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Inhalation devices and inhaled corticosteroids particle size influence on severe pneumonia in patients with chronic obstructive pulmonary disease: a nationwide cohort study

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ABSTRACT

Background Inhaled corticosteroids (ICSs) are associated with an increased risk of pneumonia among patients with chronic obstructive pulmonary disease (COPD). The introduction of extrafine particle ICS has aimed to improve the distribution of medicine in the airways by altering deposition within the lungs, potentially affecting efficacy and side effects. It remains unclear if extrafine particle ICS administration alters the risk of pneumonia compared with standard particle size ICS.

Methods An observational cohort study including all Danish COPD outpatients receiving ICS from 2010 to 2017. The primary outcome was pneumonia hospitalisation in the different ICS particle dosing regimens. The primary analysis was an adjusted Cox proportional hazards model. For sensitivity analysis, a subgroup analysis of patients receiving spray devices was done. Further, we created a propensity score matched cohort, in which we matched for the same covariates as adjusted for in the main analysis.

Results A total of 35 691 patients were included of whom 1471 received extrafine particle ICS. Among these patients, 4657 were hospitalised due to pneumonia. Patients with COPD receiving extrafine particle ICS had a lower risk of hospitalisation due to pneumonia compared with patients receiving standard particle size ICS in our primary analysis (HR 0.75; 95% CI 0.63 to 0.89; p=0.002), subgroup analysis (HR 0.54; 95% CI 0.45 to 0.65; p<0.0001) and the propensity-matched population (HR 0.72; 95% CI 0.60 to 0.87; p=0.0006).

Interpretation The use of extrafine particle ICS administration was associated with a lower risk of pneumonia hospitalisation in patients with COPD compared with those who received standard size treatment.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Inhaled corticosteroids (ICSs) are associated with an increased risk of pneumonia among patients with chronic obstructive pulmonary disease (COPD). The introduction of extrafine particle ICS has aimed to improve the distribution of medicine in the airways by altering deposition within the lungs, potentially affecting efficacy and side effects. It remains unclear if extrafine particle ICS alters the risk of pneumonia compared with standard particle size ICS.

WHAT THIS STUDY ADDS

⇒ We found that extrafine particle ICS was associated with a lower risk of pneumonia hospitalisation in patients with COPD, compared with standard particle size treatment. This study is the first ever to explore the association between ICS particle size and risk of hospitalisation due to pneumonia in a large, well-characterised cohort of COPD outpatients with complete follow-up.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our study suggests that the use of extrafine particle ICS combined with a low dose ICS for patients with COPD is associated with a lower risk of hospitalisation due to pneumonia. It seems safe for healthcare providers to prescribe extrafine particle ICS at the lowest effective dose for patients with COPD.

INTRODUCTION

Inhaled corticosteroids (ICSs), often used in combination with bronchodilators, are widely used for the treatment of chronic obstructive pulmonary disease (COPD). While ICS has been shown to reduce COPD exacerbation rates through its anti-inflammatory effects,[1] it has also been associated with an increased risk of several side effects, including pneumonia, most probably due to its immunosuppressive effects.[2 3] Mounting evidence suggests that

