DR. MEGAN RICHARDS (Orcid ID : 0000-0003-0737-389X)

Article type : Research Article

Intrapartum antibiotics and childhood asthma and allergic rhinitis: a retrospective cohort study

Megan Richards, PhD[1], Jeannette Ferber, MPH[2], Erin Swor MD[3], Toby Frescholtz MD[4], De-Kun Li, MD PhD[2], Lyndsey A. Darrow, PhD[1]

1. School of Community Health Sciences, University of Nevada, Reno, NV, USA
2. Division of Research, Kaiser Permanente Northern California, Oakland, CA, USA
3. Department of Obstetrics and Gynecology, University of Michigan, Ann Arbor, MI
4. School of Medicine, University of Nevada, Reno, NV, USA

Conflict of Interest: The authors have no conflicts of interest to disclose.

Short Title: Intrapartum antibiotics and allergic disease

ABSTRACT

Objective: This study aimed to evaluate the association between intrapartum antibiotics (IABX) and asthma and allergic rhinitis among children by ages 6, 8, and 10 years old.

Design: Retrospective cohort.

Setting and Population: Data were collected though Kaiser Permanente Northern California's (KPNC) integrated healthcare system. Children were eligible if they were born in a KPNC hospital between 1997 and 2012 and stayed enrolled through age 6.

Methods: Modified Poisson regressions with robust error variances were used to estimate risk ratios for IABX and each outcome at each follow-up age during two separate time periods [1997-2004 (n=91,739), 2005-2012 (n=108,314)].

Main outcome measures: Asthma and allergic rhinitis by ages 6, 8, and 10.

Results: The proportion of women receiving IABX increased drastically over the study period (4% in 1997 to 49% in 2011), while the incidence of asthma (8%) and allergic rhinitis (6%) stayed relatively stable. In adjusted models, risk ratios for the association between IABX and asthma and allergic rhinitis were largely compatible with the null with some slightly elevated risk ratios observed. For births from 1997-2004 risk ratios for asthma were 1.08(1.00, 1.17) at age 6, 1.05(0.97, 1.15) at age 8, and 1.08(0.99, 1.18) at age 10; for births 2005-2012, risk ratios were 1.00(95% CI: 0.95, 1.04) at age 6, 1.07(1.01, 1.12) at age 8, and 1.11(1.03, 1.20) at age 10.

Conclusions: Exposure to intrapartum antibiotics is not a strong predictor of childhood asthma or allergic rhinitis risk.

Keywords: Intrapartum antibiotics, asthma, allergic rhinitis

Tweetable Abstract: Exposure to intrapartum antibiotics is not a strong predictor of childhood asthma or allergic rhinitis risk.

INTRODUCTION

The use of intrapartum antibiotics (IABX) has increased drastically over the previous two decades and currently more than a third of women receive antibiotics during labor and delivery. The increased use of IABX is in part due to the American College of Obstetricians and Gynecologists (ACOG) 2002 guideline for the prevention of early-onset group B strep (GBS) disease, which recommends universal screening and prophylactic antibiotic treatment,[1] as well as current ACOG recommendations to administer prophylactic antibiotics to all cesarean section deliveries (C-section).[2] Antibiotics given during labor and delivery have been shown to alter the infant microbiome,[3–9] which may affect early-life immune system development and make children more susceptible to asthma and allergic diseases later in life because the microbiome plays a central role in the development of allergic diseases.[10–12]

Antibiotic exposure early in life has been associated with an increased risk of asthma and allergic rhinitis (AR), though no studies have assessed the association between intrapartum antibiotics and these outcomes. It is important to look specifically at antibiotics administered during the intrapartum period because the dose of antibiotics that infants are exposed to at this time is much greater than other early life exposure windows.[1,2,13] Two separate meta-analyses found an increased risk of asthma among children who were exposed to antibiotics in the first year of life [OR(CI): 1.27(1.12, 1.43)],[14] and an increased risk of AR associated with antibiotic exposure in the first two years of life [OR(CI): 1.23(1.13, 1.34)].[15] Similarly, studies have reported an increased risk of asthma associated with prenatal antibiotic exposure.[16,17]

The primary aim of this study was to assess the association between intrapartum antibiotics and risk of asthma and allergic rhinitis by ages 6, 8, and 10 in a large, integrated healthcare delivery system. As a secondary exposure classification, we aimed to determine if the class of antibiotics given during labor and delivery or the probable reason for receiving IABX influenced conclusions.

