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

Yun-Hang Wang, MSc, Bpharm; Viktor Wintzell Msc; Jonas Ludvigsson, MD, PhD; Henrik Svanström, PhD; Björn Pasternak, MD, PhD

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Presented by Katharine Foster

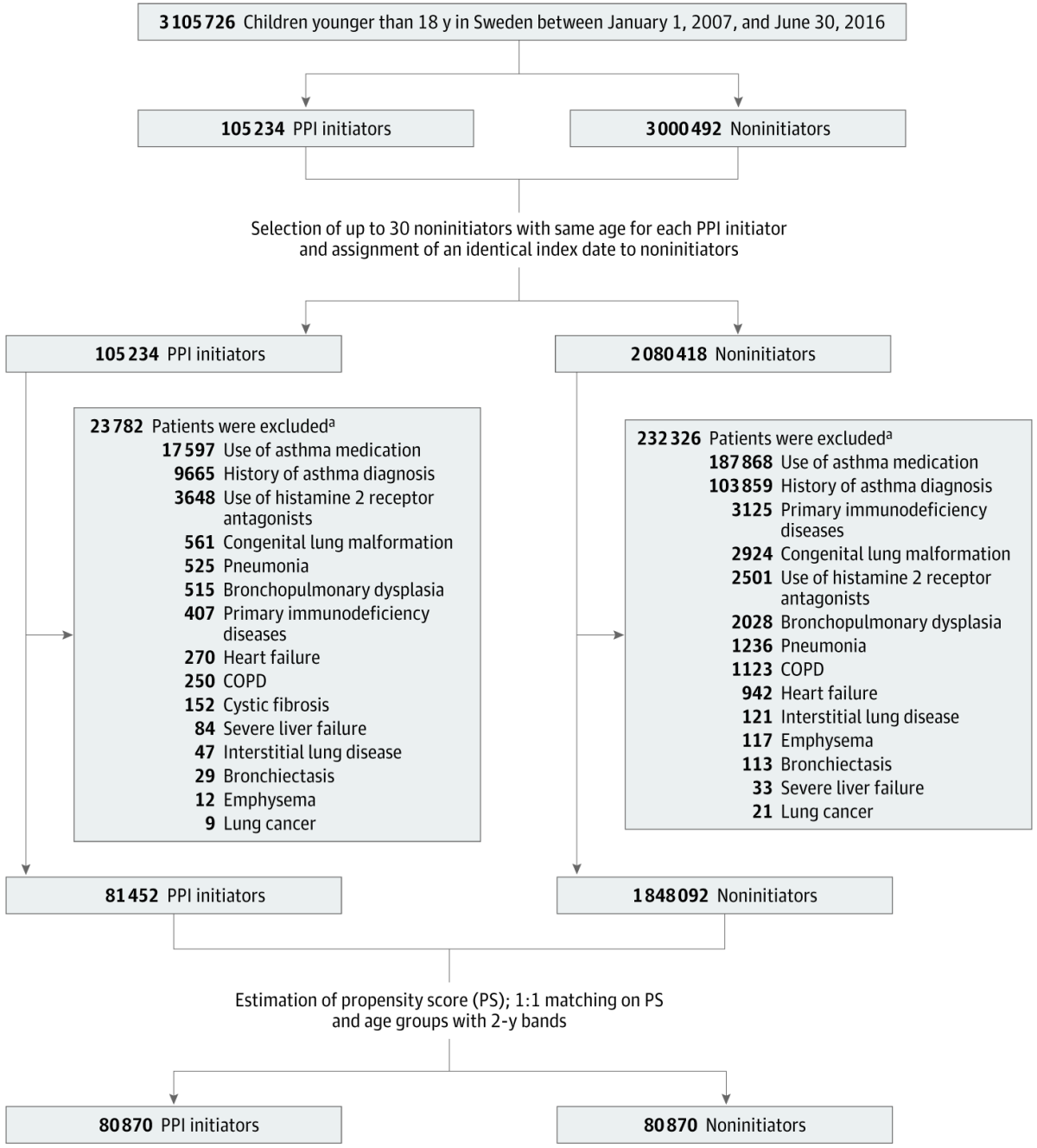
Is Proton Pump Inhibitor (PPI) Use Associated with Asthma Development in Children?

