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Early View

Original article

The risk of community-acquired pneumonia in children using gastric acid suppressants

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Title

The risk of community-acquired pneumonia in children using gastric acid suppressants

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Take home message

In this large cohort study, the use of acid suppressants in children, both PPI and H2RA, was associated with a doubled risk of CAP. This risk increased with chronic use, respiratory disease, and remained increased after discontinuation of therapy.

Abstract

With the increased use of acid suppressants, significant potential complications, such as community-acquired pneumonia are becoming more apparent. Paradoxically, in spite of an increased focus on potential complications, there is an increased use of acid suppressants in children and a lack of data specifically targeting the association between acid suppressants and community-acquired pneumonia. Our main objective was to evaluate the risk of community-acquired pneumonia in children using acid suppressants (proton pump inhibitors and/or histamine-2-receptor antagonists).

We performed a cohort study using data from the Clinical Practice Research Datalink. All patients aged 1 month to 18 years with a prescription of acid suppressants were included and matched to up to 4 unexposed children. Time-varying Cox proportional hazards models were used to estimate the risk of community-acquired pneumonia. The cohort consisted of 84,868 exposed and 325,329 unexposed children.

Current use of proton pump inhibitors and histamine-2-receptor antagonists was associated with an increased risk of community acquired pneumonia, adjusted hazard ratio 2.05 (95% CI 1.90 to 2.22) and 1.80 (95% CI 1.67 to 1.94), respectively. The risk was even greater in patients with respiratory disease. Long term use > 211 days of proton pump inhibitors and histamine-2-receptor antagonists led to a significantly greater risk of community-acquired pneumonia compared to short term use < 31 days. After cessation of therapy, the risk remained increased for the following seven months.

The use of acid suppressants in children was associated with a doubled risk of community-acquired pneumonia. This risk increased with chronic use, respiratory disease and remained increased after discontinuation of therapy.

Introduction

Acid suppressants (AS) are often prescribed in the management of symptoms of gastro-esophageal reflux (disease) in both children and adults. Over the past decades, the consumption of AS such as proton pump inhibitors (PPIs) and histamine-2 receptor antagonists (HR2As) has increased considerably. In children, a two- to eightfold increase in prescriptions of AS was observed [1-4], in spite of the increased awareness of potential adverse effects and guideline recommendations to exercise caution when prescribing for children [5]. Over the course of time, potential complications in adults became apparent: various systematic reviews and meta-analyses described an association between AS and community-acquired pneumonia (CAP) [6-9]. Although there are a number of adult studies assessing the proposed association, there are hardly any studies in children, and those that are available show conflicting results. Canani et al. performed a prospective cohort study in 186 children aged 4-36 months (47 ranitidine users, 44 omeprazole users, 95 non-users), demonstrating that the use of AS was associated with a 6-fold increased risk of CAP [10]. Blank et al. conducted a nested case-control study in 21,911 infants, comparing the risk of CAP resulting in hospitalization or death in current users and past users of PPIs [11]. Their results did not show an increased risk of CAP in current users compared to past users. However, never users were not included in this study.

Given the widespread use of AS, the significance of CAP as a serious childhood infection [12], and the paucity of data regarding the association between AS and CAP in children, there is an urgent need to assess the potential impact of AS on the risk of CAP in children. The specific objectives of this study were: (1) to evaluate the risk of developing CAP in children using PPIs and/or H2RAs, (2) to assess the influence of a chronic respiratory disease (like asthma, bronchopulmonary dysplasia (BPD) and cystic fibrosis (CF)), and (3)

to compare the risk between current, recent, past, and never users of AS, and to assess the effect of prolonged use and cessation of therapy.

Methods

Study design

We performed a cohort study, using the UK Clinical Practice Research Datalink (CPRD) GOLD, a large primary care database of anonymized medical records of 740 primary care practices. Since 1987, the CPRD has recorded data such as patient demographics, medical history, laboratory test results, medical diagnosis, and prescription details [13]. The CPRD has been extensively used and validated for pharmacoepidemiological and epidemiological research and has been shown to be representative for populations outside the UK [13, 14].