METHODS

Study Population

The study population was a subset of all singleton live births in Kaiser Permanente Northern California's (KPNC) integrated healthcare delivery system between January 1, 1997 and January 2, 2012. Multiple births were excluded because of differences in delivery characteristics and early childhood outcomes. Children were included in the retrospective cohort if they were born at a KPNC hospital and had continuous enrollment through at least age 6. Children were excluded if they were born at a contracting hospital, due to limited information on in hospital antibiotic dispensings, or if they ever received a cystic fibrosis diagnosis, because of the high use of early life antibiotics and challenges of diagnosing asthma in children with cystic fibrosis. Outcomes were assessed at ages 6, 8, and 10 years if children remained enrolled in the KPNC system through each follow-up age and reached each age by the end of 2017, the end of the study period (i.e., not administratively censored). See Figure S1 for a flow diagram of study exclusion and sample size at each follow-up age. Because of the implementation of the EPIC electronic medical record system and increase in variable collection starting in 2005, as well as the dramatic change in the indications and frequency of IABX use, the study population was divided into two study periods based on birthdate (January 1, 1997-December 31, 2004; January 1, 2005-January 2, 2012). Throughout the paper we will refer to these two time periods as the 1997 cohort and the 2005 cohort, respectively.

Intrapartum Antibiotics

Intrapartum antibiotic (IABX) data were collected through KPNC's electronic health record (EHR). IABX were defined as any intravenous antibiotic given during the delivery admission prior to the time of delivery. To account for antepartum hospitalizations, only inpatient antibiotics given within three days of delivery were classified as intrapartum; if antibiotics were given more than three days prior to birth they were considered prenatal antibiotics. Among women who received IABX, 99.7% had at least one administration within 24 hours of delivery.

IABX were categorized according to the classes of antibiotics women received. Antibiotic classes included penicillin, cephalosporin, aminoglycoside, lincosamide, macrolide, or another class of antibiotics. Indicator variables were created for each class, allowing for women to be classified as exposed to more than one class of antibiotic. In the 2005 cohort, IABX were additionally categorized based on the probable indication for receiving IABX including a positive GBS test (GBS+) during pregnancy, not having a GBS test result by time of delivery (GBS unknown), C-section, and chorioamnionitis or intra-amniotic infection (IAI), see Table S1 for International Classification of Disease (ICD) codes. From these indications, six exclusive categories were created: (1) GBS+ (2) GBS unknown (3) C-section (4) IAI (5) multiple indications (6) other/unknown.

Outcome Definitions

We chose strict disease definitions to minimize false positive outcomes, which determine bias in the risk ratio regardless of the false negative probability.[18] Asthma was defined at each follow-up age (6, 8, 10) using ICD codes from the EHR and prescription dispensing information. To be classified as an asthma case, children had to meet two criteria. First, children had to have either an inpatient discharge diagnosis code for asthma (primary code, or secondary code if the primary code was a respiratory infection, see Table S1 for list of codes), or two outpatient asthma ICD codes (ICD-9: 493; ICD-10: J45) at least 30 days apart. Second, children had to have at least two dispensings of a controller medication at least 30 days apart in their lifetime. In order to meet the case definition at each follow-up age, at least one controller medication must have been dispensed within the previous 12 months, therefore allowing children's asthma status to change between follow-up ages. AR was defined as having two AR diagnosis codes (ICD-9: 477; ICD-10: J30) at least 30 days apart; and either one AR medication, or a third AR diagnosis code. AR medications included nasal corticosteroids and second-generation antihistamines. To meet the case definition at each follow-up age, at least one diagnosis code or prescription must have been within the previous two years.

