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Association Between Proton Pump Inhibitor Use and Risk of Fracture in Children

Yun-Han Wang, MSc, BPharm; Viktor Wintzell, MSc; Jonas F. Ludvigsson, MD, PhD; Henrik Svanström, PhD; Björn Pasternak, MD, PhD

IMPORTANCE Proton pump inhibitor (PPI) use has been linked to increased risk of fracture in adults. Despite a trend in prescription of PPIs in children, there is scarce evidence regarding this safety concern in pediatric patients.

OBJECTIVE To evaluate the association between PPI use and risk of fracture in children.

DESIGN This nationwide register-based cohort study included data from Sweden from July 2006 to December 2016. Children younger than 18 years who initiated PPI use were matched on propensity score and age with those who did not initiate PPI use.

EXPOSURE Initiation of PPI use.

MAIN OUTCOMES AND MEASURES Cox regression was adopted to estimate hazard ratios (HRs) for a first fracture of any type and 5 subtypes of fracture, with follow-up for up to 5 years. To address potential residual confounding, high-dimensional propensity score matching and a direct comparison with histamine-2 receptor antagonists were performed.

RESULTS There were a total of 115 933 pairs of children included. During a mean (SD) of 2.2 (1.6) years of follow-up, 5354 and 4568 cases of any fracture occurred among those who initiated PPIs vs those who did not, respectively (20.2 vs 18.3 events per 1000 person-years; hazard ratio [HR], 1.11 [95% CI, 1.06-1.15]). Use of PPIs was associated with increased risk of upper-limb fracture (HR, 1.08 [95% CI, 1.03-1.13]), lower-limb fracture (HR, 1.19 [95% CI, 1.10-1.29]), and other fractures (HR, 1.51 [95% CI, 1.16-1.97]) but not head fracture (HR, 0.93 [95% CI, 0.76-1.13]) or spine fracture (HR, 1.31 [95% CI, 0.95-1.81]). The HRs for fracture according to cumulative duration of PPI use were 1.08 (95% CI, 1.03-1.13) for 30 days or less, 1.14 (95% CI, 1.09-1.20) for 31 to 364 days, and 1.34 (95% CI, 1.13-1.58) for 365 days or more. The association was consistent in most sensitivity analyses, including high-dimensional propensity score matching (HR, 1.10 [95% CI, 1.06-1.15]), although the analysis of PPI vs histamine-2 receptor antagonist did not reach statistical significance (HR, 1.06 [95% CI, 0.97-1.15]).

CONCLUSIONS AND RELEVANCE In this large pediatric cohort, PPI use was associated with a small but significant increased risk of any fracture. Risk of fracture should be taken into account when weighing the benefits and risks of PPI treatment in children.

Supplemental content

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Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Yun-Han Wang, MSc, BPharm, Clinical Epidemiology Division, Department of Medicine Solna, Karolinska Institutet, Eugeniahemmet T2, 171 76 Stockholm, Sweden (yun-han.wang@ki.se).

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Proton pump inhibitors (PPIs) are mainstay treatment for children with gastric acid–associated disorders, although because of limited evidence, treatment guidelines[1,2] recommending their use are mostly based on expert opinion. A substantial increase of PPI use among children in recent years has been reported,[3] despite concerns regarding the safety of these drugs in pediatric patients.[4] Children are more vulnerable to drug toxicity because of physiological immaturity and age-varied pharmacokinetics of PPIs that prolong drug metabolism.[5] Accordingly, it is critical to clarify the safety of PPIs in children.

Fracture is common during childhood[6] and might lead to higher risk of subsequent fracture in later life.[7] The use of PPIs has been proposed to increase fracture risk based on several hypothesized mechanisms, including gastric-acid inhibition leading to the impairment of calcium absorption and bone metabolism.[8] Results of observational studies among elderly adults at high baseline risk of fracture have been inconsistent, which is why it is unclear if an association between PPIs and fracture exists. A recent meta-analysis[9] of 32 observational studies in elderly adults at high baseline risk of fracture suggested that PPI use was associated with an increased risk of fracture at any site (hazard ratio [HR], 1.30 [95% CI, 1.16-1.45]), the spine (HR, 1.49 [95% CI, 1.31-1.68]), and the hip (HR, 1.22 [95% CI, 1.15-1.31]), although there was significant heterogeneity across studies, indicating inconsistency.

In children, the few published observational studies have yielded inconsistent findings. A cohort study[10] conducted in children born preterm found an increased fracture risk associated with PPI treatment during the first year of life (adjusted rate ratio, 1.43 [95% CI, 1.13-1.81]). Similarly, another cohort study[11] reported an HR of 1.23 (95% CI, 1.14-1.31) for fracture among infants who initiated PPI treatment before age 1 year, and the risk increased with the duration of PPI use. Conversely, a nested case-control study[12] that included patients aged 4 to 29 years found a significant association between PPIs and fracture risk in young adults aged 18 to 29 years (adjusted odds ratio [OR], 1.39 [95% CI, 1.26-1.53]) but not in children aged 4 to 17 years (adjusted OR, 1.13 [95% CI, 0.92-1.39]). However, the studies had limitations of study design; for instance, they did not follow PPI users from the start of treatment,[10,12] lacked data on inpatient fracture diagnoses,[11] and adjusted for only a few fracture risk factors.[10-12] This nationwide register-based cohort study aimed to investigate the association of PPIs with the risk of fracture among children, implementing a propensity score–matched, new-user design.

