BRN Reviews REVIEW

The Copenhagen City Heart Study Experience and its Key Contributions to Chronic Obstructive Pulmonary Disease

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ABSTRACT

Although the principal aim of the Copenhagen City Heart Study (CCHS) was to investigate risk factors for ischaemic heart disease, it already started including spirometry and a questionnaire on respiratory symptoms from its start in 1976. Longitudinal design including five examination rounds and follow-up of hospitalisations, mortality and medically treated exacerbations of chronic obstructive pulmonary disease (COPD) gave a great opportunity to study different aspects of the natural history of COPD. Since 1988, more than 100 papers on different aspects of obstructive lung diseases have been published. Among the most quoted are publications on lung function decline in asthma, trajectories leading to COPD, analyses describing positive association between physical activity and COPD, role of nutritional status for prognosis of COPD, and a nested intervention study showing no effect of an inhaled corticosteroid (ICS) on lung function decline among individuals with mild COPD. The present review describes some of these studies. **(BRN Rev. 2018;4(4):231-44)**

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Key words: Asthma. Chronic obstructive pulmonary disease. Epidemiology. Natural history.

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Received in original form: 28-04-2018
Accepted in final form: 30-05-2018
DOI: 10.23866/BRNRev:2017-0022

BACKGROUND

In the 1980s, COPD epidemiology in Denmark, the rest of the Nordic countries and Europe in general, was heavily influenced by the findings by Fletcher et al.[1,2] in their study of London postal workers. Although several cohort studies from England and the United States (US) had improved our understanding of chronic lung disease[3-6], they had mainly stimulated prevalence studies and analyses of cross-sectional data. With the seminal findings by Fletcher et al.[1,2], exploring longitudinal changes in lung function, the focus on assessing longitudinal decline in forced expiratory volume in one second (FEV_1) as a marker of development of airflow limitation and subsequent disease progression, enabled the study of risk factors and modifiers for an excess decline in lung function, primarily FEV_1. This of course required longitudinal assessment of lung function, but a number of cohort studies in the Nordic countries had been set up in the late 1960s and early 1970s, mainly inspired by the Framingham study[7], and among these was the Copenhagen City Heart Study (CCHS)[8]. Other cohorts in Europe and the US had been set up around the same time, the most prominent of which are listed in a review by Kohansal et al.[9].

THE COPENHAGEN STUDY

The original aim of the CCHS was to investigate the distribution of cardiovascular disease in the general population of Copenhagen and the risk factors for the incidence of heart disease and other chronic conditions. In contrast to earlier studies, the majority of the invited participants were women. The funds for the first study were provided by The Danish Heart Association, and the leading physician Anders Tybjærg Hansen, who was Professor of Cardiology at the University of Copenhagen during the 1970s, recruited two younger cardiologists, Peter Schnohr and Gorm Jensen, and a statistician, Jørgen Nyboe, to the steering committee. Initially, there were no plans to include lung function testing. However, as the study happened to take part in rooms right next to the hospital's physiology laboratory, the Danish respiratory physiologist Johan Georg suggested the cardiologists to include spirometry as one of the tests. It was accepted, and the foundation for respiratory epidemiology in Copenhagen was laid. It was taken up by another physiologist, Steffen Groth, and Peter Lange who ensured the inclusion of spirometry at subsequent visits.

For the first examination round, which was conducted from 1976 to 1978, a sample of 19,698 subjects, aged 20 years or older and living in the part of Copenhagen surrounding the Copenhagen University Hospital (Rigshospitalet), was selected at random from the national Danish Civil Registration System, after age stratification in 5-year age groups. In total, 14,223 subjects participated in the initial survey (response rate 81%). They were all re-invited to participate in later surveys along with additional subjects in the youngest age groups. The number of participants in the second survey was 12,923, in the third 10,135, 6237 in the fourth examination and, finally, 4466 in the fifth and most recent survey (Fig. 1).

Although the main focus was on cardiovascular risk factors, the first examination already included spirometry, as the Framingham Heart study suggested that reduced vital

