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Extreme restriction design as a method for reducing confounding by indication in pharmacoepidemiologic research

Matthew H. Secrest[1] | Robert W. Platt[1,2,3] | Colin R. Dormuth[4] | Dan Chateau[5] | Laura Targownik[5] | Rui Nie[1] | Carla M. Doyle[1,2] | Sophie Dell'Aniello[1] | Kristian B. Filion[1,2,6]

[1] Centre for Clinical Epidemiology, Lady Davis Research Institute, Jewish General Hospital, McGill University, Montreal, Canada

[2] Department of Epidemiology, Biostatistics and Occupational Health, McGill University, Montreal, Canada

[3] Department of Pediatrics, McGill University, Montreal, Canada

[4] Department of Anesthesiology, Pharmacology, and Therapeutics, Faculty of Medicine, University of British Columbia, Vancouver, Canada

[5] Department of Community Health Sciences, Manitoba Centre for Health Policy, College of Medicine, Faculty of Health Sciences, University of Manitoba, Winnipeg, Canada

[6] Division of Clinical Epidemiology, Department of Medicine, McGill University, Montreal, Canada

Correspondence
K. B. Filion, Departments of Medicine and of Epidemiology, Biostatistics, and Occupational Health, McGill University, Centre for Clinical Epidemiology, Lady Davis Research Institute, Jewish General Hospital 3755 Cote Ste-Catherine, H-410.1 Montreal, Quebec H3T 1E2 Canada.
Email: kristian.filion@mcgill.ca

Abstract

Purpose: Confounding by indication is a concern in observational pharmacoepidemiologic studies, including those that use active comparator, new user (ACNU) designs. Here, we present a method of restriction to an indication, which we call "extreme restriction," to reduce confounding in such studies.

Methods: As a case study, we evaluated the effect of proton pump inhibitors (PPIs) on hospitalization for community-acquired pneumonia (HCAP). PPI use has been associated with increased HCAP risk, but this association likely results from confounding by indication due to gastroesophageal reflux disease (GERD). Using the UK's Clinical Practice Research Datalink, we compared the risk of HCAP within 180 days between PPI users and histamine-2 receptor antagonist (H2RA) users in an ACNU cohort using Cox proportional hazard models with a time-fixed exposure definition adjusted for high-dimensional propensity score deciles. We then performed the same analysis on an "extremely-restricted" cohort of incident nonsteroidal anti-inflammatory drug (NSAID) users, some of whom received PPIs for prophylaxis. Because PPIs were given as prophylaxis in this population, confounding due to GERD should be limited. We compared effect estimates between ACNU and restricted cohorts to evaluate confounding in both analyses.

Results: In the ACNU cohort, PPIs were associated with an increased risk of HCAP (hazard ratio [HR]: 1.25; 95% confidence interval [CI]: 1.05, 1.47), but this association was not present in the restricted cohort (HR: 1.06; 95% CI: 0.75, 1.49).

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Prior posting and presentation: This work is the sole product of the authors and has never been submitted for publication or presented in a public setting. The case study for extreme restriction is based on a substantive article by Filion KB et al on the risk of hospitalization for community-acquired pneumonia associated with proton pump inhibitor therapy,[1] which was also presented at a Society for Epidemiologic Research conference.[2] An earlier version of the present study was presented in abstract form at the International Conference for Pharmacoepidemiology.[3]

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Conclusions: Restriction to a single indication for treatment may reduce confounding by indication in studies conducted in distributed data networks and other large databases.