Key Points

Question Is proton pump inhibitor (PPI) use associated with increased risk of fracture in children?

Findings This pediatric cohort compared 115 933 patients who initiated PPI use with 115 933 matched individuals who did not initiate use and found that PPI use was associated with an 11% increased risk of fracture, a significant difference.

Meaning These data suggest that PPI use is associated with a small increased risk of fracture in children; the findings inform safety considerations when these drugs are prescribed to pediatric patients.

Methods

Data Sources

A cohort study was conducted (eFigure 1 in the Supplement), using mandatory Swedish nationwide registers. The National Patient Register contains disease diagnoses and surgical procedures from inpatient specialist care and outpatient as well as emergency care settings across all hospitals in Sweden. The positive predictive values of disease diagnoses in the National Patient Register mostly range from 85% to 95%, including fracture assessed among patients admitted to hospital with fracture as a primary diagnosis.[13] 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. Through the Total Population Register and Statistics Sweden, demographic data and parental socioeconomic data were obtained. Registers were linked using unique personal identifiers. 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.

Study Cohort

The source population was all children in Sweden younger than 18 years during the study period (July 1, 2006, to December 31, 2016). From the source population, we identified all children who initiated PPI use, defined as patients prescribed their first PPI during the study period who had no PPI prescription in the year prior. The PPI dispensing date was defined as the index date.

The cohort was constructed using a 2-step matching approach, which served to include an appropriate comparator group (those who did not initiate use) from the source population. First, each patient who initiated PPI use was matched to up to 30 who did not, identified from those individuals in the source population who had the same age and were alive on the PPI index date. All children who did not initiate use, matched to a given child who did initiate PPI use, were assigned the same index date as this child. Second, for inclusion in the final analytical cohort, those who did initiate PPIs and those who did not were matched (1:1 ratio) on propensity score and age groups with 2-year bands. Exclusion criteria were cancer, organ transplant, congenital skeletal malformation, and birth trauma–associated fracture (all within 10 years prior to the index date), as well as severe liver failure, fracture, and fracture complication (all within 1 year prior to the index date) (eTable 1 in the Supplement).

PPI Exposure

Our primary exposure was any use of PPIs, including omeprazole, esomeprazole, pantoprazole, lansoprazole, and rabeprazole (eTable 1 in the Supplement), with the risk of fracture analyzed according to the intention-to-treat approach. We did 2

secondary analyses. First, we assessed the risk of fracture according to cumulative duration of PPI treatment during the 5-year follow-up period, measured in a time-dependent manner. Duration of PPI use was determined from the total amount of tablets in prescriptions, with each tablet assumed to correspond to 1 day of use. To take into account irregularities and gaps in continuous treatment, the length of refill gaps was permitted up to 50% of duration of the preceding prescription. If a prescription was not refilled before the preceding prescription's end date plus 50% of its duration, treatment was regarded as discontinued. Cumulative duration was categorized as 30 or fewer days, 31 to 364 days, and 365 days or more, and the risk of fracture analyzed for the full 5-year follow-up period for each category. Second, we assessed associations between individual PPIs and fracture, for which we additionally created subcohorts of each individual drug. Within each subcohort, we reestimated a drug-specific propensity score and rematched children who did and did not initiate use on propensity and age group (in 2-year age bands) by using the same algorithm as in the primary analysis.

Outcomes

The primary outcome was defined as the first diagnosis of any fracture (*International Classification of Diseases, Tenth Revision* [*ICD-10*] codes in eTable 1 in the Supplement) requiring hospitalization or acute outpatient hospital care during follow-up. The secondary outcomes were 5 subtypes of fracture according to anatomical site, including head, spine, upper limb, lower limb, and other areas (*ICD-10* codes in eTable 1 in the Supplement); each subtype was analyzed separately. In a secondary analysis, we investigated the risk of primary and secondary outcomes according to age group at the index date, including patients aged 0 days to younger than 6 months, 6 months to younger than 2 years, 2 to younger than 6 years, 6 to younger than 12 years, and 12 years or older.

Propensity Score

Potential confounders were selected based on variables reported to be associated with risk of fracture. We measured patient demographic and parental socioeconomic characteristics at index date, comorbidities in the 2 years prior to the index date, health care utilization, and comedications in the year prior to the index date (eTable 1 in the Supplement).

A propensity score–matching approach was used. Logistic regression, including all covariates in **Table 1**, was performed to estimate the propensity score. Each child who initiated PPIs was matched to a child who did not on propensity score and age group (in 2-year age bands) by using the greedy nearest neighbor matching algorithm without replacement, with a caliper of 0.2 SDs of the logit of the propensity score.[14] The standardized difference was used to assess covariate balance between the 2 groups; a covariate was considered to be well balanced if the standardized difference was less than 10%.

Statistical Analysis

The analytical cohort was followed up from the index date until first diagnosis of fracture, emigration, death, age 18 years, 5 years of follow-up, or the end of the study period (December, 31, 2016), whichever occurred first. We used Poisson models to estimate incidence rates and Cox proportional hazards regression models to quantify HRs with 95% CIs, comparing those who initiated PPI use with those who did not. A Wald test for the interaction between treatment status and time was used to examine the proportional hazards assumption. Statistical analyses were done using SAS Enterprise Guide 7.1 (SAS Institute). A 95% CI that did not overlap and a 1-sided or 2-sided *P* less than .05 were considered statistically significant.

