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Authors: Claudio Barbiellini Amidei[1], Rosanna Comoretto[1], Loris Zanier[2], Daniele Donà[3], Anna Cantarutti[4], Cristina Canova[1].

1 Unit of Biostatistics, Epidemiology and Public Health, Department of Cardio-Thoraco-Vascular Sciences and Public Health, University of Padua, Padua, Italy.

2 Epidemiological Service, Health Directorate, Friuli Venezia Giulia Region, Udine, Italy.

3 Division of Paediatric Infectious Diseases, Department for Woman and Child Health, University of Padua, Padua, Italy

4 Department of Statistics and Quantitative Methods, Milano Bicocca, Italy

Corresponding author:

Cristina Canova

Department of Cardio-Thoraco-Vascular Sciences and Public Health, University of Padua, Padua, Italy.

email address: cristina.canova@unipd.it

Take home:

Exposure to acid-suppressive medications in the first year of life is associated with a marked increase in the risk of developing childhood asthma; further studies are required to assess the causal relationship that underlies this association.

To the Editor,

Asthma is the most frequent immune-mediated chronic condition among children, and is associated with genetic risk factors as well as specific prenatal and early-life exposures(1). Gastroesophageal reflux disease (GERD) is a common paediatric condition(2), associated with bronchospasms in infants and has been considered a possible risk factor for the development of asthma, although the results are inconsistent(2,3). The treatment for GERD is based on acid-suppressive medications, mainly proton pump inhibitors (PPIs) and H2 receptor antagonists (H2RAs)(4).

Acid-suppressive medications and antibiotics can alter the human microbiome(5,6) with long-lasting effects, especially among infants(7). Microbiome alterations are considered responsible for several immune-mediated conditions, including asthma(8–10).

To the best of our knowledge, the association between acid-suppressive medication exposure in the first months of life and asthma has been explored in only one article(11).

The aim of this study was to estimate the risk of developing asthma after PPI and H2RA exposure during the first year of life in a large population-based birth cohort.

The study population was composed of children born between 1995 and 2011 in Friuli-Venezia Giulia, Italy. In this region, an integrated healthcare system, developed in the 1980s, automatically collects and pools data on healthcare services funded by the National Health Service. The drug prescription records database (coded by the Anatomical-Therapeutic-Chemical -ATC- Classification System) and mortality records were linked through a unique regional identification code to the Medical Birth Register, where data on parental socio-demographic status, pregnancy, labour, delivery and newborn birth were collected for all deliveries.

Exposure was defined as the presence of ≥1 PPI (ATC:A02BC*) or ≥1 H2RA (ATC:A02BA*) prescription in the first 6 and 12 months of life. All prescriptions were identified through the drug prescription records database that includes comprehensive information on all medications dispensed by pharmacies with medical prescriptions.

Incident asthma after the age of 3 was defined by the presence of ≥2 prescriptions in a 12-month window: short- and long-acting beta2 agonists (ATC:R03AC*); adrenergics in combination with other drugs, not anticholinergics (ATC:R03AK*); inhaled corticosteroids (ATC:R03BA*); and antileukotriene drugs (ATC:R03DC*). This definition was based on a previously validated algorithm with a positive predictive value of 78.5% (76.2-80.7) and a sensitivity of 74.5% (72.1-76.7)(12). Asthma onset was defined as the date of the first prescription in the 12-month frame. Any incident case before the age of 3 was excluded from the analyses.

Follow-up began at ≥3 years of age until death, migration, incident asthma or end of follow-up (31/12/2012).

Cox regression models were used to estimate hazard ratios (HR) and 95% confidence intervals (CI) for developing asthma, following PPI and H2RA exposure, both combined and separately. The assumption of proportional hazards was investigated by studying graphs over the log cumulative hazards function and the Schoenfeld residuals.

