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ORIGINAL RESEARCH

Effect of Exposure to Inhaled Corticosteroids on Lung Cancer Incidence – A Comparison of Earlier Study Methodology on the Financial Database of the Hungarian National Health Insurance Fund

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Background: Lung cancer (LC) is one of the main causes of death among COPD patients. Similar risk factors and pathophysiology motivated multiple retrospective studies investigating a possible risk reduction effect of inhaled corticosteroids (ICS) use among COPD patients, yet there is still no consensus on the issue.

Methods: Using the financial database of the National Health Insurance Fund, involving the overall population of Hungary, two retrospective analyses were performed between 2009 and 2019, based on the contradicting works of Suissa and Raymakers. Both analytical methods were used to recreate the study populations and compare the outcomes. Cox proportional hazard models were used to estimate the effect of ICS use on the risk of LC. The models were corrected for immortal time bias.

Results: Altogether, 96,686 and 196,560 patients were enrolled in the Suissa and Raymakers models, respectively. Average age was 65.7 (standard deviation – SD: 9.14) and 65.3 (SD: 9.37) years, with 48.4% and 56% women correspondingly. Through the study period 26.2% and 60.8% used ICS for longer than 1 year. Overall, 4941 and 8969 new LC cases were identified. Based on the adjusted Cox models ICS use had a protective effect for LC in both populations with hazard ratios being 0.77 (0.63–0.94) and 0.61 (0.53–0.7), respectively.

Conclusion: Even though the original publications reported contradicting results, in our analysis of over 200,000 patients, both reproduced models showed a significant reduction of LC risk in COPD patients using ICS therapies. Main limitation: models were adjusted for age and sex; individual smoking data were not available in the administrative database. A higher proportion of patients with predominantly asthma-coded prescriptions was observed in the ICS-exposed group of Cohort 2.

Keywords: COPD, lung cancer, inhaled corticosteroids

Introduction

Chronic obstructive pulmonary disease (COPD) ranks among the top causes of morbidity and mortality,[1–3] while lung cancer (LC) is the most prevalent cancer and the leading cause of cancer death worldwide.[4–6] Studies report 40–70% of patients with LC have a coexisting diagnosis of COPD,[7–9] representing significant overlap between these two smoking related pulmonary diseases. In addition, the correspondence between COPD and the risk of LC development is important to mention,[10] but the influence of therapeutic management of both diseases on each other's outcomes is still not clear. The role and contribution of inhaled corticosteroids (ICSs) are relevant and important since these are increasingly used in the management of COPD, particularly in patients at risk of exacerbation.[11] Researchers have raised questions on whether ICS might affect the development of LC.[12–16]

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Several biological mechanisms have been proposed through which ICS might theoretically influence lung cancer development, based on their specific pharmacological properties, which are distinct from those of systemic corticosteroids. Tobacco smoke promotes both inflammatory and mutagenic effects in the lungs, potentially inducing both lung carcinogenesis and COPD, with the NF-κB pathway serving as a key mediator central to both COPD-related inflammation and carcinogenesis.[17] ICS exert their primary anti-inflammatory effects locally within the airways through specific molecular mechanisms, including suppression of pro-inflammatory gene transcription via NF-κB inhibition and recruitment of histone deacetylase-2 (HDAC2), reduction of inflammatory cell infiltration, and inhibition of chemotactic mediators in the airway epithelium.[18,19] Exploratory mechanistic studies suggest that ICS may inhibit epithelial–mesenchymal transition (EMT), a potential link between inflammation and tissue remodeling.[20,21] At standard COPD doses, ICS have limited systemic bioavailability, ensuring that their anti-inflammatory effects remain targeted to the airways without triggering broad systemic immunosuppression.[22] Whether these mechanistic properties translate into a clinically meaningful reduction in lung cancer risk in COPD patients, however, remains to be established.

According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2025 report, evidence on the association between ICS use and LC risk in COPD is conflicting, and the document emphasizes that, based on the available data, ICS do not appear to increase or decrease the risk of LC.[11] The need for further evidence in this field has been highlighted by a systematic review and dose-response meta-analysis[23] and a comprehensive analysis of nine prospective cohorts.[24] From the aforementioned literature, two studies are outstandingly interesting for they were both performed in the same country, on a large number of patients, during long follow-up period, with methodologically rigorous designs, yet reached diametrically opposite conclusions.[15,16]

Raymakers et al from British Columbia, with 39,676 COPD patients, found that ICS use was associated with 30% reduction of LC risk (HR = 0.70 (95% CI: 0.61–0.80)). However, a further large cohort study, from Quebec by Suissa et al with 63,276 COPD patients, did not demonstrate an overall reduction of LC risk in ICS user COPD patients (HR = 1.01 (95% CI: 0.94–1.08)). In addition, Suissa drew attention to a potential methodological bias existing in Raymakers' work[25] which stems from the definition of ICS exposure as a non-time-dependent variable, which could lead to a bias, overestimating the effect of ICS. Raymakers refuted this claim and noted that cases of LC were determined in a different manner, giving another theory for the discrepancy of their results as published in a subsequently published correspondence.[25,26] They used histopathologically verified cases from a cancer registry, while Suissa et al used hospital discharge data, which may also contain other diagnoses and cause ascertainment bias which could confound the effect of ICS. The available publications and interpretations do not provide solid ground to determine the proper method and to elucidate the results. Beyond these differences, there were major discrepancies in the selection criteria for the studied population. As this could result in the enrolment of very different populations, comparison of the same outcome, using the definitions employed by the authors, could be a viable way to compare the two methodologies.

Since the question of the effect of ICS on the development of LC in COPD is still a high priority topic, and the variables used in both studies are available in the database of the Hungarian National Health Insurance Fund (NHIF), we decided to analyse the different methods employed by the two Canadian authors. We aimed to determine whether the choice of cohort definition methodology influences the estimated association between ICS use and lung cancer incidence in COPD patients, by applying both the Suissa and Raymakers methodologies to the same nationwide Hungarian administrative database.