Covariate Information

Covariate information for both mothers and children was collected from the EHR, pharmacy dispensing database, birth records, and prospectively collected breastfeeding surveys at well-child visits. Maternal covariates included age, race, education, pre-pregnancy BMI, smoking, co-morbid conditions (see Table S1), and antibiotic use during pregnancy. Infant covariates included mode of delivery, sex, gestational age, birth order, birthweight, neonatal intensive care unit admission of at least two days, breastfeeding duration, and antibiotics in the first year of life.

Statistical Analysis

The distribution of covariates by exposure and outcome groups was compared across study periods and follow-up ages. Given the interpretation advantage of risk ratios (RR) over odds ratios when the outcome is common and advantageous properties for minimizing bias from disease misclassification,[17] we used modified Poisson regression models with robust variance estimation to estimate RRs and 95% confidence intervals (CI). Confounders selected for the fully adjusted primary models differed based on outcome and study period and were informed by directed acyclic graphs. Models used to assess the association between IABX and asthma included all confounders listed above. For models estimating the risk of AR, all confounders listed above except for hypertension and diabetes variables were included. Information on pre-pregnancy BMI and breastfeeding was unavailable in the 1997 cohort and therefore not included in the models.

We conducted several sub-analyses including one restricted to children who did not have any prenatal or infant antibiotic exposures (i.e., IABX would have been the only early life antibiotic exposure). Effect modification by gestational age (preterm/full-term), maternal asthma or allergy (yes/no), and birth order (firstborn/second+ born) was examined using stratified models, which allowed for independent estimation of covariate effects within strata. Maternal asthma or allergy was defined as having any ICD codes for asthma, AR, atopic dermatitis, food allergy, or other allergies in the mothers' EHR (see Table S1). The effects of antibiotic classes were assessed using a single model that included all classes and the same covariates as the primary models. In the 2005 cohort, the association between the mutually exclusive IABX indication categories and the outcomes was assessed using models similar to the primary models.

Potential sources of bias were assessed to determine if they were affecting our results and leading to inconsistent results across time and follow-up ages. Inverse probability weights (IPW) were used to determine if missing outcome data, due to drop-out from the KPNC system, had an effect on the estimated associations. We used a weighted generalized estimating equations[19] approach using all measured variables in a logistic regression to estimate probability of dropout at each follow up age, and

then weighted subjects by their inverse probability of dropout in the main analysis to account for imbalanced loss to follow-up. Indicators for whether the child reached the specified follow-up age during the study period were included in the missingness model to account for administrative censoring. To control for potentially unmeasured familial factors, we conducted a matched sibling analysis among mothers who had at least two children born in the KPNC system with discordant IABX exposures between 1997-2012.

Results for each age (6, 8, and 10 years) are represented using subscripts (e.g. RR_6, n_6, etc.). All analyses were completed in SAS 9.4 (SAS Institute, Cary, NC). This study was approved by the Institutional Review Boards at the University of Nevada, Reno and Kaiser Permanente.

RESULTS

There were 91,739 children included in the 1997 cohort (n_8=81,714; n_{10}=73,905) and 108,314 children included in the 2005 cohort (n_8=68,353; n_{10}=36,039). The majority of attrition in the 2005 cohort was due to administrative censoring (i.e., not reaching each follow-up age by the end of the study) and not drop-out from the KPNC system. The proportion of women that received IABX increased dramatically over time (See Figure 1). In the 1997 cohort, 7% of women received IABX. In the 2005 cohort the overall proportion of women receiving IABX was 39%, with IABX steadily increasing across birth years. Women who received penicillin (the recommended treatment for GBS)[1] were administered, on average, a total of 12.0 million units (SD: 7.4) during labor and delivery. Women who received cefazolin, a cephalosporin antibiotic commonly given during C-sections,[2] had a total dose of 2.5g (SD: 3.7), on average. Unlike IABX, the proportion of children who met the case definition for asthma and AR did not differ across birth years. Across both time periods and all ages of follow up, about 8% of children met the case definition for asthma. As expected, the proportion of children meeting the case definition for AR increased across follow-up ages (age 6: 4%; age 8: 6%; age 10: 8%) but did not vary across time periods.

