

Infant Exposure to Acid Suppressant Medications Increases Risk of Recurrent Wheeze and Asthma in Childhood



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What is already known about this topic? Acid suppressant medications (ASMs) are commonly prescribed during infancy, but little is known about the relationship between ASM exposure and risk of childhood asthma and atopy.

What does this article add to our knowledge? In a cohort of children with a history of severe bronchiolitis, ASM exposure during infancy increased risk of recurrent wheeze and asthma.

How does this study impact current management guidelines? Clinicians should carefully consider the risks and benefits of ASM during infancy.

BACKGROUND: Acid suppressant medications (ASMs) are commonly prescribed in infancy. Little is known about the relationship between ASM exposure and risk of childhood asthma and atopic conditions.

OBJECTIVE: We sought to examine the association between infant ASM exposure and risk for developing recurrent wheeze, allergen sensitization, and asthma in early childhood.

METHODS: We used data from a diverse, multicenter, prospective cohort study of 921 infants with a history of bronchiolitis. ASM exposure (histamine-2 receptor antagonists and/or proton pump inhibitors) during infancy (age: <12 months) was ascertained by parent report and medical record

review. The outcomes were recurrent wheeze by age 3 years, early childhood allergen sensitization (serum specific IgE), and asthma by age 6 years. We constructed multivariable Cox proportional hazards models and multivariable logistic regression models adjusting for multiple confounders.

RESULTS: Of the 921 children in the cohort, 202 (22%) were exposed to ASMs during infancy. Compared with unexposed children, those exposed to ASM were more likely to develop recurrent wheeze by age 3 years (adjusted hazard ratio: 1.58, 95% confidence interval [CI]: 1.20-2.08, $P = .001$) and asthma by age 6 years (adjusted odds ratio: 1.66, 95% CI: 1.22-2.27, $P = .001$). ASM exposure during infancy was not significantly associated with the development of early childhood allergen sensitization (adjusted odds ratio: 1.00, 95% CI: 0.70-1.44, $P = .99$).

CONCLUSIONS: Although exposure to ASMs during infancy does not increase the risk of allergen sensitization in early childhood, ASM exposure during infancy increases the risk of recurrent wheeze and asthma during early childhood. © 2022 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2022;10:2935-40)

Key words: Acid suppressant medications; Asthma; Recurrent wheeze; Childhood

Recurrent wheeze and asthma are common conditions of childhood associated with a significant morbidity and a risk for mortality.^{1,2} Allergen sensitization (eg, allergen specific IgE [sIgE]) may predispose to atopic conditions including recurrent wheeze and childhood asthma.^{3,4}

Acid suppressant medications (ASMs), including proton pump inhibitors (PPIs) and histamine-2 receptor antagonists (H2RAs), are commonly prescribed and purchased medications in the United States.⁵⁻⁷ Infants are often prescribed ASM empirically for the treatment of gastroesophageal reflux or gastroesophageal reflux disease (GERD) despite little evidence

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Abbreviations used

ASM- Acid suppressant medication
 BMI- Body mass index
 CI- Confidence interval
 GERD- Gastroesophageal reflux disease
 H2RA- Histamine-2 receptor antagonist
 HR- Hazard ratio
 OR- Odds ratio
 PPI- Proton pump inhibitor
 sIgE- Specific IgE

for their efficacy.^{8,9} Although exposure to ASM prenatally has been associated with an increased risk of recurrent wheeze, asthma, and other atopic conditions,¹⁰⁻¹³ little is known about the association between infant ASM exposure and risk of developing childhood respiratory conditions and allergen sensitization.^{14,15}

Our objective was to examine the associations of infant ASM exposure with the risk of developing recurrent wheeze by age 3 years, allergen sensitization in early childhood, and asthma by age 6 years in a high-risk population. This study population includes children with a history of severe bronchiolitis during infancy, who are at a known increased risk of developing both recurrent wheeze and asthma in childhood.¹⁶⁻¹⁸

METHODS**Study design and study population**

The 35th Multicenter Airway Research Collaboration is an ongoing multicenter prospective cohort study of infants (age: <1 year) enrolled during hospitalization for bronchiolitis during the 2011-2014 winter seasons (see Online Repository text at www.jaci-inpractice.org). Study design and participants have been described previously.¹⁹ Infants with known heart/lung disease and those born at <32 gestational weeks were excluded.