Study population

The study cohort consisted of children aged 1 month to 18 years with at least one prescription for either a PPI or H2RA (exposed patients) during the period of data collection from 1 January 1995 to 31 December 2017. The first prescription of an AS defined the start of follow-up (index date). Each exposed patient was matched by year of birth, sex and practice to up to 4 children without a prescription for an AS (unexposed patients), using the incidence density sampling technique, and were assigned the index date of their matched exposed patient. From both the exposed and unexposed population, children with a history of active tuberculosis, malignancies or use of tuberculosis medication prior to the index date were excluded. Patients using immunosuppressant medication 6 months prior to index date and patients with a history of pneumonia 3 months prior to index date were excluded as well. Every patient was followed from his/her index date up to the end of data collection, until he/she turned 18 years old, until he/she died, or when the outcome of interest occurred; whichever came first.

The exposure of interest was the prescription of a PPI and/or H2RA. The follow-up time was stratified into periods of 30 days. Before the start of each period, exposure to either PPIs or H2RAs was determined, dividing person-time into “current use”, “recent use”, “past use”, “distant past use” and “never use”. The distribution of person-time in the different groups was based on the time that had passed since the most recent prescription: 1-30 days was defined as “current use”, 31-60 days as “recent use”, 61-210 days as “past use” and over 211 days as “distant past use”. As a result of this classification, patients were able to move between groups during follow-up. Clearly, “never users” had no history of prescription of a PPI or H2RA.

Each current use interval was further stratified by continuous duration of use. To determine continuous duration of use, the prescribed quantity and the written dosage instruction was used to estimate the duration of each PPI/H2RA prescription. Continuous duration was then defined as the time from the first continuous prescription until the start of an interval, allowing a gap of 60 days between the estimated end date of a prescription and the start of the next prescription.

Outcome of interest

The primary outcome of interest was the occurrence of CAP in the full CPRD cohort (read codes available upon request). CAP was defined according to the definition of the British Thoracic Society (BTS): persistent or repetitive fever together with chest recessions and a raised respiratory rate [15]. We selected READ codes based on the description of this clinical syndrome. We reviewed the literature to identify risk factors for the outcomes of interest. These risk factors were used as potential confounders (for the estimation of relative risks). Potential confounders were assessed in a time-dependent manner, with the exception of sex, and were collected at the start of each time interval. All variables were treated as categorical variables (with the exception of age), and we used dummy indicator variables to account for missing data. Potential confounders included age, gender, a history of pneumonia, a history

of gastro-esophageal reflux, chronic lung diseases (asthma, BPD, CF) and (severe) psychomotor disability.

Statistical analysis

Cox proportional hazard models (SAS 9.4, PHREG procedure) were used to estimate the hazard ratios (HRs) for CAP in AS users compared to never users. We tested for statistical differences between PPI use or H2RA use, applying the Wald statistic. PPI and H2RA use was stratified by time since the most recent prescription. HRs were adjusted for age, sex and potential confounders that showed a >5% change in its beta-coefficient of an age/gender-adjusted analysis or when consensus about inclusion existed within the team of researchers supported by clinical evidence from the literature.

The protocol for this study was approved by the Independent Scientific Advisory Committee (ISAC) for MHRA Database research, protocol number 18_107.

Results

Patient characteristics

A total of 447,759 patients aged 1 month to 18 years were identified in the CPRD database, consisting of 90,858 children exposed to a PPI and/or H2RA and 356,901 children unexposed to a PPI and/or H2RA at baseline. Subsequently, we excluded 14,538 unique patients (5,985 exposed children and 8,553 unexposed children) based on the following exclusion criteria: history of pneumonia 3 months prior to index date (4,100), active tuberculosis or use of medication for tuberculosis (3,921), use of immunosuppressant drugs (962) and/or malignancy (6,352). Matched cases and controls of excluded patients were excluded as well when there was no matched set of a case and at least 1 control any more (23,023). Therefore, our study cohort consisted of a total of 410,197 children, of whom 84,868 were exposed and 325,329 were unexposed at baseline.

