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**eTable 1. Definition of Covariates**

|  |  |  |
| --- | --- | --- |
| **Covariate** | **Definition** | **Missing (%)** |
| **Demographic** |  |  |
| Infant sex | Male, female | 0 (0.0) |
| Infant’s race/ethnicity | White, Black, Hispanic, Asian/Pacific Islander, other, unknown/missing | 2 953 (1.3) |
| Socioeconomic status | Health insurance coverage through government health care assistance programs such as Medicaid (Yes/No) was used as proxy for socioeconomic status. | 0 (0.0) |
| **Maternal and pregnancy** | |  |
| Education | As reported on birth certificate: less than high school, high school, some college, bachelor’s degree or higher, unknown | 2 614 (1.2) |
| Parity | Continuous | 20 681 (9.3) |
| Diabetes | Defined as any one of the following conditions: 1) a diagnosis of diabetes (International Classification of Diseases, 9th revision, Clinical Modification ICD-9-CM 249 or 250, or 10th revision ICD-10 E10, E11 or E12) during or within 24 months prior to the current pregnancy, 2) a diagnosis of gestational diabetes (ICD-9-CM 648.8, ICD-10 O24.4, O99.81), 3) a hemoglobin A1c ≥ 6.5% during or within 24 months prior to the current pregnancy. | 0 (0.0) |
| Pre-pregnancy BMI | Base body weight measured closest to the beginning of pregnancy within a time window of 6 months before and 3 months after the first week of gestation. Missing values imputed.  A maternal height <4 feet or ≥7 feet, 2 inches was considered biologically implausible and excluded from the analysis. Maternal weight data were excluded if weight was <30 lbs or ≥1000 lbs. Because implausible combinations of weight and height may be missed by the procedures described above, we additionally excluded BMI values <5 kg/m2 or ≥100 kg/m2 as implausible. | 28 420 (12.7) |
| Gestational weight gain | Calculated as difference between pre-pregnancy weight and weight measured at delivery. Missing values imputed. | 22 372 (10.0) |
| Chorioamnionitis | Defined as an ICD-9 code of 658.4x, 762.7, 658.4x or ICD-10 code of O41.12xx, P02.7, O41.10xx. | 0 (0.0) |
| Smoking during pregnancy | Smoking, no smoking | 0 (0.0) |
| Antepartum antibiotic exposure  Trimester 1/2  Trimester 3 | Maternal prescription of antibiotics during (Yes/No). Missing values were treated as not exposed.  Up to 26 completed gestational weeks. Between 27 gestational weeks and date of hospital admission for delivery. For mothers with longer or multiple inpatient stays before delivery, we defined the 3rd trimester as ending 48 hours before delivery (intrapartum). | 68 920 (30.8) 0 (0.0) |
| **Birth** |  |  |
| Year of birth | Continuous from 2007 to 2015 | 0 (0.0) |
| Birth weight | Continuous, as reported on birth record | 0 (0.0) |
| Gestational age | Gestational age at birth is based on the clinical estimate of gestational age as recorded in the maternal electronic medical records, to the nearest completed week | 0 (0.0) |
| Medical center | One of 14 KPSC medical centers in which delivery was recorded | 0 (0.0) |
| **Childhood** | |  |
| Any breastfeeding | Any breastfeeding (Yes/No) during the first 6 months after birth, obtained from unstructured progress notes using natural language processing between 2007-2010, and from surveys administered during or prior to well-child visit as described elsewhere (does this statement need a reference?) | 10 984 (4.9) |
| Neonatal antibiotics | Antibiotic exposure during the first 28 days after birth (Yes/No) | 0 (0.0) |
| Lactation antibiotics | Indirect antibiotic exposure during breastfeeding by linkage with maternal EMR (Yes/No) | 0 (0.0) |
| Childhood antibiotics | Cumulative exposure to antibiotics as time-varying count until the end of follow up | 0 (0.0) |

