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Prenatal and Infant Exposure to Acid-Suppressive Medications and Risk of Allergic Diseases in Children

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IMPORTANCE Existing observational data have indicated positive associations of acid-suppressive medication (ASM) use in prenatal and early life with allergic diseases in children; however, no study to date has accounted for confounding by indication or within-familial factors.

OBJECTIVE To evaluate the association of prenatal or infant exposure to ASMs with risk of allergic diseases in children.

DESIGN, SETTING, AND PARTICIPANTS This nationwide, cohort study included data from South Korea's National Health Insurance Service mother-child–linked database from January 1, 2007, to December 31, 2020. Participants included mother-child pairs of neonates born from April 1, 2008, to December 31, 2019.

EXPOSURES Prenatal and infant exposure to ASMs (histamine 2 receptor antagonists [H2RAs] and proton pump inhibitors [PPIs]).

MAIN OUTCOMES AND MEASURES Composite and individual outcomes of allergic diseases (asthma, allergic rhinitis, atopic dermatitis, and food allergy) in children (followed up to 13 years of age) were assessed. The ASM-exposed individuals were compared with unexposed individuals in propensity score (PS)–matched and sibling-matched analyses to control for various potential confounders and within-familial factors. Hazard ratios (HRs) with 95% CIs were estimated using Cox proportional hazards regression models.

RESULTS The study included 4 149 257 mother-child pairs. Prenatal exposure analyses included 808 067 PS-matched pairs (763 755 received H2RAs, 36 529 received PPIs) among women with a mean (SD) age of 31.8 (4.2) years. The PS-matched HR was 1.01 (95% CI, 1.01-1.02) for allergic diseases overall (asthma: HR, 1.02 [95% CI, 1.01-1.03]; allergic rhinitis: HR, 1.02 [95% CI, 1.01-1.02]; atopic dermatitis: HR, 1.02 [95% CI, 1.01-1.02]; food allergy: HR, 1.03 [95% CI, 0.98-1.07]); in sibling-matched analyses, the HRs were similar to those of PS-matched analyses but were not significant (allergic diseases: HR, 1.01; 95% CI, 0.997-1.01). Infant exposure analyses included 84 263 PS-matched pairs (74 188 received H2RAs, 7496 received PPIs). The PS-matched HR was 1.06 (95% CI, 1.05-1.07) for allergic diseases overall (asthma: HR, 1.16 [95% CI, 1.14-1.18]; allergic rhinitis: HR, 1.02 [95% CI, 1.01-1.03]; atopic dermatitis: HR, 1.05 [95% CI, 1.02-1.08]; food allergy: HR, 1.28 [95% CI, 1.10-1.49]); asthma risk (HR, 1.13; 95% CI, 1.09-1.17) remained significantly higher among children exposed to ASMs during infancy in sibling-matched analyses. The findings were similar for H2RAs and PPIs analyzed separately and were robust across all sensitivity analyses.

CONCLUSIONS AND RELEVANCE The findings of this cohort study suggest that there is no association between prenatal exposure to ASMs and allergic diseases in offspring. However, infant exposure to ASMs was associated with a higher risk of developing asthma, although the magnitude was more modest than previously reported. Clinicians should carefully weigh the benefits of prescribing ASMs to children, accompanied by subsequent close monitoring for any clinically relevant safety signals.

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Supplemental content

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The prevalence of allergic diseases has risen worldwide, especially among children and adolescents.[1,2] Great efforts have been dedicated to identifying factors associated with allergic disease,[3] and data have suggested associations between allergic diseases and acid-suppressive medication (ASM) use in fetal and early life.[4-8] Meanwhile, ASMs, including proton pump inhibitors (PPIs) and histamine 2 receptor antagonists (H2RAs), are frequently used during pregnancy to treat gastroesophageal reflux disease (GERD),[9] and in recent decades, the use of ASMs has substantially increased in both pregnant and pediatric populations.[10,11]

There is a plausible biological mechanism for the association of ASMs with allergic diseases. Acid-suppressive medications may interfere with the digestion of food antigens, resulting in the sensitization of the immune system to predispose children to allergic diseases.[12,13] Moreover, ASMs may alter the composition and function of the gut microbiome, a known predictor of allergic diseases.[14-17] In support, a growing number of epidemiological studies have reported positive associations of allergic diseases in offspring with ASM use during pregnancy and infancy (eTable 1 in the Supplement).[4-8,18-25] However, these studies did not fully address confounding by indication and within-family shared factors.[26-28] Given that asthma and GERD are often concomitant (up to 80% of patients with asthma have GERD) and asthma may induce GERD or vice versa,[29] prior findings could have been confounded by GERD rather than showing a true association between allergic diseases and ASM use.[27,30] Likewise, allergic diseases are highly heritable and affected by familial factors (eg, genetic and environmental factors)[31]; thus, lack of adjustment for familial factors is another potential source of bias.[32] However, there are limited studies that considered confounding by indication and familial factors.

Thus, we aimed to examine whether prenatal or infant exposure to ASMs was associated with allergic diseases in children using the nationwide mother-offspring–linked health care database of South Korea. We used the propensity score (PS) approach to adjust for potential confounding, including indications (eg, GERD), and sibling-matched analyses to explore the influence of factors shared within families.

Key Points

Question Is prenatal or infant exposure to acid-suppressive medication (ASM) associated with increased risk of allergic diseases in children?

Findings In this nationwide cohort study of 4 149 257 mother-child pairs that controlled for underlying conditions and within-familial factors, there was no higher risk of allergic diseases associated with prenatal exposure to ASMs, whereas infant exposure to ASMs was significantly associated with a higher risk of developing asthma.

Meaning These findings suggest that there is no association between prenatal exposure to ASMs and allergic diseases in children but that infant exposure to ASMs is associated with subsequent development of asthma.