The baseline characteristics of the cohorts are described in Table 1. The mean duration of follow-up, mean age, gender distribution and age distribution at cohort entry were similar in both cohorts. As expected, in comparison to unexposed patients, the patients in the exposed cohort were more likely to have a diagnosis of gastro-esophageal reflux 1 year prior to index date.

Risk of developing community-acquired pneumonia

An increased risk of developing CAP was found in all types of users of PPIs and H2RAs (current, recent, past and distant past users) compared to never users (Tables 2 and 3).

Current use of PPIs was associated with a 2-fold increased risk of developing CAP as compared to never use (adjusted hazard ratio (aHR) 2.05 [95% confidence interval (CI) 1.90 to 2.22]). Prolonged use of PPIs for more than 30 days was also associated with a higher risk of CAP, particularly in long-term users (> 211 days; aHR 2.34 [95% CI 2.06 to 2.67]). Moreover, the risk of CAP in continued current use > 211 days was significantly higher than

the risk in continued current use < 31 days, adjusted hazard ratio 2.53 [95% CI 2.22 to 2.88] versus adjusted hazard ratio 2.05 [95% CI 1.78-2.32], (p=0.028). After cessation of PPI treatment, the risk of CAP decreased slowly over time; in the first 7 months after discontinuation, the aHR was 1.72 [95% CI 1.53 to 1.94] for recent use, a 1.8 fold-increased risk was found for past use (aHR 1.79 [95% CI 1.66 to 1.93]), and a 1.3-fold increased risk for distant past use (aHR 1.29 [95% CI 1.23 to 1.36]).

Regarding the use of H2RAs, comparable results were found: current use of H2RAs was associated with a 1.8-fold increased risk of developing CAP compared to never use (aHR 1.80 [95% CI 1.67 to1.94]). Continued current use > 211 days led to a significantly greater risk of CAP compared to continued current use < 31 days, adjusted hazard ratio 2.63 [95% CI 2.22 to 3.11] versus adjusted hazard ratio 1.90 [95% CI 1.71-2.12], (p <0.001). Furthermore, the risk of CAP remained increased after cessation of H2RA therapy in comparison with never use.

Our analyses demonstrated no synergistic effect of the combined use of PPI and H2RA on the risk of CAP. Concomitant use of PPI and H2RA was associated with a 2.5-fold augmented risk of CAP, which did not differ much from the hazard ratios of PPIs and H2RAs separately. When current use of PPI and/or H2RA was further stratified by potential confounders, we found that the risk of CAP was even greater in patients with psychomotor disability, a history of pneumonia, or asthma (Tables 4 and 5).

Discussion

To our knowledge, this is the first large-scale study in the pediatric population assessing the effects of current, past, and long-term use of AS on the risk of developing CAP, and comparing the effects of both PPI and H2RA. We found that the use of AS in children was associated with a two-fold increased risk of acquiring CAP. This association was observed for both PPIs and H2RAs, and the increased hazard ratios of the two drug classes were quite similar. With prolonged use, the risk increased over time, especially with continued use > 211 days. Even after discontinuation of therapy, the risk remained increased for at least seven months, but decreased over time. Hazard ratios of developing CAP were even greater in AS users with psychomotor disability, a history of pneumonia, or asthma.

There are various explanations for the observed association between AS use and CAP. As an increased risk of CAP in both PPI and H2RA users was found, the observed association may be a consequence of a common denominator of these drugs, such as lowering the pH. Due to our study design, it is not possible to draw definite conclusions about causality but we hypothesize that the reduced pH leads to a change in microbiota and to the selection of more pathogenic bacteria in the airways and/or intestines. Consequently, alterations in the airway and/or gut microbiota could increase the risk of CAP.