KEYWORDS
confounding, methodology, methods, pharmacoepidemiology, restriction, study design

1 | INTRODUCTION

Confounding by indication is a well-known source of bias in observational pharmacoepidemiologic studies[1-3] and occurs when the indication for a treatment is an independent risk factor for the health outcome of interest. This source of confounding reflects discrepancies in prognostic variables between treatment groups that result from physician-prescribing practices, eg, because physicians are more likely to administer a more potent treatment to patients with more severe disease or a history of treatment failure.[4] Restriction has long been recognized as a valuable approach to minimize confounding by indication and other sources of bias.[5] In this paper, we provide a brief review of restriction to reduce bias in pharmacoepidemiologic studies. We then discuss an underutilized study design, which we refer to as "extreme restriction," that reduces confounding through restriction of the study population to a single indication for treatment. The strengths and limitations of extreme restriction are discussed from a methodological standpoint, along with examples where extreme restriction is compelling. Finally, we present extreme restriction's utility in a case study evaluating proton pump inhibitor (PPI) safety with respect to hospitalization for community-acquired pneumonia (HCAP) using data from the UK's Clinical Practice Research Datalink (CPRD).[6]

2 | RESTRICTION IN PHARMACOEPIDEMIOLOGY

In the last several decades, new standards in the design of observational pharmacoepidemiologic studies have emerged to address concerns about the divergence between observational evidence and randomized controlled trials.[7-9] Among these methodological considerations, more rigorous restriction of the study population has been particularly emphasized.[5,10-16] This may be achieved, for instance, through explicit restriction criteria[5] or the use of propensity score trimming or rigorous matching.[17,18] Restriction of the study population serves several functions: it reduces selection bias and confounding (by lowering the variation in confounder values in the study population) and ensures the validity of assumptions for causal inference.[19]

A patient's treatment history logically serves as one basis for exclusion as it can summarize a patient's medical history and disease prognosis. In the "new user" method popularized by Ray and colleagues[10] in 2003, only patients with no history of therapy during a prespecified washout period are included in the treatment group. The new user design reduces survivor bias that may arise as a result of time-varying hazards, for instance because prevalent users have a lower risk of the outcome due to a depletion of susceptible patients. Importantly, the new user design also prevents the introduction of bias from adjustment for variables affected by prior treatment. Restricting to patients with multiple prescription refills (ie, adherent patients) also reduces bias from exposure misclassification.[5]

An extension to the new user design, the active comparator, new user (ACNU) design, has emerged as the modern standard for pharmacoepidemiologic inquiries.[15] The ACNU design restricts the study population to new users of two comparable treatments with the same indications (a therapy and its "active comparator"), which may reduce selection bias and confounding because treatment indications are proxies for disease severity, health care utilization, contraindications, etc. It follows that the reduction in confounding in ACNU analyses will depend on the extent to which patients on either treatment resemble each other. In the presence of clinical equipoise between two treatments, treatment allocation may be considered independent of prognostic variables, and results of an ACNU study will mimic those of a randomized trial.[11] Though ACNU studies are less likely to be confounded by indication, this source of bias will remain if there is not an active comparator for which genuine equipoise exists. In these situations, extreme restriction of the study population to an indication that may or may not relate to the treatment of interest may reduce confounding and produce an internally valid effect estimate. An illustrative example of extreme restriction is presented by the evaluation of PPI safety with respect to HCAP.

3 | CASE STUDY BACKGROUND: PPIS AND HCAP

PPIs are widely prescribed,[20] with over 113.4 million prescriptions filled annually in the United States alone.[21] These drugs are prescribed for peptic ulcers, gastrointestinal bleeding, gastroesophageal reflux disease (GERD), and other indications to lower gastric acid production and raise intragastric pH.[22] It has been hypothesized that PPIs and other acid-suppressive drugs such as histamine-2 receptor antagonists (H2RAs) increase the risk of pneumonia by promoting bacterial colonization of the stomach and esophagus.[21] Meta-analyses[23-25] have reported that the use of PPIs increases the risk of community-acquired pneumonia (summary-adjusted risk ratio [RR][25]: 1.48; 95% confidence interval [CI]: 1.14, 1.92). However, this purported association may be confounded by indication due to GERD, a common indication for PPIs[26-28] that is thought to independently increase the risk of pneumonia.[29]

