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# Association between inhaled corticosteroids and incidence of idiopathic pulmonary fibrosis: nationwide population-based study

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## ABSTRACT

**Background** Idiopathic pulmonary fibrosis (IPF) is a progressive disease found primarily in older people, with the use of systemic steroids linked to poor outcomes. However, the role of inhaled corticosteroids (ICSs) in IPF remains unclear. This study investigated the association between ICS use and IPF risk using national insurance data, particularly in individuals with chronic airway diseases.

**Methods** Using the National Health Insurance Service-National Sample Cohort database, our study included patients diagnosed with chronic obstructive pulmonary disease or asthma. ICS exposure was assessed via treatment claims, and IPF cases were identified using broad and narrow criteria. We used inverse probability of treatment weighting (IPTW) with propensity scores for balanced covariate analysis.

**Results** Of 57 456 patients (mean age: 55.9 years, 42.3% men), 16.5% used ICS and 83.5% did not. ICS users showed higher rates of broad (0.98 vs 0.41 per 1000) and narrow IPF (0.61 vs 0.21 per 1000) than non-users. Pre-IPTW, ICS use was associated with increased IPF risk; however, this was not significant post-IPTW. Post-IPTW, both ICS dose as a continuous variable (broad adjusted HR per 100 µg/day: 1.03, 95% CI: 1.02 to 1.04; narrow adjusted HR per 100 µg/day: 1.03, 95% CI: 1.01 to 1.04 post-IPTW) and high-dose ICS (≥1000 µg/day) (broad adjusted HR: 3.89, 95% CI: 1.61 to 9.41; narrow adjusted HR: 3.99, 95% CI: 1.19 to 13.41) use correlated with an elevated IPF risk.

**Conclusion** While no overall significant association between ICS use and IPF risk was observed post-IPTW, there may be an increased risk in patients using high-dose ICS.

### WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Idiopathic pulmonary fibrosis (IPF) is a chronic and progressive interstitial lung disease with a high mortality rate. While systemic steroids have a negative impact on IPF outcomes, inhaled corticosteroids (ICS) are widely used in managing other chronic respiratory conditions, including chronic obstructive pulmonary disease (COPD) and asthma.

### WHAT THIS STUDY ADDS

⇒ This study is the first large-scale nationwide cohort study that investigates the relationship between ICS use and the incidence of IPF specifically in patients with chronic airway diseases like COPD and asthma. The findings suggest that while overall ICS use was not significantly associated with an increased risk of IPF, high doses of ICS might be linked to an elevated risk.

### HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study highlights the need for prospective research to further evaluate the dose-dependent risk of IPF with ICS use in chronic airway disease patients, potentially influencing clinical guidelines to incorporate cautious ICS management. Policymakers may need to revise recommendations to ensure the safe application of ICS, particularly at high doses, to prevent adverse outcomes in at-risk populations.

## BACKGROUND

Idiopathic pulmonary fibrosis (IPF), one of the most prevalent forms of interstitial lung disease (ILD), is a chronic and progressive interstitial pneumonia of unknown aetiology typically observed in older adults.[1 2] Characterised by rapid pulmonary function deterioration, IPF results in substantial respiratory impairment and poor prognoses, with a median survival of 3–5 years postdiagnosis.[1 3] The aetiology of IPF is multifactorial, involving both genetic predisposition and environmental factors, collectively contributing to abnormal wound-repair processes and excessive fibrotic activity in lung tissues.[4] The global burden of IPF is increasing, attributed to an ageing population and diagnostic technique advancements.[5] Current therapeutic approaches—such as the use of antifibrotics—mainly focus on slowing down disease progression and preserving lung function,[6] underscoring the importance of early diagnosis and risk factor identification to improve outcomes in patients with IPF.

While the incidence rate of IPF among patients with airway diseases is not well-established, it has been reported that the incidence of airway diseases, particularly chronic obstructive pulmonary disease (COPD), among patients with IPF is high.[7] In chronic airway diseases such as asthma and COPD, especially with type 2 inflammation, inhaled corticosteroids (ICSs) are crucial for reducing airway inflammation and hyperresponsiveness.[8 9] However, the role of steroids in ILDs presents a complex issue. While systemic steroids are known to affect IPF outcomes adversely,[10 11] their application in non-IPF ILDs, particularly connective tissue disease (CTD)-related ILDs, is a common practice for managing inflammation.[12 13] Thus, the balance of potential risks and benefits of ICS in patients with ILDs, particularly those with IPF, remains unclear. Previously, a small study including 20 patients with IPF showed that beclomethasone/formoterol improved forced expiratory volume in 1 s and forced expiratory flow at 25–75% without any significant effects on forced vital capacity, King's Brief ILD score and the 6-minute walk test—compared with a placebo.[14] However, the broader impact of ICS on the development of IPF, especially in patients with chronic airway diseases, remains unclear. Therefore, this study aimed to investigate the association between ICS use and the risk of IPF in patients with chronic airway disease using nationwide claims data.

