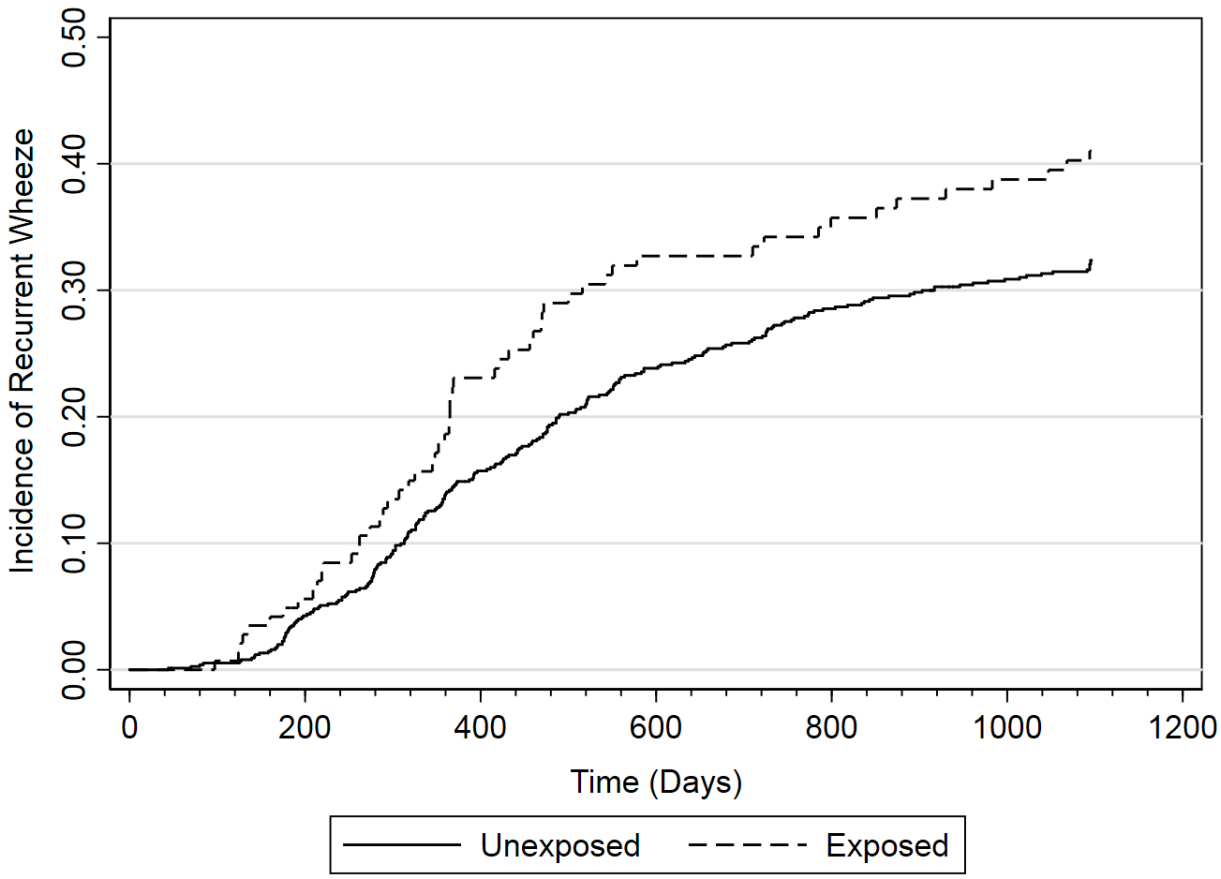
Incidence of Recurrent Wheeze
0.00
0.10
0.20
0.30
0.40
0.50
0
200
400
600
800
1000
1200
Time (Days)
Unexposed
Exposed

Online Supplement

Title: Prenatal exposure to acid suppressant medications and the risk of recurrent wheeze at 3 years of age in children with a history of severe bronchiolitis

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Detailed Methods

Study Design and Study Population

The 35th Multicenter Airway Research Collaboration (MARC-35) is a multicenter prospective cohort study of infants less than 1 year of age enrolled during an episode of severe bronchiolitis from 2011-2014. Severe bronchiolitis was defined by the need for hospitalization. The study was conducted at 17 sites in the U.S. using a standardized protocol, details of which have been previously published.(E1) Children who met the endpoint of recurrent wheeze prior to study entry were excluded.

We enrolled 1016 children in the study, of which 921 children were followed in the longitudinal cohort. The analytic cohort for the present analysis was defined as the 900 (98%) participants in the longitudinal cohort with complete exposure and outcome data. At the time of enrollment, a parent participated in a detailed in-person interview to capture demographic, parental health, perinatal and child health information. The subject's parent subsequently underwent structured telephone interview by trained study staff every 6 months. Blood samples were obtained from all participants at enrollment. Serum was analyzed for multiple parameters including total immunoglobulin E (IgE) level. Allergen testing was performed by Phadia Immunology Reference Laboratory (Portage, MI). This analysis was a pre-determined secondary analysis.