Previous strategies to control confounding by indication of the PPI-pneumonia relationship were inadequate. In a nested case-control study of only PPI-exposed patients, Laheij and colleagues observed an

adjusted RR of community-acquired pneumonia of 1.89 (95% CI: 1.36, 2.62).[30] The authors did not have access to information on the indication for PPI use, so their observed effect was likely confounded by the timing of GERD symptoms and the duration of GERD treatment, which may be protracted.[31] Time-varying GERD symptoms may also have confounded a previous case-crossover study on patients hospitalized for pneumonia after stroke (adjusted odds ratio [OR]: 1.63; 95% CI: 1.25, 2.12).[32]

A reasonable investigation would adopt the ACNU framework and compare incident PPI users to incident H2RA users, a drug class with similar indications. However, PPIs are greatly preferred to H2RAs as the primary therapy for GERD,[31,33] such that even exclusion of patients with a recorded diagnosis for GERD or related conditions would not be expected to fully eliminate confounding. Also, if H2RAs are independently associated with HCAP, the association between PPIs and pneumonia would be masked.

4 | THE EXTREME RESTRICTION DESIGN

Some indications for PPI are unrelated to GERD, allowing for the application of the extreme restriction study design. A small proportion of PPI prescriptions are given concomitantly with NSAIDs[26,27] as prophylaxis against adverse gastrointestinal effects of PPIs.[34] Because incident PPI users who are simultaneously prescribed NSAIDs are less likely to have GERD or related conditions, a comparison of PPI users to nonusers in a population of incident NSAID users is expected to be free from major confounding.

Our proposed method of extreme restriction is effective either (1) when distinct indications for a particular treatment exist and at least one of these is unassociated with the health outcome, as in the case of PPIs and HCAP, or (2) when the indication is unrelated to both treatment and health outcome, but defines a population in which the treatment is unassociated with the outcome. An example of this latter situation is given by the study of vaccine effectiveness in incident statin users.[35] Vaccine users typically have greater health-seeking behaviors and less frailty than the general population, so a study of unselected vaccine users may be confounded by other prognostic variables; restricting to incident statin users reduces confounding by reducing the variability between exposed and unexposed with respect to confounders (eg, lifestyle variables, frailty, comorbidities).

Extreme restriction can be viewed as a logical extension of the ACNU design. In an ACNU study, inclusion is defined by all indications for treatment; in an extremely-restricted design, only a single indication or pared selection of indications is used. In some cases, the extremely-restricted and ACNU study designs converge. For example, restriction to patients with type 2 diabetes who fail metformin therapy could be considered both an ACNU and extremely-restricted design, because these patients possess a distinct indication for treatment with one of many active comparators.[36]

Restriction improves internal validity at the potential cost of reduced generalizability and precision.[16] In the case study we present, generalizability is seemingly limited: Few patients use PPIs as prophylaxis, and for the remainder of PPI patients, nontreatment of excessive gastric acid is not a relevant clinical comparator.[37] But as our case study demonstrates, the reduced external validity in extreme restriction may sometimes be inconsequential, eg, because the purported biological mechanism may be applicable to all patients, regardless of indication. A potentially large number of patients may also be excluded from study in extremely-restricted designs, leading to reduced precision and power. For this reason, we expect extreme restriction to be useful for large, distributed drug safety and effectiveness networks such as the Canadian Network for Observational Drug Effect Studies (CNODES) and Sentinel.[38,39] While a major motivation for the creation of these networks was to evaluate rare diseases or rarely used drugs, their existence allows for the application of rigorous inclusion criteria to produce more internally valid study populations.

