

ONLINE APPENDICES

Online Appendix 1. Demographic and clinical characteristics by exposure status at cohort entry in a restricted cohort of new users of non-steroidal anti-inflammatory drugs.

	H2RA Analysis	
	H2RA Exposed	Unexposed*
Total Number of Patients	47,344	4,342,733
Database (%)		
Alberta	3.1	4.1
Saskatchewan	5.8	4.6
Manitoba	5.0	5.3
Ontario	61.1	21.7
Quebec	0.1	0.7
Nova Scotia	2.1	0.9
MarketScan	13.8	49.6
GPRD	9.0	13.0
Age (%) [Years] †		
40-54	16.2	41.8
55-64	10.3	23.8
65-74	41.6	19.4
75-84	26.5	12.2
85+	5.4	2.8
Women (%)	63.7	58.0
Year of Cohort Entry (%)		
1997	4.9	1.5
1998	7.0	2.5
1999	7.5	3.1
2000	8.2	4.5
2001	7.9	4.7
2002	8.0	4.7
2003	7.6	4.9
2004	6.9	4.7
2005	6.1	3.8
2006	5.9	3.9
2007	9.5	18.0
2008	9.0	18.5
2009	8.2	17.6
2010	3.2	7.6
2011	0.1	0.1
Nursing Home (%) ‡	0.6	0.8
Urban (%) §	86.9	78.8
Comorbidities (%)		

Asthma	3.8	1.9
Bronchiectasis	0.1	0.1
COPD	3.9	2.5
Diabetes	10.8	9.6
Non-hospitalized pneumonia	2.5	2.2
Hospitalizations in the Year Preceding Cohort Entry (%)		
None	92.3	93.2
One	6.1	5.6
Two	1.1	0.9
Three	0.3	0.2
Four or More	0.1	0.1
Prescriptions in the Year Preceding Cohort Entry (%)		
None	2.8	5.6
One	4.9	8.6
Two	6.7	9.9
Three	7.7	10.3
Four or More	77.9	65.6
Medications (%)		
PPI [†]	3.7	2.9
H2RA [†]	34.0	1.6
NSAIDs [†]	40.3	28.4
Immunosuppressive Agents	0.5	1.1
Influenza Vaccine ^{**}	11.0	5.6
Inhaled Bronchodilators	11.1	8.3
Inhaled Corticosteroids	10.2	13.1
Pneumococcal Vaccine ^{**}	4.5	2.4
Non-Topical Antibiotics	43.7	44.5
Non-Topical Corticosteroids	10.4	16.3

Abbreviations: COPD = Chronic Obstructive Pulmonary Disease; H2RA = Histamine-2 Receptor Antagonist; NSAIDs = Non-Steroidal Anti-Inflammatory Drugs; PPI = Proton Pump Inhibitor.

*Saskatchewan did not contribute to the PPI analysis. In addition, small differences in the unexposed groups exist in the PPI and H2RA analyses because of trimming during the estimation of high-dimensional propensity scores.

[†]Alberta, Ontario, Quebec, and Nova Scotia only contributed data for those > 66 years of age whereas MarketScan only contributed data for those aged 40-65 years.

[‡]The proportion of study participants living in nursing homes was only reported by Manitoba and Ontario.

[§]Data regarding urban/rural location were only available in Alberta, Manitoba, Nova Scotia, and Ontario.

^{||}Comorbidities and medication use are defined using data in the year prior to and including the date of cohort entry.

^{††}Denotes use in the 7-12 months before cohort entry. Use in the 6 months before cohort entry resulted in exclusion.

^{**}Vaccination data were only available for the GPRD, Manitoba, MarketScan, and Nova Scotia.

Online Appendix 2. Demographic and clinical characteristics by exposure status at cohort entry in a restricted cohort of new users of non-steroidal anti-inflammatory drugs, with analyses restricted to one, randomly-selected observation per patient.