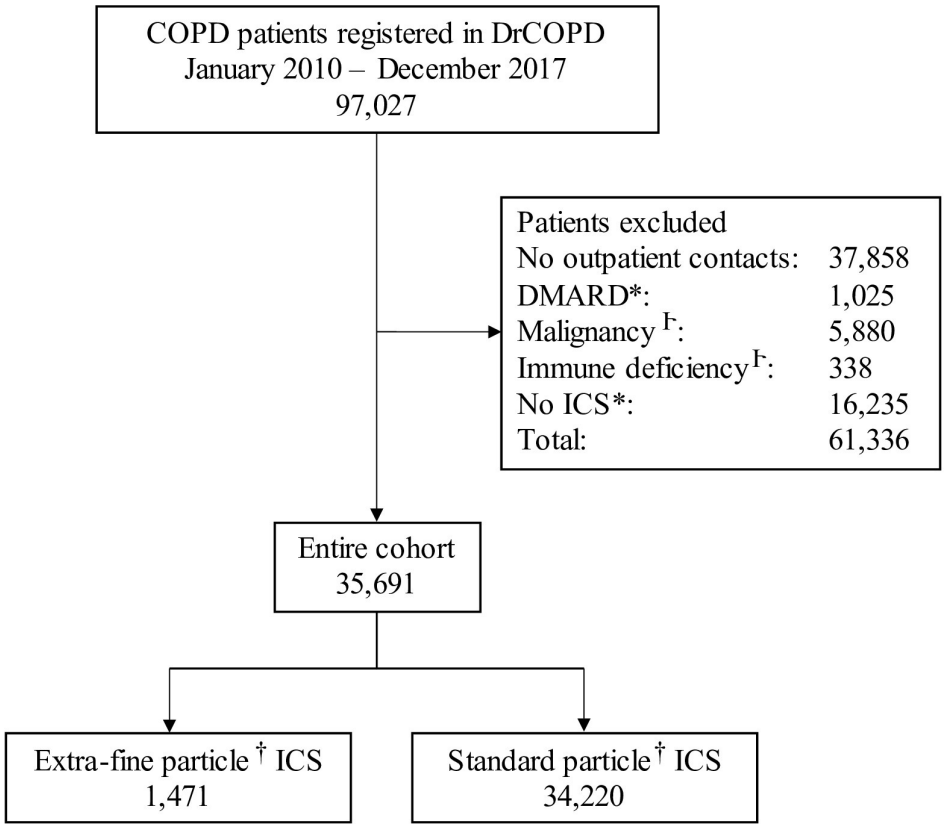

Figure 1 Flow chart of study selection criteria. Patients not followed in outpatient clinics were excluded due to lag of registrations of possible confounders such as forced expiratory volume in the first second and body mass index. Furthermore, we excluded patients receiving DMARD, patients with cancer or immune deficiencies because these are likely to affect the main outcome, risk of hospitalisation due to pneumonia. The cohort is divided into patients receiving extrafine particle ICS and standard particle ICS.

the risk of pneumonia in patients with COPD treated with ICS increases in a dose-dependent manner.[4 5]

ICS particle size is measured in median mass aerodynamic diameter (MMAD) ranging from 1 to 5 µm for commonly used ICS devices.[6] Particle size has proven to play a role in distribution within the lung.[7] Extrafine particles, defined as having an MMAD of ≤2 µm, have been shown to reach more peripheral parts of the airways to a greater extent.[8 9] It has also been reported that extrafine particles increase drug uptake due to their increased surface area.[10] Altering the aerosol size within the narrow range of 1–5 µm affects the deposition within the lungs and could potentially alter both efficacy and side effects. It remains uncertain from a theoretical perspective whether extrafine particle ICS alter the risk of pneumonia. On one hand, the improved distribution of ICS in peripheral lung sections may result in immunosuppressive effects and elevate the risk of pneumonia. However, on the other hand, extrafine particle size may result in a larger dispersion area, reducing the local concentration. Additionally, extrafine particles may facilitate faster absorption and elimination, potentially lowering the risk of pneumonia. With the increasing use of these drugs, it is important to identify safety issues that may not be uncovered in clinical randomised controlled trials

Currently, there are two available extrafine particle ICS formulations, beclometasone dipropionate hydrofluoroalkane inhaler (HFA) and extrafine ciclesonide. The evidence for clinically relevant outcomes as risk of pneumonia related to extrafine particles is still scarce, specifically regarding the risk of infection. An epidemiological study suggests that extrafine particles may be protective against pneumonia for patients with obstructive pulmonary disease, although the results are only significant in the unadjusted analysis.[11] To the best of our knowledge, no systematic studies with complete follow-up examining the effect of extrafine particle size on pneumonia risk specifically in patients with COPD have been conducted on a large scale.

In this study, we aim to determine whether extrafine ICS particles influence the risk of pneumonia admission in patients with COPD when adjusting for several confounders, including budesonide equivalent doses of ICS.

METHODS

Study design

This observational cohort study aimed to determine the effect of ICS particle size on the risk of hospitalisation

Table 1 Baseline characteristics for the entire cohort and the propensity-matched population.