Methods

Data Source

We conducted a nationwide population-based cohort study using the National Health Insurance Service (NHIS) database of South Korea (from January 1, 2007, to December 31, 2020), which represents the entire Korean population (>50 million people).[33] The NHIS database includes comprehensive information on sociodemographic data, inpatient and outpatient health care utilization (diagnoses, procedures, and prescriptions), health examinations, and vital statistics (eAppendix 1 in the Supplement). The mother-child-linked cohort was built and provided by the NHIS, which was constructed using a unique insurance identification number shared within a family.[34,35] The start of pregnancy was estimated based on the delivery date or diagnoses of preterm birth using a previously validated algorithm to estimate the gestational age in administrative databases.[36] The overall positive predictive value for diagnostic records in claims data was 82% according to a previous validation study.[37] This study was approved by the institutional review board of Sungkyunkwan University. The requirement for informed consent was waived as this study used deidentified administrative data. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.[38]

Study Cohorts

We first identified all pregnancy episodes in women that resulted in live births between April 1, 2008, and December 31, 2019. We then constructed 2 study cohorts, each with different exclusion criteria. First, for prenatal exposure analyses, we excluded women younger than 19 years or older than 44 years and women who had no ASM prescription during pregnancy but received 1 or more ASMs within 30 days before pregnancy to minimize misclassification caused by their receiving ASMs before pregnancy but taking them during pregnancy. Second, for infant exposure analyses, we excluded children followed up for less than 1 year after birth; children with a diagnosis of respiratory conditions (eg, congenital lung malformation, bronchiectasis), primary immunodeficiency disease, heart failure, or severe liver failure in the first 6 months of life (definitions are given in eTable 2 in the Supplement)[6]; and children with any study outcome in the first 6 months of life.

In addition, we constructed sibling-matched cohorts based on the mother's unique identification number to control for unmeasured, within-family genetic, lifestyle, and social confounders.[28,39] Within these cohorts, we identified only siblings with discordant exposure (ASM) status. An inconsistent finding between the overall and sibling cohorts implied that findings from the overall cohort were likely to be subject to familial confounding.

Exposure to ASMs

Exposure to ASMs was defined as 1 or more prescriptions for a PPI or H2RA (Anatomical Therapeutic Chemical classification system code A02BC or A02BA). For prenatal exposure

analyses, exposure was defined as 1 or more ASM prescriptions at any time during pregnancy. The comparative group was defined as women who had no ASM prescription from 30 days before pregnancy to the delivery date. For infant exposure analyses, exposure was defined as 1 or more ASM prescriptions during the first 6 months of life among offspring. The comparative group was defined as infants having no ASM prescription during this period.

Outcomes

Development of allergic diseases among children was defined using *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* (*ICD-10*) codes, recorded by a physician, as the primary diagnosis from either an inpatient or outpatient setting, including primary and specialist care. The primary outcome, allergic diseases, was a composite end point of asthma, allergic rhinitis, atopic dermatitis, and food allergy (detailed definitions are given in eTable 2 in the Supplement). Asthma was defined as having 2 or more asthma diagnosis records within 1 year and receiving 2 or more independent prescriptions for asthma medications with gaps of more than 2 weeks within 1 year.[40,41] Allergic rhinitis, atopic dermatitis, and food allergy were defined using the appropriate *ICD-10* codes with 2 or more claims within 1 year.[42-46] The secondary outcomes were the individual components of the primary outcome.

For prenatal exposure analyses, the outcomes were measured after birth until outcome onset, death, or the end of the study period (December 31, 2020), whichever came first (up to 13 years of age). For infant exposure analyses, the outcomes were measured from 6 months after birth until outcome onset, death, or the end of the study period, whichever came first (up to 13 years of age).

Covariates

For prenatal exposure analyses, we included the following covariates as potential confounders or their surrogates: maternal age at delivery, income level, urban living, maternal conditions (eg, asthma, allergic rhinitis, and atopic dermatitis), co-medication use in fetal life (eg, antibiotics, antidepressants), measures of health care utilization (eg, obstetric comorbidity index,[47,48] number of outpatient visits), parity, plurality, birth year, and birth season. We measured maternal conditions diagnosed at least once in inpatient settings or twice in outpatient settings from 6 months before pregnancy to the day before delivery. Co-medication use was defined as a drug prescribed 3 or more days after the start of pregnancy to the day before delivery. Health care utilization was measured during the 6 months before pregnancy. In addition, history of maternal smoking and body mass index (BMI) were measured using the most recent health examination records before or during pregnancy; these were considered only for sensitivity analyses due to a high prevalence of missing data (restricted study cohort to subset with smoking and BMI data). Body mass index was classified according to the World Health Organization Asia-Pacific standard BMI.[49] For infant exposure analyses, we included the following covariates: ASM exposure in fetal life, child sex, birth weight, feeding type (eg, breastfeeding, formula feeding), respiratory diagnosis at birth, infant indications for ASMs, obstetric conditions (eg, preterm birth, cesarean birth), and all aforementioned maternal characteristics from the prenatal exposure analyses (eTable 2 in the Supplement gives detailed variable definitions).

Statistical Analysis

We performed 1:1 (for ASMs and H2RAs) or 1:4 (for PPIs) PS matching with the digit-based greedy matching algorithm (eighth digit to first digit [8 to 1]) without replacement.[50,51] The PS, the probability of receiving exposure, was derived using a multivariable logistic regression model by including all covariates as independent variables. Covariate balance between groups was assessed using the standardized mean difference (SMD), in which an absolute value of less than 0.1 implied no important imbalances (PS distributions are shown in eFigures 1 and 2 in the Supplement).

In the PS-matched cohort, we used Cox proportional hazards regression models to estimate hazard ratios (HRs) with 95% CIs for each study outcome. In the sibling-matched cohort, we used stratified Cox proportional hazards regression models with a separate stratum for each mother to account for correlation among sibling pairs. In each outcome model, we further adjusted variables that remained imbalanced (ie, absolute SMD ≥0.1) after matching to address potential residual confounding and deaths were treated as censoring events. The Cox proportional hazards regression assumption was tested with Schoenfeld residuals and was not violated for the primary outcome.