	PPI Analysis		H2RA Analysis	
	PPI Exposed	Unexposed*	H2RA Exposed	Unexposed*
Total Number of Patients	68,268	2,914,279	30,193	3,050,116
Database (%)				
Alberta	5.8	3.7	3.2	3.6
Saskatchewan	0	0	6.0	4.2
Manitoba	2.8	4.8	5.2	4.6
Ontario	30.9	18.6	56.3	17.9
Quebec	1.0	0.6	0.1	0.6
Nova Scotia	0.4	0.9	2.3	0.9
MarketScan	31.5	59.7	17.8	57.1
GPRD	27.8	11.6	9.1	11.2
Age (%) [Years] †				
40-54	27.5	45.7	19.1	45.9
55-64	21.6	25.5	11.7	25.3
65-74	29.3	16.4	39.9	16.5
75-84	17.0	9.9	23.9	9.9
85+	4.6	2.5	5.4	2.5
Women (%)	61.9	57.5	63.1	57.4
Year of Cohort Entry (%)				
1997	0.2	1.3	5.6	1.6
1998	0.5	2.1	7.1	2.3
1999	0.6	2.5	7.2	2.7
2000	1.5	3.8	8.1	4.0
2001	2.2	3.9	7.8	4.1
2002	2.9	3.8	7.5	4.0
2003	4.1	3.9	7.0	4.0
2004	5.2	3.7	6.4	3.9
2005	6.3	2.9	5.5	3.0
2006	7.9	2.9	5.4	3.1
2007	17.9	20.2	10.0	19.6
2008	22.0	20.6	9.6	20.0
2009	21.8	19.9	9.1	19.3
2010	6.9	8.5	3.6	8.4
2011	0.0	0.0	0.1	0.1
Nursing Home (%) ‡	0.8	1.1	0.9	1.1
Urban (%) §	85.2	78.2	86.1	78.2
Comorbidities (%)				
Asthma	2.5	1.6	3.5	1.6
Bronchiectasis	0.1	0.0	0.1	0.0
COPD	3.0	2.1	3.9	2.2
Diabetes	10.0	9.7	11.0	9.6

Non-hospitalized pneumonia	2.3	2.2	2.6	2.2
Hospitalizations in the Year Preceding Cohort Entry (%)				
None	91.6	93.3	91.7	93.2
One	6.9	5.6	6.6	5.6
Two	1.1	0.9	1.2	0.9
Three	0.3	0.2	0.4	0.2
Four or More	0.1	0.1	0.2	0.1
Prescriptions in the Year Preceding Cohort Entry (%)				
None	4.5	5.7	3.3	6.2
One	6.8	8.9	5.6	9.2
Two	7.9	10.1	7.0	10.3
Three	8.7	10.3	8.1	10.4
Four or More	72.2	65.1	76.0	63.9
Medications (%)				
PPI [†]	22.8	3.2	3.9	3.1
H2RA [†]	2.6	1.5	30.5	1.5
NSAIDs [†]	24.8	21.0	33.2	20.8
Immunosuppressive Agents	1.4	1.2	0.6	1.2
Influenza Vaccine ^{**}	18.6	4.5	8.5	4.3
Inhaled Bronchodilators	11.2	8.1	11.0	8.0
Inhaled Corticosteroids	12.0	14.3	10.8	13.9
Pneumococcal Vaccine ^{**}	10.7	1.9	3.9	1.9
Non-Topical Antibiotics	42.9	45.2	43.6	44.7
Non-Topical Corticosteroids	14.1	18.0	11.1	17.4

Abbreviations: COPD = Chronic Obstructive Pulmonary Disease; H2RA = Histamine-2 Receptor Antagonist; NSAIDs = Non-Steroidal Anti-Inflammatory Drugs; PPI = Proton Pump Inhibitor.

*Saskatchewan did not contribute to the PPI analysis. In addition, small differences in the unexposed groups exist in the PPI and H2RA analyses because of trimming during the estimation of high-dimensional propensity scores.

[†]Alberta, Ontario, Quebec, and Nova Scotia only contributed data for those ≥ 66 years of age whereas MarketScan only contributed data for those aged 40-65 years.

[‡]The proportion of study participants living in nursing homes was only reported by Manitoba and Ontario.