	Entire cohort (n=35 691)		Propensity-matched population* (n=7986)	
	Standard particles ICS† (n=34 220)	Extrafine particles ICS† (n=1471)	Standard particle size ICS† (n=6654)	Extrafine particles ICS† (n=1332)
Age, years, median (IQR)	70.7 (62.9–77.8)	69.1 (61.5–76.2)	69.0 (61.3–76.6)	69.1 (61.4–75.9)
Male, n (%)	15 481 (45.2)	646 (43.9)	2934 (44.1)	590 (44.3)
BMI, kg/m^2, median (IQR)	25.0 (21.0–29.0)	25.0 (21.5–29.0)	25.0 (22.0–29.0)	25.0 (21.5–29.0)
BMI unknown, n (%)	2460 (7.2)	89 (6.1)	–	–
Active	10 818 (31.6)	404 (27.5)	1958 (29.4)	393 (29.5)
Former	19 960 (58.3)	885 (60.2)	4266 (64.1)	858 (64.4)
Never	1066 (3.1)	84 (5.7)	430 (6.5)	81 (6.1)
Unknown	2375 (6.9)	98 (6.7)	–	–
FEV1 (%), median (IQR)	45.0 (33.0–59.0)	46.0 (34.0–60.0)	46.0 (33.0–60.0)	45.0 (33.5–60.0)
GOLD stages 1–4 according to FEV1 (%), n (%)				
≥ 80	1465 (4.3)	70 (4.8)	351 (5.3)	62 (4.7)
79–50	11 643 (34.0)	520 (35.4)	2495 (37.5)	500 (37.5)
49–30	12 145 (35.5)	520 (35.4)	2488 (37.4)	510 (38.3)
<30	6377 (18.6)	268 (18.2)	1320 (19.8)	260 (19.6)
Unknown	2590 (7.6)	93 (6.3)	–	–
AECOPD-Hosp, n (%)				
0	22 354 (65.3)	1044 (71.0)	4350 (65.4)	943 (70.8)
1	7376 (21.6)	241 (16.4)	1413 (21.2)	220 (16.5)
≥2	4490 (13.1)	186 (12.6)	891 (13.4)	169 (12.7)
≥1 All-cause-hosp, n (%)	21 702 (63.4)	837 (56.9)	4204 (63.2)	759 (57.0)
OCS treatments, n(%)				
0	16 948 (49.5)	601 (40.9)	2720 (40.9)	536 (40.2)
1	4087 (11.9)	180 (12.2)	805 (12.1)	168 (12.6)
≥2	13 185 (38.5)	690 (46.9)	3129 (47.0)	628 (47.1)
Prophylactic OCS, n (%)	3501 (10.2)	185 (12.6)	820 (12.3)	161 (12.1)

Additional baseline characteristics can be found in online supplemental table 5.
*Propensity matched cohort. Propensity matching was done using a greedy match algorithm matching up to five controls receiving standard particle size ICS per case receiving extrafine particles. Matching was done on the following variables: age, sex, smoking status, forced expiratory volume in the first second, BMI, daily use of ICSs in budesonide equivalent dose, number of oral corticosteroids treatments and overlapping asthma.
†Devices containing beclomethason hydrofluoroalkane solutions or ciclesonide sprays were categorised as extrafine particles, all other ICS devices were categorised as standard particle size.
AECOPD, acute exacerbation of chronic obstructive pulmonary disease; BMI, body mass index; FEV1, forced expiratory volume in the first second; GOLD, Global Initiative for Chronic Obstructive Lung Disease; Hosp, hospitalisation; ICS, inhaled corticosteroids; OCS, oral corticosteroids.

due to pneumonia. The study population consisted of patients with COPD followed in outpatient clinics.

The following were excluded:

1. Patients with only in hospital registrations, as these registrations do not include essential patient characteristics used for adjusted analysis, such as forced expiratory volume in the first second (FEV1).
2. Patients with a history of malignant neoplasm or severe immunodeficiency within the past 5 years (indicated by International Classification of Diseases (ICD) codes listed in online supplemental table 1.
3. Patients who had been prescribed a disease-modifying antirheumatics drug within the past 12 months (indicated by Anatomical Therapeutic Chemical codes listed in online supplemental table 2.
4. Patients with no redeemed ICS prescriptions the year prior to cohort entry.

Cohort entry was defined as the date of the initial outpatient clinic visit. The primary outcome was hospitalisation due to pneumonia, as indicated by ICD-10 codes J12–18. Patients were followed for 1 year from cohort entry or until the first hospitalisation due to pneumonia,

Table 2 Characteristics of ICS consumption the year prior to cohort entry based on redeemed prescriptions

	ICS standard particles*, (n=34 220)	ICS extrafine particles*, (n=1471)
Daily ICS dose†, µg, median (IQR)	657.5 (315.6–1315.1)	670.7 (328.8–1150.7)
ICS exposure groups‡, n (%)		
Low(<420 µg/day)	11 514 (33.6)	469 (31.9)
Moderate (420–986 µg/day)	11 474 (33.5)	543 (36.9)
High (>986 µg/day)	11 232 (32.8)	459 (31.2)
No of prescriptions, median (IQR)	5 (3–9)	6 (3–10)
ICS type users, n (%)		
Beclomethasone	34 (0.1)	0
Beclomethasone HFA	0	1197 (81.4)
Budesonide	18 010 (52.6)	0
Fluticasone propionate	15 746 (46.0)	0
Fluticasone furoate	384 (1.1)	0
Ciclesonide	0	274 (18.6)
Momethasone	46 (0.1)	0

