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Association between proton pump inhibitor use and risk of pneumonia in children: nationwide self-controlled case series study in Sweden

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ABSTRACT

Objective To evaluate the association between use of proton pump inhibitors (PPIs) and risk of pneumonia in children.

Design Nationwide register-based self-controlled case series study.

Setting Sweden, July 2006 to December 2016.

Participants Children aged <18 years who were treated with PPIs and had a hospitalisation or hospital emergency care visit for pneumonia within 1 year before and 2 years after PPI initiation.

Main outcomes and measures The primary analysis examined the risk of pneumonia during the risk period (ongoing PPI treatment), the pre-exposure period (≤30 days preceding PPI treatment) and the postexposure period (days 1–365 after PPI discontinuation), comparing to the unexposed period. Conditional Poisson regression was used to estimate incidence rate ratios (IRRs) and 95% CIs.

Results A total of 2356 cases of pneumonia were included. Compared with the unexposed period, the risk of pneumonia was significantly increased during ongoing PPI treatment, with an adjusted IRR of 1.40 (95% CI 1.21 to 1.62). The risk of pneumonia was also increased in the pre-exposure period (adjusted IRR, 1.80, 95% CI 1.51 to 2.13), but not in the postexposure period (adjusted IRR 0.98, 95% CI 0.89 to 1.08). Dividing the risk period by time since treatment initiation, the increased risk of pneumonia was highest in the first 30 days (adjusted IRR 1.63, 95% CI 1.35 to 1.97), remained during days 31–90 (adjusted IRR 1.32, 95% CI 1.04 to 1.69), but waned in days ≥91 (IRR 1.06, 95% CI 0.79 to 1.41).

Conclusions and relevance An increased risk of pneumonia was observed both immediately before and immediately after PPI initiation. This pattern of association can likely be explained by an underlying risk of pneumonia due to factors transiently present at the time around PPI initiation. Thus, our findings do not support a causal relationship between PPI use and risk of pneumonia.

Strengths and limitations of this study

- The main strengths of this study are the use of nationwide data ensuring generalisability and a large sample size enabling precision of the estimates.
- Employment of the self-controlled case series method permitted within-individual comparisons which controlled for time-invariant confounders and reduced selection bias.
- The study did not investigate mild to moderate pneumonia cases that were likely managed in primary care.
- Unmeasured confounders cannot be fully ruled out, including time-varying risk factors for pneumonia.
- Information regarding over-the-counter drugs, drug use during hospitalisation and patients' adherence to proton pump inhibitors was unavailable.

INTRODUCTION

Proton pump inhibitors (PPIs) are widely effective in the treatment of gastric acid-related disorders. In the recent decade, use of PPIs has increased markedly among children[1] and these drugs are frequently prescribed off-label.[2] There are growing safety concerns about PPI use in children, with a potential increased risk of pneumonia representing one such concern.

Among adults, a number of meta-analyses of observational studies and small randomised controlled trials[3–6] found that PPIs were linked to an increased risk of pneumonia; notably, the greatest increase in risk has been observed within 30 days after PPI initiation. However, given substantial heterogeneity in the meta-analyses[3–6] and null associations shown in the most recent studies,[7 8] whether PPIs are associated with the risk of pneumonia in adults remains debated.

In children, only two population-based studies[9 10] have examined this drug safety issue. A recent cohort study[10] observed a twofold increased risk of pneumonia within the first 30 days of current use of PPIs, as compared with non-use, whereas a nested case–control study found a neutral association when comparing current PPI use to past

use.[9] The discrepancies between the two studies can probably be explained by sample variation, potential selection bias, or protopathic bias, which is particularly prone to contribute to a higher risk of pneumonia occurring in the immediate period after PPI initiation. Accordingly, whether PPI use is associated with risk of pneumonia in children is not fully understood. We aimed to investigate the association between PPI use among children and the risk of pneumonia by conducting a nationwide register-based self-controlled case series (SCCS) study.