All models were adjusted for year of birth, sex, maternal age (≤24, 25–29, 30–34, 35–39, or ≥40 years), maternal education (up to 8th grade, 13th grade, or university), gestational age (≤28, 29–35, or ≥36 weeks), and birth weight (<2500 g, or ≥2500 g). To reduce a potential confounding effect, we also included antibiotic utilization in the first year of life, as categorical variable (0, 1, 2, ≥3) in the models.

A cumulative-dose response association was assessed considering prescriptions of acid-suppressive medications as a continuous variable in the models. A sensitivity analysis was performed for asthma onset at age ≥6.

Among the 111,414 individuals (679,658 person/years) who met the inclusion criteria, incident asthma was identified in 19,424 subjects, with median age at diagnosis of 4 years (mean: 4.6, SD: 2.4), followed up to 15 years.

In the first 12 months of life, 1,764 (1.58%) children, were prescribed 2,731 acid-suppressive medications. These medications were more common among asthmatic children (2.17%) than among non-asthmatic children (1.46%). Overall, 150 (0.13%) infants were prescribed ≥1 PPI and 1,651 (1.48%) were prescribed ≥1 H2RA.

We found an increased risk of developing asthma after exposure to acid-suppressive medications in the first year of life (adj2HR 1.60 95%CI 1.45-1.77), even after adjusting for antibiotic exposure. Risks following exposure in the first 6 months of life were slightly higher (adj2HR 1.67 95%CI 1.51-1.85), even after adjusting for all available confounding variables. All results showed a significant cumulative-dose response relationship (p-trend <0.001), although elevated risks were present even at low doses. Exposure to PPIs was associated with higher risks than exposure to H2RAs.

When considering asthma onset at age ≥6, we identified 74,207 subjects (≥6 years of follow-up), of which 4,071 were incident asthma cases. Elevated risks persisted (adj2HR 1.46 95%CI 1.24-1.91), even after adjusting for antibiotic exposure (adj3HR 1.44 95%CI 1.11-1.86).

The only previous article that investigated the association between exposure to acid-suppressive medications and asthma, observed similar results to those we found, with increased risks of 1.41 (95%CI 1.31-1.52) for PPIs and 1.25 (95%CI 1.21-1.29) for H2RAs(11,13). Nevertheless, the study by Mitre et al focused exclusively on exposures in the first 6 months of life and identified outcomes immediately after exposure.

Some studies have found that acid-suppressive medications were associated with the development of other immune-mediated diseases, which further suggests the presence of actual interference with the immune system(11,13). Various mechanisms have been investigated, but the exact pathophysiological process remains unclear. Growing evidence suggests that a relevant role could be played by the microbiota. Early-life exposure to antibiotics, as well as acid-suppressive medications, induces long-lasting effects on the intestinal microbiota(5) that have been linked to the development of different allergic conditions(11). One possible mechanism consists of an increased production of short-chain fatty acids that modulate the innate immune response with an increase in regulatory T-cell populations, thereby promoting immune-mediated disorders(14). Murine studies have shown that acid-suppressive medications are associated with increased immunoglobulin E production and could therefore predispose to the development of asthma(15).

Patients exposed to PPIs were associated with higher risks of asthma, which could be explained by a greater effectiveness in reducing gastric acidity, thereby strongly interfering with protein digestion and consequently changing antigen exposure to the immune system in the intestine(8). A possible mechanism concerning H2RAs would be interference with the kinetics of histamine, which plays a major role in immune-mediated responses(16).