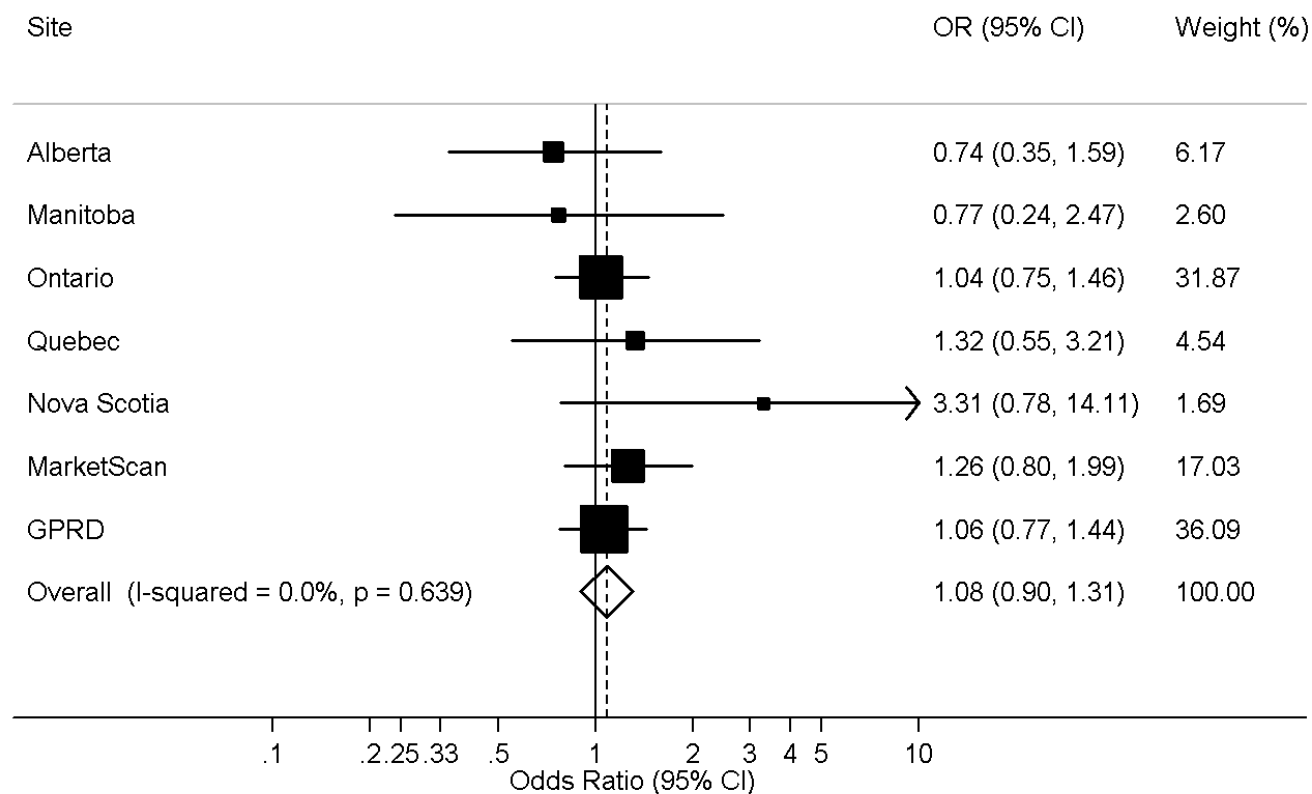
[§]Data regarding urban/rural location were only available in Alberta, Manitoba, Nova Scotia, and Ontario.

^{||}Comorbidities and medication use are defined using data in the year prior to and including the date of cohort entry.