**eTable 2. Sensitivity analyses exclusions**

|  |  |  |
| --- | --- | --- |
| **Exclusions** | **Rationale and Definition** | **Excluded N (%)** |
| **Sensitivity 1:** Healthy term cohort | Rationale: Explore impact of children who were born prematurely, with high or low birth weight, and/or with complex health conditions on effect size.  Low/high birth weight was defined based on the 2000 to 2015 race/ethnicity- and sex-specific nomogram (internal standard); birth weight below the 5th percentile or higher than the 95th percentile for gestational age | 22 198 (9.9) |
|  | Preterm birth was defined as gestational age <37th week | 17 191 (7.7) |
|  | Neonatal sepsis was defined as having a positive blood or cerebrospinal fluid culture in first 72 hours with > 5 days of antibiotic therapy. Prolonged inpatient stay was defined as NICU admission > 5 days or total stay > 7 days. | 11 567 (5.2) |
|  | Complex care conditions were defined according to CCC classification system V2 of the 9 categories (cardiovascular, respiratory, neuromuscular, renal, gastrointestinal, hematologic or immunologic, metabolic, other congenital or genetic, and malignancy).20,21 | 21 607 (9.7) |
|  | Any of the conditions above | 49 467 (22.1) |
| **Sensitivity 2:** GBS IAP antibiotics only | Rationale: To investigate if GBS IAP alone or exposure to other antibiotics such as for treatment of chorioamnionitis explains the association between exposure and childhood BMI.  Infants were not excluded but reclassified as exposed to other intrapartum antibiotics. GBS IAP was defined as penicillin G, ampicillin, cefazolin, clindamycin and/or vancomycin ≥4 hours before delivery only. No other antibiotics allowed (except skin prophylaxis for Cesarean section). | Reclassified: 4302 (10.8) of GBS IAP |
| **Sensitivity 3:** Homogenous groups with regard toGBS colonization: | Rationale: To examine whether GBS colonization may have an effect in addition to antibiotic prophylaxis  Using GBS colonization status (positive, negative, unknown) based on bacteriological screening and standard cultures conducted from vaginal-rectal swabs and urine samples, infants were excluded as follows:  Vaginal delivery: No antibiotic exposure: if GBS status positive or unknown GBS IAP: If GBS status negative or unknown Other antibiotic exposure: if GBS status positive or unknown  Cesarean delivery: GBS IAP: If GBS status negative or unknown Other antibiotic exposure: if GBS status positive or unknown | 7270 11728 6041  3897 14300 |
| **Sensitivity 4:** No antepartum antibiotic exposure | Rationale: To eliminate the effect of antepartum antibiotic exposure on risk for GBS colonization  Children born to women with any antibiotic exposure during pregnancy but before intrapartum period were excluded | 79824 |

**eTable 3: Duration and route of intrapartum antibiotic administration\***

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Vaginal delivery** | | **Cesarean delivery** | |
|  | **GBS IAP** | **Other** | **GBS IAP** | **Other** |
| Children (N) | 31263 | 11425 | 8366 | 58684 |
| Unique Antibiotics (N) | 35083 | 13843 | 18300 | 65670 |
| **Duration of antibiotic administration (min)** |  |  |  |  |
| Median (IQR) | 610 (412, 920) | 101 (45, 171) | 879 (484, 1417) | 32 (18, 54) |
| **Administration route (%)** |  |  |  |  |
| Intravenous | 31263 (100.00) | 11214 (98.15) | 8366 (100.00) | 58635 (99.90) |
| Oral | 0 (0.00) | 211 (1.85) | 0 (0.00) | 49 (0.10) |
| **Antibiotic agent (%)\*** |  |  |  |  |
| Ampicillin | 9331 (26.60) | 5267 (38.05) | 3390 (18.52) | 2420 (3.69) |
| Azithromycin | 329 (0.94) | 87 (0.63) | 425 (2.32) | 1468 (2.24) |
| Cefazolin$ | 1187 (3.38) | 998 (7.21) | 4666 (25.50) | 38135 (58.07) |
| Clindamycin | 1687 (4.81) | 692 (5.00) | 960 (5.25) | 3128 (4.76) |
| Gentamycin | 2006 (5.72) | 2376 (17.16) | 1415 (7.73) | 1897 (2.89) |
| Penicillin G | 19988 (56.97) | 4105 (29.65) | 4317 (23.59) | 803 (1.22) |
| Vancomycin | 332 (0.95) | 72 (0.52) | 103 (0.56) | 73 (0.11) |
| Other | 223 (0.64) | 246 (1.78) | 138 (0.75) | 210 (0.32) |
| Surgical prophylaxis agent (cefazolin, clindamycin) not recorded | 0 (0.00) | 0 (0.00) | 2886 (15.77) | 17536 (26.70) |