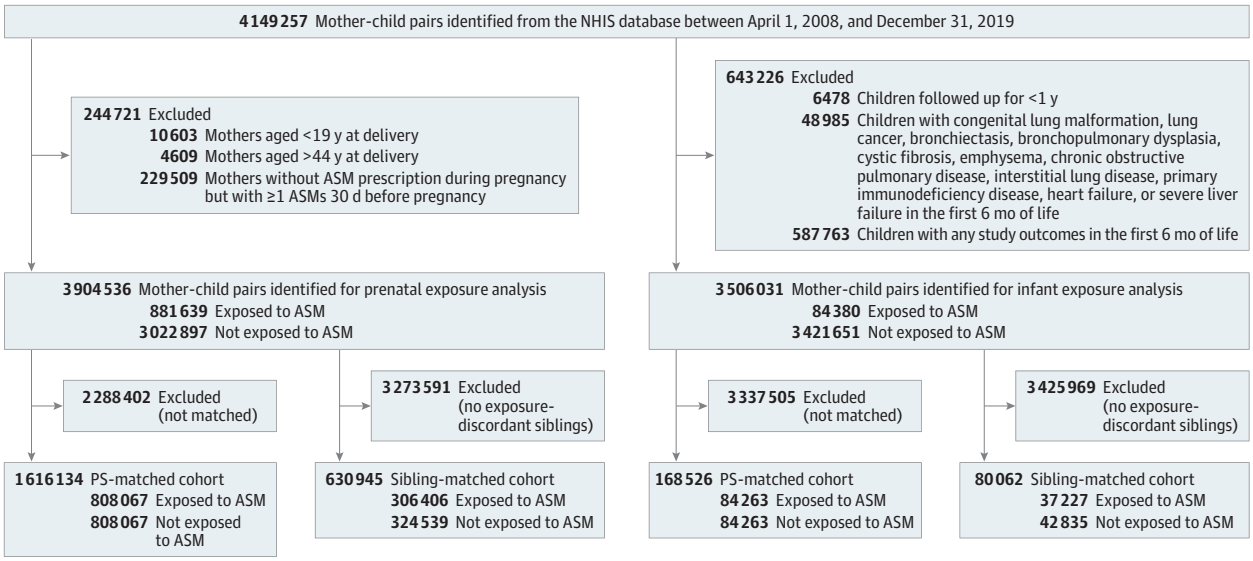
We performed various secondary and sensitivity analyses to test the validity of the primary analyses (more details are given in eAppendices 2-4 and eTables 3 and 4 in the Supplement). Robust SE was used to account for correlations in women with multiple pregnancies and found no considerable change in 95% CIs in the primary analysis. Thus, we did not include correlation structures in our analyses. A 95% CI not overlapping 1.0 was considered statistically significant. All analyses were performed using SAS, version 6.1 (SAS Institute Inc).

Results

Prenatal Exposure Analyses

Of 4 149 257 mother-child pairs, we included 3 904 536 pairs for prenatal exposure analyses, of whom 881 639 (22.6%) were prenatally exposed to ASMs (**Figure 1**). After 1:1 PS matching, there were 808 067 pairs of women (mean [SD] age, 31.8 [4.2] years) prenatally exposed and unexposed to ASMs (763 755 received H2RAs, and 36 529 received PPIs); balance was achieved for all covariates with absolute SMDs less than 0.1 (**Table** and eTable 5 in the Supplement). With a mean (SD) follow-up of 2.6 (2.7) years in both groups, the incidence rate difference of allergic diseases was 5.4 per 1000 person-years (incidence rates: 306.1 per 1000 person-

Figure 1. Flowchart of Study Cohort Identification



ASM indicates acid-suppressive medication; NHIS, National Health Insurance Service; PS, propensity score.

years vs 300.7 per 1000 person-years in prenatally ASM-exposed vs unexposed children) (**Figure 2**). The PS-matched HRs were 1.01 (95% CI, 1.01-1.02) for allergic diseases overall, 1.02 (95% CI, 1.01-1.03) for asthma, 1.02 (95% CI, 1.01-1.02) for allergic rhinitis, 1.02 (95% CI, 1.01-1.02) for atopic dermatitis, and 1.03 (95% CI, 0.98-1.07) for food allergy in prenatally ASM-exposed children vs unexposed children. The PS-matched HRs for all allergic outcomes for exposure to PPIs (n = 42 575) and H2RAs (n = 804 212) analyzed separately were comparable with those from the primary analysis.

Infant Exposure Analyses

We identified 3 506 031 mother-child pairs for infant exposure analyses, of whom 84 380 (2.4%) were exposed to ASMs during early infancy (Figure 1). In the PS-matched cohort of 84 263 pairs of infants exposed and unexposed to ASMs (mean [SD] follow-up: 3.5 [2.8] years and 3.6 [2.8] years, respectively), all covariates had absolute SMDs less than 0.1 (Table and eTable 5 in the Supplement). The incidence rate difference of allergic diseases was 12.8 per 1000 person-years (incidence rates: 218.1 per 1000 person-years vs 205.2 per 1000 person-years in children exposed to ASMs during infancy -vs those unexposed) (**Figure 3**). Unlike prenatal exposure analyses, PS-matched HRs for risk of asthma (1.16; 95% CI, 1.14-1.18) and food allergy (1.28; 95% CI, 1.10-1.49) were moderately increased but not substantially for allergic diseases overall (HR, 1.06; 95% CI, 1.04-1.07), allergic rhinitis (HR, 1.02; 95% CI, 1.01-1.03), or atopic dermatitis (HR, 1.05; 95% CI, 1.02-1.08) in children exposed to ASMs during infancy vs those unexposed. When comparing children exposed to PPIs (n = 7496) or H2RAs (n = 74 188) during infancy with those unexposed, the estimates for allergic diseases overall and its components were similar to those of the primary analysis.