## METHODS

### Data source

To conduct this study, we used the updated National Health Insurance Service-National Sample Cohort (NHIS-NSC, V.2.2) sampled from the National Health Insurance (NHI) database in 2006. This cohort represented 2.2% of the South Korean population in 2002.[15] This database, useful for public health experts and policymakers, was collected retrospectively (2002–2005) and prospectively (2007–2019), including new births and removing deceased or emigrated individuals. It comprehensively records insurance eligibility, medical history, healthcare provider details and health examination data.

### Study population

Our study included patients diagnosed with COPD (J42-44, excluding J43.0 (emphysema)) or asthma (J45-J46)—according to the Korean Standard Classification of Diseases codes (KCD)—who underwent multiple medical visits within 1 year from the first diagnosis and used respiratory medications at least twice in that year. We excluded J43.0 (emphysema) as it refers to a structural change often found incidentally on CT, without causing airflow obstruction. These medications included ICSs, long-acting muscarinic antagonists (LAMAs), ICS/long-acting beta-agonists (LABA), short-acting beta-agonists (SABA), xanthine, leukotriene receptor antagonists (LTRA) and systemic steroids.

In our NHIS-NSC cohort including 100 000 participants, we initially screened 354 762 individuals who had COPD or asthma between 2002 and 2019 (figure 1). After applying exclusion criteria, such as an age of <18 years (n=86 085), lack of a national health examination for baseline covariates (n=46 947), a diagnosis of COPD or asthma during the washout period (2002 or 2003), used to exclude individuals with potential pre-existing IPF before cohort entry, a follow-up period of <1 year (diagnosis in 2019) (n=6980), an IPF diagnosis before the date of initial assignment of the IPF diagnosis code (n=130) and missing major covariates (n=1464), we finalised a cohort of 57 456 patients.

### Exposure assessment

Exposure in our study was determined using NHI treatment claims, classifying participants as 'ICS users' or 'non-ICS users' based on their medication records. ICS doses were standardised to fluticasone equivalents (50 mg), with equivalency ratios established for other steroids (budesonide at 80 mg, ciclesonide at 32 mg and beclomethasone at 100 mg).[16–19] The mean daily dose was calculated by dividing the total medication quantity by the prescription duration to assess dose-dependent associations.

### Outcome assessment

The primary outcome of our study was identifying IPF cases using KCD code J84.18 (other interstitial pulmonary diseases with fibrosis), requiring at least one hospitalisation or two outpatient visits with this code, corroborated by chest CT scans within 3 months of the date of initial assignment of the IPF diagnosis code (broad definition) and consistent with previous claims database studies.[20 21] We focused on J84.18 for greater diagnostic specificity, as other codes in the J84 category include ILD not specific to IPF. We incorporated the Rare Intractable Diseases (RID) registration code (V236) because of its strict and reliable criteria for narrow definitions. The government's RID programme—which supports patients with rare diseases—includes stringent criteria for IPF requiring a surgical lung biopsy or chest CT to exclude other ILD causes, consistent with methods used in prior research employing the RID database.[22–24] Since the RID code for IPF was available from 2011, the narrow definition for IPF was evaluated from 2011.

In our study, the index date for ICS users was their first ICS prescription, while that for non-ICS users was the first prescription date of other respiratory medications. Covariates were recorded on the index date. Follow-up began on the date of first ICS prescription for ICS users and on the date of initial IPF diagnosis for non-users, and continued until the earliest occurrence of death, insurance withdrawal or the study end date (31 December 2019).