In vitro studies showed the presence of proton pumps in mucous glands of the human lung [16] and indicated the presence of H2 receptors in the bronchus [17]. An altered pH of the mucous secretions in the lungs may alter the respiratory flora, and may cause the selection of more pathogenic micro-organisms, thereby increasing the risk of CAP [18].

A *second* hypothesis for the association between AS and CAP is crosstalk between the intestines and the lung, referred to as the gut-lung axis, suggesting that alterations in the intestinal microbiota can influence the lungs and vice versa [19, 20]. Although the understanding of the gut-lung axis is still premature, it is known that PPIs can induce

intestinal dysbiosis [21], and several studies showed that alterations of gut microbiota can influence the course of respiratory infections. Schuijt et al. showed that disruption of the gut microbiota impairs immune responses and worsens the course of pneumococcal pneumonia [22]. On the other hand, a systematic review and meta-analysis described how the administration of probiotics may positively influence the course and incidence of respiratory infections in children [23]. The effect of intestinal dysbiosis on the lungs could be the consequence of translocation of gastric bacteria into the lungs through (non-acid) gastro-esophageal reflux with micro-aspiration [24], or result from alterations in the immune response by bacterial products produced in the colon due to the dysbiosis [19, 20].

A *third* proposed mechanism is that AS are able to directly alter the function and quantity of cellular components of the immune system, possibly resulting in increased susceptibility to infection. *In vitro* studies have demonstrated that PPIs inhibit the cytotoxic activity of natural killer cells and impair the function of neutrophils, while famotidine, a H2RA, has been shown to increase the number of inflammatory cells in bronchoalveolar lavage fluid [25-28]. However, with this proposed mechanism, we cannot explain the prolonged increased risk after discontinuation of therapy, as the altered immune response seems to be an on-off phenomenon.

As a *fourth* hypothesis, it was proposed more recently that the observed association is strongly influenced by confounders such as patients' characteristics, comorbidity or protopathic bias [29, 30]. However, in our analysis, we adjusted for possible confounders such as age, sex, GERD and history of pneumonia, after which the risk of developing CAP remained increased in AS users. Moreover, we tried to lower the risk of protopathic bias by examining the effects of prolonged use of AS. With an increased exposure time to AS, the hazard ratios increased, while the risk gradually decreased after stopping AS therapy. These findings do not support protopathic bias, although we cannot completely rule out the possibility.

When looking at *possible risk modifiers*, hazard ratios of developing CAP were even greater in children using AS with psychomotor disability, a history of pneumonia or asthma. In children with psychomotor disability, the increased risk of CAP may be due to impaired swallowing function, poor oral status, and recurrent aspiration [31, 32]. Recurrent CAP may result from various causes such as structural airway anomalies, immunodeficiency, aspiration, and asthma [33]. In children with asthma, CAP is also a more prevalent condition, possibly as a consequence of poor asthma control resulting in inflammation and intraluminal obstruction [33]. The use of inhaled corticosteroids is also associated with an increased risk of pneumonia [34].

Interestingly, a diagnosis of GERD in current users of our cohort was not associated with an increased risk of developing CAP, which may be explained by two factors. First, GERD is often over-diagnosed or misdiagnosed by primary physicians [35]. Secondly, the increased risk of CAP may not directly be the consequence of aspiration after full-column non-acid reflux, but result from the possible effect of AS on mucous pH and gut and lung microbiota.