Sibling-Matched Analysis

Sibling-matched cohorts included 630 945 mother-child pairs and 80 062 infants for the prenatal and infant exposure analyses, respectively (Figure 1; characteristics are shown in eTables 6 and 7 in the Supplement). For sibling-matched prenatal exposure analyses, the HRs were similar to those of PS-matched analyses but were not statistically significant for allergic diseases overall (HR, 1.01; 95% CI, 0.997-1.01) and the individual components (**Figure 4**). For sibling-matched infant exposure analyses, risk of asthma (HR, 1.13; 95% CI, 1.09-1.17) remained significantly increased.

Secondary and Sensitivity Analyses

Results of secondary analyses are shown in eTables 8 and 9 in the Supplement. Results from all sensitivity analyses were largely consistent with the main findings (eTables 10 and 11 in the Supplement).

Discussion

Principal Findings

In this large, population-based cohort study, we found no meaningful associations between prenatal exposure to ASMs and risk of allergic diseases in offspring in both PS-matched and sibling-matched analyses. Unlike prenatal exposure, infant exposure to ASMs was associated with higher risk of allergic diseases, especially asthma (HR, 1.16; 95% CI 1.14-1.18) and food allergy (HR, 1.28; 95% CI, 1.10-

Table. Characteristics of Mothers and Children Stratified by Exposure to Acid-Suppressive Medications During Pregnancy and Infancy After Propensity Score Matching[a]

Characteristic	Prenatal exposure analysis			Infant exposure analysis		
	Exposed (n = 808 067)	Unexposed (n = 808 067)	SMD	Exposed (n = 84 263)	Unexposed (n = 84 263)	SMD
Follow-up time, mean (SD), y	2.6 (2.7)	2.6 (2.7)	NA	3.5 (2.8)	3.6 (2.8)	NA
Mother						
Age at delivery, mean (SD), y	31.8 (4.2)	31.7 (4.2)	0.01	31.9 (4.3)	31.9 (4.4)	0.00
Income level, quartile						
First	148 956 (18.4)	147 025 (18.2)	0.03	15 921 (18.9)	15 992 (19.0)	0.00
Second	202 568 (25.1)	201 104 (24.9)		20 967 (24.9)	20 821 (24.7)	
Third	284 918 (35.3)	287 824 (35.6)		29 832 (35.4)	29 683 (35.2)	
Fourth	171 625 (21.2)	172 114 (21.3)		17 543 (20.8)	17 767 (21.1)	
Urban living	561 048 (69.4)	561 039 (69.4)	0.00	55 812 (66.2)	55 840 (66.3)	0.00
Condition						
Asthma	38 826 (4.8)	37 031 (4.6)	0.01	1413 (1.7)	1440 (1.7)	0.00
Allergic rhinitis	326 986 (40.5)	328 354 (40.6)	0.00	14 818 (17.6)	15 039 (17.8)	−0.01
Atopic dermatitis	21 011 (2.6)	19 928 (2.5)	0.01	530 (0.6)	518 (0.6)	0.00
Autoimmune disease	4951 (0.6)	4689 (0.6)	0.00	301 (0.4)	275 (0.3)	0.01
Gastroesophageal reflux disease	116 988 (14.5)	112 216 (13.9)	0.02	8433 (10.0)	8481 (10.1)	0.00
Peptic ulcer	60 838 (7.5)	58 701 (7.3)	0.01	4439 (5.3)	4493 (5.3)	0.00
Helicobacter pylori infection	220 (0.03)	222 (0.03)	0.00	21 (0.02)	19 (0.02)	0.00
Gastritis and duodenitis	396 465 (49.1)	409 197 (50.6)	−0.03	29 989 (35.6)	30 394 (36.1)	−0.01
Diabetes	110 915 (13.7)	105 843 (13.1)	0.02	5515 (6.5)	5767 (6.8)	−0.01
Hypertension	43 452 (5.4)	40 900 (5.1)	0.01	3034 (3.6)	2996 (3.6)	0.00
Anemia	234 370 (29.0)	234 511 (29.0)	0.00	10 449 (12.4)	10 421 (12.4)	0.00
Affective disorder	11 673 (1.4)	11 042 (1.4)	0.01	699 (0.8)	697 (0.8)	0.00
Nonaffective psychosis	974 (0.1)	950 (0.1)	0.00	112 (0.1)	127 (0.2)	−0.01
Co-medications in fetal life						
Antibiotics	452 086 (55.9)	461 054 (57.1)	−0.02	39 853 (47.3)	40 144 (47.6)	−0.01
Antidepressants	5669 (0.7)	5102 (0.6)	0.01	557 (0.7)	540 (0.6)	0.00
Antidiabetic drugs	9582 (1.2)	9191 (1.1)	0.01	1311 (1.6)	1337 (1.6)	0.00
Immunosuppressants	2173 (0.3)	2064 (0.3)	0.00	223 (0.3)	205 (0.2)	0.00
NSAIDs	172 564 (21.4)	167 710 (20.8)	0.02	12 853 (15.3)	12 820 (15.2)	0.00
Opioid analgesics	220 760 (27.3)	221 037 (27.4)	0.00	18 677 (22.2)	18 746 (22.2)	0.00
Systemic corticosteroids	96 404 (11.9)	92 272 (11.4)	0.02	8326 (9.9)	8438 (10.0)	0.00
Health care utilization						
Obstetric comorbidity index, mean (SD)	0.7 (1.0)	0.7 (1.0)	0.03	0.8 (1.1)	0.8 (1.1)	0.00
Outpatient visits, mean (SD), No.	6.3 (6.2)	6.2 (5.9)	0.01	6.0 (6.2)	6.1 (6.4)	−0.01
Emergency department visits	60 411 (7.5)	58 866 (7.3)	0.01	6049 (7.2)	6224 (7.4)	−0.01
Hospital admissions	58 755 (7.3)	56 261 (7.0)	0.01	6746 (8.0)	6691 (7.9)	0.00
Obstetric condition						
Nulliparity	396 713 (49.1)	396 775 (49.1)	0.00	39 836 (47.3)	39 552 (46.9)	0.01
Multifetal	34 342 (4.2)	29 858 (3.7)	0.03	6142 (7.3)	6333 (7.5)	−0.01
Preterm birth	NA	NA	NA	19 668 (23.3)	19 868 (23.6)	−0.01
Cesarean birth	NA	NA	NA	42 040 (49.9)	41 940 (49.8)	0.00
Birth year						0.00
2008-2011	268 195 (33.2)	272 338 (33.7)	0.03	30 045 (35.7)	30 326 (36.0)	0.00
2012-2015	298 243 (36.9)	297 779 (36.9)		31 028 (36.8)	30 893 (36.7)	
2016-2019	241 629 (29.9)	237 950 (29.4)		23 190 (27.5)	23 044 (27.3)	