The distribution of maternal characteristics was similar in the 1997 cohort compared to the 2005 cohort (Table 1, Table S2). In the 2005 cohort compared to the 1997 cohort, there was a larger proportion of mothers who were Asian or Pacific Islander, had more than 16 years of education, had any health condition, and delivered via C-section. In both cohorts, women were more likely to receive IABX if they had a C-section, were older, had more years of education, had asthma or allergies, or if their child was preterm, had a birthweight <2500g, or was the first born. In the 2005 cohort, when pre-pregnancy BMI data were available, women were more likely to receive IABX if they had higher BMIs.

Asthma

Unadjusted estimates for the association between IABX and asthma were elevated and once adjusted for covariates, showed less evidence that IABX are associated with childhood asthma. Risk ratios were consistent across ages in the 1997 cohort [RR_6(CI): 1.08(1.00, 1.17); RR_8(CI): 1.05(0.97, 1.15); RR_{10}(CI): 1.08(0.99, 1.18)] (See Figure 2; Table S3). In the 2005 cohort, the risk ratios were highest for asthma assessed at age 10 [RR_6(CI): 1.00(0.95, 1.04); RR_8(CI): 1.07(1.01, 1.12); RR_{10}(CI): 1.11(1.03, 1.20)]. Restricting the sample to children who were not exposed to prenatal or infant antibiotics resulted in risk ratios that were slightly higher, but more uncertain, than the primary adjusted model for both time periods and all age cohorts (Table S3). There was no statistical evidence that the association between IABX and asthma varied by gestational age, maternal asthma or allergy status, or birth order.

Allergic Rhinitis

Both unadjusted and adjusted estimates for the association between IABX and AR were higher in the 1997 cohort than in the 2005 cohort (See Figure 2; Table S3). In the 1997 cohort, adjusted estimates showed a positive association between IABX and AR [RR_6(CI): 1.12(1.00, 1.25); RR_8(CI): 1.13(1.03, 1.24); RR_{10}(CI): 1.05(0.96, 1.15)]; in the 2005 cohort, adjusted estimates were all close to an RR of 1.00. Restricting the sample to children who were unexposed to prenatal or infant antibiotics, estimates for the 1997 cohort increased, whereas estimates for the 2005 cohort decreased. In analyses stratified by gestational age, maternal asthma or allergy status, or birth order there were no statistically significant differences in the risk ratios across strata.

IABX Classes and Indications

When IABX exposure was categorized based on the class of antibiotics a woman received, results did not show consistent patterns across time periods or follow-up ages (See Figure 3; Table S4). There was suggestive evidence that exposure to lincosamide antibiotics increased the risk of childhood asthma, however estimates were imprecise with wide confidence intervals. There were no indication categories for IABX that showed consistent associations with either asthma or AR (See Figure S2; Table S5).

Bias Assessments

Using IPW we did not observe evidence of bias due to drop-out from the KPNC system (Table S7). In a matched-sibling analysis spanning both time periods (n=31,401), there was not a consistently increased risk of asthma [RR_6(CI): 1.00(0.83, 1.13; RR_8(CI): 1.01(0.86, 1.18); RR_{10}(CI): 1.09(0.88, 1.34)] or AR [RR_6(CI): 0.94(0.79, 1.11); RR_8(CI): 0.96(0.81, 1.13); RR_{10}(CI): 1.04(0.84, 1.29)] among siblings who were exposed to IABX compared to siblings who weren't exposed to IABX.

DISCUSSION

Motivated by the increased use of IABX, evidence that IABX impact the infant gut microbiome, and limited research into the long-term effects of IABX, we investigated the effects of IABX on the incidence of asthma and AR in childhood. In a large, longitudinal cohort of 200,053 mother-child pairs the risk of asthma and AR was about the same for children born to women receiving IABX compared to those who did not. For asthma at follow-up ages of 8 and 10 in the 2005 cohort, we observed a 5-11% relative increase in risk with exposure to IABX; although these associations were modest and inconsistent, a slight increase in risk due to IABX cannot be ruled out. Elevated risk ratios for AR were isolated to the 1997 cohort, a time in which IABX use was less common, with no evidence of an association in more recent years. The largely null results observed do not warrant changes to the current guidelines for IABX administration, which are important to the prevention of maternal and infant infections.

