed an increased risk of respiratory hospitalisations and death despite taking pulmonary and nonpulmonary diseases into account in symptomatic individuals with normal spirometry without known airway disease. Increased risks could already be observed during the first 2 years of follow-up, for never-smokers alone, for each symptom separately, and with a clear positive dose–response relationship between number of symptoms and risk.

Strengths of the present study include a large contemporary population-based cohort study with randomly selected individuals with a long and complete follow-up, and information on clinically relevant outcomes. Furthermore, we had information on pulmonary and nonpulmonary disease with related risk factors.

A potential limitation of the present study is that we only have information on lung function and chronic respiratory symptoms at the baseline examination, and not during follow-up; however, since the increased risks could already be observed after a short follow-up time for all clinical outcomes, we believe that this information would be of minor relevance to the aim of this study. Another potential limitation is that the available chronic respiratory symptoms are somewhat nonspecific and could reflect nonrespiratory disease. However, the present study also reflects a true clinical setting, where patients seek medical assistance with nonspecific symptomatology. Nonetheless, all types of symptoms were associated with all respiratory outcomes with comparable risk estimates in separate analyses. In addition, results were similar when adjusting for nonpulmonary diseases, including cardiovascular disease, diabetes and cancer. Another potential limitation is that we were unable to determine symptom severity and thereby disease severity. It seems unlikely that we have missed individuals with substantial symptoms, but more likely that we have included more individuals with mild symptoms due to the setting. Nonetheless, individuals with mild symptoms will only dilute an association and attenuate the risk estimates, and therefore cannot explain our observations. Furthermore, there was a clear positive dose–response relationship with all outcomes according to number of symptoms. Lastly, another potential limitation is that although ICD codes are reported by a medical doctor, there will inevitably be misclassification. However, this type of misclassification is likely to be nondifferential and would bias towards the null, and therefore cannot explain our positive results.

Clinical implications of the present study relate to diagnosis and treatment of airway disease in general practice. Normal spirometry alone in symptomatic individuals is not sufficient to preclude airway disease. We suggest that these individuals should be reassessed within a short time period, and if symptoms persist they should be offered further investigations for airway disease and, if relevant, also effective treatment options for smoking cessation. Future studies should investigate what type of treatment should be offered to these individuals.

In conclusion, chronic respiratory symptoms are associated with respiratory hospitalisations and death in individuals with normal spirometry without known airway disease.

Author contributions: Y. Çolak and S. Afzal had full access to all data in the study and had final responsibility for the decision to submit for publication. Y. Çolak, B.G. Nordestgaard, J. Vestbo, P. Lange and S. Afzal contributed to the study concept and design. Y. Çolak, B.G. Nordestgaard, J. Vestbo, P. Lange and S. Afzal collected, analysed or interpreted the data. Y. Çolak wrote the draft manuscript. Y. Çolak, B.G. Nordestgaard, J. Vestbo, P. Lange and S. Afzal revised the manuscript for important intellectual content. Y. Çolak did the statistical analyses. B.G. Nordestgaard obtained funding. B.G. Nordestgaard provided administrative, technical or material support. S. Afzal supervised the study.

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