(continued)

Table. Characteristics of Mothers and Children Stratified by Exposure to Acid-Suppressive Medications During Pregnancy and Infancy After Propensity Score Matching[a] (continued)

Characteristic	Prenatal exposure analysis			Infant exposure analysis		
	Exposed (n = 808 067)	Unexposed (n = 808 067)	SMD	Exposed (n = 84 263)	Unexposed (n = 84 263)	SMD
Birth season[b]						
Spring	206 765 (25.6)	208 906 (25.9)	0.00	20 148 (23.9)	20 103 (23.9)	0.00
Summer	202 970 (25.1)	201 084 (24.9)		21 921 (26.0)	22 017 (26.1)	
Autumn	202 789 (25.1)	201 968 (25.0)		22 169 (26.3)	22 306 (26.5)	
Winter	195 543 (24.2)	196 109 (24.3)		20 025 (23.8)	19 837 (23.5)	
Smoking						
Current	18 928 (2.3)	18 130 (2.2)	0.02	1806 (2.1)	1830 (2.2)	0.02
None or past	372 495 (46.1)	383 286 (47.4)		37 918 (45.0)	37 241 (44.2)	
Missing data	416 644 (51.6)	406 651 (50.3)		44 539 (52.9)	45 192 (53.6)	
Body mass index, mean (SD)[c]						
Underweight	54 474 (6.7)	54 144 (6.7)	0.02	5195 (6.2)	5044 (6.0)	0.00
Normal	233 371 (28.9)	242 227 (30.0)		23 403 (27.8)	23 188 (27.5)	
Overweight	49 775 (6.2)	51 255 (6.3)		5154 (6.1)	5115 (6.1)	
Obesity	52 953 (6.6)	52 855 (6.5)		5867 (7.0)	5641 (6.7)	
Missing data	417 494 (51.7)	407 586 (50.4)		44 644 (53.0)	45 275 (53.7)	
Infant						
ASM use in fetal life	NA	NA	NA	17 140 (20.3)	17 236 (20.5)	0.00
Sex						
Female	NA	NA	NA	35 984 (42.7)	35 902 (42.6)	0.00
Male	NA	NA	NA	48 279 (57.3)	48 361 (57.4)	0.00
Birth weight, g						
<1500	NA	NA	NA	3611 (4.3)	2832 (3.4)	0.06
1500-2499	NA	NA	NA	9353 (11.1)	10 189 (12.1)	
≥2500	NA	NA	NA	67 114 (79.6)	67 046 (79.6)	
Missing data	NA	NA	NA	4185 (5.0)	4196 (5.0)	
Feeding						
Breast	NA	NA	NA	31 514 (37.4)	31 446 (37.3)	0.00
Formula	NA	NA	NA	14 312 (17.0)	14 245 (16.9)	
Mixed	NA	NA	NA	30 016 (35.6)	30 152 (35.8)	
Missing data	NA	NA	NA	8421 (10.0)	8420 (10.0)	
Respiratory diagnosis at birth	NA	NA	NA	12 843 (15.2)	13 128 (15.6)	−0.01
Indications						
Gastroesophageal reflux disease	NA	NA	NA	10 707 (12.7)	11 336 (13.5)	−0.02
Peptic ulcer	NA	NA	NA	788 (0.9)	464 (0.6)	0.05
Gastritis and duodenitis	NA	NA	NA	9884 (11.7)	10 233 (12.1)	−0.01
Helicobacter pylori infection	NA	NA	NA	0	0	0.00

Abbreviations: ASM, acid-suppressive medication; NA, not applicable; NSAIDs, nonsteroidal anti-inflammatory drugs; SMD, standardized mean difference.

[a] Data are presented as number (percentage) of mothers or infants unless otherwise indicated.

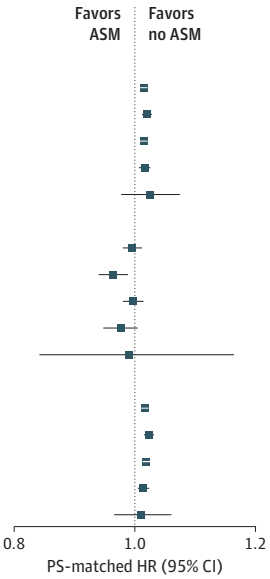
[b] Spring was from March to May; summer, June to August; autumn, September to November; and winter, December to February.

[c] Calculated as weight in kilograms divided by height in meters squared. Underweight was less than 18.5; normal, 18.5 to 22.9; overweight, 23.0 to 24.9; and obesity, 25.0 or more.