In 1997 only 4% of births received IABX, whereas in 2005 this increased to 22% and to 49% in 2011. This 12-fold increase in IABX administration was not accompanied by a corresponding change in the proportion of children meeting our asthma or AR case definitions, which was flat over the study period. The drastic increase in IABX administration is most likely due to the 2002 ACOG committee opinion recommending IABX for all women who are colonized with GBS, as well as the ACOG practice bulletin recommending administration of prophylactic antibiotics to all women undergoing C-section delivery. This is perhaps the strongest evidence in our study against an effect of IABX on asthma or AR. Instead, it may indicate that the inconsistent results across time periods are due to differences in unmeasured confounders, for example, temporal differences in the reasons a woman was prescribed IABX. Children born before universal GBS screening and prophylactic antibiotic treatment for C-section were exposed to IABX for different reasons. If a mother received IABX prior to the issuance of these two guidelines, it was most likely because she had at least one risk factor for or early sign of maternal or neonatal infection.[20] If these factors are also associated with a greater risk of asthma and AR in childhood, this may explain the higher risk ratios for the infants born in earlier years.

There is a wealth of evidence demonstrating that the use of IABX reduces neonatal GBS infection, surgical site infection after C-section, and improves birth outcomes for women with IAI, and the results in the KPNC population suggest this common practice does not increase the risk of asthma and AR later in life. However, it is possible that the risk of asthma or AR varies across antibiotic classes because each class of antibiotics differentially impacts the infant microbiome.[9] In our analyses, the class most suggestively associated with asthma was lincosamide antibiotics, although confidence intervals

were wide. This is a potentially noteworthy finding because lincosamide antibiotics are most commonly recommended for women who have a suspected penicillin allergy.[1,2] Although penicillin allergies have not been associated with other allergic diseases, there may be other characteristics of these mothers that are associated with their children's asthma or AR risk.

There has been extensive research into the possible effects of antibiotics during pregnancy and infancy on atopic disorders such as asthma and AR, but this study is the first to focus on IABX, which represent relatively high doses of antibiotics at the time of birth. For the prevention of neonatal infection with GBS, ACOG recommends a 5 million unit loading dose of penicillin, followed by 2-3 million units every four hours until birth.[1] Comparatively, to treat a bacterial infection in adults the recommended dose of penicillin is 200,000 to 500,000 units every four to six hours.[13] Our results reassuringly show that IABX are unlikely to increase the risk of these common childhood outcomes. However, among multiple comparisons we did observe several modest positive associations which, if causal, could be important on a population level. Future studies should attempt to replicate these findings in other large cohorts.

We chose strict outcome definitions requiring multiple diagnosis codes and medication dispensings to define the outcomes, which increased the specificity of outcome classification, and reduced bias in the risk ratio due to outcome misclassification.[18] However, because of the strict definition there is the possibility that children with mild asthma or AR were misclassified leading to an outcome group more weighted toward severe disease. We assessed many potential sources of bias including selection bias due to drop out from the KPNC system (IPW analysis) and confounding by familial factors (sibling analysis). We did not find evidence of selection bias and there was a not a consistently elevated association between IABX and the outcomes among discordant siblings. This may indicate that there are unmeasured familial covariates that are driving the small positive associations reported in the primary models.

CONCLUSION

In this study we observed little evidence that IABX increases the risk of asthma or AR in early childhood. Some positive associations were observed for asthma which may motivate future studies, but risk ratios were all close to 1 and positive results should be interpreted in light of multiple comparisons. Stratified analyses did not show an increased risk of asthma or AR associated with IABX in any subgroup. Although the use of IABX increased over the 15-year study period, there was not a corresponding increase in the prevalence of asthma and AR. To the best of our knowledge this is the first study to

assess the association between IABX and asthma or AR in childhood and fills an important gap in the literature on early life antibiotic exposures. Our study adds to the limited research on the long-term effects of IABX, use of which has increased dramatically in recent years to affect half of all deliveries in the US.