- PPI usage is common and increasing among children.[1]
- PPIs inhibit gastric acid secretion which alters the lung and gut microbiome [2] and has been associated with increased risk of asthma flares. [3]
- Alternately, suppressed acid-mediated breakdown of antigens in the stomach can increase sensitization of the immune system to allergens.[4]
- Only 1 comparative study has investigated the risk of asthma development following exposure to PPI or H_2RA during the 1st six months of life among ~80,000 infants and found a hazard ratio (HR) of 1.41 (95% CI, 1.31-1.52) of asthma development in infants. [5]

1. Hales CM, Kit BK, Gu Q, Ogden CL. Trends in prescription medication use among children and adolescents—United States, 1999-2014. *JAMA*. 2018;319(19):2009-2020. doi:10.1001/jama.2018. 5690
2. Levy EI, Hoang DM, VandenplasY.Theeffects ofprotonpumpinhibitorsonthemicrobiomein young children. *Acta Paediatr*. 2020;109(8):1531- 1538. doi:10.1111/apa.15213
3. Hufnagl K,Pali-SchöllI, Roth-WalterF, Jensen-Jarolim E. Dysbiosis of the gut and lung microbiomehasaroleinasthma.*Semin Immunopathol*. 2020;42(1):75-93. doi:10.1007/ s00281-019-00775-y
4. Schöll I, Untersmayr E, Bakos N, Roth-Walter F, Gleiss A, Boltz-Nitulescu G, Scheiner O, Jensen-Jarolim E. Antiulcer drugs promote oral sensitization and hypersensitivity to hazelnut allergens in BALB/c mice and humans. Am J Clin Nutr. 2005 Jan;81(1):154-60. doi: 10.1093/ajcn/81.1.154. PMID: 15640475. Mitre E, Susi A, Kropp LE, Schwartz DJ, Gorman GH, Nylund CM. Association Between Use of Acid-Suppressive Medications and Antibiotics During Infancy and Allergic Diseases in Early Childhood. JAMA Pediatr. 2018 Jun 4;172(6):e180315. doi: 10.1001/jamapediatrics.2018.0315. Epub 2018 Jun 4. PMID: 29610864; PMCID: PMC6137535.
5. Mitre E, Susi A, Kropp LE, Schwartz DJ, Gorman GH, Nylund CM. Association Between Use of Acid-Suppressive Medications and Antibiotics During Infancy and Allergic Diseases in Early Childhood. JAMA Pediatr. 2018 Jun 4;172(6):e180315. doi: 10.1001/jamapediatrics.2018.0315. Epub 2018 Jun 4. PMID: 29610864; PMCID: PMC6137535.

Methods

- Propensity score-matched cohort study
- Propensity score determined by demographic, socioeconomic characteristics, > 2 years of comorbidities (including atopy), health care usage & co-medications used 1 year prior.
  Goal of <10% standardized difference between matched cohort in 2-year age bands.
- Primary outcome = incident asthma determined by diagnosis or two independent prescriptions for asthma medications filled within 90 days



Results

- PPI use was associated with a 57% increased risk of asthma.
- Regardless of time from PPI initiation to diagnosis, PPI was significantly associated with asthma diagnosis.
- All types of PPI were associated with increased risk.