Further evidence suggested a possible causal relationship, related to an increased risk of asthma in the offspring, following exposure to acid-suppressive medications during pregnancy(13)

The main limitation of this study is possible confounding by indication and severity, as it was not possible to distinguish the effect of GERD or its severity from the effect of acid-suppressive medications. Moreover, although acid-suppressive medications and anti-asthmatic drugs require a medical prescription, we cannot rule out a possible differential misclassification related to the tendency of some families to overmedicate their children. A further limitation is the lack of data to adjust for parental smoking as well as the cooccurrence of allergic diseases in the child. Nevertheless, we believe the risk of reverse causation linked to GERD being responsible of asthma, as well as early asthmatic symptoms or allergic conditions that may mimic GERD clinical manifestations in the infant should be reduced by the longitudinal study design, with a clear

separation between exposure and incident asthma among children aged ≥3. Moreover, higher risks were observed after exposure in the first 6 months of life, therefore, further away from treatment for GERD, and only 17 (4.02%) of the exposed children were treated for GERD with acid-suppressive medications the year before being identified as asthmatics. Although we used a surrogate outcome by defining asthma through medication use, the inclusion of only incident asthma after the age of 3 and 6 years, reduced the risk of misclassification(17) by limiting the possibility of identifying children with bronchospasms due to GERD or viral infections, which are common in early childhood(18).

This study observed an association between exposure to acid-suppressive medications in the first months of life and the subsequent development of asthma. Based on our findings it would seem advisable to use these medicines at the minimally effective dose and for the shortest time necessary. Limits to this study relate to the impossibility of ruling out whether the observed effect is related to GERD, which is treated with acid-suppressive medications, or if these medications, by altering the human microbiome or through other pathophysiological mechanisms, predispose patients to the development of asthma. Future studies with data on clinically assessed GERD, that take into account the severity of the disease, could allow to compare differences in risks of developing asthma among children treated and non-treated with acid-suppressive medications, possibly clarifying the actual underlying causal association.

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Table 1 Risk of asthma onset among subjects 3 years old or above following exposure to acid-suppressive medication in the first 12 and 6 months of life.

Acid-suppressive medication	Asthma cases N = 19,424	Persons-years	Adj1 HR (95% CI)	Adj2 HR (95% CI)	Adj3 HR (95% CI)
First 12 months of life					
No	19,002	671,538	1	1	1
Yes	422	8,119	1.62 (1.47-1.78)	1.60 (1.45-1.77)	1.58 (1.43-1.74)
1*	300	5,899	1.58 (1.35-1.77)	1.56 (1.38-1.75)	1.53 (1.36-1.72)
2*	69	1,246	1.72 (1.35-2.17)	1.75 (1.38-2.22)	1.72 (1.36-2.19)
≥3*	53	974	1.75 (1.33-2.29)	1.73 (1.32-2.27)	1.68 (1.28-2.21)
p-trend			<0.001	<0.001	<0.001
PPI					
No	19,388	679,138	1	1	1
Yes	36	519	1.91 (1.37-2.64)	1.88 (1.35-2.61)	1.82 (1.32-2.53)
H2RA					
No	19,024	671,978	1	1	1
Yes	400	7,680	1.63 (1.48-1.80)	1.62 (1.46-1.79)	1.59 (1.44-1.76)
First 6 months of life					
No	19,026	672,373	1	1	1

Yes	398	7,285	1.68 (1.52-1.86)	1.67 (1.51-1.85)	1.66 (1.50-1.84)
1*	289	5,438	1.63 (1.45-1.84)	1.61 (1.43-1.82)	1.60 (1.42-1.80)
2*	73	1,261	1.76 (1.40-2.22)	1.83 (1.45-2.30)	1.82 (1.44-2.30)
≥3*	36	586	1.98 (1.43-2.74)	1.91 (1.37-2.66)	1.87 (1.35-2.61)
p-trend			<0.001	<0.001	<0.001
PPI					
No	19,394	679,304	1	1	1
Yes	30	354	2.19 (1.53-3.14)	2.17 (1.52-3.11)	2.14 (1.45-3.06)
H2RA					
No	19,044	672,668	1	1	1
Yes	380	6,990	1.68 (1.52-1.86)	1.67 (1.51-1.86)	1.66 (1.50-1.84)

Adj1: gender, year of birth; Adj2: gender, year of birth, maternal age at birth, gestational age and weight at birth; Adj3: Adj2 and antibiotics. *References are subjects with no prescription for acid-suppressive medications.