1.49); the risk of asthma remained significantly higher (HR, 1.13; 95% CI, 1.09-1.17), whereas there was no significant difference in risk of food allergy in sibling-matched analyses. Based on the upper limit of the 95% CI from the adjusted estimate from sibling-matched analyses, we ruled out the possibility of a more than 17% increase in the risk for asthma associated with ASM use. Secondary analyses did not show any notable heterogeneity in effect estimates between PPIs and H2RAs, exposure timing, cumulative dose, and formulation type. The findings were robust across all sensitivity analyses, strengthening the reliability of our main results.

Figure 2. Risk of Allergic Diseases in Children Following Exposure to Acid-Suppressive Medications (ASMs) During Pregnancy in Propensity-Score (PS)–Matched Analyses

ASM, allergic disease	Exposed		Unexposed		Incidence rate difference/ 1000 PY	HR (95% CI)	
	Events, No.	Incidence rate, per 1000 PY	Events, No.	Incidence rate, per 1000 PY		Crude	PS matched
Any ASM[a]							
Any	631 771	306.1	629 776	300.7	5.4	1.11 (1.10-1.11)	1.01 (1.01-1.02)
Asthma	247 956	59.6	245 098	58.2	1.5	1.06 (1.06-1.06)	1.02 (1.01-1.03)
Allergic rhinitis	552 936	193.5	550 678	190.3	3.2	1.13 (1.13-1.14)	1.02 (1.01-1.02)
Atopic dermatitis	159 915	33.5	158 094	32.8	0.7	1.04 (1.04-1.05)	1.02 (1.01-1.02)
Food allergy	3827	0.7	3748	0.6	0.0	1.12 (1.08-1.16)	1.03 (0.98-1.07)
PPI only[b]							
Any	27 300	326.8	110 012	327.7	-0.9	1.12 (1.11-1.13)	1.00 (0.98-1.01)
Asthma	9290	56.3	38 798	57.9	-1.6	0.90 (0.89-0.92)	0.96 (0.94-0.99)
Allergic rhinitis	23 949	217.6	96 964	217.6	0.1	1.22 (1.21-1.23)	1.00 (0.98-1.01)
Atopic dermatitis	6461	35.5	26 674	35.8	-0.3	0.97 (0.95-1.00)	0.98 (0.95-1.00)
Food allergy	187	0.9	766	0.9	0.0	1.35 (1.19-1.55)	0.99 (0.84-1.16)
H2RA only[c]							
Any	599 553	305.5	596 773	299.5	6.0	1.10 (1.10-1.11)	1.02 (1.01-1.02)
Asthma	237 405	59.9	233 840	58.2	1.7	1.07 (1.07-1.07)	1.02 (1.02-1.03)
Allergic rhinitis	524 733	192.5	521 421	188.5	4.0	1.12 (1.12-1.13)	1.02 (1.02-1.02)
Atopic dermatitis	152 398	33.5	150 768	32.8	0.6	1.05 (1.04-1.05)	1.01 (1.01-1.02)
Food allergy	3591	0.7	3568	0.6	0.0	1.10 (1.06-1.14)	1.01 (0.96-1.06)



Squares indicate hazard ratios (HRs), with horizontal lines indicating 95% CIs. H2RA indicates histamine 2 receptor antagonist; PPI, proton pump inhibitor; PY, person-years.

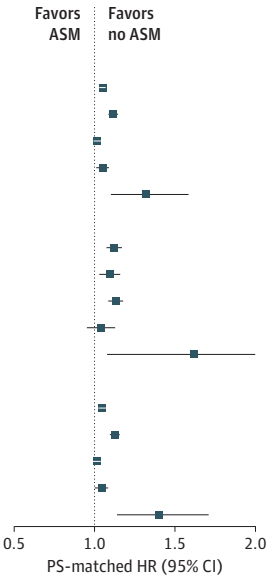
[a] Exposed: 808 067; unexposed: 808 067 (1:1 matching).

[b] Exposed: 36 529; unexposed: 146 116 (1:4 matching).

[c] Exposed: 763 755; unexposed: 763 755 (1:1 matching).

Figure 3. Risk of Allergic Diseases in Children Following Exposure to Acid-Suppressive Medications (ASMs) During Infancy in Propensity-Score (PS)–Matched Analyses

ASM, allergic disease	Exposed		Unexposed		Incidence rate difference/ 1000 PY	HR (95% CI)	
	Events, No.	Incidence rate, per 1000 PY	Events, No.	Incidence rate, per 1000 PY		Crude	PS matched
Any ASM[a]							
Any	63 696	218.1	62 174	205.2	12.8	1.10 (1.09-1.10)	1.06 (1.05-1.07)
Asthma	27 364	56.7	24 416	48.5	8.2	1.23 (1.22-1.25)	1.16 (1.14-1.18)
Allergic rhinitis	55 103	147.7	54 407	144.5	3.2	1.04 (1.03-1.05)	1.02 (1.01-1.03)
Atopic dermatitis	11 901	20.1	11 383	19.0	1.0	1.05 (1.04-1.07)	1.05 (1.02-1.08)
Food allergy	374	0.6	292	0.4	0.1	1.35 (1.22-1.50)	1.28 (1.10-1.49)
PPI only[b]							
Any	5703	249.0	22 237	219.8	29.1	1.23 (1.20-1.26)	1.13 (1.10-1.17)
Asthma	2249	56.4	8550	50.4	6.0	1.18 (1.13-1.23)	1.10 (1.05-1.15)
Allergic rhinitis	5060	178.2	19 636	157.8	20.4	1.24 (1.21-1.28)	1.13 (1.10-1.17)
Atopic dermatitis	1088	22.8	4232	21.2	1.7	1.16 (1.09-1.23)	1.06 (0.99-1.13)
Food allergy	44	0.8	119	0.5	0.3	1.86 (1.38-2.50)	1.52 (1.07-2.15)
H2RA only[c]							
Any	56 228	215.6	54 856	204.0	11.6	1.09 (1.08-1.09)	1.06 (1.04-1.07)
Asthma	24 359	56.7	21 649	48.7	8.0	1.24 (1.23-1.26)	1.16 (1.14-1.18)
Allergic rhinitis	48 556	145.4	47 870	143.1	2.3	1.03 (1.02-1.03)	1.01 (1.00-1.03)
Atopic dermatitis	10 510	19.8	9931	18.7	1.1	1.05 (1.03-1.07)	1.06 (1.03-1.09)
Food allergy	309	0.5	261	0.4	0.1	1.25 (1.12-1.40)	1.18 (1.00-1.39)



Squares indicate hazard ratios (HRs), with horizontal lines indicating 95% CIs. H2RA indicates histamine 2 receptor antagonist; PPI, proton pump inhibitor; PY, person-years.