Methods

Overview

Our research aimed to compare the different study methodology of Suissa and Raymakers to determine whether ICS use influences the development of LC in COPD patients. All patients in the NHIF database who had at least one container of inhalative maintenance and/or reliever treatment for asthma or COPD in the period of 2009–2019 were investigated. Later data were excluded, due to the disturbing effect on routine patient care of the COVID-19 pandemic. Our research group had earlier used this database to investigate long-term outcomes of COPD[27,28] and asthma.[29,30] As Hungary has a single insurer healthcare system, this database encompasses the whole population of Hungary, collecting data on all

procedures and treatments, including medication prescriptions, further details of the database had been described in our earlier publications. Based on Act No. 80/1997 on mandatory health insurance coverage, NHIF has the right to handle individual patients' data and based on Act 63/2012 on the reuse of public data, has the right to share aggregate data on a claim basis. As per this legislation, it is not possible to obtain the data of individual patients or results that come from aggregating the data of less than 10 patients. The NHIF is compelled by law to uphold the anonymity of the individual patients, so an individual consent form is not required for the study's approval process by the Ethics Committee. The study was approved by the National Scientific and Research Ethics Committee of Hungary (ETT-TUKEB), under docket number IV/2651-4/2021/EKU and it was conducted in accordance with the Helsinki Declaration.

Cohort Definitions

The cohort formation steps described by Suissa and Raymakers were followed. These steps are detailed in the respective publications; however, to highlight the main differences we present the main steps below.

For the Suissa population (Cohort 1) we enrolled patients who were: above 50 years of age; had at least three different prescriptions for long-acting muscarinic antagonist (LAMA) or long-acting beta-2 agonist (LABA) within 12 months during the study duration; had no prescription for LABA, LAMA or ICS one year prior to inclusion (wash-in period); had no lung cancer (LC) diagnosis prior to enrolment.

To create the Raymakers (Cohort 2) population, the following criteria were used: above 50 years of age; had at least three different prescriptions for LAMA, short-acting muscarinic antagonist (SAMA) or short-acting beta-2 agonist (SABA) within 12 months during the study duration; had no prescription for SABA, SAMA or LAMA one year prior to inclusion (wash-in period); had no diagnosis of LC prior to enrolment. The last criterion was not originally included in the Raymakers study but to ensure better comparability of the two studied populations, it was included in our analysis.

In both cohorts, the date of the first of the three prescriptions was considered the index date. Wash-in periods were calculated from this date. As data was only available from 01.01.2009, the earliest date for patient inclusion was 01.01.2010.

Follow-Up and Exposure

All patients were followed from the index date until death, diagnosis of LC, or the end of study period (12.31.2019). The wash-in period was used to ensure the enrolment of incident COPD patients. Protopathic and latency periods were applied in the same manner as described in previous publications of Suissa and Raymakers.[16,17] For easier understanding a brief explanation is provided here.

Protopathic bias occurs if a medication is prescribed inadvertently for a disease that had not been diagnosed. As LC can also cause respiratory symptoms (usually attributed to COPD), the prescription of inhaled medication could happen due to an undiagnosed LC. For this reason, all patients without at least 12 months of follow-up after the index date had been excluded.

Information on ICS use was derived from prescription data of medications containing beclomethasone, budesonide, fluticasone, and ciclesonide alone or in combination (no other ICS was available in the included period). Dose equivalences were based on the GINA equivalence table, which has remained consistent across guideline versions.[31] To determine exposure, a one-year latency period was applied, meaning that all LC events that happened in the one-year window following the first prescription for ICS containing medication were considered as unexposed to ICS. This was done to provide a realistic timeframe for the effect of ICS on development of cancer. To avoid immortal time bias, cautioned by Suissa, ICS exposure was defined as a time-dependent variable through the follow-up.

Graphical representation of cohort formation and information to help understand latency and protopathic periods and exposure are shown in Figure 1.

Collected Data and Outcomes

Baseline data (at the index date or one year prior) included age, gender, number of hospitalisation events due to any cause, COPD or cardiovascular disease (CVD), number of moderate or severe exacerbations, comorbidities, Charlson comorbidity index (CCI), oral glucocorticoid (OCS) therapy use and prior use of ICS-LABA combinations. Exacerbations were defined as use of OCS or hospitalisation with the International Classification of Diseases (ICD-10) code of COPD (J44).

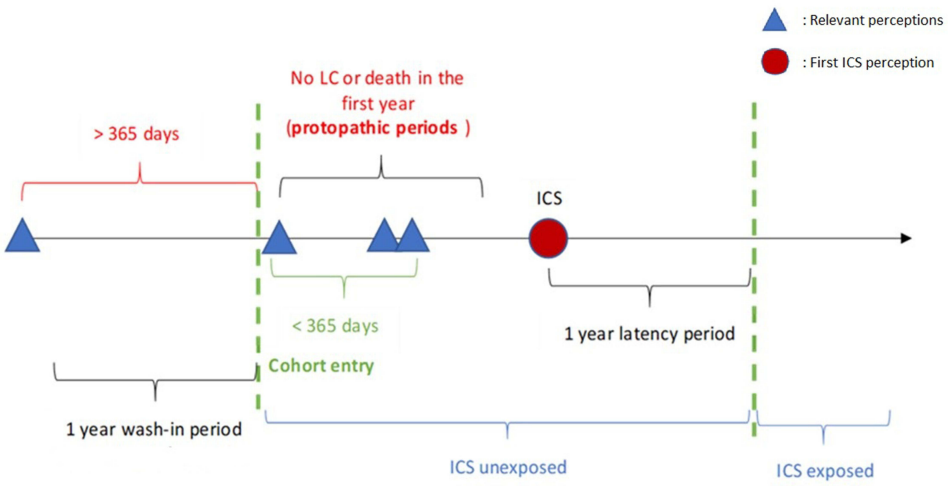

Figure 1 Graphical depiction of cohort formation and the most relevant definitions.

