



# Cesarean Delivery and the Risk of Childhood Allergic Rhinitis

Megan Richards, PhD<sup>1</sup>; Jeannette Ferber, MPH<sup>2</sup>; De-Kun Li, MD, PhD<sup>2</sup>; Lyndsey Darrow, PhD<sup>1</sup>

<sup>1</sup>School of Community Health Sciences, University of Nevada, Reno; <sup>2</sup>Division of Research, Kaiser Permanente Northern California



Kaiser Permanente Division of Research

## Cesarean delivery was not associated with allergic rhinitis at follow-up ages of 6, 8 or 10 in a large contemporary US cohort.

### Background

- Allergic rhinitis (AR) is the most common allergic disease worldwide and prevalence has increased over the last century
- Vaginal delivery is one of the earliest sources of microbial exposure for infants
- Early life microbial differences may increase susceptibility to allergic rhinitis later in life
- Previous meta-analysis (Bager, 2014) reported a pooled odds ratio of 1.24 (1.08, 2.43) for the association between C-section and AR

### Objectives

Examine the association between C-section and AR at ages 6, 8, and 10 in a large US cohort using electronic medical records, pharmacy dispensing data, state birth records, and prospectively collected breastfeeding surveys.

### Methods

**Study Population:** Children born in Kaiser Permanente Northern California integrated healthcare system between 2005 and 2014 with follow-up through at least 6 years of age

**Exposure:** Cesarean delivery, overall and sub-classified by the following attributes for births after 2008:

- Exposure to labor
- Exposure to maternal vaginal microbiota
- Medical indication for C-section

**Outcome:** Allergic rhinitis at ages 6, 8, and 10

- Two AR diagnosis codes (ICD-9: 477; ICD-10: J30) at least 30 days apart
- And either: one AR medication (nasal corticosteroid or second generation antihistamine), or a third AR diagnosis code
- At least on diagnosis code or prescription within the last two years

### Statistical Methods

- Modified Poisson regression models with robust variance estimation
- Adjusted for maternal age, education, race, pre-pregnancy BMI, smoking, prenatal antibiotics, maternal asthma and allergies, gender, gestational age, birth weight, NICU admission, birth order, and breastfeeding
- Stratification by potential effect modifiers
- Effect of C-section overall ("primary" model) and estimated separately by exposure to labor, exposure to microbiota, and indication for C-section
- Assessment of bias due to missing data, loss to follow-up, and intrapartum antibiotics