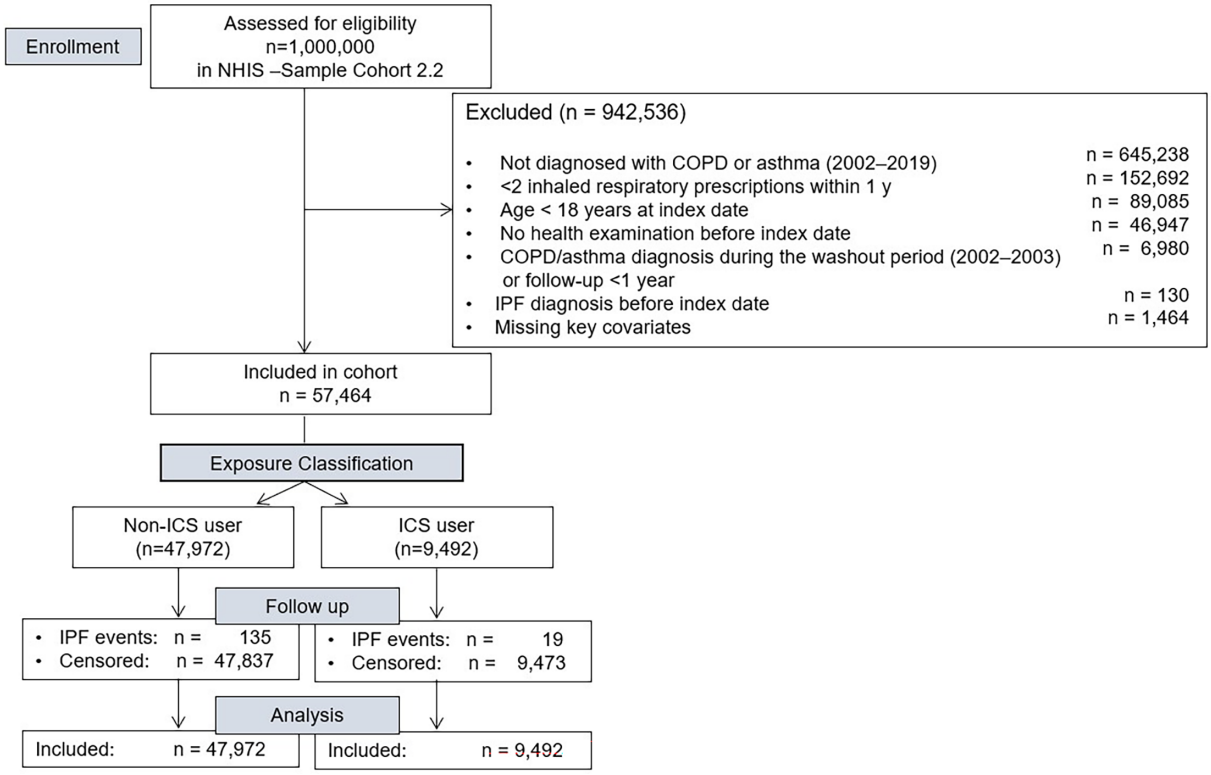


**Figure 1** Patient Enrolment. COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroids; IPF, idiopathic pulmonary fibrosis; NHIS, National Health Insurance Service.

## Statistical analysis

We compared the baseline characteristics of ICS and non-ICS users using t-tests and $\chi^2$ tests. To balance any differences, we used the propensity score method to perform inverse probability of treatment weighting (IPTW).[25] Propensity scores were calculated using a generalised linear model with a binomial distribution, including covariates known to affect the risk and prognosis of IPF, such as baseline demographics, smoking status, comorbidities and prior treatments.[26] We applied stabilised weights to estimate the average treatment effect in the population, which helps suppress large variance and improve the robustness of our estimates.[27] The IPTW-adjusted weights were then used in a Cox proportional hazards (PH) regression model to assess the association between ICS use and IPF outcomes, without further adjustment for covariates. This approach minimised the risk of over-adjustment, as the IPTW process balanced the covariates across groups prior to analysis. A standardised mean difference (SMD) below 0.10 post-IPTW indicated balanced covariates between the groups (online supplemental figure S1).

We calculated the incidence of IPF as cases per 1000 person-years. The IPF risk was calculated using Cox PH models to calculate both unadjusted (before IPTW) and adjusted (after IPTW) HRs with 95% CIs. Kaplan-Meier survival curves were plotted to illustrate IPF incidence over time, and group comparisons were made using the log-rank test. To address potential bias from early diagnosis and to minimise immortal time bias, we conducted landmark analyses at 6 months, 1 year and 2 years. Only patients who survived to each of these time points were included in the analysis, ensuring that ICS exposure and IPF development were evaluated without the influence of survival prior to ICS initiation.

Continuous ICS users were defined as those receiving at least one ICS prescription every 30 days during follow-up. The mean daily ICS doses were used as variables either in a continuous form or transformed into categorical values. For the continuous analysis, the doses were converted to calculate the HR per 100 µg/day. For the categorical analysis, the mean daily ICS doses—converted to fluticasone equivalents—were categorised into three groups: high (1000 µg/day), medium (500–999 µg/day) and low (<500 µg/day). In addition, we used subgroup analyses to identify specific ICS-user groups with a higher risk of IPF, considering factors such as sex, age, smoking status (never vs ever), income level (low (0–3) vs middle (4–7) vs high (8–10)), underlying airway disease (asthma or COPD, both), systemic cumulative steroid use (methylprednisolone <250 mg vs ≥250 mg)[28] and the Charlson Comorbidity Index (CCI) score (<2 vs ≥2).[29]

All statistical analyses were conducted using SAS Enterprise Guide V.8.3 (SAS Institute, Cary, North Carolina, USA) and R Studio V.4.3.0 (RStudio Inc, Boston, Massachusetts, USA). For IPTW and Cox PH modelling, we used the R package's 'WeightIt' (V.0.10.2; Greifer, 2020) and 'survival' (V.3.2–7; Therneau, 2020) to ensure