METHODS

Data sources

For this SCCS study, we used data from four mandatory nationwide Swedish registers; a unique anonymised identifier for individuals enabled linkage of data between registers. The National Patient Register records information on all hospital admissions, and hospital outpatient visits, with comprehensive disease diagnoses and surgical procedures in Sweden. The validity of disease diagnoses in National Patient Register has been established, with the positive predictive values generally ranging from 85% to 95%.[11] The Prescribed Drug Register contains prescription drug records from all Swedish pharmacies, covering details on the drug type, drug quantity and dispensing date. The Cause of Death Register includes data on causes of death and date of death. Demographic data were obtained through the Total Population Register.

Case definition

The primary outcome was defined as any diagnosis of pneumonia captured from hospital admission or emergency outpatient care visits (International Statistical Classification of Diseases and Related-Health Problems, 10th Revision (ICD-10): J12.x–J18.x) at age <18 years. The outcome dates were assigned as the dates of hospital admission or emergency outpatient care visits for pneumonia. A subsequent pneumonia occurring more than 30 days after the date of discharge for a previous pneumonia was defined as an independent event.

Selection of cohort

We identified episodes with PPI treatment from a source cohort of all children aged <18 years in Sweden, 1 July 2006 to 31 December 2016, who had no use of PPI within 1 year before 1 July 2006. The study unit was episodes, defined as a time interval of up to 1 year before PPI index date and up to 2 years after PPI index date. Each individual could contribute with multiple non-overlapping episodes to the study cohort, and for each episode, the first dispensing date of PPI during that episode served as index date. The start of each episode was defined as birthdate, date of immigration or 1 year before the index date, whichever came latest.

Exclusion criteria were any history of tuberculosis and/or cystic fibrosis (ICD-10: E84.x, A15.x, A16.x, A17.x, A18.x, A19.x), cancer (ICD-10: C00.x–C97.x), chronic kidney disease (ICD-10: N18.x), HIV infection (ICD-10: B20.x, B21.x, B23.x, B24.x), interstitial lung disease (ICD-10: J84.x), primary immunodeficiency disease (ICD-10: D70.0, D70.4, D71.x, D72.0, D76.1, D80.x, D81.x, D82.x, D83.x, D84.x, E70.3, G11.3), severe liver disease (ICD-10: B15.0, B16.0, B16.2, B19.0, K70.4, K72.x, K76.6, I85.x), any solid organ transplantation (Swedish surgery codes (KVÅ codes): KAS, FQA, FQB, GDG, JJC) before the date of pneumonia and any record of use of other anti-acid agents (Anatomical Therapeutic Chemical (ATC) codes: A02BA, A02A) between 1 year before the start of an episode until the end of an episode.

Exposure

Our exposure was any use of oral PPIs, including esomeprazole, lansoprazole, omeprazole, pantoprazole, and rabeprazole (ATC codes: A02BC, A02BD, M01AE52). Duration of PPI use was measured from the total amount of tablets dispensed, with each tablet assumed to correspond to 1 day of use. We defined patients as continuously treated with PPIs as long as they refilled prescriptions, allowing for a gap between prescriptions of up to 30 days.

We split episodes into four separate periods (figure 1): (1) the pre-exposure period, defined as the interval between 30 days before index date until index date. The pre-exposure period was designed to take into account time-varying factors that could potentially change probability of PPI use as well as the risk of an event. (2) The risk period, defined as the time of ongoing PPI treatment, starting from the day after the index date until the estimated end of treatment. Further, we divided risk periods into 1–30, 31–90 and ≥91 days to evaluate any temporal change in the direction or magnitude of association for risk of pneumonia with ongoing PPI use. (3) The postexposure period, defined as the interval of 1 to 365 days after PPI discontinuation. (4) The unexposed period, defined as the remaining observation time that was not part of any of the aforementioned time periods, that is, all time before the pre-exposure periods and after the postexposure periods; this represented the unexposed reference category.