Contribution of Authorship: MR and LAD designed the study and research questions. JF and DL were responsible for data acquisition and management. MR, JF, and LAD designed and conducted the statistical analyses. ES and TF provided important obstetric guidance. MR drafted the paper, which was revised and approved by all authors.

Source of Funding: This work was supported by the National Institutes of Allergy and Infectious Disease [grant number R01AI122266]

Acknowledgments: This work was supported by the National Institutes of Allergy and Infectious Disease [grant number R01AI122266]. This work was presented at the 2020 Society for Epidemiologic Virtual Research Conference, on December 16-18, 2020.

Ethical Approval: This study was approved by the Institutional Review Boards at the University of Nevada, Reno and Kaiser Permanente on January 21, 2021 [849756-9].

REFERENCES

1. American College of Obstetricians and Gynecologists. Prevention of Group B Streptococcal Early-Onset Disease in Newborns: ACOG Committee Opinion Summary, Number 782. *Obstet Gynecol*. 2019;134(1):206-210. doi:10.1097/AOG.0000000000003335

2. American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 199: Use of Prophylactic Antibiotics in Labor and Delivery. *Obstet Gynecol*. 2018;132(3):e103-e119. doi:10.1097/AOG.0000000000002833

3. Stearns JC, Simioni J, Gunn E, et al. Intrapartum antibiotics for GBS prophylaxis alter colonization patterns in the early infant gut microbiome of low risk infants. *Sci Rep*. 2017;7. doi:10.1038/s41598-017-16606-9

4. Mazzola G, Murphy K, Ross RP, et al. Early Gut Microbiota Perturbations Following Intrapartum Antibiotic Prophylaxis to Prevent Group B Streptococcal Disease. *PloS One*. 2016;11(6):e0157527. doi:10.1371/journal.pone.0157527

5. Corvaglia L, Tonti G, Martini S, et al. Influence of Intrapartum Antibiotic Prophylaxis for Group B Streptococcus on Gut Microbiota in the First Month of Life. *J Pediatr Gastroenterol Nutr*. 2016;62(2):304-308. doi:10.1097/MPG.0000000000000928

6. Nogacka A, Salazar N, Suárez M, et al. Impact of intrapartum antimicrobial prophylaxis upon the intestinal microbiota and the prevalence of antibiotic resistance genes in vaginally delivered full-term neonates. *Microbiome*. 2017;5(1):93. doi:10.1186/s40168-017-0313-3

7. Azad MB, Konya T, Persaud RR, et al. Impact of maternal intrapartum antibiotics, method of birth and breastfeeding on gut microbiota during the first year of life: a prospective cohort study. *BJOG Int J Obstet Gynaecol*. 2016;123(6):983-993. doi:10.1111/1471-0528.13601

8. Tapiainen T, Koivusaari P, Brinkac L, et al. Impact of intrapartum and postnatal antibiotics on the gut microbiome and emergence of antimicrobial resistance in infants. *Sci Rep*. 2019;9. doi:10.1038/s41598-019-46964-5

9. Coker MO, Hoen AG, Dade E, et al. Specific class of intrapartum antibiotics relates to maturation of the infant gut microbiota: a prospective cohort study. *BJOG Int J Obstet Gynaecol*. 2020;127(2):217-227. doi:10.1111/1471-0528.15799

10. Fujimura KE, Lynch SV. Microbiota in Allergy and Asthma and the Emerging Relationship with the Gut Microbiome. *Cell Host Microbe*. 2015;17(5):592-602. doi:10.1016/j.chom.2015.04.007

11. Lee S-Y, Lee E, Park YM, Hong S-J. Microbiome in the Gut-Skin Axis in Atopic Dermatitis. *Allergy Asthma Immunol Res*. 2018;10(4):354-362. doi:10.4168/aair.2018.10.4.354

12. Pascal M, Perez-Gordo M, Caballero T, et al. Microbiome and Allergic Diseases. *Front Immunol*. 2018;9. doi:10.3389/fimmu.2018.01584