**Table 1** Baseline demographics before and after IPTW

| Characteristic | ICS users | Non-ICS users | P value* | SMD before IPTW | SMD after IPTW |
|---|---|---|---|---|---|
| Number of patients | 9492 (16.5) | 47 972 (83.5) | | | |
| Age | 59.2±15.5 | 55.3±14.8 | <0.001 | 0.258 | 0.055 |
| Male | 4081 (43.0) | 20 211 (42.1) | 0.120 | −0.009 | −0.014 |
| Smoking status | | | | | |
| Never | 6030 (63.5) | 33 722 (70.3) | <0.001 | −0.068 | −0.003 |
| Former | 1625 (17.1) | 5545 (11.6) | | 0.056 | 0.007 |
| Current | 1837 (19.4) | 8705 (18.2) | | 0.012 | −0.003 |
| BMI | 24.3±3.7 | 24.0±14.7 | <0.001 | 0.026 | 0.016 |
| Income | | | | | |
| Medical aid | 454 (4.8) | 281 (0.6) | <0.001 | 0.042 | 0.000 |
| Low | 2051 (21.6) | 10 559 (22.0) | | −0.004 | −0.001 |
| Middle | 3183 (33.5) | 17 668 (36.8) | | −0.033 | −0.001 |
| High | 3804 (40.1) | 19 464 (40.6) | | −0.005 | 0.002 |
| Comorbidity | | | | | |
| COPD | 570 (6.0) | 5477 (11.4) | <0.001 | −0.054 | 0.009 |
| Asthma | 6818 (71.8) | 36 160 (75.4) | | −0.036 | −0.011 |
| Both COPD and asthma | 2104 (22.2) | 6335 (13.2) | | 0.090 | 0.002 |
| Diabetes mellitus | 1350 (14.2) | 5521 (11.5) | <0.001 | 0.027 | 0.007 |
| Dyslipidaemia | 2224 (23.4) | 7154 (14.9) | <0.001 | 0.085 | 0.009 |
| Hypertension | 3126 (32.9) | 13 083 (27.3) | <0.001 | 0.057 | 0.007 |
| Ischaemic heart disease | 801 (8.4) | 2570 (5.4) | <0.001 | 0.031 | 0.031 |
| Arrhythmia | 312 (3.3) | 923 (1.9) | <0.001 | 0.014 | 0.002 |
| Heart failure | 269 (2.8) | 598 (1.3) | <0.001 | 0.016 | 0.001 |
| Obstructive sleep apnoea | 17 (0.18) | 41 (0.09) | 0.009 | 0.001 | 0.000 |
| Gastro-oesophageal reflux | 3220 (33.9) | 10 281 (21.4) | <0.001 | 0.125 | 0.011 |
| Emphysema | 156 (1.6) | 224 (0.5) | <0.001 | 0.012 | 0.001 |
| Infection | 19 (0.20) | 26 (0.05) | <0.001 | 0.002 | 0.000 |
| NTM | 11 (0.12) | 11 (0.01) | <0.001 | 0.001 | 0.000 |
| Fungal infection | 3 (0.03) | 7 (0.01) | 0.251 | 0.000 | 0.000 |
| IPA | 3 (0.03) | 7 (0.01) | 0.251 | NC | NC |
| Renal failure | 130 (1.4) | 227 (0.5) | <0.001 | NC | NC |
| Malignancy | 566 (6.0) | 1754 (3.7) | <0.001 | NC | NC |
| CCI score≥2 | 4088 (43.1) | 18 751 (39.1) | <0.001 | 0.040 | 0.006 |
| Medication | | | | | |
| ICS only | 4358 (45.9) | NA | | | |
| ICS/LABA | 6863 (72.3) | NA | | | |
| LABA only | 2238 (23.6) | 19 986 (41.7) | <0.001 | −0.181 | −0.007 |
| LABA/LAMA | 150 (1.6) | 163 (0.3) | <0.001 | 0.012 | 0.001 |
| LAMA only | 1612 (17.0) | 1341 (2.8) | <0.001 | 0.142 | 0.002 |
| SABA | 5071 (53.4) | 16 630 (34.7) | <0.001 | 0.188 | 0.031 |
| Xanthine | 4267 (45.0) | 26 914 (56.1) | <0.001 | −0.112 | −0.005 |
| LTRA | 6545 (69.0) | 28 862 (60.2) | <0.001 | 0.088 | 0.023 |
| Systemic steroid | 2760 (29.1) | 22 741 (47.4) | <0.001 | −0.183 | −0.026 |

Data were summarised using mean±SD or number (%). Among the variables, items included in other variables were not separately calculated (NC) for IPTW.
*The p value for the difference was calculated using t-tests and $\chi^2$ test.
BMI, body mass index; CCI, Charlson Comorbidity Index; COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroids; IPA, invasive pulmonary aspergillosis; IPTW, inverse probability of treatment weighting; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; NA, not applicable; NC, not calculated; NTM, non-tuberculous mycobacteria; SABA, short-acting beta-agonist; SMD, standardised mean difference.