Statistical analysis

For each episode, patients were followed up from the start of an episode until age 18 years, death, emigration, any new PPI-prescription after the end of the risk period, 2 years after the index date, or 31 December 2016, whichever came first. Given the case definition, person-time from date of hospital admission or contact until 30 days after hospital discharge was not included in the analyses, because patients were not at risk of the outcome during this time interval.

The association between risk of pneumonia and PPI use was investigated by comparing the rates of pneumonia in the pre-exposure, risk and postexposure periods with that in the unexposed period. Conditional Poisson regression models were performed to estimate

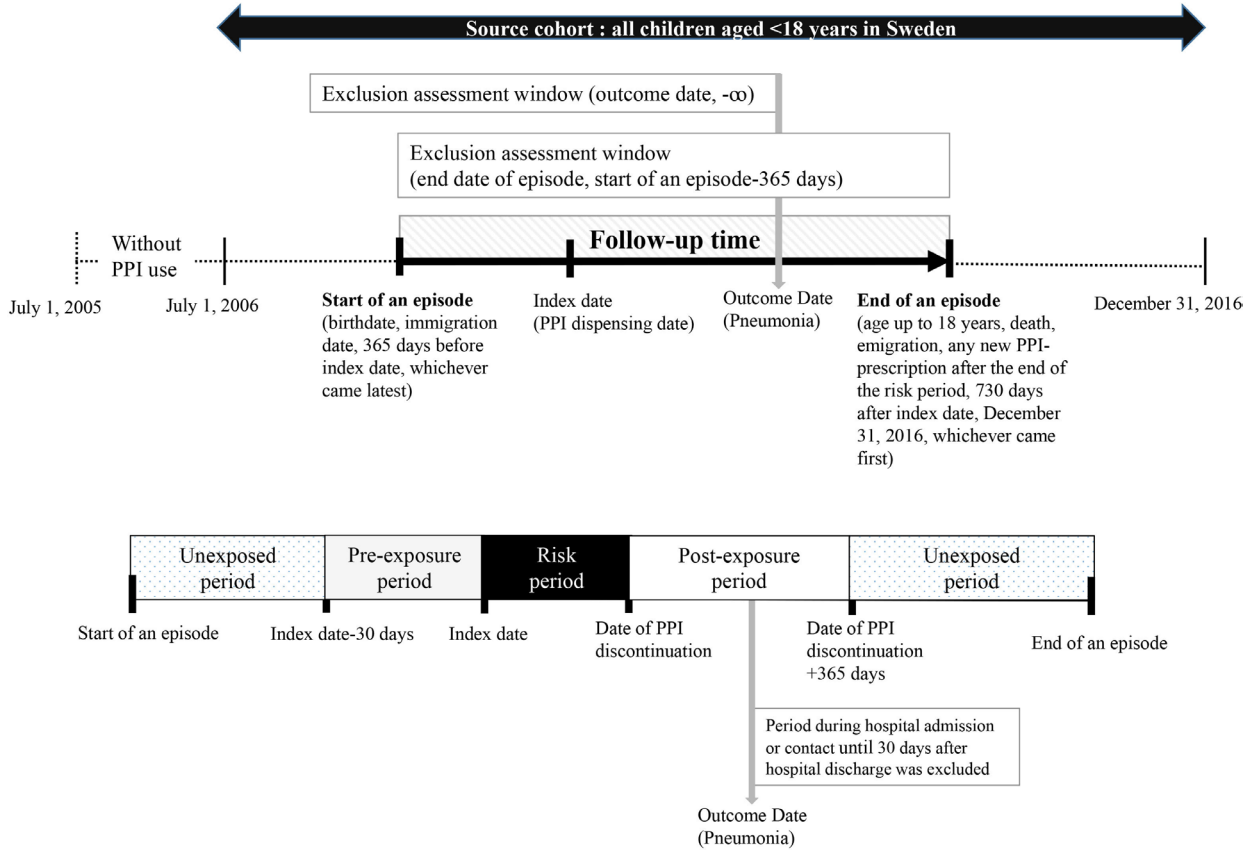

Figure 1 Schematic depiction of study design for self-controlled case series. PPI, proton pump inhibitor.

the crude and adjusted incidence rate ratios (IRRs) and corresponding 95% CIs. For adjusted models, the time periods were divided by treatment status and by age with 1-year bands and season (March–May, June–August, September–November, December–February).