Table 2. Main Results of Associations Between PPI Use and Risk for Asthma

Analysis	PPI initiators (n = 80 870)		Noninitiators (n = 80 870)		Absolute risk difference in incidence (95% CI)[a]	HR (95% CI)
	No. of events	Incidence rate[a]	No. of events	Incidence rate[a]		
Primary analysis	4428	21.8	2818	14.0	7.9 (7.1-8.7)	1.57 (1.49-1.64)
Secondary analyses						
Asthma definition						
Diagnosis of asthma	863	4.3	561	2.8	1.5 (1.1-1.8)	1.53 (1.38-1.70)
2 Asthma drug prescription fills within 90 d	3565	17.6	2257	11.2	6.4 (5.7-7.1)	1.57 (1.49-1.66)
Timing of asthma onset (days after treatment initiation)						
≤90	592	29.5	365	18.2	11.3 (8.3-14.3)	1.62 (1.42-1.85)
91-180	576	29.3	333	16.9	12.4 (9.4-15.4)	1.73 (1.52-1.98)
≥181	3260	20.0	2120	13.1	6.9 (6.0-7.8)	1.53 (1.45-1.62)
Individual drugs[b]						
Esomeprazole	1250	52.2	777	31.8	20.4 (16.8-24.1)	1.64 (1.50-1.79)
Lansoprazole	305	37.4	204	25.1	12.2 (6.8-17.6)	1.49 (1.25-1.78)
Omeprazole	2854	16.8	1985	11.8	5.0 (4.2-5.8)	1.43 (1.35-1.51)
Pantoprazole	37	17.4	16	7.5	10.0 (3.3-16.6)	2.33 (1.30-4.18)

Abbreviations: HR, hazard ratio; PPI, proton pump inhibitor.

[a] Calculated as events per 1000 person-years.

[b] Rabeprazole was not analyzed due to small sample size (n = 6). The numbers of matched pairs of each subcohort were 11 305 for esomeprazole, 3219 for lansoprazole, 65 860 for omeprazole, and 821 for pantoprazole.

Results

Table 3. Associations Between PPI Use and Risk for Asthma, Stratified by Cumulative Duration of PPI Use

Initiation status	Person-years (% of total person-years)	No. of events	Incidence rate[a]	Absolute risk difference in incidence (95% CI)[a]	HR (95% CI)
None	201 971.1 (100)	2818	14.0	1 [Reference]	1 [Reference]
Time since initiation, d					
≤30	111 331.6 (55)	2419	21.7	7.8 (6.8-8.8)	1.52 (1.44-1.61)
31-364	88 829.9 (44)	1939	21.8	7.9 (6.8-9.0)	1.51 (1.42-1.60)
≥365	2707.9 (1)	70	25.9	11.9 (5.8-18.0)	1.59 (1.25-2.02)

Abbreviations: HR, hazard ratio; PPI, proton pump inhibitor.

[a] Calculated as events per 1000 person-years.

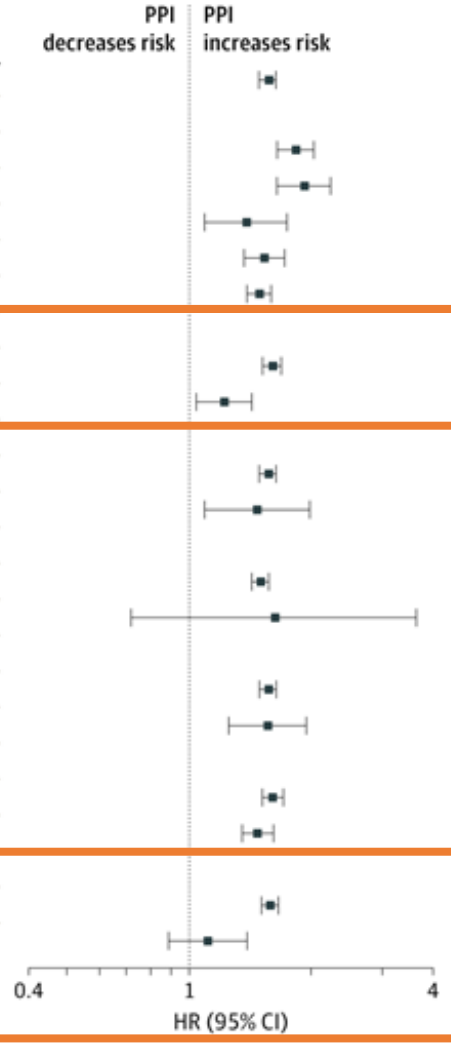
- Cumulative duration of PPI use (< 1 month, 1 to 12 months, > 12 months) and risk of asthma were significantly associated, regardless of the cumulative duration of PPI use.