We enrolled 1016 participants, of whom 921 were followed longitudinally. At enrollment, a parent or guardian completed a detailed in-person interview to capture demographic, parental, perinatal, and child health information. The subject's parent/guardian subsequently underwent a structured telephone interview by trained study staff every 6 months through age 6 years. In addition, participants were invited to attend an in-person examination in early childhood (age range: 36-67 months, median age: 45 months). At enrollment, blood samples and nasopharyngeal aspirates were collected using a standardized protocol. Blood samples were collected again at the early childhood examination.

A comprehensive medical record review was completed by trained physician chart reviewers, including a review of all available medical records in the first year of life: hospitalizations, primary care visits, specialist visits, emergency department visits, and urgent care visits.

The study was approved by the institutional review board at each participating site and conducted in accordance with Good Clinical Practice Standards. Written informed consent was obtained from the parent or guardian of each participant during enrollment.

Exposure

Data on infant exposure to ASM were obtained from a combination of 2 sources: parent report and comprehensive medical record review. ASM use includes H2RA and PPIs. At the age 12-month interview, parents were asked, "Some children are given H2RAs or PPIs for reflux (heartburn). Since your child was born, until his/her

first birthday, approximately what was the total length of time (in weeks) that he/she took H2RA or PPIs for any reason." In addition, trained physician chart reviewers abstracted the duration of H2RA or PPI use within the first year of participants' life from all available medical records. We defined infant exposure to ASM (PPI or H2RA) as ASM use >0 weeks in duration before age 12 months, ascertained by the physician review of both data sources (parent report and medical record review). If the duration of exposure was not known on the combined outcome but data from the medical record review indicated the use of ASM, participants were considered exposed to ASM.

Covariates

Covariates obtained from parent interview at enrollment included infant age at enrollment, sex, race and ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, and other), health insurance type, maternal history of asthma, paternal history of any atopic conditions, prenatal exposure to ASM, prenatal smoke exposure, smoke exposure in the home reported at enrollment, premature birth (≤ 37 weeks and >32 weeks of gestational age), and mode of delivery. Median household income by ZIP code was obtained by linking the home ZIP code at enrollment with median household income estimates from Esri Business Analyst Desktop (Esri, Redlands, Calif). Nasopharyngeal aspirates were tested for respiratory syncytial virus types A and B using real-time reverse-transcriptase polymerase chain reaction. Data on factors related to severity of bronchiolitis including intensive care unit admission, use of continuous positive airway pressure, apnea, and length of hospitalization (days) were obtained from the review of medical records from participants' index hospital visit. Infant eczema was ascertained based on parent-reported data (at enrollment and the age 12-month interview) and the physician review of medical records.²⁰ Infant body mass index (BMI)-for-age z -scores were calculated using 6-month height and weight measurements abstracted from the infant medical chart review. Infant obesity was defined as having a BMI-for-age z -score of ≥ 1.64 .²¹

Outcomes

Recurrent wheeze by 3 years of age was defined per the 2007 National Institutes of Health asthma guidelines using parent-reported data through age 36 months as (1) having at least 2 corticosteroid-requiring exacerbations within 6 months, or (2) having at least 4 wheezing episodes within 1 year, each lasting at least 1 day and affecting sleep.^{17,22}

Serum samples from early childhood were analyzed for total IgE level and allergen sensitization by sIgE by ImmunoCAP at the Phadia Immunology Reference Laboratory (Portage, Mich). Infancy and early childhood samples (median age 42 months) were tested for food sIgE to cow's milk, egg white, peanut, cashew nut, and walnut. In addition, early childhood samples were tested for sIgE to grasses, trees, weeds, molds, cat, dog, cockroach, mouse, and dust mites (*Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*). sIgE ≥ 0.35 kU/L was considered positive. We used sIgE results from early childhood to create several variables: food allergen sensitization (yes or no), aeroallergen sensitization (yes or no), any allergen sensitization (ie, food or aeroallergen; yes or no), and number of allergens with sensitization (0, 1, 2, or ≥ 3).