To explore potential effect modifiers for risk of any fracture, we conducted 6 subgroup analyses stratified by sex; use of comedications including systemic corticosteroids, inhaled corticosteroids, opioids, and antidepressants; and an empirical disease risk score (DRS). The DRS was developed to quantify the baseline risk of fracture for each individual in the matched cohort, and the subgroup analysis was stratified by the quartile of DRS.[15] Specifically, for DRS establishment, we initially used Cox proportional hazards regression to evaluate the association between each variable listed in Table 1 (with the exclusion of calendar year) and risk of fracture and obtained relevant coefficient values. The DRS was calculated as a 5-year probability of developing fracture by applying the estimated coefficient values and setting the status of PPI to no use.

To test the robustness of study findings, we adopted several sensitivity analyses. First, to potentially increase specificity of the outcome definition, we restricted to primary diagnosis of fracture as outcome. Second, we assessed fracture risk with maximum 1-year and 3-year follow-up periods, respectively. Third, to address confounding by indication by *Helicobacter pylori* infection (which might be associated with decreased bone mineral density[16]), we excluded patients who received PPI as part of triple therapy for *H pylori* eradication. Furthermore, to address confounding by indication, we repeated all analyses that presented a significant association in the primary study, comparing those who initiated PPI use vs those who initiated histamine-2 receptor antagonist (H_2RA) use. Clinicians commonly prescribe H_2RAs as antacid agents, which share clinical indications with PPIs and are less potent. We hypothesized that H_2RA use had no association with fracture in children, based on limited data.[10,11] For this analysis, the derivation of propensity score was based on the covariates listed in Table 1 and same procedures as in the primary analysis. For the analysis, inverse probability of treatment weighting was used (given the lower number of children who used H_2RAs, matching would have led to a substantial loss of those who used PPIs; details in eMethods 1 and eFigure 4 in the Supplement). Fifth, to account for the influence of residual confounding, we used high-dimensional propensity score matching (details in eMethods 2 and eTable 5 in the Supplement).[17] Furthermore, we excluded patients who had any hospital admission within 14 days before the index date. Finally, we adopted the rule-out approach to evaluate the influence of an unmeasured confounder on study findings.[18]

Table 1. Baseline Characteristics of Children Who Did vs Did Not Use Proton Pump Inhibitors (PPIs) Before and After Matching

Characteristic	Before Propensity Score Matching, No. (%)			After Propensity Score Matching, No. (%)		
	Children Who Used PPIs (n = 117 234)	Children Who Did Not Use PPIs (n = 2 373 292)	Standardized Difference, %	Children Who Used PPIs (n = 115 933)	Children Who Did Not Use PPIs (n = 115 933)	Standardized Difference, %
Age, mean (SD), y	12.6 (5.0)	11.5 (5.6)	19.0	12.6 (5.0)	12.6 (5.0)	0.4
Age group						
0 d-<6 mo	4442 (3.8)	133 903 (5.6)	8.8	4388 (3.8)	4388 (3.8)	0
6 mo-<2 y	4552 (3.9)	141 389 (6.0)	9.6	4292 (3.7)	4292 (3.7)	0
2-<4 y	2543 (2.2)	82 511 (3.5)	7.9	2367 (2.0)	2367 (2.0)	0
4-<6 y	3415 (2.9)	102 404 (4.3)	7.5	3297 (2.8)	3297 (2.8)	0
6-<8 y	5520 (4.7)	149 236 (6.3)	6.9	5415 (4.7)	5415 (4.7)	0
8-<10 y	8488 (7.2)	194 773 (8.2)	3.6	8360 (7.2)	8360 (7.2)	0
10-<12 y	12 182 (10.4)	236 373 (10.0)	1.4	12 058 (10.4)	12 058 (10.4)	0
12-<14 y	15 004 (12.8)	243 353 (10.3)	8.0	14 818 (12.8)	14 818 (12.8)	0
14-<16 y	24 318 (20.7)	387 490 (16.3)	11.4	24 196 (20.9)	24 196 (20.9)	0
16-<18 y	36 770 (31.4)	701 860 (29.6)	3.9	36 742 (31.7)	36 742 (31.7)	0
Sex						
Female	71 626 (61.1)	1 137 595 (47.9)	26.7	70 849 (61.1)	71 328 (61.5)	0.8
Male	45 608 (38.9)	1 235 697 (52.1)	26.7	45 084 (38.9)	44 605 (38.5)	0.8
Calendar year						
2006-2009	32 263 (27.5)	727 757 (30.7)	6.9	31 918 (27.5)	31 047 (26.8)	1.7
2010-2013	44 830 (38.2)	810 988 (34.2)	8.5	44 230 (38.2)	44 433 (38.3)	0.4
2014-2016	40 141 (34.2)	834 547 (35.2)	1.9	39 785 (34.3)	40 453 (34.9)	1.2
Birth region						
Scandinavia	104 096 (88.8)	2 009 814 (84.7)	12.1	102 902 (88.7)	103 017 (88.9)	0.3
Rest of Europe	2707 (2.3)	98 671 (4.2)	10.5	2693 (2.3)	2510 (2.2)	1.1
Outside Europe	10 399 (8.9)	262 756 (11.1)	7.4	10 306 (8.9)	10 377 (9.0)	0.2
Missing value	32 (0.03)	2051 (0.1)	2.5	32 (0.03)	29 (0.03)	0.2
Parental education, y[a]						
≤9	7507 (6.4)	125 703 (5.3)	4.7	7399 (6.4)	7525 (6.5)	0.4
10-12	49 304 (42.1)	858 535 (36.2)	12.1	48 772 (42.1)	49 017 (42.3)	0.4
≥13	58 409 (49.8)	1 245 196 (52.5)	5.3	57 757 (49.9)	57 615 (49.7)	0.2
Missing value	2014 (1.7)	143 858 (6.1)	22.6	2005 (1.7)	1776 (1.5)	1.6
Parental income, by quartile, $[a,b]						
<23 388.10	28 593 (24.4)	546 293 (23.0)	3.2	28 161 (24.3)	28 333 (24.4)	0.3
23 388.10-<29 768.93	30 362 (25.9)	546 315 (23.0)	6.7	30 001 (25.9)	30 188 (26.0)	0.4
29 768.93-<38 335.44	29 309 (25)	547 357 (23.1)	4.5	29 018 (25.0)	29 103 (25.1)	0.2
≥38 335.44	26 622 (22.7)	550 048 (23.2)	1.1	26 408 (22.8)	26 318 (22.7)	0.2
Missing value	2348 (2.0)	183 279 (7.7)	26.8	2345 (2.0)	1991 (1.7)	2.3
Comorbidities						
Cardiovascular disease	1813 (1.6)	9748 (0.4)	11.6	1639 (1.4)	1458 (1.3)	1.4
Diabetes	878 (0.8)	9239 (0.4)	4.8	872 (0.8)	775 (0.7)	1.0
Asthma	7060 (6.0)	64 615 (2.7)	16.2	6902 (6.0)	6602 (5.7)	1.1
Thyroid disease	784 (0.7)	5304 (0.2)	6.7	762 (0.7)	642 (0.6)	1.3
Other inflammatory diseases[c]	3345 (2.9)	5865 (0.3)	21.2	2976 (2.6)	2355 (2.0)	3.6
Renal disease	884 (0.8)	1172 (0.05)	11.2	644 (0.6)	567 (0.5)	0.9
Anemia	1403 (1.2)	3686 (0.2)	12.7	1215 (1.1)	1052 (0.9)	1.4
Neurological disorder	4091 (3.5)	20 908 (0.9)	17.9	3718 (3.2)	3476 (3.0)	1.2
Celiac disease	1268 (1.1)	8609 (0.4)	8.5	1228 (1.1)	1103 (1.0)	1.1
Psychiatric disorder[d]	5279 (4.5)	47 993 (2.0)	14.0	5254 (4.5)	4814 (4.2)	1.9
Fall	13 223 (11.3)	167 696 (7.1)	14.6	13 084 (11.3)	13 143 (11.3)	0.2