Lung cancer was defined as first inpatient, outpatient care or medication prescription with ICD-10 code of LC (C34). ICS use was further detailed based on the length of continuous therapy and daily dose used. Length was calculated based on the days of therapy covered by a single prescription, calculated from the daily dosage and type of medications, multiplied by the number of prescriptions. A maximum of 30 days gap was accepted between two prescriptions for consideration of continuous therapy. Daily dose was calculated by the cumulative, fluticasone equivalent dose of all prescriptions, divided by the cumulative days of continuous treatment (including the gaps as well). Based on length and dosage, three groups were created: 0 – below 2 years, 2 – below 4 years, 4 years or longer; 0–500 mcg/day, 501–1000 mcg/day, over 1000 mcg/day.

Finally, to further investigate the enrolled patient populations, an analysis was done to determine what is the rate of prescriptions in patients with both J44 (COPD) and J45 (asthma) ICD-10 codes for both cohorts. The ratio of prescriptions based on J44 and J45 (J44/J45 ratio) was calculated: ratio of 1 indicates a higher chance of COPD patients' enrolment, while a ratio close to 0 indicates a higher chance of inclusion of asthma patients. Details of this analysis are shown in Supplementary Material 1.

Statistical Analysis

Baseline characteristics were compared between patients who received inhaled corticosteroid (ICS) therapy (at any time during follow-up) and those who did not, within each cohort. Categorical variables were compared using chi-square tests and continuous variables with ANOVA. A p-value <0.05 was considered statistically significant.

The expected number of lung cancer events per 1000 patients per year was estimated for each therapy group (exposed vs non-exposed, and subgroups defined by therapy duration and average daily dose). Crude incidence rates and person-years were calculated for each group, and their ratio was used to derive incidence rates.

To examine the association between ICS therapy and lung cancer incidence while addressing censoring, Cox proportional hazards regression models were applied. Two model variants were used: a crude model including only ICS exposure, and an adjusted model incorporating age and sex as fixed covariates, while ICS therapy was modelled as a time-dependent covariate to avoid immortal time bias in both models. Reference categories were defined as male sex, age 50–59 years, and non-ICS exposure. Due to population size constraints, the regression models were executed on 10 disjoint random samples, with aggregated results presented (details of this method are presented in Supplementary Material 2). The outputs included log10-transformed hazard ratio estimates, standard errors, hazard ratios with 95% confidence intervals, and p-values. Given the observational, non-randomized nature of the dataset, these findings are limited to associative conclusions without implying causality, as potential confounding factors beyond age and sex could not be fully controlled.

Suissa and Raymakers also incorporated a substantial number of additional covariates in their model. While there is some overlap among these, notable differences also exist. Upon reviewing their results, we observed that the hazard ratio (HR) associated with ICS use changed only marginally after including the additional covariates. Therefore, as we did not see a medical rationale for the inclusion of these parameters, for the sake of simplicity, our models were adjusted only for patient sex and age. As part of the sensitivity analyses, we examined the impact of considering or disregarding latency and protopathic periods on our results. The results of these analyses are detailed in Supplementary Material 3.

Results

Cohort Formation

During the studied period, 1,031,791 patients had at least one prescription for inhaled medications (maintenance and/or reliever) with either J44 or J45 codes. With the use of cohort formation criteria from Cohort 1, 131,294 patients met initial criteria, and after exclusions, detailed in Figure 2, 113,653 patients were ultimately enrolled. After the application of the 1 year protopathic period this number decreased to the final population of 96.686 who were followed for an average of 1741.5 days (4.77 years). Using the criteria of Cohort 2, 296,974 patients met initial criteria, and 225.115 patients were enrolled. Similarly, with the application of the protopathic period, the final population of 196.560 patients was created and followed for an average of 1823.3 days (4.99 years). Details of cohort formation for both populations is shown in Figure 2.

Descriptive Results

With the application of the one-year latency period 25.341 (26.2%) patients were ICS exposed in Cohort 1, and 119.417 patients (60.8%) in Cohort 2. There were multiple statistically significant differences within both cohorts between ICS exposed and not exposed populations. Notably in Cohort 1, there were more female patients (51.4% vs 47.3%) who had more COPD related events (hospitalisation 0.09 vs 0.05 event/person and exacerbations – 1 or more 12.3% vs 8.7%) but suffered from lower overall burden of comorbidities, based on the CCI (1.81 vs 1.88) in the population exposed to ICS. In Cohort 2 similar differences were seen, with a markedly higher proportion of female patients (60.2% vs 49.5%), higher COPD related burden (0.06 vs 0.04 events of COPD related hospitalisations/person and 10.5% vs 7.8% who had one or more exacerbations) and lower CCI (1.81 vs 1.84). All detailed differences and p values are shown in Tables 1 and 2.