Asthma by age 6 years was defined by using a previously validated epidemiologic definition of asthma in childhood. This included using parent-reported data through age 6 years and clinician

TABLE I. Demographic and clinical characteristics by exposure to acid suppressant medications (ASM) during infancy

Characteristics	Overall (n = 920), n (%)	ASM exposed (n = 202), n (%)	ASM unexposed (n = 718), n (%)	P value*
Age at enrollment (mo)				.07
<2	272 (30)	70 (35)	202 (28)	
≥2	648 (70)	132 (65)	516 (72)	
Sex				.21
Female	368 (40)	73 (36)	295 (41)	
Race and ethnicity				<.001
Non-Hispanic White	400 (43)	114 (56)	286 (40)	
Non-Hispanic Black	210 (23)	39 (19)	171 (24)	
Hispanic	275 (30)	46 (23)	229 (32)	
Other	35 (4)	3 (2)	32 (4)	
Health insurance				.002
Public or none	546 (59)	101 (50)	445 (62)	
Private	372 (41)	101 (50)	271 (38)	
Median household income estimated by ZIP code at enrollment				.13
<\$40,000	314 (34)	60 (30)	254 (35)	
≥\$40,000	606 (66)	142 (70)	464 (65)	
Maternal history of asthma	195 (21)	44 (22)	151 (21)	.85
Maternal history of any atopic condition†	510 (55)	111 (55)	399 (56)	.88
Prenatal ASM exposure	144 (16)	57 (29)	87 (12)	<.001
Prenatal smoke exposure	125 (14)	24 (12)	101 (14)	.39
Smoke exposure at home reported at enrollment	138 (15)	26 (13)	112 (16)	.34
Premature birth (≤37 wk)	171 (19)	52 (26)	119 (17)	.003
Born by C-section	311 (34)	73 (36)	238 (34)	.48
Respiratory syncytial virus infection at enrollment	751 (82)	159 (79)	592 (82)	.23
Severity of bronchiolitis (intensive care unit, intubation, continuous positive airway pressure, or apnea)	146 (16)	51 (25)	95 (13)	<.001
Hospital length of stay, median (interquartile range) (d)	2 (1-3)	2 (2-4)	2 (1-3)	.002‡
Hospital length of stay (d)				.07
<3	552 (60)	110 (54)	442 (62)	
Obesity at age 6 mo				.08
Not obese	688 (75)	163 (81)	525 (73)	
Obese	92 (10)	14 (7)	78 (11)	
Missing	140 (15)	25 (12)	115 (16)	

Results are counts and column percentages, unless otherwise indicated.

*P values from the χ^2 or Fisher exact test, as appropriate. Bold text denotes $P < .05$.

†Asthma, allergic rhinitis, eczema, food allergy, medication allergy, or other allergy.

‡P values from the Kruskal-Wallis test. Bold text denotes $P < .05$.

diagnosis of asthma by age 6 years with either asthma medication use or asthma symptoms during age 5-5.9 years.²³

Statistical analysis

For each outcome (recurrent wheeze, allergen sensitization, and asthma), the analytic cohort was defined as participants in the cohort with complete exposure and outcome data. For the recurrent wheeze analysis, we excluded 7 participants for whom ASM exposure may have occurred after the development of recurrent wheeze. To examine the associations of ASM exposure with covariates, we performed bivariate analyses using χ^2 tests, Fisher's exact tests, and Kruskal-Wallis tests, as appropriate.

We used multivariable Cox proportional hazards models to examine the associations between ASM exposure and recurrent wheeze by age 3 years, with unadjusted, partially adjusted, and adjusted multivariable models. The assumption of proportional hazards was verified using Schoenfeld residuals for all the Cox

proportional hazards. Cox models were stratified by sex because hazards were not proportional by sex according to Schoenfeld residuals. We plotted the association of ASM exposure and recurrent wheeze by age 3 years using the adjusted Cox proportional hazards model using the Kaplan-Meier estimator plot.