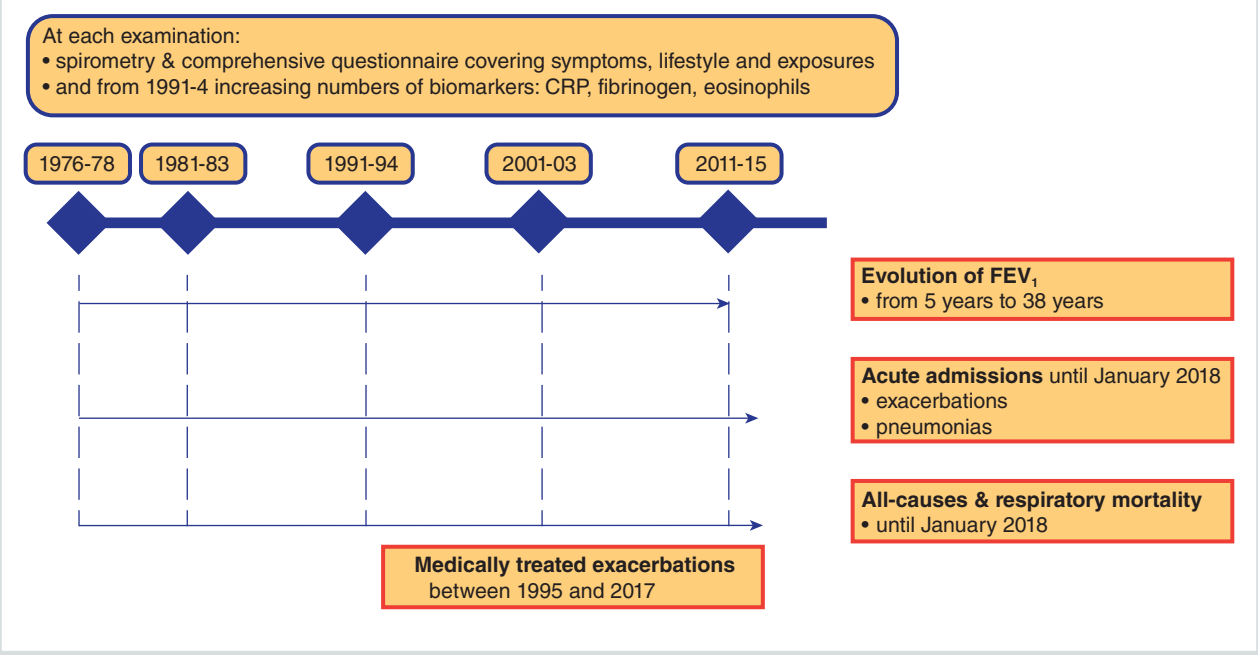

Figure 1. Flow chart of The Copenhagen City Heart Study.
CRP: C-reactive protein; FEV_1: forced expiratory volume in one second.

capacity may be a predictor for heart failure and perhaps also for ischaemic heart disease[10]. Thus, spirometry was performed at all examinations of the CCHS: pre-bronchodilator measurements only in the first, second, fourth and fifth examination, whereas post-bronchodilator values were additionally obtained in the third examination in the subgroup of participants with FEV_1/forced vital capacity (FVC) < 0.7. At the initiation of the study, smoking prevalence in Copenhagen in both men and women was more than 50% and the participants answered a detailed questionnaire on their smoking habits, including the type of tobacco smoked (cigarettes, cheroots, cigars and pipe) and whether they inhaled or not. In addition, the questionnaire included information on asthma and chronic bronchitis. During the evolution of the study, the respiratory questionnaire was expanded to include an increasing number of respiratory symptoms and questions on recurrent respiratory infections. The participants also gave blood for various analyses and for biobanking.

All participants were subsequently followed through linkage with Danish registries on vital status and hospital admission. For analyses of medically treated exacerbations of COPD, the CCHS database was linked with the Danish Prescription Registry, which holds complete information on all out-of-hospital dispensed prescriptions.

SMOKING AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE

During the 1980s, following the seminal study of Fletcher et al.[1], which defined two overlapping but distinct syndromes, the more benign hypersecretory disorder (defined by presence of chronic mucus hypersecretion = chronic bronchitis) and the more serious obstructive syndrome (defined as chronic airflow limitation), the tendency was to investigate these two conditions separately, rather than combining them into COPD[1]. This was also the case in the CCHS. At that time there was an interest in whether filter cigarettes were less harmful than plain cigarettes and whether reduction in the number of cigarettes smoked had some health advantages. In this context, the early publications from CCHS showed that lung function decline was not affected by the presence of filters and that inhalation habits did not affect lung function decline in cigarette smokers[11,12]. In pipe smokers however, respiratory symptoms and lung function decline were less pronounced in those who reported not to inhale while smoking. The CCHS studies focusing on the number of cigarettes smoked, smoking cessation and reduction could demonstrate a dose-dependent relationship with regard to lung function decline and a beneficial effect of quitting on both lung function decline and remittance of respiratory symptoms[13,14]. Reducing smoking had some effect in younger light smokers but not in the elderly nor in the heavy smokers.

Subsequent studies focused on the possible sex differences in the susceptibility to smoking and suggested that smoking may have a slightly higher impact on the lung function of females than males, and that females suffer a higher risk of being admitted to hospital for COPD[15].