(continued)

Table 1. Baseline Characteristics of Children Who Did vs Did Not Use Proton Pump Inhibitors (PPIs) Before and After Matching (continued)

Characteristic	Before Propensity Score Matching, No. (%)			After Propensity Score Matching, No. (%)		
	Children Who Used PPIs (n = 117 234)	Children Who Did Not Use PPIs (n = 2 373 292)	Standardized Difference, %	Children Who Used PPIs (n = 115 933)	Children Who Did Not Use PPIs (n = 115 933)	Standardized Difference, %
Health care utilization						
No. of hospital admissions						
0	111 523 (95.1)	2 356 219 (99.3)	25.4	111 048 (95.8)	111 314 (96.0)	1.2
1	4021 (3.4)	14 881 (0.6)	20.0	3712 (3.2)	3387 (2.9)	1.6
≥2	1690 (1.4)	2192 (0.1)	15.5	1173 (1.0)	1232 (1.1)	0.5
No. of outpatient visits						
0	49 879 (42.6)	1 752 755 (73.9)	66.9	49 867 (43.0)	49 235 (42.5)	1.1
1	23 793 (20.3)	333 793 (14.1)	16.6	23 746 (20.5)	24 348 (21.0)	1.3
≥2	43 562 (37.2)	286 744 (12.1)	60.8	42 320 (36.5)	42 350 (36.5)	0.1
No. of emergency department visits						
0	101 486 (86.6)	2 299 199 (96.9)	38.1	101 350 (87.4)	101 715 (87.7)	1.0
1	10 402 (8.9)	64 153 (2.7)	26.7	10 092 (8.7)	9504 (8.2)	1.8
≥2	5346 (4.6)	9940 (0.4)	26.8	4491 (3.9)	4714 (4.1)	1.0
No. of drugs used						
0	36 737 (31.3)	1 429 789 (60.2)	60.6	36 722 (31.7)	36 442 (31.4)	0.5
1	23 649 (20.2)	420 499 (17.7)	6.3	23 587 (20.4)	24 110 (20.8)	1.1
≥2	56 848 (48.5)	523 004 (22.0)	57.6	55 624 (48.0)	55 381 (47.8)	0.4
Comedications						
Cardiovascular drugs[e]	1123 (1.0)	4215 (0.2)	10.4	967 (0.83)	911 (0.79)	0.5
Anticoagulants	417 (0.4)	1679 (0.1)	6.2	386 (0.33)	340 (0.29)	0.7
Growth hormone therapy	205 (0.2)	1949 (0.1)	2.6	195 (0.2)	135 (0.12)	1.4
Contraceptives	16 310 (13.9)	122 394 (5.2)	30.1	16 264 (14.0)	16 176 (14.0)	0.2
Thyroid treatment	908 (0.8)	6461 (0.3)	7.0	881 (0.8)	761 (0.7)	1.2
Calcium/vitamin D supplement	761 (0.7)	2520 (0.1)	8.9	677 (0.6)	572 (0.5)	1.2
Asthma medication	15 107 (12.9)	154 218 (6.5)	21.7	14 723 (12.7)	14 451 (12.5)	0.7
Systematic glucocorticosteroid	5172 (4.4)	32 572 (1.4)	18.2	4848 (4.2)	4106 (3.5)	3.3
Nonsteroidal anti-inflammatory drug	9815 (8.4)	49 020 (2.1)	28.6	9533 (8.2)	9021 (7.8)	1.6
Antipsychotics	722 (0.6)	4564 (0.2)	6.7	713 (0.6)	602 (0.52)	1.3
Antidepressants	3099 (2.6)	17 719 (0.8)	14.7	3080 (2.7)	2800 (2.4)	1.5
Benzodiazepine receptor agonist	1752 (1.5)	6324 (0.3)	13.2	1562 (1.4)	1465 (1.3)	0.7
Attention-deficit/ hyperactivity disorder drugs	3110 (2.7)	35 882 (1.5)	8.0	3100 (2.7)	2730 (2.4)	2.0
Opioids	2136 (1.8)	11 523 (0.5)	12.5	2086 (1.8)	1763 (1.5)	2.2
Antiepileptics	2135(1.8)	9484 (0.4)	13.6	1927 (1.7)	1658 (1.4)	1.9
Antihistamine	12 973 (11.1)	132 706 (5.6)	19.9	12 770 (11.0)	12 223 (10.5)	1.5