**Table 2** Cox proportional analysis for the risk of IPF according to ICS use

| | Broad IPF definition | | | | Narrow IPF definition | | | |
|---|---|---|---|---|---|---|---|---|
| | Unadjusted HR (95% CI) | P value | Adjusted (IPTW) HR (95% CI) | P value | Unadjusted HR (95% CI) | P value | Adjusted (IPTW) HR (95% CI) | P value |
| ICS uses | 1.70 (1.02 to 2.82) | 0.041 | 1.18 (0.62 to 2.63) | 0.680 | 1.91 (1.00 to 3.66) | 0.049 | 1.38 (0.48 to 3.95) | 0.552 |
| Landmark analysis | | | | | | | | |
| 6 months | 2.22 (1.22 to 4.04) | 0.009 | 1.27 (0.58 to 2.78) | 0.554 | 2.21 (1.00 to 4.90) | 0.050 | 1.20 (0.46 to 3.09) | 0.708 |
| 1 year | 1.43 (0.64 to 3.19) | 0.388 | 0.85 (0.26 to 2.78) | 0.790 | 1.61 (0.55 to 4.70) | 0.386 | 0.73 (0.17 to 3.18) | 0.676 |
| 2 years | 1.01 (0.24 to 4.31) | 0.987 | 0.64 (0.11 to 3.82) | 0.624 | 1.76 (0.40 to 7.87) | 0.457 | 1.20 (0.18 to 7.89) | 0.849 |
| Daily dose analysis | 1.04 (1.02 to 1.05) | <0.001 | 1.03 (1.01 to 1.04) | 0.001 | 1.03 (1.01 to 1.06) | 0.010 | 1.03 (1.01 to 1.05) | 0.001 |
| Three groups | | | | | | | | |
| Non-ICS | reference | | reference | | | | reference | |
| 1000 µg/day | 6.94 (2.80 to 17.22) | <0.001 | 3.66 (1.34 to 9.96) | 0.011 | 7.44 (2.30 to 24.10) | <0.001 | 4.67 (1.33 to 16.40) | 0.016 |
| 500–999 µg/day | 1.47 (0.54 to 4.02) | 0.456 | 0.55 (0.18 to 1.72) | 0.304 | 1.31 (0.32 to 5.42) | 0.711 | 0.54 (0.11 to 2.69) | 0.451 |
| <500 µg/day | 1.29 (0.29 to 5.72) | 0.448 | 1.25 (0.46 to 3.39) | 0.666 | 1.62 (0.72 to 3.61) | 0.242 | 1.46 (0.39 to 5.41) | 0.570 |
| Duration | | | | | | | | |
| Non-ICS | reference | | reference | | | | reference | |
| Intermittent use | 1.77 (0.91 to 3.44) | 0.091 | 1.66 (0.62 to 4.46) | 0.316 | 1.90 (0.80 to 4.49) | 0.144 | 1.82 (0.47 to 7.10) | 0.387 |
| Continuous use | 1.62 (0.81 to 3.24) | 0.172 | 0.60 (0.28 to 1.32) | 0.207 | 1.93 (0.82 to 4.56) | 0.134 | 0.83 (0.32 to 2.15) | 0.701 |

*NA: Not applicable because no event occurred
ICS, inhaled corticosteroids; IPF, idiopathic pulmonary fibrosis; IPTW, Inverse probability of treatment weighting.