In addition, in two subgroup analyses, we tested whether the association between risk of pneumonia and PPI use varied by sex and age at PPI initiation (categorised as 1–5, 6–13 and ≥14 years). Likelihood ratio tests were used to calculate the interaction effect within the subgroups.

In order to assess the robustness of study findings, several sensitivity analyses were conducted. First, to test the assumption of SCCS that the occurrence of the event would not censor or alter observation periods, we excluded patients who died during follow-up. Second, in the SCCS design, the events must be independent within individuals. We, therefore, further restricted to the first occurrence of pneumonia during the first episode. Third, we extended the interval between two pneumonia events to at least 90 days, which is suggested to be the time taken for patients to recover from pneumonia.[12] Forth, we redefined the length of pre-exposure periods to 90 days to minimise the pre-exposure time bias. That is, the risk of the unexposed period was possibly mixed with a high pre-exposure risk, leading to a higher risk of the unexposed period thereby diluting the relative risks associated with all other time periods. Next, to potentially improve the accuracy of the pneumonia definition, we restricted the analysis to cases with a primary diagnosis of pneumonia and cases hospitalised for pneumonia, respectively. Additionally, to further examine assumptions of the episode-based study design, we limited the unexposed period to the time before the pre-exposure period and time after postexposure period, separately, as well as restricted to the first episode for each individual. Further, given that systemic glucocorticoids are a potential risk factor for pneumonia,[13] and PPIs might be considered for gastroprotection in patients treated with corticosteroids, we restricted the analysis to patients without systemic glucocorticoid treatment (ATC codes: H02AB) between 90 days before the start of an episode until the end of an episode. In addition, we restricted the analysis to patients who were not concomitantly treated with antibiotics for H. pylori eradication (clarithromycin, amoxicillin, metronidazole or tetracycline (ATC codes: A02BD06, J01FA09, J01CA04, P01AB01, J01AA)) within 14 days before PPI initiation or 14 days after PPI discontiunation. Finally, we calculated the E-value for the lower bound of the CI to quantify the minimum effect of potential unmeasured confounding that would be needed to move the 95% CI to include the null.[14]

All data management was performed in SAS Enterprise Guide, V.9.4 (SAS Institute) and statistical analyses were conducted using STATA V.16 (StataCorp), respectively. A 95% CI that did not overlap 1.00

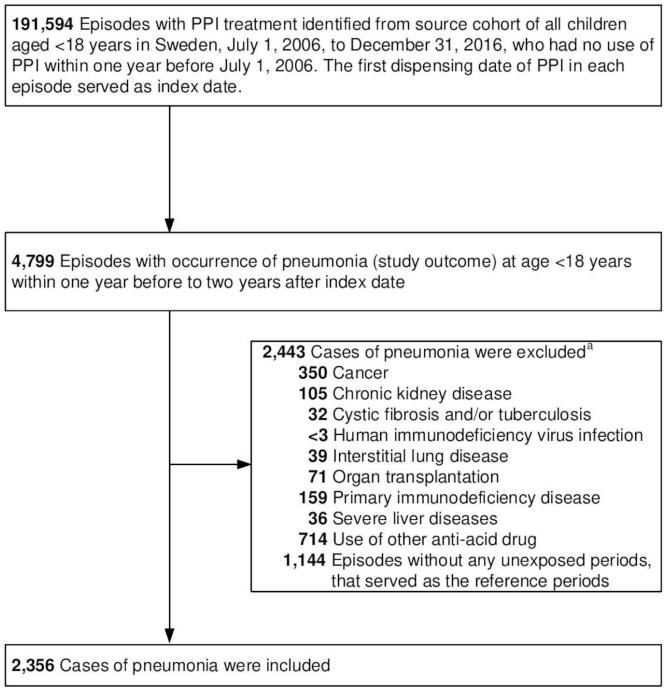

Figure 2 Flow chart of study population selection. [a]Some patients met multiple exclusion criteria. PPI, proton pump inhibitor.

and two-tailed p<0.05 were considered statistically significant.