Our data add to the growing evidence that the use of AS is associated with the development of CAP. In the literature on adult patients, multiple papers reported on this association.In a large systematic review and meta-analysis, including 6,351,656 participants, Lambert et al. observed a 1.5-fold increased risk of developing CAP in patients using PPIs [9]. A second meta-analysis, performed by Johnstone et al, in around 1 million patients demonstrated similar results, with an 1.4-fold increased risk of CAP with PPI use [7]. Eom et al. also found a significant association between PPI and CAP, with an 1.3-fold increased risk, and a 1.2-fold increased risk of hospital-acquired pneumonia in H2RA users [8]. In our study with children, we found even greater risk ratios for the association between AS and CAP than in these studies in adults.

So far, only 2 pediatric studies were performed specifically targeting this association, showing conflicting results. Canani et al. found a negative association between AS and CAP

in a small group of 186 children aged 4-36 months, who were prescribed a PPI or H2RA for 2 months [10]. At the 4-month follow-up, they found a six-fold increased risk of developing CAP with either PPI or H2RA use. Blank et al. performed a nested case-control study in 21,911 infants, demonstrating that current use of PPI in infants does not increase the risk of CAP compared to past use [11]. It is likely that they did not observe an increased hazard when comparing current use to past use, as in our study past use was still associated with an increased risk of acquiring CAP. In addition, their primary outcome was CAP or lower respiratory tract infection leading to hospitalization or death, which clearly differs from the definition of CAP in the general population in our study.

Our study has several strengths. The main strength is that this is the first large study in children to examine this association, in which the effect of prolonged use and cessation of therapy were assessed too. In addition, we studied the role of *both* PPI and H2RA use and were able to compare the hazard ratios on CAP related to these two drugs. Our results are likely to be generalizable as the CPRD database population has been shown to be representative for the UK population, as well as populations outside the UK [13, 14].

Our study also has several limitations. Due to its observational nature, the results may be biased by exposure and/or outcome misclassification. Also, residual confounding cannot be completely excluded as it is possible that possible confounders were underreported. Due the study design we cannot establish a causal relationship between the use of AS and CAP. Moreover, we were not able to discriminate between a viral or bacterial origin of CAP in our study due to the study design.

In conclusion, this study showed that the use of AS in children, both PPIs and H2RAs, is associated with an average 2-fold increased risk of acquiring CAP. The risk of CAP further increased over time with continued use > 211 days. After cessation of therapy, the risk remained increased for at least 7 months. Patients with psychomotor disability, a history of pneumonia, or asthma using an AS had an even greater risk of CAP.

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Contributors

LS, QJ, FV, ED, EG, JC and JD designed the study. JD, FV and LS were responsible for the data extraction. LS, QJ, MB, FV, ED and JD wrote the paper. LS and QJ performed a systematic review of the literature on this subject. All authors critically revised the article and approved the final version.

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Data sharing

CPRD Gold Data for this study has been sublicensed from the Medicines and Healthcare products Regulatory Agency by Utrecht University and is subject to an agreement that does not allow further sharing with others. However, CPRD Gold data, either for original or replication studies, is available from the licensor to any team of researchers who meet appropriate qualifications, subject to a priori scientific approval of the study protocol by ISAC and the availability of a sublicensing agreement. Data dictionaries of exposures and outcomes are available for auditing purposes.

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Table 1 - Baseline characteristics of the AS users and the controls at cohort entry in the study

Characteristics	Study population (n=410,197)			
	AS users (n=84,868)	%	Non-users (n=325,329)	%
Mean follow-up time, years (SD)	3.7	3.1	3.6	3.1
Female sex	45,212	53.3	173,533	53.3
Mean age at index date, years (SD)	9	6.8	8.9	6.7
History of disease				
Pneumonia [a]	13,026	15.3	39,794	12.2
GE-reflux [b]	18,258	21.5	4,032	1.2
Asthma	11,058	13.0	32,012	9.8
BPD	86	0.1	44	0.0
CF	346	0.4	56	0.0
Psychomotor disability	505	0.6	352	0.1

Data are presented as n (%), unless stated otherwise. Abbreviations: GE-reflux: gastro-oesophageal reflux, BPD: bronchopulmonary dysplasia, CF: cystic fibrosis. [a] *History of pneumonia more than 3 months prior to index date.* [b] *History of GE-reflux within 1 year of index date.*