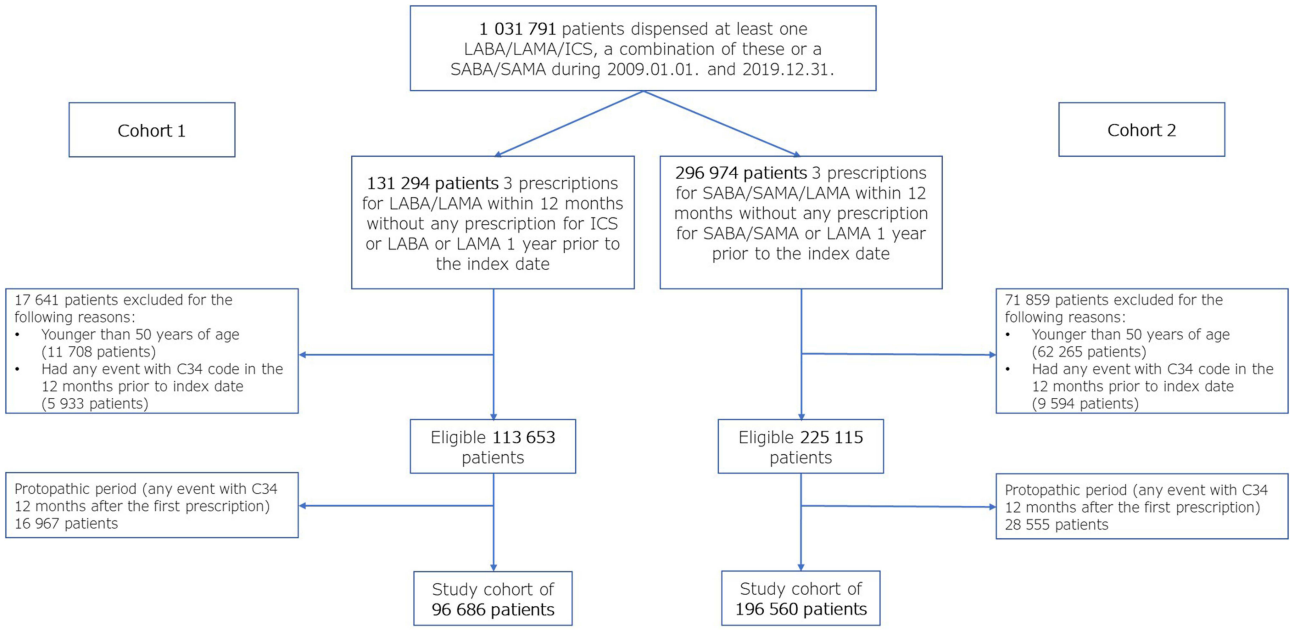

Figure 2 Details of cohort formation for both populations. Enrolment criteria of Cohort 1 correspond to Suissa's and Cohort 2 to Raymakers's selection criteria.

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Table 1 Baseline Characteristics of Cohort 1. Hospitalisations, Exacerbations, Previous ICS-LABA Therapy Use, and Comorbidities Were Assessed 1 Year Prior to Index Date

	No ICS	ICS	Total	P-value
Number of patients	71345	25,341	96,686	
Follow-up time mean (days) (SD)	1606.67 (886.31)	2121.20 (852.83)	1741.52 (906.35)	<0.001
Females (%)	33,769 (47.3)	13,026 (51.4)	46,795 (48.4)	<0.001
Age mean (SD) - index date	66.05 (9.24)	64.58 (8.79)	65.66 (9.14)	<0.001
Age group (%)				<0.001
50–59	19,435 (27.2)	8371 (33.0)	27,806 (28.8)	
60–69	27,536 (38.6)	9643 (38.1)	37,179 (38.5)	
70+	24,374 (34.2)	7327 (28.9)	31,701 (32.8)	
Hospitalization mean (SD)				
Any reason	0.62 (1.19)	0.63 (1.15)	0.63 (1.18)	0.562
COPD-related	0.05 (0.26)	0.09 (0.36)	0.06 (0.29)	<0.001
CVD-related	0.14 (0.52)	0.12 (0.49)	0.14 (0.52)	<0.001
Exacerbation (%)				<0.001
Zero	65087 (91.2)	22,214 (87.7)	87,301 (90.3)	
One	4665 (6.5)	2253 (8.9)	6918 (7.2)	
Two or more	1593 (2.2)	874 (3.4)	2467 (2.6)	
Combination therapy (ICS + LABA) (%)	0	0	0	0
Oral glucocorticoid use (%)	3318 (4.7)	1545 (6.1)	4863 (5.0)	<0.001
Comorbidity (%)				
Myocardial infarction	3519 (4.9)	1060 (4.2)	4579 (4.7)	<0.001
Heart failure	11822 (16.6)	3921 (15.5)	15,743 (16.3)	<0.001
Peripheral vascular disease	10073 (14.1)	2945 (11.6)	13,018 (13.5)	<0.001
Cerebrovascular disease	13253 (18.6)	4308 (17.0)	17,561 (18.2)	<0.001
Diabetes	14014 (19.6)	4526 (17.9)	18,540 (19.2)	<0.001
Renal disease	2283 (3.2)	658 (2.6)	2941 (3.0)	<0.001
Cancer (not lung)	5846 (8.2)	1686 (6.7)	7532 (7.8)	<0.001
Metastatic cancer	383 (0.5)	109 (0.4)	492 (0.5)	0.046
Dementia	869 (1.2)	245 (1.0)	1114 (1.2)	0.001
Rheumatoid disease	1216 (1.7)	458 (1.8)	1674 (1.7)	0.293
Peptic ulcer	317 (0.4)	99 (0.4)	416 (0.4)	0.287
Liver disease	1898 (2.7)	633 (2.5)	2531 (2.6)	0.171
Hemiplegia or paraplegia	314 (0.4)	99 (0.4)	413 (0.4)	0.327
Charlson comorbidity index mean (SD)	1.88 (1.61)	1.81 (1.53)	1.87 (1.59)	<0.001

Abbreviations: COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; ICS, inhaled corticosteroids; LABA, long-acting beta agonist; SD, standard deviation.

Table 2 Baseline Characteristics of Cohort 2. Hospitalisations, Exacerbations, Previous ICS-LABA Therapy Use, and Comorbidities Were Assessed 1 Year Prior to Index Date