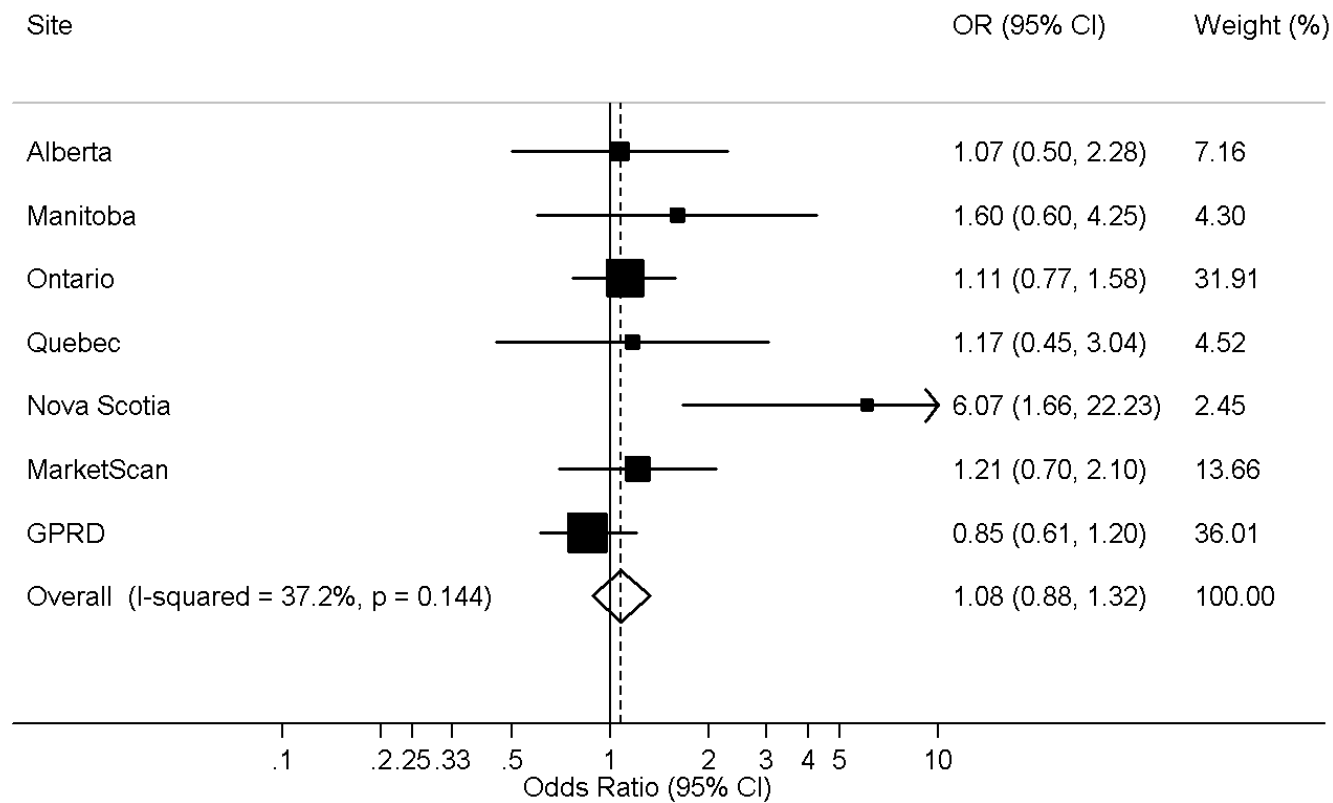
[¶]Denotes use in the 7-12 months before cohort entry. Use in the 6 months before cohort entry resulted in exclusion.