*Spray devices containing beclomethason HFA solutions or ciclesonide are categorised as extrafine particles, all other ICS devices are categorised as standard particle size.
†Based on ICS accumulated budesonide equivalent dose 1 year prior to cohort entry. Budesonide equivalent dose was calculated using ratios summarised in online supplemental table 3.
‡ICS exposure groups (low, moderate and high) were made by dividing the population into three equally big groups based on the ICS budesonide equivalent dose.
HFA, hydrofluoroalkane inhaler; ICS, inhaled corticosteroid.

or death. The study period was from 2010 to 2017. The study protocol is available online.[12]

Data collection

Data were obtained from the following registries:

1. The Danish Register of COPD (DrCOPD) was used to identify individuals with COPD who were followed in outpatient clinics. The diagnosis of COPD was validated by both spirometry testing and consultation with a respiratory specialist. DrCOPD is a nationwide database that includes individual patient data, such as severity of airflow obstruction, body mass index (BMI) and smoking status, for all outpatient visits and hospitalisations due to exacerbations of COPD.[13]
2. The Danish National Patient Registry contains data on all hospital admissions since 1977 and all hospital outpatient visits since 1995. This database was used to identify hospitalisations due to pneumonia and characterise comorbidities in the study population.[14]
3. The Danish National Database of Reimbursed Prescriptions (DNDRP) was used to identify prescribed and redeemed medication, including exposure to ICS. The DNDRP is nationwide and includes data on all reimbursed prescriptions redeemed at Danish community and hospital-based outpatient pharmacies.[15]

Data on age, BMI, smoking status, Medical Research Council dyspnoea score and FEV1 were gathered at the first outpatient visit. If a value was missing the first non-missing value from a subsequent outpatient visit was used. Information on comorbidities presented in the baseline was collected 5 years prior to cohort entry. Medication data were based on redeemed prescriptions the year prior to cohort entry.

Exposure to ICS and ICS particle size

All prescriptions for ICS, either as monotherapy or in combination with bronchodilators, redeemed 365 days prior to cohort entry were identified. The dosages of all ICS medications were converted to budesonide-equivalent doses (factors used are summarised in online supplemental table 3). The yearly accumulated budesonide equivalent doses were used to calculate daily ICS use, which was then used to divide the cohort into three equally sized exposure groups: low, moderate and high.

ICS particle size was classified into two categories: standard particle size (MMAD>2) and extrafine particle size (MMAD≤2). Currently, there are two types of ICS with extrafine particle formulations available: beclomethasone HFA solutions and extrafine ciclesonide sprays. In cases where patients were prescribed more than one type of ICS, they were categorised according to the type of ICS they had received the most of.

Statistical analysis

The risk of hospitalisation due to pneumonia associated with ICS particle size was estimated using an adjusted Cox proportional hazard regression model. The following variables were included in the model as covariates: age (categories: <62 years, 62–69 years, 70–77 years

Table 3 Results from the Cox proportional hazard regression model on the risk of hospitalisation due to pneumonia