Results

- The risk of asthma was highest for ages < 6 months and 6 months to < 2 years, those without atopy, and those without systemic corticosteroid use.

- No difference seen for history of lower respiratory tract infection, GERD, analgesic use, nor systemic antibiotic use.

Subgroup	PPI initiators			Noninitiators			Hazard ratio (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	80870	4428	21.8	80870	2818	14.0	1.57 (1.49-1.64)	
Age group								
0 d to <6 mo	3205	942	153.4	3205	555	83.0	1.83 (1.65-2.03)	
6 mo to <2 y	2094	482	113.8	2094	272	58.2	1.91 (1.65-2.22)	
2 y to <6 y	2954	170	24.1	2954	123	17.4	1.38 (1.09-1.74)	<.001
6 y to <12 y	18244	780	17.5	18244	492	11.5	1.53 (1.37-1.72)	
≥12 y	54373	2054	14.6	54373	1376	9.8	1.49 (1.39-1.59)	
Atopic disease								
No	76607	4066	21.1	76877	2544	13.2	1.60 (1.52-1.68)	.001
Yes	4263	362	34.7	3993	274	28.6	1.22 (1.04-1.43)	
Lower respiratory tract infection								
No	80256	4321	21.4	80283	2747	13.7	1.57 (1.49-1.64)	.68
Yes	614	107	76.9	587	71	52.3	1.47 (1.09-1.98)	
Gastroesophageal reflux disease								
No	78634	4115	20.8	80804	2812	13.9	1.50 (1.43-1.57)	.84
Yes	2236	313	60.3	66	6	36.9	1.62 (0.72-3.63)	
Analgesic use								
No	77279	4216	21.8	77596	2692	13.9	1.57 (1.49-1.64)	.95
Yes	3591	212	23.4	3274	126	15.0	1.56 (1.25-1.94)	
Systemic antibiotic use								
No	60093	3224	21.6	59880	1994	13.5	1.60 (1.52-1.70)	.10
Yes	20777	1204	22.5	20990	824	15.3	1.47 (1.35-1.61)	
Systemic corticosteroid use								
No	78244	4246	21.6	78711	2686	13.7	1.58 (1.51-1.66)	.003
Yes	2626	182	27.4	2159	132	24.7	1.11 (0.89-1.39)	



Discussion

- Strengths:
  - 1st comprehensive investigation of the association between PPI use and risk of asthma in a large and unselected nationwide population of children and adolescents using advanced analytical methods.
  - Additional analysis with high-dimensional propensity score matching correlated well with the initial HR (HR, 1.48; 95% CI, 1.41- 1.55).
  - Extensive sensitivity analysis to avoid confounding
- Only comparative study showed, among a retrospective cohort of ~80,000 children in the US followed over ~4.5 years, an adjusted HR for risk of asthma in infants who received PPIs in the first 6 months of life was 1.41 (95% CI, 1.31-1.52), but did not distinguish risk based on duration of therapy and only adjusted in analysis for prematurity, delivery methods and sex.[5]

5. Mitre E, Susi A, Kropp LE, Schwartz DJ, Gorman GH, Nylund CM. Association Between Use of Acid-Suppressive Medications and Antibiotics During Infancy and Allergic Diseases in Early Childhood. JAMA Pediatr. 2018 Jun 4;172(6):e180315. doi: 10.1001/jamapediatrics.2018.0315. Epub 2018 Jun 4. PMID: 29610864; PMCID: PMC6137535.

Discussion

- Limitations:
  - Unable to capture mild intermittent asthma diagnosis from primary care settings
  - Unable to know if subject filled or took their PPI prescriptions
  - Cannot accommodate for patients treated with PPI for symptoms of asthma
  - Does not capture hospitalization or over the counter PPI use
  - Unable to capture microbiota data, prenatal exposures, nor genetic & environmental factors (ie pollution)

Thank you to ISAAI for the opportunity to present.

Questions?