**Figure 1: Demographic characteristics at age 6**

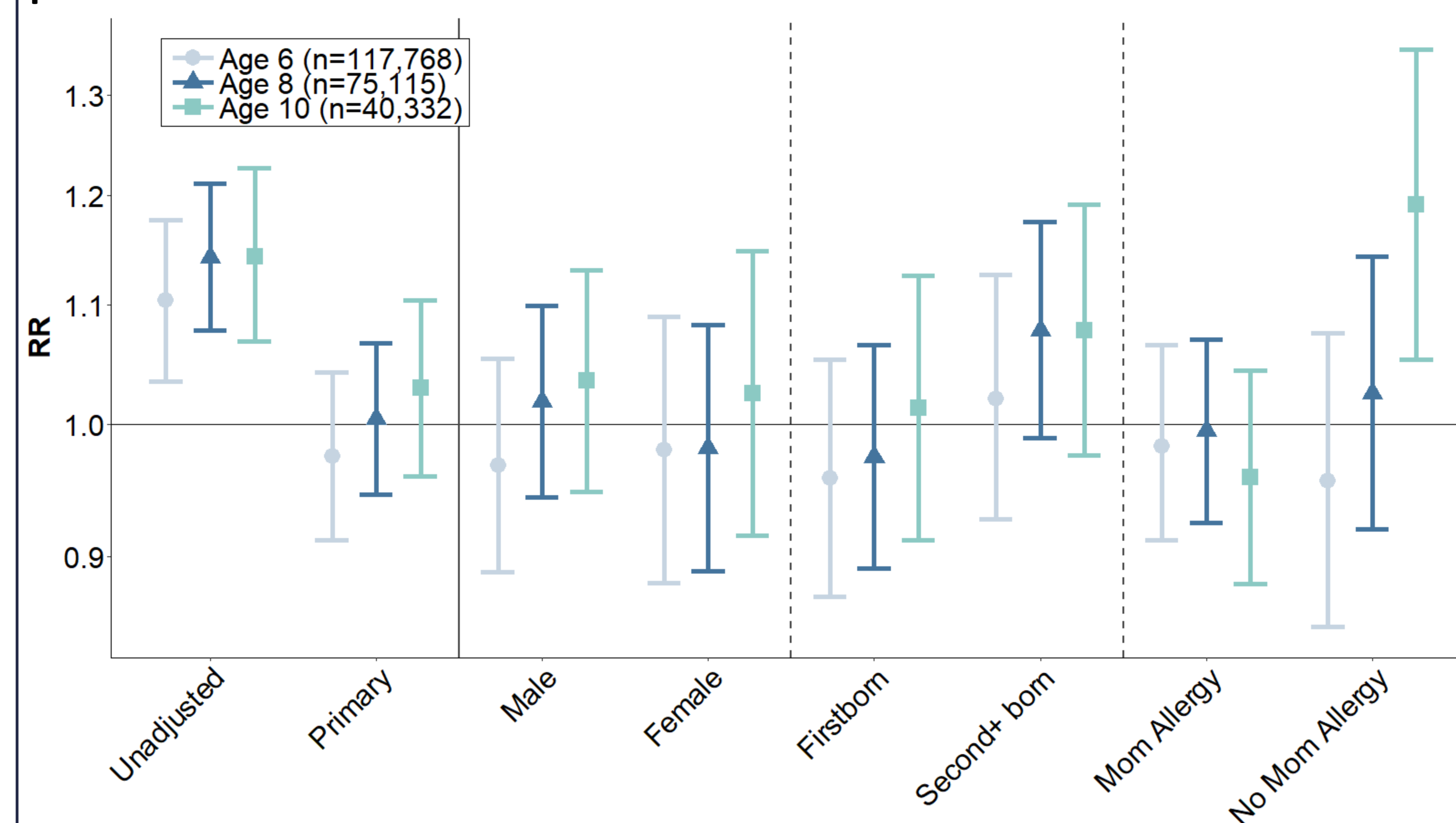
|                                 | % Total <sup>a</sup><br>n = 117,768 | % C-section <sup>b</sup><br>n = 31,708 | % AR <sup>b</sup><br>n = 4,450 |
|---------------------------------|-------------------------------------|--|--------------------------------|
| <b>Maternal Characteristics</b> |                                     |  |                                |
| Age                             |                                     |  |                                |
| <25                             | 10.3%                               | 17.8%                                  | 4.0%                           |
| 25-29                           | 27.5%                               | 22.2%                                  | 3.6%                           |
| 30-34                           | 35.5%                               | 26.9%                                  | 3.7%                           |
| 35-39                           | 21.2%                               | 33.9%                                  | 3.9%                           |
| 40+                             | 5.4%                                | 41.3%                                  | 4.1%                           |
| Education                       |                                     |  |                                |
| <12 years                       | 4.9%                                | 23.6%                                  | 3.8%                           |
| 12-15 years                     | 44.0%                               | 26.6%                                  | 4.2%                           |
| 16+ years                       | 50.1%                               | 27.4%                                  | 3.4%                           |
| Race                            |                                     |  |                                |
| White                           | 40.8%                               | 26.5%                                  | 3.1%                           |
| Black                           | 5.9%                                | 33.0%                                  | 6.9%                           |
| API                             | 26.6%                               | 26.4%                                  | 3.8%                           |
| Hispanic                        | 22.4%                               | 26.6%                                  | 4.0%                           |
| Other                           | 4.3%                                | 27.4%                                  | 4.1%                           |
| Pre-pregnancy BMI               |                                     |  |                                |
| Underweight                     | 2.0%                                | 17.3%                                  | 3.5%                           |
| Normal                          | 45.3%                               | 22.8%                                  | 3.6%                           |
| Overweight                      | 24.4%                               | 28.4%                                  | 4.0%                           |