Patient and public involvement

No patients were involved in setting the research question, nor in the design, conduct, or interpretation of the study. The study is based on anonymised nationwide register data, and no dissemination of results directly to study participants is planned.

RESULTS

Among 191 494 episodes with PPI treatment in children aged <18 years during the study period, we identified 4799 episodes during which pneumonia occurred. After implementing the exclusion criteria, a total of 2356 cases were included (figure 2); the median age at PPI initiation was 3.6 (IQR 1.2–11.5) years and half were male.

Of the total 2356 cases, 155 cases occurred in the pre-exposure period, 284 cases occurred in the risk period, 744 cases in the postexposure period and 1173 cases occurred during time unexposed to PPI treatment. Compared with the unexposed period, the adjusted IRRs were 1.80 (95% CI 1.51 to 2.13) for the pre-exposure period, 1.40 (95% CI 1.21 to 1.62) for the risk period and 0.98 (95% CI 0.89 to 1.08) for the postexposure period. After dividing the risk period into time intervals, the adjusted IRRs for pneumonia were 1.63 (95% CI 1.35 to 1.97) for day 1 to 30 since the start of the risk period, 1.32 (95% CI 1.04 to 1.69) for day 31–90 and 1.06 (95% CI 0.79 to 1.41) for ≥91 days (table 1).

In subgroup analyses (table 2), while testing the association between pneumonia and PPI use by sex, no significant interactions were found. On the other hand, when age at index date was stratified by categories of 1–5, 6–13 and ≥14 years, the adjusted IRR for pneumonia were significantly different across the three age groups in the pre-exposure period (p<0.01 for interaction) and postexposure period (p<0.01 for interaction). During the pre-exposure period, the highest IRR was observed in the age group ≥14 years (adjusted IRR 3.11, 95% CI 2.30 to 4.21), followed by 6–13 years (adjusted IRR 2.35, 95% CI 1.67 to 3.30) and 1–5 years (adjusted IRR 1.14, 95% CI 0.87 to 1.49). Whereas during the postexposure period, the highest IRR was observed in the age group 1–5 years (1.05, 95% CI 0.93 to 1.20), followed by 0.98 (95% CI 0.79 to 1.22) for 6–13 years and 0.76 (95% CI, 0.60 to 0.96) for ≥14 years.

Figure 3 shows the results of sensitivity analyses, which were all consistent with our main findings. Finally, the E-value for the lower bound of the CI for the risk period was 1.71. Hence, to move the CI to include 1.0, rendering the estimate non-significant, an unmeasured confounder

Table 1 Main results of association between PPI use and risk for pneumonia

Period*	No of events	Person-years of observation	Crude incidence rate ratio (95% CI)	Adjusted incidence rate ratio† (95% CI)
Unexposed period	1173	1956.5	Reference	Reference
Pre-exposure period	155	122.2	1.84 (1.55 to 2.18)	1.80 (1.51 to 2.13)
Risk period	284	306.0	1.43 (1.23 to 1.65)	1.40 (1.21 to 1.62)
1–30 days	127	104.8	1.70 (1.41 to 2.05)	1.63 (1.35 to 1.97)
31–90 days	76	80.4	1.33 (1.04 to 1.69)	1.32 (1.04 to 1.69)
≥91 days	81	120.4	1.05 (0.79 to 1.39)	1.06 (0.79 to 1.41)
Postexposure period	744	1268.3	1.00 (0.91 to 1.10)	0.98 (0.89 to 1.08)

*The risk period was defined as current use of PPI; the pre-exposure period was a time period of 30 days before PPI initiation; the postexposure period was a time period of up to 365 days after PPI discontinuation; the unexposed period was the remaining time within a time frame of up to 1 year before and 2 years after PPI initiation.
†Adjusted for age with 1-year bands and season.
PPI, proton pump inhibitor.