With the increase of the duration of the CCHS, new possibilities for analyses became apparent. In 2006, approximately 30 years after the initiation of the study, we focused on the risk of developing COPD in relation to smoking and changes in smoking habits. Within the study population, we identified approximately 8045 men and women aged 30-60 years with normal lung function at baseline and followed their lung function and mortality from COPD. The 25-year incidence of moderate and severe COPD was 20.7% in continuous smokers and 3.6% in never smokers, and 92% of the COPD-related deaths occurred in subjects who were current smokers at the beginning of the follow-up period. Smoking cessation, especially early in the follow-up period, decreased the risk of developing COPD substantially compared with continuous smoking. Overall, the absolute risk of developing COPD defined as presence of chronic airflow limitation was at least 25%, which is higher than was previously estimated[16] (Fig. 2). These findings were in line with findings from Northern Sweden[17].

OTHER RISK FACTORS AFFECTING DEVELOPMENT AND PROGRESSION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

It is a well-known clinical phenomenon that patients with a low body mass index (BMI) suffer a poorer prognosis than those with maintained BMI. However, on a population level, a high BMI carries the major mortality risk[18], albeit not for respiratory mortality

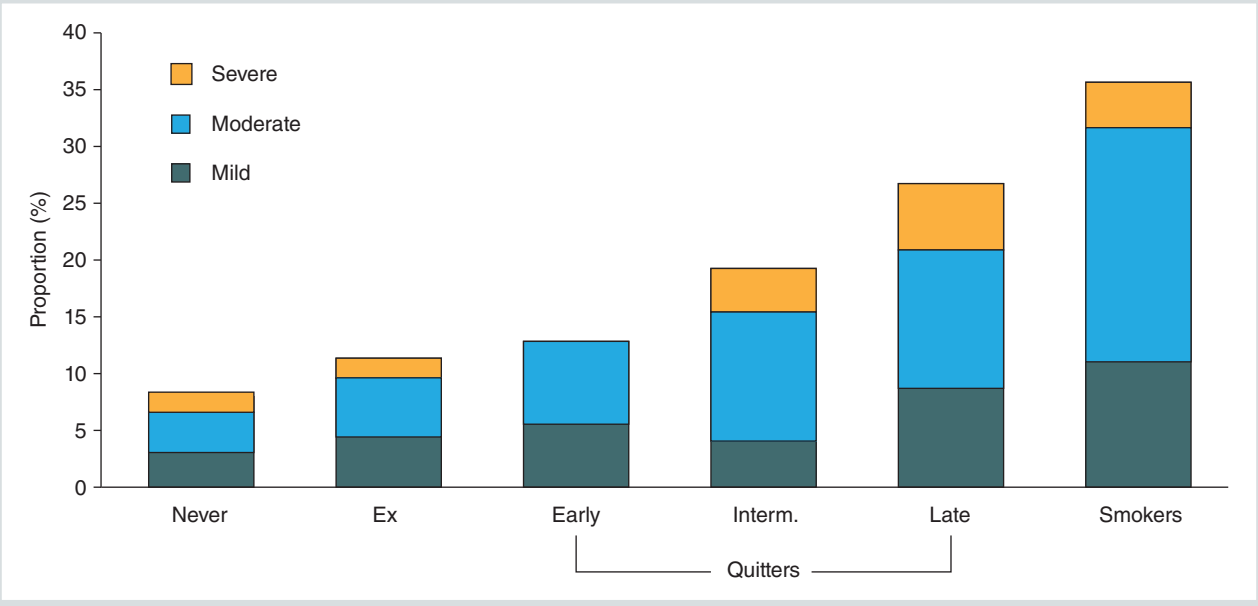

FIGURE 2. Cumulative incidence of COPD according to GOLD 1-4 grades for men and women combined *(reproduced with permission from Løkke A et al.[16]. © 2018 BMJ Publishing Group Ltd & British Thoracic Society. All rights reserved).*
COPD: chronic obstructive pulmonary disease; GOLD: Global Initiative for Obstructive Lung Disease; Interm.: intermediate.

according to more recent surveys[17]. In the CCHS, we could show a clear association between low BMI and respiratory as well as overall mortality, whereas in subjects with severe airflow limitation there was a steady increase in survival with increasing BMI[20].

In a subsequent longitudinal analysis, we found that five-year changes in BMI were also associated with mortality although not as strongly as baseline BMI. In subjects with severe airflow limitation, an increase in BMI was associated with improved prognosis in those with a BMI < 25kg/m^2, whereas the opposite was true for those being overweight or obese[21].