KEY POINTS

- Restriction of the study population to patients with a single indication (ie, "extreme restriction") may reduce confounding by indication in pharmacoepidemiologic studies that use large databases.
- Large distributed health networks such as the Canadian Network for Observational Drug Effects Studies and other organizations with data on very large populations are well suited for analysis of more restricted and internally valid study populations

Settings for extreme restriction are wide-ranging. One example reported by Dormuth and colleagues[40] concerns statin potency and the risk of incident diabetes. Most patients with a history of cardiovascular disease are indicated for statin treatment. These patients also possess characteristics that predict future type 2 diabetes, so a naïve comparison of high potency statin users to low potency statin users would be confounded by indication. Dormuth et al restricted to a single, well-defined indication for the secondary prevention of cardiovascular disease and observed a moderate increase in the risk of incident diabetes with high-dose statin use, consistent with the clinical trial literature.[40] Hypertensive patients who commence dual instead of single antihypertensive therapy may represent another homogeneous and restricted group to be leveraged in drug safety studies. As discussed above, we also consider indications that are orthogonal to the study drug of interest to be extreme restriction designs. For instance, one may study classes of anticoagulants in a population of new users of antihyperglycemic drugs to control for comorbidities/frailty.

Extreme restriction may be ill advised in several circumstances, most notably when the sample size is limited, either because of the nature of the source population or the indication for treatment. In situations where heterogeneity of the population persists after restriction, the internal validity of the study may not be sufficiently improved to justify a restricted design. Finally, if there is substantial effect modification due to the indication on which the cohort is restricted, the results would not be generalizable to the larger study population. Thus, in studies of drug safety, judgment must be exercised in determining the value of a harm signal which might only apply to the highly selected group of patients included in the analysis.

5 | CASE STUDY: PROTON PUMP INHIBITORS AND HOSPITALIZATION FOR COMMUNITY-AQCUIRED PNEUMONIA

In our previous work, we found no clinically significant effect of PPIs (summary-adjusted OR for eight CNODES sites: 1.05; 95% CI: 0.89, 1.25) on the risk of HCAP in an analysis of extremely-restricted cohorts of incident NSAID users.[41] For this case study, we expanded upon our previous work, first by conducting an ACNU comparison of PPIs and H2RAs. We then repeated our analysis on an extremely-restricted cohort of NSAID users, comparing prophylactic PPI users to PPI nonusers. We also conducted several exploratory analyses on additional comparator drugs unrelated to PPIs to establish the upper bounds of residual confounding by gastroesophageal conditions. We first used a random selection from the reference population matched on prescription date as an exploratory comparator group (Section S1). Additional exploratory comparator drugs (ie, treatments for glaucoma/ocular hypertension, osteoporosis, depression, and hypothyroidism) were also considered, the details of which can be found in the supplement to this manuscript (Section S1).

5.1 | Study population

We acquired patient-level electronic medical record data from the UK via the CPRD[6] (linked to the UK Hospital Episode Statistics and Office for National Statistics databases). We constructed an unrestricted cohort of adults who were newly prescribed a PPI or H2RA between 1 January 1999 and 31 December 2015. We then excluded patients who (1) were younger than 40 years old at cohort entry, (2) had an insufficient duration (<1 year) of continuous observation within the database prior to cohort entry, (3) were hospitalized for a length of stay of ≥2 days within the 30 days prior to cohort entry (to eliminate cases of hospital-acquired pneumonia) or were hospitalized on the cohort entry date, (4) had a diagnosis of pneumonia or influenza in the year prior to cohort entry, (5) had received tuberculosis medication at any time prior to cohort entry, (6) had a history of cancer in the year prior to cohort entry (treatments for these may augment pneumonia risk), (7) had received a prescription for a PPI or an H2RA at any point prior to cohort entry, and/or (8) received a simultaneous prescription for a PPI and an H2RA on the date of cohort entry. Cohort entry was defined as the date of prescription for the PPI or H2RA. We developed high-dimensional propensity score models (see Section 5.4), removing instrumental variables (ie, those with an absolute estimated log-odds >1 in models with a C-statistic >0.8) manually, and then trimmed the areas of nonoverlap of the propensity score distributions.[42]

We also formed an "extremely-restricted cohort" comprised of patients who received an NSAID prescription of ≥28 days duration between 1 January 1998 and 31 December 2015 and did not meet any of exclusion criteria 1 to 6 above. Cohort entry was defined as the date of new NSAID prescription. The restricted cohort further excluded patients with a prescription for a PPI, an H2RA, or a nonaspirin NSAID (any route of administration, prescription duration) at any point prior to cohort entry and was trimmed to the areas of high-dimensional propensity score overlap, as in the unrestricted cohort.