We used multivariable logistic regression models to examine the associations between ASM exposure and early childhood allergen sensitization outcomes, using unadjusted, partially adjusted, and adjusted models. Similarly, we used unadjusted, partially adjusted, and adjusted multivariable logistic regression models to examine the association between ASM exposure and asthma by age 6 years. All covariates included in the models were determined *a priori* based on the current understanding of the biologic model.^{13,14} All models accounted for potential clustering by site using robust standard errors.

Because of potential effect modification, we assessed for interaction by race and ethnicity, infant eczema, and prenatal ASM

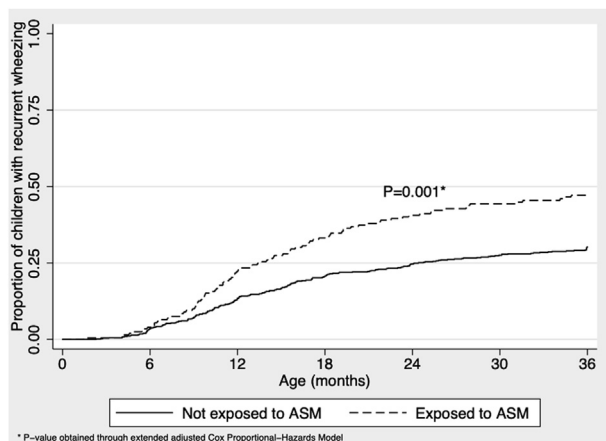


FIGURE 1. Incidence of recurrent wheeze by age 3 years by acid suppressant medication (ASM) exposure during infancy.

exposure by adding product terms to the parsimonious partially adjusted models. We performed a sensitivity analysis using a stricter definition of exposure, in which we defined those with unknown ASM exposure from the combined outcome and known exposure from the medical record review, as unexposed to ASM. To evaluate for a possible dose-response relationship, we performed additional sensitivity analyses modeling duration of ASM exposure as a continuous variable (weeks of exposure) and a categorical variable (<2 weeks, ≥2 weeks and <10 weeks, ≥10 weeks and <28 weeks, ≥28 weeks). All analyses were performed using Stata 15.1 (Stata Corp, College Station, Texas). All *P* values were 2-tailed, with *P* < .05 considered statistically significant.

RESULTS

Recurrent wheeze

Among 920 participants in the cohort with data available for the ASM exposure, 202 (22%) were exposed to ASM during infancy. Of these 202 participants, 178 had ASM exposure duration data available, with a median duration of ASM use of 13.7 weeks (interquartile range: 4-31 weeks). Most exposed children (177 of 202, 77%) had a documented diagnosis of GERD or reflux during the first year of life. The exposed infants were more likely to be non-Hispanic White, privately insured, exposed to ASM prenatally as compared with those who were not exposed to ASM (Table I). Similar associations of ASM exposure with characteristics were observed when descriptive analysis was limited to the allergen sensitization analytic cohort (Table E1, available in this article's Online Repository at www.jaci-inpractice.org). In the allergen sensitization analytic cohort, a higher proportion of participants exposed to ASM were age <2 months at enrollment (40%) compared with participants unexposed to ASM (28%).

The analytical cohort for the recurrent wheeze analysis included 913 longitudinal cohort participants. Overall, 289 (32%) participants developed recurrent wheeze by age 3 years. Among participants exposed to ASM during infancy, 84 of 195 (43%) developed recurrent wheeze, compared with 205 of 718 (29%) among those unexposed. Infants exposed to ASM had a significantly higher rate of developing recurrent wheeze by age 3 years during infancy in the unadjusted model (hazard ratio

[HR]: 1.65, 95% confidence interval [CI]: 1.28-2.12, *P* < .001, Figure 1, Table II). This association persisted after adjustment for multiple covariates (adjusted HR: 1.58, 95% CI: 1.20-2.08, *P* = .001).