\* Because infants can be exposed to more than one antibiotic, the percent may exceed 100%.

**eTable 4.**

Body mass index difference between children without exposure to antibiotics (None), children exposed to intrapartum antibiotic prophylaxis as recommended for the prevention of perinatal group B streptococcal disease (GBS IAP) and any other type or duration of intrapartum antibiotic administration (Other) stratified by delivery mode for the sensitivity analysis cohorts#.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Vaginal delivery** | | | **Cesarean delivery** | |
| **Child’s age (years)** | **None (BMI, kg/m2)** | **GBS IAP (Δ BMI, kg/m2)** | **Other (Δ BMI, kg/m2)** | **Other (BMI, kg/m2)** | **GBS IAP (Δ BMI, kg/m2)** |
| **Sensitivity 1, N** |  |  |  |  |  |
| (‘Healthy’ children only) | 95288 | 22534 | 8778 | 42082 | 5282 |
| 0.0 | 13.39 (0.0159) | -0.07 (-0.09, -0.05) | -0.05(-0.07, -0.02) | 13.36 (0.0265) | -0.11 (-0.15, -0.07) |
| 1.0 | 17.29 (0.0162) | 0.02 (-0.00, 0.04) | 0.04 (0.00, 0.08) | 17.35 (0.0267) | 0.01 (-0.04, 0.06) |
| 2.0 | 16.50 (0.0164) | 0.02 (-0.00, 0.05) | 0.05 (0.01, 0.08) | 16.54 (0.0271) | 0.08 (0.02, 0.13) |
| 3.0 | 16.19 (0.0168) | 0.04 (0.01, 0.07) | 0.05 (0.01, 0.09) | 16.25 (0.0279) | 0.08 (0.02, 0.13) |
| 4.0 | 16.05 (0.0176) | 0.06 (0.03, 0.09) | 0.04 (-0.00, 0.09) | 16.14 (0.0291) | 0.10 (0.03, 0.18) |
| 5.0 | 15.96 (0.0196) | 0.08 (0.02, 0.13) | 0.01 (-0.06, 0.09) | 16.08 (0.0322) | 0.19 (0.07, 0.31) |
| **Sensitivity 2, N** |  |  |  |  |  |
| (GBS IAP antibiotics only) | 113693 | 28832 | 13856 | 60555 | 6495 |
| 0.0 | 13.38 (0.015) | -0.28 (-0.30, -0.26) | -0.28 (-0.30, -0.25) | 13.23 (0.023) | -0.32 (-0.37, -0.28) |
| 1.0 | 17.30 (0.015) | 0.08 (0.06, 0.10) | 0.10 (0.07, 0.13) | 17.38 (0.023) | 0.06 (0.01, 0.10) |
| 2.0 | 16.51 (0.015) | 0.07 (0.05, 0.10) | 0.07 (0.04, 0.10) | 16.57 (0.023) | 0.09 (0.05, 0.14) |
| 3.0 | 16.20 (0.016) | 0.10 (0.07, 0.12) | 0.07 (0.04, 0.11) | 16.27 (0.024) | 0.11 (0.06, 0.17) |
| 4.0 | 16.05 (0.016) | 0.11 (0.09, 0.15) | 0.08 (0.03, 0.12) | 16.16 (0.025) | 0.17 (0.10, 0.24) |
| 5.0 | 15.97 (0.018) | 0.12 (0.07, 0.17) | 0.06 (0.00, 0.12) | 16.09 (0.028) | 0.27 (0.16, 0.38) |