For both the unrestricted and restricted cohorts, patients were followed until incident HCAP or censoring due to whichever of the following occurred first: end of follow-up (180 days), death from any cause, hospitalization of ≥2 days in duration, withdrawal from the database, or end of study period (31 December 2015). We conducted two sensitivity analyses. In one sensitivity analysis, follow-up in the comparator group was censored at PPI initiation; patients were only able to contribute one observation in this analysis. In another sensitivity analysis, we performed a logistic regression with HCAP within 180 days as the outcome, using the same adjustment variables as in the primary, Cox analysis.

5.2 | Exposure assessment

Exposure was fixed at cohort entry. In the unrestricted cohort, patients were considered exposed if they received a PPI at cohort entry and unexposed if they received an H2RA at cohort entry. In the extremely-restricted cohort, patients were considered exposed if they received a PPI prescription on the cohort entry date and unexposed if they did not.

5.3 | Outcome assessment

The outcome for all analyses was HCAP within 180 days. We defined HCAP as a diagnosis in the primary or secondary position of pneumonia as defined by International Classification of Disease, 10th revision codes (J09.X1, J10, J11, J12-J18, J85.1, B01.2, B05.2, and B25.0) within the first 2 days of hospital admission, with an event requiring a length of stay >1 day or a death on the admission date. The event date was the hospital admission date.

5.4 | Statistical analysis

In our primary analyses, we used Cox proportional hazard models to estimate hazard ratios (HRs) and 95% CIs for the effect of PPI use on HCAP. All outcome regression models were adjusted for age, sex, previous (>1 year) pneumonia/influenza, and deciles of high-dimensional propensity score.[43] Several variables were forced into the propensity score model: body mass index, alcohol abuse, smoking status, history of certain comorbidities at baseline (asthma, bronchiectasis, chronic obstructive pulmonary disease, diabetes), use of select medications (immunosuppressive agents, influenza vaccine, inhaled bronchodilators, inhaled corticosteroids, pneumococcal vaccine, systemic antibiotics, oral corticosteroids), hospitalization in the previous year, use of >4 medications in the previous year, number of hospitalizations in the previous year, and >4 physician visits in the previous year.

SAS software version 9.4 was used for all analyses.

TABLE 1 Characteristics of PPI users versus H2RA users in the ACNU cohort at cohort entry[a]