Sensitization

The analytical cohort for the allergen sensitization analysis included 610 participants, of whom 176 (29%) developed food sensitization, 163 (27%) developed aeroallergen sensitization, and 252 (42%) were sensitized to a food or aeroallergen. Among participants exposed to ASM during infancy, 51 of 128 (40%) developed sensitization to a food or aeroallergen, compared with 201 of 478 (42%) among those unexposed. Exposure to ASM was not significantly associated with food sensitization, aeroallergen sensitization, or any (food or aeroallergen) sensitization, in the unadjusted, partially adjusted, or adjusted model (Table II). For example, the adjusted odds ratio (OR) for food or aeroallergen sensitization associated with infant ASM exposure was 1.00 (95% CI: 0.70-1.44, *P* = .99).

Asthma

The analytical cohort for the asthma analysis included 861 participants, of whom 239 (28%) developed asthma by age 6 years. Among participants exposed to ASM in infancy, 64 of 189 (34%) developed asthma by age 6 years, compared with 175 of 672 (26%) among those unexposed. The odds of developing asthma by age 6 years were significantly higher among those exposed to ASM during infancy in the unadjusted model (OR: 1.45, 95% CI: 1.09-1.94, *P* = .01, Table II). This association persisted after adjustment for multiple covariates (adjusted OR: 1.66, 95% CI: 1.22-2.27, *P* = .001).

Effect modification

We found evidence that the association of infant ASM exposure and recurrent wheeze by age 3 years was modified by prenatal ASM exposure in the partially adjusted model (*P* interaction = .004). Specifically, infant ASM exposure was associated with increased rate of recurrent wheeze among participants without prenatal ASM exposure in the partially adjusted model (HR: 1.96, 95% CI: 1.46-2.63, *P* < .001), but not among those with prenatal ASM exposure (HR: 0.78, 95% CI: 0.45-1.37, *P* = .39). There was no evidence of interaction between prenatal and infant ASM exposure in relation to development of any allergen sensitization (*P* interaction = 0.22) or asthma (*P* interaction = .91) in the partially adjusted models. Furthermore, we did not find evidence of interaction in the associations of infant ASM exposure with recurrent wheeze, allergen sensitization, or asthma across race and ethnicity or infant eczema in the partially adjusted models (all *P* interactions > .1).

The associations of infant ASM exposure with recurrent wheeze by age 3 years and asthma by age 6 years persisted using the stricter ASM definition in adjusted models (Table E2, available in this article's Online Repository at www.jaci-inpractice.org). Using ASM exposure as a continuous variable in the multivariable model, participants with a 4-week increase in ASM exposure during infancy were 1.14 times more likely to develop asthma by age 6 years (adjusted OR: 1.14, 95% CI: 1.02-1.29, *P* = .02). In addition, participants with longer than 28 weeks of ASM exposure had increased odds of asthma by age 6 years compared with those with less than 2 weeks of ASM exposure, suggesting a dose-response relationship (partially

TABLE II. Models of acid suppressant medication (ASM) exposure during infancy and development of recurrent wheeze, allergen sensitization, and asthma

Outcomes	Outcome, n (%)	Unadjusted	P value	Partially adjusted*	P value	Adjusted†	P value
Recurrent wheeze by age 3 y‡							
Exposed	84 (43)	1.65 (1.28-2.12)	<.001	1.62 (1.25-2.10)	<.001	1.58 (1.20-2.08)	.001
Unexposed	205 (29)	1.00 (ref)		1.00 (ref)		1.00 (ref)	
IgE sensitization in early childhood: food§							
Exposed	36 (28)	0.94 (0.56-1.58)	.82	1.00 (0.63-1.61)	.99	1.02 (0.65-1.61)	.94
Unexposed	140 (29)	1.00 (ref)		1.00 (ref)		1.00 (ref)	
IgE sensitization in early childhood: aeroallergen§							
Exposed	35 (27)	1.03 (0.64-1.66)	.91	1.07 (0.66-1.74)	.78	1.11 (0.65-1.89)	.71
Unexposed	128 (27)	1.00 (ref)		1.00 (ref)		1.00 (ref)	
IgE sensitization in early childhood: any (food or aeroallergen)§							
Exposed	51 (40)	0.91 (0.59-1.41)	.68	0.96 (0.64-1.43)	.84	1.00 (0.70-1.44)	.99
Unexposed	201 (42)	1.00 (ref)		1.00 (ref)		1.00 (ref)	
Asthma by age 6 y§							
Exposed	64 (34)	1.45 (1.09-1.94)	.01	1.58 (1.19-2.09)	.002	1.66 (1.22-2.27)	.001
Unexposed	175 (26)	1.00 (ref)		1.00 (ref)		1.00 (ref)	