| Obese                           | 19.3%                               | 36.8%                                  | 4.4%                           |
| Prenatal Antibiotics            |                                     |  |                                |
| Yes                             | 29.6%                               | 28.3%                                  | 4.6%                           |
| No                              | 70.4%                               | 26.4%                                  | 3.5%                           |
| Allergic Rhinitis               |                                     |  |                                |
| Yes                             | 42.7%                               | 28.0%                                  | 5.1%                           |
| No                              | 57.3%                               | 26.1%                                  | 2.8%                           |
| <b>Child Characteristics</b>    |                                     |  |                                |
| Gender                          |                                     |  |                                |
| Male                            | 51.2%                               | 28.1%                                  | 4.5%                           |
| Female                          | 48.8%                               | 25.7%                                  | 3.0%                           |
| Gestational Age                 |                                     |  |                                |
| Preterm                         | 6.7%                                | 39.9%                                  | 4.6%                           |
| Full-term                       | 93.3%                               | 26.0%                                  | 3.7%                           |
| Birth order                     |                                     |  |                                |
| 1st born                        | 42.4%                               | 28.6%                                  | 4.5%                           |
| 2nd born                        | 36.8%                               | 26.4%                                  | 3.4%                           |
| 3rd+ born                       | 21.8%                               | 23.3%                                  | 2.8%                           |
| Breastfeeding                   |                                     |  |                                |
| None                            | 10.0%                               | 31.0%                                  | 3.8%                           |
| <3 mos.                         | 19.7%                               | 28.8%                                  | 4.1%                           |
| 3-6 mos.                        | 11.9%                               | 27.1%                                  | 4.2%                           |
| >6 mos.                         | 45.6%                               | 25.2%                                  | 3.6%                           |
| Missing                         | 12.9%                               | 26.7%                                  | 3.6%                           |