	Entire cohort		Subgroup analysis*		Propensity matched‡	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Extrafine particles ICS	0.75 (0.63 to 0.89)	0.002	0.54 (0.45 to 0.65)	<0.0001	0.72 (0.60 to 0.87)	0.0006
ICS exposure groups†						
Low (<420 µg/day)	ref	–	ref	–	Ref	–
Moderate (420–986 µg/day)	1.11 (1.03 to 1.21)	0.01	1.07 (0.90 to 1.27)	0.5	1.25 (1.06 to 1.48)	0.008
High (>986 µg/day)	1.35 (1.25 to 1.47)	<0.0001	1.14 (0.96 to 1.34)	0.1	1.25 (1.05 to 1.49)	0.01
Male	1.16 (1.09 to 1.23)	<0.0001	1.32 (1.18 to 1.48)	<0.0001	1.22 (1.07 to 1.38)	0.002
Age group						
<62	ref	–	ref	–	ref	–
62–69	1.39 (1.25 to 1.54)	<0.0001	1.35 (1.10 to 1.66)	0.005	1.35 (1.10 to 1.65)	0.003
70–77	1.90 (1.72 to 2.11)	<0.0001	1.56 (1.28 to 1.91)	<0.0001	1.97 (1.62 to 2.39)	<0.0001
>77	2.96 (2.67 to 3.28)	<0.0001	2.37 (1.95 to 2.89)	<0.0001	2.81 (2.30 to 3.43)	<0.0001
BMI class, kg/m^2						
<18.5	1.30 (1.18 to 1.43)	<0.0001	1.23 (1.05 to 1.44)	0.01	1.26 (1.03 to 1.54)	0.03
18.5–24.9	ref	–	ref	–	ref	–
25–29.9	0.90 (0.83 to 0.97)	0.006	0.96 (0.84 to 1.11)	0.6	0.88 (0.76 to 1.03)	0.1
30–34.9	0.87 (0.78 to 0.96)	0.007	0.93 (0.77 to 1.13)	0.4	0.81 (0.66 to 0.99)	0.04
≥35	1.12 (0.97 to 1.26)	0.1	1.05 (0.82 to 1.3)	0.7	1.14 (0.90 to 1.45)	0.29
Gold stage according to FEV1(%),						
≥ 80	ref	–	ref	–	ref	–
79–50	1.26 (1.03 to 1.55)	0.02	1.46 (0.94 to 2.27)	0.1	1.38 (0.92 to 2.07)	0.1
49–30	1.76 (1.44 to 2.15)	<0.0001	1.91 (1.2 to 3.0)	0.004	1.87 (1.26 to 2.79)	0.002
<30	2.37 (1.93 to 2.91)	<0.0001	2.37 (1.52 to 3.7)	0.0001	2.81 (1.87 to 4.23)	<0.0001
Smoking status						
Active	1.12 (1.045 to 1.19)	0.003	1.11 (0.98 to 1.26)	0.1	0.88 (0.66 to 1.17)	0.07
Former	ref	–	ref	–	ref	–
Never	0.91 (0.75 to 1.09)	0.3	1.03 (0.75 to 1.42)	0.8	1.15 (0.99 to 1.32)	0.4
No of OCS treaments						
0	ref	–	ref	–	ref	–
1	1.30 (1.18 to 1.44)	<0.0001	1.18 (0.98 to 1.42)	0.09	1.31 (1.06 to 1.62)	0.01
≥2	1.67 (1.56 to 1.78)	<0.0001	1.52 (1.34 to 1.72)	<0.0001	1.62 (1.40 to 1.87)	<0.0001
Asthma	1.03 (0.96 to 1.11)	0.3	1.01 (0.89 to 1.16)	0.9	1.05 (0.92 to 1.20)	0.5

*This analysis was only caried out on patients receiving ICS spray treatment.
†ICS exposure groups (low, moderate and high) were made by dividing the population into three equally big groups based on the ICS budesonide equivalent dose.
‡Propensyty matching using a greed match algorithm with up to five controls per case. Matching was done on the following variables: age, sex, smoking status, FEV1, BMI, ICS group, OCS group and asthma diagnosis.
BMI, body mass index; FEV1, forced expiratory volume in the first second; ICS, inhaled corticosteroid; OCS, oral corticosteroid.

and >77 years), sex (categories: male and female), Gold stage according to FEV1% (categories: ≥80%, 79%–50%, 49%–30% and <30%), BMI class (categories: <18.5 kg/m^2, 18.5–24.9 kg/m^2, 25–29.9 kg/m^2, 30–34.9 kg/m^2 and ≥35 kg/m^2), smoking status (categories: active, former and never), number of oral corticosteroids treatments during the previous year (categories 0, 1 and ≥2), diagnosed with asthma (categories: yes and no), and ICS exposure group (categories low <420 µg/day, moderate 420–986 µg/day and high >986 µg/day).

All variables for the Cox analysis were tested for the proportional hazard assumption using Schoenfeld residual plots. The linearity assumption was not met for FEV1%, age, ICS dosage or BMI when used as continuous variables in the analysis. This was handled by penalised splines with five knots. However, for easier interpretation,

Table 4 Table of events of hospitalisation due to pneumoniae or death by exposure to extrafine particle size ICS or standard particle size ICS during the 1-year follow-up

	Standard* ICS	Extrafine* ICS	Total
No event, n (column percentage)	26 571, 77.7%	1212, 82.4%	27 783
Hospitalisation due to pneumonia, n (column percentage)	4513, 13.2%	144, 9.8%	4657
Death, n (column percentage)	3136, 9.2%	115, 7.8%	3251
Total	34 220	1471	35 691

*Devices containing beclomethason hydrofluoroalkane solutions or ciclesonide sprays were categorised as extrafine particles, all other ICS devices were categorised as standard particle size.
ICS, inhaled corticosteroid.

continuous variables were converted to categorical in the presented analysis since this did not affect the HR for the main outcome. Death was right censored in the model. Missing data for the Cox analysis were handled by complete case analysis. A cumulative incidence function was performed for graphical presentation.