BMI, Body mass index.

*The partially adjusted model adjusts for sex, race and ethnicity, insurance, and median household income estimated using ZIP code at enrollment.

†The adjusted model adjusts for variables in the partially adjusted model and age at enrollment (<2 months vs ≥2 months), maternal asthma, prenatal ASM exposure, preterm birth, mode of delivery, respiratory syncytial virus infection at enrollment, and bronchiolitis severity. Models of IgE sensitization were additionally adjusted for atopic dermatitis during infancy. The model for asthma by age 6 years was additionally adjusted for obesity at age 6 months (BMI-for-age z-score <1.64 vs ≥1.64).

‡Results are hazard ratios and 95% confidence intervals from Cox proportional hazards models. Bold text denotes $P < .05$.§Results are odds ratios and 95% confidence intervals from logistic regression models. Bold text denotes $P < .05$.

adjusted P trend = .01) (Table E3, available in this article's Online Repository at www.jaci-inpractice.org).

DISCUSSION

In this large prospective cohort of US children at high-risk for recurrent wheeze and asthma, we found that infant exposure to ASM further increases risk of both recurrent wheeze and asthma in childhood. Infant ASM exposure was not associated with increased risk of allergen sensitization in early childhood.

These findings are consistent with recent publications reporting an increased risk of allergic disease with exposure to ASM. Prenatal exposure to ASM has been associated with childhood asthma, but less is known about exposure during infancy.^{11,12} In a large administrative claims database of children in the United States, those prescribed H2RAs (approximately 17%) or PPIs (approximately 2%) in the first 6 months of life had an increased risk of allergic conditions in childhood including asthma and food allergy.²⁴ In a nationwide study in Sweden, children (age ≤17 years) were matched by age and propensity score for treatment with PPI. The PPI exposed children had a significantly increased risk of asthma with infants and toddlers having the highest risk.²⁵ In our cohort, we report that 22% of infants were exposed to ASMs during infancy.²⁴ Despite little evidence of efficacy and recommendations to limit use from the American Academy of Pediatrics "Choosing Wisely" campaign (2014), use of ASM among infants is not rare.^{26,27}

The mechanism underlying this association is not yet known, but proposed mechanisms include risk of allergen sensitization (eg, allergen sIgE) and deleterious alterations in the airway and gut microbiota are possible.¹⁴ The risk of allergen sensitization has been shown to occur in mice and a small subset of adults

treated with ASM.^{15,28} However, in our study, we found no evidence of increased allergen sensitization in early childhood to food or aeroallergens. This finding suggests that development of sensitization in early childhood may not be the underlying mechanism for increased risk of recurrent wheeze and allergic asthma.

The airway and gastrointestinal microbiota in early childhood are increasingly identified as important in the pathogenesis of the airway respiratory infection, allergic disease, recurrent wheezing, and asthma.²⁹⁻³³ ASMs, like antibiotics, have been shown to alter the microbiota.³⁴ Alterations in the microbiota may be responsible for the increased risk and should be further studied as both exposure to ASM and the microbiota are potentially modifiable.

