

# Correspondence

## Observational Studies of Inhaled Corticosteroids in Chronic Obstructive Pulmonary Disease: Misconstrued Immortal Time Bias

To the Editor:

The recent article by Kiri and colleagues on the effect of inhaled corticosteroids (ICS) in the treatment of chronic obstructive pulmonary disease (COPD) claims to present “results from two observational designs free of immortal time bias” (1). This erroneous claim reflects a grave misunderstanding of immortal time bias (2–4).

In the propensity scores cohort design, Kiri and coworkers correctly intend in their METHODS to use “only patients whose treatment status was defined on the same day of discharge” to define ICS exposure status. They thus correctly identify, from the cohort of 4,398 subjects, all 1,091 patients who were prescribed ICS on the day of discharge. However, the nonusers of ICS were then incorrectly taken as merely the 538 patients “who were never exposed to ICS in their entire follow-up period.” To comply with the METHODS, they should have used all 3,307 patients from the cohort who were not prescribed ICS on the day of discharge. Consequently, these patients would be followed for up to 1 year until the first of the outcome dates or the date of ICS, since they are unexposed to ICS until that point. By excluding the 2,769 patients who were not prescribed ICS on the day of discharge but received an ICS later in the year of follow-up, the authors excluded a crucial component of follow-up time (unexposed and immortal), thus introducing a significant degree of immortal time bias in the results.

Table 1 shows approximate figures estimated on the basis of 675 patients with an outcome event of hospitalization for COPD or all-cause death occurring in the cohort of 4,398 subjects. The table shows that by the biased approach, where only the 538 patients not prescribed ICS during the entire year of follow-up are used to define the ICS-unexposed group, the rate ratio of the outcome of hospitalization for COPD or all-cause death with ICS is 0.70, which corresponds to the value found by the authors. The corrected approach, which uses all 3,307 patients who did not receive ICS on the day of discharge as the ICS-unexposed

group, as defined in METHODS, produces a rate ratio of 1.48. This difference stems from the 450 person-years of unexposed and immortal follow-up time arising from the 2,769 patients who were excluded outright by the biased approach. Thus, had the authors followed the correct method they described—namely, to use “only patients whose treatment status was defined on the day of discharge” and not peek into the future to define exposure—they would have included all 3,307 such patients in the non-ICS group. This unjustified exclusion resulted in an immortal time bias that could never be redressed by even the most sophisticated techniques of data analysis.

The nested case-control approach is limited by its exposure definition of ICS in the 6-month period prior to the outcome event, thus subject to information bias. Indeed, since the death of patients with COPD is oftentimes preceded by numerous and lengthy hospitalizations, cases but not control subjects will appear to be “unexposed” to ICS in the 6-month period prior to death simply because they were in the hospital and could not receive an ICS prescription from their general practitioner. The resulting rate ratio will be systematically biased downwards by such information bias.

In conclusion, such state-of-the-art methods as propensity scores and nested case-control designs are powerless against immortal time bias or information bias. In the study by Kiri and coworkers, the propensity scores approach should be properly redone using the entire unexposed cohort, as stated in their METHODS. The nested case-control analysis should provide detailed documentation on the duration of all hospitalizations in the 6-month period prior to the index date for cases and control subjects. Unless the correct reanalyses of these data demonstrate otherwise, the results and conclusions of the article by Kiri and coworkers are untenable.

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**TABLE 1. SOURCE OF IMMORTAL TIME BIAS IN SELECTION OF THE INHALED CORTICOSTEROID-UNEXPOSED COHORT FOR THE PROPENSITY SCORES ANALYSIS BY KIRI AND COLLEAGUES**

	No. Subjects	No. Outcome Events*	Person-years	Rate (per 100/yr)	Rate Ratio
<i>Biased approach</i>					
ICS on Day 0	1,091	409	886.5	46.1	0.70
No ICS in follow-up	538	266	405.0	65.7	1.0
					(reference)
<i>Corrected approach</i>					
ICS on Day 0	1,091	409	886.5	46.1	1.48
No ICS on Day 0	3,307	266	855.0	31.1	1.0
					(reference)
No ICS in follow-up	538	266	405.0	65.7	
ICS on Days 1–90	2,561	0	320.0	0.0	
ICS on Days 91–365	208	0	130.0	0.0	

Definition of abbreviation: ICS = inhaled corticosteroids.

\* Hospitalization for chronic obstructive pulmonary disease or all-cause death.

## References

1. Kiri VA, Pride NB, Soriano JB, Vestbo J. Inhaled corticosteroids in chronic obstructive pulmonary disease: results from two observational designs free of immortal time bias. *Am J Respir Crit Care Med* 2005; 172:460–464.
2. Suissa S. Effectiveness of inhaled corticosteroids in chronic obstructive pulmonary disease: immortal time bias in observational studies. *Am J Respir Crit Care Med* 2003;168:49–53.
3. Suissa S. Inhaled steroids and mortality in COPD: bias from unaccounted immortal time. *Eur Respir J* 2004;23:391–395.
4. Suissa S, Ernst P. Bias in observational study of the effectiveness of nasal corticosteroids in asthma. *J Allergy Clin Immunol* 2005;115:714–719.

From the Authors:

We thank Dr. Suissa for his interest in our article, in which we used two different designs to analyze observational data on chronic obstructive pulmonary disease (COPD) and the use of inhaled corticosteroids (ICS) (1). Our designs were chosen because of recent concerns that some earlier analyses could have been subject to bias due to unbalanced baseline characteristics