For sensitivity analysis, we used a subgroup Cox analysis looking only at patients receiving spray inhalers. This analysis was performed to rule out that the differences we found were due to comparing spray and powder devices, since all extrafine particle ICSs are formulated as sprays, while standard particle size is currently formulated both as spray and powder devices. Although it is worth noting that extrafine particle ICS can also be formulated as dry powder, such products were not included in our cohort. We adjusted for the same variables as in the main analysis. Furthermore, we did a propensity-matched cohort matched on the same variables adjusted for in the main analysis. We used a greedy match method with up to five controls per case and a logistic propensity score calliper of 0.25.[16] We applied a Cox proportional hazards model while adjusting for the same variables matched for in the propensity-matched cohort.

The majority of statistical analyses were made using SAS V.9.4 statistical software. Penalised splines and graphs were made using R V.4.1.3, (packages: survminer V.0.4.9 and survival V.3.5-0).

Patient and public involvement

We have integrated patient representatives into our steering committee for crucial input on trial designs and observational studies. We also conducted an international survey on COPD trial outcomes with active participation from patients, their families and advocacy groups. Whenever we conduct nationwide studies, we keep the public informed via press releases and discussions with the Danish lung patient organisation.

RESULTS

We included 35 691 patients with COPD followed in outpatient clinics, of which 1471 received an ICS with an extrafine particle formulation. The eligibility processes are shown in figure 1. Baseline characteristics are presented in table 1. Patients receiving extrafine particles had similar baseline characteristics compared with patients receiving standard particle size ICS, although trending to be slightly younger, having higher FEV1 and increased prevalence of asthma. The median daily dose of ICS in budesonide equivalent doses for patients with COPD receiving extrafine particle ICS was 671 µg compared with 657 µg for the patients receiving standard particle size ICS. The most common ICS types for patients receiving standard particle size ICS were budesonide and fluticasone propionate, and the most prescribed ICS type for extrafine particles was Beclomethasone HFA. An overview of ICS consumption is shown in table 2.

The adjusted Cox model on the entire cohort showed that patients treated with extrafine particle ICS had a lower risk of hospitalisation due to pneumonia (HR 0.75; 95% CI 0.63 to 0.89; p=0.002). The risk was lower for the subgroup analysis looking only at patients receiving spray inhalation (HR 0.54; 95% CI 0.45 to 0.65, p<0.0001), the Cox model performed on the propensity-matched cohort, revealed similar results to the adjusted analysis performed on the entire cohort (HR 0.72; 95% CI 0.60 to 0.87 p=0.0006). Results from the primary analysis and the sensitivity analysis are presented in table 3. Furthermore, high use of ICS, male, high age, low BMI, low FEV1% and active smoking were associated with increased risk of hospitalisation due to pneumonia. A supplementary analysis, accounting for the same variables as in the primary analysis, with the addition of the year of cohort entry treated as a continuous variable, was conducted. The time-adjusted HR for the use of extrafine particle ICS was consistent with the main analysis (HR 0.78; 95% CI 0.66 to 0.94; p=0.009). The unadjusted results from the entire cohort are presented in online supplemental table 4. A total of 4657 patients had an event of hospitalisation due to pneumonia in the 1-year follow-up period. Crude number of events and deaths are shown in table 4.

Ninety per cent of the patients in the entire cohort had full data completeness for all the variables used in the adjusted analysis. Missing data for individual parameters are shown in table 1.

A cumulative incidence curve for the entire cohort, patients receiving spray ICS and the propensity-matched cohort are shown in figure 2. All three curves show