[a] Covariate based on the parent with the highest achieved education and income, respectively.

[b] Converted from Swedish kronor (1 = $0.1037); in Swedish currency, brackets are less than 225 673 kronor, 225 673 to less than 287 242 kronor, 287 242 to 369 747 kronor, and 369 747 kronor or more.

[c] Inflammatory bowel disease, rheumatoid arthritis, and other inflammatory polyarthropathies.

[d] Anxiety, depression, bipolar disorder, schizophrenia, and attention-deficit/ hyperactivity disorder.

[e] Cardiovascular medication, including β-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, diuretics, and calcium channel blockers.

Results

Patient Selection

From the source population, which included 3 621 940 children during the study period, 117 234 children who initiated PPI use and 2 373 292 who did not were eligible for matching (eFigure 2 in the Supplement). After 1-to-1 matching on propensity score and age, 115 933 pairs of children who did vs did not initiate PPI use were included in the study cohort. The mean (SD) age of children who used PPIs was 12.6 (5.0) years, and 71 626 (61.1%) were girls; and all baseline characteristics were

Table 2. Associations Between Proton Pump Inhibitors (PPIs) Use and Risk for Any Fracture and Fracture Subtypes

	Children Who Used PPIs (n = 115 933)		Children Who Did Not Use PPIs (n = 115 933)		
Fracture Type	No. of Events	Incidence Rate[a]	No. of Events	Incidence Rate[a]	Hazard Ratio (95% CI)
Any	5354	20.2	4568	18.3	1.11 (1.06-1.15)
Head	203	0.7	206	0.8	0.93 (0.76-1.13)
Spine	88	0.3	63	0.2	1.31 (0.95-1.81)
Upper limb	3755	14.0	3283	13.0	1.08 (1.03-1.13)
Lower limb	1407	5.2	1112	4.3	1.19 (1.10-1.29)
Other fracture	144	0.5	90	0.3	1.51 (1.16-1.97)

[a] Events per 1000 person-years.

well balanced between the 2 groups (Table 1). The mean (SD) follow-up time was 2.2 (1.6) years among those who initiated PPIs and 2.3 (1.7) years among those who did not. The proportional hazards assumption was not violated for primary and secondary outcomes.

Primary Analysis

As demonstrated in **Table 2**, PPI initiation was associated with increased risk of any fracture (HR, 1.11 [95% CI, 1.06-1.15]). With respect to subtypes of fracture, PPI initiators were at increased risk of fracture of the upper limb (HR, 1.08 [95% CI, 1.03-1.13]), lower limb (HR, 1.19 [95% CI, 1.10-1.29]), and other sites (HR, 1.51 [95% CI, 1.16-1.97]), but there were no significant associations with head fractures (HR, 0.93 [95% CI, 0.76-1.13]) and spine fractures (HR, 1.31 [95% CI, 0.95-1.81]).

Secondary Analyses

In the analysis according to age group (**Figure 1**), significantly increased risks for any fracture were observed only among patients who started PPIs at age 6 years or older. The HRs for any fracture were 1.14 (95% CI, 1.08-1.22) and 1.09 (95% CI, 1.03-1.15) in the age groups 6 to younger than 12 years and 12 years or older, respectively. Patients who were 12 years or older had increased risk of fracture of the spine (HR, 1.46 [95% CI, 1.01-2.11]), lower limb (HR, 1.21 [95% CI, 1.08-1.35]), and other sites (HR, 1.72 [95% CI, 1.26-2.35]). In the secondary analysis assessing the association between cumulative duration of PPI treatment and risk of any fracture (**Table 3**), the HRs were 1.08 (95% CI, 1.03-1.13) for PPI treatment duration of 30 days or fewer, 1.14 (95% CI, 1.09-1.20) for 31 to 364 days, and 1.34 (95% CI, 1.13-1.58) for 365 days or more.