However, many factors other than smoking and BMI impact respiratory health. Inspired by not least the Whitehall studies from London showing a marked influence of socioeconomic status (SES) on health, we used education and income as proxies for SES and found that low SES was associated with a mean FEV_1 almost 300mL lower than in individuals with high SES, a feature independent of age[22]. Low SES was also associated with higher risk of respiratory admissions and when refined using social position instead of the crude SES categories, the associations remained[23]. A more recent study investigated how long-term prognosis of established COPD is influenced by SES[24]. Adjusting for sex, age, FEV_1 in percentage of predicted values, dyspnoea, frequency of previous exacerbations and smoking, we observed that shorter school education (in comparison with university education), was associated with a higher risk of

COPD exacerbations (approximate hazard ratio [HR] 1.6) and all-cause mortality (approximate HR 2). Our conclusion was that even in an economically well-developed country with a tax-funded health care system as Denmark, low SES is associated with a poorer prognosis of COPD.

Together with groups from Barcelona and Maastricht, the CCHS data were analysed to investigate the association between the level of physical activity and changes in physical activity and the development and prognosis of COPD. The analyses suggested that individuals with COPD who engage in regular physical activity have a lower risk of both COPD admissions and mortality[25]. Longitudinal lung function analyses showed that moderate-to-high levels of regular physical activity were associated with reduced lung function decline and a lower COPD risk among smokers[26]. The relationship between changes in physical activities and outcomes was more complex: in participants with COPD with low baseline physical activity, no differences were found in survival between unchanged or increased physical activity at follow-up. However, a decline to low physical activity at follow-up was associated with an increased mortality risk in subjects with and without COPD[27]. Overall, the observational data from CCHS suggest that it is important to assess and encourage physical activity in the earliest stages of COPD in order to maintain the physical activity level as high as possible, as this is associated with better prognosis. Several other studies focused on additional risk factors. One study of importance for the clinician showed a significant association between gastro-oesophageal reflux and exacerbations[28].

THE IMPORTANCE OF CHRONIC BRONCHITIS

One of the main issues in COPD epidemiology – and the focus on the London study by Fletcher et al.[1] – was the association between chronic bronchitis (chronic mucus hypersecretion [CMH]) and decline in lung function. The background was the British Hypothesis, claiming an association between recurrent lower respiratory tract infections and the development of chronic airflow limitation. This hypothesis was rejected by Fletcher et al.[1] using CMH as a proxy for recurrent bronchial infections, and the notion of CMH being an innocent bystander was supported by the frequently quoted mortality study by Peto et al.[29] showing that CMH provided very little prognostic information regarding mortality once FEV_1 was taken into account.

However, the prevalence of CMH was considerably lower in Copenhagen than in the London study and it was therefore likely that a "true association" could have been overlooked in the London study where the higher prevalence could be viewed as a response to higher levels of air pollution and therefore "noise". The first Copenhagen analyses focused on mortality and showed that, although there was only a small excess mortality associated with CMH in subjects with good lung function, the excess mortality associated with CMH was significant in those with low FEV_1[30]. Prescott et al.[31] subsequently showed that the excess mortality in those with CMH was likely due to terminal pneumonia/infectious exacerbations and in a specific analysis of risk factors for pneumonia admission in the general population, CMH was also a risk factor[32]. Subsequent analyses of CMH and FEV_1 decline

showed a significant association contrasting the findings by Fletcher et al[1]. (Fig. 3) as well as an association with increased risk of hospital admission, and we hypothesised that CMH may be a marker of ongoing inflammation rather than infection[33]. A subsequent paper showed that, although CMH is associated with FEV_1 decline, presence of CMH per se is not indicative of pre-COPD as suggested by the Global Initiative for Obstructive Lung Disease (GOLD) when launching GOLD grade 0[34], the main reason being that a significant number of smokers without CMH went on to develop COPD, and pointing to an at-risk population would carry the risk of wrongly labelling other smokers at not being at risk[35].

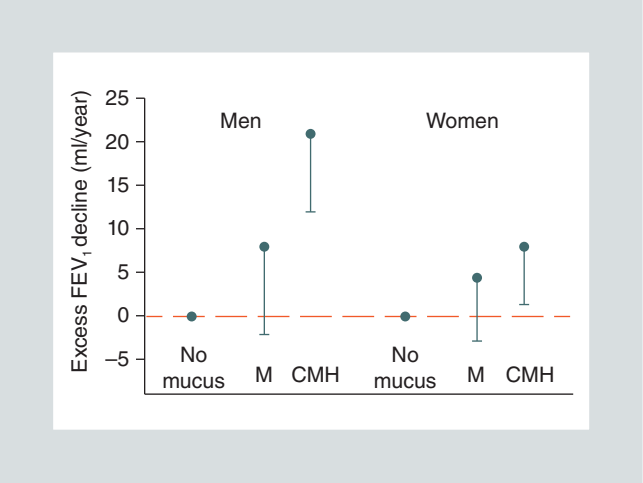

Figure 3. Association between mucus hypersecretion and FEV_1-decline *(reproduced with permission from Vestbo J et al.[33]. © 2018 American Thoracic Society).*
CMH: chronic mucus hypersecretion; FEV_1: forced expiratory volume in one second; M: mucus secretion.