	PPI Users		H2RA Users	
	n 471 987	%	n 66 310	%
Age				
40-44	58 404	12.4	9582	14.5
45-49	59 876	12.7	8378	12.6
50-54	58 936	12.5	8371	12.6
55-59	57 466	12.2	8104	12.2
60-64	60 566	12.8	7839	11.8
65-69	53 075	11.2	6855	10.3
70-74	43 241	9.2	6076	9.2
75-79	34 832	7.4	5088	7.7
80-84	25 043	5.3	3366	5.1
≥85	20 548	4.4	2651	4.0
Women	262 114	55.5	38 369	57.9
Year of cohort entry				
1999-2004	84 791	18.0	44 221	66.7
2005-2009	174 603	37.0	15 273	23.0
2010-2015	212 593	45.0	6816	10.3
BMI				
<30	311 926	66.1	43 279	65.3
≥30	110 431	23.4	12 168	18.4
Missing	49 630	10.5	10 863	16.4
Smoking				
Smoker	288 743	61.2	37 320	56.3
Nonsmoker	170 934	36.2	23 921	36.1
Missing	12 310	2.6	5069	7.6
Alcohol abuse	29 854	6.3	2746	4.1
Comorbidities				
Asthma	62 197	13.2	8017	12.1
Bronchiectasis	2279	0.5	259	0.4
COPD	38 434	8.1	5976	9.0
Diabetes	68 542	14.5	5826	8.8
Previous (>1 yr) pneumonia or influenza	46 462	9.8	5877	8.9
Hospitalizations in the year preceding cohort entry				
0	424 711	90.0	59 881	90.3
1	36 498	7.7	4816	7.3
2	7462	1.6	1082	1.6
3	2085	0.4	345	0.5
≥4	1231	0.3	186	0.3
Prescription history				
NSAID use on day of cohort entry	118 876	25.2	6623	10.0
Medications				
Immunosuppressive agents	4457	0.9	598	0.9
Influenza vaccine	44 867	9.5	6941	10.5
Inhaled bronchodilators	64 490	13.7	8306	12.5
Inhaled corticosteroids	47 742	10.1	6158	9.3
Pneumococcal vaccine	6019	1.3	837	1.3
Systemic antibiotics	187 104	39.6	25 389	38.3
Systemic corticosteroids	36 316	7.7	4837	7.3

[a]Numbers refer to the study population after exclusion criteria and high-dimensional propensity score trimming. The ACNU cohort is defined by new users of PPIs or H2RAs.

Abbreviations: ACNU, active comparator new user[15]; BMI, body mass index; COPD, chronic obstructive pulmonary disease; H2RA, histamine-2 receptor antagonist; n, number; NSAID, nonsteroidal anti-inflammatory drug; PPI, proton pump inhibitor; yr, year.

TABLE 2 Characteristics of PPI + NSAID users versus NSAID-only users in the restricted cohort at cohort entry[a]

	PPI + NSAID Users		NSAID-Only Users	
	n 16 141	%	n 185 235	%
Age				
40-44	1758	10.9	38 256	20.7
45-49	1945	12.1	33 509	18.1
50-54	2090	12.9	29 206	15.8
55-59	2023	12.5	24 837	13.4
60-64	2368	14.7	20 875	11.3
65-69	2035	12.6	13 759	7.4
70-74	1518	9.4	9867	5.3
75-79	1102	6.8	7336	4.0
80-84	714	4.4	4486	2.4
≥85	588	3.6	3104	1.7
Women	8391	52.0	94 471	51.0
Year of cohort entry				
1999-2004	941	5.8	74 696	40.3
2005-2009	4459	27.6	66 696	36.0
2010-2015	10 741	66.5	43 843	23.7
BMI				
<30	10 635	65.9	117 181	63.3
≥30	3679	22.8	34 423	18.6
Missing	1827	11.3	33 631	18.2
Smoking				
Smoker	9355	58.0	98 807	53.3
Nonsmoker	6427	39.8	71 861	38.8
Missing	359	2.2	14 567	7.9
Alcohol abuse	1032	6.4	8031	4.3
Comorbidities				
Asthma	1581	9.8	16 807	9.1
Bronchiectasis	62	0.4	409	0.2
COPD	760	4.7	6951	3.8
Diabetes	2298	14.2	13 365	7.2
Previous (>1 yr) pneumonia or influenza	1053	6.5	10 643	5.7
Hospitalizations in the year preceding cohort entry				
0	15 227	94.3	176 782	95.4
1	751	4.7	7021	3.8
2	122	0.8	1095	0.6
3	33	0.2	231	0.1
≥4	8	0.0	106	0.1
Prescription history				
NSAID use on day of cohort entry	16 141	100.0	185 235	100.0
Medications				
Immunosuppressive agents	80	0.5	498	0.3
Influenza vaccine	1190	7.4	10 031	5.4
Inhaled bronchodilators	1464	9.1	14 473	7.8
Inhaled corticosteroids	1080	6.7	10 476	5.7
Pneumococcal vaccine	182	1.1	1473	0.8
Systemic antibiotics	4796	29.7	51 944	28.0
Systemic corticosteroids	645	4.0	4409	2.4

[a]Numbers refer to the study population after exclusion criteria and high-dimensional propensity score trimming. The extremely-restricted cohort is defined by new users of NSAIDS with or without PPIs.