[a] Exposed: 84 263; unexposed: 84 263 (1:1 matching).

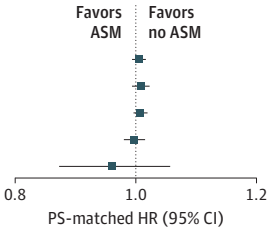
[b] Exposed: 7496; unexposed: 29 984 (1:4 matching).

[c] Exposed: 74 188; unexposed: 74 188 (1:1 matching).

Figure 4. Risk of Allergic Diseases in Children Following Prenatal and Infant Exposure to Acid-Suppressive Medications (ASMs) in Sibling-Matched Analyses

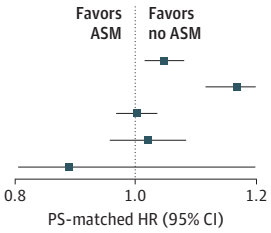
A Prenatal exposure analyses

Allergic disease	Exposed (n = 306 406)		Unexposed (n = 324 539)		Incidence rate difference/ 1000 PY	HR (95% CI)	
	Events, No.	Incidence rate, per 1000 PY	Events, No.	Incidence rate, per 1000 PY		Crude	Adjusted
Any	242 193	324.2	263 844	319.9	4.3	1.00 (1.00-1.01)	1.01 (1.00-1.01)
Asthma	93 821	60.9	107 234	61.5	-0.6	0.95 (0.95-0.96)	1.01 (1.00-1.02)
Allergic rhinitis	214 240	210.9	234 051	203.3	7.6	1.02 (1.02-1.03)	1.01 (1.00-1.02)
Atopic dermatitis	56 500	32.1	66 860	33.6	-1.6	0.91 (0.90-0.92)	1.00 (0.98-1.01)
Food allergy	1315	0.6	1429	0.6	0.0	1.01 (0.94-1.09)	0.96 (0.88-1.06)



B Infant exposure analyses

Allergic disease	Exposed (n = 37 227)		Unexposed (n = 42 835)		Incidence rate difference/ 1000 PY	HR (95% CI)	
	Events, No.	Incidence rate, per 1000 PY	Events, No.	Incidence rate, per 1000 PY		Crude	Adjusted
Any	28 315	223.3	32 832	215.9	7.4	1.04 (1.03-1.06)	1.03 (1.00-1.05)
Asthma	11 831	56.0	13 041	50.6	5.5	1.09 (1.07-1.12)	1.13 (1.09-1.17)
Allergic rhinitis	24 587	153.7	28 852	152.6	1.1	1.01 (0.99-1.03)	0.98 (0.96-1.01)
Atopic dermatitis	4911	19.1	6068	19.8	-0.7	0.95 (0.92-0.99)	0.99 (0.94-1.04)
Food allergy	150	0.5	158	0.5	0.1	1.12 (0.89-1.40)	1.01 (0.75-1.36)



Squares indicate hazard ratios (HRs), with horizontal lines indicating 95% CIs. PS indicates propensity score; PY, person-years.

Comparison With Previous Studies

Prenatal Exposure to ASMs and Allergic Diseases

Two meta-analyses,[4,5] both including 8 observational studies, showed that prenatal exposure to ASMs was associated with a higher risk of asthma in offspring compared with no prenatal exposure (pooled risk ratios, 1.45 [95% CI, 1.35-1.56][4] and 1.36 [95% CI, 1.16-1.61][5]). However, existing studies did not account for potential confounding by indication and within-family shared factors, which are important factors associated with allergic diseases. In the current study, which controlled for numerous potential confounders, including indications (eg, GERD), we found no meaningful associations between prenatal ASM use and allergic diseases in offspring. Thus, our findings suggest that the previous findings may have been confounded by unmeasured factors.

Infant Exposure to ASMs and Allergic Diseases

We found significantly higher risk of allergic diseases associated with infant ASM use, but the risk was substantially lower than in existing literature. One cohort study of US data[8] found that the use of H2RAs and PPIs in the first 6 months of life was associated with elevated risk of asthma (HR, 1.41; 95% CI, 1.31-1.52), allergic rhinitis (HR, 1.44; 95% CI, 1.35-1.52), atopic dermatitis (HR, 1.12; 95% CI, 1.09-1.14), and food allergy (HR, 2.18; 95% CI, 2.04-2.33), and a similar risk of food allergy was also found in another cohort study of US children.[52] Two cohort studies using data from Italy[7] and Sweden[6] found parallel risk of asthma associated with ASM use in the first 6 months of life (Italy: HR, 1.66 [95% CI, 1.50-1.84]; Sweden: HR, 1.83 [95% CI, 1.65-2.03]). Nevertheless, our estimates were generally smaller in magnitude (HRs ranged from 1.02 [allergic rhinitis] to 1.28 [food allergy]) than those of prior studies (HRs ranged from 1.12 [allergic rhinitis] to 2.59 [food allergy]).[8] This may be due to regional factors (eg, ethnicity, insurance system, and medication use behavior); for instance, the present study had different prescription patterns with fewer days prescribed for PPIs (median, 7-day [IQR, 4-15 days]) and H2RAs (median, 4 days [IQR, 3-7 days]) compared with a US cohort study (PPIs: median, 60 days [IQR, 30-91 days]; H2RAs: median, 60 days [IQR, 39-92 days]).[8] Moreover, the differences in the rates of exposure or outcome incidence and duration of follow-up could have led to inconsistent findings among studies. For instance, compared with previous studies, the current study generally had lower exposure rates of PPIs, comparable incidence rates of asthma and allergic rhinitis, substantially lower rates of atopic dermatitis and food allergy (eTable 12 in the Supplement), and a shorter follow-up duration for allergic diseases overall but a longer duration for asthma (eTable 13 in the Supplement). Nevertheless, we additionally controlled for indications of ASMs and familial factors, had diagnosis and prescription data from all settings (including inpatient and outpatient and primary and specialist care), and had minimal exposure misclassification (PPIs were unavailable as over-the-counter medications); these factors were not or were only partially accounted for in previous studies.[6-8] Our findings therefore provide a comprehensive investigation of the association between ASM use during infancy and the risk of allergic diseases in childhood, complemented with advanced epidemiological and analytical methods that address previously unaccounted factors or limitations.