Table 2 – Use of proton pump inhibitors and risk of community-acquired pneumonia

Exposure	**No. of CAP events**	**IR** (/1000 py's)	**Age/sex adjusted HR**	**95% CI**		**Fully adjusted HR** *	**95% CI**	
Never PPI or H2RA	21,471	19.1	Reference			Reference		
PPI use by time since last prescription								
Current: 1-30 days	739	68.4	2.66	2.47	2.86	2.05	1.90	2.22
Recent: 31-60 days	288	45.2	2.13	1.89	2.39	1.72	1.53	1.94
Past: 61-210 days	729	36.9	2.12	1.97	2.28	1.79	1.66	1.93
Distant past: > 211 days	1,588	19.8	1.39	1.32	1.46	1.29	1.23	1.36
Current PPI use by duration of use								
1-30 days	186	41.8	2.29	1.99	2.65	1.89	1.63	2.18
31-60 days	75	80.1	2.22	1.77	2.79	1.81	1.44	2.27
61-210 days	241	95.1	2.62	2.30	2.97	2.04	1.79	2.32
> 211 days	237	82.0	3.32	2.92	3.77	2.34	2.06	2.67
Current use of both PPI and H2RA	73	111.1	3.47	2.76	4.36	2.52	2.00	3.18

*Abbreviations: PPI: proton pump inhibitor, H2RA: histamine-2 receptor antagonist, CAP: community-acquired pneumonia, IR: incidence rate, py's: person years, HR: hazard ratio, CI: confidence interval. * Adjusted for age, sex, history of pneumonia, gastro-oesophageal reflux 1 year before, asthma, bronchopulmonary dysplasia, cystic fibrosis. All analyses are adjusted for use of H2RA.*

Table 3 – Use of histamine-2 receptor antagonists and risk of community-acquired pneumonia

Exposure	**No. of CAP events**	**IR** (/1000 py's)	**Age/sex adjusted HR**	**95% CI**		**Fully adjusted HR** *	**95% CI**	
Never PPI or H2RA	21,471	19.1	Reference			Reference		
H2RA use by time since last prescription								
Current: 1-30 days	780	85.4	2.28	2.12	2.45	1.80	1.67	1.94
Recent: 31-60 days	491	77.3	2.04	1.87	2.23	1.68	1.53	1.85
Past: 61-210 days	1,479	66.6	1.95	1.85	2.06	1.65	1.55	1.74
Distant past: > 211 days	3,943	26.4	1.24	1.20	1.29	1.19	1.15	1.23
Current H2RA use by duration of use								
1-30 days	330	68.2	2.04	1.83	2.27	1.90	1.71	2.12
31-60 days	77	87.6	1.95	1.56	2.44	1.83	1.46	2.29
61-210 days	237	110.8	2.45	2.15	2.78	2.27	1.99	2.58
> 211 days	136	106.4	3.09	2.61	3.66	2.63	2.22	3.11
Current use of both PPI and H2RA	73	111.1	3.47	2.76	4.36	2.52	2.00	3.18

*Abbreviations: PPI: proton pump inhibitor, H2RA: histamine-2 receptor antagonist, CAP: community-acquired pneumonia, IR: incidence rate, py's: person years, HR: hazard ratio, CI: confidence interval. * Adjusted for age, sex, history of pneumonia, gastro-oesophageal reflux 1 year before, asthma, bronchopulmonary dysplasia, cystic fibrosis. All analyses are adjusted for use of H2RA.*

Table 4 - Current use of PPI and risk of community-acquired pneumonia, stratified by confounders