Abbreviations: ACNU, active comparator new user[15]; BMI, body mass index; COPD, chronic obstructive pulmonary disease; H2RA, histamine-2 receptor antagonist; NSAID, nonsteroidal anti-inflammatory drug; PPI, proton pump inhibitor; yr, year.

5.5 | Results

We identified a total of 471 987 PPI users and 66 310 H2RA users in the unrestricted cohort after propensity score trimming (Tables 1 and S1). Although most baseline covariates were well balanced between exposure groups, PPI users were more likely to have diabetes, be obese, enter the cohort in later years, and receive an NSAID prescription as prophylaxis on the date of cohort entry than H2RA users. The restricted cohort of NSAID users contained 16 141 patients who received a prophylactic PPI and 185 235 PPI nonusers (Tables 2 and S2). The imbalances in diabetes and obesity between exposure groups were similar in the restricted and unrestricted cohorts, with PPI users more likely to possess these comorbidities. In addition, PPI users were more likely to be older than nonusers.

In the ACNU cohort, the crude incidence of HCAP among PPI users was 8.5 per 1000 person-years (95% CI: 8.1, 8.9), compared with 5.5 per 1000 person-years (95% CI: 4.7, 6.4) among H2RA users (Table 3). An increased risk of HCAP among PPI users was observed after adjustment in the ACNU analysis, with an HR of 1.25 (95% CI: 1.05, 1.47). In the restricted cohort, the crude incidence rates of HCAP were somewhat lower than in the ACNU cohort for both the PPI exposed (6.1 per 1000 person-years, 95% CI: 4.6, 8.2) and unexposed (2.9 per 1000 person-years, 95% CI: 2.6, 3.3) patients, likely because of the exclusion of patients with GERD. The risk of HCAP associated with PPI use was greatly reduced in the extremely-restricted analysis, with a HR of 1.06 (95% CI: 0.75, 1.49). The extremely-restricted cohort had lower precision and wider log-CIs than the ACNU cohort: 0.69 and 0.34, respectively.

The results for the analyses of exploratory comparator groups varied (see the supplement to this manuscript). The random sample from the CPRD and incident ocular glaucoma medication users led to the greatest adjusted HRs: 1.94 (95% CI: 1.55, 2.43) and 2.62 (95% CI: 2.02, 3.40), respectively. The results of the sensitivity analysis wherein unexposed patients were censored at PPI initiation were similar to those in the primary analysis (Table S14). Use of a logistic regression outcome model, as in our previous work,[41] produced results consistent with those in the primary analysis (Table S15).

6 | DISCUSSION

In this study, we evaluated residual confounding in ACNU and extreme restriction designs. Assuming that the true effect of PPIs on HCAP is null,[41] our extremely-restricted analysis produced an absolute bias reduction of 19% relative to the ACNU analysis and altered the interpretation of the results. The ACNU analysis provides evidence of an adverse effect of PPIs on the risk of HCAP significant to an alpha of 0.05, while the restricted analysis does not support this effect. However, because of the lower precision in the extremely-restricted design, clinically significant effects (eg, HRs >1.2) still fall within the 95% CIs of the restricted analysis. Our method of extreme restriction demonstrably reduced the estimated effect of PPIs on HCAP, and did so despite imbalances in certain baseline characteristics of PPI exposed and unexposed groups that suggested the presence of residual confounding. The exploratory analyses suggested that residual confounding could lead to effect estimates as high as ~2, compared with which even the ACNU analysis was less confounded. Our results were robust to censoring at PPI initiation in the comparator group and to modeling HCAP as a binary outcome in a logistic regression instead of a time-to-event outcome in a Cox model.