NATURAL HISTORY OF OBSTRUCTIVE LUNG DISEASE

The longitudinal design of the CCHS allows studies describing long-term prognosis of respiratory diseases. One of the early studies focused on lung function decline in individuals with self-reported asthma from the first to the third examination, comprising three measurements of lung function over a 15-year period[36]. The analyses showed that the decline in FEV_1 was greater among the subjects with asthma than among those without the disease. This was observed among both men and women, and among both smokers and non-smokers. Consequently, at the age of 60, a 175-cm-tall non-smoking man without asthma had an average FEV_1 of 3 litres, as compared with 2 litres for a man of similar age and height who smoked and had asthma.

The revised GOLD document from 2011[37] introducing the clinical COPD groups A-D inspired us to investigate the ability of this new classification to predict hospitalisations and mortality due to COPD. In these analyses we combined the CCHS with its "sister study", the Copenhagen General Population Study. The latter is a prospective epidemiologic study that recruits more than 100,000 subjects, representative of the general population, and collects genotypic and phenotypic data of relevance to a wide range of health-related problems. With regard to the questionnaire and the examination of the participants, this study uses a similar methodology as CCHS. The analyses showed that, in comparison with the previous uni-dimensional GOLD stratification based on lung function only (GOLD 1-4), the new multi-dimensional A-D stratification identified a higher number of individuals at substantial risk of exacerbations and disease progression and thus needing special attention[38]. Interestingly, we found that the survival of group B was poorer that of group C, despite lower lung function in the latter (Fig. 4). Thus, severe dyspnoea was associated with poor

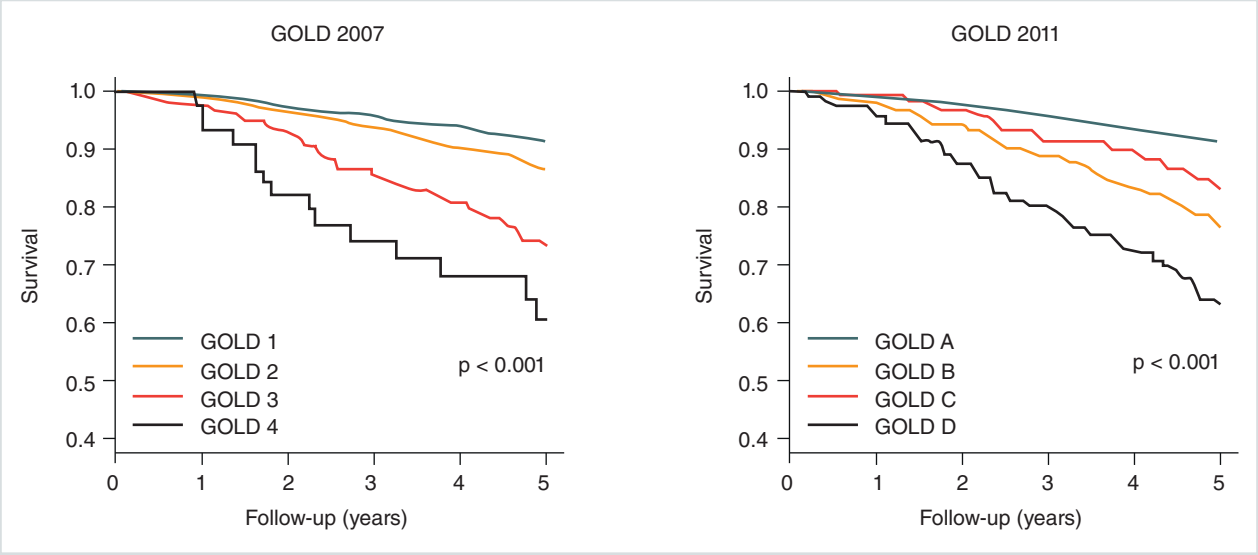

Figure 4. Survival according to GOLD 2007 and GOLD 2011 classification *(reproduced with permission from Lange P et al.[38]. © 2018 American Thoracic Society).*
GOLD: Global Initiative for Obstructive Lung Disease.

survival irrespective of level of lung function and warrant special attention. Our results suggested that the poor prognosis associated with more severe dyspnoea symptoms in group B could be due to presence of cardiovascular disease and cancer in this subgroup.