Table 2 Subgroup analyses of association between PPI use and risk of pneumonia

	Unexposed period*		Pre-exposure period*		Risk period*		Postexposure period*	
	No of events	Adjusted incidence rate ratio†	No of events	Adjusted incidence rate ratio† (95% CI)	No of events	Adjusted incidence rate ratio† (95% CI)	No of events	Adjusted incidence rate ratio† (95% CI)
Sex								
Male	592	Reference	85	1.80 (1.42 to 2.28)	145	1.39 (1.13 to 1.72)	367	0.97 (0.84 to 1.11)
Female	581	Reference	70	1.79 (1.39 to 2.31)	139	1.40 (1.13 to 1.73)	377	1.00 (0.87 to 1.15)
P value for interaction				0.80		0.91		0.74
Age group‡								
1–5 years	643	Reference	61	1.14 (0.87 to 1.49)	119	1.21 (0.97 to 1.50)	481	1.05 (0.93 to 1.20)
6–13 years	275	Reference	40	2.35 (1.67 to 3.30)	84	1.64 (1.22 to 2.20)	144	0.98 (0.79 to 1.22)
≥14 years	255	Reference	54	3.11 (2.30 to 4.21)	81	1.58 (1.18 to 2.10)	119	0.76 (0.60 to 0.96)
P value for interaction				<0.01		0.11		<0.01

*The risk period was defined as current use of PPI; the pre-exposure period was a time period of 30 days before PPI initiation; the postexposure period was a time period of up to 365 days after PPI discontinuation; the unexposed period was the remaining time within a time frame of up to 1 year before and 2 years after PPI initiation.
†Adjusted for age with 1 year bands and season.
‡Age was measured at index date.
PPI, proton pump inhibitor.