Our study has several strengths, including the application high-dimensional propensity scores, use of a validated outcome algorithm, an intention-to-treat study design, sensitivity analyses, and a broad set of exploratory analyses encompassing several comparator groups not commonly thought to augment HCAP risk.

Several limitations are noteworthy, including exposure misclassification due to the availability of over-the-counter PPIs in the UK, the potential for PPI prescriptions to be given to the unexposed during follow-up (our sensitivity analysis explored the potential effect of this), and the analysis of prescriptions issued rather than filled. Despite our use of high-dimensional propensity scores and rigorous statistical adjustment, some residual confounding is possible. In addition, we removed suspected instrumental variables empirically from our propensity score models, which may have introduced bias through the removal of noninstruments. The inflation of type I error is also a concern given the number of statistical tests performed. Finally, while our choice of exploratory comparator drugs was made to minimize the risk

TABLE 3 Fully-adjusted HRs comparing PPI use to nonuse in the ACNU and extremely-restricted cohorts

	Patients	HCAP	PYs	IR[a]	Adjusted HR (95% CI)[b]
ACNU cohort					
H2RA users	66 310	168	30 702	5.5 (4.7, 6.4)	1.00 (Ref)
PPI users	471 987	1820	214 652	8.5 (8.1, 8.9)	1.25 (1.05, 1.47)
Extremely-restricted cohort					
NSAID-only users	185 235	258	87 759	2.9 (2.6, 3.3)	1.00 (Ref)
PPI + NSAID users	16 141	45	7321	6.1 (4.6, 8.2)	1.06 (0.75, 1.49)

Abbreviations: ACNU, active comparator new user[15]; CI, confidence interval; H2RA, histamine-2 receptor antagonist; HCAP, hospitalization for community acquired pneumonia; HR, hazard ratio; IR, incidence rate; NSAID, nonsteroidal anti-inflammatory drug; PPI, proton pump inhibitor; PY, person-years; Ref, reference.

[a]Per 1000 person-years.

[b]Adjusted for age, sex, previous (>1 year) pneumonia/influenza, and deciles of high-dimensional propensity score.

of pneumonia in the unexposed group; several of these drugs, such as selective serotonin reuptake inhibitors, may in fact serve as a proxy for comorbidities that augment HCAP risk (eg, obesity), rendering comparisons of our primary results to the exploratory results less informative.

Our method of extreme restriction itself may be limited in its applicability. Finding indications for treatment that are unrelated to the outcome may be hard in clinical practice; operationalizing studies based on these indications may also be troublesome. Extreme restriction is not a panacea, and extremely-restricted analyses can still be subject to residual confounding. Finally, even in situations where an extremely-restricted design is possible, it may be unnecessary if the potential for confounding in other study designs is low; extreme restriction comes at the cost of decreased generalizability and sample size and is thus less attractive when other valid designs are available.

7 | CONCLUSIONS

Extreme restriction to an indication or pared set of indications may reduce confounding by indication in studies conducted in distributed data networks and other large databases.

ETHICS STATEMENT

This study received ethics approval from the institutional review board at the Montreal Jewish General Hospital and the Independent Scientific Advisory Committee of the CPRD (protocol 16_238RMn2).

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CONFLICT OF INTEREST

RWP has received personal fees from Amgen, AbbVie, Pfizer, and Novartis. LP has served on the advisory boards for Pfizer, Takeda, AbbVie, and Janssen; has received speaking fees from Janssen, Takeda, and Pfizer; and has received grant support from Pfizer and AbbVie. The other authors declare no conflicts of interest.

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ORCID

Matthew H. Secrest https://orcid.org/0000-0002-0939-4902
Robert W. Platt https://orcid.org/0000-0002-5981-8443
Kristian B. Filion https://orcid.org/0000-0001-6055-0088

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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