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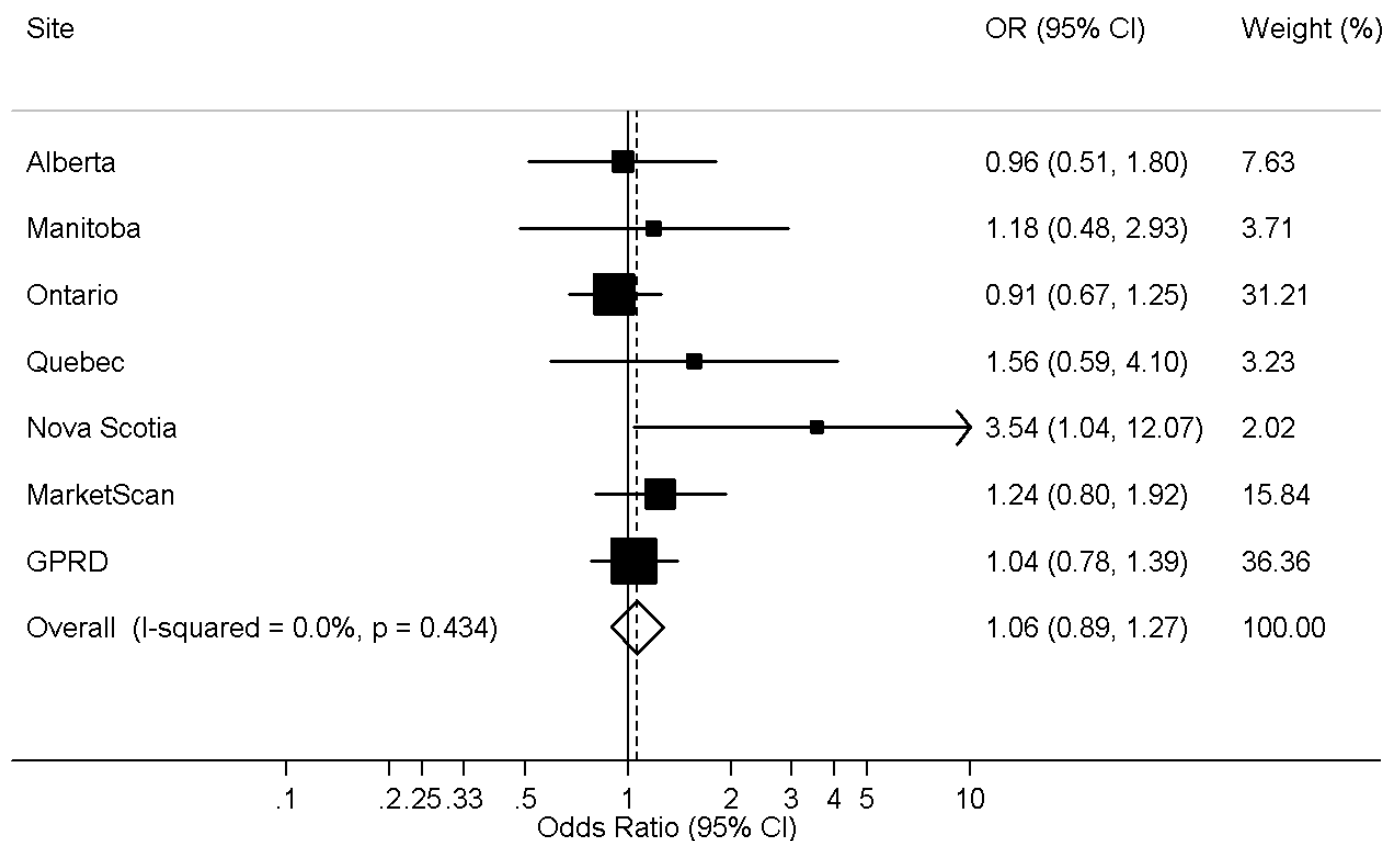
Online Appendix 3. Sensitivity analysis examining the association between the use of proton pump inhibitors and the 6-month cumulative incidence of hospitalization for community-acquired pneumonia in a restricted cohort of new users of non-steroidal anti-inflammatory drugs, with analysis restricted to one random-observation per patients. Analyses were adjusted for age, sex, previous non-hospitalized pneumonia, prescription of proton pump inhibitors, histamine-2 receptor antagonists, and non-steroidal anti-inflammatory drugs in the 7 to 12 months prior to cohort entry, and high-dimensional propensity score decile. Abbreviations: CI = Confidence Interval; GPRD = General Practice Research Database; OR = Odds Ratio.