| **Sensitivity 3, N** |  |  |  |  |  |
| (Homogenous groups with regard toGBS colonization) | 106423 | 19535 | 5384 | 44384 | 4469 |
| 0.0 | 13.43 (0.0157) | -0.11 (-0.13, -0.09) | -0.27(-0.31, -0.24) | 13.37 (0.0258) | -0.13 (-0.18, -0.09) |
| 1.0 | 17.33 (0.0159) | 0.04 (0.02, 0.07) | 0.09 (0.05, 0.14) | 17.40 (0.0260) | 0.01 (-0.05, 0.07) |
| 2.0 | 16.54 (0.0162) | 0.04 (0.01, 0.07) | 0.10 (0.05, 0.15) | 16.59 (0.0263) | 0.06 (0.00, 0.12) |
| 3.0 | 16.23 (0.0166) | 0.07 (0.04, 0.10) | 0.09 (0.04, 0.14) | 16.29 (0.0272) | 0.08 (0.02, 0.15) |
| 4.0 | 16.09 (0.0174) | 0.10 (0.06, 0.13) | 0.09 (0.03, 0.15) | 16.18 (0.0286) | 0.14 (0.06, 0.22) |
| 5.0 | 16.00 (0.0193) | 0.09 (0.03, 0.14) | 0.10 (0.00, 0.20) | 16.12 (0.0317) | 0.25 (0.11, 0.40) |
| **Sensitivity 4, N** |  |  |  |  |  |
| (No antepartum antibiotic exposure) | 76711 | 17906 | 7067 | 37190 | 4733 |
| 0.0 | 13.43 (0.0157) | -0.27 (-0.29, -0.24) | -0.17(-0.21, -0.14) | 13.37 (0.0258) | -0.25 (-0.30, -0.20) |
| 1.0 | 17.33 (0.0159) | 0.08 (0.05, 0.11) | 0.06 (0.02, 0.10) | 17.40 (0.0260) | 0.09 (0.03, 0.15) |
| 2.0 | 16.54 (0.0162) | 0.07 (0.05, 0.10) | 0.05 (0.01, 0.09) | 16.59 (0.0263) | 0.11 (0.05, 0.17) |
| 3.0 | 16.23 (0.0166) | 0.09 (0.06, 0.12) | 0.07 (0.02, 0.11) | 16.29 (0.0272) | 0.12 (0.06, 0.19) |
| 4.0 | 16.09 (0.0174) | 0.11 (0.07, 0.15) | 0.07 (0.02, 0.13) | 16.18 (0.0286) | 0.16 (0.08, 0.23) |
| 5.0 | 16.00 (0.0193) | 0.12 (0.06, 0.18) | 0.06 (-0.02, 0.15) | 16.12 (0.0317) | 0.21 (0.09, 0.34) |

# Sensitivity analysis cohort exclusions and reclassifications see eTable2.

Full Model adjustment for demographics, maternal and birth-related factors included infant sex, gestational age at birth, birth weight, infant’s race/ethnicity (White, Black, Hispanic, Asian or Pacific Islander, other or unknown), year of birth, medical center of birth, maternal education, parity, maternal diabetes, maternal pre-pregnancy BMI, maternal gestational weight gain, maternal smoking during pregnancy, antepartum antibiotic exposure, neonatal antibiotic exposure, any breastfeeding, indirect antibiotic exposure during breastfeeding, and childhood antibiotic exposure.