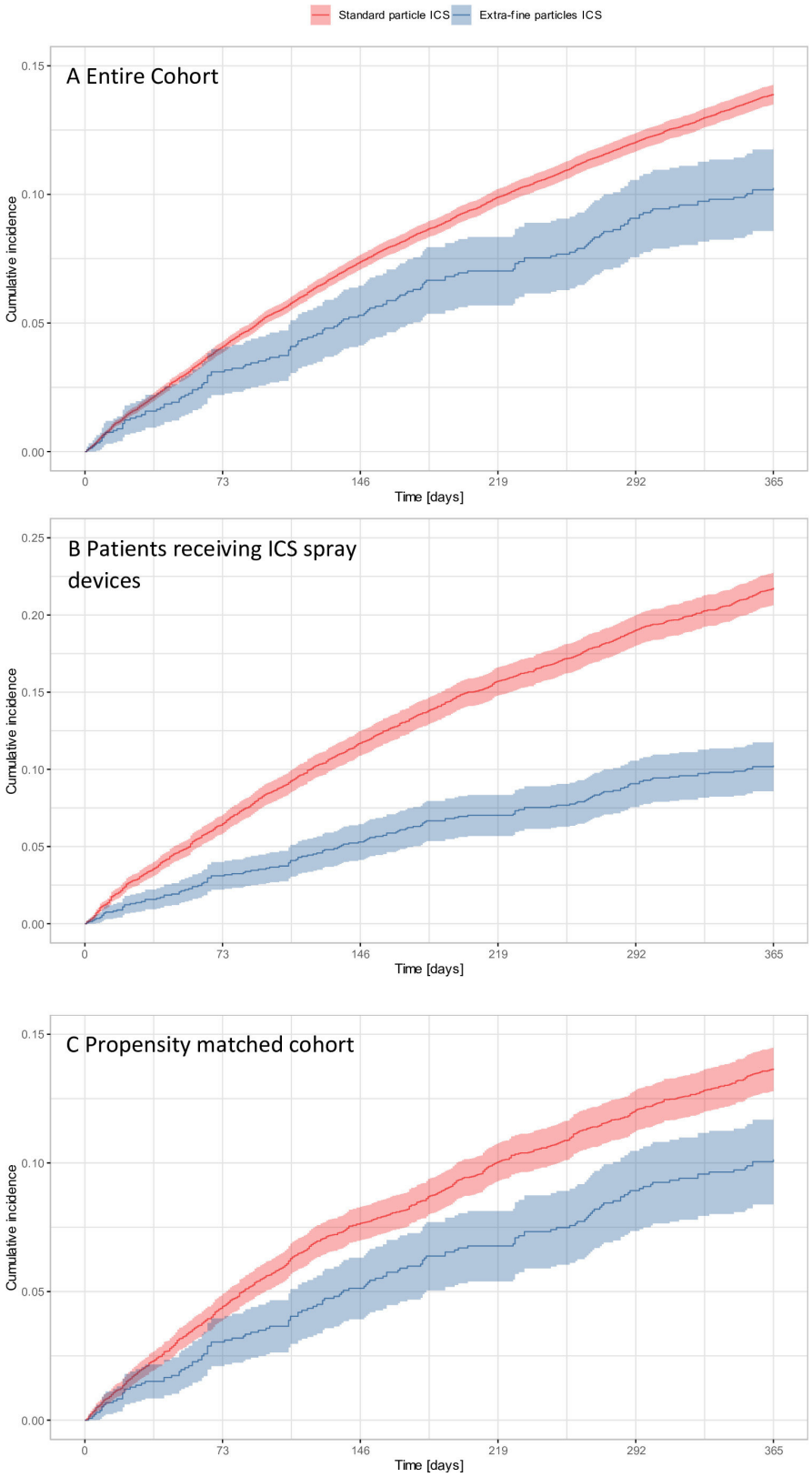

Figure 2 Cumulative incidence of hospitalisation due to pneumonia 365 days after the first outpatient visit for patients receiving standard particle size and extrafine particle size inhaled corticosteroids (ICS). (A) entire cohort, (B) Subgroup analysis on the part of the cohort consisting of patients receiving ICS spray devices, since all extrafine particle ICS devices are sprays. (C) Propensity matched cohort. Propensity matching was done using a greedy match algorithm matching up to five controls receiving standard particle size ICS per case receiving extrafine particle ICS. Matching was done on the following variables: age, sex, smoking status, forced expiratory volume in the first second, body mass index, daily use of inhaled corticosteroids in budesonide equivalent dose, number of oral corticosteroids treatments and overlapping asthma.

higher accumulated incidence of hospitalisation due to pneumonia for patients receiving standard particle size ICS compared with extrafine particle ICS.

DISCUSSION

To our knowledge, this is the first study focusing on the risk of hospitalisation due to pneumonia for patients with COPD related to ICS particle size. Among patients with COPD using ICS, we found a strong association between receiving ICS in an extrafine particle formulation and having a lower risk of pneumonia hospitalisation. The result was robust for the adjustments made in the main analysis. In addition, the subgroup analysis, excluding patients not receiving spray devices, showed an even lower HR of hospitalisation due to pneumonia for the patients treated with extrafine particle ICS. Furthermore, we did a propensity-matched cohort for sensitivity analysis with similar HRs to the main analysis.