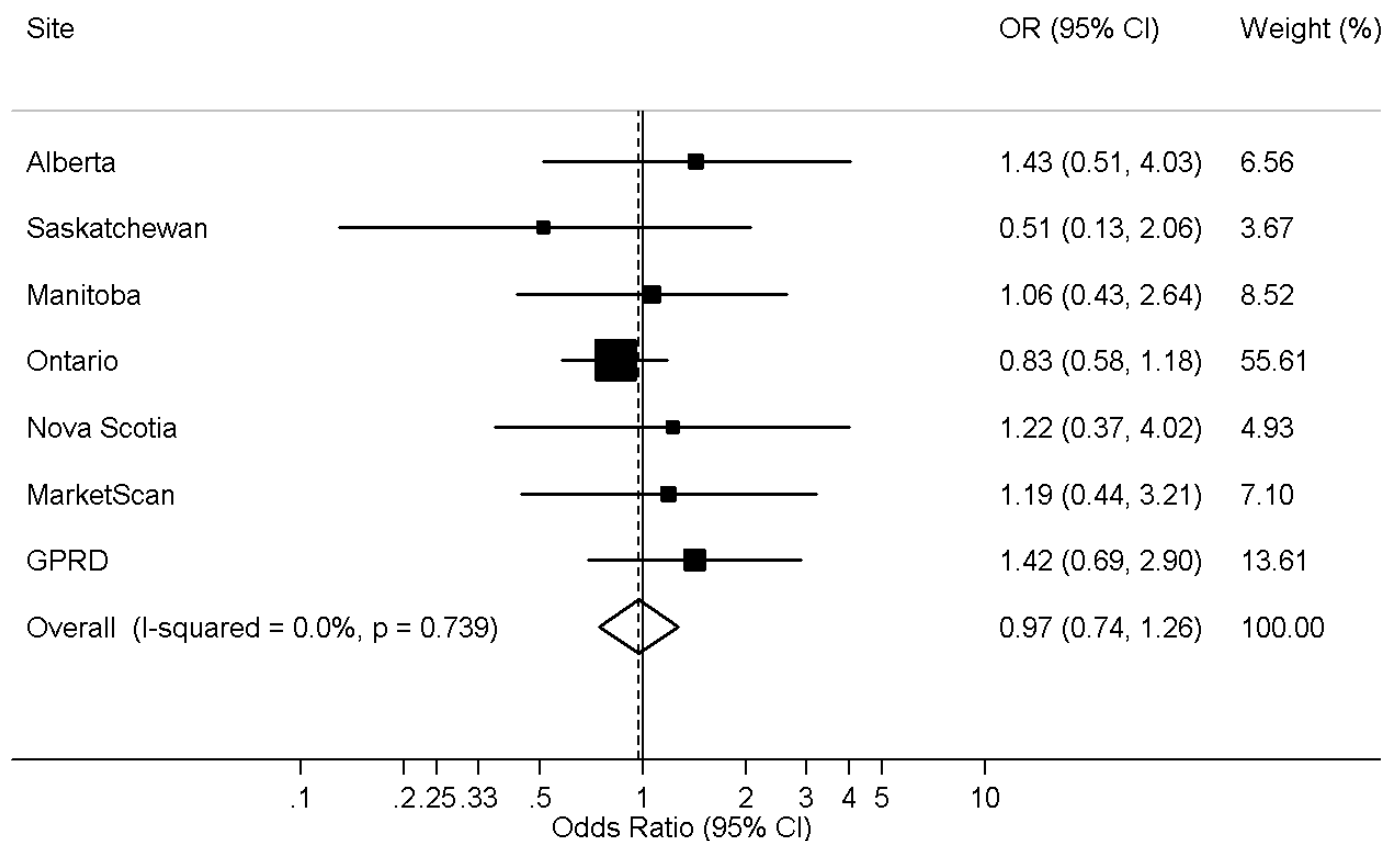
Online Appendix 4. Sensitivity analysis examining the association between the use of proton pump inhibitors and the 6-month cumulative incidence of hospitalization for community-acquired pneumonia in a restricted cohort of new users of non-steroidal anti-inflammatory drugs and excluding users of proton pump inhibitors, histamine-2 receptor antagonists, and non-steroidal anti-inflammatory drugs in the year prior to cohort entry. Analyses were adjusted for age, sex, previous non-hospitalized pneumonia, and high-dimensional propensity score decile. Abbreviations: CI = Confidence Interval; GPRD = General Practice Research Database; OR = Odds Ratio.