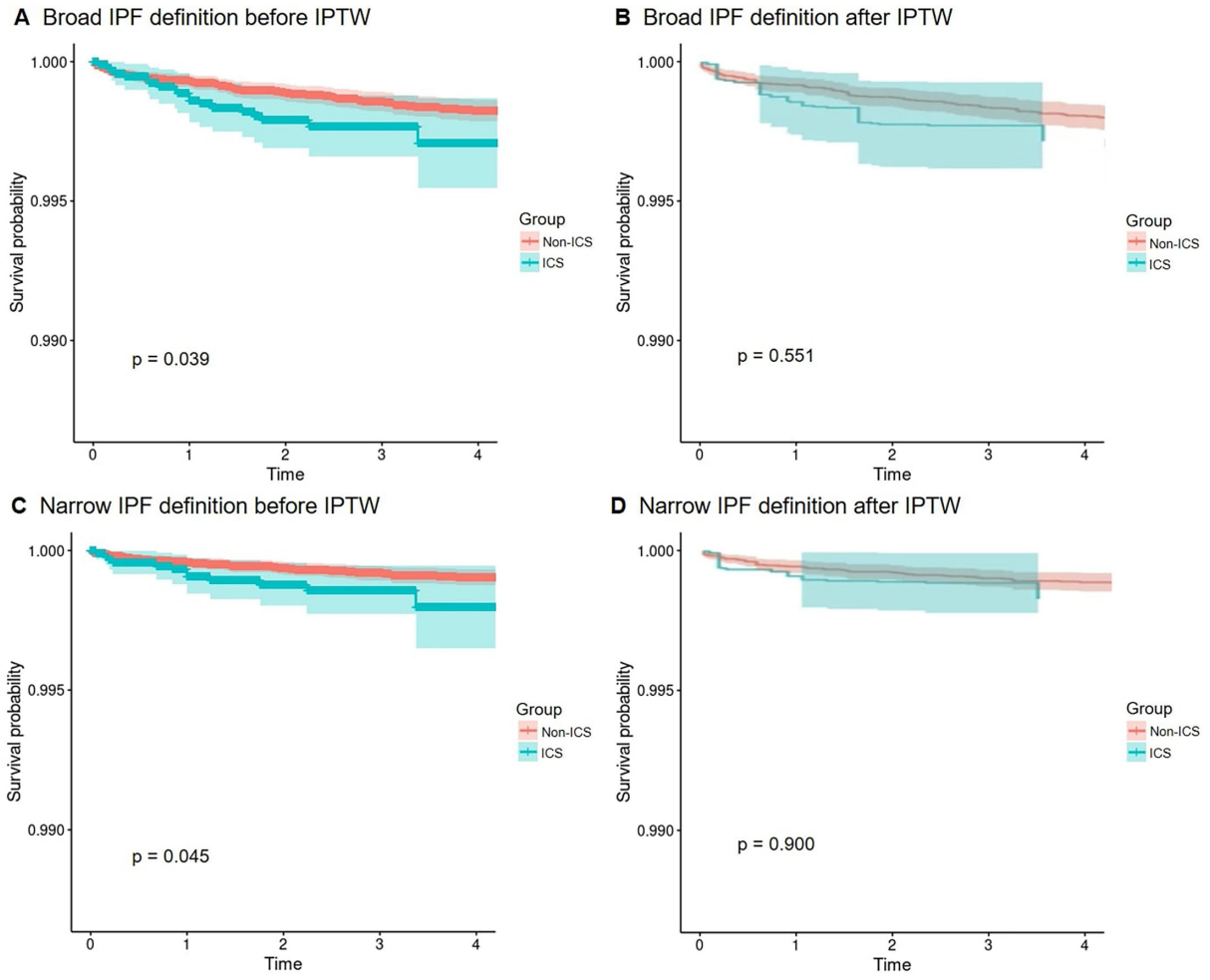


**Figure 2** Cumulative incidence of IPF. (A) Broad IPF definition before IPTW matching, (B) broad IPF definition after IPTW matching, (C) narrow IPF definition before IPTW matching and (D) narrow IPF definition after IPTW matching. The cumulative incidence of IPF was illustrated with a Kaplan-Meier curve, with the x and y axes adjusted to scale. Group differences were assessed using the log-rank test. ICS, inhaled corticosteroids; IPF, idiopathic pulmonary fibrosis; IPTW, inverse probability of treatment weighting.

methodological rigour and reproducibility. Statistical significance was set at p<0.05.

### Patient and public involvement

Patients or the public were not involved in the design, conduct, reporting or dissemination plans of our research.

## RESULTS

### Baseline demographics

In our cohort (n=57 456), the mean age was 55.9 years, with 42.3% being men and 69.2% reporting never having smoked. Within the cohort, 9492 individuals (16.5%) were using ICS, and 47 972 (83.5%) were non-ICS users (table 1).

Before applying IPTW matching, compared with non-ICS users, ICS users were older and had a higher proportion of former and current smokers. They also had a higher body mass index, an increased prevalence of medical aids and more frequent underlying comorbidities, including diagnoses of both COPD and asthma simultaneously, as well as diabetes mellitus, dyslipidaemia and hypertension. Furthermore, ICS users received more prescriptions for LAMA, SABA and LTRA but fewer prescriptions for LABA, xanthine and systemic steroids. The prescription details for ICS users can be found in online supplemental table S1. Over a median follow-up of 6.1 years (IQR: 3.1–9.7 years), 667 (7.0%) deaths occurred among ICS users and 4823 (10.1%) occurred among non-ICS users. Following IPTW matching, the covariates were well-balanced, with all SMDs below 0.1 (online supplemental figure S1).

### Incidence of IPF based on ICS treatment status

We observed 154 cases of broad IPF (0.41 per 1000 people) and 83 cases of narrow IPF (0.22 per 1000 people). ICS users had significantly higher incidences of both broad (0.89 vs 0.38 per 1000 people) and narrow IPF (0.56 vs 0.20 per 1000 people) than non-ICS users (online supplemental table S2). Additionally, high-dose ICS users had significantly higher rates for both broad (3.73 per 1000

Table 3 Subgroup analysis for the risk of IPF according to ICS use

| | | Broad IPF definition | | | Narrow IPF definition | | |
|---|---|---|---|---|---|---|---|
| | Number | Event | Adjusted (IPTW) HR (95% CI) | P value | Event | Adjusted (IPTW) HR (95% CI) | P value |
| Age | | | | | | | |
| ≥ 65 years | 16775 | 100 | 1.61 (0.70 to 3.71) | 0.267 | 56 | 1.78 (0.58 to 5.46) | 0.317 |
| < 65 years | 40689 | 54 | 0.06 (0.01 to 0.48) | 0.008 | 27 | 0.12 (0.02 to 0.95) | 0.044 |
| Sex | | | | | | | |
| Male | 24292 | 107 | 1.10 (0.41 to 2.99) | 0.850 | 59 | 1.33 (0.37 to 4.75) | 0.665 |
| Female | 33172 | 47 | 1.32 (0.45 to 3.87) | 0.612 | 24 | 1.38 (0.32 to 6.01) | 0.669 |
| Smoking | | | | | | | |
| Never | 39752 | 89 | 1.02 (0.39 to 2.62) | 0.973 | 49 | 0.53 (0.15 to 1.83) | 0.314 |
| Ever | 17712 | 65 | 1.36 (0.39 to 4.69) | 0.628 | 34 | 2.70 (0.71 to 10.23) | 0.144 |
| Incomes | | | | | | | |
| Low (0–3rd) | 13345 | 30 | 0.88 (0.29 to 2.69) | 0.820 | 18 | 1.16 (0.31 to 4.30) | 0.826 |
| Middle (4–7) | 20851 | 61 | 1.09 (0.27 to 4.43) | 0.909 | 29 | 1.42 (0.21 to 9.61) | 0.718 |
| High (8–10) | 23268 | 63 | 1.46 (0.62 to 3.39) | 0.472 | 36 | 1.41 (0.46 to 4.35) | 0.544 |
| Underlying airway disease | | | | | | | |
| Asthma | 42978 | 73 | 0.39 (0.11 to 1.42) | 0.152 | 45 | 0.47 (0.11 to 2.08) | 0.321 |
| COPD | 6047 | 30 | 3.00 (0.75 to 11.95) | 0.119 | 14 | 3.00 (0.48 to 18.61) | 0.088 |
| Both | 8439 | 51 | 1.12 (0.40 to 3.15) | 0.830 | 24 | 1.29 (0.44 to 3.83) | 0.643 |
| Systemic steroid | | | | | | | |
| Use (cumulative PD dose ≥250 mg) | 25501 | 67 | 0.81 (0.30 to 2.18) | 0.670 | 38 | 1.35 (0.45 to 4.05) | 0.592 |
| None (cumulative PD dose <250 mg) | 31963 | 87 | 1.31 (0.50 to 3.47) | 0.585 | 45 | 1.36 (0.34 to 5.36) | 0.664 |
| CCI | | | | | | | |
| ≥ 2 | 22839 | 81 | 0.82 (0.34 to 1.99) | 0.665 | 43 | 0.65 (0.18 to 2.37) | 0.519 |
| < 2 | 34625 | 73 | 1.55 (0.50 to 4.79) | 0.445 | 40 | 2.40 (0.64 to 9.04) | 0.196 |