The underlying mechanism behind the lower risk of pneumonia for patients with COPD treated with extrafine particles remains unclear. Patients receiving extrafine particle ICS were comparable to those receiving other formulations, but slightly younger and healthier, nevertheless the results were robust for the adjusted analysis. Patients receiving extrafine particle ICS did on average receive a higher median budesonide equivalent daily dose, potentially leading to a higher risk of pneumonia in contrast to our results. The risk of pneumonia may be lower due to smaller particle size leading to increased passive absorption or different liposolubility properties affecting elimination.

To date, no clinical trials have been conducted comparing extrafine particle ICS to standard particle size ICS for patients with COPD. Previous studies mainly focus on patients with asthma or obstructive pulmonary disease in general. Registry studies pooling obstructive lung diseases might confound the results, due to the different risks of pneumonia related to ICS treatment for patients with asthma and COPD[17] and corresponding different prescription patterns for these two separate disease entities. A register study investigated the risk of pneumonia for patients with obstructive lung disease and showed a lower risk of pneumonia in patients stepping up to extrafine particle ICS compared with standard size particle ICS.[11] However, this risk reduction was not significant in the adjusted analysis. Furthermore, this study was limited to a selected group of patients, excluding patients receiving budesonide. Another study examined the effectiveness of extrafine particles compared with standard size particles and did not show differences in the risk of pneumonia, however, they only found very few cases of pneumonia (four confirmed).[18] Similarly, one-third study showed no difference in incidence of pneumonia for patients with COPD receiving triple therapy with or without extrafine particle ICS, although based on few outcomes.[19]

Our study has several strengths. We included more than 35 000 patients with COPD followed in outpatient clinics receiving ICS. We had approximately 1400 patients receiving extrafine particle ICS of which about 10% had a hospitalisation due to pneumonia. This dataset contains information on multiple confounders including age, BMI, smoking status and FEV1 enabling adjustments and matching. We have complete data for the primary outcome, redeemed prescriptions and death. The baseline characteristics of patients treated with extrafine particle ICS, compared with those receiving standard particle size ICS, were quite similar. Although there are no clear clinical guidelines for prescribing extrafine particle ICS, one might expect more ill patients to receive this treatment. However, the baseline data do not support this hypothesis. This similarity in baseline characteristics makes our study somewhat less reliant on adjustments. Data completeness was high for all the variables used for adjustment. Most patients with missing data had missing data on multiple parameters (FEV1, BMI, smoking status) at the same time, and these patients had a similar age to patients with full data completeness, this indicates most of the missing data is due to registration problems, indicating data are missing completely at random. The hypothesis was tested with different sensitivity analyses with similar robust results.

Although our study has several strengths, some limitations deserve consideration. The diagnosis of pneumonia was based on hospitalisation records and may be subject to misclassification by clinicians, leading to potential under-reporting or over-reporting of the outcome. However, it is unlikely that the ICS particle size would affect the accuracy of the pneumonia diagnosis, and as such, any bias attributed to this possible misclassification would most likely be non-differential. Furthermore, ICD-10 codes have previously been validated as a method for identifying hospitalisations due to pneumonia.[20] The study used data on redeemed prescriptions rather than actual medication intake, which may probably result in an overestimation of ICS consumption. However, this error is likely to be small given that it is based on multiple collected prescriptions and is unlikely to significantly impact the primary outcome. A potential criticism of our study design is that the comparison between the two groups was not solely based on ICS particle size, but also on the type of ICS used (budesonide, fluticasone, etc). Previous studies have indicated a possible excess risk of pneumonia associated with fluticasone.[21] However, when accounting for dose equivalency, such associations to fluticasone cannot be reproduced, and the biological correlate to such a notion seems less clear.[4] While our study cohort consisted of patients with COPD followed in outpatient clinics by pulmonologists, treated with ICS, we believe that the influence of particle size on pneumonia risk is likely to hold relevance across broader COPD patient populations. However, caution should be exercised when generalising our findings to patients with COPD followed by general practitioners, as they may

exhibit lower pneumonia hospitalisation rates. As with other prospective studies, it is not possible to rule out remaining residual confounding.

In conclusion, we found that extrafine particle ICS for patients with COPD is strongly associated with a lower risk of hospitalisation due to pneumonia compared with standard particle size ICS. The signal was robust through three different adjusted models. Until randomised controlled trials can inform us further, ICS formulations with extrafine particles, using the lowest possible dose, seem like a safe choice, in patients with COPD at high risk of this serious adverse effect to corticosteroids.

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Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants but according to Danish law, separate ethical approval for patient registry studies is not required. Therefore, a specific reference number or ID from an ethics committee or institutional board has not been provided for this study. According to Danish law, obtaining informed consent is not required when using data from the Danish Patient Registry that has been anonymised through encryption.

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