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 study subject.

Exposure

The maternal use of ASM (PPI or H2RA) during pregnancy was obtained from the parent by questionnaire at enrollment. The following questions were used to determine exposure status:

- "When pregnant with your child, did you/the biological mother take H2 blockers or proton pump inhibitors for gastroesophageal reflux (heartburn, GERD) or ulcers? Examples were provided. Respondents were instructed not to include antacids.
- If the response was yes, they were asked "How many months of the pregnancy did you/she take these medications?"

Outcome

Recurrent wheeze by 3 years of age was defined per the 2007 NIH asthma guidelines: 1) having at least 2 corticosteroid-requiring exacerbations within 6 months, or 2) having at least 4 wheezing episodes within one year, each lasting at least one day and affecting sleep.[E2] This outcome was continually assessed by structured telephone interviews with the parents every 6 months for the first 36 months of life. For all breathing problems detailed information was gathered including date of onset of symptoms, duration of symptoms, effect on sleep, medical care received, and medications used.

Covariates

At enrollment, the parent provided detailed information regarding multiple covariates including demographics of race/ethnicity (non-Hispanic white (NHW), non-Hispanic black (NHB),

Hispanic and other), insurance status, maternal and paternal history of allergic conditions (asthma, allergic rhinitis, food allergy and eczema), maternal smoking during pregnancy, gestational age at birth, child's birth weight, multiple gestation (e.g. twin), mode of delivery, maternal use of antibiotics during pregnancy and child's health prior to study enrollment. Household income at enrollment was estimated based on median household income by ZIP code obtained from Esri ArcGIS Business Analyst Desktop (Redlands, CA).

Statistical Analysis

Summary data on demographics and maternal factors were compared using Pearson's χ^2 for categorical variables and Mann-Whitney U test for continuous variables as appropriate. Unadjusted and adjusted hazard ratios (HR) were calculated using Cox proportional hazards modeling stratified by the age of the child at enrollment. The assumption of proportional hazards was verified using Schoenfeld residuals. The hazards for age at enrollment were not proportional over time, thus all multivariable models were specified to stratify by age. Two adjusted models were performed to assess for the effect of potential confounders. The first model adjusted for sociodemographic factors including sex, race/ethnicity and median household income. The fully adjusted model adjusted for sex, race/ethnicity, median household income, maternal history of atopy (asthma, allergic rhinitis, food allergy or eczema), maternal smoking during pregnancy, gestational age at birth, multiple gestation (e.g. twin), mode of delivery and maternal use of antibiotics during pregnancy prior to labor. All covariates included in the model were determined *a priori* based on the current understanding of the biologic model. We performed stratified analysis by race/ethnicity (NHW, NHB and Hispanic) including full adjustment for the potential confounders listed above. Additionally, we performed analysis based on duration of exposure to

ASM during pregnancy (No ASM use, < 2 months of use and ≥ 2 months of use) including full adjustment for potential confounders. Statistical significance was determined by a two-sided $P<0.05$.

Results

The exposed cohort was primarily composed of 65% (93/144) NHW children who were insured privately and had a median household income ≥ $40,000/year. (Table E1) There were no significant differences between the ASM exposed and unexposed groups in the types of viral pathogens isolated during the initial bronchiolitis event. There was no significant difference in the severity of initial bronchiolitis event (ICU admission and intubation). (Table E2)

Although statistical power was low, we performed an exploratory analysis in different racial/ethnic groups and found an adjusted HR above 1.00 for all three major groups: NHW 1.07 (95%CI, 0.69-1.66), NHB 1.34 (95%CI, 0.65-2.79), and Hispanics 2.16 (95%CI 1.07-4.39); the excess risk among Hispanics with prenatal exposure to ASM was statistically significant ($P_{interaction} = 0.045$).

References

E1. Hasegawa K, Stewart CJ, Celedon JC, Mansbach JM, Tierney C, Camargo CA Jr. Serum 25-hydroxyvitamin D, metabolome, and bronchiolitis severity among infants: a multicenter cohort study. Pediatr Allergy Immunol. 2018;29(4):441-45.

E2. Expert Panel Report 3 (EPR-3): guidelines for the diagnosis and management of asthma-summary report 2007. J Allergy Clin Immunol. 2007;120(5 Suppl):S94-138.