CCI, Charlson comorbidity index; COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroids; IPF, idiopathic pulmonary fibrosis; IPTW, Inverse probability of treatment weighting; PD, prednisolone.

people) and narrow (2.24 per 1000 people) IPF incidence than those non-ICS users. However, low daily ICS exhibited a higher incidence rate for the narrow IPF definition (0.47 per 1000 people) than other doses. Moreover, both intermittent and continuous ICS usage resulted in higher broad and narrow IPF rates than non-ICS users.

### Association between ICS and IPF risk

Before IPTW, ICS use was associated with an increased risk of broad (unadjusted HR: 1.70, 95% CI: 1.02 to 2.82) and narrow IPF (unadjusted HR: 1.91, 95% CI: 1.00 to 3.66) definitions (table 2 and figure 2a and b). However, post-IPTW matching showed no significant association between ICS use and IPF risk in either definition, and this trend remained consistent across all landmark analyses (table 2 and figure 2c and d).

In both pre-IPTW and post-IPTW analyses, a significant association with IPF risk was consistently observed for continuous daily mean ICS dose, with an adjusted HR of 1.03 (95% CI: 1.01 to 1.04) for the broad definition and 1.03 (95% CI: 1.01 to 1.05) for the narrow definition per 100 µg/day. When categorised into three dosage levels post-IPTW, high-dose daily ICS use was significantly associated with IPF in both definitions (broad: adjusted HR: 3.66, 95% CI: 1.14 to 9.96; narrow: adjusted HR: 4.67, 95% CI: 1.33 to 16.40) compared with non-ICS users. Nevertheless, in duration-based analyses, no significant associations were observed after IPTW adjustment.

### Subgroup analysis

In patients aged ≥65 years, no significant association between ICS use and risk of IPF was observed (table 3). Conversely, in patients aged <65 years, ICS use demonstrated reduced risk of IPF in both broad (adjusted HR: 0.06, 95% CI: 0.01 to 0.45) and narrow IPF definitions (adjusted HR: 0.12, 95% CI: 0.02 to 0.95, p=0.053). In COPD patients, ICS use showed a marginally significant increased risk for narrowly defined IPF (adjusted HR: 3.00, 95% CI: 0.48 to 18.61, p=0.088), but not for broadly defined IPF. However, no significant findings were observed in other subgroups based on sex, smoking status, income, systemic steroid use or CCI.

## DISCUSSION

To our knowledge, this study was the first large nationwide cohort study to investigate the association between ICS use and IPF incidence in chronic airway diseases. Our findings suggest that ICS use did not significantly increase the overall IPF risk on adjusted analysis, although high doses of ICS were associated with an elevated risk of IPF. These findings are consistent across various IPF definitions and identified high-risk groups.

Our study found that after adjusting for covariates, ICS use was not significantly associated with an increased IPF incidence in chronic airway diseases. However, high-dose ICS use increases IPF incidence, with the highest ICS daily dose group having a greater risk of developing IPF compared with the non-users. The risk of developing concurrent chronic airway diseases, particularly COPD, is not well-documented but is suggested to be significant. Recent research from Korean claims databases reports that about 37% of patients with other chronic airway diseases also had COPD, marking the highest prevalence among comorbidities.[30] Furthermore, meta-analyses of 23 studies have shown COPD prevalence rates ranging from approximately 6% to 67%.[7] This indicates a considerable overlap between COPD and IPF, despite their clear clinical, radiological and pathological distinctions. Both conditions share significant pathophysiological features, such as accelerated ageing of pulmonary fibrotic tissue, potentially due to telomere dysfunction or genetic predispositions and exacerbated by oxidative damage from tobacco smoke.[31] Our study suggests that high-dose ICS might impact the development of IPF, particularly in COPD patients with significant airway remodelling and chronic conditions. This association indicates that high-dose ICS could exacerbate pulmonary fibrosis in susceptible individuals, emphasising the need for cautious use of these medications in patients at risk for IPF.