13. Mayo Clinic. Penicillin (Oral Route, Injection Route, Intravenous Route, Intramuscular Route). Published July 1, 2020. Accessed August 4, 2020. https://www.mayoclinic.org/drugs-supplements/penicillin-oral-route-injection-route-intravenous-route-intramuscular-route/proper-use/drg-20062334

14. Penders J, Kummeling I, Thijs C. Infant antibiotic use and wheeze and asthma risk: a systematic review and meta-analysis. *Eur Respir J*. 2011;38(2):295-302. doi:10.1183/09031936.00105010

15. Ahmadizar F, Vijverberg SJH, Arets HGM, et al. Early-life antibiotic exposure increases the risk of developing allergic symptoms later in life: A meta-analysis. *Allergy*. 2018;73(5):971-986. doi:10.1111/all.13332

16. Lapin B, Piorkowski J, Ownby D, et al. Relationship between prenatal antibiotic use and asthma in at-risk children. *Ann Allergy Asthma Immunol Off Publ Am Coll Allergy Asthma Immunol*. 2015;114(3):203-207. doi:10.1016/j.anai.2014.11.014

17. Popovic M, Rusconi F, Zugna D, et al. Prenatal exposure to antibiotics and wheezing in infancy: a birth cohort study. *Eur Respir J*. 2016;47(3):810-817. doi:10.1183/13993003.00315-2015

18. Rothman K, Greenland S, Lash T. *Modern Epidemiology*. 3rd Edition. LIPPINCOTT WILLIAMS & WILKINS; 2008.

19. Lin G, Rodriguez RN. Weighted Methods for Analyzing Missing Data with the GEE Procedure. :8.

20. Schrag S, Gorwitz R, Fultz-Butts K, Schuchat A. Prevention of perinatal group B streptococcal disease. Revised guidelines from CDC. *MMWR Recomm Rep Morb Mortal Wkly Rep Recomm Rep*. 2002;51(RR-11):1-22.

TABLE/FIGURE LEGENDS

Table 1. Table 1. Characteristic of the KPNC population, age 6

[a] Percents represent the percent of the total population that is within each category (i.e. column percents)

[b] Percents represent the row percents (i.e. the percent of participants within each category that had IABX, asthma or AR)

Abbreviations: API, Asian or Pacific Islander; AR, allergic rhinitis; BMI, pre-pregnancy body mass index; C-section, cesarean delivery; IABX, intrapartum antibiotics; KPNC, Kaiser Permanente Northern California; MAA, maternal asthma or allergies

Figure 1. Proportion of births receiving intrapartum antibiotics over time

Intrapartum antibiotic use increased over time throughout the study period. Lines at the bottom of the figure depict the birth years that are included in each follow-up age analysis. For example, children born in 2008 are included in the 2005 cohort for follow-up age 6 and 8.

Figure 2. Risk ratio and 95% confidence interval estimates for the association between intrapartum antibiotics and asthma and allergic rhinitis (AR).

Covariates for all models include: maternal age, race, education, pre-pregnancy BMI (2005 only), smoking, allergy and asthma status, antibiotic use during pregnancy, mode of delivery, birthweight, sex, birth order, NICU admission, breastfeeding (2005 only), and antibiotics in the first year of life. Additional covariates in asthma models include: gestational diabetes, type II diabetes, pre-pregnancy hypertension, pregnancy induced hypertension

Figure 3. Risk ratios and 95% confidence intervals for the association between antibiotic class and asthma

All classes of antibiotics were included in the model.

Model adjusted for maternal age, race, education, pre-pregnancy BMI (2005 only), smoking, allergy and asthma status, gestational diabetes, type II diabetes, pre-pregnancy hypertension, pregnancy induced hypertension, antibiotic use during pregnancy, mode of delivery, birthweight, sex, birth order, NICU admission, breastfeeding (2005 only), and antibiotics in the first year of life.