<sup>a</sup> Percents represent the percent of the total population (column percent)

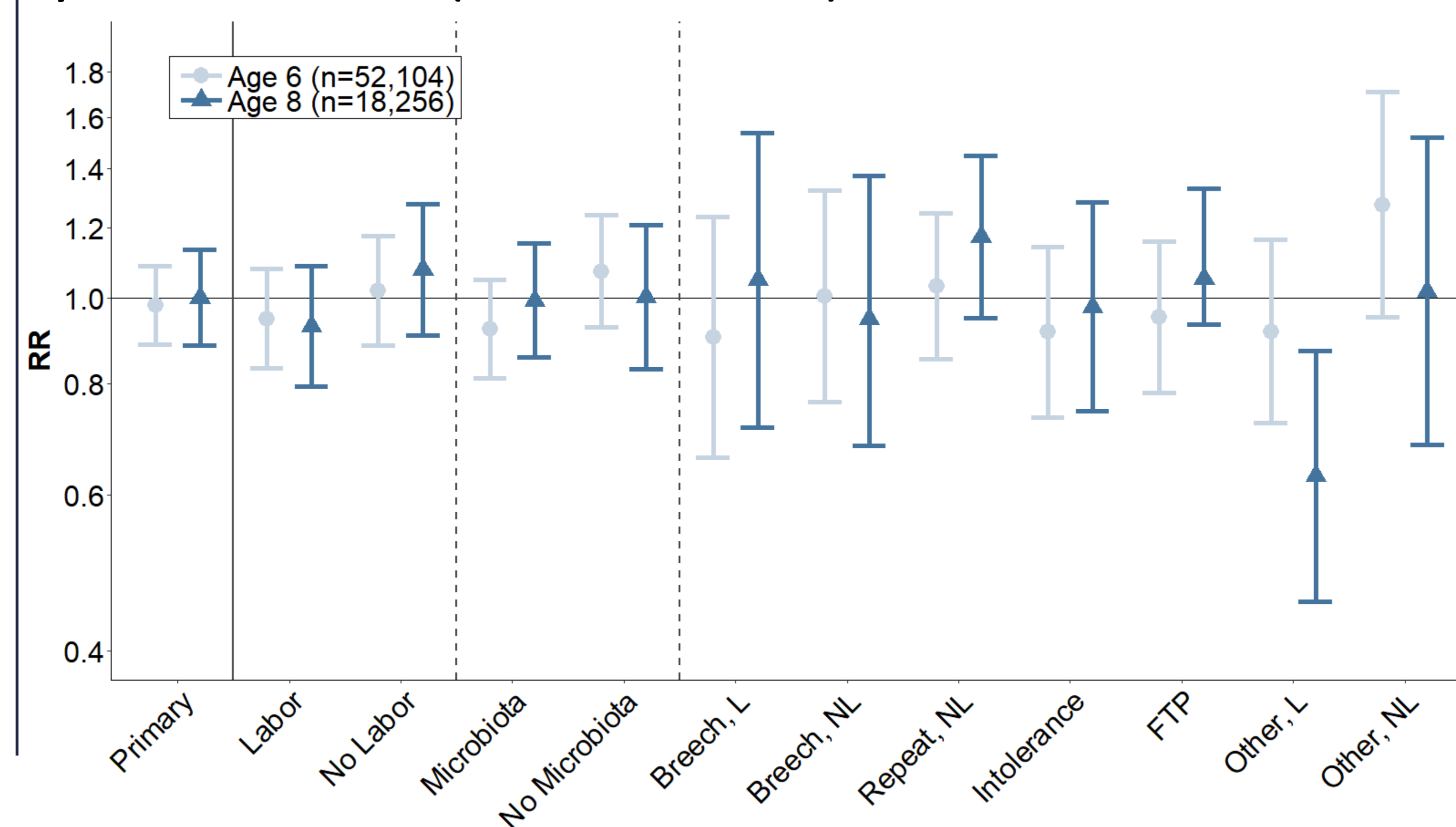
<sup>b</sup> Percents represent the percent of individuals in each covariate category born via C-sections or meeting the AR case definition at age 6.

### Results

**Figure 1: Risk ratios for the association between C-section and AR, stratified by potential effect modifiers**



**Figure 2: Risk ratios for the association between C-section and AR, subdivided by C-section attributes (for births after 2008)**



### Discussion

- The proportion of children meeting the AR case definition at each follow-up age was 3.8% at age 6, 6.8% at age 8, and 9.2% at age 10.
- C-section delivery accounted for about 27% of deliveries among all follow-up age groups
- Despite an unadjusted association between C-section and AR, after adjustment there was no association between C-section and AR [RR<sub>6</sub>(CI): 0.98(0.91, 1.04); RR<sub>8</sub>(CI): 1.00(0.95, 1.07); RR<sub>10</sub>(CI): 1.03(0.96, 1.10)]. Stratification by potential effect modifiers yielded similar estimates.
  - There was modest evidence of an increased risk of AR associated with C-section among younger siblings [RR<sub>10</sub>(CI): 1.08(0.98, 1.19)] and children born to mothers without allergies [RR<sub>10</sub>(CI): 1.19(1.05, 1.35)].
- Children born via C-section in the "other, labor" category were less likely to develop AR at age 8 [RR<sub>10</sub>(CI): 0.63 (0.45, 0.87)] compared to vaginally delivered children.
- Bias analyses indicated that consideration of missing data, loss to follow-up, intrapartum antibiotics, or alternate AR case definitions yielded similar estimated associations.
- Strengths of the analysis include: (1) large sample size in a contemporary US cohort, (2) thorough examination of potential sources of bias, (3) adjustment for often excluded confounders

**Abbreviations:** API, Asian/Pacific Islander; AR, allergic rhinitis; BMI, body mass index; C-section, cesarean section delivery; FTP, failure to progress; ICD, International Classification of Disease; KPNC, Kaiser Permanente Northern California; L, labor; NL, no labor