Table E1. Baseline characteristics of infants hospitalized for bronchiolitis by prenatal acid
Data are expressed as n (%) unless otherwise indicated suppressant medication exposure and development of recurrent wheeze

Demographics	**Analytical cohort (n=900)**	**ASM exposed with recurrent wheeze (n=56)**	**ASM exposed without recurrent wheeze (n=88)**	**ASM unexposed with recurrent wheeze (n =233)**	**ASM unexposed without recurrent wheeze (n=523)**	**P value**
Age at Enrollment-*months* [median(IQR)]	3.22 (1.67-6.00)	4.47 (2.62-7.52)	2.94 (1.38-5.63)	3.58 (2.07-6.08)	2.96 (1.51 – 5.91)	0.47
Sex						0.92
Female	361 (40)	20 (36)	35 (40)	95 (41)	211 (40)	
Male	539 (60)	36 (64)	53 (60)	138 (59)	312 (60)	
Race/Ethnicity						<0.001
Non-Hispanic White	396 (44)	32 (57)	61 (69)	104 (45)	199 (38)	
Non-Hispanic Black	201 (22)	10 (18)	12 (14)	62 (27)	117 (22)	
Hispanic	268 (30)	13 (23)	14 (16)	60 (26)	181 (35)	
Other	35 (4)	1 (2)	1 (1)	7 (3)	26 (5)	
Insurance Status						<0.001
Private	367 (41)	29 (52)	59 (67)	84 (36)	195 (38)	
Public	519 (58)	25 (45)	29 (33)	146 (63)	319 (61)	
Uninsured	12 (1)	2 (4)	0	2 (1)	8 (2)	
Median Household Income						0.17
< $40,000 per year	304 (34)	14 (25)	23 (26)	81 (35)	186 (36)	
≥ $ 40,000 per year	596 (66)	42 (75)	65 (74)	152 (65)	337 (64)	
Gestational Age at Birth						<0.001
> 40 weeks	352 (39)	20 (36)	18 (20)	93 (40)	221 (42)	
> 37 to 40 weeks	382 (42)	20 (36)	39 (44)	101 (43)	222 (43)	
> 34 to 37 weeks	134 (15)	10 (18)	29 (33)	28 (12)	67 (13)	
> 32 to 34 weeks	32 (4)	6 (11)	2 (2)	11 (5)	13 (2)	
Birth Weight						0.041
< 5 lbs	57 (6)	7 (13)	6 (7)	20 (9)	24 (5)	

≥ 5 lbs	838 (94)	49 (88)	82 (93)	211 (91)	496 (95)	
Mode of Delivery						0.07
Vaginal	589 (66)	28 (50)	57 (65)	160 (69)	344 (66)	
C- Section	310 (34)	28 (50)	31 (35)	73 (31)	178 (34)	
Multiple Birth (i.e. twin)						< 0.001
Yes	41 (5)	6 (11)	10 (11)	6 (3)	19 (4)	
No	859 (95)	50 (89)	78 (89)	227 (97)	504 (96)	
Maternal Antibiotics Prior to Labor						0.010
Yes	242 (27)	22 (40)	30 (35)	67 (29)	123 (24)	
No	647 (73)	33 (60)	55 (65)	161 (71)	398 (76)	
Maternal Smoking During Pregnancy						0.065
Yes	123 (14)	14 (25)	11 (13)	34 (15)	64 (12)	
No	776 (86)	42 (75)	77 (88)	199 (85)	458 (88)	
Maternal History of Asthma						<0.001
Yes	192 (21)	24 (43)	21 (24)	60 (26)	87 (17)	
No	702 (79)	32 (57)	66 (76)	171 (74)	433 (83)	
Maternal History of Atopic Condition*						< 0.001
Yes	208 (23)	22 (39)	28 (32)	61 (26)	97 (19)	
No	689 (77)	34 (61)	59 (68)	172 (74)	424 (81)	

*Atopic conditions include asthma, allergic rhinitis, food allergy and eczema. Abbreviations- ASM: acid suppressant medications, C-section: cesarean section.

Table E2. Viral pathogens and severity of initial bronchiolitis event by prenatal acid suppressant medication exposure

Characteristics of initial bronchiolitis event	**ASM Exposed (n=144)**	**ASM Unexposed (n=756)**	**P value**
Viral Pathogen*			
HRV	31 (22)	152 (20)	0.70
RSV A	86 (60)	445 (59)	0.85
RSV B	29 (20)	180 (24)	0.34
Human metapneumovirus	7 (5)	40 (5)	0.83
Coronavirus	5 (6)	48 (6)	0.72
Adenovirus	5 (3)	37 (5)	0.46
Mycoplasma	2 (1)	9 (1)	0.84
Influenza A	2 (1)	6 (1)	0.49
Influenza B	2 (1)	3 (0.4)	0.14
Parainfluenza 1	0	4 (1)	0.38
Parainfluenza 2	0	2 (0.2)	0.54
Parainfluenza 3	3 (2)	16 (2)	0.98
ICU Admission			0.98
Yes	21(15)	111 (15)	
No	123(85)	645 (85)	
Intubation			0.33
Yes	3 (2)	28 (4)	
No	141 (98)	728 (96)	

Abbreviations: HRV: human rhinovirus, ICU: Intensive care unit, RSV: respiratory syncytial virus. *Children could have no virus detected, one virus or multiple viruses detected.

Figure Legend

Figure E1. Incidence of recurrent wheeze from birth to age 3 years by prenatal exposure to acid suppressant medications