This study has several limitations including the observational study design that precludes strong statements about causality. Despite our extensive efforts to control for potential confounding, the possibility of unmeasured confounding remains. Misclassification of the exposure is possible but minimized by our use of data from both the parent reported use and medical record review. Our cohort comprises children who are at high-risk for developing recurrent wheeze and subsequent asthma due to their history of severe bronchiolitis. Although the study sample limits the generalizability of our results, it is important to note that severe bronchiolitis is the most common cause for infant hospitalization.¹⁸ It is important to study this high-risk population as these children are at increased risk for recurrent wheeze and asthma and thus, targeted interventions may be warranted. The relationship between ASM exposure and development of severe bronchiolitis is not yet known, but of considerable interest. However, this relationship is not likely to bias the results of our study as all participants shared a history of severe bronchiolitis.

CONCLUSIONS

Exposure to ASM during infancy increases the risk of developing recurrent wheeze and asthma in children with a history of severe bronchiolitis. Infant exposure to ASM does not increase the risk of allergen sensitization in early childhood, suggesting that other mechanisms such as alterations in the microbiota may underlie these findings. ASMs should be used in infants only when necessary, and all prescribers should consider the risks and benefits before initiation of therapy.

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ONLINE REPOSITORY

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TABLE E1. Demographic and clinical characteristics by exposure to acid suppressant medications (ASMs) during infancy, among participants in the allergen sensitization analysis

Characteristics	Overall (n = 610), n (%)	ASM exposed (n = 129), n (%)	ASM unexposed (n = 481), n (%)	P value*
Age at enrollment (mo)				.01
<2	187 (31)	51 (40)	136 (28)	
≥2	423 (69)	78 (60)	345 (72)	
Sex				.46
Female	249 (41)	49 (38)	200 (42)	
Race and ethnicity				.009
Non-Hispanic White	254 (42)	69 (53)	185 (38)	
Non-Hispanic Black	145 (24)	28 (22)	117 (24)	
Hispanic	192 (31)	31 (24)	161 (33)	
Other	19 (3)	1 (1)	18 (4)	
Health insurance				.05
Public or none	361 (59)	67 (52)	294 (61)	
Private	247 (41)	62 (48)	185 (39)	
Median household income estimated by ZIP code at enrollment				.14
<\$40,000	218 (36)	39 (30)	179 (37)	
≥\$40,000	392 (64)	90 (70)	302 (63)	
Maternal history of asthma	131 (22)	25 (20)	106 (22)	.51
Maternal history of any atopic condition†	332 (54)	67 (52)	265 (55)	.52
Prenatal ASM exposure	95 (16)	36 (29)	59 (13)	<.001
Prenatal smoke exposure	65 (11)	11 (9)	54 (11)	.36
Smoke exposure at home reported at enrollment	85 (14)	16 (12)	69 (14)	.57
Premature birth (≤37 wk)	119 (20)	33 (26)	86 (18)	.05
Born by C-section	206 (34)	44 (34)	162 (34)	.99
Respiratory syncytial virus infection at enrollment	505 (83)	102 (79)	403 (84)	.21
Severity of bronchiolitis (intensive care unit, intubation, continuous positive airway pressure, or apnea)	104 (17)	34 (26)	70 (15)	.002‡
Hospital length of stay, median (interquartile range) (d)	2 (1- 3)	2 (2- 4)	2 (1-3)	.003
Hospital length of stay				.13
<3 d	357 (59)	68 (53)	289 (60)	
Obesity at age 6 mo				.57
Not obese	470 (77)	103 (80)	367 (76)	
Obese	62 (10)	10 (8)	52 (11)	
Missing	78 (13)	16 (12)	62 (13)	

Results are counts and column percentages, unless otherwise indicated.

*P values from the χ^2 or Fisher exact test, as appropriate. Bold text denotes $P < .05$.

†† Asthma, allergic rhinitis, eczema, food allergy, medication allergy, or other allergy.

‡P values from the Kruskal-Wallis test. Bold text denotes $P < .05$.