Table 1. Characteristic of the KPNC population, age 6

	1997 Cohort				2005 Cohort			
	Total[a]	IABX[b]	Asthma[b]	AR[b]	Total[a]	IABX[b]	Asthma[b]	AR[b]
	n=91,739	n=6514	N=7236	N=3868	n=108,314	n=42,041	N=8082	N=4209
Maternal age (years)								
<25	15.5%	6.4%	7.3%	3.3%	10.2%	36.7%	8.7%	4.3%
25-29	28.0%	6.7%	8.3%	4.4%	27.4%	37.3%	7.2%	3.7%
30-34	33.0%	7.3%	7.7%	4.1%	35.7%	38.5%	7.2%	3.8%
35-39	19.0%	7.6%	8.1%	4.4%	21.2%	41.2%	7.7%	4.1%
40+	4.5%	8.6%	7.7%	3.8%	5.4%	43.6%	7.2%	4.1%
Maternal education								
<12 years	6.8%	4.2%	7.1%	3.0%	4.8%	32.4%	7.8%	4.0%
12-15 years	51.9%	6.7%	8.0%	4.1%	43.7%	38.8%	8.3%	4.3%
16+ years	37.7%	7.7%	7.7%	4.3%	50.5%	39.4%	6.7%	3.5%
Missing	3.6%	12.8%	9.5%	4.8%	1.1%	39.9%	8.4%	4.5%
Maternal race								
White	48.1%	7.0%	6.8%	3.9%	42.4%	37.5%	6.0%	3.2%
Black	5.4%	7.5%	11.2%	5.7%	6.1%	46.0%	12.3%	7.4%
API	20.0%	7.3%	8.8%	4.4%	27.8%	40.1%	7.9%	3.9%
Hispanic	22.4%	6.7%	8.4%	3.9%	23.0%	37.8%	8.4%	4.2%
Other	4.1%	9.5%	9.1%	4.1%	0.7%	37.6%	7.0%	3.6%
Maternal BMI (kg/m^2)[c]								
Underweight	-	-	-	-	2.1%	36.9%	5.6%	3.2%
Normal	-	-	-	-	45.6%	37.5%	6.6%	3.6%
Overweight	-	-	-	-	24.3%	41.0%	7.7%	4.2%
Obese	-	-	-	-	19.1%	46.9%	9.3%	4.6%
Missing	-	-	-	-	8.8%	22.2%	7.4%	3.1%
MAA								
No	77.2%	6.5%	7.0%	3.7%	44.5%	37.2%	5.2%	2.7%
Yes	22.9%	9.1%	10.8%	5.5%	55.5%	40.2%	9.3%	4.9%
C-Section								
No	81.8%	6.4%	7.5%	3.9%	74.0%	29.3%	7.0%	3.8%
Yes	18.2%	10.3%	9.6%	4.8%	26.0%	65.8%	8.7%	4.2%
Infant Gender								
Male	51.0%	7.3%	9.8%	5.0%	51.2%	39.5%	9.0%	4.6%

Female	49.0%	6.9%	5.9%	3.2%	48.8%	38.1%	5.8%	3.1%
Preterm								
Yes (<37 weeks)	6.2%	24.4%	12.0%	4.5%	6.7%	66.3%	12.2%	4.7%
No (≥37 weeks)	93.8%	6.0%	7.6%	4.2%	93.3%	36.8%	7.1%	4.3%
Birth order								
1st born	40.0%	10.4%	8.2%	5.1%	42.1%	43.5%	7.6%	4.6%
2nd born	36.2%	5.1%	8.1%	3.9%	36.2%	35.7%	7.5%	3.6%
3rd+ born	23.8%	4.7%	7.0%	2.7%	21.7%	34.9%	7.1%	3.0%

[a] Percents represent the percent of the total population that is within each category (column percents)

[b] Percents represent the row percents (the percent of participants within each category that had IABX/asthma/AR)

[c] BMI categories are as follows: underweight (<18.5 kg/m^2); normal (18.5-24.9 kg/m^2); overweight (25-29.9 kg/m^2); obese (≥ 30 kg/m^2)

Abbreviations: API, Asian or Pacific Islander; AR, allergic rhinitis; BMI, pre-pregnancy body mass index; C-section, cesarean delivery; IABX, intrapartum antibiotics; KPNC, Kaiser Permanente Northern California; MAA, maternal asthma or allergies