Exposure	No. of CAP events	IR (/1000 py's)	Age/sex adjusted HR	95% CI		Fully adjusted HR *	95% CI	
Never PPI or H2RA	21,471	19.1	Reference			Reference		
Current PPI use: 1-30 days	739	68.4	2.66	2.47	2.86	2.05	1.90	2.22
Per confounder								
History of pneumonia								
Yes	171	83.8	5.80	4.99	6.75	3.92	3.37	4.57
No	568	64.8	2.28	2.09	2.48	1.86	1.71	2.03
Gastro-oesophageal reflux [a]								
Yes	257	104.7	2.16	1.91	2.44	2.03	1.79	2.30
No	482	57.7	3.02	2.76	3.30	2.41	2.20	2.64
Asthma								
Yes	106	56.1	4.29	3.54	5.19	3.13	2.58	3.79
No	633	71.0	2.50	2.30	2.70	2.03	1.87	2.21
Bronchopulmonary dysplasia								
Yes	<5	189.5	3.22	1.04	9.99	2.47	0.80	7.65
No	736	68.2	2.66	2.47	2.86	2.08	1.93	2.25
Cystic fibrosis								
Yes	30	65.2	2.62	1.83	3.75	2.17	1.51	3.10
No	709	68.5	2.66	2.47	2.87	2.13	1.97	2.30
Psychomotor disability								
Yes	66	193.4	7.88	6.19	10.04	6.80	5.34	8.66
No	673	64.3	2.49	2.31	2.69	2.02	1.86	2.18

*Abbreviations: PPI: proton pump inhibitor, H2RA: histamine-2 receptor antagonist, CAP: community-acquired pneumonia, IR: incidence rate, py's: person years, HR: hazard ratio, CI: confidence interval. [a] History of GE-reflux 1 year before. * Adjusted for age, sex, history of pneumonia, gastro-oesophageal reflux 1 year before, asthma, bronchopulmonary dysplasia, cystic fibrosis. All analyses are adjusted for use of H2RA.*

Table 5 - Current use of H2RA and risk of community-acquired pneumonia, stratified by confounders

Exposure	No. of CAP events	IR (/1000 py's)	Age/sex adjusted HR	95% CI		Fully adjusted HR *	95% CI	
Never PPI and H2RA	21,471	19.1	Reference			Reference		
Current H2RA use: 1-30 days	780	85.4	2.28	2.12	2.45	1.80	1.67	1.94
Per confounder								
History of pneumonia								
Yes	103	104.3	5.47	4.51	6.64	3.91	3.22	4.75
No	677	83.1	2.09	1.93	2.25	1.68	1.55	1.82
Gastro-oesophageal reflux [a]								
Yes	353	107.2	2.09	1.88	2.33	2.02	1.81	2.24
No	427	73.1	2.45	2.23	2.70	2.17	1.97	2.39
Asthma								
Yes	51	58.9	3.46	2.63	4.56	2.62	1.99	3.45
No	729	88.2	2.22	2.06	2.39	1.80	1.67	1.95
Bronchopulmonary dysplasia								
Yes	6	276.3	4.86	2.18	10.82	3.63	1.63	8.06
No	774	85.0	2.27	2.11	2.44	1.81	1.67	1.95
Cystic fibrosis								
Yes	12	110.9	2.68	1.52	4.72	2.34	1.33	4.13
No	768	85.1	2.27	2.11	2.44	1.82	1.68	1.96
Psychomotor disability								
Yes	43	270.0	8.25	6.11	11.12	7.02	5.20	9.48
No	737	82.1	2.19	2.03	2.35	1.77	1.63	1.91

*Abbreviations: PPI: proton pump inhibitor, H2RA: histamine-2 receptor antagonist, CAP: community-acquired pneumonia, IR: incidence rate, py's: person years, HR: hazard ratio, CI: confidence interval. [a] History of GE-reflux 1 year before. * Adjusted for age, sex, history of pneumonia, gastro-oesophageal reflux 1 year before, asthma, bronchopulmonary dysplasia, cystic fibrosis. All analyses are adjusted for use of PPI.*