	No ICS	ICS	Total	P-value
Number of patients	77143	119,417	196,560	
Follow-up time mean (days) (SD)	1557.19 (887.78)	1995.14 (928.27)	1823.26 (937.31)	<0.001
Females (%)	38,148 (49.5)	71,927 (60.2)	110,075 (56.0)	<0.001
Age mean (SD)	65.99 (9.41)	64.79 (9.30)	65.26 (9.37)	<0.001
Age group (%)				<0.001
50–59	21,525 (27.9)	40,231 (33.7)	61,756 (31.4)	
60–69	29,251 (37.9)	42,904 (35.9)	72,155 (36.7)	
70+	26,367 (34.2)	36,282 (30.4)	62,649 (31.9)	
Hospitalization mean (SD)				
Any reason	0.63 (1.24)	0.59 (1.13)	0.61 (1.17)	<0.001
COPD-related	0.04 (0.24)	0.06 (0.28)	0.05 (0.26)	<0.001
CVD-related	0.14 (0.52)	0.10 (0.42)	0.11 (0.46)	<0.001
Exacerbation (%)				<0.001
Zero	71114 (92.2)	106,821 (89.5)	177,935 (90.5)	
One	4430 (5.7)	8992 (7.5)	13,422 (6.8)	
Two or more	1599 (2.1)	3604 (3.0)	5203 (2.6)	
Combination therapy (ICS + LABA) (%)	2550 (3.3)	32,763 (27.4)	35,313 (18.0)	<0.001
Oral glucocorticoid use (%)	3204 (4.2)	7468 (6.3)	10,672 (5.4)	<0.001
Comorbidity (%)				
Myocardial infarction	3695 (4.8)	3871 (3.2)	7566 (3.8)	<0.001
Heart failure	12485 (16.2)	16,287 (13.6)	28,772 (14.6)	<0.001
Peripheral vascular disease	10639 (13.8)	12,834 (10.7)	23,473 (11.9)	<0.001
Cerebrovascular disease	14510 (18.8)	21,538 (18.0)	36,048 (18.3)	<0.001
Diabetes	15316 (19.9)	21,861 (18.3)	37,177 (18.9)	<0.001
Renal disease	2518 (3.3)	3014 (2.5)	5532 (2.8)	<0.001
Cancer (not lung)	6381 (8.3)	8445 (7.1)	14,826 (7.5)	<0.001
Metastatic cancer	446 (0.6)	508 (0.4)	954 (0.5)	<0.001
Dementia	968 (1.3)	1258 (1.1)	2226 (1.1)	<0.001
Rheumatoid disease	1325 (1.7)	2233 (1.9)	3558 (1.8)	0.014
Peptic ulcer	347 (0.4)	456 (0.4)	803 (0.4)	0.023
Liver disease	2094 (2.7)	2908 (2.4)	5002 (2.5)	<0.001
Hemiplegia or paraplegia	388 (0.5)	484 (0.4)	872 (0.4)	0.002
Charlson comorbidity index mean (SD)	1.84 (1.63)	1.81 (1.53)	1.82 (1.57)	0.001

Abbreviations: COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; ICS, inhaled corticosteroids; LABA, long-acting beta agonist; SD, standard deviation.

There were relevant differences among the percentages of J45 codes of ICS exposed and not exposed groups in Cohorts 1 and 2. In Cohort 1, the percentage of patients who had their prescriptions for maintenance therapy with J45 code over 50% of all times (more prevalent prescriptions for asthma than for COPD) was 5.5% in the non-exposed and 10.0% in the ICS exposed groups. At the same time, in Cohort 2 the same proportions were 7.8% for non-exposed and 44.3% for ICS exposed groups. The distribution of J45/J44 prescriptions in all populations is shown in Supplementary Material 1.

LC was documented in 4941 (5.11%) cases in Cohort 1, of which 1075 (21.8%) happened in the ICS exposed group, while in Cohort 2 overall 8969 (4.56%) LC cases were reported, out of which 4487 (50.0%) happened in the ICS exposed group.

The crude LC incidence rates were the following: in Cohort 1, among ICS exposed patients 13.6 LC cases/1000 patients/year, for ICS non-exposed patients 12.3 events/1000 patients/year; in Cohort 2, among ICS exposed patients 9.6 events/1000 patients/year, for ICS non-exposed patients 13.6 events/1000 patients/year. Most patients received ICS for a shorter time (0–2 years) and lower dosage (<500 mcg fluticasone propionate equivalent), and the majority of LC events happened in the lower dose/shorter period ICS populations. The exact values are shown in Table 3. As shown in Table 1 and Table 2, there were significant differences across multiple parameters between the ICS exposed and not exposed groups, including age and sex, so adjusting to these factors can relevantly alter the crude LC incidence rate. Finally, the crude incidence rate does not account for the time-dependent modeling of ICS exposure and the one-year latency period applied in the Cox regression.

Model Results

Both in the crude and age plus sex adjusted model in both cohorts, a significant reduction of LC risk was shown in patients exposed to ICS with HR = 0.77 (95% confidence interval – 95% CI: 0.63; 0.94) in Cohort 1 and HR = 0.61 (95% CI: 0.53; 0.7) in Cohort 2. Also in these models, for both cohorts, a significant decrease of risk was observed in females (Cohort 1 HR = 0.69, 95% CI: 0.58; 0.82; Cohort 2 HR = 0.64, 95% CI: 0.56; 0.74), while a significant increase of risk was observed in the age group 60–69, compared to reference of 50–59 years of age. All results of the adjusted models are shown in Table 4.

Table 3 Number of LC Incidence (Events), Person-years of Follow-Up and Incidence Rates for Cohorts 1 and 2

	Cohort 1			Cohort 2		
	Number with Events	**Person-Years**	**Rate/1000/Year**	**Number with Events**	**Person-Years**	**Rate/1000/Year**
Any ICS Use						
None	3866	314,048.7	12.3	4482	329,114.7	13.6
Any ICS	1075	78,950.7	13.6	4487	469,082.9	9.6
Time since ICS initiation						
None	3866	314,048.7	12.3	4482	329,114.7	13.6
0–2 years	820	43,867.2	18.7	3048	227,205.1	13.4
>2–4 years	188	20,084.3	9.4	996	119,182.8	8.4
>4 years	67	15,001.3	4.5	443	122,695.0	3.6
Mean daily dose (mcg)						
None (reference)	3866	314,120.2	12.3	4484	329,352.4	13.6
>0 to <500 mcg	956	74,204.0	12.9	3882	439,927.0	8.8
500 to <1000 mcg	103	4468.9	23.0	554	27,882.9	19.9
≥1000 mcg	16	209.4	76.4	49	1035.2	47.3

Table 4 Age and Gender Adjusted Models of ICS Exposure's Effect on Lung Cancer Incidence in COPD Patients