In analyses of individual PPIs, omeprazole was associated with an increased risk of any fracture (HR, 1.08 [95% CI, 1.03-1.13]), whereas the HR for any fracture was not significantly increased for esomeprazole (HR, 1.05 [95% CI, 0.94-1.16]), lansoprazole (HR, 1.06 [95% CI, 0.90-1.25]), and pantoprazole (HR, 1.31 [95% CI, 0.88-1.99]) (eTable 2 in the Supplement).

Subgroup and Sensitivity Analyses

The results of subgroup analyses are shown in **Figure 2**; there were no significant interactions across subgroups. Our primary findings remained robust in most sensitivity analyses (Figure 2), including analyses restricted to primary diagnosis of outcome (HR, 1.10 [95% CI, 1.06-1.14]), redefining maximum follow-up to 1 and 3 years (1 year: HR, 1.08 [95% CI, 1.01-1.15]; 3 years: HR, 1.12 [95% CI, 1.07-1.17]), excluding patients who started PPI-containing triple therapy for *H pylori* eradication (HR, 1.11 [95% CI, 1.06-1.15]), and excluding patients with any record of hospitalization within 14 days before the index date (HR, 1.10 [95% CI, 1.06-1.15]). The fracture HR from the analysis with high-dimensional propensity score matching was 1.10 (95% CI, 1.06-1.15). The rule-out approach indicated that potential unmeasured confounding would have to be relatively strong to explain the observed association; for instance, if the prevalence of an unmeasured confounder would be about twice as high among those who initiated PPI use than those who did not, an odds ratio for the association between an unmeasured confounder and PPI initiation of at least 2.0 would be required to explain the observed association (eFigure 3 in the Supplement).[18]

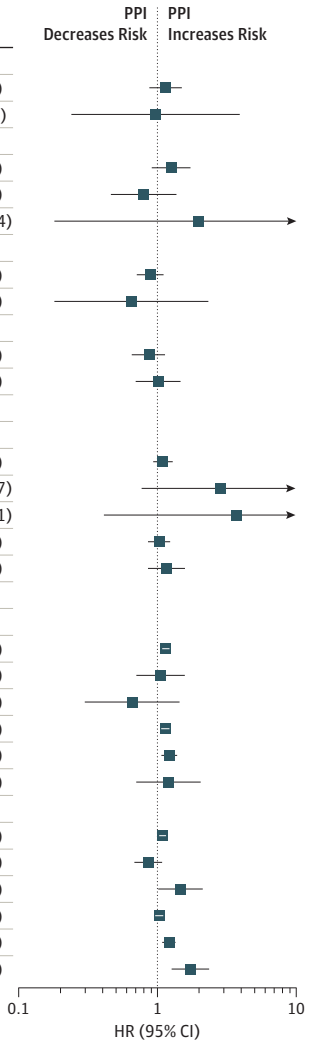
For the comparative analysis (eTables 3 and 4 and eFigure 5 in the Supplement), among 111 184 patients treated with PPI vs 20 737 with H_2RA, we observed no significant association between PPI and risk of any fracture (weighted HR, 1.06 [95% CI, 0.97-1.15]), an upper-limb fracture (weighted HR, 1.04 [95% CI, 0.94-1.14]), and any other fracture (weighted HR, 1.00 [95% CI, 0.58-1.71]), whereas the weighted HR for lower limb fracture was 1.22 (95% CI, 1.03-1.44). In analyses of fracture according to selected age categories, there were no significant associations apart from an increased risk of lower-limb fracture in the age category of 6 to younger than 12 years. In the analysis of cumulative duration (eTable 4 in the Supplement), the point estimates of the HRs for any fracture were nominally increased across all categories, but only the category with 31 to 365 days was statistically significant (weighted HR, 1.10 [95% CI, 1.00-1.21]). Lastly, the weighted HR for risk of any fracture was 1.10 (95% CI, 1.01-1.19) when comparing omeprazole with H_2RA (eTable 4 in the Supplement).

Discussion

In this nationwide cohort study of children, PPI initiation, as compared with noninitiation, was associated with a statistically significant 11% relative increase in risk of any fracture. The association was driven by fractures of upper limbs, lower limbs, and other sites; appeared to be mainly restricted to children 6 years and older; and seemed to be somewhat more pronounced with a longer cumulative duration of PPI use. Point

Figure 1. Associations Between Proton Pump Inhibitor (PPI) Use and Risks for Any Fracture and Fracture Subtypes, Stratified by Age