With the longer follow-up, it became possible to examine trajectories of FEV_1 leading to COPD. The inspiration for this came from two sources: first, Fletcher & Peto's BMJ paper[2] contained a figure showing how initial low lung function could be a risk factor for chronic airflow limitation later in life; secondly, several studies of cohorts of COPD patients had shown that decline in FEV_1 was much lower than anticipated given their COPD[39-42]. This resulted in one of the most interesting and challenging CCHS projects. In this study, the CCHS database was combined with the Framingham Offspring Cohort and the Lovelace Smokers Cohort. The participants were subdivided into 4 trajectories defined based on lung function ($FEV_1 \geq 80\%$ or $< 80\%$ of the predicted value) at inclusion into the cohort and the presence or absence of COPD at the last study visit[43]. Among 657 participants with FEV_1 of less than 80% of the predicted value before 40 years of age, 174 (26%) had COPD after 22 years of observation, whereas among 2207 persons who had a baseline FEV_1 of at least 80% of the predicted value before 40 years of age, 158 (7%) developed COPD.

Approximately half of the 332 persons with COPD at the end of the observation period had had a normal FEV_1 before 40 years of age and a rapid decline in FEV_1 (53 ml/yr), whereas the remaining half had had a low FEV_1 in

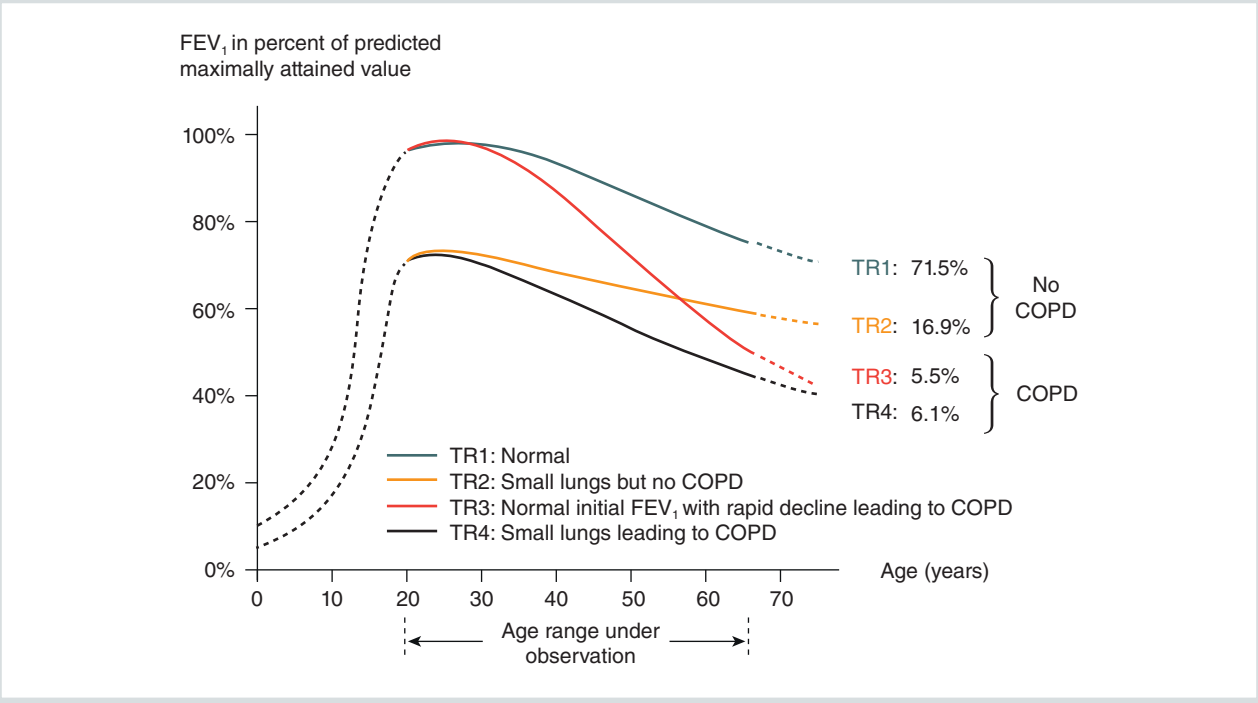

FIGURE 5. Distribution of individuals into four FEV_1-trajectories *(reproduced with permission from Lange P et al.[43])*.
COPD: chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in one second. TR: trajectories.

early adulthood and a subsequent normal decline in FEV_1 (27 ml/yr), despite similar smoking exposure (Fig. 5). This study confirmed previous hypothesis that low FEV_1 in early adulthood is an important risk factor for COPD and that accelerated decline in FEV_1 is not an obligate feature of COPD.