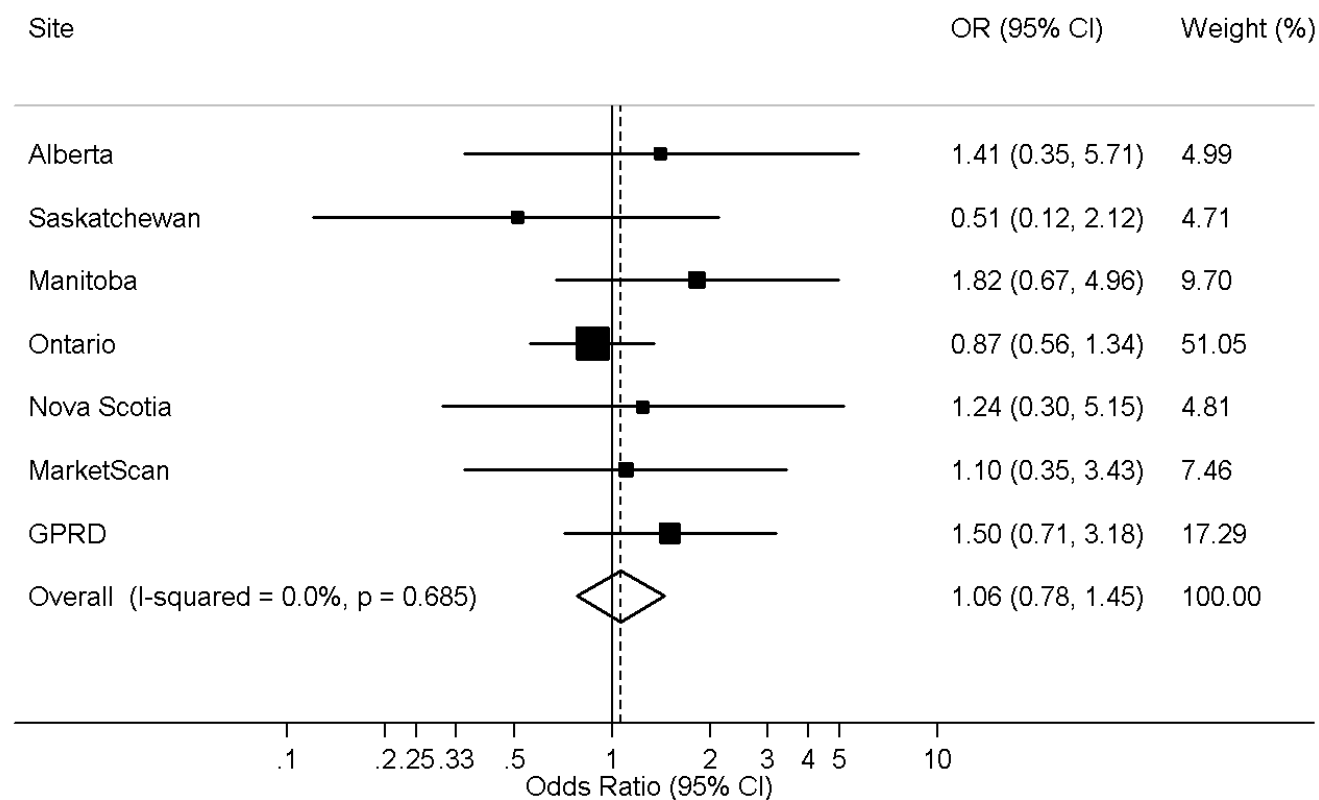
Online Appendix 5. Sensitivity analysis examining the association between the use of proton pump inhibitors and the 6-month cumulative incidence of hospitalization for community-acquired pneumonia in a restricted cohort of new users of non-steroidal anti-inflammatory drugs and excluding cross-overs. Analyses were adjusted for age, sex, previous non-hospitalized pneumonia, prescription of proton pump inhibitors, histamine-2 receptor antagonists, and non-steroidal anti-inflammatory drugs in the 7 to 12 months prior to cohort entry, and high-dimensional propensity score decile. Abbreviations: CI = Confidence Interval; GPRD = General Practice Research Database; OR = Odds Ratio.



Online Appendix 6. Sensitivity analysis examining the association between the use of histamine-2 receptor antagonists and the 6-month cumulative incidence of hospitalization for community-acquired pneumonia in a restricted cohort of new users of non-steroidal anti-inflammatory drugs, with analysis restricted to one random-observation per patients. Analyses were adjusted for age, sex, previous non-hospitalized pneumonia, prescription of proton pump inhibitors, histamine-2 receptor antagonists, and non-steroidal anti-inflammatory drugs in the 7 to 12 months prior to cohort entry, and high-dimensional propensity score decile. Abbreviations: CI = Confidence Interval; GPRD = General Practice Research Database; OR = Odds Ratio.



Online Appendix 7. Sensitivity analysis examining the association between the use of histamine-2 receptor antagonists and the 6-month cumulative incidence of hospitalization for community-acquired pneumonia in a restricted cohort of new users of non-steroidal anti-inflammatory drugs and excluding users of proton pump inhibitors, histamine-2 receptor antagonists, and non-steroidal anti-inflammatory drugs in the year prior to cohort entry. Analyses were adjusted for age, sex, previous non-hospitalized pneumonia, and high-dimensional propensity score decile. Abbreviations: CI = Confidence Interval; GPRD = General Practice Research Database; OR = Odds Ratio.



Online Appendix 8. Sensitivity analysis examining the association between the use of histamine-2 receptor antagonists and the 6-month cumulative incidence of hospitalization for community-acquired pneumonia in a restricted cohort of new users of non-steroidal anti-inflammatory drugs and excluding cross-overs. Analyses were adjusted for age, sex, previous non-hospitalized pneumonia, prescription of proton pump inhibitors, histamine-2 receptor antagonists, and non-steroidal anti-inflammatory drugs in the 7 to 12 months prior to cohort entry, and high-dimensional propensity score decile. Abbreviations: CI = Confidence Interval; GPRD = General Practice Research Database; OR = Odds Ratio.