TABLE E2. Models of acid suppressant medication (ASM) exposure (strict definition) during infancy and development of recurrent wheeze, allergen sensitization, and asthma

Outcomes	Outcome, n (%)	Unadjusted	P value	Partially adjusted*	P value	Adjusted†	P value
Recurrent wheeze by age 3 y‡							
Exposed	71 (26)	1.72 (1.30-2.27)	<.001	1.70 (1.28-2.26)	<.001	1.61 (1.19-2.17)	.002
Unexposed	79 (13)	1.00 (ref)		1.00 (ref)		1.00 (ref)	
IgE sensitization in early childhood: food§							
Exposed	23 (24)	0.78 (0.42-1.43)	.42	0.84 (0.49-1.46)	.54	0.85 (0.51-1.41)	.53
Unexposed	140 (29)	1.00 (ref)		1.00 (ref)		1.00 (ref)	
IgE sensitization in early childhood: aeroallergen§							
Exposed	25 (27)	0.99 (0.56-1.76)	.98	1.06 (0.58-1.92)	.85	1.12 (0.60-2.08)	.73
Unexposed	128 (27)	1.00 (ref)		1.00 (ref)		1.00 (ref)	
IgE sensitization in early childhood: any (food or aeroallergen)§							
Exposed	35 (37)	0.82 (0.50-1.35)	.43	0.88 (0.55-1.39)	.58	0.91 (0.61-1.36)	.66
Unexposed	201 (42)	1.00 (ref)		1.00 (ref)		1.00 (ref)	
Asthma by age 6 y§							
Exposed	45 (20)	1.29 (0.89-1.88)	.18	1.45 (1.01-2.08)	.05	1.46 (1.02-2.09)	.04
Unexposed	99 (17)	1.00 (ref)		1.00 (ref)		1.00 (ref)	

BMI, Body mass index.

*The partially adjusted model adjusts for sex, race and ethnicity, insurance, and median household income estimated using ZIP code at enrollment.

†The adjusted model adjusts for variables in the partially adjusted model and age at enrollment (<2 months vs ≥2 months), maternal asthma, prenatal ASM exposure, preterm birth, mode of delivery, respiratory syncytial virus infection at enrollment, and bronchiolitis severity. Models of IgE sensitization were additionally adjusted for atopic dermatitis during infancy. The model for asthma by age 6 years was additionally adjusted for obesity at age 6 months (BMI-for-age z-score <1.64 vs ≥1.64).

‡Results are hazard ratios and 95% confidence intervals from Cox proportional hazards models. Bold text denotes $P < .05$.

§Results are odds ratios and 95% confidence intervals from logistic regression models. Bold text denotes $P < .05$.

TABLE E3. Sensitivity analysis models of duration of infant acid suppressant medication (ASM) exposure and asthma by age 6 years

Infant ASM exposure	Total, (n = 896), n (%)	Unadjusted	P value	P trend*	Partially adjusted†	P value	P trend*	Expanded adjusted‡	P value	P trend*
ASM (categorical)				.05			.01			.02
ASM <2 wk	746 (83)	1.00 (ref)	—		1.00 (ref)	—		1.00 (ref)	—	
ASM ≥2 wk and <10 wk	44 (5)	1.21 (0.66-2.22)	.53		1.34 (0.74-2.44)	.33		1.33 (0.82-2.14)	.25	
ASM ≥10 wk and <28 wk	52 (6)	0.91 (0.40-2.06)	.82		1.01 (0.44-2.30)	.99		1.04 (0.45-2.41)	.93	
ASM ≥28 wk	54 (6)	1.75 (1.14-2.70)	.01		2.11 (1.31-3.40)	.002		2.09 (1.22-3.59)	.007	

Results are odds ratios and 95% confidence intervals from logistic regression models.

Bold text denotes $P < .05$.

BMI, Body mass index.

*P trends were obtained using a continuous version of the midpoint of each ASM exposure duration category for each model. Bold text denotes $P < 0.05$.

†The partially adjusted model adjusts for sex, insurance, race and ethnicity, and median household income estimated using ZIP code at enrollment.

‡The adjusted model adjusts for variables in the partially adjusted model and age at enrollment (<2 months vs ≥2 months), preterm birth, mode of delivery, maternal asthma, bronchiolitis severity, respiratory syncytial virus infection, prenatal ASM exposure, and obesity at age 6 months (BMI-for-age z-scores <1.64 vs ≥1.64).