After the publication of the Global Initiative for Asthma (GINA)- GOLD document on asthma-COPD overlap syndrome (ACOS) in 2014, we revisited the question of long-term prognosis in individuals with asthmatic features and those with COPD. We expanded the observation period and analysed both FEV_1 decline for 18 years and hospital admissions and survival for 22 years. We defined six different subgroups: healthy never-smokers, ever-smokers without asthma and COPD, those with asthma with low cumulated smoking exposure and no airflow limitation, those with COPD, those with asthma-COPD overlap (ACO) with asthma onset before the age of 40 years, and those with ACO with asthma onset after the age of 40 years. The estimated decline in FEV_1 in ACO with early-onset asthma was 27 mL, which did not differ significantly from the decline of 21 mL per year in healthy never-smokers. FEV_1 decline in individuals with ACO with late-onset asthma was 50 mL and in the COPD group we observed an annual decline of 40 mL. Hazard ratios for hospital admissions due to exacerbations of asthma or COPD were highest in

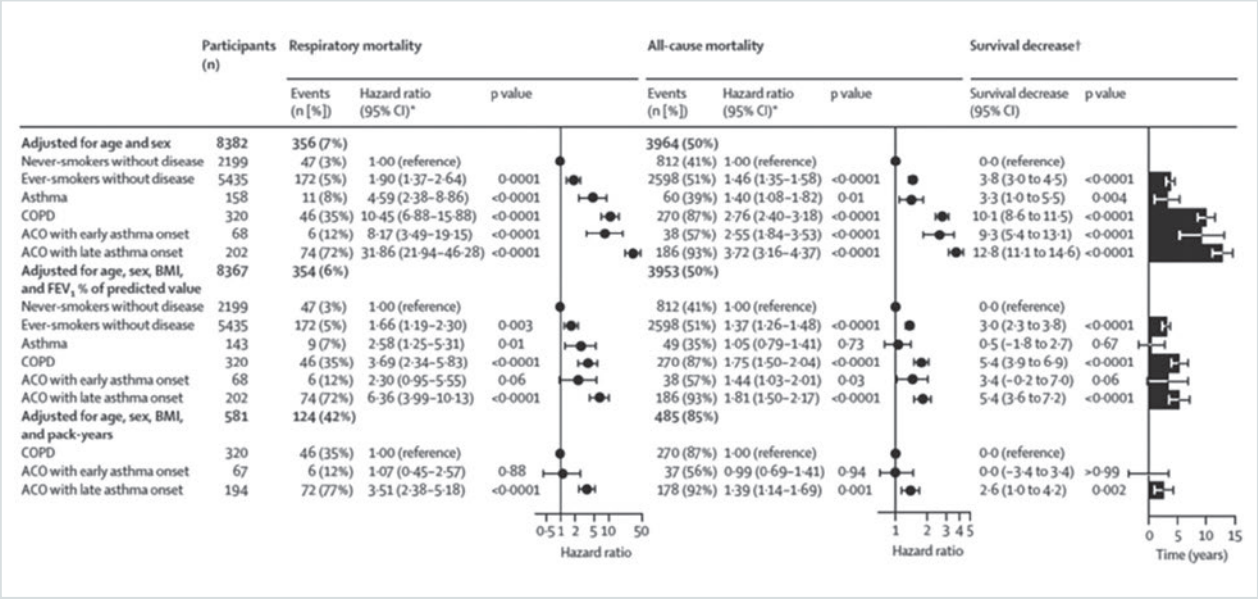

FIGURE 6. Risk of respiratory and total mortality according to the type of obstructive lung disease *(reproduced with permission from Lange P et al.[44]).*

ACO: asthma-chronic obstructive pulmonary disease overlap; BMI: body-mass index; CI: confidence interval; COPD: chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in one second.

ACO with late-onset asthma and this group also had shortest life expectancy (Fig. 6). We concluded that the prognosis of individuals with ACO seems to be affected by the age of recognition of asthma, being worst in those with asthma onset after 40 years of age[44].

BIOMARKERS

There is a need for biomarkers in COPD. Spirometry is required for diagnosis and contains information for categorisation and determining the prognosis; however, the heterogeneity of COPD makes FEV_1 alone a poor disease characteristic[45]. Markers of systemic inflammation were believed to be of value for predicting prognosis, disease progression and possibly other concomitant diseases. Fibrinogen was in the CCHS associated with level of FEV_1 and risk of hospital admission as well as decline in FEV_1[46]. Whereas the latter has not been confirmed in longitudinal studies of COPD patients[40], fibrinogen is now accepted as a marker of increased risk of exacerbations[47]. C-reactive protein (CRP) is also associated with lung function and risk of admission[48] and more detailed analysis using the concept of Mendelian randomisation showed that it is not elevated CRP per se that carries the risk, but rather underlying factors affecting both CRP and risk[49]. As it is unlikely that a single biomarker will ever fulfil all expectations in COPD, patterns of biomarkers have been examined. Using three levels of three easily accessible inflammatory biomarkers

– white blood cell count, fibrinogen and CRP – we found a clear association between increased systemic inflammation and risk of a number of important comorbidities in COPD[50]. Using the same biomarkers, we also found that systemic inflammation was associated with exacerbations, even after adjusting for history of exacerbations[51]. However, as exacerbations are rare events on a population level, it was the negative predictive value rather than the positive predicted value that was of importance. That patterns of inflammation rather than single markers may be of predictive value in COPD was also to some extent seen in the Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points (ECLIPSE) study of patients with moderate-to-very-severe COPD[52,53].