	Cohort 1				Cohort 2			
	Coefficient	**Standard Error**	**Hazard Ratio (95% CI Interval)**	**P-value**	**Coefficient**	**Standard Error**	**Hazard Ratio (95% CI Interval)**	**P-value**
ICS use								
None (reference)								
Any ICS use	−0.26	0.1	0.77 (0.63; 0.94)	0.011	−0.49	0.07	0.61 (0.53; 0.7)	<0.001
Gender								
Male (reference)								
Female	−0.37	0.09	0.69 (0.58; 0.82)	<0.001	−0.44	0.07	0.64 (0.56; 0.74)	<0.001
Age								
50–59 (reference)								
60–69	0.29	0.11	1.34 (1.08; 1.66)	0.006	0.28	0.08	1.32 (1.13; 1.55)	<0.001
70–79	0.13	0.12	1.14 (0.9; 1.44)	0.313	0.14	0.09	1.15 (0.96; 1.37)	0.126
80+	−0.32	0.24	0.73 (0.45; 1.16)	0.174	−0.21	0.17	0.81 (0.58; 1.13)	0.206

Notes: Hazard ratios are highlighted in green if the parameter significantly decreases the risk of LC development, while the ones highlighted in red significantly increase the risk of LC.

When comparing the length of therapy, ICS exposure of 0–2 years corresponded to a significant decrease in LC risk in both cohorts (Cohort 1 HR = 0.74, 95% CI: 0.6; 0.92; Cohort 2 HR = 0.58, 95% CI: 0.5; 0.66). Medium length of ICS use (2–4 years) corresponded to a significant decrease of LC risk in Cohort 2 (HR = 0.73, 95% CI: 0.57; 0.92), while long-term ICS exposure (>4 years) corresponded to an increase in risk for LC in Cohort 1 (HR = 1.88, 95% CI: 1.04; 3.38; Table 5). Of

Table 5 Age and Gender Adjusted Models of ICS Therapy of Length and Dose's Effect on Lung Cancer Incidence in COPD Patients

	Cohort 1				Cohort 2			
	Coefficient	**Standard Error**	**Hazard Ratio (95% CI Interval)**	**P-value**	**Coefficient**	**Standard Error**	**Hazard Ratio (95% CI Interval)**	**P-value**
Time since ICS initiation								
None (reference)								
0–2 years	−0.3	0.11	0.74 (0.6; 0.92)	0.008	−0.55	0.07	0.58 (0.5; 0.66)	<0.001
>2–4 years	−0.08	0.24	0.92 (0.58; 1.48)	0.746	−0.32	0.12	0.73 (0.57; 0.92)	0.006
>4 years	0.63	0.3	1.88 (1.04; 3.38)	0.038	−0.2	0.17	0.82 (0.59; 1.14)	0.237
Mean daily dose since ICS initiation, mcg								
None (reference)								
>0 to <500 mcg	−0.25	0.11	0.78 (0.63; 0.97)	0.019	−0.51	0.07	0.6 (0.52; 0.69)	<0.001
500 to <1000 mcg*	–	–	–	–	−0.09	0.16	0.91 (0.67; 1.25)	0.584
≥1000 mcg*	–	–	–	–	–	–	–	–

Notes: *Results for the 500 mcg to <1000 mcg and ≥1000 mcg/day fluticasone equivalent dose group could not be reported due to insufficient case numbers and data protection constraints of the NHIF. Hazard ratios are highlighted in green if the parameter significantly decreases the risk of LC development, while the ones highlighted in red significantly increase the risk of LC.

particular note, this finding should be interpreted with caution, as the number of events in this subgroup was small (n = 67) and the confidence interval is wide, indicating substantial uncertainty around this estimate.

Evaluation of the effect of ICS dose was limited, as a low number of cases used high doses of ICS. In both cohorts most patients used low doses of ICS, and in both cohorts low dose ICS exposure (>0 to <500 mcg) corresponded to a significant decrease of LC risk (in Cohort 1 HR = 0.78, 95% CI: 0.63; 0.97; Cohort 2 HR = 0.6, 95% CI: 0.52; 0.69). Details of the models of ICS therapy length and dose are shown in Table 5. High ICS dose usage was observed in a very low number of cases; thus, the data of this group were not available due to data protection regulations of the NHIF.

To show the comparison of our results and the research data of Suissa and Raymakers, Figure 3 shows the HRs and corresponding confidence intervals for ICS exposure and ICS therapy length and dose in our cohorts and those of the two original works. In the original work of Raymakers et al ICS therapy length and dose were assessed as continuous variables while in Suissa's and our work these variables were assessed as categorical. For this reason, the dose and therapy length results of Raymakers were excluded from this Figure.

Our sensitivity analysis aimed at determining the impact of the applied latency and protopathic periods. As shown in Supplementary Material 3, omitting the latency period influenced the outcomes, mainly reducing the protective effect of ICS, or in some cases reversing it. The impact of the protopathic period appeared to be dependent on the application of a latency period: when a latency period was applied, including the protopathic period resulted in a less favorable effect of ICS. Conversely, when no latency period was applied, the observed effect of ICS therapy was less sensitive to whether the protopathic period was included. Excluding the protopathic period significantly affected the final cohort size.