Age Group/ Fracture Type	PPI Initiators		Noninitiators		HR (95% CI)
	No. of Events	Incidence Rate, Events per 1000 Person-Years	No. of Events	Incidence Rate, Events per 1000 Person-Years	
0 d-<6 mo (n = 4388 vs n = 4388)					
Any fracture	116	8.6	98	7.5	1.14 (0.87-1.49)
Head	4	0.3	4	0.3	0. 97 (0.24-3.90)
Spine	0	-	0	-	NA
Upper limb	87	6.4	67	5.1	1.25 (0.91-1.72)
Lower limb	24	1.8	29	2.2	0.80 (0.46-1.37)
Other	2	0.1	1	0.1	1.95 (0.18-21.54)
6 mo-<2 y (n = 4292 vs n = 4292)					
Any fracture	153	11.0	168	12.4	0.88 (0.71-1.10)
Head	4	0.3	6	0.4	0.65 (0.18-2.32)
Spine	0	-	0	-	NA
Upper limb	97	6.9	110	8.0	0.86 (0.65-1.13)
Lower limb	59	4.2	57	4.1	1.01 (0.70-1.46)
Other	0	-	1	0.1	NA
2-<6 y (n = 5664 vs n = 5664)					
Any fracture	324	17.5	282	16.0	1.09 (0.93-1.28)
Head	9	0.5	3	0.2	2.83 (0.77-10.47)
Spine	4	0.2	1	0.1	3.69 (0.41-33.01)
Upper limb	233	12.4	215	12.1	1.03 (0.85-1.23)
Lower limb	88	4.6	72	4.0	1.16 (0.85-1.58)
Other	0	-	3	0.2	NA
6-<12 y (n = 25 833 vs n = 25 833)					
Any fracture	2275	28.2	1854	24.6	1.14 (1.08-1.22)
Head	50	0.6	44	0.6	1.04 (0.70-1.57)
Spine	11	0.1	15	0.2	0.66 (0.30-1.44)
Upper limb	1737	21.2	1420	18.6	1.14 (1.06-1.22)
Lower limb	550	6.5	418	5.3	1.22 (1.07-1.38)
Other	31	0.4	24	0.3	1.20 (0.70-2.04)
≥12 y (n = 75 756 vs n = 75 756)					
Any fracture	2486	18.0	2166	16.6	1.09 (1.03-1.15)
Head	136	1.0	149	1.1	0.86 (0.68-1.08)
Spine	73	0.5	47	0.4	1.46 (1.01-2.11)
Upper limb	1601	11.5	1471	11.2	1.03 (0.96-1.10)
Lower limb	686	4.9	536	4.0	1.21 (1.08-1.35)
Other	111	0.8	61	0.5	1.72 (1.26-2.35)



The *P* values for interaction between age group and risk of any fracture, head, spine, upper limb, lower limb fracture were 0.84, 0.41, 0.49, 0.47, 0.18, and 0.12, respectively. HR indicates hazard ratio; NA, not available.

Table 3. Associations Between Proton Pump Inhibitor Use and Risk for Any Fracture, Stratified by Cumulative Duration

Cumulative Duration	Person-Years (% of Total Person-Years)	No. of Events	Incidence Rate[a]	Hazard Ratio (95% CI)
No use	249 837.8 (100)	4568	18.3	1 [Reference]
≤30 d	145 415.9 (55.0)	2852	19.6	1.08 (1.03-1.13)
31-364 d	113 231.0 (42.8)	2357	20.8	1.14 (1.09-1.20)
≥365 d	5945.1 (2.2)	145	24.5	1.34 (1.13-1.58)

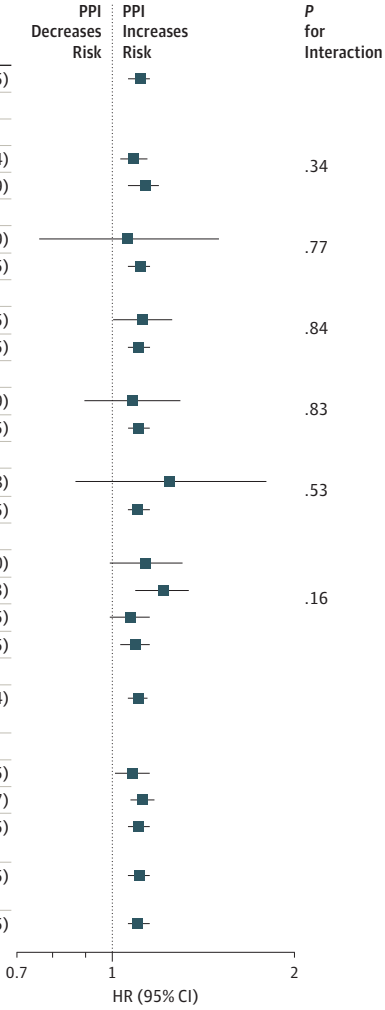
[a] Events per 1000 person-years.

estimates for all individual PPIs were greater than 1.0, although the HR was significantly increased only for omeprazole, the dominating PPI in this cohort. Most sensitivity analyses, including high-dimensional propensity score matching, were consistent with the primary results. Although there was no significant difference in the risk of any fracture between users of PPI vs H_2RA, some associations persisted, such as risk of lower limb fracture. The absence of a significant association vs H_2RA should be cautiously interpreted, because it could reflect residual confounding, limited statistical power, or a true effect of H_2RA on fracture.

A recent meta-analysis of observational studies in adults[9] supported a positive association between PPI use and risk of fracture, but there was significant heterogeneity (I^2: 78.6%;

Figure 2. Subgroup and Sensitivity Analyses of Associations Between Proton Pump Inhibitor (PPI) Use and Risks for Any Fracture