Biological Plausibility

With exact pathophysiological mechanisms unclear to date, there are several hypotheses with regard to the association of ASMs with allergic diseases. One hypothesis includes decreased gastric acid, subsequently impairing peptic digestion to mask food antigens as allergens and facilitate immunoglobulin E production to predispose children to allergic disease.[53,54] Another hypothesis involves the dysbiosis of the gut and lung, which influences asthma pathogenesis by promoting bronchial hyperresponsiveness and bronchoconstriction.[55] Moreover, there is accumulating evidence that crosstalk between the gut and the lung, the so-called gut-lung axis, is important for maintaining immune homeostasis.[56,57] Thus, dysbiosis of the gut and the lung and their bidirectional exchange caused by ASMs in infancy might increase the risk of asthma onset. Furthermore, given that the lung microbiome is primarily shaped during very early life, infant exposure to ASMs can readily alter its composition to affect asthma development.[16,58,59] Whereas infant exposure to ASMs affects the newborn directly, prenatal ASM use, which primarily alters the mother's physiological system, indirectly affects the offspring. Thus, these different mechanisms can possibly explain the heterogeneous findings between the 2 exposures in this study.

Strengths and Limitations

A strength of this comprehensive study is use of a nationwide database of 4 149 257 mother-child pairs to investigate the association between prenatal and infant ASM exposure separately and the risk of allergic diseases in children. The large samples with adequate power allowed for analyses by drug class (PPI, H2RA) and its dose-response relationship and sibling-matched analyses with precision. We also identified exposure to ASMs that was free from recall bias by using routinely collected electronic prescribing records. Moreover, we conducted sibling-matched analyses and various sensitivity analyses (eg, restricting the study cohort to patients with ASM-related indications) to address the possibility of confounding by underlying conditions, familial factors, or exposure and outcome misclassification. In addition, a deterministic linkage of records between mothers and offspring based on algorithms developed by the NHIS further enhanced the accuracy and reliability of our findings.

Several limitations should be kept in mind when interpreting the results. First, exposure misclassification was possible given the uncertainty of whether patients actually took the ASM prescribed. However, in the sensitivity analysis that used 2 or more ASM prescriptions, we found similar results to our primary analyses, providing support. Exposure misclassification, although minimal, was also possible as low-dose H2RAs are restrictively available over-the-counter purchases in Korea; PPIs are only available with prescriptions. Second, the possibility of outcome misclassification cannot be ruled out as our outcomes were based on relevant *ICD-10* diagnosis codes. However, the outcome definitions adopted in this study have been widely used in several previous clinical studies[42-46] and also well validated across various claims data.[60-62] Moreover, a Korean validation study found a high positive predictive value for overall diagnoses in the database (approximately 82%),[37] suggesting that the diagnostic records are fairly valid, under reasonable assumption. Third, the NHIS database is not primarily used for research purposes, and thus, factors that may have affected the risk of study outcomes (eg, smoking) were available for only a subset of participants; the result of the sensitivity analysis restricted to women with smoking and BMI data indicated that these factors were unlikely to affect the interpretation of our findings. Fourth, because we used population data from South Korea, it is unclear whether the results are generalizable to or replicable in other populations. Fifth, protopathic bias may have been possible in infant exposure analyses, as some patients may present with early asthmatic symptoms that mimic GERD clinical manifestation. However, this is unlikely to explain our observed association, as we observed a consistently significant association in the sensitivity analysis that redefined asthma as an incident case after age 2 years. Sixth, this study had a shorter follow-up for allergic diseases overall than a prior study.[8] Yet, the study had longer follow-up for the individual outcome of asthma than existing studies,[6,7] supporting the validity of our findings by having sufficient follow-up for patients to an age when the disease of interest typically presents. Seventh, our study cohort was restricted to women with pregnancies resulting in live births; however, as existing data showed no association of ASM use with live birth,[63] this study had little potential for collider bias (ie, spurious negative associations of prenatal exposure with allergic diseases in children).[64] Eighth, despite applying several advanced epidemiological methods, including a sibling-matched analysis, in common with other pharmacoepidemiological studies using a claims database, residual confounding from disease severity, socioeconomic status (eg, educational level), and microbiome or environmental data (eg, air pollution) may still have been present.

Conclusions

This study's findings suggest that there is no association between prenatal exposure to ASMs and risk of allergic diseases in offspring. However, our data suggest that infant exposure to ASMs is associated with a higher risk of developing asthma compared with no ASM exposure, although the magnitude of the association was more modest than previously reported. Clinicians should therefore carefully weigh the benefits of prescribing ASMs to children against its small but potential risk of asthma, accompanied by subsequent close monitoring for any clinically relevant safety signals.

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Acquisition, analysis, or interpretation of data: Noh, Jeong, E-Y. Choi, Pasternak, Nordeng, Bliddal, Man, Yon, Shin.
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