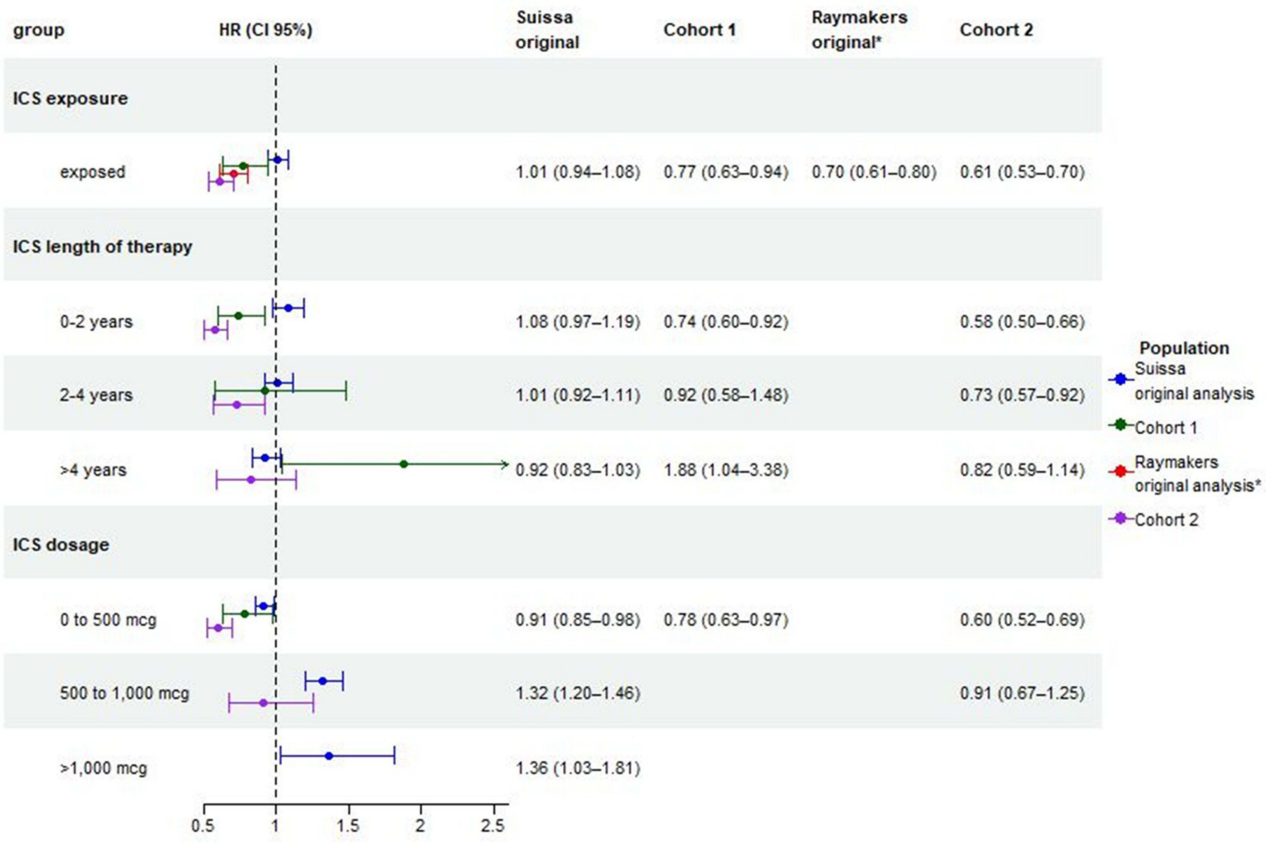

Figure 3 Forest plot showing the HRs and corresponding 95% CIs from the original works of Suissa, Raymakers and our age and gender adjusted models. *Raymakers et al presented results only for ICS exposure.

Discussion

Glucocorticoids (GC) are widely used as potent anti-inflammatory agents, as they – among many other effects – reduce immune cell recruitment and proinflammatory cytokine production, and potentially protect against cancer in early, pre-tumour environments.[32–35] However, during chronic inflammation prolonged GC signalling may impair tissue repair, suppress anti-tumour immunity, promote immune checkpoint expression, and favour tumour cell survival.[36–38] Thus, dysregulated inflammation and long-term glucocorticoid exposure can shift the immune environment from tumour-suppressive to tumour-promoting. In accordance with this, some researchers have found that long-term glucocorticoid exposure might be associated with a higher risk of cancer when administered orally.[39–41] However, in COPD glucocorticoid substances are administered as a maintenance therapy via inhalation, thus have markedly reduced systemic side effects. This generates the question of whether the local anti-inflammatory treatment, by suppressing chronic inflammation of the airways in COPD patients, can reduce the risk of lung cancer development. Some researchers observed in retrospective data analyses that ICS use in COPD was associated with a lower risk of lung cancer.[12,13,15,42–44] Two meta-analyses also indicated that ICS use in COPD was associated with a reduced risk of lung cancer, although the potential protective effect might be questioned due to biases in the included studies.[14]

In our study, we aimed to compare the methodology and outcomes of two large, population-based, retrospective studies, assessing the effect of ICS use on the risk of incident LC in COPD, by recreating these populations and evaluating the outcomes in the database of the Hungarian NHIF. Our results show that in both study cohorts the incidence of LC was significantly lower in the ICS exposed groups as compared to patients who never received ICS. These findings strengthen the earlier assumption that the use of ICS might have a beneficial effect in preventing LC in COPD patients.

Our results of general ICS exposure are in concordance with the findings of Raymakers but are in contrast with the findings of Suissa. However, evaluating the effect of ICS, depending on the dose used by the patients, we can conclude that all studies show a significant decrease in the risk of LC with the lowest dosage (0–500 mcg fluticasone propionate equivalent). We must highlight that in current (and previous) treatment guidelines the use of high dose ICS is not recommended in COPD, so based on the equivalence table of Global Initiative for Asthma (GINA) document, only low or medium dose ICS is used in COPD. This is equivalent to the lowest dose category in our study, meaning that the currently accepted doses of ICS used in COPD treatment could have a potential risk reduction effect of LC incidence.

The divergent findings between our Cohort 1 and Suissa's original study, despite using the same methodology, warrant consideration. Several factors may explain this discrepancy. First, population-level differences likely play a role: Hungary has one of the highest lung cancer incidence rates in Europe,[45–47] with potentially different stage distribution at diagnosis and different smoking patterns compared to Quebec. Second, healthcare system differences may influence outcomes – Hungary's single-payer system captures all COPD patients regardless of socioeconomic status, whereas the Quebec database primarily included patients aged ≥65 years or welfare recipients. Third, the study periods differed (2009–2019 vs 2000–2015), during which COPD treatment guidelines and ICS prescribing patterns evolved substantially – most notably, the use of higher doses of ICS had been shown not to be effective in COPD treatment, resulting in very low prevalence of high ICS dose usage in our populations. Nonetheless, our results in both cohorts align more closely with those of Raymakers et al, despite using Suissa's methodology in Cohort 1, suggesting that population-level factors may have a stronger influence on the observed association than the specific analytical approach employed.