Blood eosinophils have attracted significant attention recently as it may be a theragnostic marker for ICS in COPD. This is difficult to evaluate in epidemiology. However, population studies can add to the general knowledge of this biomarker, and in Copenhagen, blood eosinophils were associated with an increased risk in both asthma[54] and COPD[55]; for the latter, absolute counts had better predictive value than relative eosinophil counts, with optimal prediction cut off at 340 x 10^9 cells/L. Recently, we have also shown that eosinophils are associated with an increased risk of pneumonia without any obvious interaction with treatment with ICS[56].

THE COPENHAGEN CITY LUNG STUDY

As mentioned, treatment effects can be difficult to assess in observational studies as not least bias by indication can be difficult to adjust for. We assessed the effect of statins on risk of exacerbation and found a protective effect with statins reducing the risk of exacerbations by 33%[57]. This contrasts with the findings of the Simvastatin Therapy for Moderate and Severe COPD (STATCOPE) trial[58] and subsequent analyses actually confirmed that the effect was only seen in those excluded from the randomised trial: i.e., those where statins may already be indicated for cardiovascular reasons.

It is, nevertheless, possible to do randomised controlled trials nested in a population study. The advantage is that this can often reduce the recruitment bias often seen in controlled trials[59,60]; the downside is that any marked intervention effect may affect subsequent observational follow-up findings. With the remarkable impact of ICS on course and prognosis in asthma and Dutch studies indicating an effect of systemic steroids on the prognosis of COPD[61,62], the path was opened for long-term controlled trials of ICS in COPD with disease progression as the outcome. In parallel with the European Respiratory Society Study on Chronic Obstructive Pulmonary Disease (EUROSCOP)[63] and the Inhaled Steroids in Obstructive Lung Disease in Europe (ISOLDE) trial[64], we chose to examine the effect of a relatively high dose of inhaled budesonide on FEV_1 decline in subjects in the Copenhagen Heart Study with irreversible airflow limitation[65]. This study was called the Copenhagen City Lung Study and investigated lung function decline during three years in 290 patients who were randomly assigned to budesonide, 800 µg plus 400 µg daily for six months followed by 400 µg twice daily. The estimated rates of decline did not differ significantly

(difference 3 ml/yr). In this population with quite mild COPD, we observed 155 exacerbations in the budesonide group and 161 in the placebo group. Thus, the results of the Copenhagen City Lung Study added to the rather pessimistic view on ICS in mild COPD, possibly worth revisiting after recent trials and re-analyses[66-68].

COMMENT

A longitudinal study is often known from its scientific outputs; however, the real work does not come from the analyses and manuscripts but from the daily running of the study and the goodwill of the participants and their willingness to invest time in the examinations. The CCHS benefitted from starting at a time when the willingness to participate was likely higher than today where attrition rates seem to be shrinking. Also, staff loyal to the study has ensured the continuity and stability and has helped overcome challenges over the years - but things like change of spirometer, changing register coding (changing of International Classification of Diseases [ICD] codes), and changing legislation have provided occasional headaches. In an ideal world – not least a world with better research funding – more frequent examinations with more time for each participant would have been desirable, but all in all this study has served its purpose well.

Finally, we have had the luxury of only summarising the respiratory research in the CCHS. Many hundreds of papers in other areas have been published; searches on authors like Gorm Jensen, Peter Schnohr, Børge Nordestgaard, Eva Prescott and Merete Appleyard will provide a long list of publications, not least in the cardiovascular area.

CONCLUSIONS

The longitudinal nature, the considerable size and the possibility of linking study data with various Danish health registries have allowed the CCHS to publish more than 100 papers on different aspects of asthma and COPD during the last 30 years. In particular, the CCHS has contributed to a better understanding of factors affecting the development, the course of lung function and the prognosis of this disease.

CONFLICTS OF INTEREST

Dr. Lange reports personal fees from Chiesi Pharmaceuticals, personal fees from Boehringer-Ingelheim, personal fees from AstraZeneca, grants and personal fees from GSK, outside the submitted work; Dr. Vestbo reports personal fees from Chiesi Pharmaceuticals, personal fees from Boehringer-Ingelheim, personal fees from Novartis, personal fees from AstraZeneca, outside the submitted work.

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