It is known that steroids negatively impact the prognosis of IPF,[10] but their effect on the incidence of IPF is not well understood. There could be several factors for the impact of ICS on the development of IPF. The association between ICS use and increased IPF risk may relate to changes in the lung microbiome. ICS users often show a microbiome with more certain microbes.[32–35] Durack *et al* found that asthma patients on medium-dose ICS had an increased relative abundance of *Neisseria* genera when compared with a placebo group.[32] Similar increases in *Streptococcus pneumoniae* in sputum were noted in COPD studies following ICS use.[32] Molyneaux *et al* observed higher bacterial levels, including *Neisseria* sp and *Streptococcus* sp in bronchoalveolar lavage samples of patients with IPF compared with healthy controls.[36] Meanwhile, Guidi *et al* revealed that ICS can stimulate the production of specific fibroblast growth factors (FGFs) such as FGF2, FGF4 and FGF18 in bronchial airway epithelial cells, both in vivo and in vitro.[37] These FGFs, particularly FGF2, FGF9 and FGF18, are known to be upregulated in IPF lungs and play a pivotal role in modulating fibroblast activity.[38] This leads to an intensified inflammatory response in lung tissue, characterised by increased production of profibrotic cytokines and tissue remodelling processes. Such changes are significant factors that could potentially increase the risk of developing IPF.

In this study, we observed that using ICS decreased the risk of IPF in individuals aged <65 years. Although the reasons for this finding remain elusive, it is imperative to consider that the incidence of IPF in younger individuals is relatively low.[5] Consequently, some cases initially diagnosed and recorded as IPF might represent other types of ILD. This potential misclassification could contribute to the observed decrease in IPF risk among younger patients. Non-IPF ILDs—particularly CTD-ILD or interstitial pneumonia with autoimmune features—typically involve significant inflammatory processes.[39 40] Although our study had limited sample sizes to determine the risk in non-IPF ILDs conclusively, ICS could potentially have a protective effect in these conditions due to their anti-inflammatory properties.

The relatively low ICS use observed in our cohort is consistent with previous real-world data from Korea. A nationwide study using the Health Insurance Review and Assessment database reported an overall ICS prescription rate of 22.6% among patients with asthma, with nearly half of institutions prescribing ICS to less than 10% of their patients.[41] Several factors contribute to the low ICS use in South Korea, including cultural preference for oral medications over inhalers, time constraints limiting inhaler education during clinical visits and complex insurance reimbursement policies. In addition, in COPD management, ICS is not a primary treatment choice but is selectively prescribed only for patients with frequent exacerbations, according to international and local guidelines.[42 43] This selective prescribing pattern, combined with the Korean healthcare delivery system, likely explains the low ICS use observed in patients with both asthma and COPD in our cohort.

Despite providing valuable insights, our study had certain limitations. First, being a retrospective observational study, it cannot establish causation and unaccounted confounding factors may exist, including other IPF risk factors. Considering this, we conducted an IPTW analysis with a wide range of covariates, including health

examination data. In the unadjusted analysis, ICS use appeared to be associated with an increased IPF incidence. However, after adjustment for baseline differences such as age, smoking status and comorbidities, this association was no longer significant, suggesting that the initial association was likely driven by confounding factors. Second, using claims data carries the risk of misclassification for IPF diagnosis. To address this, we employed a narrow definition of IPF diagnosis using the RID code, strengthening the reliability of our findings. In addition, although we enhanced diagnostic specificity by restricting IPF definitions to strict ICD-10 and CT-based criteria, some IPF cases may have been misclassified under other J84 codes, potentially leading to underestimation. However, such non-differential misclassification would likely bias results toward the null rather than exaggerating the association.[44] Future studies may consider sensitivity analyses including broader J84 classifications. Third, our study might have had selection bias because of using an NHI sample cohort. However, this cohort does represent the entire Korean population nationally, and the examination data used were government-provided and cost-free, ensuring its representativeness. Finally, since our research focused solely on Koreans, it may have limited applicability to other regions or racial groups. Therefore, further studies involving diverse populations would be beneficial. Despite these limitations, our study's strengths lie in comprehensive national insurance dataset utilisation and advanced statistical methods to investigate the relationship between ICS use and IPF risk.

## CONCLUSION

Our study found no significant overall association between ICS use and IPF risk after adjustment, though high-dose ICS use was associated with increased IPF risk in some subgroups. Given the widespread use of ICS in managing chronic respiratory diseases, careful consideration of its use, particularly at high doses, is necessary. Future prospective studies are needed to further investigate this potential risk and clarify the dose-response relationship.

**Contributors** HL: data curation (lead); formal analysis (lead); methodology (equal); software (lead); visualisation (equal); writing – original draft (equal); writing – review and editing (equal). HYY: conceptualisation (lead); data curation (equal); formal analysis (equal); funding acquisition (lead); investigation (equal); methodology (equal); project administration (lead); resources (lead); software (equal); supervision (lead); validation (lead); visualisation (equal); writing – original draft (equal); writing – review and editing (equal). HYY acts as the guarantor of this study and is responsible for the overall content.

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