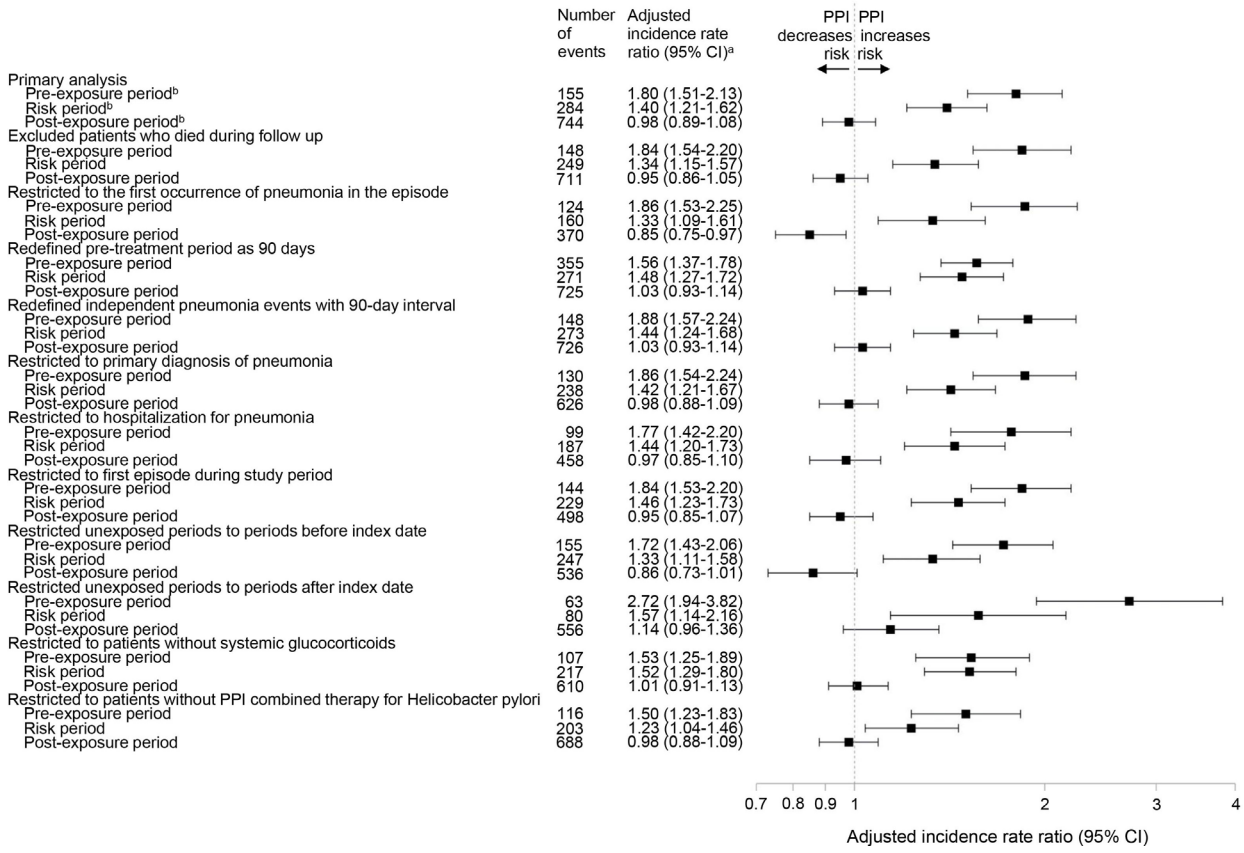

Figure 3 Sensitivity analyses of association between PPI use and risk of pneumonia. [a]Adjusted for age with 1-year bands and season. [b]The risk period was defined as current use of PPI; the pre-exposure period was a time period of 30 days before PPI initiation; the postexposure period was a time period of up to 365 days after PPI discontinuation; the unexposed period was the remaining time within a time frame of up to 1 year before and 2 years after PPI initiation. IRR, incidence rate ratio; PPI, proton pump inhibitor.

would have to have an association with both PPI and risk of pneumonia by an IRR of at least 1.71.

DISCUSSION

In this nationwide SCCS study of a paediatric population, we observed a 40% elevated risk of pneumonia during ongoing PPI use compared with the unexposed period with no PPI use. The increased risk was only observed within the first 90 days since start of PPI treatment, but not later. This, together with the 80% elevated risk of pneumonia during the period immediately before PPI initiation suggests that the relationship between PPI use and pneumonia is not causal. The pattern of observed associations was consistent in all sensitivity analyses and subgroups stratified by sex, whereas heterogeneity of the association was observed between age groups.

The association between PPIs and risk of pneumonia has been explored extensively in adults, but results remains inconclusive. Previous meta-analyses of observational studies and smaller randomised controlled trials[3–6] reported increased risks of pneumonia of 36% to 49% with PPI therapy. The increased risk was found to be driven by the first 30 days of PPI use. Similar to these previous adult studies, we found that PPI use was associated with a 40% increased risk of pneumonia, compared with the unexposed period, and the strongest magnitude of the association was observed in the first 30 days of treatment.

While PPIs are proposed to moderate the risk of pneumonia by altering microbiota in the gut and airway through inhibition of gastric acid,[15] it is largely unknown if short-term use of PPIs achieves changes of the microbiome that are clinically significant. A trial with 14 participants showed that a month-long treatment course with PPIs was not associated with a change in diversity of microbiota.[16] Similarly, a recent observational study that enrolled 20 children found no significant change in the total number of predominant gut microbiota after a 4 to 8 weeks' course of PPI treatment.[17] These data suggest that our observed associations during the risk period are unlikely to be biologically plausible, at least if the putative mechanism is alteration of the microbiome. If PPIs were truly related to an increased risk of pneumonia due to alteration of the gut microbiome, a risk increase that is observed immediately after PPI initiation should probably not be expected; further, the increased risk should persist with longer-term use of PPIs. However, in our study, the strongest magnitude of association within the risk period was observed in the first 30 days of ongoing PPI treatment

and no association was observed in the period of ongoing PPI treatment longer than 90 days since PPI initiation. Hence, the significant association with short-term PPI use should be cautiously interpreted. It might, for instance, reflect protopathic bias; that is, patients presenting prodromes of undiagnosed pneumonia, such as cough and chest pain, could have been potentially prescribed PPI treatment for misdiagnosed reflux disease.