Analysis	PPI Initiators			Noninitiators			HR (95% CI)	P for Interaction
	No. of Patients	No. of Events	Incidence Rate, Events per 1000 Person-Years	No. of Patients	No. of Events	Incidence Rate, Events per 1000 Person-Years		
Primary result	115 933	5354	20.2	115 933	4568	18.3	1.11 (1.06-1.15)	
Subgroup analysis								
Sex								
Male	45 084	2913	26.5	44 605	2499	24.5	1.08 (1.03-1.14)	.34
Female	70 849	2441	15.8	71 328	2069	14.0	1.13 (1.06-1.19)	
Antidepressant								
Yes	3080	76	18.0	2800	60	17.1	1.06 (0.76-1.49)	.77
No	112 853	5278	20.3	113 133	4508	18.3	1.11 (1.06-1.15)	
Inhaled glucocorticosteroid								
Yes	12 867	701	23.2	12 179	565	20.8	1.12 (1.00-1.25)	.84
No	103 066	4653	19.9	103 754	4003	18.0	1.10 (1.06-1.15)	
Systemic glucocorticosteroid								
Yes	4848	293	25.3	4106	205	23.3	1.08 (0.90-1.29)	.83
No	111 085	5061	20.0	111 827	4363	18.1	1.10 (1.06-1.15)	
Opioid								
Yes	2086	79	23.4	1763	48	18.9	1.24 (0.87-1.78)	.53
No	113 847	5275	20.2	114 170	4520	18.3	1.10 (1.06-1.15)	
Disease risk score, by quantile								
Quantile 1 (the lowest value)	28 914	448	9.5	29 052	376	8.4	1.13 (0.99-1.30)	.16
Quantile 2	28 989	846	12.8	28 972	670	10.6	1.21 (1.09-1.33)	
Quantile 3	28 923	1406	20.9	29 050	1256	19.6	1.07 (0.99-1.15)	
Quantile 4 (the highest value)	29 107	2654	31.6	28 859	2266	29.2	1.09 (1.03-1.15)	
Sensitivity analysis								
Restricted to primary diagnosis of fracture	115 651	5072	19.0	115 725	4359	17.5	1.10 (1.06-1.14)	
Redefined maximum follow-up period								
1-y	115 933	2003	20.3	115 933	1806	18.8	1.08 (1.01-1.15)	
2-y	115 933	4316	20.2	115 933	3705	18.1	1.12 (1.07-1.17)	
Adopted high-dimensional propensity score matching	115 655	5370	20.3	115 655	4500	18.5	1.10 (1.06-1.15)	
Excluded PPI-based triple therapy for *H pylori*	114 687	5305	20.2	115 933	4568	18.3	1.11 (1.06-1.15)	
Excluded any hospitalization within 14 d before the index date	109 670	5008	20.2	114 927	4531	18.3	1.10 (1.06-1.15)	



H pylori indicates *Helicobacter pylori*; HR, hazard ratio; PPI, proton pump inhibitor.

$P < .001$) across studies, indicating inconsistency of the association. Also, most of the studies included in the meta-analysis had issues with confounding control. Furthermore, data from the most recent observational studies and a trial[19-21] found no significant association between PPI use, including long-term use of PPIs, and risk of fracture. There are limited data regarding a potential fracture risk associated with PPI use across all pediatric ages. A nested case-control study[12] reported a null association between any use of PPI and risk of any fracture among children aged 4 to younger than 18 years. Two cohort studies[10,11] of infants enrolled from the US military health care system showed significant association between PPI exposure in the first year of life and fracture. Both studies, however, adjusted for a limited number of covariates, leaving the possibility of residual confounding. By comprehensively investigating this safety concern using advanced methods, our large study substantially expands on previous data. Although the mechanism of PPI-associated fracture risk is unclear, one proposed mechanism is that PPI might inhibit gastric acid, leading to malabsorption of calcium and vitamin B_{12} as well as hypergastrinemia.[8]

The study has several strengths. By using Swedish registers, it includes a large, nationwide cohort of children, and this is why results are likely generalizable to similar populations. Including more than 115 000 children exposed to PPIs enabled ample statistical power for examining the primary outcome, as evident from the narrow 95% CIs. The study expands on information about the risk of fracture and subtypes of fracture in children of different age groups, by duration of PPI use and for individual PPIs.

Limitations

The study had limitations. Despite the implementation of several advanced epidemiological methods, residual confound-

ing cannot be ruled out, given that some important information on drug use and factors for bone health were not captured in registers, such as daily dose, race/ethnicity, body mass index, bone mineral density, and physical activity. Moreover, we cannot exclude potential confounding by indication, since indications for PPI use could not be readily captured through the available data sources. However, we expect this potential confounding to be minimized in our sensitivity analysis, which used a comparative design with H_2RA as the reference. Furthermore, exposure misclassification is a possibility, because information on over-the-counter medication was not available and exposure status was based on filled prescriptions rather than actual drug use. Finally, the results of secondary analyses might have insufficient statistical power. For instance, there was a low number of fracture events for spine fractures and certain individual drugs.

Conclusions

In this large pediatric cohort, PPI use was associated with a small but statistically significant increased risk of any fracture. Risk of fracture should be taken into account when weighing the benefits and risks of PPI treatment in children.

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Author Affiliations: Clinical Epidemiology Division, Department of Medicine, Solna, Karolinska Institutet, Stockholm, Sweden (Wang, Wintzell, Svanström, Pasternak); Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden (Ludvigsson); Department of Pediatrics, Örebro University Hospital, Örebro, Sweden (Ludvigsson); School of Medicine, Division of Epidemiology and Public Health, University of Nottingham, Nottingham, United Kingdom (Ludvigsson); Celiac Disease Center, Department of Medicine, Columbia University College of Physicians and Surgeons, New York, New York (Ludvigsson); Department of Epidemiology Research, Statens Serum Institut, Copenhagen, Denmark (Svanström, Pasternak).

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Concept and design: Wang, Wintzell, Pasternak.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Wang.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Wang.
Obtained funding: Pasternak.
Administrative, technical, or material support: Wang, Wintzell, Pasternak.
Supervision: Pasternak.

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