**eTable 5:**

Attributable body weight difference from birth to 5 years of age in children from sensitivity analysis 1 cohort (‘Healthy, term cohort’) unexposed to intrapartum antibiotics (None), exposed to intrapartum antibiotic prophylaxis as recommended for the prevention of perinatal group B streptococcal disease (GBS) and exposed to any other type or duration of intrapartum antibiotic administration (Other) stratified by delivery mode.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Vaginal delivery** | | | **Cesarean delivery** | |
|  | **None (weight gain, kg)** | **GBS (Δ weight gain, kg)** | **Other (Δ weight gain, kg)** | **Other (weight gain, kg)** | **GBS (Δ weight gain, kg)** |
| Total cohort, N | 95288 | 22534 | 8778 | 42082 | 5282 |
|  | Reference |  |  | Reference |  |
| Full Model | 15.98 | 0.16 (0.15, 0.17) | 0.05 (0.03, 0.06) | 16.15 | 0.23 (0.21, 0.26) |

Using the Full Model (Covariates through childhood) adjustment for demographics, maternal and birth-related factors included infant sex, gestational age at birth, birth weight, infant’s race/ethnicity (White, Black, Hispanic, Asian or Pacific Islander, other or unknown), year of birth, medical center of birth, maternal education, parity, maternal diabetes, maternal pre-pregnancy BMI, maternal gestational weight gain, maternal smoking during pregnancy, antepartum antibiotic exposure, neonatal antibiotic exposure, breastfeeding, indirect antibiotic exposure during breastfeeding, and childhood antibiotic exposure.



**eFigure 1:** Study flow chart

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**eFigure 2**: Crude body mass index (BMI), delta BMI, and their 95% CIs for children unexposed to intrapartum antibiotics (None), children exposed to intrapartum antibiotic prophylaxis as recommended for the prevention of perinatal group B streptococcal disease (GBS) and any other type or duration of intrapartum antibiotic administration (Other) stratified by delivery mode

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**eFigure 3**: Adjusted body mass index (BMI), delta BMI, and their 95% CIs for sensitivity analysis 1 cohort (‘Healthy, term cohort’) unexposed to intrapartum antibiotics (None), exposed to intrapartum antibiotic prophylaxis as recommended for the prevention of perinatal group B streptococcal disease (GBS) and any other type or duration of intrapartum antibiotic administration (Other) stratified by delivery mode

Using the Full Model (Covariates through childhood) adjustment for demographics, maternal and birth-related factors included infant sex, gestational age at birth, birth weight, infant’s race/ethnicity (White, Black, Hispanic, Asian or Pacific Islander, other or unknown), year of birth, medical center of birth, maternal education, parity, maternal diabetes, maternal pre-pregnancy BMI, maternal gestational weight gain, maternal smoking during pregnancy, antepartum antibiotic exposure, neonatal antibiotic exposure, any breastfeeding, indirect antibiotic exposure during breastfeeding, and childhood antibiotic exposure.





**eFigure 4**: Comparison of adjusted BMI between the exposure to antibiotics during antepartum, intrapartum and postpartum periods for sensitivity analysis 1 cohort (‘Healthy, term cohort’).

#Indirect antibiotic exposure through breastfeeding by a mother using antibiotics during the first 3 months of a child’s life. The estimate for childhood exposure is per 14-day episode of antibiotic use.

Using the Full Model (Covariates through childhood) adjustment for demographics, maternal and birth-related factors included infant sex, gestational age at birth, birth weight, infant’s race/ethnicity (White, Black, Hispanic, Asian or Pacific Islander, other or unknown), year of birth, medical center of birth, maternal education, parity, maternal diabetes, maternal pre-pregnancy BMI, maternal gestational weight gain, maternal smoking during pregnancy, antepartum antibiotic exposure, neonatal antibiotic exposure, any breastfeeding, indirect antibiotic exposure during breastfeeding, and childhood antibiotic exposure.

The reference point reflects a population mean BMI at age 5 of 15.96 (SD 0.019) kg/m2 for vaginally delivered children unexposed to intrapartum antibiotics (None) and 16.08 (SD 0.032) kg/m2 for children delivered by Cesarean section and exposed to other intrapartum antibiotics (Other).