We observed that patients were at an 80% increased risk of pneumonia in the 30-day period immediately before PPI initiation, as compared with the unexposed period. One possible explanation is that a transient deterioration of patients' underlying health status could have contributed to an increased risk of pneumonia, and that this also contributed to an increased probability of initiating PPI treatment. This underlying risk would then have persisted during the initial phase of PPI treatment, but would subsequently have been attenuated as underlying health status improved. Hence, this pattern of risk argues against a causal association between PPI and risk of pneumonia and rather points to the possibility of confounding or another source of bias. In line with our observations, one previous study showed a higher risk of pneumonia in the 30 days before (IRR 1.92, 95% CI 1.84 to 2.00) than in the 30 days after starting PPI treatment (IRR 1.19, 95% CI 1.14 to 1.25) in an SCCS analysis and a reduced risk of pneumonia with PPIs in a prior event rate ratio analysis (HR 0.91, 95% CI 0.83 to 0.99).[18] Another study found that PPI use was not only associated with an increased risk of pneumonia but also other common diseases thought to be unrelated to PPIs.[19] Furthermore, recent evidence,[7 8] especially a large-scale randomised controlled trial[8] did not find a significant difference in risk of pneumonia between patients randomised to pantoprazole and placebo. Given the scarcity of previous data in children,[9 10] our study substantially expands on the understanding of this drug safety concern in the paediatric population.

The main strengths of this study are the use of nationwide data ensuring generalisability and a large sample size enabling precision of the estimates, and the employment of an SCCS design, permitting within-individual comparisons which controlled for time-invariant confounders and reduced selection bias. A series of assumptions for the SCCS design were met, as the results were robust in sensitivity analyses.

The study also has some limitations. First, our study was based on pneumonia cases that were of sufficient severity to warrant hospitalisation or hospital emergency visit. Most mild to moderate pneumonia cases are likely managed in primary care, and our study results are not necessarily generalisable to that setting. Second, the outcome definition was based on ICD-10 codes, hence assuming a clinical diagnosis of pneumonia; the possibility of outcome misclassification cannot be ruled out. Third, given the observational nature of this study, unmeasured confounders may have introduced bias to our findings, in particular time-varying risk factors for pneumonia. Furthermore, exposure misclassification may exist since information on over-the-counter drugs and medication use during hospitalisation was unavailable. Finally, we estimated the duration of PPI treatment based on filled prescriptions, but did not have information on the actual time the drugs were taken.

Conclusions

An increased risk of pneumonia was observed both immediately before and immediately after PPI initiation. This pattern of association can likely be explained by an underlying risk of pneumonia due to factors transiently present at the time around PPI initiation. Thus, our findings do not support a causal relationship between PPI use and risk of pneumonia.

Contributors Y-HW and BP had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: Y-HW, HS, BP. Acquisition, analysis or interpretation of data: Y-HW, HS, VW, JFL and BP. Drafting of the manuscript: Y-HW. Critical revision of the manuscript for important intellectual content: Y-HW, HS, VW, JFL and BP. Statistical analysis: Y-HW. Obtained funding: BP. Study supervision: BP. BP acts as a guarantor for the manuscript.

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Disclaimer The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Competing interests HS has received consulting fees from Celgene and is employed by IQVIA, outside of the submitted work. JFL coordinates, on behalf of the Swedish IBD quality register (SWIBREG); a study that has received funding from Janssen corporation. The other authors declare no conflicts of interest.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval The study was approved by the Regional Ethics Committee in Stockholm, Sweden, which did not require informed consent because this was a registry-based study.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data may be obtained from a third party and are not publicly available. Raw data may be obtained following permission from the register holders.

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