A particularly interesting aspect is the observed association of LC development with the length of ICS use in COPD, which mainly showed a distinctly varied picture in both the works of Suissa and Raymakers, and in our cohorts. We must highlight the results of Cohort 1, which showed an increase in LC risk with long treatment (>4 years). However, it is also important to note that the number of events was very low in this population. These results raise the possibility that the impact of glucocorticoids on LC risk is strongly influenced by the inhaled dose and the length of exposure. This observation may reflect the dual nature of glucocorticoid effects on carcinogenesis. While short-term anti-inflammatory action may suppress early tumor-promoting inflammation, prolonged exposure could impair anti-tumor immunity and tissue repair mechanisms, as we have discussed above.

In our exploratory analysis, the proportions of enrolled patients with asthma and COPD were evaluated in both cohorts. We found that in Cohort 2 there was a difference between ICS exposed and not exposed populations in the proportion of patients

having mostly asthma prescriptions (shown on Supplementary Figures 4–6). This could mean that in the ICS exposed groups, a larger proportion of asthma patients were enrolled, which could lead to a bias in our results, as asthmatics generally have lower risk of LC than COPD patients. However, no similar difference was observed in Cohort 1, retaining our overall conclusions (as presented on Supplementary Figures 1–3). We do not presume that this might have biased our results, as similar case was described in the results of Raymakers in their original work; their subsequent analysis showed that the exclusion of patients with events with J45 codes (asthma) resulted in similar outcomes as their main analysis. Notably, Suissa et al themselves cited asthma patient inclusion as a potential source of bias in observational studies reporting a protective ICS effect – yet our Cohort 1, following the Suissa methodology with minimal asthma contamination (10.0% of ICS-exposed patients), also demonstrated a statistically significant protective association, suggesting that the observed effect cannot be solely attributed to the inclusion of asthma patients with a lower baseline lung cancer risk.

Our sensitivity analysis aimed at determining the effect of the applied latency and protopathic periods. As shown in Supplementary Material 3, discarding latency period had a strong effect on the outcomes, mainly reducing the protective effect of ICS or even reversing it. On the other hand, discarding protopathic period had little effect on the outcomes, however it significantly affected the final cohort numbers. Based on these findings, the application of both methods is important for the final analysis. Detailed comparisons of these changes in the model are shown in Supplementary Figures 7–9 for Cohort 1 (overall exposure, length of therapy and average daily dose showed similar changes depending on the presence or absence of protopathic and latency periods), and on Supplementary Figures 10–12 for Cohort 2 (similar effects seen for all exposure definitions).

There are relevant limitations to our study. First, our aim was to make possible a comparison of the aforementioned publications, which resulted in the use of a limited model. Inclusion of further confounders to investigate their effect is a necessary next step to strengthen our conclusion. Furthermore, the use of a multi-state model instead of simple censoring in case of the protopathic period would provide a more sophisticated outcome. Finally, through database analysis, it is not possible to access patient level data (like smoking history), histologically validate LC occurrence, or validate the COPD diagnosis by spirometry. Smoking history is possibly the most relevant of these missing parameters, as it has the most documented effect on the risk of lung cancer development, as discussed above. Unfortunately, smoking is not reported in the financial database by any reliable proxy, as there is no reimbursed activity linked to any code that is applicable to all smokers. This is a limitation shared by both original publications we aimed to replicate. In Cohort 1, where patients were identified based on LAMA and/or LABA use – medications exclusively indicated for COPD – smoking history is likely to be similarly distributed across exposure groups, potentially limiting its role as a differential confounder. In Cohort 2, where a higher proportion of asthma patients was present in the ICS-exposed group (44.3%), the potential confounding effect of smoking cannot be excluded to the same extent. Finally, our lung cancer outcome definition, based on the first occurrence of ICD-10 C34 code across inpatient, outpatient and prescription records, may be subject to outcome misclassification, and a sensitivity analysis incorporating different outcome definitions would be warranted in future studies.

Strengths of our study stem from the large patient numbers enrolled, and the fact that, as Hungary has a single-insurance based healthcare system, the evaluation of the whole COPD population of the country is possible. This is a unique opportunity which helps to diminish potential confounders that might affect other databases which only cover parts of a country's population, based on, for example geography, income status, specific populations etc.

Conclusion

In our work of recreating two large, population based cohort studies, we have found that ICS exposure decreased the risk of lung cancer in COPD patients, with lower dose of ICS and shorter treatment period. At the same time, extended ICS exposure increased LC risk. While the observational design precludes definitive causal conclusions, the consistency of the protective association across both methodological approaches and the large sample size provide a rationale for further investigation, ideally through prospective studies with detailed smoking history and histologically confirmed outcomes.

Data Sharing Statement

The data analyzed in this study were obtained from the financial database of National Health Insurance Fund of Hungary and is not available from the authors. Derived data supporting the findings of this study are available from the corresponding author upon reasonable request.

Ethics Approval and Consent to Participate

The study was approved by the National Scientific and Research Ethics Committee of Hungary (ETT-TUKEB), under docket number IV/2651-4/2021/EKU and it was conducted in accordance with the Helsinki Declaration. As the study was approved on a national level, no additional institutional ethics' committee approval was needed.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

B. Santa is an employee of Chiesi Hungary Kft. Dr Laszlo Nemeth reports personal fees from Semmelweis University, Budapest, outside the submitted work. T. Balázs reports consultancy fees paid to his institution from Chiesi Hungary Kft., outside the submitted work. V. Müller reports personal fees or grants from Chiesi, Astra Zeneca, Berlin Chemie Menarini, Boehringer Ingelheim, TEVA, and Pfizer, during the conduct of the study. All other authors have no relevant conflict of interest to declare regarding the study.

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